A clinical perspective of childhood glaucoma: an exploration of genotypes, phenotypes, and quality of life

By

Mr Lachlan Wheelhouse Knight
BHSc, MOrth

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SUMMARY

Childhood glaucoma describes a group of chronic vision-threatening conditions with disease-onset occurring between birth and 18 years. It is a leading cause of irreversible childhood vision impairment and blindness and is typically associated with genetic variants with a Mendelian pattern of inheritance, some of which are known to be associated with systemic disease or a syndrome. Childhood glaucoma requires complex and specialised lifelong surgical and conservative management, and if the disease is not treated promptly, irreversible vision-impairment or blindness is the likely outcome. Treatment does not guarantee a safeguard from visual morbidity and close monitoring throughout one's lifespan is required. This means that childhood glaucoma has the potential to cause a considerable impact on quality of life for the individual and their caregivers at any time. Despite this, evidence-based clinical practice guidelines for the multidisciplinary management of childhood glaucoma do not yet exist. Instead, current guidelines are largely based on clinician experience and consensus. This is the result of several gaps in knowledge regarding the ocular and systemic phenotypic heterogeneity of childhood glaucoma, the genetic landscape of the condition, the impact of the condition on family planning, and the impact of the condition on the quality of life of children and adults with childhood glaucoma, and their caregivers. This thesis addressed these gaps in knowledge to help inform the management of childhood glaucoma. My original contributions to knowledge included the delineation of the phenotypic and genotypic heterogeneity of childhood glaucoma in the largest population of predominantly European ancestry and a novel report of the long-term clinical outcomes in the two genes most commonly implicated in congenital-onset glaucoma: *CYP1B1* and *TEK*. I further provided an original exploratory analysis of the systemic associations of childhood glaucoma with respect to the underlying molecular diagnoses. In addition, I provided a novel and in-depth insight of the psychosocial implications of childhood glaucoma from the perspectives of children and adults with the condition, and their caregivers. This resulted in the successful development of the first childhood glaucoma patient-reported outcome measure that can provide an accurate assessment of quality of life in adults with childhood glaucoma: the CGQoL-14. This translational research has led to a proposed framework for a family-centred multidisciplinary approach to the management of childhood glaucoma. This will serve to ensure that any individual impacted by childhood glaucoma is provided with the highest level of care and achieves the best possible clinical and quality of life outcomes.

DECLARATION

I certify that this thesis:

1. Does not incorporate without acknowledgment any material previously submitted for a degree or diploma in any university; and
2. The research within will not be submitted for any other future degree or diploma without the permission of Flinders University; and
3. To the best of my knowledge and belief, does not contain any material previously published or written by another person except where due reference is made in the text.

Signed: Lachlan Wheelhouse Knight

Date: 27 October 2022

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THESIS OUTCOMES

Peer-reviewed first-authored publications arising from Doctoral candidature

1. **Knight LSW**, Ruddle JB, Taranath DA,... Siggs OM,* Souzeau E,* Craig JE.* Childhood and early onset glaucoma classification and genetic profile in a large Australasian disease registry. ***Ophthalmology***. 2021;128(11):1549-1560.
2. **Knight LSW**, Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. Quality of life in adults with childhood glaucoma: an interview study. ***Ophthalmol Glaucoma***. 2022;5(3):325-36.
3. **Knight LSW,** Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. The caregiver experience in childhood glaucoma: an interview study. ***Ophthalmol Glaucoma***. 2022;5(5):531-43.
4. **Knight LSW**, Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. Quality of life in children with glaucoma: A qualitative interview study in Australia. ***BMJ Open***. 2022:12(7):e062754

Other peer-reviewed first-authored manuscript published during Doctoral candidature

1. **Knight LSW**, Mullany S, Taranath DA,... Souzeau E, Craig JE, Siggs OM. The phenotypic spectrum of *ADAMTSL4*-associated ectopia lentis: Additional cases, complications, and review of the literature. ***Mol Vis****.* 2022;28:257-268.

Peer-reviewed co-authored manuscripts published during Doctoral candidature

1. Prem Senthil M, **Knight LSW**, Taranath DA,… Siggs OM, Souzeau E, Craig JE. Comparison of anterior segment abnormalities in individuals with *FOXC1* and *PITX2* variants. ***Cornea***. 2022;41(8):1009-1015.
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8. Marshall H, Berry EC, Diaz-Torres S, Mullany S, Schmidt J, Thomson D, Nguyen TT, **Knight LSW**,… Craig JE. Association between body mass index and primary open-angle glaucoma in three cohorts. ***Am J Ophthalmol***. 2023;245(1):126-133.

Conference presentations

1. “Quality of life in children and adults with childhood glaucoma: An interview study.” *The Association for Research in Vision and Ophthalmology 2022* (Denver).
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6. “No one ever asked me that: Quality of life in adults with childhood glaucoma.” *The 77th Orthoptics Australia Annual Conference 2022* (virtual).
7. “Chronicles of the hidden patient: The caregiver experience in childhood glaucoma.” *The 77th Orthoptics Australia Annual Conference 2022* (virtual).
8. “The kids are alright: Quality of life in children with glaucoma.” *Australian and New Zealand Glaucoma Society Congress 2022* (virtual).

9. “No one ever asked me that: Quality of life in adults with childhood glaucoma.” *Australian and New Zealand Glaucoma Society Congress 2022* (virtual).
10. “Chronicles of the hidden patient: The caregiver experience in childhood glaucoma.” *Australian and New Zealand Glaucoma Society Congress 2022* (virtual).
11. “Childhood and early-onset glaucoma classification and genetic profile in a large Australasian disease registry.” *The Association for Research in Vision and Ophthalmology 2021* (virtual).
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Talks

1. Hear the voice of our youngsters with glaucoma, Glaucoma Australia, held online, 9 March 2022 (Invited Speaker)
2. Childhood glaucoma classifications and genetics: an overview, Orthoptics Australia Journal Club, held online, 18 May 2021
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8. Orthoptics Australia Research Grant 2020
9. Flinders Foundation PhD top-up scholarship 2019

Other media raising awareness of my research throughout Doctoral candidature

1. Rhiannon Bowman. Research lets children with glaucoma tell their story. Insight Magazine. Published September 12, 2022. https://www.insightnews.com.au/research- lets-children-with-glaucoma-tell-their-story/
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ABBREVIATIONS

ANZRAG	Australian and New Zealand Registry of Advanced Glaucoma
ARS	Axenfeld-Rieger syndrome
ASD	Anterior segment dysgenesis
BCVA	Best-corrected visual acuity
BMI	Body mass index
CarCGQoL	Caregivers of Children with Congenital Glaucoma QoL Questionnaire
CGQoL-14	Childhood Glaucoma Quality of Life-14
CI	Confidence interval
CCT	Central corneal thickness
CGRN	Childhood Glaucoma Research Network
DIF	Differential item functioning
IOP	Intraocular pressure
Glau-QoL 36	Glaucoma Quality of Life-36
HTG	High tension glaucoma
HR-QoL	Health-related quality of life
HVF	Humphrey Visual Field test
IQR	Interquartile range
JOAG	Juvenile open-angle glaucoma
MD	Mean deviation
MNSQ	Mean square standardised residual
NEI-VFQ 25	National Eye Institute Visual Function Questionnaire 25
NF1	Neurofibromatosis Type 1
NTG	Normal tension glaucoma
OHT	Ocular hypertension
PACG	Primary angle closure glaucoma
PCA	Principal components analysis
PCG	Primary congenital glaucoma

PedsQL	Pediatric Quality of Life Inventory
POAG	Primary open-angle glaucoma
PROM	Patient-reported outcome measure
PSI	Person separation index
QoL	Quality of life
SG-A	Secondary glaucoma associated with an acquired condition
SG-C	Secondary glaucoma following cataract surgery
SG-O	Secondary glaucoma associated with a non-acquired ocular anomaly
SG-S	Secondary glaucoma associated with non-acquired systemic disease
SWS	Sturge Weber syndrome
VR-QoL	Vision-related quality of life
WHOQoL-BREF	World Health Organization Quality of Life questionnaire—Abbreviated version
WHO	World Health Organization

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CHAPTER 1 AN INTRODUCTION TO CHILDHOOD GLAUCOMA

Glaucoma is a term used to describe a heterogeneous group of chronic vision-threatening optic neuropathies mediated by intraocular pressure (IOP).[1] It is characterised by optic nerve head atrophy and specific patterns of visual field loss.[1] The condition can be diagnosed in an individual of any age, and it is often subcategorised dependent upon the age of disease onset. The term 'adult-onset glaucoma' is given where glaucoma is diagnosed at age 40 years or older. It is the most studied form of glaucoma due to its considerable estimated global prevalence of 3.5% in the adult population aged 40–80 years, and being one of the leading causes of irreversible and preventable visual impairment worldwide.[2,3] Meanwhile, 'early-onset glaucoma' is the term used to describe glaucoma diagnosed prior to age 40 years and 'childhood glaucoma', a subset of early-onset disease, has disease onset occurring at any age from birth to less than 18 years of age.[4] Although these are relatively rare glaucomatous entities, childhood glaucoma is a leading cause of irreversible childhood blindness worldwide and accounts for an estimated 6.9% of childhood vision impairment.[5] My thesis predominantly explores childhood glaucoma.

In addition to being relatively rare, childhood glaucoma is considered a uniquely different condition to later-onset forms of disease for several other reasons.[4] Firstly, it is typically associated with genetic variants with a Mendelian pattern of inheritance, some of which are known to be associated with systemic disease or a syndrome.[6] Monogenic inheritance can also cause later-onset glaucoma, although they account for a small proportion of cases. Multifactorial aetiologies including complex polygenic and environmental risk factors more often contribute to later-onset forms of glaucoma.[1,7] Secondly, childhood glaucoma presents a lifetime risk of visual impairment and the prognosis is often less favourable than later-onset disease. If the disease begins during the critical period of visual development (infancy or early childhood), it can cause damage to the visual system beyond the optic nerve.[4,8] Children with disease onset before the age of three years are further susceptible to having impaired corneal integrity (e.g., corneal enlargement, oedema and scarring or Haab striae) or high amounts of myopia as raised IOP causes pathological enlargement of the infant eye.[8–10] Thirdly, surgical intervention is frequently required immediately upon diagnosis and may be followed by several years of topical antiglaucoma therapies (i.e., eye drops) and further surgery to control IOP and maintain vision status.[11] Finally, the young age of onset, the long-term management, disease sequelae and uncertain visual outcome of childhood glaucoma may pose unique emotional, social, or physical impacts on the individual and the caregiver throughout the lifespan.[12]

Despite these differences between childhood and later-onset forms of glaucoma, high-quality evidence-based clinical practice guidelines for childhood glaucoma do not exist.[13] Historically, management protocols for this ocular condition were developed from consensus and clinician experience.[14] In 2013, the ninth World Glaucoma Association Consensus agreed that the literature detailing the diagnostic criteria, classification, and treatment of childhood glaucoma needed updating to assist clinicians with provision of the most optimum level of care.[4] Later, in 2020, the World Health Organization (WHO) continued to advocate for the development of clinical practice guidelines for congenital glaucoma to facilitate provision of universal healthcare for this rare condition.[15] To help inform the management of childhood glaucoma, the areas of interest of my thesis include characterisation of the disease, genetic aetiologies, the clinical outcomes, and its impact on QoL. These are aligned with the topics of priority research in other ophthalmic childhood conditions as determined by the WHO Vision 2020 initiative, which aimed to reduce the prevalence of preventable childhood vision impairment and blindness.[16] My original contributions to knowledge directly contributed to a limited body of literature within these areas.

1.1 Pathophysiology of childhood glaucomas

The pathogenesis of glaucoma is related to the imbalance between aqueous humour production and drainage. This process modulates IOP.[17,18] Aqueous humour is a clear fluid that serves to provide nutrients to surrounding ocular tissues and maintain the shape of the eye. It is produced within the non-pigmented epithelial cells of the ciliary body, in the posterior chamber of the anterior segment.[18] From there, the aqueous humour circulates through the pupillary space and into the anterior chamber of the anterior segment. Drainage then occurs at the iridocorneal angle via one of two pathways: the conventional (Figure 1.1A) or the uveoscleral pathway (Figure 1.1B).[18] The conventional pathway refers to drainage of aqueous humour through the trabecular meshwork and into Schlemm's canal. It is then absorbed into the episcleral veins (Figure 1.1A). This pathway accounts for approximately 80% of aqueous humour drainage, and includes the Schlemm's canal and trabecular meshwork.[19] As per Figure 1.1B, the uveoscleral outflow refers to drainage of aqueous humour via other surrounding structures including the ciliary body and iris root, and is ultimately absorbed into the choroidal and scleral veins or episcleral tissue.[18] In glaucoma, the structures of the conventional pathway are typically implicated.[17]

Figure 1.1 has been removed due to Copyright restrictions

Figure 1.1. Aqueous humour outflow pathways

The conventional outflow pathway (A) and the uveoscleral outflow pathway (B) (Source: Goel et al. 2010[18])

If IOP rises, it can cause damage to the optic nerve at the level of the lamina cribrosa.[20] The lamina cribrosa is the anatomical site where the retinal ganglion cell axons, which relay visual information to the visual cortex via the lateral geniculate nucleus, exit the eye.[17,21] Chronically raised IOP can cause compression or deformation of the lamina cribrosa which may block axonal transport with consequent ganglion cell injury and apoptosis.[17] Degeneration and apoptosis of retinal ganglion cells may also occur from mitochondrial dysfunction, oxidative stress, vascular dysfunction, inflammation or neurotoxic factors.[22] Thinning of the lamina cribrosa and retinal ganglion cell loss contribute to the characteristic optic nerve head cupping and thinning of the neuroretinal rim seen in glaucoma.[17,20] Retinal ganglion cell degeneration further causes the characteristic progressive visual field loss seen in glaucoma.[17] Visual field loss typically begins in the midperiphery, with advanced glaucoma leaving only a central field of vision.[17]

Central visual acuity may also be threatened by raised IOP in childhood glaucoma.[11,23] Pathological increases in IOP in an elastic infant eye can cause corneal irregularities from breaks in Descemet's membrane of the cornea (Haab striae) and corneal oedema.[9] Increased IOP results in abnormal axial length elongation with subsequent myopia.[10] These pathological changes can result in secondary stimulus deprivation or anisometropic amblyopia (i.e., insults to the developing visual system).[11,23]

Aetiologies of chronically raised IOP in childhood glaucoma can be broadly divided into primary and secondary. This is determined on the basis of whether there are primary developmental defects in the aqueous humour outflow pathway (trabecular meshwork or Schlemm's canal) or if there are other secondary causes for disruption to aqueous humour outflow. Subclassifications of primary and secondary childhood glaucoma include open-angle glaucoma or closed angle-glaucoma. This is

determined by whether the iridocorneal angle is anatomically open or closed, thereby physically blocking the flow of aqueous humour.

1.1.1 Primary childhood glaucoma

Primary open-angle childhood glaucoma may result from arrested development of the conventional outflow pathway without a known secondary cause.[24] It may include maldevelopment of the trabecular meshwork and iridotrabecular junction,[25] or maldevelopment of the Schlemm's canal.[26] The trabecular meshwork typically develops between the 12th and 22nd week of embryogenesis and is mostly derived from neural crest cells.[27] It is hypothesised that during the third trimester the layers of the trabecular meshwork become abnormally compressed and thickened. This obstructs the aqueous humour outflow.[24] Meanwhile, Schlemm's canal arises from the mesoderm (via vascular endothelial cells).[27–29] The structure is visible from 16 weeks gestation, and reaches adult-like development by eight years of age.[30] Maldevelopment of Schlemm's canal is similarly associated with aqueous humour outflow obstruction with consequent increased IOP.[26]

Maldevelopment of the structures of the conventional aqueous humour pathway with raised IOP is typically associated with glaucoma arising before age 3 years. This is termed primary congenital glaucoma (PCG),[25] but may also be referred to as primary infantile glaucoma,[10] isolated trabeculodysgenesis,[25] or congenital glaucoma.[31] PCG is further associated with pathological corneal and axial length changes as mentioned above.[9] Thickened and compact trabecular meshwork has also been observed in individuals with primary open-angle glaucoma diagnosed between the ages of 4 years and up to 35–40 years, without ocular enlargement or corneal changes.[32–34] Glaucoma with an onset between these ages is coined juvenile open-angle glaucoma (JOAG). However, goniodysgenesis may not be observed in all individuals with JOAG.[35] The integrity of the trabecular meshwork may also be compromised from oxidative stress, and consequently cause raised IOP and retinal ganglion cell death.[36,37] Retinal ganglion cell loss may also occur from multifactorial aetiologies as discussed above (e.g., vascular dysfunction).[22] Ocular enlargement and corneal changes are not seen in JOAG as the sclera and cornea become more mature and become less elastic with age.[38]

1.1.2 Secondary childhood glaucoma

Secondary glaucomas may be caused by several developmental anomalies in other ocular structures (e.g., iridocorneal dysgenesis and disorders of the lens) or an acquired condition. The pathogenesis of glaucoma varies between these causes and are summarised below.

Iridocorneal dysgenesis refers to developmental anomalies of the iris or cornea.[25] Glaucoma associated with iridocorneal dysgenesis can be described as open or closed angle, and is typically seen in conditions including aniridia, Peters anomaly and Axenfeld-Rieger syndrome (ARS).[25] Aniridia describes a rare ocular condition whereby there is a varying degree of iris hypoplasia from almost total absence to mild hypoplasia.[39] In aniridia, a layer of iris tissue may extend over the trabecular meshwork and obstruct aqueous outflow (open-angle glaucoma) or there may be iris adhesions to the trabecular meshwork which can contract over time and narrow the iridocorneal angle (closed-angle glaucoma).[40] In Peters anomaly, a condition where there is an absence of the corneal endothelium and Descemet's membrane, iris adhesions to the lens may form and physically obstruct aqueous humour outflow.[41,42] Physical obstruction of the aqueous humour outflow by iridocorneal dysgenesis is also considered in the pathogenesis of ARS-associated glaucoma. ARS describes a condition with ocular anomalies with or without a series of characteristic systemic features that have a neural crest cell origin.[43] Other terms used to describe this disease spectrum have included Axenfeld-Rieger anomaly, Axenfeld anomaly or syndrome, and Rieger anomaly or syndrome.[43,44] Specific iridocorneal dysgenesis seen in ARS include a prominent Schwalbe ring (also called a posterior embryotoxon) with attached iris strands, iris stromal hypoplasia, corectopia (displaced pupil) and pseudopolycoria (multiple pupils).[43–45] Varying degrees of developmental arrest of the trabecular meshwork and Schlemm's canal have been observed in individuals with ARS and may contribute to glaucoma pathogenesis.[43] Iridocorneal dysgenesis may also occur in congenital rubella with consequent glaucoma.[46]

The most common lenticular disorder implicated in childhood glaucoma is ectopia lentis. Ectopia lentis refers to dislocation of the lens due to disattenuation of the ciliary zonules.[47] These are essential for holding the lens in place.[47] It may occur in association with a connective tissue disease (e.g., Marfan syndrome, Weill-Marchesani syndrome) or may occur because of trauma.[48] The mechanism of glaucoma in ectopia lentis is due to pupillary block.[48] This is a process whereby weakening zonules results in anterior displacement of the lens with a consequent increase in iridolenticular contact and obstruction of aqueous humour outflow.[48]

Secondary open-angle or closed-angle childhood glaucomas may be caused by uveitis, corticosteroid use, trauma, tumours, and intraocular surgery. In uveitic open-angle glaucoma, inflammatory cells in the trabecular meshwork can mechanically block aqueous humour outflow, whilst uveitic closed-angle glaucoma may occur secondary to posterior synechiae between the iris and lens or iris and cornea.[49] Corticosteroid use, either used for uveitis treatment, or other inflammatory conditions, can cause open-angle glaucoma.[49,50] Evidence suggests that corticosteroids can alter the structure and function of the trabecular meshwork or increase the deposition of extracellular matrix proteins, all of which result in

reduced aqueous humour outflow.[50] Blunt ocular trauma may cause open-angle glaucoma, via angle recession or obstruction of the trabecular meshwork due to inflammatory, pigmentary, or red blood cells.[51] Trauma may also result in closed-angle glaucoma from ectopia lentis.[51] Intraocular tumours may cause glaucoma depending upon the exact tumour (e.g., ciliary body, iris, choroid, retina). In broad terms, open-angle glaucoma may be due to invasion of the tumour into the iridocorneal angle or iris neovascularisation, whilst angle-closure may occur due to anterior displacement of the iris from tumour growth.[52] Finally, intraocular surgery, particularly in the context of congenital or childhood cataract, may cause open-angle glaucoma.[53] Hypotheses for glaucoma following cataract surgery include the obstruction of the trabecular meshwork by lens debris,[54] or the alteration of the structure and function of the trabecular meshwork following exposure to lens epithelial cells.[55] Glaucoma and cataracts have also been hypothesised to be a part of a congenital syndrome.[56] Overall, it is apparent that there are various disease mechanisms involved in childhood glaucoma and these result in different subtypes of the condition.

1.2 The phenotypes of childhood glaucoma

Multiple attempts to classify subtypes of childhood glaucoma based on their underlying pathophysiology have been made throughout the literature.[9,25,57] This has resulted in many different terms being used to describe the same disease. For example, to describe primary open-angle childhood glaucoma, the terms '*primary childhood glaucoma*', '*primary developmental glaucoma'* and '*primary genetically determined glaucoma*' have been used.[9,25,57] To describe secondary glaucoma, terms have included '*secondary glaucoma', 'secondary childhood glaucoma'* and *'secondary developmental glaucoma'*.[9,25,57] Moreover, various ages have been used to classify the subtype of primary glaucoma (i.e., PCG or JOAG). A diagnosis of PCG has included an age of disease onset between birth and 12 months of age,[10] or birth to 3 years of age,[31,58] whilst a diagnosis of JOAG in the context of childhood glaucoma has included an age of disease onset from age 3–18 years,[58] 4–20 years,[59] or 5–18 years.[60] JOAG is also a term used to describe disease onset between 4–40 years,[61] 10–30 years,[62] 10–35 years,[63] or even 10-40 years.[34] The use of these different diagnostic terms and diagnostic criteria has been problematic because it prevents more accurate estimates of the epidemiology of childhood glaucoma and measurement of clinical outcomes.

To address these issues, the Childhood Glaucoma Research Network (CGRN) developed a classification system in 2013 describing the subtypes of childhood glaucoma and their diagnostic criteria (Figure 1.2).[4] These have been adopted by the World Glaucoma Association and the American Board of Ophthalmology.[4] As per Figure 1.2, diagnosis and classification of childhood glaucoma depends on clinical investigations including IOP measurement, posterior segment examination and visual field

testing (to assess for optic nerve head cupping and extent of optic nerve head damage, respectively), anterior segment examination and gonioscopy (to observe for ocular anomalies including iridocorneal dysgenesis) and corneal diameter measurement and cycloplegic refraction (to determine abnormal stretching and elongation of the eye).[4,38] The presence of two or more signs indicative of glaucomatous damage are required for a diagnosis of glaucoma.[4] A general history taking is also required to ascertain the age of onset, and determine whether there is possible acquired cause including cataract or trauma or possible associated systemic disease.[4,38]

As per the CGRN criteria, primary childhood glaucoma includes PCG and JOAG. PCG is further classified as neonatal onset (diagnosis between 0–1 months of age), infantile onset (diagnosis >1–24 months), or late onset or late recognition of disease (diagnosed >2 years).[4] JOAG is generally considered to be diagnosed from age 4 years in the absence of corneal changes, as corneal enlargement usually occurs prior to age 3 years.[38,64] Meanwhile, secondary childhood glaucomas have been grouped dependent upon whether there is secondary glaucoma associated with a non-acquired ocular anomaly (SG-O; e.g., iridocorneal dysgenesis, lenticular disorders), secondary glaucoma associated with a non-acquired systemic disease (SG-S; e.g., Marfan syndrome, Weill-Marchesani syndrome), secondary glaucoma associated with an acquired condition (SG-A; e.g., uveitis, trauma), or secondary glaucoma following cataract surgery (SG-C). Because glaucoma following cataract surgery is a common and well-known cause of secondary glaucoma, it was given its own category, rather than being grouped with SG-A.[53] The development of this classification system has since enabled uniformity in childhood glaucoma research.[64,65]

Figure 1.2 has been removed due to Copyright restrictions

Figure 1.2. Classifications of childhood glaucoma

A systematic flowchart for classifying childhood glaucoma developed by the CGRN (Source: Thau et al. 2018)[64]

IOP: Intraocular pressure, c/d: cup-disc ratio, K: corneal changes, AL: axial length, VF: visual field

Despite the introduction of a new and unified classification system, childhood glaucoma remains a challenging disease to study because of its relative rarity. Incidence rates of childhood glaucoma are not well-reported, with one study of a Minnesotan population reporting an incidence of 1/43,575.[59] This statistic, however, is confounded by the inclusion of all cases diagnosed <20 years of age, in contrast to the CGRN criteria which considered that childhood glaucoma is diagnosed at <18 or ≤16 years of age.[4] The same study reported an incidence of PCG of 1/68,254 live births.[59] This is much lower than other studies that have reported the incidence of PCG. An incidence rate for PCG has been reported to be 1/18,500–38,000 in other European populations including Australia,[10,66,67] and 1/3,300 in southern Indian,[68] 1/2,500 in Middle Eastern,[69] and 1/1,200 in Slovakian Gypsy populations.[70] Incidence rates are higher in countries where consanguinity or founder effects are more common.[66,69,70] Incidence rates of other childhood glaucoma subtypes are seldom reported. The incidence of non-acquired developmental ocular anomalies (e.g., aniridia, ARS, Peters anomaly) and systemic conditions (e.g., Neurofibromatosis

Type 1 [NF1] and Sturge Weber syndrome [SWS]) that are commonly encountered in association with childhood glaucoma, and their prevalence of secondary glaucoma are summarised in Table 1.1. The incidence of childhood cataracts and prevalence of aphakic glaucoma is also presented in Table 1.1.

Table 1.1. Incidence rates of common conditions associated with childhood glaucoma and the prevalence of secondary glaucoma

Condition	Incidence of disease	Prevalence of secondary glaucoma	References
Aniridia	1/64,000 to 1/96,000	6–75% of individuals, with onset at any age	39,71,72
ARS	1/200,000	~50% of individuals, with onset typically in childhood or young adulthood	43,73
Peters anomaly	1/150,000	33–50% of individuals, with onset typically in childhood	42,74
NF1	1/2,500 to 1/4,500	16% of individuals with NF1, or 23% of individuals with orbito-facial NF1 only, with onset typically between birth and 13 years	75–77
SWS	1/50,000	30–71% of individuals, with 67–72% of glaucoma presentations <24 months of age	78–80
Childhood cataract	1/18,000 to 1/36,000	0–57% of eyes, with a ~32% risk of glaucoma if surgery is done at age <9 months, and ~4% risk of glaucoma if surgery is done at age ≥9 months of age, at 10 years following surgery.	81–84

ARS: Axenfeld-Rieger syndrome, NF1: Neurofibromatosis Type 1, SWS: Sturge-Weber syndrome

Several studies have reported the contribution of each childhood glaucoma subtypes using the CGRN criteria to determine which subtypes were more prevalent.[65,85–91] Table 1.2 reports these population-based studies in their respective regions and countries, each with the two most common classifications of childhood glaucoma reported, excluding glaucoma suspects. PCG appeared to be the most prevalent subtype of childhood glaucoma reported by the majority of the studies.[65,86,88–91] Across all studies, PCG has an overall prevalence rate of 5–55%.[65,85–91] This was followed by SG-A (10–38%) and SG-O (5–29%).[65,85–91] Prevalence rates were lower in JOAG (1–20%), SG-S (1–19%) and SG-C (2–18%).[65,85–91] Childhood glaucoma appeared to be more prevalent in males.[65,85–91] Of note, the age of childhood glaucoma disease onset has been defined at different ages. This disagreement is reflected in the CGRN guidelines, which determined that childhood glaucoma may be defined as onset <18 years of age in the United States of America but ≤16 years of age in the United Kingdom, Europe and United Nations Children's Fund regions.[4] This may have led to an underestimation of the number of individuals with later-onset disease subtypes, and in particularly JOAG, in the contribution to disease patterns. There is a current paucity of studies investigating the distribution of disease in a European setting and none have reported the distribution of disease in an Australian cohort. Two small studies which utilised the CGRN

classifications were conducted in the United States of America, although the proportion of individuals with European ancestry were not reported.[65,85] Individuals of European ancestry in a large international study continued to be seldom represented (20.3%).[91]

Table 1.2. Contribution of childhood glaucoma subtypes per population with respect to the CGRN classifications

Study population, location	Cases reported (n)	Glaucoma suspects (n)	Glaucoma cases (n)	Two most common diagnostic classifications† (%)	European ancestry (n, %)	Male: Female	Age cut-off for diagnosis (years)
European setting							
Tertiary Childhood Centre, Florida, USA[65]	201	79	122	1. PCG (32%) 2. SG-A (23%)	n/a	1.3:1	n/a
Tertiary Childhood Centre, Akron, USA[85]	108	50	58	1. SG-A (38%) 2. JOAG (29%)	n/a	1.9:1	≤18
Non-European setting							
Tertiary University Ophthalmology Centre, São Paulo, Brazil[86]	496	66	430	1. PCG (51%) 2. SG-C (15%)	n/a	1.3:1	<18
Two Tertiary Ophthalmic Centres, Thailand[87]	423	85	338	1. SG-O (29%) 2. PCG (26%)	n/a	1.4:1	<16
Tertiary Childhood Centre, South India[88]	275	0	275	1. PCG (39%) 2. SG-O (17%)	n/a	1.4:1	<16
Tertiary Childhood Centre, Dakhelia, Egypt[89]	207	0	207	1. PCG (55.1%) 2. SG-A (29.5%)	n/a	1.8:1	<16
Ophthalmologic National Reference Centre, Colombia[90]	89	0	89	1. PCG (47%) 2. JOAG (20%)	n/a	1:1	<16
Global setting							
Multicentre international cohort[91]	441	0	441	1. PCG (43%) 2. SG (46%)‡	89 (20.3%)	1.5:1	<18

USA: United States of America; PCG: primary congenital glaucoma; SG-A: secondary glaucoma associated with an acquired condition; n/a: not available; JOAG: juvenile open-angle glaucoma; SG-C: secondary glaucoma following cataract surgery; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; SG: secondary glaucoma.

†The percentages reported have been calculated amongst individuals with glaucoma only. Only the two most common diagnostic classifications have been listed for brevity.

‡The proportion of individuals with each subtype of secondary glaucoma (i.e., SG-O, SG-A, SG-C, SG-S) were not reported.

The differences in the distribution of disease subtypes and the male preponderance observed in the aforementioned studies[65,85–91] may be due to the disease presentation or population characteristics, including access to care and the genetic landscape. For example, the higher rates of PCG may be

because early-onset disease (typically prior to age 3 years) is associated with signs of epiphora, photophobia, corneal haze, buphthalmos or blepharospasm, which may prompt a caregiver to seek urgent medical attention.[38] There is also a genetic basis: PCG is considered familial in 10–40% of cases and often follows an autosomal recessive transmission.[92] This explains why PCG is higher in populations where parental consanguinity is more common due to marriage practices (e.g., India and Egypt).[88,89] None of the aforementioned studies which utilised the CGRN criteria, however, have studied the genetic landscape of their populations.[65,85–91] Investigation of the molecular diagnoses underpinning childhood glaucoma, with respect to the CGRN classifications, can support our understanding of the genetic basis of disease and their associated phenotypic spectrum.

1.3 Genetics of childhood glaucoma

Childhood glaucoma is most commonly associated with genetic variants with an autosomal recessive or autosomal dominant Mendelian pattern of inheritance.[6,7] Although there is phenotypic variability, each gene is most commonly associated with one CGRN disease classification.[6,7] Many genes have been associated with childhood glaucoma, with the most common ones including: *CYP1B1*, *TEK,* and *LTBP2* for PCG; *MYOC* and *EFEMP1* for JOAG; and *FOXC1, PITX2, PAX6* and *CPAMD8* for SG-O.[6,7,93] Variants in these genes can be associated with variable disease expressivity and age-related penetrance. This results in a broad phenotypic spectrum with varying degrees of anterior segment dysgenesis (ASD; a collective term to describe trabeculodysgenesis, Schlemm's canal dysgenesis, iridocorneal dysgenesis and lens anomalies)[94] and consequent overlap between CGRN classifications. The phenotypic spectrum of several of these genes may include extraocular features, with variable expressivity, dependent on the underlying function of the gene. The varied disease-spectrum arising from pathogenic variants in each of these genes has important implications for understanding disease patterns and disease aetiologies. The disease-spectrum can also guide genetic testing practices and clinical management of childhood glaucoma.[8] The ocular and systemic phenotypic spectrum of the most common genes implicated in childhood glaucoma are therefore herein reviewed with respect to their underlying function.

1.3.1 Cytochrome P450 family 1 subfamily B polypeptide 1 (*CYP1B1*)

The *CYP1B1* gene was first discovered to be implicated in autosomal recessive PCG in 1997.[95] It has since been attributed to varying prevalence rates of PCG dependent on the population studied. Biallelic *CYP1B1* variants have been implicated in 15–22% of individuals with PCG of European ancestry.[96,97] This is relatively low compared to PCG populations where parental consanguinity may be more common. The prevalence of biallelic *CYP1B1* variants in Indian populations with PCG is 30–33%,[98,99]

and increases to 75–96% in Middle Eastern populations with PCG.[100–102] This is expected for an autosomal recessive trait and highlights that genetic causes of PCG are inherently dependent upon the genetic architecture of the population being studied.

Deleterious biallelic variants in the *CYP1B1* gene do not exclusively cause PCG. Although less common, the phenotypic spectrum of *CYP1B1* includes other forms of primary glaucoma including JOAG and adult-onset primary open-angle glaucoma (POAG; defined as disease onset ≥40 years).[61,95,103–105] Biallelic *CYP1B1* variants account for 0–3.3% of JOAG diagnosed up to the age of 35–40 years,[61,105–107] whilst few cases of POAG have been reported.[104] Meanwhile, some cases of iridocorneal dysgenesis including Peters anomaly,[108–115] ectropion uveae with partial aniridia,[116] complete aniridia,[117] ocular ARS (iridocorneal adhesions, posterior embryotoxon, anterior iris insertion),[118,119] microphthalmia and sclerocornea,[108] have been reported. The contribution of biallelic *CYP1B1* variants in SG-O overall, however, has not been reported.

The varied *CYP1B1*-associated ocular disease spectrum is yet to be explained by the gene's function. Murine studies have demonstrated that knockdown or inhibition of the activity of the CYP1B1 protein is associated with abnormal structural organisation of the trabecular meshwork and an increased susceptibility to oxidative stress.[120] This leads to apoptosis of trabecular meshwork cells and modulation of aqueous outflow through the conventional pathway.[120] This finding may assist in explaining the pathogenesis of primary glaucoma. However, it is unknown whether CYP1B1 is involved in the development of other ocular tissues that could give rise to iridocorneal dysgenesis.[121–124] The gene has other functions including the metabolism of steroids, including oestrogen, carcinogens, retinoic acid and melatonin, but the relevance of these functions in glaucoma pathogenesis is unknown.[121–124] Further functional studies and additional reports of *CYP1B1*-associated ocular disease will assist in understanding the contribution of the gene in ocular disease.

Extraocular features of *CYP1B1*-associated ocular disease have been seldom reported. Among individuals with ocular findings suggestive of ARS,[118,119] one infant was reported to have a broad nasal bridge and protruding umbilicus.[119] Whilst a broad nasal bridge and umbilical anomalies are often observed in ARS,[125–132] these features may just be typical of an infant.[133,134] It is therefore unclear whether these systemic features are part of a *CYP1B1*-associated disease spectrum. Meanwhile, *CYP1B1* polymorphisms have been implicated in the susceptibility to developing cancers.[135–137] In particular, these include hormone-mediated cancers such as prostate and breast cancer.[135] However, these polymorphisms have not been implicated in childhood glaucoma and may therefore not be relevant to individuals with childhood glaucoma. Investigation of the systemic features in a cohort with

CYP1B1-associated ocular disease could help to determine if any potential associated features require investigation and consequent clinical management.

1.3.2 Tunica interna endothelial cell kinase (*TEK*)

Heterozygous loss-of-function variants in the *TEK* gene (formerly known as *TIE2*) were first implicated in autosomal dominant PCG in 2016.[26] Because of its relatively recent discovery, it has only been attributed to 5% of PCG cases (10/189) in an international cohort of predominantly European ancestry.[26] A Han Chinese study further reported that *TEK* variants accounted for 5.5% (11/200) of PCG cases.[138] However, gain-of-function and benign *TEK* variants, which are not involved in the disease pathogenesis, were included in their prevalence calculation and therefore does not provide an accurate measure of the contribution of the gene to PCG disease.[138] After removing these individuals, the prevalence rate equates to 2.0% (4/200) of PCG cases. The proportion of other childhood glaucoma subtypes explained by loss-of-function *TEK* variants is not known. However, heterozygous loss-of-function *TEK* variants have been found to have incomplete penetrance and variable age-related onset of disease within the same pedigree.[26,139] This included two cases of JOAG and POAG each.[26,139] Although based off few reports, the *TEK*-associated glaucoma spectrum appears to only include primary glaucomas: PCG, JOAG and POAG.[26,138,139] Further reports and characterisation of its ocular phenotype are needed to support this.

The phenotype of primary glaucoma is explained by the function of the gene. TEK is a receptor to the angiopoietin ligands ANGPT1 and ANGPT2.[140] The ANGPT1/2-TEK pathway is critical for the development of Schlemm's canal, with murine studies demonstrating that TEK haploinsufficiency[26] or complete knockout of ANGPT1[141] results in a hypoplastic Schlemm's canal and a subsequent glaucomatous phenotype.[26,141] The role of TEK in the development of other ocular structures including the cornea, iris and ciliary body has not been reported. This may be because Schlemm's canal has a distinct embryological origin to the other structures, arising from the mesoderm, instead of neural crest cells.[27–29] This may further explain why SG-O does not appear to be part of the *TEK*-associated ocular disease spectrum.

The TEK receptor gene has several extraocular regulatory functions, but it is unclear if these are associated with systemic disease in *TEK*-associated glaucoma. Other functions of the TEK gene include lymphangiogenesis, heart development and vascular stabilisation,[140,142,143] with murine studies demonstrating that complete knockout of *TEK* results in cardiac defects and embryonic lethality.[26,143] Conversely, gain-of-function *TEK* variants have been found to cause cutaneo-mucosal and other venous malformations,[26,144] the majority of which occur on the tongue, lip and buccal mucosa.[144] More recently,

TEK has been implicated in osteogenesis, bone mineralization and bone regeneration, although its exact role remains unknown.[145,146] Inhibition of *TEK* in mice blocks osteogenic differentiation and mineralisation of bone marrow stem cells.[145] Only one pedigree with *TEK*-associated PCG has been reported to have systemic features.[139] Frequent findings in family members included Legg-Calve-Perthes disease, a hip disorder characterised by necrosis of the femoral head due to a disruption to its vascular supply,[147] and ovarian cysts.[139] However, this family had a co-occurring pathogenic variant in *SVEP1;* a gene that is responsible for cell adhesion processes and is highly expressed in osteogenic tissue, the placenta and epidermis.[148,149] It is therefore unclear whether the systemic features observed in the aforementioned family are associated with the extraocular functions of *TEK*, *SVEP1* or other environmental or genetic factors. Characterisation of systemic features in these individuals requires further investigation. This may assist in determining the clinical management of individuals with a loss-of-function *TEK* variant.

1.3.3 Latent transforming growth factor-β-binding protein 2 (*LTBP2*)

Deleterious biallelic *LTBP2* variants were first described in association with autosomal recessive PCG in 2009.[150,151] However, several individuals in these reports diagnosed with PCG had features of SG-O, including ectopia lentis, and SG-S, including features of connective tissue disorders (arachnodactyly, joint hypermobility and tall stature).[150,151] In 2019, Morlino and colleagues,[152] summarised the phenotypic spectrum of 60 reported cases of *LTBP2*-associated disease and confirmed that *LTBP2* is associated with three CGRN phenotypes: PCG, SG-O and SG-S. The most common ocular phenotype in SG-O included ectopia lentis and microspherophakia, whilst common systemic features in SG-S included a high-arched palate, cardiac anomalies and tall stature.[150,151,153–158] Biallelic *LTBP2* variants have further been implicated in Weill-Marchesani syndrome, which features short stature, brachydactyly and joint stiffness.[155] A case of JOAG was later reported.[159] An exact prevalence of *LTBP2*-associated disease in either of these glaucoma phenotypes in any population has not yet been calculated. It does appear that like *CYP1B1, LTBP2*-associated disease is more prevalent in populations where parental consanguinity and founder effects are more common. This includes populations of Middle Eastern and Roma/Gypsy ancestry.[150–152] Clinicians should be aware of its variable presentation and assess the presence of these ocular and extraocular features to help determine the likely genetic diagnosis and ensure appropriate clinical management.

The pathogenesis of the varied *LTBP2*-associated disease spectrum is unclear. It has been proposed that LTBP2 proteins may interact with fibrillin-1 in microfibril formation for ciliary zonule development and may have a role in maintaining the elasticity of the ciliary body.[150,160] Deleterious *LTBP2* variants may therefore alter the structural support and architecture of the iridocorneal angle, including the

trabecular meshwork, resulting in a phenotype of PCG or SG-O (ectopia lentis).[150] LTBP2 is further expressed in multiple extraocular tissues including the dermis, lung, heart, testes, spleen, and skeletal muscle, where a structural role within elastic fibres is considered but not defined.[161–163] This may provide an explanation for extraocular findings suggestive of a connective tissue disease.

1.3.4 Myocilin (*MYOC*)

MYOC was first associated with autosomal dominant JOAG in 1997.[164] Since then, it has become the most common gene associated with JOAG and POAG, accounting for 8–36% of cases diagnosed up to age 40 years[165,166] and 2-4% of POAG.[167] Both inter- and intra-familial variable disease penetrance and variable age of disease onset have been observed. To some degree, the varied age at onset depends upon the variant, with some variants associated with a younger age of onset than others. For example, variant p.Gly367Arg is typically associated with disease onset in childhood or early adulthood (range: 7–51 years),[168–170] whilst p.Gln368Ter has a mean age of onset of 54.8±13.7 years.[171]

MYOC-associated disease is reported to be restricted to the eye,[172] although its exact pathogenesis is not fully understood.[173] Current evidence supports that gain-of-function *MYOC* variants lead to aggregate protein misfolding in the endoplasmic reticulum of the trabecular meshwork.[174] This is considered to cause trabecular meshwork cell apoptosis and subsequent glaucoma.[174] Morphological changes in the trabecular meshwork are further supported by findings of thickened trabecular meshwork in individuals with *MYOC* variants.[33] This may lead to obstruction of aqueous humour outflow and increased IOP. Systemic features have not been reported although it is unclear whether this is due to a lack of investigation or because systemic features do not truly exist. Investigation of systemic features is required to confirm this.

1.3.5 EGF-containing fibulin-like extracellular matrix protein 1 (*EFEMP1*)

Heterozygous pathogenic *EFEMP1* variants were first associated with autosomal dominant JOAG in 2020.[93] Like *MYOC*, variable glaucomatous disease penetrance and a variable age of disease onset have been observed.[93,175–177] Approximately 50 known individuals with glaucoma and a predicted pathogenic *EFEMP1* missense or stop-loss variant, all of whom have non-European ancestry, have been reported.[93,175–177] JOAG (i.e. disease onset <40 years) is the more common glaucomatous phenotype reported, followed by POAG,[93,175–177] with a mean age of disease onset of 16 years (range: 3–43).[175] There have been no reports of PCG. An additional *EFEMP1* missense variant (p.Arg345Trp) has been exclusively associated with an autosomal dominant macular dystrophy, Malattia Leventinese (also known as Doyne honeycomb retinal dystrophy) without glaucoma.[178]

The pathogenesis of *EFEMP1* variants associated with glaucoma is not yet understood.[175] The extracellular matrix protein fibulin-3, the product of *EFEMP1*, has high expression in the trabecular meshwork, optic nerve and neural retina, where it is considered to provide structural support.[179,180] It has been proposed that like *MYOC*, glaucomatous disease is due to a gain-of-function mechanism with protein aggregation and protein retention in the trabecular meshwork. This may obstruct aqueous humour outflow and raise IOP.[175] This hypothesis is supported by studies of fibulin-3 knockout mice that had normal trabecular meshwork and IOP, and no glaucomatous optic neuropathy.[180] Fibulin-3 is also expressed in the human heart, placenta, lung and fibroblasts,[181] where it is believed to have a possible role in skeletal development and elastic tissue development and maintenance.[182] Few adults with biallelic loss-of-function *EFEMP1* variants without glaucoma have demonstrated systemic features suggestive of a Marfan-like connective tissue disease.[183,184] In contrast, systemic features have seldom been reported or investigated in individuals with *EFEMP1*-associated glaucoma.[93,175–177] Systemic features have been reported in only one individual with *EFEMP1*-associated glaucoma but this individual had a concurrent *COL11A1* variant (Stickler syndrome).[177] It is therefore unclear if systemic features are associated with *EFEMP1*-associated glaucoma and further research is required to support this.

1.3.6 Complement component 3- and pregnancy zone protein-like alpha-2-macroglobulin domain-containing protein 8 (*CPAMD8*)

Biallelic *CPAMD8* variants are associated with autosomal recessive ocular disease with variable expressivity and penetrance.[101,111,185–188] First documented in 2016 in association with arrested PCG and ASD without glaucoma,[185] *CPAMD8*-associated disease has only been reported in 21 known individuals.[101,111,185–188] Despite its relatively rarity, the ocular phenotype has already been expanded to include PCG, JOAG, POAG, SG-O and ASD without glaucoma, with the most common ASD features being lens anomalies (early-onset cataract, ectopia lentis) and iridocorneal dysgenesis (iris stromal hypoplasia, ectropion uveae, iridodonesis, iris transillumination).[101,111,185–188] Biallelic *CPAMD8* variants account for 3.9% of childhood glaucomas (diagnosis between birth to <18 years) and 1.4% of JOAG (diagnosed between 18 and 40 years).[186] The average age at glaucoma diagnosis is 9.2±14.9 years [range: 0–35], although *CPAMD8*-associated SG-O may begin before the age of 3 years and present with PCG-like signs including corneal clouding and buphthalmos.[186] This can lead to a diagnosis of PCG instead of SG-O as corneal clouding can prevent an accurate assessment of the anterior segment (i.e., gonioscopy).[186]

The pathophysiology of *CPAMD8*-associated disease is not fully understood. It has been made challenging to understand the role of *CPAMD8* because it is not present in rodent genomes.[185] Instead, the variable ocular phenotype of *CPAMD8*-associated disease is supported by the finding of *CPAMD8*

transcript in the lens, iris and cornea in humans at 22 weeks' gestation.[185] This suggests that CPAMD8 has a role in neural crest cell differentiation and periocular mesenchyme development.[185] CPAMD8 is considered to have an additional role in innate and acquired immunity, with high protein expression in the kidney, brain and testis, and low expression in the heart, liver and small intestine.[189] This may explain why *CPAMD8* polymorphisms have been implicated in autoimmune diseases including multiple sclerosis,[190] and Crohn's disease.[191] However, the significance of this role of *CPAMD8* in glaucoma pathogenesis is not known, as these polymorphisms are not implicated in the ocular phenotype. No systemic features have been reported in those with *CPAMD8*-associated ocular disease.[101,111,185–188] Further characterisation of the ocular and systemic phenotype in individuals with *CPAMD8*-associated ocular disease may assist in understanding the role of *CPAMD8*. This also has the potential to identify if individuals may benefit from management of possible associated systemic features.

1.3.7 Forkhead box C1 (*FOXC1*) and Paired-like homeodomain transcription factor 2 (*PITX2*)

Deletions and sequence variants (i.e., missense, nonsense, frameshift, splice-site, copy number variants) in *FOXC1* and *PITX2*, and duplications of *FOXC1*, have long been established to be associated with autosomal dominant ARS.[125–130] Pathogenic variants in *FOXC1* and *PITX2* account for 40–71% of ARS and demonstrate variable expressivity of ocular and systemic features.[111,125,126,192] The ocular phenotype of *FOXC1*-associated and *PITX2*-associated ARS typically includes corectopia, pseudopolycoria, ectropion uveae, posterior embryotoxon, iris hypoplasia, peripheral anterior synechiae and iris processes,[193] whilst systemic features involve organs and structures of neural crest cell origin (e.g., dental, cardiac, craniofacial skeletal abnormalities).[125–130,132,192]

There are key differences in the ocular phenotypes between the genes. *FOXC1*-associated disease is associated with a significantly earlier age of glaucoma onset compared to *PITX2*-associated disease (6.0±13.0 years [range: 0–37 years] vs 18.0±10.6 years [range: 1–48 years], respectively).[130] This is an important differentiating feature, particularly as the earlier age of onset in *FOXC1*-associated glaucoma may lead to a misdiagnosis of PCG, similar to *CPAMD8*-associated disease.[194] The rate of glaucoma, however, is not significantly different, with approximately 61–74% and 53–66% of *PITX2*-associated and *FOXC1*-associated disease developing glaucoma, respectively.[130,192,195] These are both higher than the commonly quoted 50% risk of glaucoma in ARS.[43,73] Other ocular features, including iris hypoplasia and pseudopolycoria are significantly more prevalent in *PITX2*-associated disease compared to *FOXC1*-associated disease.[130,193] Variants in *FOXC1* can also result in Peters anomaly,[196,197] aniridia,[197–204] JOAG,[200] and PCG,[200,205] while *PITX2* variants may cause aniridia,[126,199,206] Peters anomaly or isolated iris hypoplasia,[126,206–208] although there are currently insufficient reports to suggest that the rates of these ocular phenotypes are significantly different between the two cohorts.

Systemic features can also vary between each genetic cohort.[125–130,132] Specific systemic features that are more common in *PITX2*-associated disease include dental (missing teeth, small teeth) and umbilical anomalies (redundant umbilical skin, inguinal or umbilical hernia).[125,127,130,132,192] Few individuals have also been reported to have gastrointestinal issues and developmental delay.[125,130,132] Meanwhile, congenital heart defects, crowded teeth, hearing loss and skeletal anomalies are more common in *FOXC1*-associated disease.[192] Less frequent features observed in *FOXC1*-associated disease have included short stature, arachnoid cysts, hydrocephalus, intellectual disability and developmental delays.[125,126,130,132,195] Both genetic cohorts may also exhibit features of facial dysmorphism, with telecanthus, hypertelorism, and low-set ears being significantly more common in those with a *FOXC1* variant.[132] Finally, few individuals from either cohort have been found to exhibit cerebral small vessel disease and it has been proposed that these findings may be associated with an increased risk of stroke.[192,209] Ongoing investigation of the differences in systemic features between these two cohorts can continue to assist with clinical management of this condition and provide guidance for genetic testing.

The phenotypic spectrum observed in *FOXC1*-associated and *PITX2*-associated disease is explained by their underlying functions. *FOXC1* is a member of the forkhead box transcription factors which encode DNA-binding proteins required for cell proliferation and migration during the development of several organ systems and structures.[210] These include development of the anterior segment of the eye,[211] the cardiovascular system,[212] the renal system,[212,213] meninges, dental structures and cranial bones.[214,215] *PITX2* encodes a homeobox transcription factor that regulates the expression of other genes required for the development of the anterior segment,[216,217] dental structures,[218] the heart,[217] and pituitary gland.[217] *PITX2* is also involved in the closure of the ventral body wall (of which defects give rise to umbilical hernias),[217] and development of mandibular and maxillary bones.[218] Interestingly, *FOXC1* and *PITX2* transcription factors are colocalised during ocular development and *FOXC1* is regulated by the *PITX2* transcript, *PITX2A*.[219] The functional link between these genes may explain why variants in the genes result in a similar ocular phenotype.[219]

1.3.8 Paired box gene 6 (*PAX6*)

Deleterious variants in *PAX6* were first associated with aniridia in 1992.[220] Since then, *PAX6* pathogenic variants have accounted for approximately 90% of aniridia cases and are transmitted in an autosomal dominant mode of inheritance.[221] The majority of cases have a positive family history although sporadic aniridia has been reported in up to 44% of cases.[222] The phenotypic spectrum of *PAX6*-associated aniridia includes nystagmus, keratopathy, cataract and foveal hypoplasia, whilst 26–28% develop glaucoma.[222,223] The mean age at glaucoma diagnosis is 25.0±17.3 years, with approximately 30% of

cases presenting in the first or second decade of life.[223] Deleterious *PAX6* variants may also cause other, less common ocular phenotypes. These include Peters anomaly,[224] optic nerve malformations (e.g., coloboma, optic nerve hypoplasia),[225] congenital cataract, foveal hypoplasia, ARS and microphthalmia.[226]

The ocular phenotypic spectrum of *PAX6*-associated disease is explained by the gene function. The *PAX6* gene is often referred to as 'the master regulator of the eye', as it codes transcription factors required for ocular development.[227] The ocular phenotypes observed in *PAX6*-associated disease appear to be determined by the dosage of PAX6 transcription factor.[228] Aniridic phenotypes are most often due to a premature stop codon (i.e., nonsense, frameshift and splice site) and PAX6 haploinsufficiency which greatly alter the gene dosage and its regulatory network.[227] Meanwhile, non-aniridic phenotypes are more often associated with missense variants that impair DNA binding resulting in the preservation of a subset of downstream targets rather than haploinsufficiency.[227,229]

The *PAX6* gene is expressed in extraocular tissues including the pancreas and brain although the significance of these findings in *PAX6*-associated ocular disease is not clear.[230] Murine models have supported a role of *PAX6* in pancreatic development,[231,232] and few cases of metabolic conditions including diabetes mellitus and obesity, presumed to be related to this function, have been reported in humans with *PAX6*-associated aniridia.[223,233–236] The significance of PAX6 expression in the brain is not fully understood, although a role in neurodevelopment has been proposed.[237] This may explain the prevalence of neurodevelopmental disorders including learning difficulties, intellectual disability, autism spectrum disorder, and ataxia reported in individuals with *PAX6*-associated aniridia.[223,238–241] Systemic features are observed if there is a concurrent deletion of *PAX6* and the adjacent *WT1* gene. This results in a condition known as WAGR syndrome (Wilms tumour, aniridia, genitourinary malformations and intellectual disability),[242] whilst additional deletion of the *BDNF* gene results in WAGRO syndrome (WAGR syndrome with obesity).[243]

1.3.9 Genes associated with syndromic childhood glaucoma

There are many genetic syndromes associated with childhood glaucoma. The most frequent genetic syndromes encountered throughout this thesis include neurocutaneous syndromes, NF1 and SWS. NF1 describes an autosomal dominant disorder caused by pathogenic variants in the *NF1* gene.[244] Its gene product, neurofibromin, is a tumour suppressant predominantly expressed in cells with neural crest cell origin, including Schwann cells and melanocytes.[245] Altered gene function typically results in benign tumours involving Schwann-like cells (optic nerve gliomas, neurofibromas) and melanocytes (iris Lisch nodules and cafe-au-lait spots).[245] Other systemic features include developmental delay, learning

difficulties and skeletal abnormalities (e.g., osteopenia, short stature).[245,246] Childhood glaucoma is a rare complication of NF1 (16%, Table 1.1)[77] and is theorised to be caused by infiltration of neurofibromas into the iridocorneal angle, abnormal development or absence of the trabecular meshwork or Schlemm's canal, or secondary angle closure secondary to ciliary body and choroidal thickening.[247,248]

SWS is a disorder of neural crest cell migration and differentiation, and is caused by somatic pathogenic variants in *GNAQ*.[249] It gives rise to vascular malformations in the eyes, skin and meninges, and is typically characterised by a unilateral facial port-wine stain with unilateral and ipsilateral glaucoma, and leptomeningeal angiomas.[78,79] Bilateral cases have been observed.[78] Other systemic features may include epilepsy, learning difficulties and hemiplegia.[78] Childhood glaucoma is more prevalent in SWS than NF1 (30–71% vs 16%, respectively, Table 1.1),[78,79] although its pathogenesis is not fully understood. Aqueous humour imbalance is considered to be associated with raised episcleral venous pressure caused by episcleral arteriovenous shunts,[78,79,250] hypersecretion of aqueous humour by the ciliary body or choroidal angioma,[79] or trabeculodysgenesis with or without iridodysgenesis.[78,79] Glaucoma onset is <24 months of age in 67–72% if trabeculodysgenesis is found.[78,79]

Other less common genetic syndromes associated with childhood glaucoma include connective tissue disorders, metabolic disorders and chromosomal disorders among many other rare disorders.[4,251] Connective tissue disorders associated with childhood glaucoma may include Weill-Marchesani syndrome (associated with biallelic pathogenic variants in *ADAMTS10*,[252] *ADAMTS17,*[253] or *LTBP2*,[155] or heterozygous *FBN1* pathogenic variants[254]),[255] Marfan syndrome (heterozygous *FBN1* variants),[256] and Stickler syndrome (ocular and systemic features observed with heterozygous *COL2A1*[257] and *COL11A1*[258] pathogenic variants, and homozygous *COL9A1*,[259] *COL9A2*,[260] and *COL9A3*,[261] pathogenic variants; non-ocular features observed with heterozygous *COL11A2* pathogenic variants[262]).[263] Metabolic disorders associated with childhood glaucoma can include homocystinuria (biallelic pathogenic variants in *CBS*[264])[265] and Lowe syndrome (X-linked recessive pathogenic variants in *OCRL1*[266]).[267] Few cases of childhood glaucoma have also be observed in Down syndrome, a chromosomal disorder characterised by an extra chromosome 21 (trisomy 21[268]).[255,269]

1.4 Management of childhood glaucoma

Because of the varied aetiologies of childhood glaucoma, many of which are genetic, current recommendations for the optimum management of the condition advise multidisciplinary care from ophthalmologists, paediatricians, and clinical geneticists.[8,255] This is primarily to ascertain the appropriate clinical and molecular diagnosis, determine the presence of systemic features, and ensure effective and appropriate disease management and treatment.[8,255] Anaesthesiologist input is further

necessary where examinations under general anaesthetic or intraocular surgery is required.[38,255] The treatment of childhood glaucoma and management of systemic features is reviewed below with respect to the roles of these recommended specialists. The specific treatments for underlying ocular conditions associated with childhood glaucomas (e.g., inflammatory treatments for uveitis, chemotherapy for ocular tumours) are not discussed.

1.4.1 Treatment

Childhood glaucoma often requires medical therapy and surgical interventions to control IOP, alongside visual rehabilitation to treat associated amblyopia.[8] In PCG, first-line intervention is usually surgery, whilst topical antiglaucoma medications (i.e., eye drops) are often used to stabilise IOP prior to surgery.[8,270] Medical therapy is often considered the first line treatment in JOAG and secondary glaucomas,[8,270] although glaucoma surgery is frequently required to control IOP.[31] Glaucoma surgery is required in 80–100% of children with PCG,[11,31,91] 40–70% of individuals with JOAG,[31,91] and 11–80% of individuals with secondary glaucoma.[31,91] The goal of treatment is to typically achieve optimal IOP control without progressive optic neuropathy.[11,66]

The choice of medical therapies typically follows a hierarchy. Topical beta-adrenergic antagonists (β-blockers) are considered first, followed by topical or oral carbonic anhydrase inhibitors.[270] If these medications are unsuccessful, other topical medications are tried in order of preference: adrenergic agonists, prostaglandin analogues, miotics and combination therapies.[270] Sometimes more than one medical therapy is needed to control IOP.[270] However, each medication comes with the potential for systemic side effects and may be contraindicated.[270,271] For example, β-blockers may cause bronchospasm and are contraindicated in children with asthma, whilst oral carbonic anhydrase inhibitors may cause metabolic acidosis and are contraindicated in children with impaired renal or hepatic functions.[270,271] It is therefore recommended that a child undergoes review from a paediatrician to examine for any systemic disease and is monitored for possible medication side effects.[270,271]

There are several types of glaucoma surgeries that aim to lower IOP. However, there is a paucity of randomised surgical trials which guide ophthalmologists in their selection.[272,273] This is due to disease rarity and variability. Consensus surveys and large international cohort studies have described that angle surgeries (i.e., goniotomy or trabeculotomy) or combined trabeculotomy/trabeculectomy are most effective for the surgical management of PCG,[11,91,273] while angle surgeries or trabeculectomy are preferred in JOAG.[11,91,273] For secondary glaucomas, trabeculectomy, combined trabeculotomy/trabeculectomy, glaucoma drainage device implantation, or cyclodestructive laser are often considered the first-line surgery with the exception of SWS-associated glaucoma, where angle

surgery is recommended.[66,91,273] The function of these surgeries are summarised in Table 1.3. There is no established surgical algorithm available to determine the choice of surgery after failure,[11,272,273] and although rare, surgical complications can occur (e.g., vitreous haemorrhage, endophthalmitis or retinal detachment).[66,272] If the individual develops a blind and painful eye, enucleation or evisceration of the eye may be considered.[274]

Table 1.3. Description of the surgical procedures used in childhood glaucoma

Surgery category	Surgery	Procedure
Enhance innate aqueous humour outflow (also called angle surgeries)	Goniotomy	Incision of the trabecular meshwork to allow outflow into Schlemm's canal. This is performed in the absence of corneal clouding.[275]
	Trabeculotomy	Rupturing of the inner wall of Schlemm's canal resulting in a direct route to the anterior chamber. This can be performed in the presence of corneal clouding.[276] Variations of this procedure exist: conventional trabeculotomy (up to one third of Schlemm's canal incised) or circumferential trabeculotomy (360 degree incision).[277]
Create an external aqueous outflow pathway	Trabeculectomy	Creation of an aqueous outflow channel from the anterior chamber to a conjunctival filtering bleb.[278] Antimetabolites mitomycin-C and 5-fluorouracil, are often used intraoperatively and postoperatively, respectively, to prevent scarring of the bleb.[31,66,279]
	Combined trabeculotomy/ trabeculectomy	A procedure whereby trabeculotomy and trabeculectomy are performed simultaneously.[280]
	Glaucoma drainage device	An implant which shunts aqueous humour from a tube situated in the anterior chamber to an external reservoir (a plate).[281] The Baerveldt[282] and Ahmed implants[283] are typically used in childhood glaucoma dependent on surgeon preference.[91,272]
Reduce aqueous production	Cyclodestruction	Involves ablation of the ciliary epithelium. Several forms of cyclodestructive procedures exist: cyclocryotherapy,[284] transscleral,[285] and endoscopic laser cyclophotocoagulation.[286] Transscleral cyclodiode laser is typically preferred as it has less surgical complications.[287]

Visual rehabilitation to treat amblyopia may also be required if glaucoma causes an insult to the developing visual system during the critical period of visual development.[8] Risk factors for amblyopia in childhood glaucoma include unilateral affliction, strabismus, corneal scarring, cataract, and uncorrected refractive error (e.g., myopia, astigmatism, anisometropia).[11,23,288] Full-time spectacle correction with or without occlusion therapy or atropine therapy is undertaken as appropriate during the critical period of vision development to maximise vision potential (usually up until age 6–9 years).[8,23]

1.4.2 Genetic testing

Genetic testing is currently recommended in the multidisciplinary care of childhood glaucoma.[8,289,290] This is because it can assist with genotype-phenotype correlations, refine clinical diagnoses, guide

management, and enable accurate counselling for the risk to other family members or the risk of recurrence in subsequent offspring.[8,289,290] The value of genetic testing is best exemplified by *FOXC1*-associated glaucoma, which is usually associated with SG-O (ARS). This condition can present prior to age 3 years, with a clinical presentation similar to PCG, with corneal clouding and buphthalmos.[194] The presence of corneal clouding, in addition to challenges associated with assessing a non-compliant young child, can prevent an accurate assessment for ocular anomalies consistent with ARS (i.e., gonioscopy). This can lead to a diagnosis of PCG instead of SG-O.[194] Genetic confirmation of *FOXC1* in this example is helpful because it would refine the clinical diagnosis to probable SG-O with ARS instead of PCG and prompt appropriate referral for investigation and management of systemic features associated with ARS. Finally, identification of the *FOXC1* variant in a parent, or lack thereof if *de novo*, would inform the likelihood of transmission in current and subsequent offspring (i.e., 50% in autosomal dominant disease).[194]

Genetic testing is not always successful and it is considered that a large proportion of childhood glaucomas are yet to be explained by a molecular diagnosis.[6] An exact rate of genetic testing success does not exist because of the limited availability of genetic testing and the relative rarity of these molecular diagnoses.[6] Two European cohort studies have attempted to deduce the relative prevalence of molecular diagnoses with respect to all individuals with childhood glaucoma and their CGRN classification. These included a German study of 29 children,[113] and a Swiss study of 18 individuals with childhood glaucoma.[291] Their findings are limited by small sample sizes such that any estimates of genetic testing success and the contribution of a molecular diagnosis to a CGRN subtype may be limited.[291] Other studies have instead examined the contribution of either one gene in one CGRN phenotype (e.g., *CYP1B1* in PCG)[108] or the contribution of many genes in one CGRN phenotype (e.g., SG-O).[111] This does not offer an overall success rate for a molecular diagnosis in childhood glaucoma due to the genetic and phenotypic heterogeneity of the condition.

1.4.3 Systemic features

A child with glaucoma may require input from a paediatrician or medical subspecialist for investigation and management for systemic features or syndromes associated with childhood glaucoma.[255] This may be guided by the results of a clinical ophthalmic examination or genetic testing, particularly where a certain molecular diagnosis has been made.[8] For example, individuals diagnosed with ocular features suggestive of ARS (with or without identification of deleterious *FOXC1* or *PITX2* variants) may require referral to medical subspecialities including cardiology, endocrinology, craniofacial, dental and orthopaedics.[292] Individuals with sporadic aniridia require radiological examination to assess for Wilms tumour where genetic testing has not yet excluded deletion of *WT1*.[293]

Subspecialist referral pathways have not yet been recommended for individuals diagnosed with other glaucomas with developmental anomalies, including PCG or JOAG (which have arrested development of the trabecular meshwork or Schlemm's canal). This could be because there are no established systemic features associated with these clinical diagnoses or because there has been insufficient investigation or reporting of these. Midha and colleagues reported systemic associations in 5.9% of children with primary glaucoma, with congenital heart disease and global development delay each having a prevalence of 1.8%.[255] However, genetic testing was not performed in this study, making it difficult to establish if these conditions were related to a true diagnosis of primary glaucoma, or were part of a genetic condition or syndrome that could change the diagnosis from PCG to SG-O or SG-S.[255] Subspecialist referral pathways have similarly not been recommended for individuals with a certain molecular diagnosis including *CYP1B1*, *TEK, CPAMD8* and *MYOC*. This is because it remains unclear whether systemic features are part of the disease spectrum in the genes, as discussed above. Investigation of systemic features in these clinical and genetic cohorts is needed to ascertain whether subspecialities may be needed in the care of children with childhood glaucoma.

1.5 Outcomes of childhood glaucoma

The management of childhood glaucoma is complex. Accordingly, the treatment and visual outcomes of the condition may vary. The rarity of childhood glaucoma, its underlying genetic causes, varied surgical and nonsurgical treatments and clinical outcomes may also result in potentially devastating impacts on quality of life (QoL).[12] The treatment, visual, and QoL outcomes in childhood glaucoma are therefore reviewed.

1.5.1 Treatment outcomes

Successful control of IOP from topical antiglaucoma medication with or without surgery is variable. Quantifiable success rates are complicated by the rarity of the condition, small sample sizes, the length of follow-up, the treatment preferences of specialists, and specialists' experience. More specifically, surgical success depends on many variables including the surgical technique used, the surgeon experience, the child's age, the structure of the eye, the severity of disease, the glaucoma subtype and the number of previous surgeries performed.[11,272,274] Broadly, in individuals with PCG, where surgery is typically the first line of treatment, IOP control may be achieved in 40–94% following one surgical procedure with or without topical medication at one year.[66,294,295] In comparison, 80–86% of individuals with secondary glaucoma may be controlled with topical medications only or topical medications with surgery at one year.[66,296] Success rates typically decrease as the number of years post-surgery increases.[11,295–297]

The ability to control IOP may depend on the underlying molecular diagnoses and consequent disease severity. However, the literature comparing IOP treatment outcomes in genetic cohorts is relatively scarce. One study reported that significantly more glaucoma surgeries have been required to control IOP in *PITX2*-associated SG-O compared to *FOXC1*-associated SG-O, and indicated that the former results in more severe disease.[195] Biallelic pathogenic variants in *CYP1B1* are also considered to cause more severe PCG and may require additional topical medications or glaucoma surgeries to control IOP compared to eyes without *CYP1B1* pathogenic variants.[298–300] It is unknown, however, if individuals without *CYP1B1* pathogenic variants in these studies harboured other genetic variants associated with PCG as these were not screened for (e.g., *TEK*).[298–300] Comparative studies of treatment outcomes in other genetic childhood glaucomas have not been done.

1.5.2 Visual outcomes

Visual outcomes in childhood glaucoma are highly variable and are often measured by best-corrected visual acuity (BCVA) rather than visual field data.[10,11,23,31,87,88,91,301,302] This is likely owing to a child's inability to accurately perform a visual field test. It is difficult to establish if BCVA outcomes are better in one subtype compared to another due to small sample sizes, variable ages at presentation and the length of follow-up at BCVA measurement.[10,11,23,31,87,88,91,301,302] Worse BCVA outcomes have instead been associated with worse vision at diagnosis, unilateral disease, a diagnosis of glaucoma at <3 months of age and amblyopia.[10,11,23] Amblyopia causes approximately 50% of vision loss in childhood glaucoma.[23] Because amblyopia is a condition associated with an insult to the developing visual system during the critical period of visual development, individuals with earlier disease onset, such as PCG, may report worse BCVA than individuals with later-onset disease. In support of this, normal BCVA (≥6/12 or ≥0.3 logMAR) has been reported in only 4%–46% of individuals with PCG compared with 77% of individuals with JOAG, while 18%–51% of individuals with secondary disease reported normal BCVA owing to a variable age of disease onset.[11,88,301,302]

The visual outcomes may depend on the molecular diagnosis and the consequent disease severity. For example, individuals with *PITX2*-associated glaucoma are more likely to have BCVA worse than 6/12 compared to *FOXC1*-associated glaucoma due to the former causing more severe glaucomatous disease.[195] Severe glaucomatous field loss is usually seen in individuals with pathogenic *MYOC* variants,[303,304] and poor BCVA is often reported in *PAX6*-associated disease due to associated foveal hypoplasia, nystagmus, cataract and keratopathy (mean: 1.0 logMAR or equivalent Snellen measurement of 6/60).[223] Disease complications in *CPAMD8*-associated disease, including glaucoma, early-onset cataract and retinal detachment, have contributed to variable BCVA (decimal: 0.42±0.32, or equivalent mean Snellen measurement of 6/15) and visual field outcomes (mean deviation: −8.92±9.90

dB).[186] Reports of BCVA have seldom been reported in individuals with biallelic pathogenic *CYP1B1* variants,[61,298–300,305] or pathogenic *TEK* variants,[26,138,139] despite being among the most common genes implicated in PCG,[26,96,97,138] and PCG being the most common subtype of childhood glaucoma in several populations.[65,86,88–91]

1.5.3 Quality of life outcomes

The long-term management, disease sequelae and uncertain visual outcomes in childhood glaucoma may pose emotional, social, or physical impacts. However, there is a paucity of literature investigating QoL in childhood glaucoma. Few studies have quantitatively measured the impact of the condition on QoL in children,[306–310] and adults[311,312] with childhood glaucoma, and their caregivers.[313–318] Quantitative measurement of QoL may be attained using patient-reported outcome measures (PROMs).[319] These are defined as a measure of a patient's own interpretation of the status of their condition.[319] There have been several QoL PROMs used throughout childhood glaucoma QoL research in children and adults with the condition.[306–312] Broadly, the PROMs used either measured generic health-related QoL (HR-QoL), which is not considered sensitive for measuring matters faced by individuals with a vision-threatening disease;[311,320] vision-related QoL (VR-QoL) which consider vision-specific impacts on QoL;[320,321] or disease-specific QoL, which considers the specific impact the disease may have on QoL.[320–322] No study which measured QoL in children or adults has utilised a childhood glaucoma disease-specific QoL PROM. This is because a childhood glaucoma-specific PROM does not exist for these population groups. The lack of glaucoma-specific PROMs and the limitation of the findings from previous studies are discussed below.

1.5.3.1 Quality of life in children with glaucoma

There are few studies that have quantitatively measured the impact of childhood glaucoma in children.[306–310] Only two studies measured HR-QoL,[309,310] and used either the Pediatric Quality of Life Inventory (PedsQL) version 4.0,[323] or the Kidscreen-27 Questionnaire,[324] which were developed for children with none, acute or chronic health conditions. Four studies measured VR-QoL,[306–309] and all used the Impact of Vision Impairment for Children Questionnaire, which was developed for children with vision impairment.[325] Because none of these PROMs were specifically developed for children with glaucoma, they lack specificity and may not accurately measure QoL in this cohort. Nonetheless, it has been reported that children with glaucoma who have lower BCVA in the better-seeing eye experienced worse VR-QoL,[306–309] and HR-QoL,[309] compared to normal-sighted children. Despite this, children with bilateral disease did not measure significantly different VR-QoL or HR-QoL compared to those with unilateral disease and normal BCVA in their non-affected eye in several studies.[306,307,309,310] This

contradiction implies that children with unilateral disease may experience poor VR-QoL or HR-QoL for reasons other than BCVA. This may include glare or contrast sensitivity, which are associated with reduced visual function in adults with adult-onset glaucoma.[326] Glare and contrast sensitivity have not been assessed as potential influential covariables in VR-QoL or HR-QoL.[306–309] Appropriate evaluation of the impact of these symptoms of childhood glaucoma is required to resolve these conflicting reports.

Investigations of QoL in children with glaucoma have also shown that a younger age is associated with worse HR-QoL.[309,310] It has been hypothesised that there is a survivor bias in childhood glaucoma, whereby children who have had the condition longer and are therefore older, adapted better and reported a better HR-QoL.[309,310] In contrast, studies that investigated QoL in children with other chronic diseases such as cystic fibrosis[327] and type 1 diabetes,[328] reported that older children may experience worse QoL compared to their younger counterparts. This was considered to be due to adolescents experiencing more issues regarding body image, disease-management and treatment burden. These issues are yet to be explored thoroughly in the context of children with glaucoma.

1.5.3.2 Quality of life in adults with childhood glaucoma

Two studies have investigated the QoL impact of childhood glaucoma in adults with PCG,[311,312] whilst none are yet to evaluate QoL in other forms of childhood glaucoma. One study in Iran used the National Eye Institute Visual Function Questionnaire 25 (NEI-VFQ 25)[329] to measure VR-QoL in Iranian adults with PCG.[312] A high mean deviation on visual field testing (i.e., more visual field loss) was associated with worse VR-QoL in this cohort.[312] However, this PROM was developed for adults with vision impairment secondary to any cause of vision loss, and may not be specific enough to measure the impact of childhood glaucoma. The second study evaluated HR-QoL in an Indian cohort with PCG,[311] and used the World Health Organization Quality of Life Questionnaire—Abbreviated version (WHOQoL-BREF).[330] The same study also measured life satisfaction, using the 5-item Satisfaction with Life Scale.[331] No clinical variable (e.g., BCVA, use of topical medications) was associated with either HR-QoL or life satisfaction measures.[311] A lower education and rural residence was associated with worse HR-QoL and not being married was associated with lower life satisfaction.[311] Because of the quantitative nature of the study, it cannot be determined if low education, rural residence or not being married were associated with having childhood glaucoma (e.g., *did having low BCVA prevent adequate access to learning materials?*) or due to other reasons. Neither PROM used in this study was developed for use in childhood glaucoma and may again lack specificity for disease-specific issues encountered in childhood glaucoma. Moreover, neither study had investigated the impact of childhood glaucoma on family planning, which is critical in the context of a predominantly inherited disease.

Contrary to the proposed hypothesis of a survivor bias, age was not associated with QoL in adults with PCG.[311,312] Instead, decreasing QoL with increasing age has been reported in individuals who were diagnosed with glaucoma between ages 15-40 years (i.e., a diagnosis of JOAG).[332] In this study, it was hypothesised that young adults experienced a better QoL than their older counterparts because they were able to better adapt to changing situations, had better cognition and were socially well-connected.[332] Young adults may have also lacked an understanding of their prognosis and have different priorities at the time of the study or their diagnosis.[332] This hypothesis could further be influenced by the finding that amongst those with JOAG, higher QoL was associated with better visual acuity. However, the relationship between QoL, age and visual acuity was not established.[332] In contrast, younger adults with adult-onset glaucoma have demonstrated higher levels of treatment nonadherence,[333] and increased levels of anxiety of the future of their glaucoma.[334] Further evaluation into the behaviour and attitudes of adults with childhood glaucoma is required to establish if younger adults are at risk of developing non-compliant behaviours and experiencing anxiety.

1.5.3.3 Quality of life in caregivers of an individual with childhood glaucoma

A diagnosis of childhood glaucoma can be a stressful and traumatic experience for caregivers. This may be compounded by the disease's chronicity, uncertain visual prognosis, surgical interventions and frequent examinations under anaesthetic, instillation of topical medications and monitoring of amblyopia therapy.[12] Despite this, few studies have investigated the impact of childhood glaucoma on the QoL of caregivers.[313–318] In addition, the majority of these studies have investigated the experience of caregivers of children with PCG only.[313,314,316–318] Several studies utilised an appropriately developed PROM (the Caregivers of Children with Congenital Glaucoma QoL PROM [CarCGQoL])[316] which provided a validated and accurate measure of caregiver QoL in childhood glaucoma.[313,315,317] The use of the CarCGQoL demonstrated that the event of surgery and anaesthesia had independently caused significant caregiver stress,[317] while worse QoL in an Indian cohort of caregivers was associated with a child's older age and longer duration of disease.[313] This contradicts the survivor bias theory in children with glaucoma,[309,310] and could be due to concerns regarding their child's marriage prospects and other socio-cultural pressures.[313] It has been reported that 44–69% of caregivers have experienced depressive symptoms,[313,314] and 76% experienced moderate or severe caregiver burden.[314] However, there were no clinical or demographic variables associated with these findings. It is unclear as to how clinicians can address potential risk factors for depression and high caregiver burden, and best support caregivers of children with glaucoma. Furthermore, no studies have evaluated the use of coping strategies or the impact of the condition on family planning.

1.6 This thesis

Childhood glaucoma describes a rare group of phenotypically and genetically heterogeneous ocular conditions. It is a leading cause of childhood blindness,[5] and poses a potentially significant impact on QoL owing to its complex management and varied treatment and visual outcomes. Development of the best approach to managing childhood glaucoma has been hindered by the disease rarity, the limited availability of genetic testing, the scarce literature detailing genetic characterisation of disease and QoL outcomes, and the historically low prioritisation in global health initiatives compared to other childhood ocular conditions.

To assist with advancing the care of individuals with childhood glaucoma and their families, this thesis will address several gaps in knowledge in the areas of clinical and genetic characterisation of disease, clinical outcomes in genetic disease, and the impact of childhood glaucoma on QoL. My original contribution to knowledge includes the characterisation of the subtypes of childhood glaucoma and its genetic landscape in a large Australasian population using one of the largest worldwide single cohorts with childhood glaucoma. This thesis will provide an original contribution to the delineation of the phenotypic spectrum associated with known childhood glaucoma genes by investigating their ocular and systemic features. A unique investigation of disease outcomes amongst genetic cohorts with PCG is undertaken alongside an original and in-depth qualitative exploration of the psychosocial impact of childhood glaucoma from the perspectives of the child, adult, and their caregiver. Using this information, this thesis describes the development of a novel childhood glaucoma-specific measure of QoL designed for adults with childhood glaucoma. Finally, this thesis will summarise how these areas of childhood glaucoma are pertinent to the clinical management of childhood glaucoma.

CHAPTER 2 METHODS

2.1 Introduction

This thesis details seven interrelated studies which explore various components of the clinical approach to childhood glaucoma. These components, and consequent studies, can be broadly divided into an exploration of genotype-phenotype correlations and an inquiry into the impact of the condition on QoL. This thesis adopts quantitative and qualitative methods suitable for each respective inquiry. The shared quantitative and qualitative techniques adopted throughout each study are summarised in this chapter for reference. Each study recruited participants through the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) which is herein described. Unique study design features and analytical techniques are detailed in the corresponding chapters.

2.2 Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG)

2.2.1 Referral pathway and glaucoma diagnosis

The ANZRAG was established in 2007 with the aim of identifying clinical and genetic risk factors implicated in the development of severe glaucomatous disease.[335] It evolved to recruit individuals with glaucoma of any severity and glaucoma suspects. The ANZRAG continues to recruit individuals with any form of primary or secondary glaucoma with disease onset at any age, and those with features of ASD. With respect to individuals with childhood glaucoma, earlier phases of recruitment targeted developmental forms of the disease (i.e., PCG, JOAG, and SG-O) and excluded those with acquired disease or SG-C. This has changed upon commencement of this thesis whereby all forms of childhood glaucoma are now actively recruited.

The methods and recruitment strategies involved in the ANZRAG have been described previously by Souzeau and colleagues,[335] and are herein discussed for reference in the context of childhood glaucoma. In brief, participants were referred to the registry by their treating specialist or via self-referral pathways with subsequent verification of glaucomatous disease. Pathways for referral included a paper or online submission (www.anzrag.com.au). Participation in the registry required a description of the clinical details to confirm a diagnosis of glaucoma, ASD, or glaucoma suspect. Clinical information included the subtype of glaucoma, age at glaucoma diagnosis, maximum IOP, BCVA, refraction, central corneal thickness (CCT), vertical cup:disc ratio, visual field mean deviation and presence of central field loss, and surgical history. Additional information pertaining to corneal findings (e.g., presence of Haab striae, corneal oedema, increased in corneal diameter), and axial length (for measurement of abnormal growth of an infant eye),[336] were provided by clinicians or requested where necessary to confirm a

diagnosis of PCG.[4] Registry staff ensured consistent data recording and requested information from the specialist, or reviewed case notes, to complete any missing records where possible to confirm diagnosis. Participants, or their parent or guardian, were specifically asked to self-report their continental ancestry (i.e., European, including European Australian and European New Zealanders, or non-European, including Asian, Middle Eastern, African, South or Central American and Oceanian), and any known family history of any subtype of glaucoma, defined as the presence of a fourth degree or closer relative affected by glaucoma.

Glaucoma severity was defined as advanced or non-advanced as per the ANZRAG protocol where appropriate.[171,335] Advanced glaucoma was defined as having visual field loss related to glaucoma with at least two out the four central squares having a pattern standard deviation <0.5% or a mean deviation of <-15 dB on a Humphrey 24-2 visual field test (HVF). Where visual field testing could not be performed, advanced glaucoma was defined as the loss of BCVA due to glaucoma. If an individual did not meet these criteria, but still had a diagnosis of glaucoma, the term non-advanced glaucoma was used. Because a HVF is not frequently performed by individuals with childhood glaucoma, owing to either a young age or poor visual acuity, BCVA was often used as a proxy for disease severity throughout this thesis. The level of vision impairment was categorised according to the International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision).[337] These are presented in Table 2.1.

Table 2.1. Classification of severity of vision impairment

Vision impairment category	BCVA (Snellen)
No vision impairment	≥6/12
Mild vision impairment	<6/12 – ≥6/18
Moderate vision impairment	<6/18 – ≥6/60
Severe vision impairment or blindness	<6/60 – ≥6/120
Blindness	<6/120 – CF
	HM or LP
	NLP

BCVA: Best-corrected visual acuity; CF: count fingers; HM: hand movements; LP: light perception; NLP: no light perception

2.2.2 Genetic testing

Upon receipt of informed written consent, participants provided a blood or saliva sample for DNA extraction. Targeted genetic testing, whole exome sequencing and/or whole genome sequencing were

performed on collected samples as they were received, such that the most recent samples are yet to be tested. Venous blood specimens were collected in EDTA tubes and DNA was extracted by a QIAcube automated system using QIAamp DNA Blood Mini kit (Qiagen, Chadstone, VIC, Australia). Saliva specimens were collected into an Oragene DNA Self-Collection kit (DNA Genotek Inc., Ottawa, ON, Canada), with DNA isolated as per manufacturer's instructions.

2.2.2.1 Targeted genetic testing

Targeted genetic testing was based on the clinical diagnosis (e.g., *CYP1B1* sequencing for PCG, *MYOC* sequencing for JOAG, *FOXC1*/*PITX2* sequencing and copy number variant analysis for ARS). In addition, some cohorts previously had targeted genetic testing for specific genes. This included 160 individuals with JOAG had *CYP1B1* sequencing,[61] and 86 individuals with JOAG and normal-tension glaucoma (NTG; glaucoma associated with IOP <21 mmHg) had *TBK1* copy number variant analysis and *OPTN* sequencing for p.Glu50Lys.[338]

2.2.2.2 Exome and genome sequencing

Whole exome and whole genome sequencing were performed as previously described,[186,339] on individuals who did not have a molecular diagnosis via targeted genetic testing. Exome capture was performed using the Agilent SureSelect system (version 4 or version 5), and exome and genome sequencing were performed on an Illumina HiSeq or NovaSeq device by an external provider (Macrogen Inc, Seoul, Korea). Raw sequence reads were mapped to the human reference genome (hg19) using the Burrows-Wheeler Aligner, with variants called using the Genome Analysis Toolkit (GATK) and annotated using ANNOVAR.

All genetic results reported in this thesis were validated and classified by the National Association of Testing Authorities-accredited laboratories of SA Pathology at the Flinders Medical Centre (Bedford Park, SA, Australia). Variant classification was performed according to the 2015 American College of Medical Genetics guidelines,[340] with all genetic results returned to participants by a qualified genetic counsellor (supervisor ES).

2.3 Classification of glaucoma

Glaucoma classifications of individuals reported throughout this thesis were determined based on individuals' age of diagnosis and whether their disease was primary or secondary. Individuals with a diagnosis of glaucoma between ages 0 to <18 years were assigned a diagnosis of childhood glaucoma, those diagnosed from age 18 to <40 years were assigned a diagnosis of early-onset glaucoma and those diagnosed at age 40 years and above were considered to have late-onset disease.

Participants with childhood glaucoma were assigned one of the following six CGRN classifications where appropriate:[4]

2.3.1 Primary glaucoma

a. PCG, defined as open-angle glaucoma with neonatal onset (0–1 month of age), infantile onset (1–24 months of age), late onset or late recognition of disease (>2 years of age), or spontaneously arrested PCG. The absence of ASD, systemic disease or an acquired condition confirmed a diagnosis of PCG.[4] Spontaneously arrested PCG was diagnosed in the presence of buphthalmos and Haab striae, with normal IOP, normal appearing optic discs, and no corneal oedema.[4]
b. JOAG, more broadly considered in this thesis as a diagnosis of open-angle glaucoma occurring from age 4 to <40 years of age, without corneal features (i.e., Haab striae, oedema, buphthalmos), ASD, systemic disease or history of an acquired condition. Individuals were further reported to have either NTG (described as maximum recorded IOP ≤21 mmHg) or high-tension glaucoma (HTG, maximum recorded IOP >21 mmHg) in the affected eye/s, where possible and relevant.

2.3.2 Secondary glaucoma

a. Glaucoma associated with acquired conditions (SG-A), where glaucoma is secondary to a condition that is not present at birth.
b. Glaucoma associated with non-acquired ocular anomalies (SG-O), where glaucoma is secondary to a non-acquired condition that is predominantly ocular.
c. Glaucoma associated with non-acquired systemic disease (SG-S), where glaucoma develops in the presence of a disease that is predominantly systemic, with or without ocular manifestations.
d. Glaucoma following cataract surgery (SG-C), where cataract surgery precedes glaucoma onset regardless of any co-existing ocular or systemic abnormality.

As per the CGRN classification, individuals were classified as having SG-O, even in the presence of systemic disease, if the disorder was predominantly ocular. This includes individuals with ARS.[4] Individuals with only posterior embryotoxon and no systemic features were not considered to have ARS.[341] When an individual had ASD that did not fit a specific phenotype, the term ‘unclassified ASD’ was used, as recommended by Idrees and colleagues.[94] Individuals with primary angle-closure glaucoma (PACG) diagnosed in childhood were classified as having SG-O as this entity is caused by anatomical disorders of the iris, lens and retrolenticular structures.[17]

2.4 Quantitative statistical methods

Quantitative methods are concerned with the quantification of observations and control of empirical variables to statistically determine causal or correlational relationships between data.[342] Statistical analysis, however, is not always possible, particularly where sample sizes are small or there is not a suitable control or comparative group.[343] This was an anticipated issue in the study of a rare condition such as childhood glaucoma.

2.4.1 Methodology

Quantitative methods are generally underpinned by positivist and post-positivist philosophies, which both consider that knowledge is largely developed upon objective measurement of a phenomena.[342] A goal of positivist and post-positivist inquiry is to establish generalisations about observable phenomena. The difference between the two philosophies is that positivism serves to verify a theory using rigorous study design and testing, whilst post-positivism believes that biases are inevitable and that one can never truly measure and understand all phenomena.[342] The post-positivist philosophy was adopted for the works of thesis. This is because biases such as recruitment and population biases are inevitable in the study of a rare disease.

2.4.2 Statistical analysis

Several statistical tests are used throughout this thesis and are described in more detail within each respective chapter. The choice of which statistical test to conduct depended on the research question being asked, the variables being used in the analysis and the nature of their data (i.e., parametric or nonparametric).[344–346] For example, if the research question was to determine the frequency of glaucoma subtypes within a certain population, then the number of individuals with a certain glaucoma subtype was analysed and reported, rather than the number of eyes with an ocular phenotype, as demonstrated in Table 1.2.[65,85–91] If the research question was to determine the impact of vision on QoL, then the relationship between QoL and the BCVA of the better eye was analysed, rather than the BCVA of the worse eye, as the former is a better indicator of disease severity.[345] This is common practice amongst studies investigating QoL in childhood glaucoma.[306,307,309,310]

If the research question was to determine the relationship between a certain genotype and the severity of ocular disease, it is not always suitable to use the better or worse affected eye in the statistical model. This is because it cannot be assumed that the disease impacts each eye similarly.[345,346] It is also not suitable to include both eyes from one individual in the statistical model, as this can lead to an overestimate the effect size and the significance of the findings (i.e., increase the risk of type I

errors).[346,347] It is instead best practice to account for any inter-eye correlation using a mixed effects linear regression or a generalised estimating equation.[345] The former is preferred where there is missing data.[345] A mixed effects linear regression model controls for the random effect of the inter-eye correlation and the fixed effects of any covariate (e.g., age of the participant).[345] Confounding covariates including age of the participant and gender are controlled for in multivariable linear and logistic regression models throughout this thesis dependent upon whether the data is continuous or binary, respectively.[348] Software packages including SPSS version 27.0 for Windows (IBM/SPSS Inc, Chicago, IL, USA) and R version 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria) were used throughout this thesis to conduct appropriate statistical testing.

2.5 Qualitative methods

Qualitative methods describe a group of procedures that aim to describe and interpret an individual's experience with a phenomenon (e.g., childhood glaucoma).[342] Qualitative methods were adopted throughout this thesis to explore QoL issues encountered and the lived experiences of those impacted by childhood glaucoma. Because the techniques adopted were similar across Chapters 6, 7 and 8, they are summarised here for reference.

2.5.1 Methodology

The execution of qualitative methods and the interpretation of the results depends upon the research paradigm chosen.[342] As per the Consolidated Criteria for Reporting Qualitative Research, it is pertinent that the methodological orientation and theory of the researcher is reported in qualitative research.[349] Identifying the research paradigm used to approach the data is key in assuring the ethical integrity of the research.[350] To guide selection of the most appropriate research paradigm, the strengths and limitations of each paradigm used in qualitative research, as discussed by Ponterotto[342] and Braun and Clarke,[351] are summarised in Table 2.2.

Table 2.2. Research paradigms

Paradigm	What it involves	When to use it	Strengths	Limitations
Positivist	Systematic observation and description of a phenomenon	Study aim is to create an explanation for, and prediction about, the phenomenon/lived experience	▪ Can draw generalisations from data ▪ Data can be represented quantitatively ▪ Research findings can be replicated ▪ Suitable if there is a theoretical interest in the topic	▪ The researcher is absolutely objective (i.e., no data interpretation is involved) ▪ Generalisation risks losing the value and meaning of an individual's own experience
Post-positivist	Systematic observation and description of a phenomenon	Study aim is to create an explanation for, and prediction about, the phenomenon/lived experience	▪ Can draw generalisations from data ▪ Acknowledges researcher objectivity is not entirely possible ▪ Data can be represented quantitatively ▪ Suitable if there is a theoretical interest in the topic	▪ Generalisation risks losing the value and meaning of an individual's own experience ▪ Research findings may not be absolutely replicable
Constructivist -interpretivist	Description of a phenomenon with deep reflection and co-construction of meaning with the participant	Study aim is to create a shared understanding of the phenomenon/ lived experience with the participant	▪ Acknowledges that one participant's reality is equally important as others ▪ Develops a deep understanding of the phenomenon ▪ Data not usually represented quantitatively	▪ Does not allow a theoretical interest to be established *a priori* ▪ Generalisations are not possible ▪ Results are subjective/cannot be replicated easily ▪ Timely
Critical-ideological	Description of a phenomenon within a social-historical context that reflect the researcher's values	Study aim is to study a lived experience of oppressed groups of people and empower them to create democratic change	▪ Acknowledges that one participant's reality is equally important as others ▪ Provides very detailed accounts of an individual's experience ▪ Data not usually represented quantitatively ▪ Unbiased by prior literature	▪ Does not allow a theoretical interest to be established *a priori* ▪ Generalisations are not possible ▪ Results are subjective/cannot be replicated easily ▪ Timely

Based on the strengths and limitations of the research paradigms presented in Table 2.2, the post-positivist research paradigm was chosen to best describe the approach used to explore the phenomena of living with childhood glaucoma. This approach was considered most suitable because a theoretical interest as to how childhood glaucoma may impact an individual's QoL was already established. This was formed by prior literature and my own clinical and research experience. Post-positivism further allows the calculation and reporting of the number of individuals represented within each meaningful set of qualitative data (i.e., a theme).[342] This was considered useful in enhancing the readability of qualitative findings for researchers and clinicians and was favoured over the use of commonly used terms such as 'some' or 'many'.[352] Post-positivism also acknowledges that the researchers' experiences may influence data collection and interpretation (i.e., researcher objectivity is not entirely possible).[342] This was important to recognise because, unlike positivism, it accepts that the research findings may not be entirely replicable.

Selection of the most appropriate paradigm to underpin the methods requires a researcher to constantly and critically self-reflect. Reflection is a core skill in research design and offers a way to legitimise and validate research proceedings.[353] It is further considered a necessary practice to maintain the ethics of the research, particularly because the way in which the data was analysed and presented is dependent upon the research paradigm chosen.[350,353] Reflection regarding the selection of the correct research paradigm was demonstrated throughout the works of this thesis. Previous publications arising from the works of this thesis cited the use of interpretative phenomenological analysis, which falls under the constructivist-interpretivist paradigm (Table 2.2).[354,355] Interpretive phenomenological analysis is centred on three principles: idiographic (the study of an individual), the double hermeneutic (the theory that a researcher's interpretation of a phenomena is based upon the participants' own understanding of what it means to live with the phenomena) and phenomenology (the study of lived experiences).[356] Upon deeper reflection, it was realised that the research had moved away from a purist idiographic description, which requires a detailed report of a single individual's experience rather than just the study of it, to a nomothetic (population-central/generalised) description of the phenomena.[342,356] Generalisations about the research findings were instead made so that broad recommendations for the care of any individual impacted by the condition could be provided, and a childhood glaucoma-specific QoL PROM could be developed. Generalisations are more consistent with a post-positivist paradigm (Table 2.2).[342] The double hermeneutic was initially considered applicable to my research as meaning from the participants' words and phrases needed to be generated. However, it was later realised that the double hermeneutic required a substantially more in-depth analysis of the impact of the researcher-participant relationship, the wider social context, and the nuances of each participant's responses (e.g., *why did the participant say, 'I had to'? Were they feeling pressure from something or someone? What or whom? Why?*).[356] Instead, a relatively objective approach was maintained and a descriptive analysis (e.g., counting words or phrases) was provided without interpretation of the meaning of a phrase or response outside of what was discussed with the participant. This type of analysis is more consistent with a post-positivist approach.[342] A post-positivist paradigm is also suitable for phenomenology (i.e., the study of lived experiences).[342]

2.5.2 Semi-structured interviews

Semi-structured one-on-one interviews or focus groups are a suitable method for qualitative inquiry which aims to understand social phenomena. They enable researchers to develop a deep understanding of an individual's experiences and thought processes.[357] Because of the COVID-19 pandemic and its restrictions on group gatherings, one-on-one semi-structured interviews were used to explore the QoL issues and lived experiences of childhood glaucoma in several cohorts instead of focus groups. These

cohorts included: 1) children with glaucoma (Chapter 6);[358] 2) adults with childhood glaucoma (Chapter 7);[355] and 3) parents and caregivers (henceforth referred to as caregivers) of individuals with childhood glaucoma (Chapter 8).[354] Semi-structured interview guides for each of these cohorts were developed based on prior literature investigating QoL in childhood glaucoma.[306–317] Instruments used to measure QoL in these studies for the development of interview questions were also consulted. This included the PedsQL,[323] Kidscreen-27 questionnaire,[324] Impact of Vision Impairment for Children Questionnaire,[325] NEI-VFQ 25,[329] WHOQOL-BREF,[330] and CarCGQoL.[316] Other QoL instruments designed for use for adults with adult-onset glaucoma were further consulted. This included the Glaucoma Quality of Life-36 (Glau-QoL 36),[359] the Symptom Impact Glaucoma,[360] and the Glaucoma Quality of Life-15.[361] Finally, literature detailing the broader experience of caring for a child with a vision-impairment was considered.[362] The interview guides for each cohort are provided in Appendix A.

All interviews were conducted in the English language. Of the 96 interviews conducted, only six were conducted by one other individual (BR; a health counsellor) as part of their higher research degree in counselling. These interviews were included in the analyses. No participants were under the clinical care of either interviewer. Participants (and their caregiver where the participant was a child) were informed that both interviewers were completing a higher research degree. One-on-one semi-structured interviews occurred via telephone or Cisco WebEx videoconferencing (Milpitas, California, USA), subject to the participant's preference. Interviews were audio-recorded and transcribed verbatim. In keeping with a nomothetic post-positivist approach, interviews continued until thematic saturation was achieved.[342] Thematic saturation was defined as the point where no new information was gained from subsequent interviews.[363] It was assessed with respect to whether the depth of responses already obtained created a rich insight into the meaning of the theme or subtheme.[364] These criteria are analogous to the self-assessed questions of: "*have I heard it all?"* and "*do I understand it all?*".[364] Once thematic saturation was achieved, additional interviews with individuals already recruited to the studies were conducted to confirm saturation had been reached. Recruitment ceased thereafter.

2.5.3 Data analysis

A general inductive approach was used to identify QoL themes.[365] The general inductive approach is not tied to any research paradigm unlike thematic analysis or phenomenology whereby the calculation and reporting of the number of individuals represented within each theme is not considered a valid technique to interpret data.[351,366] The general inductive approach has been widely adopted, and has been used to explore issues impacting individuals with ophthalmic disease,[367] and the lived experience

of patients and caregiver in the context of other chronic diseases including arthritis, heart disease, and cancer.[368–370]

This process began with close reading and familiarisation of the transcripts.[365] All interview transcripts were then systematically coded using QSR NVivo 12 (QSR International Pty Ltd, Melbourne, VIC, Australia). This was done at the same time as study recruitment to monitor for thematic saturation. Specific segments of texts with similar or repetitive patterns of meaning were coded to form a major theme or subtheme.[365,371] Themes and subthemes were then refined in an iterative process, and appropriate participant quotations were selected which conveyed the essence of the theme or subtheme.[365] To enhance the readability of qualitative findings, major themes were abbreviated to be consistent with previous ophthalmic QoL research,[372–374] and qualitative data were reported quantitatively, as previously discussed.[352] This facilitated pattern recognition and transparency of findings for the reader.[352] The prominence of QoL themes was determined by the number of participants who raised issues connected to the corresponding theme. To ensure that interpretation of the data was credible, stakeholder coding checks were frequently and separately performed with three co-researchers, two of whom were co-supervisors (BR and co-supervisors MPS and ES).[365] Neither were treating specialists. Any discrepancies between researchers were resolved by discussion.

2.5.4 Patient and public involvement

An important aspect of patient-centred outcome research, such as QoL research, is to involve participants in formulating the research question and design.[375] In March 2020 during World Glaucoma Week, the research aims and design were presented at a national childhood glaucoma support group meeting prior to conducting the research. This was hosted by Glaucoma Australia, a national charity organisation which supports individuals diagnosed with glaucoma (see Thesis Outcomes; the Glaucoma Australia Congenital Support Group Morning Tea 2020). Engagement with attendees assisted in affirming that the research topic was relevant and there was interest to participate. Attendees' responses further informed the development of the interview guides. Attendees were keen to see research findings disseminated back to the childhood glaucoma community. In March 2022 during World Glaucoma Week, an invitation was extended by Glaucoma Australia to host an online public seminar for the childhood glaucoma community and provide feedback on the research findings of QoL in children with glaucoma (see Thesis Outcomes; Hear the Voice of Our Youngsters with Glaucoma). Dissemination of research findings pertaining to the adult and caregiver cohorts will occur in future.

2.6 Conclusion

The methods that are frequently used throughout this thesis were summarised. This chapter provides a point of reference for participant recruitment, glaucoma diagnosis and classification, genetic testing, and data analysis techniques.

CHAPTER 3 THE PHENOTYPIC AND GENETIC HETEROGENEITY OF CHILDHOOD AND EARLY-ONSET GLAUCOMA

Published manuscript

The contents of this chapter have been published in a peer-reviewed manuscript of which I am the first author: **Knight LSW**, Ruddle JB, Taranath DA,... Siggs OM,* Souzeau E,* Craig JE.* Childhood and early onset glaucoma classification and genetic profile in a large Australasian disease registry. ***Ophthalmology***. 2021;128(11):1549-60.

My contributions to the manuscript involved the research conception and design (60%), data collection including review of referrals, case note review and data extraction from paper and electronic records (70%), generation of a dataset (100%), data analysis including statistical analysis (90%), interpretation of the data (60%), and drafting the manuscript (100%). Jamie Craig, Emmanuelle Souzeau and Owen Siggs contributed equally to the manuscript including study concept and research design (35%), data collection (20%), interpretation of the data (30%), critically revising the contents of the manuscript, project funding and supervision. Jonathan Ruddle further contributed to research design (5%), data collection/participant recruitment (5%), interpretation of the data (5%), critically revising the contents of the manuscript and supervision. Ayub Qassim, Sean Mullany and James Breen were involved in data analysis including statistical analysis (10%) and critical revision of the contents of the manuscript. As the ANZRAG is a multicentre study, several other co-authors assisted with participant recruitment/data collection and critical revision of the manuscript. This included Deepa Taranath, Ivan Goldberg, James Smith, Glen Gole, Mark Chiang, Faren Willett, Guy D'Mellow, James Elder, Andrea Vincent, Sandra Staffieri, Lisa Kearns, David Mackey, and Susie Luu.

The introduction and methods of this manuscript have been edited to fit the structure of this thesis.

3.1 Introduction

The term 'early-onset glaucoma' encompasses a heterogenous group of vision-threatening optic neuropathies with onset before age 40 years.[7] Childhood glaucoma represents a subcategory of early-onset glaucoma defined as disease onset <18 years of age.[2] The different subtypes of childhood glaucoma have previously been described using various definitions and classification systems that lacked consensus. To address this issue, the CGRN recently developed a classification system describing the subtypes of childhood glaucoma, which has been adopted by the World Glaucoma Association and the American Board of Ophthalmology.[4]

In accordance with the CGRN classification, primary glaucoma includes PCG and JOAG, while secondary glaucomas are subcategorized depending on their underlying pathology. These secondary glaucomas include SG-O (e.g., ARS, Peters anomaly), SG-S (e.g., NF1, SWS, connective tissue disorders), and SG-A (e.g., uveitis, trauma, or intraocular surgery). Glaucoma that occurs following surgery for childhood cataract (i.e., SG-C) falls under a separate classification.[4]

Childhood glaucoma is most commonly associated with single genetic variants with a Mendelian pattern of inheritance.[6,7] The most common genes implicated are: *CYP1B1, LTBP2,* and *TEK* for PCG; *MYOC* and *EFEMP1* for JOAG; and *FOXC1, PITX2, PAX6* and *CPAMD8* for SG-O.[6,7,93] Variants in these genes are usually associated with strong age-related penetrance and variable expressivity, which contributes to a broad phenotypic spectrum and overlap between clinical entities. Consequently, these genes are also commonly implicated in glaucomatous disease diagnosed between the ages of 18 and 40 years (defined as early-onset disease).[6,7] Other genes typically implicated in early-onset disease include *TBK1* and *OPTN*, which are associated with NTG.[338,376] The genetic heterogeneity of childhood and early-onset glaucomas, coupled with the difficulty of accurately establishing clinical diagnoses in young individuals, highlights the importance of genetic testing in this cohort.[194]

To the best of my knowledge, the genetic findings of the phenotypes described by the CGRN have not been reported in a large cohort of individuals with childhood and early-onset glaucoma. In addition, none are yet to report the diagnostic yield of genetic testing in these cohorts. This is likely owing to the limited availability of genetic testing and relative rarity of these molecular diagnoses. The ANZRAG is well-positioned to overcome these limitations.

My original contribution to knowledge was a detailed report of the genetic results and diagnostic yield in one of the largest international cohorts of individuals with childhood or early-onset glaucoma from the ANZRAG, with respect to their CGRN classification.

3.2 Methods

3.2.1 Participants

Participants included in this study were sourced from the ANZRAG as previously described (Chapter 2).[335] Maximum recorded IOP and age at glaucoma diagnosis were recorded for each individual by the referring clinician. Family history of glaucoma and continental ancestry were recorded as described in Chapter 2.

All participants who were referred to the registry since its establishment in 2007 to October 2020 and who had a clinical diagnosis of glaucoma between the ages of 0 and <40 years were included. Individuals with a diagnosis of glaucoma from the ages of 0 to <18 years were assigned a diagnosis of childhood glaucoma and those diagnosed from age 18 to <40 years were considered to have early-onset glaucoma. Glaucoma suspects were not included. Participants in either cohort were subsequently assigned one of the six CGRN classifications as outlined in Chapter 2. The CGRN classifications, although developed for childhood glaucoma, were also applied to the early-onset cohort because no formalised system for glaucoma diagnosis in individuals diagnosed between the ages of 18 and <40 years exists.

An 'Unclassified' category was additionally assigned to individuals for circumstances where it could not be determined if their glaucoma was primary or secondary due to an insufficient view of the ocular structures or unavailable medical records.

Ethics approval was obtained through the Southern Adelaide Clinical Human Research Ethics Committee (2021/HRE00032). The study adhered to the revised Declaration of Helsinki (2013) and the National Health and Medical Research Council statement of ethical conduct in research involving humans (2018).

3.2.2 Genetic testing

Participants, or their parent or guardian, provided informed written consent. Participants then provided a blood or saliva sample for DNA extraction. Targeted genetic testing and/or exome or genome sequencing were performed on collected samples as they were received as outlined in Chapter 2. Briefly, targeted genetic testing was based on the clinical diagnosis (e.g., *CYP1B1* sequencing for PCG) whilst some cohorts previously had targeted genetic testing for specific genes. This included *CYP1B1* sequencing in 160 individuals with JOAG,[61] and *TBK1* copy number variant analysis and *OPTN* sequencing for p.Glu50Lys in 86 individuals with JOAG and NTG.[338] If a molecular diagnosis was not achieved with targeted genetic testing, whole exome or genome sequencing was performed as

previously described (Chapter 2).[186,339] The majority of the molecular diagnoses presented have been previously published and are identified in the results accordingly.[26,61,130,139,141,186,303,338,377,378]

3.2.3 Statistical analysis

All calculations were performed using SPSS version 27.0 for Windows. Data normality was assessed using the Shapiro-Wilk test. Continuous variables were expressed as median [interquartile range (IQR)]. Categorical data were expressed as counts and percentages. Statistical analyses of European ancestry and family history were performed on probands only to provide a more accurate representation of the data among families. The chi-square test with Yates' correction for continuity or Fisher exact test was used for categorical variables as appropriate. Standardised adjusted residuals were used during post hoc analyses to interpret any statistical significance. Gender distribution was assessed using a binomial test with the exact Clopper-Pearson 95% confidence interval (CI), where the probability of male gender is 0.49 based on Australian and New Zealand census data.[379,380] The median test was applied to non-parametric continuous variables, with post-hoc pairwise analyses using the Bonferroni adjustment. A *P* value of <0.05 was considered statistically significant. Multiple testing adjustments were not used beyond post hoc pairwise analyses because all analyses were exploratory in nature.

3.3 Results

3.3.1 Clinical diagnosis and classification

A total of 1219 eyes of 660 individuals with childhood or early-onset glaucoma were included. Exact clinical phenotypes per classification are reported in Appendix B, Table B1. Bilateral disease was reported in 86.7% of individuals (566/653), and 55.8% of individuals (368/660) were male, representing a male:female ratio of 1.26:1 (95% CI: 0.519–0.596, p<0.001). A positive family history of glaucoma was reported in 59.9% of probands (344/574) and 76.2% of probands (428/562) self-reported European ancestry.

3.3.1.1 Childhood glaucoma

Of the whole cohort, 533 eyes of 290 individuals (43.9%) were classified as having childhood glaucoma (Table 3.1). Primary glaucoma was more common than secondary glaucoma (223/290, 76.9% vs 63/290, 21.7%). Four individuals had unclassified glaucoma (1.4%). PCG was the most common subtype (167/290, 57.6%), followed by JOAG (56/290, 19.3%). Infantile PCG was the most common PCG subtype (89/167, 53.3%, Appendix B, Table B1). Of those with JOAG, 80.4% (45/56) had HTG (Appendix B, Table B1). Bilaterality was significantly different across all subtypes (p<0.001), where those with SG-S were least likely to have bilateral disease (1/6, 16.7%) compared with JOAG (53/56,

94.6%, p<0.001). Gender distribution did not significantly differ between subgroups (p=0.61), although an overall male:female ratio of 1.28:1 was found in the childhood cohort (95% CI: 0.503–0.620, p=0.008). The PCG cohort recorded a higher male:female ratio of 1.46:1 (95% CI: 0.514–0.668, p=0.005). A positive family history of glaucoma was significantly different across subgroups (p=0.004). It was most commonly reported in probands with JOAG (29/45, 64.4%) and less commonly reported in probands with PCG (50/140, 35.7%, p=0.007). Parental consanguinity was self-reported in eight individuals with childhood glaucoma, of whom five had PCG. Median maximum IOP was highest in those with SG-A (48 [46–49] mmHg) but differences in IOP across subgroups did not reach statistical significance (p=0.07). However, there was a statistically significant difference in the median age of disease diagnosis across subtypes (p<0.001). The median age of those with SG-O (3 [0.2–8] years) was significantly different to both PCG (0.25 [0–0.6] years, p<0.001) and JOAG cohorts (14 [12–16] years, p<0.001).

Table 3.1. Demographic and clinical characteristics of individuals with childhood glaucoma

	PCG	JOAG	SG-A	SG-O	SG-S	SG-C	Unclassified	Total	p-value
All cases n (%)	167 (57.6)	56 (19.3)	3 (1.0)	49 (16.9)	6 (2.1)	5 (1.7)	4 (1.4)	290 (100.0)	-
Eyes n (%)	303 (56.8)	109 (20.5)	5 (0.9)	93 (17.4)	7 (1.3)	8 (1.5)	8 (1.5)	533 (100.0)	-
Bilateral n (%)	138/165 (83.6)	53/56 (94.6)	2/3 (66.7)	44/49 (89.8)	1/6 (16.7)	3/5 (60.0)	4/4 (100.0)	245/288 (85.1)	**<0.001**[a]
Male gender n (%)	99/167 (59.3)	28/56 (50.0)	2/3 (66.7)	28/49 (57.1)	2/6 (33.3)	3/5 (60.0)	1/4 (25.0)	163/290 (56.2)	0.61[a]
Probands n (%)	148 (59.2)	45 (18.0)	3 (1.2)	41 (16.4)	6 (2.4)	5 (2.0)	2 (0.8)	250 (100.0)	-
Family history n (%)	50/140 (35.7)	29/45 (64.4)	0/3 (0.0)	20/39 (51.3)	3/6 (50.0)	2/5 (40.0)	2/2 (100.0)	106/240 (44.2)	**0.004**[a]
European ancestry n (%)	104/138 (75.4)	30/44 (68.2)	3/3 (100.0)	26/39 (66.7)	4/6 (66.7)	3/4 (75.0)	1/2 (50.0)	171/236 (72.5)	0.72[a]
Highest recorded IOP (mmHg)*	30 (24–40)	40 (27–46)	48 (46–49)	35 (27–45)	31 (30–38)	37 (22–49)	40 (n/a)	32 (25–40)	0.07[b]
Age at diagnosis (years)*	0.25 (0–0.6)	14 (12–16)	6 (5–6)	3 (0.2–8)	0 (0–4)	11 (0–15)	4 (3–6)	0.6 (0–7)	**<0.001**[b]

PCG: Primary congenital glaucoma; JOAG: Juvenile open-angle glaucoma; SG-A: secondary glaucoma associated with an acquired condition; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; SG-S: secondary glaucoma associated with a systemic condition; SG-C: secondary glaucoma following cataract surgery; IOP: intraocular pressure; n/a: not available
Totals for each variable may not equal the total number of cases due to missing data. Bold values indicate statistical significance (p<0.05). All cases include probands and non-probands. European ancestry and family history were calculated for probands only.
*Highest recorded intraocular pressure (IOP) and age at diagnosis (years) are presented as median (IQR).
[a]Fisher's Exact Test, [b]Median test

3.3.1.2 Early-onset glaucoma

A total of 686 eyes of 370 individuals (56.1%) were diagnosed with early-onset glaucoma (Table 3.2). JOAG was the most prevalent subtype (271/370, 73.2%). Of these, 78.6% (213/271) had HTG and 8.1% (22/271) had NTG (Appendix B, Table B1). Bilaterality was significantly different across all subtypes (p<0.001), with those with JOAG more likely to have bilateral involvement (247/266, 92.9%) compared with individuals with SG-A (33/49, 67.3%, p<0.001). An overall male:female ratio of 1.24:1 was found across all early-onset glaucoma cases (95% CI: 0.502–0.605, p=0.008). The distribution of gender was significantly different between groups (p=0.002); SG-A was more common in male individuals (36/49, 73.5%) compared with JOAG (147/271, 54.2%, p=0.04). Family history was also significantly different between groups (p=0.007); probands with SG-A were least likely to report a family history of glaucoma

(25/45, 55.6%) compared with those with JOAG (187/246, 76.0%, p=0.03). Differences in IOP between subgroups also reached statistical significance (p=0.002). Those with JOAG had a lower median maximum recorded IOP (29 [23–38] mmHg) compared with those with an associated acquired condition (36 [30–48] mmHg, p=0.03) and non-acquired ocular anomalies (39 [28–45] mmHg, p=0.02). The median maximum IOP recorded was 15 [14–17] mmHg among individuals with NTG compared with 32 [26–40] mmHg among those with HTG (Appendix B, Table B1). The median age of diagnosis of disease also reached statistical significance between groups (p=0.03). Those with non-acquired systemic disease had the youngest median age of disease diagnosis (23 [21–30] years) but post-hoc analyses did not show statistical significance between specific groups.

Table 3.2. Demographic and clinical characteristics of individuals with early-onset glaucoma

	JOAG	SG-A	SG-O	SG-S	SG-C	Total	p-value
All cases n (%)	271 (73.2)	49 (13.2)	44 (11.9)	5 (1.4)	1 (0.3)	370 (100.0)	-
Eyes n (%)	513 (74.8)	82 (12.0)	79 (11.5)	10 (1.5)	2 (0.3)	686 (100.0)	**-**
Bilateral n (%)	247/266 (92.9)	33/49 (67.3)	35/44 (79.5)	5/5 (100.0)	1/1 (100.0)	321/365 (87.9)	**<0.001[a]**
Male gender n (%)	147/271 (54.2)	36/49 (73.5)	22/44 (50.0)	0/5 (0.0)	0/1 (0.0)	205/370 (55.4)	**0.002[a]**
Probands n (%)	250 (72.7)	49 (14.2)	40 (11.6)	4 (1.2)	1 (0.3)	344 (100.0)	**-**
Family history n (%)	187/246 (76.0)	25/45 (55.6)	24/39 (61.5)	2/3 (66.7)	0/1 (0.0)	238/334 (71.3)	**0.007[a]**
European ancestry n (%)	190/242 (78.5)	37/45 (82.2)	25/34 (73.4)	4/4 (100.0)	1/1 (100.0)	257/326 (78.8)	0.76[a]
Highest recorded IOP (mmHg)*	29 (23–38)	36 (30–48)	39 (28–45)	35 (29–47)	23 (n/a)	30 (24–40)	**0.002[b]**
Age at diagnosis (years)*	34 (29–37)	32 (30–37)	31 (25–35)	23 (21–30)	20 (n/a)	33 (28–36)	**0.03[b]**

JOAG: juvenile open-angle glaucoma; SG-A: secondary glaucoma associated with an acquired condition; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; SG-S: secondary glaucoma associated with a systemic condition; SG-C: secondary glaucoma following cataract surgery; IOP: intraocular pressure; n/a: not available.

Totals for each variable may not equal the total number of cases due to missing data. Bold values indicate statistical significance (p<0.05). All cases include probands and non-probands. European ancestry and family history were calculated for probands only.

*Highest recorded intraocular pressure (IOP) and age at diagnosis (years) are presented as median (IQR).

[a]Fisher's Exact Test, [b]Median test

3.3.1.3 Differences in childhood and early-onset glaucoma cohorts

Laterality (p=0.34) and gender (p=0.90) were similarly distributed in childhood and early-onset cohorts. Probands with early-onset glaucoma showed a higher prevalence of European ancestry than probands with childhood glaucoma, but this did not reach statistical significance (78.8% vs 72.5%, respectively, p=0.10). A positive family history of glaucoma was more likely to be reported in probands with early-onset glaucoma compared with probands with childhood glaucoma (71.3% vs 44.2%, respectively, p<0.001). The distribution of exact clinical phenotypes per cohort is shown in Appendix B, Table B1. The distribution of age at diagnosis and highest recorded IOP per glaucoma subtype per cohort are shown in Appendix C, Figure C1 and Appendix C, Figure C2, respectively.

3.3.2 Genetic results

A total of 506 (506/594, 85.2%) probands underwent genetic testing, of whom 36.8% (186/506) underwent targeted genetic testing and 63.2% (320/506) underwent whole exome or genome sequencing. A molecular diagnosis was determined in 24.7% (125/506). The diagnostic yield was 37.6% (83/221) in probands with childhood glaucoma and 14.7% (42/285) in probands with early-onset glaucoma. Genetic diagnoses were achieved through targeted genetic testing in 75.2% (94/125) of probands and whole exome or genome sequencing in 24.8% (31/125). Genetic results are presented and discussed in the context of the whole cohort's clinical diagnosis and CGRN classification (see Appendix B, Table B2 for distribution of molecular diagnoses per cohort). Genetic results confirmed the clinical diagnosis in 89.6% (112/125) of probands. The remaining 10.4% (13/125) of probands underwent re-examination and were found to have other ocular and/or systemic features consistent with their molecular diagnosis and consequently had a change in clinical diagnosis. A molecular diagnosis for glaucoma was not achieved in any individual with SG-A or SG-C. The distribution of associated genes per glaucoma subtype per proband, after reclassification, are presented in Figure 3.1. Appendix C, Figure C3 conversely shows the distribution of glaucoma subtypes per associated gene.

3.3.2.1 PCG

The majority of probands with PCG (135/148, 91.2%) were genetically tested and 30.4% were given a molecular diagnosis (41/135). Biallelic variants in *CYP1B1* (n=21, 15.6%), *CPAMD8* (n=5, 3.7%) and *COL18A1* (n=1, 0.7%), and heterozygous variants in *TEK* (n=8, 5.9%), *FOXC1* (n=5, 3.7%) and *ANGPT1* (n=1, 0.7%) were found. One individual with homozygous biallelic variants in *CYP1B1* reported parental consanguinity. Biallelic variants in *CYP1B1* were present in 7 of 80 male and 14 of 55 female probands with PCG who underwent genetic testing (p=0.02).

After genetic diagnosis, 24.4% of PCG probands (10/41) had a reclassification of their clinical diagnosis based on re-examination. All individuals with *FOXC1* variants were consequently found to have features of ARS and were reclassified to have SG-O. One individual did not have any evident ocular features of ARS following thorough re-examination but based on systemic features associated with ARS, was reclassified into this category with other individuals with ARS.[194] Four of the five probands with biallelic *CPAMD8* variants were found to have features consistent with unclassified ASD,[186] and the individual with biallelic *COL18A1* variants was subsequently discovered to have Knobloch syndrome. These individuals were also reclassified to have SG-S.

3.3.2.2 JOAG

Collectively, 15.5% of tested JOAG probands across both cohorts (39/252) received a molecular diagnosis, including 30.8% (12/39) of those with childhood-onset and 12.7% (27/213) of those with early-onset glaucoma.

The results consisted of biallelic variants in *CYP1B1* (n=8, 3.2%) and *CPAMD8* (n=1, 0.4%), and heterozygous variants in *MYOC* (n=24, 9.5%), *FOXC1* (n=2, 0.8%), *TBK1* (n=2, 0.8%), *OPTN* (n=1, 0.4%) and *COL2A1* (n=1, 0.5%). Upon re-examination, the individual with *CPAMD8* was found to have unclassified ASD,[186] and the individual with a *COL2A1* variant had a history of retinal detachment and joint problems consistent with Stickler syndrome. One of the two individuals with a *FOXC1* variant,[194] who was from the childhood cohort, had a revised diagnosis of ARS upon re-examination whilst the other individual did not have any ocular anomalies or systemic features consistent with ARS.

3.3.2.3 SG-O

A molecular diagnosis was determined in 56.5% of probands (39/69) with SG-O, including 71.1% (27/38) of those with childhood-onset and 38.7% (12/31) of those with early-onset glaucoma. The most frequent variants found included heterozygous variants in *FOXC1* (n=14, 20.3%), *PITX2* (n=12, 17.4%) and *PAX6* (n=7, 10.1%). Less frequent findings included biallelic variants in *LTBP2* (n=2, 2.9%), *TMEM98* (n=2, 2.9%), *SLC4A11* (n=1, 1.4%), and *CPAMD8* (n=1, 1.4%).

All individuals with an original clinical diagnosis of SG-O and *FOXC1* variants had ARS,[130] and all individuals with *PAX6* variants had phenotypes consistent with aniridia.[377] All individuals with *PITX2* variants, except one, had ARS, whereas the remaining individual had Peters' anomaly.[130] Meanwhile, *TMEM98* variants were found in individuals with nanophthalmos,[378] and *SLC4A11* variants in an individual with congenital hereditary endothelial dystrophy. Biallelic *LTBP2* variants were associated with microspherophakia in one individual who reported parental consanguinity, and widespread

peripheral anterior synechiae, high myopia and phacodonesis in another. The latter individual was determined to have unclassified ASD. The individual with biallelic variants in *CPAMD8* also had unclassified ASD.[186]

3.3.2.4 SG-S

A total of 71.4% of probands (5/7) with an original clinical diagnosis of SG-S were given a molecular diagnosis. Two individuals with NF1 were found to have heterozygous variants in *NF1*, one of whom reported parental consanguinity. Genetic results also confirmed the clinical diagnoses of Weill-Marchesani syndrome (*ADAMTS17*), Nail Patella syndrome (*LMX1B*) and Stickler syndrome (*COL2A1*) in one individual each. No molecular diagnosis was determined for the other two probands who had a clinical diagnosis of SWS.

3.3.2.5 Unclassified glaucoma

One of two probands (50%) with this classification underwent genetic testing. This individual was found to have biallelic *LTBP2* variants with a history of aphakia following removal of congenital cataracts and glaucoma onset by one year of age. It could not be ascertained whether glaucoma preceded or followed cataract surgery.

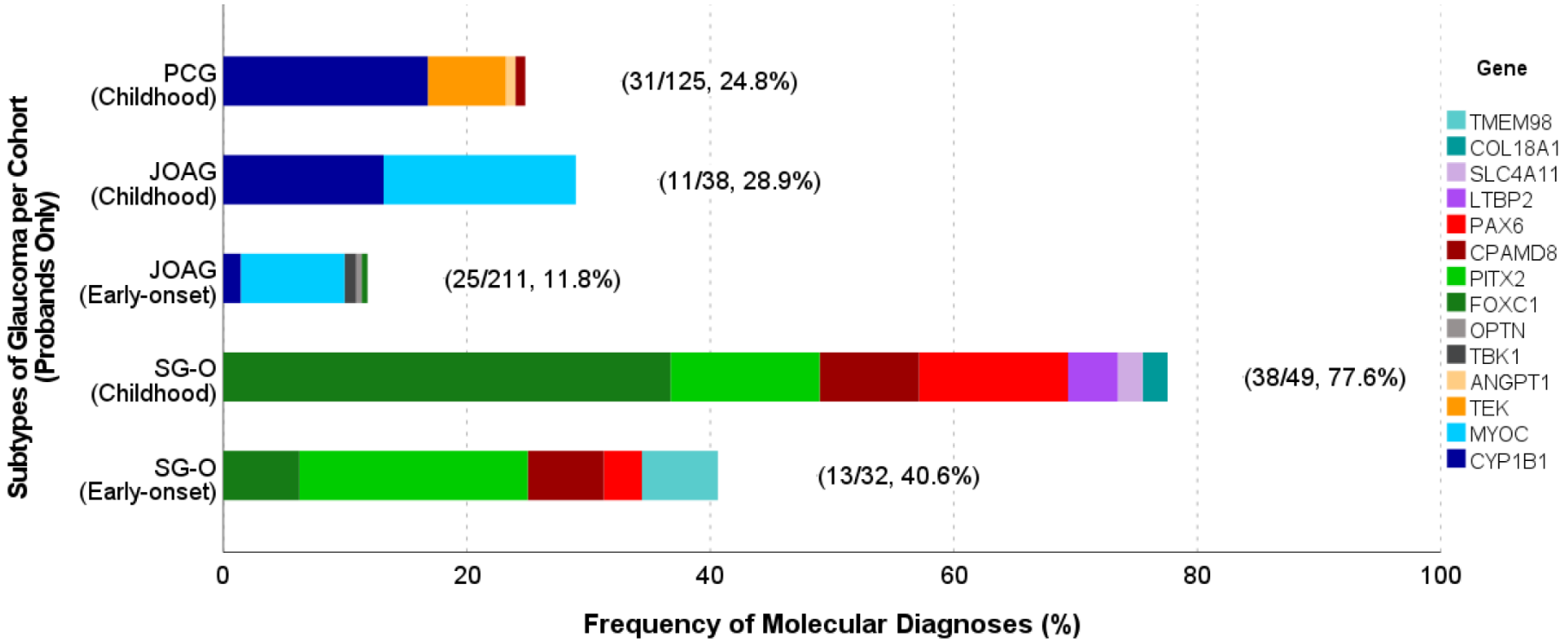

Figure 3.1. Frequencies of molecular diagnoses in tested probands stratified by CGRN classification (after reclassification post-genetic diagnosis)

The number of genetically tested probands who had a molecular diagnosis within each cohort is included after each respective bar. SG-A and SG-C were excluded because no molecular diagnoses were determined. SG-S and unclassified glaucoma classifications were also excluded because of the small number of probands.

PCG: primary congenital glaucoma; JOAG: Juvenile open-angle glaucoma; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly

3.3.3 Genotype-phenotype correlations

The demographic and clinical characteristics of cases associated with each gene are presented in Table 3.3. Biallelic variants in *CYP1B1* (n=29, 23.2%) and heterozygous variants in *MYOC* (n=24, 19.2%) and *FOXC1* (n=21, 16.8%) were the most common in all probands with a molecular diagnosis (n=125). Bilateral glaucoma was least common in individuals with *TEK* (9/12, 75.0%) and *NF1* variants (1/2, 50%). Overall, a molecular diagnosis was less prevalent in males than females (73/168, 43.5% vs 95/168, 56.5%). The number of females with biallelic *CYP1B1* variants was twice the number of males (24/36, 66.7% vs 12/36, 33.3%, 95% CI: 0.490–0.814, p=0.03). *LTBP2* mutations were exclusively found in individuals of self-reported Middle Eastern ancestry in our dataset, and 28.6% of *CYP1B1* variants were identified in probands of non-European descent.

The median age at glaucoma diagnosis was lowest in individuals with *CPAMD8* (0 [0–17] years), *TEK* (0.17 [0.0–0.25] years) and *CYP1B1* variants (0.14 [0–8] years), which is consistent with those who were clinically diagnosed with PCG. The median age at glaucoma diagnosis was highest in individuals with variants in *OPTN* (33 [30–35] years) and *MYOC* (29 [15–35] years), and *TBK1* copy number variants (30 [25–38] years). These variants were found exclusively in individuals with JOAG with the exception of one non-proband with a *MYOC* variant and PCG. The lowest median maximum IOP was recorded in individuals with *TBK1* copy number variants (13 [13–14] mmHg) and *OPTN* variants (18 [17–18] mmHg), consistent with their diagnoses of NTG. *TBK1* copy number variants and *OPTN* variants were respectively found in 14.3% (2/14) and 7.1% (1/14) of probands with NTG, respectively, all of whom had European ancestry.

Table 3.3. Demographic and clinical characteristics of genetic cohorts with childhood or early-onset glaucoma

Gene (Inheritance)	All cases n (%)	Eyes n (%)	Bilateral n (%)	Male gender n (%)	Probands n (%)	European ancestry n (%)	Family history n (%)	Highest recorded IOP (mmHg)*	Age at diagnosis (years)*	Cases described elsewhere
CYP1B1 (AR)	36 (21.4)	70 (21.7)	35/35 (100.0)	12/36 (33.3)	29 (23.2)	20/28 (71.4)	15/28 (53.6)	38 (30–40)	0.14 (0–8)	61
MYOC (AD)	36 (21.4)	71 (22.0)	35/36 (97.2)	16/36 (44.4)	24 (19.2)	21/24 (87.5)	24/24 (100.0)	40 (29–45)	29 (15–35)	303
FOXC1 (AD)	28 (16.7)	53 (16.4)	25/28 (89.3)	13/28 (46.4)	21 (16.8)	13/20 (65.0)	14/21 (66.7)	32 (24–41)	2.8 (0.11–14)	130,194
PITX2 (AD)	15 (8.9)	29 (9.0)	14/15 (93.3)	8/15 (53.3)	12 (9.6)	12/12 (100.0)	8/12 (66.7)	40 (28–52)	14 (8–21)	130
TEK (AD)	12 (7.1)	21 (6.5)	9/12 (75.0)	7/12 (58.3)	8 (6.4)	8/8 (100.0)	2/8 (25.0)	27 (22–37)	0.17 (0.0–0.25)	26,139
CPAMD8 (AR)	9 (5.4)	18 (5.6)	9/9 (100.0)	4/9 (44.4)	7 (5.6)	6/7 (85.7)	5/7 (71.4)	40 (38–44)	0 (0–17)	186
PAX6 (AD)	7 (4.2)	13 (4.0)	6/7 (85.7)	4/7 (57.1)	7 (5.6)	7/7 (100.0)	4/6 (66.7)	42 (39–48)	8 (4–14)	377
TBK1 (AD)	6 (3.6)	11 (3.4)	5/6 (83.3)	3/6 (50.0)	2 (1.6)	2/2 (100.0)	2/2 (100.0)	13 (13–14)	30 (25–38)	338
LTBP2 (AR)	5 (3.0)	10 (3.1)	5/5 (100.0)	2/5 (40.0)	3 (2.4)	0/3 (0.0)	3/3 (100.0)	40 (40–43)	4 (1–4)	-
OPTN (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	1/2 (50.0)	1 (0.8)	1/1 (100.0)	1/1 (100.0)	18 (17–18)	33 (30–35)	-
COL2A1 (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	1/2 (50.0)	2 (1.6)	2/2 (100.0)	2/2 (100.0)	29 (23–35)	25 (21–28)	-
TMEM98 (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	1/2 (50.0)	2 (1.6)	1/1 (100.0)	2/2 (100.0)	41 (40–42)	26 (21–31)	378
LMX1B (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	0/2 (0.0)	1 (0.8)	1/1 (100.0)	1/1 (100.0)	45 (29–60)	30 (30–30)	-
NF1 (AD)	2 (1.2)	3 (0.9)	1/2 (50.0)	0/2 (0.0)	2 (1.6)	1/2 (50.0)	1/2 (50.0)	35 (32–38)	0.0 (0–0)	-

ADAMTS17 (AR)	1 (0.6)	2 (0.6)	1/1 (100.0)	0/1 (0.0)	1 (0.8)	1/1 (100.0)	0/0 (0.0)	47 (n/a)	18 (n/a)	-
ANGPT1 (AD)	1 (0.6)	2 (0.6)	1/1 (100.0)	0/1 (0.0)	1 (0.8)	1/1 (100.0)	0/1 (0.0)	29 (n/a)	0.30 (n/a)	[141]
COL18A1 (AR)	1 (0.6)	2 (0.6)	1/1 (100.0)	1/1 (100.0)	1 (0.8)	0/1 (0.0)	1/1 (100.0)	22 (n/a)	11 (n/a)	-
SLC4A11 (AR)	1 (0.6)	2 (0.6)	1/1 (100.0)	0/1 (0.0)	1 (0.8)	0/1 (0.0)	0/1 (0.0)	41 (n/a)	0.20 (n/a)	-
Total	**168 (100.0)**	**323 (100.0)**	**156/167 (93.4)**	**73/168 (43.5)**	**125 (100.0)**	**97/122 (79.5)**	**85/122 (69.7)**	**35.5 (27–44)**	**9 (0.17–25)**	

AR: Autosomal recessive, AD: Autosomal dominant, IOP: intraocular pressure; n/a: not available
Totals for each variable may not equal the total number of cases due to missing data. All cases include probands and non-probands. European ancestry and family history were calculated for probands only.
*Highest recorded IOP (mmHg) and age at diagnosis (years) are presented as median (IQR).

3.4 Discussion

The CGRN classification system for childhood glaucoma offers well-defined guidelines and enables reproducible and transparent categorisation of individuals with the disease.[4] It has since been adopted by several studies,[65,85–91] enabling thorough and accurate comparisons of childhood glaucoma phenotypes in other populations. In this study, we did not include individuals who were glaucoma suspects as it is not the primary aim of the ANZRAG to recruit these individuals. To the best of our knowledge, this cohort represents the largest childhood glaucoma cohort of European ancestry, and one of the largest international cohorts reported (290 cases). Previous published studies that used the CGRN classification include cohorts from Ohio, USA (108 cases),[85] Miami, Florida (201 cases),[65] Egypt (207 cases),[89] South India (275 cases),[88] Thailand (423 cases),[87] Brazil (496 cases),[86] and an international study (441 cases) that included cohorts from India, United States, United Kingdom, Saudi Arabia, Ghana, Singapore, Israel and Germany, comprising just 89 cases of European ancestry.[91]

The spectrum of childhood glaucoma diagnoses in a given study depends on the composition of the population studied and potential recruitment biases. In this study, PCG was the most prevalent subtype of childhood glaucoma (57.6%) whereas SG-A was the least common (1.0%). Given that a major goal of our glaucoma registry (ANZRAG) is to identify the genetic causes of glaucoma, individuals with acquired childhood glaucoma were not historically actively recruited (e.g., traumatic and uveitic glaucoma), explaining the lower representation of cases in this group. Individuals with SG-S or SG-C were similarly not actively recruited. Other studies applying the CGRN classifications reported PCG among 5 to 55% of their childhood glaucoma cohort,[65,85–91] similar to this study. The estimated incidence of PCG in Australia is 1/30,000 births,[10] but incidence figures increase up to 9-fold in populations with higher rates of parental consanguinity.[66] The high proportion of PCG cases in our cohort may be explained by a recruitment bias or may reflect the diverse ethnic background of the population studied, with 24.6% of PCG cases self-reporting non-European ancestry. The population of Australia and New Zealand is just over 30 million, thus a rate of PCG affecting 1/30,000 would suggest there would be 1,000 cases of PCG (all ages) in the two countries, of whom we have recruited 167 (16.7% of the predicted total).

The lack of classification systems for individuals with early-onset glaucoma (defined here as disease diagnosis from age 18 to <40 years) makes it difficult to understand the underlying causes of disease in this heterogeneous group. Moreover, global prevalence rates appear to discount this age group, with reports typically including only individuals aged 40 years and above.[3] We therefore opted to apply the CGRN classifications to early-onset glaucoma cases in this study. This process was simple, and

individuals were assigned a diagnostic category without overlap. With this classification, JOAG was the most common diagnosis (73.3%), followed by SG-A (13.4%). Birla et al.[381] emphasised that individuals diagnosed with glaucoma under 40 years of age require a more formalised phenotypic classification system. Using a cluster analysis based on iris and angle morphology, they reported angle abnormalities in two-thirds of individuals with JOAG.[381] Such features may represent an otherwise distinct ocular phenotype that may be crucial for genetic analyses. The findings from this study support the use of a unified classification system to group phenotypically diverse early-onset glaucomas which is offered by the CGRN classification system.[4] Further subtyping of ocular anomalies is encouraged under each CGRN classification and enables a better understanding of disease phenotypes and genetic diagnoses in this age group.

Previous studies have reported on the contribution of specific genes in childhood glaucoma (e.g., *CYP1B1*),[108] or the diagnostic yield using exome sequencing in some glaucoma subtypes (e.g., ASD).[111] However, no studies have reported the diagnostic yield in a comprehensive cohort of heterogeneous childhood or early-onset glaucoma. In total, pathogenic variants in 18 genes were reported across the entire cohort. Targeted genetic testing was successful in identifying a variant in 75.2% of probands with a molecular diagnosis, whilst exome or genome sequencing was required to identify variants in the remaining probands. Similar to inherited retinal diseases and congenital cataracts, the genetic heterogeneity in our cohort supports the use of a comprehensive gene panel testing approach inclusive of all genes with evidence of association to childhood and early-onset glaucoma. Additional screening for variants in the *CHRDL1* gene may be indicated where an individual has megalocornea and a diagnosis of PCG is under consideration.

Biallelic *CYP1B1* variants were the most common genetic diagnosis in PCG (15.6%). This is similar to the prevalence reported by other studies on populations of European ancestry (15–22%),[96,97] yet lower than other populations with high consanguinity, as expected for variants associated with an autosomal recessive trait.[382] We found a significant gender difference in those with *CYP1B1* variants and PCG, with a male:female ratio of 1:2, while in the whole PCG cohort the male:female ratio was 1.46:1. Previous studies have reported the same trend of male preponderance in PCG,[65,86,89] whereas two studies also reported a higher proportion of females with *CYP1B1* variants and PCG.[383,384] This raises the possibility that one or more unidentified genes causing PCG in males may be sex linked. Additionally, the higher proportion of females with *CYP1B1* variants may be related to the fact that *CYP1B1* variants have been found to reduce the metabolism of 17β-oestradiol, an estrogen steroid hormone found within the trabecular meshwork.[385] Its role in PCG pathogenesis, however, is not yet fully understood and additional studies are needed to understand the sex bias observed in this study. Meanwhile, one-third

of PCG probands had a family history of glaucoma. This reflects the current genetic landscape of PCG caused by variants in genes inherited in an autosomal recessive manner (e.g. *CYP1B1*)[95] or an autosomal dominant manner with incomplete penetrance (e.g. *TEK*).[26]

Heterozygous variants in *MYOC* were the major genetic cause of JOAG (9.5%). The ANZRAG group previously reported *MYOC* variants in 17% of 103 individuals with JOAG with advanced visual field loss, highlighting that *MYOC* variants are associated with more severe disease in primary glaucoma.[303] *MYOC* is otherwise reported in 8–36% of JOAG cases and variants are typically associated with HTG,[165,166] while *TBK1* and *OPTN* variants are typically associated with early-onset NTG, consistent with our study results.[338,376] Biallelic variants in *CYP1B1* were implicated in 3.2% of probands with JOAG, similar to previously reported results by our group.[61] Meanwhile, heterozygous pathogenic variants in *EFEMP1* were not reported in individuals in this study with JOAG.

The highest diagnostic yield was achieved in probands with SG-O (56.5%). This is not surprising considering that the majority of this cohort comprised individuals with ARS, which has a reported diagnostic yield of 40–71% of ARS,[111,125,126,192] mainly accounted for by variants in *FOXC1* and *PITX2*. The diagnostic yield improved once probands were reclassified into this category, most of whom had an initial clinical diagnosis of PCG. The challenges associated with ASD diagnoses with subtle features, that can be clinically diagnosed as PCG in individuals with variants in *FOXC1,* has been previously reported by the ANZRAG group.*[194]* The difficulty of examining the anterior segment to diagnose ASD in infants and the absence of some associated systemic features (e.g., dental anomalies) in infants can make clinical diagnoses of PCG and ASD challenging and highlights the importance of genetic testing in reaching an accurate diagnosis. This is illustrated by one individual in this study diagnosed with PCG and a heterozygous variant in *FOXC1* with systemic features consistent with ARS (hearing loss, congenital heart defect) yet no ocular features of ARS found on detailed examinations under anaesthesia. Despite the absence of ocular features, this individual was reclassified as having SG-O based on the presence of systemic features and genetic results consistent with ARS. A heterozygous variant in *FOXC1* was also found in an individual with JOAG who had no ocular or systemic features consistent with ARS. This phenomenon has been reported before in two other cases of JOAG,[200] although both individuals were reported as having posterior embryotoxon. Although posterior embryotoxon is not considered as a diagnostic feature in ARS,[341] it may represent a subtle ocular phenotype in such individuals. Individuals with PCG and biallelic *CPAMD8* variants were reclassified as having SG-O, and the subtype of unclassified ASD, as described before.[186] Biallelic variants in *CPAMD8* have been reported elsewhere in individuals with unclassified ASD[111,185,187,188] and PCG.[101,188] Currently, ASD is the more common found ocular phenotype in individuals with biallelic *CPAMD8*

variants.[101,111,185–188]

The number of individuals with SG-S in our cohort was low, most likely explained by the fact that the ANZRAG did not initially aim to recruit these individuals. However, this cohort may represent an underdiagnosed group as illustrated by the individual with a clinical diagnosis of JOAG but a genetic diagnosis indicative of Stickler syndrome (heterozygous *COL2A1* variant). This is supported by a recent study reporting systemic abnormalities in 12.9% of individuals with childhood glaucoma,[255] and emphasises the importance of referring individuals to a genetic service for a thorough medical examination to refine clinical diagnosis. Our cohort otherwise reported a molecular diagnosis in 71.4% of individuals, with the remaining two genetically undiagnosed probands having SWS. SWS is caused by somatic variants in *GNAQ*, and consequently individuals with SWS require biopsy of an affected tissue (typically skin) for molecular diagnosis.[249]

Reaching a molecular diagnosis has several benefits for affected individuals and their families. In this study, 10.4% of individuals had a change of clinical diagnosis based on genetic results. These individuals and their family members can now be accurately counselled about the mode of inheritance and the risks for relatives. At-risk family members can benefit from predictive genetic testing, and parents of affected cases can consider reproductive options. Individuals with syndromic glaucoma can benefit from appropriate referrals for the management of associated systemic features that require specialised care. Finally, future therapeutic approaches may be gene-specific similar to inherited retinal diseases, highlighting the relevance of molecular diagnosis in precision medicine.

Study limitations include missing clinical and demographic information for some participants. Furthermore, clinical diagnoses of participants were obtained by the treating specialists, which may have introduced some variation or bias. However, this reflects a genuine representation of the clinical diagnostic landscape of childhood and early-onset glaucoma across Australasia. Genetic testing is an ongoing process of the ANZRAG and is therefore not complete for all individuals included in this study who may have been recruited but full genetic analyses were not yet available. Furthermore, a known limitation of exome and genome sequencing is the insufficient coverage of some exons or gene regions.[194] Therefore, it is possible that some disease-causing variants in known or novel glaucoma genes were not sufficiently covered or interrogated, including deep intronic variants, copy number variants and structural variants. This may have led to an underestimated diagnostic rate in this cohort. Additionally, our recruitment is somewhat biased toward individuals with glaucoma suspected to be genetic in origin as this was the original design of the ANZRAG. Consequently, those with acquired glaucoma, including those with glaucoma following ocular trauma or cataract surgery, may be underrepresented, and we expect the prevalence of these conditions to be higher in the wider

population. Finally, the genetic architecture of a cohort depends on its ancestry. Our cohort is predominantly of European ancestry, although 23.8% of the cohort reported a different ancestry, which reflects the diverse ancestral lineage of individuals in Australasia. The prevalence of different glaucoma subtypes and diagnostic yield in populations of non-European ancestry should be reported in future studies.

In conclusion, the present study reported the glaucoma phenotypes in the largest Australasian cohort under the age of 40 years, according to the CGRN classification system. It is also the largest study to ascribe genetic findings according to these criteria. A diagnostic yield of 37.6% in probands with childhood glaucoma and 14.7% in probands with early-onset glaucoma was identified. These findings contribute to our understanding of childhood and early-onset glaucoma phenotypes and their genetic basis. The diagnostic yield in this rare and heterogeneous disease supports the need for international collaborative efforts to identify new genetic associations. The results emphasise the importance of accurate clinical diagnosis and the genetic heterogeneity of the disease, and supports the development of a childhood and early-onset genetic testing panel that will ultimately become critical in the age of gene therapy for glaucoma.

CHAPTER 4 CLINICAL OUTCOMES IN *TEK*- AND *CYP1B1*-ASSOCIATED GLAUCOMA

4.1 Introduction

Genetic testing has the potential to support the clinical management of childhood glaucoma and aid the prognostication of clinical outcomes. It has previously been demonstrated that individuals with *PITX2* variants may have worse visual outcomes than individuals with *FOXC1* variants and may benefit from closer monitoring for disease progression.[195] Close monitoring and early interventions is similarly relevant to individuals with *MYOC* variants who can progress to severe visual field loss.[303,304] Individuals with *PAX6* variants can benefit from closer monitoring for the development of common disease complications including early-onset cataract, and keratopathy,[223] while those with *CPAMD8* variants may benefit from monitoring for early-onset cataract, retinal detachment and ectopia lentis.[101,111,185–188] Despite being identified as the most common genes implicated in PCG (Chapter 3),[386] the clinical course of glaucoma caused by biallelic pathogenic *CYP1B1* variants and heterozygous loss-of-function *TEK* variants have not been well described.

The paucity of literature detailing the clinical outcomes in *TEK*-associated and *CYP1B1*-associated disease is likely owing to the relatively uncommon prevalence of these genetic diagnoses and the limited availability of testing in many cases. Previous studies reporting genotype-phenotype correlations of *CYP1B1* have usually been confined to one type of glaucoma (e.g., PCG),[298,299,387,388] and are limited by the lack of statistical correction for the inclusion of both eyes from one individual and age at last examination,[298,299,387,388] and small sample sizes.[298,299,387] This can result in an overestimate of the effect size.[346,347] Other literature detailing the outcomes of *CYP1B1*-associated glaucoma have attempted to overcome these limitations by including individuals with heterozygous *CYP1B1* variants in their analyses.[300,305,389] However, there is limited evidence supporting an autosomal dominant Mendelian pattern of inheritance in *CYP1B1*-associated disease.[95,100–102,390,391] Similarly, there is limited evidence regarding the long-term clinical outcomes and severity of *TEK*-associated glaucoma, likely owing to its relatively recent discovery.[26] Qiao and colleagues[138] have previously attempted to compare the clinical characteristics between individuals with *CYP1B1* and *TEK* variants, but their analysis was limited by the inclusion of individuals with PCG and included benign and gain-of-function *TEK* variants, which are not implicated in *TEK*-associated glaucoma. There is a need to address these gaps in knowledge and provide a detailed understanding of disease outcomes in these genetic cohorts.

My original contribution to knowledge was a detailed comparison of the clinical characteristics and long-term disease outcomes in one of the largest international cohorts of individuals with *TEK*-associated and *CYP1B1*-associated glaucoma.

4.2 Methods

4.2.1 Participants

All participants in the ANZRAG identified to have pathogenic biallelic *CYP1B1* variants or a pathogenic heterozygous *TEK* variant were included in this study. Individuals identified to have only one *CYP1B1* variant (i.e., carriers) were excluded as there is limited evidence supporting an autosomal dominant Mendelian pattern of inheritance in *CYP1B1*-associated glaucoma.[95,100–102,390,391] Recruitment for this registry has been described previously (Chapter 2).[335] Clinical details at the last examination were obtained from participants' treating glaucoma specialists. Participants, or their parent/guardian, were asked to provide self-reported continental ancestry and family history of glaucoma, as outlined in Chapter 2. Participants' glaucoma phenotypes were classified according to the CGRN classifications as outlined in Chapter 2 if they had disease onset <40 years. Individuals were further classified as having POAG (defined as open-angle glaucoma diagnosed at ≥40 years) or glaucoma suspects with ocular hypertension (OHT) if IOP had measured >21 mmHg on two separate occasions.[4]

BCVA was recorded in logMAR values. Visual acuity recordings of 'count fingers', 'hand movements', 'light perception' and 'no light perception' were assigned logMAR values of 2.1, 2.4, 2.7 and 3.0, respectively.[392] Visual acuity was omitted from analyses in cases where BCVA was affected by disease unrelated to glaucoma (e.g., age-related macular degeneration). Due to the difficulty obtaining reliable vertical cup-to-disc ratios in individuals with PCG, and observations of reversal of optic disc cupping after IOP-lowering intervention in children,[393] and adults,[394] vertical cup-to-disc ratios were not included in the analysis. There is limited evidence supporting that reversal of optic disc cupping is associated with long-term functional outcomes including BCVA and HVF.[393,394] HVF results were included in analyses if BCVA was ≥0.5,[395] and the participant was aged >10 years,[396] to optimise data reliability. Data regarding glaucoma surgeries were classified as followed:

1. Incisional glaucoma surgeries, including any procedure whereby an incision was made (e.g., trabeculectomy, trabeculotomy, goniotomy, drainage device implantation)
2. Glaucoma procedures, including any incisional, laser or other non-incisional procedure (e.g., bleb needling, adjustment of drainage device); and

3. Advanced glaucoma procedures, including incisional surgeries and cyclodestructive lasers, as the latter is often considered where glaucoma is refractory to incisional surgeries, or the risks of additional incisional surgeries is considered too high.[397]

The success of each glaucoma intervention including surgeries, procedures, and use of topical antiglaucoma medication was not analysed. This is because the study was retrospective and measurements of glaucomatous disease progression at regular intervals before and after each intervention could not be obtained or calculated for all individuals. Ethical approval was obtained through the Southern Adelaide Clinical Human Research Ethics Committee (2021/HRE00032). The study adhered to the revised tenets of the Declaration of Helsinki (2013) and the National Health and Medical Research Council statement of ethical conduct in research involving humans (2018).

4.2.2 Genetic testing for *CYP1B1* and *TEK* variants

Participants, or their parent/guardian, provided written informed consent to participate in the ANZRAG. As part of their involvement, participants provided a blood or saliva sample for DNA analysis as previously described (Chapter 2). Probands and their family members underwent targeted genetic sequencing, whole exome, or whole genome sequencing, subject to testing availability. All genetic results were independently validated at the National Association of Testing Authorities-accredited laboratory (SA Pathology, Bedford Park, South Australia, Australia).

All *TEK* and *CYP1B1* variants were reported using GRCh37/hg19 reference coordinates, and transcripts were annotated against canonical reference transcripts (NM_000459.5 [*TEK*]; NM_000104.4 [*CYP1B1*]). For the purpose of this study only, all protein-truncating *TEK* and *CYP1B1* variants (i.e., essential splice site, frameshift, and nonsense) were considered pathogenic.[398] Non-truncating (i.e., missense or alternate codon) variants were considered to be pathogenic if they met the threshold of: (1) global and ancestry-matched allele frequency <0.0001 for autosomal dominant genes (i.e., *TEK*), or <0.002 for autosomal recessive genes (i.e., *CYP1B1*), as provided as provided in the Genome Aggregation Database (gnomAD v.2.1.1; https://gnomad.broadinstitute.org), (2) Combined Annotation-Dependent Depletion (CADD v.1.6; https://cadd.gs.washington.edu/snv) Phred-scaled score ≥20 (i.e., in the top 1% of the most deleterious variants in the human genome),[399] and (3) were present in at least one glaucoma-affected individual. Allele frequency thresholds were determined based on the highest population allele frequency of variants considered pathogenic or likely pathogenic in the ClinVar database. These included *TEK*: c.448G>T (p.Glu150*) and *CYP1B1*: c.182C>A (p.Gly61Glu) variants.

The *CYP1B1* variant, c.1103G>A (p.R368H) was considered pathogenic in this study despite its maximum ancestry matched allele frequency being >0.002 (South Asian allele frequency 0.03035 and

Ashkenazi Jewish allele frequency 0.02259). A recent study questioned the pathogenicity of this variant due to its high carrier frequency and low penetrance for PCG in a Saudi Arabian population.[101] However, the possibility that this variant is associated with later disease onset could not be excluded,[101] and functional studies support an impact on protein function.[400–402] We have therefore included *CYP1B1* p.R368H in our primary analyses but have performed additional analyses excluding it to assess its impact on the result findings.

4.2.3 Statistical analysis

All calculations were performed using R version 4.1.0. Data normality was assessed using the Shapiro-Wilk test. Continuous variables were expressed as median (IQR) unless otherwise specified. Categorical data were expressed as counts and percentages. Statistical analysis of self-reported ancestry and family history were performed on probands only to provide a more accurate representation of the data among families. Standardised adjusted residuals were used during post hoc analyses to interpret any statistical significance. The chi-square test with continuity correction or Fisher exact test was used for categorical variables and the Mann-Whitney U test or Mood's median test was applied to non-parametric continuous variables where appropriate. When analysing differences in clinical variables measured per eye, data were tested in a linear mixed effect regression statistical model to account for the inclusion of two eyes of one individual and the inclusion of multiple individuals from the same families influencing our findings. A binomial or a Poisson mixed effect model was used for binary outcomes or count data, respectively. To account for the age at last examination, multivariable models including this variable in the mixed effect model were also performed. Models were fitted using the functions *lmer* and *glmer* from the package *lme4* (version 1.1.28), and statistical significance tests were performed using Satterthwaite's degrees of freedom method as implemented in the package *lmerTest* (version 3.1.3). A *P* value of <0.05 was considered statistically significant. Multiple testing corrections were not applied as all statistical tests were exploratory in nature.

4.3 Results

4.3.1 Genotype-phenotype correlations

There were 87 participants from 51 families included in the study. Exome sequencing identified a total of 20 rare variants in the *TEK* gene across 43 participants from 20 families. The phenotype of each individual is listed in Appendix B, Table B3. Genetic variant information and determination of their pathogenicity are also provided in Appendix B, Table B3. Five of these families (Families 1, 2, 4, 6 and 7; Appendix B, Table B3) have been reported previously.[26,139] The pedigrees of these families are illustrated in Appendix C, Figure C4. Meanwhile, 20 variants in the *CYP1B1* gene across 44 participants

from 31 families were identified. The phenotype of each individual is listed in Appendix B, Table B4 and the pedigrees of these families are illustrated in Appendix C, Figure C5. Amongst all participants, 19/44 (43.2%) were homozygotes and 25/44 (56.8%) were compound heterozygotes (Appendix B, Table B4). One participant harboured a unique *CYP1B1* deletion which was inherited by paternal uniparental isodisomy, and has previously been reported by the ANZRAG group,[403] as have a further three participants with biallelic variants in *CYP1B1* and JOAG.[61]

Participants harbouring a *TEK* variant were significantly older at the time of the last examination than participants with biallelic *CYP1B1* variants (*TEK*: 41.7 years [range: 1.6–89.0] vs *CYP1B1*: 32.3 years [range: 0.2–74.8], p=0.03). Probands reported to have a *TEK* variant were more likely to be of self-reported European ancestry compared with probands with biallelic variants in *CYP1B1*, but statistical significance was not reached (18/20, 90.0% vs 20/31, 64.5%, p=0.09). A family history of glaucoma was otherwise similar between probands in the two cohorts (*TEK*: 10/20, 50.0% vs *CYP1B1*: 16/31, 51.6%, p=1.0); however, probands with biallelic variants in *CYP1B1* were significantly more likely to report a family history of PCG (*TEK*: 1/20, 5.0% vs *CYP1B1*: 10/31, 32.3%, p=0.03). Overall, there were more males in the *TEK* cohort compared with the *CYP1B1* cohort (27/43, 62.8% vs 16/43, 37.2%, p=0.04).

Amongst the 43 participants who were *TEK* heterozygotes, 24/43 (55.8%) were clinically diagnosed with glaucoma as per Figure 4.1. This included 18/43 (41.9%) participants who were diagnosed with PCG, 1/43 (2.3%) with JOAG and 5/43 (11.6%) with POAG. A further 4/43 (9.3%) participants had OHT whilst 15/43 (34.9%) did not have glaucoma or OHT at the time of the last examination (Figure 4.1). The median age of participants without glaucoma at the time of the last examination was 39.0 years (range: 10.0–85.4).

Amongst the 44 participants who were found to have biallelic *CYP1B1* variants, 42/44 (95.5%) were diagnosed with glaucoma. This included 28/44 (63.6%) participants who were diagnosed with PCG, 11/44 (25.0%) with JOAG, 1/44 (2.3%) with POAG and 2/44 (4.5%) with SG-O (including one participant with PACG and one participant with Peters anomaly). Two participants (2/44, 4.5%), aged 16.0 and 32.3 years at the time of their last examination, did not have glaucoma (Figure 4.1).

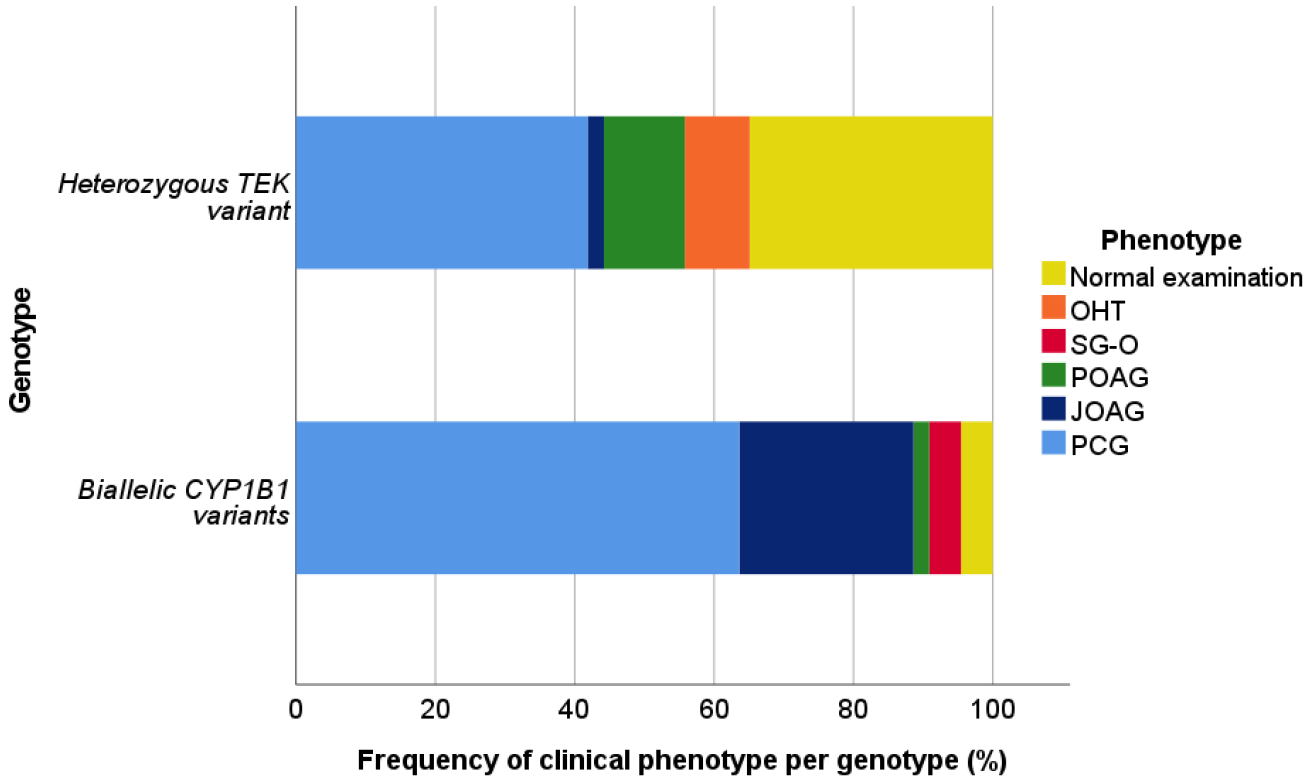

Figure 4.1. The phenotypic variability associated with *TEK* and *CYP1B1*

OHT: ocular hypertension; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; POAG: primary open-angle glaucoma; JOAG: juvenile open-angle glaucoma; PCG: primary congenital glaucoma

4.3.2 Demographic and clinical characteristics

To further elucidate the disease profile of *TEK*- and *CYP1B1*-associated glaucoma, the demographic characteristics of participants in either cohort with a diagnosis of glaucoma were compared in Table 4.1. The overall penetrance of any type of glaucoma between the two cohorts was significantly different after adjusting for age at last examination and inclusion of multiple individuals from the same family (*TEK*: 24/43, 55.8% vs *CYP1B1*: 42/44, 95.5%, p<0.001). Furthermore, there were significantly fewer females with glaucoma and a *TEK* variant than females with glaucoma and biallelic variants in *CYP1B1* (8/24, 33.3% vs 27/42, 64.3%, respectively, p=0.03).

Table 4.1. Comparison of demographic characteristics of participants with *CYP1B1*-associated glaucoma and *TEK*-associated glaucoma

Variable	*CYP1B1* (n, %)	*TEK* (n, %)	p-value
Sex among all participants (F:M ratio; % female)	27:17 (61.4)	16:27 (37.2)	**0.04[a]**
Total participants with glaucoma	42/44 (95.5)	24/43 (55.8)	**<0.001[b]**
Sex among participants with glaucoma (F:M ratio; % female)	27:15 (64.3)	8:16 (33.3)	**0.03[a]**
Self-reported ancestry (European)*	20/31 (64.5)	18/20 (90.0)	0.09[a]
Family history of glaucoma*	16/31 (51.6)	10/20 (50.0)	1.0[a]
Family history of PCG*	10/31 (32.3)	1/20 (5.0)	**0.03[c]**

F: female; M: male; PCG: primary congenital glaucoma
*Self-reported ancestry and family history of glaucoma and PCG were calculated for the number of probands only. Bold values indicate statistical significance (p<0.05).
[a]Chi-square test with continuity correction, [b]Linear mixed effect regression adjusted for age at last examination and inclusion of multiple individuals from the same family, [c]Fisher exact test

The differences in clinical characteristics per eye per cohort were further analysed as shown in Table 4.2. A total of 42 glaucomatous eyes from 24 participants from the *TEK* cohort and a total of 77 glaucomatous eyes from 39 participants from the *CYP1B1* cohort were analysed. Follow-up clinical data were not available for three participants with biallelic *CYP1B1* variants and bilateral disease (one with PCG and two with JOAG).

After adjusting for age at the last examination and the inclusion of multiple individuals from one family, participants with *TEK*-associated glaucoma were less likely to have bilateral disease compared with those with *CYP1B1*-associated glaucoma (18/24, 75.0% vs 41/42, 97.6%, respectively, p=0.01). Eyes with *TEK*-associated glaucoma had significantly better logMAR BCVA (0.2 [0.0–0.6] vs 0.8 [0.2–2.4], p=0.03) and thinner CCT (548 µm [525–570] vs 609 µm [568–674], p=0.04) compared with eyes with *CYP1B1*-associated glaucoma. Eyes with *TEK*-associated glaucoma also recorded a lower maximum IOP (30 mmHg [22–37] vs 39 mmHg [31–46], p=0.02). Meanwhile, eyes with *TEK*-associated glaucoma were less myopic than eyes with *CYP1B1*-associated glaucoma although this finding did not reach statistical significance (spherical equivalent: -1.00 dioptres [-3.25–0.0] vs -2.0 dioptres [-7.00—0.00], respectively, p=0.12). Age at diagnosis, IOP at last examination and IOP at diagnosis were not significantly different between both groups (Table 4.2).

After excluding participants aged <10 years, the inability to obtain reliable HVF data was significantly more likely in eyes with *CYP1B1*-associated glaucoma than eyes with *TEK*-associated glaucoma (47/66,

71.2% vs 11/32, 34.4%, respectively, p=0.04). The main reason for this in either cohort was BCVA <0.50 logMAR (*CYP1B1*: 35/47, 74.5% and *TEK*: 6/11, 54.5%). Additional reasons are outlined in Appendix B, Table B5. In eyes in which a HVF was completed, the median HVF mean deviation was not significantly different between the two groups (p=0.78, Table 4.2).

With respect to treatments, the proportion of eyes in either cohort requiring any glaucoma drainage procedure was relatively equal (*TEK*-associated glaucoma: 35/42, 83.3% vs *CYP1B1*-associated glaucoma: 69/77, 89.6%, p=0.93). However, eyes with *TEK*-associated glaucoma reported a lower median number of glaucoma procedures (Figure 4.2A), incisional glaucoma surgeries (Figure 4.2B) and advanced glaucoma procedures (Figure 4.2C) than eyes with *CYP1B1*-associated glaucoma, although these did not reach statistical significance after adjusting for age at last examination and the inclusion of multiple individuals from the same family (Table 4.2). Additionally, there were fewer eyes with *TEK*-associated glaucoma that required implantation of a glaucoma drainage device (*TEK*-associated glaucoma: 4/42, 9.5% vs *CYP1B1*-associated glaucoma: 25/77, 32.5%, p=0.67). Moreover, the number of topical anti-glaucoma medications being used at the time of the last review was lower in eyes in the *TEK*-associated glaucoma cohort (*TEK*-associated glaucoma: 0 [0–1] vs *CYP1B1*-associated glaucoma: 1 [1–2], p<0.001). Glaucoma complications were otherwise not different between both cohorts (Table 4.2). Complications included enucleation, evisceration or phthisis bulbi (p=0.08), and the presence of cataracts (p=0.53) or corneal disease (p=0.63).

A sub-analysis was performed for probands with glaucoma only to confirm that the inclusion of multiple individuals from the same family did not impact on the overall findings (Appendix B, Table B6). Although this resulted in a smaller sample size, the same trends in clinical outcome data were observed. Differences in maximum recorded IOP (p=0.01), logMAR BCVA (p=0.02), and the number of topical medications being used at the time of the last examination (p<0.001) remained statistically significant (Appendix B, Table B6). Statistically significant differences in the proportion of eyes requiring enucleation, evisceration or phthisis bulbi was additionally observed (p=0.02). Significant differences in female sex were no longer observed, however, there remained to be a higher proportion of females with *CYP1B1*-associated glaucoma compared to the proportion of females with *TEK*-associated glaucoma (19/31, 31.3% vs 7/20, 35.0%, p=0.12). Similarly, eyes with *TEK*-associated glaucoma remained to have thinner CCTs than eyes with *CYP1B1*-associated glaucoma although statistical significance was no longer achieved (552 µm [532–572] vs 608 µm [556–665], p=0.16).

Table 4.2. Comparison of clinical characteristics of eyes with *CYP1B1*-associated glaucoma and *TEK*-associated glaucoma

Clinical characteristic	*CYP1B1*	*TEK*	p-value	Adjusted for age at last examination
Bilateral disease	41/42 (97.6)	18/24 (75.0)	**0.008**[a†]	**0.01**
Age at diagnosis (years)*	0.2 (0–47)	0.3 (0–70)	0.15[b]	-
Age at last examination (years)*	33.8 (0.2–74.8)	46.4 (1.6–89.0)	0.30[c]	-
IOP at last examination (mmHg)	18 (14–22)	17 (12–21)	0.22[b]	0.47
IOP at diagnosis (mmHg)[‡]	34 (27–40)	30 (23–37)	0.54[b]	-
Maximum recorded IOP (mmHg)	39 (31–46)	30 (22–37)	**0.002[b]**	**0.02**
BCVA (LogMAR)	0.8 (0.2–2.4)	0.2 (0.0–0.6)	0.07[b]	**0.03**
BCVA <6/60[§]	29/75 (38.7)	7/40 (17.5)	0.07[b]	**0.03**
Unable to obtain reliable visual field data among participants aged >10 years	47/66 (71.2)	11/32 (34.4)	**0.01[b]**	**0.04**
HVF mean deviation (decibels)	-1.72 (-4.15–0.00)	-1.74 (-6.07–0.12)	0.88[b]	0.78
Spherical equivalent (dioptres)	-2.0 (-7.0–0.00)	-1.00 (-3.25–0.0)	0.14[b]	0.12
CCT (µm)	609 (568–674)	548 (525–570)	**0.004**[b]	**0.04**
Treatment characteristic per eye				
Had a glaucoma procedure	69/77 (89.6)	35/42 (83.3)	0.75[b]	0.93
Number of glaucoma procedures*	3 (0–31)	1 (0–16)	0.06[b]	0.34
Number of incisional glaucoma surgeries*	2 (0–7)	1 (0–5)	0.09[b]	0.47
Number of advanced surgical procedures*	2 (0–8)	1 (0–6)	0.07[b]	0.33
Glaucoma drainage device implanted	25/77 (32.5)	4/42 (9.5)	0.63[b]	0.67
Number of topical anti-glaucoma medications at last review	1 (1–2)	0 (0–1)	**0.007[b]**	**<0.001**
Complications[ſ]				
Enucleation, evisceration or phthisis bulbi	9/77 (12.0)	3/42 (7.1)	0.77[b]	0.08
Cataract	27/68 (39.7)	19/39 (48.7)	0.58[b]	0.53
Corneal disease	17/68 (25.0)	5/39 (12.8)	0.74[b]	0.63

IOP: intraocular pressure; BCVA: best-corrected visual acuity, HVF: Humphrey Visual Field; CCT: central corneal thickness.
Nonparametric continuous variables are presented as median (IQR) unless otherwise indicated (*).
*Data presented as a range. Bold values indicate statistical significance (p<0.05).
[a]Fisher exact test, [b]Linear mixed effect regression adjusting for the inclusion of two eyes of one individual and the inclusion of multiple individuals from the same families, [c]Mood's median test
[†]The variance explained by the random effect of family relatedness in the model was incompatible with the linear mixed effect regression model.
[‡]IOP at diagnosis was only available for 15 eyes with *CYP1B1*-associated glaucoma and 16 eyes with *TEK*-associated glaucoma.
[§]LogMAR visual acuity testing was not possible in two eyes from an individual with *CYP1B1*-associated glaucoma as the eyes belonged to an infant. BCVA in two eyes with *TEK*-associated glaucoma were affected by age-related macular degeneration and were therefore excluded from this analysis.
[ſ]Enucleated eyes were excluded from analysis of cataract and corneal disease

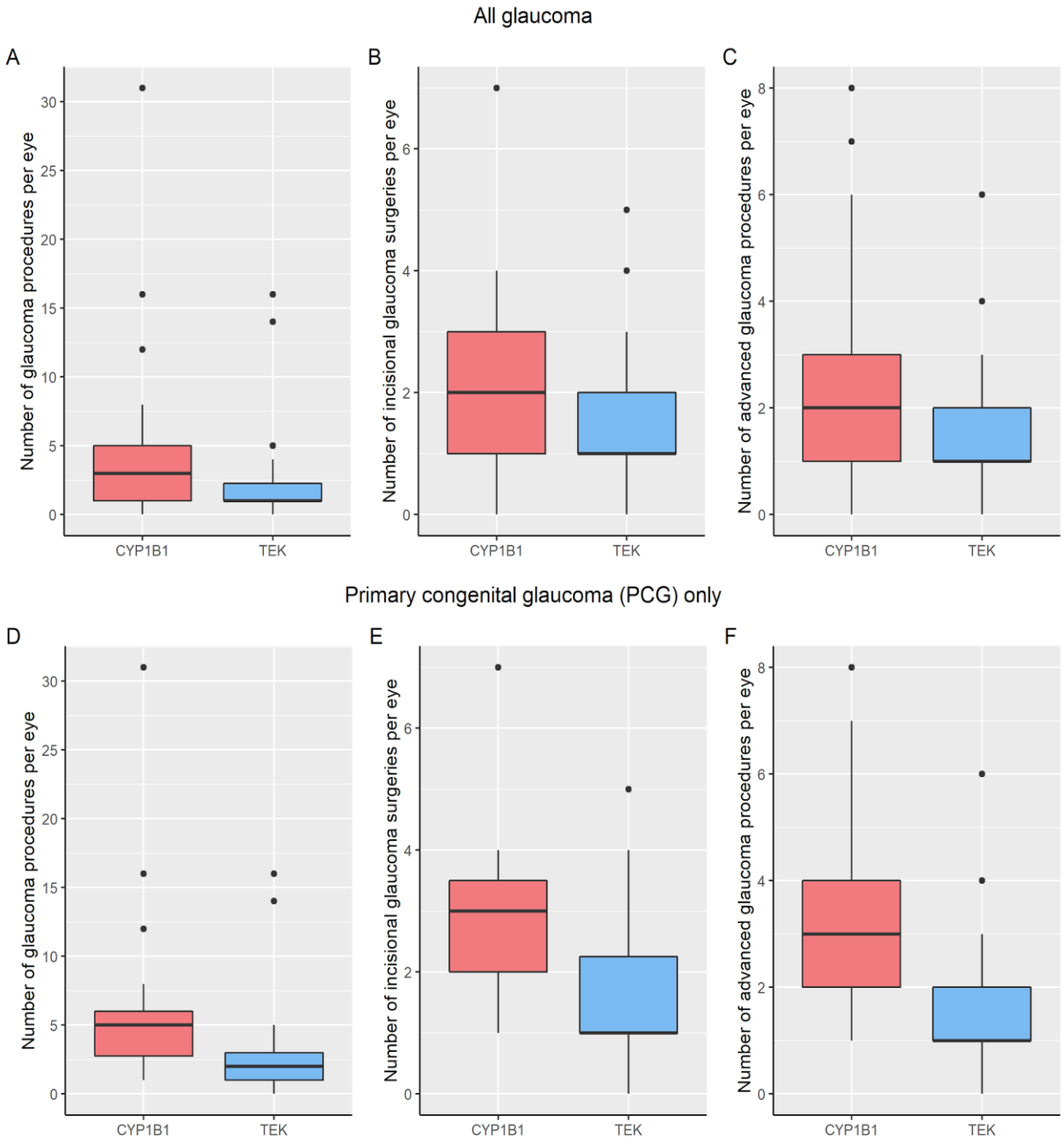

Figure 4.2. Glaucoma surgeries per eye with glaucoma and PCG stratified by genotype
These box plots demonstrate the number and type of glaucoma surgeries per eye with glaucoma in all glaucomatous eyes (A-C) and PCG-only eyes (D-F) per genotype. Glaucoma procedures included any incisional, laser or other non-incisional procedure. Incisional glaucoma surgeries included any procedure whereby an incision was made. Advanced glaucoma procedures included incisional surgeries and cyclodestructive laser procedures.
PCG: primary congenital glaucoma

4.3.3 Primary congenital glaucoma

PCG was the most common phenotype recorded in either cohort among those with glaucoma (*TEK*: 18/24, 75.0% vs *CYP1B1*: 28/42, 66.7%, p=0.67). Because of this, and to allow comparison of past and future literature pertaining to PCG,[26,138,139] a sub-analysis of the clinical variables among those with a PCG phenotype only (henceforth referred to as *TEK*-PCG and *CYP1B1*-PCG for brevity) was performed. Among participants with PCG, female sex (*TEK*: 6/18, 33.3% vs *CYP1B1*: 17/28, 60.7%, p=0.13) and self-reported European ancestry (*TEK*: 12/14, 85.7% vs *CYP1B1*: 13/22, 59.1%, p=0.14) were not significantly different between either cohort. The differences in clinical characteristics per eye per PCG cohort were further analysed as shown in Table 4.3.

The median age at diagnosis of *TEK*-PCG was significantly older compared with *CYP1B1*-PCG (2.5 months [range: 0–30]) vs 0 months [0–60], respectively p=0.03). Participants with *TEK*-PCG were significantly more likely to have infantile-onset PCG than neonatal or late-onset disease compared with those with *CYP1B1*-PCG (12/18, 66.7% vs 7/28, 25.0%, respectively, p=0.01) and were less likely to have bilateral disease compared with participants with *CYP1B1*-PCG (12/18, 66.7% vs 27/28, 96.4%, respectively, p=0.02). The median age at the last examination between cohorts was otherwise similar (p=0.74, Table 4.3). A total of 30 eyes from 18 participants with *TEK*-PCG and 53 eyes from 27 participants with *CYP1B1*-PCG were further analysed (Table 4.3).

After adjusting for age at the last examination and the inclusion of multiple individuals from one family, eyes with *TEK*-PCG had better logMAR BCVA at the last examination (0.3 [0.0–0.8] vs 1.1 [0.6–2.7], p=0.004). The maximum-recorded IOP was also significantly lower in eyes with *TEK*-PCG compared with eyes with *CYP1B1*-PCG (31 mmHg [24–40] vs 40 mmHg [31–46], p=0.03). In addition, there was a trend for eyes with *TEK*-PCG to have a thinner CCT (554 µm [527–576] vs 602 µm [557–712], p=0.18) and a lower myopic refraction compared with eyes with *CYP1B1*-PCG (spherical equivalent: -0.50 dioptres [-2.25–0.0] vs -2.0 dioptres [-7.0–-0.25], p=0.05). Neither parameter, however, was statistically significant.

With respect to treatments, the proportion of eyes in either cohort requiring any glaucoma drainage procedure was relatively equal (*TEK*-PCG: 29/30, 96.7% vs *CYP1B1*-PCG: 52/53, 98.1%, p=0.69). One eye in the *CYP1B1*-PCG cohort was not operated on as the eye was phthisical at presentation. Eyes with *TEK*-PCG reported a lower median of glaucoma procedures than eyes with *CYP1B1*-PCG, although this was not significantly different (*TEK*-PCG: 2 [range: 0–16] vs 5 [range: 1–31], p=0.06; Figure 4.2D). However, eyes with *TEK*-PCG required significantly less incisional glaucoma surgeries (*TEK*-PCG: 1 [range: 0–5] vs 3 [range: 1–7], p=0.046; Figure 4.2E) and advanced glaucoma procedures

(1 [range: 0–6] vs 3 [range: 1–8], p=0.02; Figure 4.2F) than eyes with *CYP1B1*-PCG, as presented in Figure 4.2 and Table 4.3. Fewer eyes with *TEK*-PCG also had a glaucoma drainage device implanted (*TEK*-PCG: 4/30, 13.3% vs *CYP1B1*-PCG: 21/53, 39.6%, p=0.33). Furthermore, fewer topical anti-glaucoma medications were being used at the time of the last review in eyes with *TEK*-PCG (*TEK*-PCG: 0 [0–1] vs *CYP1B1*-PCG: 1 [1–2], p=0.007), despite IOP at last examination being similar (p=0.92). Glaucoma complications were otherwise not significantly different between both cohorts (Table 4.3), although the proportion of eyes with corneal disease in the *TEK*-PCG cohort was approximately half of that in eyes with *CYP1B1*-PCG (4/27, 14.8% vs 14/44, 31.8%, respectively, p=0.60).

A sub-analysis was performed for probands with PCG only to confirm that the inclusion of multiple individuals from the same family did not impact on the overall findings (Appendix B, Table B7). The same trends in clinical outcome data were observed. Differences in age at diagnosis (p=0.03), maximum recorded IOP (p=0.02), logMAR BCVA (p=0.01), the number of advanced glaucoma procedures (p=0.047), and the number of topical medications being used at the time of the last examination (p=0.006) remained statistically significant. Statistically significant differences in the proportion of eyes requiring enucleation, evisceration or phthisis bulbi was additionally observed (p=0.047). The proportion of individuals with bilateral disease between cohorts was no longer significantly different although there continued to be less individuals with bilateral disease in the *TEK*-PCG cohort compared to the *CYP1B1* cohort (11/14, 78.6% vs 22/22, 100.0%, respectively, p=0.05). Similarly, eyes with *TEK*-PCG continued to require less incisional glaucoma surgeries than eyes with *CYP1B1*-PCG although statistical significance was no longer achieved (median [range]: 3 [1–7] vs 1 [0–5], p=0.09; Appendix B, Table B7).

Table 4.3. Comparison of clinical characteristics per PCG-eye per gene

Clinical characteristic	*CYP1B1*-PCG	*TEK*-PCG	p-value	Adjusted for age at last examination
Bilateral disease	27/28 (96.4)	12/18 (66.7)	**0.02[a]**	**0.02**
Age at diagnosis (months)*	0 (0–60)	2.5 (0–30)	**0.03[b]†**	**-**
Age at last examination (years)*	24.0 (0.17–74.8)	27.4 (1.6–82.5)	0.74[b]	-
IOP at last examination (mmHg)	17 (14–20)	18 (14–21)	0.86[a]	0.92
IOP at diagnosis (mmHg)‡	30 (26–38)	32 (25–41)	0.42[a]	-
Maximum recorded IOP (mmHg)	40 (31–46)	31 (24–40)	**0.02**[a]	**0.03**
BCVA (LogMAR)	1.1 (0.6–2.7)	0.3 (0.0–0.8)	**0.03**[a]	**0.004**
BCVA <6/60§	26/51 (51.0)	7/30 (23.3)	**0.043[a]**	**0.01**
Unable to obtain reliable visual field data among participants aged >10 years	38/42 (90.5)	10/22 (45.5)	**<0.001**[a]	**<0.001**
HVF mean deviation (decibels)	-2.44 (-3.78–-1.15)	-1.51(-3.46–-0.26)	0.69[a]	0.83
Spherical equivalent (dioptres)	-2.0 (-7.0–-0.25)	-0.50 (-2.25–0.0)	0.06[a]	0.05
CCT (µm)	602 (557–712)	554 (527–576)	**0.04**[a]	0.18
Treatment characteristic per eye				
Had glaucoma procedure	52/53 (98.1)	29/30 (96.7)	0.68[a]	0.69
Number of drainage procedures*	5 (1–31)	2 (0–16)	**0.02[a]**	0.06
Number of incisional glaucoma surgeries*	3 (1–7)	1 (0–5)	**0.007[a]**	**0.046**
Number of advanced glaucoma procedures*	3 (1–8)	1 (0–6)	**0.01[a]**	**0.02**
Glaucoma drainage device implanted	21/53 (39.6)	4/30 (13.3)	0.63[a]	0.33
Number of topical anti-glaucoma medications at last review	1 (1–2)	0 (0–1)	**0.02[a]**	**0.007**
Complicationsˈ				
Enucleation, evisceration or phthisis bulbi	9/53 (17.0)	3/30 (10.0)	0.41[a]	0.17
Cataract	21/44 (47.7)	11/27 (40.7)	0.52[a]	0.29
Corneal disease	14/44 (31.8)	4/27 (14.8)	0.74[a]	0.60

PCG: primary congenital glaucoma; IOP: intraocular pressure; BCVA: best-corrected visual acuity; HVF: Humphrey Visual Field; CCT: central corneal thickness.
Nonparametric continuous variables are presented as median (IQR) unless otherwise indicated (*).
*Data presented as a range. Bold values indicate statistical significance (p<0.05).
[a]Linear mixed effect regression adjusting for the inclusion of two eyes of one individual and the inclusion of multiple individuals from the same families, [b]Mann Whitney U test
†The variance explained by the random effect of family relatedness in the model was incompatible with the linear mixed effect regression model.
‡IOP at diagnosis was only available for 5 eyes with *CYP1B1*-PCG and 11 eyes with *TEK*-PCG.
§LogMAR visual acuity testing was not possible in two eyes from a *CYP1B1*-PCG participant as the eyes belonged to an infant.
ˈEnucleated eyes were excluded from analysis of cataract and corneal disease.

4.3.4 Non-PCG primary glaucoma severity

Because worse disease outcomes may be related to the early age of disease onset as observed in participants with PCG, I sought to analyse the clinical outcomes in participants with JOAG or POAG (referred to collectively as non-PCG primary glaucoma). This analysis included 12 eyes of six participants with a heterozygous *TEK* variant and 20 eyes of 10 participants with biallelic *CYP1B1* variants.

Participants with heterozygous variants in *TEK* were significantly older at the time of their last examination compared with those with biallelic variants in *CYP1B1* (median age: 82.3 years [range: 74.8–89.0] vs 36.1 years [range: 16.8–64.4], respectively, p=0.007). The median age at diagnosis of non-PCG primary glaucoma was significantly older in participants with a *TEK* variant compared with participants with biallelic variants in *CYP1B1* (45 years [35–70] vs 17 years [5–46], respectively, p=0.007). After adjusting for inclusion of multiple individuals from the same family, those with a *TEK* variant were significantly more likely to have a cataract than participants with *CYP1B1* variants (8/12, 66.7% vs 4/20, 20.0%, respectively, p<0.001). Median CCT was thinner in the *TEK* cohort compared to the *CYP1B1* cohort (541 µm [526–552] vs 624 µm [584–634], respectively, p=0.003) and the maximum-recorded IOP in eyes with a *TEK* variant was lower (27 mmHg [21–30] vs 37 mmHg [30–40], p=0.02). There were, however, no adjustments for age at the last examination due to multicollinearity in the model. There were no significant differences in any other clinical variable. A sub-analysis for probands only was not performed as there were only two non-probands with JOAG included in the above analysis.

4.3.5 Exclusion of the *CYP1B1* c.1103G>A (p.R368H) variant

The *CYP1B1* c.1103G>A (p.R368H) variant was reported in 13/44 (29.5%) participants (Appendix B, Table B4). Of these, 8/13 (61.5%) participants had PCG, 3/13 (23.1%) had JOAG and 1/13 (7.7%) had PACG. In addition, one parent of a child with PCG, both of whom had the variant, did not have glaucoma at age 32.3 years.

A sub-analysis between *CYP1B1* and *TEK* clinical outcomes excluding the participants with the p.R368H variant was performed (Appendix B, Table B8). Differences in statistical significance of demographic and clinical features between the two genetic cohorts, among participants and eyes with glaucoma, were similar. Differences in disease penetrance (p=0.004), sex amongst participants with glaucoma (p=0.03), disease laterality (p=0.005), maximum recorded IOP (p=0.03), logMAR BCVA (p=0.01), CCT (p=0.03), and the number of topical medications being used at the time of the last examination (p=0.001) remained statistically significant (Appendix B, Table B8). Statistically significant

differences in the number of advanced glaucoma procedures (p=0.04) was additionally observed (Appendix B, Table B8).

Differences between clinical phenotypes in participants and eyes with the p.R368H variant and those with other biallelic *CYP1B1* variants were further analysed. After adjusting for family relatedness, the median age at diagnosis in participants with the p.R368H variant was similar to participants with other *CYP1B1* variants (p.R368H: 0.1 years [range: 0–47] vs other *CYP1B1*: 0.2 years [range: 0–46], respectively, p=0.45). Meanwhile, participants harbouring the p.R368H variant were significantly younger at the time of the last examination than participants with other *CYP1B1* variants (p.R368H: 11.7 years [range: 0.2–59.5] vs other *CYP1B1*: 35.1 years [range: 6.5–74.8], p=0.04). After adjusting for age at last examination and family relatedness, the number of incisional surgeries (p.R368H: 1 [range: 0–4] vs other *CYP1B1*: 2 [range: 0–7], p=0.048) and the number of advanced surgical procedures (p.R368H: 1 [range: 0–7] vs other *CYP1B1*: 2 [0–8], p=0.046) were higher in individuals with other *CYP1B1* variants compared to those with the p.R368H variant. There were no significant differences in any other demographic or clinical variable after accounting for age at last examination.

4.4 Discussion

This study reported a novel and detailed description of the relative severity of *TEK*-associated glaucoma compared with *CYP1B1*-associated glaucoma. To the best of my knowledge, this work describes the largest cohort of individuals with *TEK*-associated glaucoma and one of the largest cohorts of individuals with biallelic *CYP1B1*-associated glaucoma of predominantly European ancestry.

In this study, eyes with biallelic variants in *CYP1B1* exhibited a significantly greater maximum recorded IOP. Overall, the *CYP1B1*-associated glaucoma cohort had a median maximum-recorded IOP of 9 mmHg more than the *TEK*-associated glaucoma cohort. This result, however, is difficult to interpret due to the retrospective nature of the study and the potential effects of treatment that could not be controlled for. In contrast, there was no significant difference in the IOP at diagnosis between cohorts, although this analysis was based on a limited number of observations due to the unavailability of several medical records at diagnosis. Despite these limitations, it remains possible that IOP is more challenging to control in eyes with *CYP1B1*-associated glaucoma. This is because this cohort were significantly more likely to remain on topical anti-glaucoma medication than participants with *TEK*-associated glaucoma. Similarly, eyes with *TEK*-PCG required significantly fewer glaucoma procedures, incisional glaucoma surgeries and advanced glaucoma procedures overall. This trend represents clinically significant findings, particularly as IOP is the only modifiable risk factor for glaucoma progression and guides disease management.[17] Previous studies have otherwise demonstrated that a small subset of

participants with *CYP1B1*-PCG and *TEK*-PCG had IOPs of up to 30–40 mmHg at their most recent clinical examination.[139,404,405] Whilst this is not representative of the maximum-recorded IOP or IOP at diagnosis, it is important to acknowledge that there is variability between participants and that their clinical treatment course may vary accordingly.

Eyes with *TEK*-associated glaucoma were less likely to have severe vision impairment (i.e., <6/60), compared with the *CYP1B1* cohort. The majority of eyes with severe vision impairment had PCG and participants with *CYP1B1*-PCG were significantly more likely to be diagnosed earlier than those with *TEK*-PCG. Children diagnosed with glaucoma earlier than 3 months of age are known to have worse visual outcomes compared with children diagnosed later.[11] Furthermore, eyes with *CYP1B1*-PCG were more myopic. Myopia is the most common refractive error in eyes with PCG.[10,11,406] It is well accepted that increased IOP results in axial elongation and subsequent myopia in an elastic infant eye.[10] Conversely, there were no differences observed in refraction between cohorts of participants with non-PCG glaucoma in this cohort (i.e., JOAG and POAG) likely owing to the rigidity of an adult eye. It has been reported that individuals with at least one variant in *CYP1B1* may have a more severe form of JOAG, with an earlier age of onset and worse mean deviation on visual field testing, compared with individuals without the variant.[61] The availability of reliable visual field data in this study, however, was limited. Nevertheless, it appears that clinical outcomes are more favourable for those with *TEK*-associated glaucoma than *CYP1B1*-associated glaucoma.

There were additional clinically differentiating features between the two cohorts. Participants with *TEK*-associated glaucoma were more likely to have unilateral disease. Amongst all reported individuals with *TEK*-associated glaucoma, almost half had unilateral disease (30/63, 47.6%),[26,138,139] while *CYP1B1*-associated glaucoma was almost always bilateral, consistent with previous reports.[101,407] Furthermore, CCTs were consistently thicker in eyes with *CYP1B1*-associated glaucoma in proband and non-proband analyses. Whilst a recent genome-wide association study identified a *CYP1B1* variant associated with variation in CCT,[408] thicker corneas could reflect endothelial dysfunction or subclinical corneal edema.[409] In this study, the proportion of eyes in the *CYP1B1* cohort with corneal disease was almost double compared with eyes with *TEK*-associated glaucoma. This observation may be explained by the higher proportion of eyes with *CYP1B1*-associated glaucoma that underwent more surgical procedures and those that were implanted with a glaucoma drainage device. Drainage device implantation, in particular, is a well-known risk factor for corneal decompensation, with patients with an implant requiring corneal monitoring.[410] Furthermore, differences in CCT have consequences for accurate IOP measurement, and emphasises the need for ongoing and accurate measurement of corneal thickness in this cohort.[411]

A sex bias was observed amongst those studied, whereby among those with glaucoma, there were significantly more females with biallelic *CYP1B1* variants than heterozygous *TEK* variants. This could be possibly explained by the biochemical function of CYP1B1, which is involved in metabolising an estrogen steroid hormone required for trabecular meshwork synthesis (17β-oestradiol).[385] A similar sex bias has been observed in other studies in children with PCG and variants in *CYP1B1*,[383,384,386] despite PCG being more commonly observed in males.[65,86,386]

Variability in the disease phenotype, clinical characteristics, and disease severity may be due to the influence of other genetic modifiers that are yet to be discovered. This may be especially relevant in the case of *TEK*, where 35% did not have glaucoma or OHT at the time of the last examination. This may be explained in part by delayed disease onset (e.g., five *TEK* heterozygotes were diagnosed later in life with POAG) such that individuals who were unaffected at the time of the study may develop disease later. Variants in other genes in the ANGPT1/2-TEK pathway may also contribute to differences in disease penetrance and expressivity, as has recently been proposed for *SVEP1*.[139] Other rare and common variants may be relevant here, including rare *ANGPT1* variants associated with PCG,[141] and common *ANGPT1* variants associated with IOP.[412] Variants in *SVEP1* and *ANGPT2* have also been associated with POAG risk.[413] However, no participant in this study was found to harbour a rare variant in *ANGPT1, ANGPT2,* or *SVEP1.* Other possible sources of variation include classes of *TEK* variants yet to be discovered, such as deep intronic or structural variants not captured during exome sequencing, or common variants beyond the TEK-ANGPT pathway, which have collectively been shown to influence the penetrance of a moderate effect size variant in *MYOC* (p.Gln368Ter).[414] Nonetheless, the identity of these modifying factors, whether they are genetic or non-genetic, will be important to our understanding of glaucoma pathogenesis.

This study did not aim to ascertain whether certain types and combinations of variants resulted in more severe disease in either cohort due to the limited sample size to observe significant associations. Previous studies have proposed that null *CYP1B1* variants may be associated with a more severe PCG phenotype than non-null variants.[300,305,415] However, interpretation of the findings is limited by the small number of observations and/or the lack of statistical analyses of outcome data, including adjusting for the number of eyes and age at last examination. Berraho and colleagues[388] performed statistical analysis and reported no significant differences in the proportion of eyes with severe PCG between cohorts with biallelic null and non-null *CYP1B1* variants. Meanwhile, no studies have yet investigated whether the type of pathogenic *TEK* variant affects disease severity.[26,138,139] Given the rarity of these diseases and molecular diagnoses, international collaboration is required to achieve adequate sample

size for analysis of whether the type of variant or combination of variants are associated with disease severity.

Additional studies are required to determine the pathogenicity of the *CYP1B1* variant, c.1103G>A (p.R368H). Its role in PCG pathogenesis was recently questioned in a Saudi Arabian study which reported a high allele frequency and low disease penetrance.[101] However, this study did not test the influence of this variant on later-onset forms of glaucoma,[101] and *in vitro* studies have demonstrated a functional impact of the p.R368H variant.[400–402] In the current study, 23% of participants with the p.R368H variant were diagnosed with JOAG and one with POAG. A sub-analysis excluding individuals with this variant was undertaken and the findings were relatively unchanged. However, it was found that eyes with the p.R368H variant required a lower number of incisional surgeries and advanced glaucoma procedures than eyes with other *CYP1B1* variants. This result was difficult to interpret as it was based on a small sample size and there were no significant differences in any other demographic or clinical variable.

This study highlights several benefits for genetic testing in individuals with glaucoma. It assists clinicians in providing a more reliable disease prognosis, particularly as those with *TEK*-associated glaucoma had more favourable outcomes than those with *CYP1B1*-associated glaucoma. Genetic testing and counselling also enable individuals and caregivers to make informed family planning decisions in the context of childhood glaucoma. The ANGPT1/2-TEK pathway is also the target of an investigational topical therapy for POAG,[416,417] although this and other targeted therapies may well be more effective in individuals with *TEK*-associated glaucoma described here.

There are several limitations to this study. These include missing data for some participants due to the retrospective nature of the study. This inhibited the inability to analyse the vertical cup:disc ratio at diagnosis and limited the ability to interpret IOP findings. Furthermore, clinical outcomes may have been influenced by the availability of ophthalmic care, different lengths of disease duration and follow-up, treatment adherence, having multiple individuals from the same family affected by glaucoma, and the treating specialists' surgical experience and treatment preferences. However, statistical testing corrected for the differences in age at last examination between cohorts and correction for family relatedness reduced the influence of any possible familial factors. A sub-analysis of probands only confirmed the same trends in data observed. Although this study described the largest cohort of individuals with heterozygous variants in *TEK,* and one of the largest cohorts to investigate the clinical outcomes of individuals with biallelic variants in *CYP1B1*, comparison between both cohorts may be limited due to the rarity of both conditions. The rate of unaffected individuals with biallelic *CYP1B1* variants or heterozygous *TEK* variants may also be underestimated because not all family members

within each pedigree have yet undergone genetic testing. This may have also affected the analysis of disease severity and penetrance. Furthermore, functional evidence is required to support the pathogenicity for some *TEK* variants included in this study and will be an aim of future research. Finally, the cohort was predominantly of European ancestry, and validation of these findings in other populations will be required.

In conclusion, the present study demonstrated that heterozygous *TEK* variants were associated with less severe glaucoma, and had a lower penetrance, than individuals with biallelic *CYP1B1* variants. More work is required to understand the determinants of disease penetrance and expressivity in both settings, which will be critical for our understanding of glaucoma pathogenesis. Overall, the characterisation of these cohorts has important implications for their future clinical management, including accurate prognostication, treatment, and counselling.

CHAPTER 5 AN EXPLORATION OF SYSTEMIC FEATURES IN CHILDHOOD GLAUCOMA

5.1 Introduction

The optimum approach in the management of childhood glaucoma requires multidisciplinary care from ophthalmologists, paediatricians, and clinical geneticists.[8,255] This is primarily to ascertain the appropriate clinical and molecular diagnosis, determine the presence of systemic features and ensure effective disease management.[8,255] However, guidance pertaining to what systemic features to investigate in childhood glaucoma is hindered by the scarce literature documenting comorbid systemic disease. Reports of systemic features in primary childhood glaucomas, including PCG and JOAG are relatively absent.[255] Meanwhile, secondary glaucomas, including SG-O (e.g., ARS) have well-documented multisystem involvement.[44,45] The lack of systemic associations with primary glaucomas could be because there truly are none associated with the condition, or there has been insufficient investigation or reporting of these in this relatively rare disorder. The ANZRAG is well-placed to address this gap in knowledge as it provides one of the largest childhood glaucoma cohorts with well characterised ocular phenotypes and molecular diagnoses.

There are many well-known genes associated with non-acquired childhood glaucomas (i.e., PCG, JOAG, SG-O, SG-S) that have key regulatory functions that may influence the development of non-ocular organ systems. This includes *FOXC1* and *PITX2*, which regulate neural crest cell differentiation.[210,216,217] Pathogenic variants in these genes typically result in an ocular phenotype of SG-O, alongside systemic features of ARS including, but not limited to, dental, cardiac and craniofacial skeletal abnormalities.[125–127,130,132,192,195] Similarly, it has been suggested that pathogenic variants in *LTBP2* cause a connective tissue disease phenotype.[152,155] Meanwhile, reports of extraocular features in genes associated with PCG (e.g., *CYP1B1, TEK*) and JOAG (e.g., *MYOC*) are lacking. Investigation and characterisation of systemic features in these cohorts may improve clinical and molecular diagnostic rates and may add insight into the biological mechanisms and genetic pathways underpinning development of glaucoma.[251]

Understanding what systemic features may manifest in non-acquired glaucomas and their associated molecular diagnoses can facilitate referral pathways for effective management of systemic disease. Early referral to medical subspecialities including cardiology, endocrinology, craniofacial, and orthopaedics for individuals diagnosed with *FOXC1* and *PITX2*-associated ARS is already recommended.[292] Conversely, subspecialist referral pathways have not yet been recommended for

individuals diagnosed with PCG, JOAG or other certain molecular diagnoses. The primary aim of the present study was to explore the presence of systemic features in the different subtypes of non-acquired childhood glaucomas and compare the prevalence of these features between primary and secondary glaucoma subtypes, to ascertain whether additional referrals to subspecialists may be recommended for certain subtypes. The secondary aim was to evaluate systemic features in genes typically associated with these conditions and generate hypotheses regarding potential associations between multisystem involvement and molecular diagnoses.

My original contribution to knowledge was a systematic exploratory investigation of systemic features in a large cohort of individuals with primary and secondary childhood glaucoma, and cohorts with a molecular diagnosis associated with childhood glaucoma.

5.2 Methods

5.2.1 Participants

This was a survey-based phenotypic and molecular exploratory study. Participants were drawn from the ANZRAG using a non-probability convenience sampling technique. This is a technique which describes the selection of participants from a subset of an entire population that is readily accessible for the purposes of the research (i.e., participants with childhood glaucoma enrolled in the ANZRAG were invited to participate because their contact information was easily accessible and they were known to have had genetic testing).[418] All participants were required to have up-to-date contact information. To address the primary aim of the study, participants were included if they had a diagnosis of non-acquired childhood glaucoma as per the criteria outlined in Chapter 2. The categories included were:

1. Primary glaucoma: PCG or JOAG
2. Secondary glaucoma: SG-S or SG-O

If the molecular diagnosis resulted in a reclassification of the glaucoma subtype as previously discussed in Chapter 3,[386] the participant was analysed according to their reclassified diagnosis. Participants with SG-A were not included as they were not expected to have systemic features associated with their glaucoma diagnosis. SG-C were also not included as their glaucoma was considered to be acquired from cataract surgery.

To address the secondary aim of the study, those with a molecular diagnosis commonly associated with childhood glaucoma within the ANZRAG cohort, who did not have a diagnosis of childhood glaucoma, were also included. This is because pathogenic variants in genes may exhibit variable age-related penetrance of glaucoma (Chapter 3 and 4),[7,26,130,139,186,386] such that systemic features may precede any

glaucoma diagnosis. The genetic cohorts invited to participate were determined on the basis of achieving a likely sample size of n≥5 per genetic cohort to avoid possible over-reporting of systemic features in smaller groups. This resulted in the additional recruitment of individuals without childhood glaucoma who had biallelic pathogenic variants in *CYP1B1* or *CPAMD8*, or had heterozygous pathogenic variants in *MYOC, TEK, FOXC1, PITX2* or *PAX6*. Individuals with biallelic pathogenic variants in *LTBP2* without childhood glaucoma were not included as contact information was not available for several of these individuals within the ANZRAG cohort. Participants with a molecular diagnosis and glaucoma were assigned a glaucoma classification dependent on the age of disease onset (childhood: 0–<18 years or early-onset: 18–<40 years) and their phenotype, as per the CGRN criteria (Methods, Chapter 2).[4] Participants with a molecular diagnosis and primary open-angle glaucoma diagnosed ≥40 years of age were assigned a diagnosis of POAG. Participants with a molecular diagnosis and ASD without childhood or early-onset glaucoma were assigned a diagnosis of ASD only. Participants with a molecular diagnosis who had not developed glaucoma and did not have ASD were assigned a classification of either OHT (if IOP ≥21 mmHg) or unaffected (if IOP ≤21 mmHg). If the molecular diagnosis resulted in a reclassification of the glaucoma subtype (as per Chapter 3),[386] the participant was categorised according to their reclassified diagnosis as described above. The categories were:

1. Primary disease: PCG, JOAG (childhood or early-onset), POAG or OHT.
2. Secondary disease: SG-S or SG-O (childhood or early-onset), or ASD only; and
3. Unaffected.

Ethics approval was obtained through the Southern Adelaide Clinical Human Research Ethics Committee (2020/HRE00891). The study adhered to the revised Declaration of Helsinki (2013) and the National Health and Medical Research Council statement of ethical conduct in research involving humans (2018).

5.2.2 Survey design

A systemic health survey, which included questions regarding the presence of current or previous systemic features, was distributed in the English language (Appendix D). The survey was designed by including questions related to prior reports of specific systemic features associated with the most common molecular diagnoses in childhood glaucomas and general questions about health to explore potential novel associations. This was done to increase the sensitivity for detecting known systemic associations which may be common to developmental pathways important for both the eye and other tissues. This included systemic features reported in individuals with pathogenic variants in:

1. *FOXC1*: musculoskeletal or connective tissue features (skeletal abnormalities, short stature [as inferred from height]), cardiovascular features (stroke, cardiac defects), genitourinary features (reproductive, renal), neurodevelopmental features (hydrocephalus, intellectual disability, developmental delays), hearing loss and renal features.[125,126,130,132,195,209]
2. *PITX2*: dental features, hernias, gastrointestinal or umbilical features.[125,127,130,132]
3. *LTBP2*: musculoskeletal or connective tissue features including tall stature (as inferred from height), cleft lip/palate, bone fractures (as a proxy for possibly reduced bone mineral density), joint or skeletal abnormalities;[152,155] and
4. *PAX6* or WAGR syndrome: neurodevelopmental features (intellectual disability, autism spectrum disorder), genitourinary features, diabetes mellitus and obesity (as inferred from BMI).[233,234,238–242]

Additional questions were included to cover other general health (e.g., cancers, skin abnormalities) or mental health issues and create a broad health questionnaire. The age at which a bone fracture was diagnosed, or a hearing aid implanted, were collected to ascertain age-related associations.

In keeping with the recommendations of medical research survey development, common themes were grouped together.[419] These included the themes of glaucoma diagnosis and treatment history, growth and developmental history, and general health history. Glaucoma diagnosis and treatment history were collected for the purposes of updating ANZRAG records for future research (questions 6–12 in Appendix D, Health Survey D1 and questions 5–9 in Appendix D, Health Survey D2). As such, the results from these questions were not reported in this study but were used throughout Chapters 6–9 to support demographic characteristics of potential participants. Survey questions were reviewed by four paediatric glaucoma ophthalmologists (including supervisors JEC and JBR) and two childhood glaucoma genetic experts (supervisors ES and OMS).

A modified health survey had been developed for individuals with *FOXC1* or *PITX2* variants within the ANZRAG who had participated in a previous study led by a supervisor (ES).[130] This previous study investigated glaucomatous and systemic features in individuals with *FOXC1* and *PITX2* variants.[130] Additional data regarding systemic features was provided in a consequent manuscript which investigated facial dysmorphism in individuals with *FOXC1* and *PITX2* variants, for which I was a co-author.[132] These studies similarly utilised a health survey to ascertain systemic features associated with the condition, such that the modified survey excluded questions previously asked for individuals who had completed the previous survey (Appendix D, Health Survey D2). Answers provided by respondents in the aforementioned studies,[130,132] were included in this study where possible. Each survey was

designed for distribution in print and electronic formats. The electronic health survey was designed using Qualtrics software (Provo, Utah, US).

5.2.3 Data collection

The survey, along with an invitation letter outlining the purpose of the study, were distributed via post or email, subject to participants' preferred method of contact for ANZRAG communications. Participants who received a postal survey were provided a return-paid envelope to improve response rates.[420] Where an individual was aged <18 years, the survey was addressed to the individual's parent or caregiver. Data collection extended from December 2020 to July 2022.

The following features were assessed using "Yes" or "No" answers: skeletal or bony abnormalities, cleft lip, cleft palate, joint abnormalities, hernia, bone fracture, reproductive or genital problems, kidney problems, missing teeth, extra teeth, small teeth, abnormally shaped teeth, heart defects or problems, stroke or ministroke, hydrocephalus, developmental delay, learning difficulties, behavioural problems, mental health issues or mood disorders, gut or stomach problems, hearing loss, hearing aid, unusual skin lesions such as scars, bumps, spots or birthmarks, diabetes and type of diabetes, cancer and extra skin on the belly button. The following features were further assessed by open-ended questions: type of skeletal or bony abnormalities, type of joint abnormalities, type of bone fracture (the bone fractured, the number of fractures and age at the fracture), type of reproductive or genital problems, type of gut or stomach problem, type of kidney problems, type of heart defect or problem, type of mood disorder or mental health issues, type of skin lesion, type of cancer and other features.

Body mass index (BMI) was calculated using participants' height and weight (kilograms/metres^2).[421] The WHO BMI classifications were assigned based on normative values for adults (aged ≥20 years) and children (aged 0–<5 years and 5–19 years).[421–423] Child normative BMI classifications were sex specific.[422,423] As per current recommendations,[424] normative height percentiles for child participants aged 0–2 years were calculated according to the WHO chart for children aged 0–2 years.[425] For participants aged >2 years, the Centers for Disease Control and Prevention 2–20 years Growth Chart for males and females were used.[426] For participants aged >20 years, normative 20-year-old height percentiles were used.[426] Short stature was defined as a height below the third percentile and tall stature was defined as height above the 97th percentile for age and sex.[427] BCVA was collected from participants' ANZRAG record.

When reporting data, systemic features were aggregated into groups of diseases for brevity. These included musculoskeletal or connective tissue features (cleft lip, cleft palate, joint or skeletal abnormalities [including short or tall stature], hernia and bone fracture), neurodevelopmental features

(development delays, learning difficulties, behavioural disorders and mental health issues or mood disorders), cardiovascular features (cardiac defects and stroke) and genitourinary features (reproductive and renal features). Questions that were answered by <20% of participants were not reported. This included questions 13–15 (Appendix D, Health Survey D1) and questions 10–12 (Appendix D, Health Survey D2) about birth.

5.2.4 Statistical analysis

The Shapiro-Wilk test was used to assess for a normal distribution of quantitative data. Normally distributed data were expressed as means and standard deviations, whilst non-normal distributed variables were expressed as medians and IQR. The chi-square test with continuity correction or Fisher exact test were used for categorical variables and the Mann-Whitney U test or median test were applied to non-parametric continuous variables where appropriate. Multivariable linear regression or Firth's logistic regression was performed to compare the presence of systemic features in individuals with primary and secondary glaucoma whilst adjusting for age at survey completion and sex. Firth logistic regression is suitable for small datasets and reduces the chance of a type I error by penalising the likelihood ratio.[428,429] A *P* value <0.05 was considered statistically significant. Bonferroni adjustment for multiple correction testing was not performed as all analyses were exploratory in nature. All statistical tests were performed using SPSS package version 27.0, except for Firth's logistic regression, which was performed using R version 4.1.0 with the *logistf* package (version 1.24.1).

A separate analysis of probands only was not performed due to possible varied expression of systemic features within a pedigree from a possible underlying molecular diagnosis associated with glaucoma, as per previous studies.[130,192,430] Similarly, family relatedness was not corrected for within the logistic regression model. All questions that were not answered by participants were recorded as missing and were not included in analyses. Responses to 'other' systemic features (Question 41, Appendix D, Health Survey D1 and Question 28, Appendix D, Health Survey D2) were analysed with the respective systemic feature where appropriate.

5.3 Results

5.3.1 Participants

A total of 439 surveys were distributed and 131/439 (29.8%) were completed. The median age of participants was 36.9 years (IQR: 18.0–62.4) and 77/131 (58.8%) were female. Distribution via email received a significantly higher response rate compared to post (70/139, 50.4% vs 61/300, 20.3%, respectively, p<0.001). The difference in age between participants and non-participants was not

significantly different (median [IQR]: 36.9 years [18.0–62.4] vs 39.7 years [17.5–59.5], respectively, p=0.70) and there was no significant difference in sex among those who did or did not complete the survey (females: 77/131, 58.8% vs 150/308, 48.7%, respectively, p=0.07). Non-participants were significantly more likely to be of self-reported non-European ancestry compared to participants (60/305, 19.7% vs 14/131, 10.7%, respectively, p=0.03). The presence of a molecular diagnosis was not significantly higher in participants compared to non-participants (89/131, 67.9% vs 180/308, 58.4%, respectively, p=0.08). Among non-participants, 31/308 (10.1%) had completed a health survey in the aforementioned studies investigating systemic features in *FOXC1* and *PITX2*.[130,132] The responses of these individuals were included where possible. Subsequently, survey responses from a total of 162 participants were analysed.

5.3.2 Systemic features per childhood glaucoma subtype

Among all respondents, 107/162 (66.0%) had childhood glaucoma. Demographic characteristics across each childhood glaucoma subgroup are presented in Table 5.1. Most participants had PCG (51/107, 47.7%). Of these individuals, 24/51 (47.1%) had a molecular diagnosis. Most individuals with a diagnosis of SG-O had a molecular diagnosis (30/32, 93.8%) whilst almost half of participants with JOAG (8/17, 47.1%) had a molecular diagnosis. The most common phenotype amongst those diagnosed with SG-O was ARS (21/32, 65.6%), followed by unclassified ASD (6/32, 18.8%). All participants with ARS (21/21, 100.0%) had a molecular diagnosis. These individuals had a pathogenic or likely pathogenic variant in either *FOXC1* (14/21, 66.7%) or *PITX2* (7/21, 33.3%). Participants with SG-S were the youngest at the time of survey completion (median: 11.6 years [IQR: 2.4–15.7]) whilst those with JOAG were the oldest (median: 28.9 years [IQR: 23.1–47.6]) as per Table 5.1. Those with PCG had the highest prevalence of unilateral or bilateral BCVA <6/60 (24/45, 53.3%).

Table 5.1. Demographic characteristics per childhood glaucoma subtype

Characteristic[†]	PCG	JOAG	SG-O	SG-S	Total
Number of individuals	51/107 (47.7)	17/107 (15.9)	32/107 (29.9)	7/107 (6.5)	**107/107 (100.0)**
Age at survey completion, years (median, IQR)	26.7 (11.5–46.7)	28.9 (23.1–47.6)	25.8 (11.3–40.1)	11.6 (2.4–15.7)	**25.8 (13.1–44.3)**
Female sex	26/51 (51.0)	9/17 (52.9)	16/32 (50.0)	4/7 (57.1)	**55/107 (51.4)**
European ancestry	44/51 (86.3)	14/17 (82.4)	28/32 (87.5)	6/7 (85.7)	**92/107 (86.0)**
Probands	45/51 (88.2)	15/17 (88.2)	26/32 (81.3)	7/7 (100.0)	**93/107 (86.9)**
Molecular diagnosis	24/51 (47.1)	8/17 (47.1)	30/32 (93.8)	3/7 (42.9)	**65/107 (60.7)**
CYP1B1	12/51 (23.5)	2/17 (11.8)	1/32 (3.1)	0/7 (0.0)	**15/107 (14.0)**
TEK	11/51 (21.6)	0/17 (0.0)	0/32 (0.0)	0/7 (0.0)	**11/107 (10.3)**
MYOC	0/51 (0.0)	6/17 (35.3)	0/32 (0.0)	0/7 (0.0)	**6/107 (5.6)**
CPAMD8	0/51 (0.0)	0/17 (0.0)	5/32 (15.6)	0/7 (0.0)	**5/107 (4.7)**
FOXC1	0/51 (0.0)	0/17 (0.0)	14/32 (43.8)	0/7 (0.0)	**14/107 (13.1)**
PITX2	0/51 (0.0)	0/17 (0.0)	7/32 (21.9)	0/7 (0.0)	**7/107 (6.5)**
PAX6	0/51 (0.0)	0/17 (0.0)	3/32 (9.4)	0/7 (0.0)	**3/107 (2.8)**
Other	1/51 (2.0)[‡]	0/17 (0.0)	0/32 (0.0)	3/7 (0.0)[§]	**4/107 (3.7)**
Unilateral or bilateral BCVA <6/60	24/45 (53.3)	1/17 (5.9)	12/31 (38.7)	4/5 (80.0)	**41/98 (41.8)**

PCG: primary congenital glaucoma; JOAG: juvenile open-angle glaucoma; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; SG-S: secondary glaucoma associated with a non-acquired systemic condition; IQR: interquartile range; BCVA: best-corrected visual acuity

[†]All values presented as n (%) unless otherwise specified.

[‡]Included *ANGPT1* (1/51, 2.0%)

[§]Included *NF1* (2/7) and a chromosome 7 deletion (del7q11.22q21.11; 1/7)

The systemic features across each childhood glaucoma subtype were analysed and are presented in Table 5.2. As per Table 5.2, musculoskeletal and connective tissue features were the most common group of systemic features reported across all ocular subtypes. The most notable findings are further detailed per glaucoma subtype.

5.3.2.1 PCG

Among participants with PCG, 43/51 (84.3%) reported at least one systemic feature (Table 5.2). Bone fractures were the only systemic feature to be most commonly reported by the PCG cohort compared to other cohorts (23/51, 45.1%; Table 5.2). Participants with a bone fracture were significantly more likely to have unilateral or bilateral BCVA <6/60 than participants who did not report a bone fracture (16/22, 72.7% vs 8/23, 34.8%, p=0.02). Formal BCVA was not recorded in six participants owing to their young age at the time of the study. Sex was not significantly different between individuals who did or did not report a bone fracture (female: 10/23, 43.5% vs 16/28, 57.1%, p=0.49). Participants who reported

a bone fracture were older than those who did not, although this did not reach significance (median [IQR]: 40.8 years [18.7–61.1] vs 19.7 years [4.3–36.9], respectively, p=0.21).

For interest, a sub-analysis was performed to determine if any systemic features were more common among those with PCG with or without a molecular diagnosis (Appendix B, Table B9). After adjusting for age at last follow-up and sex, the overall prevalence of any systemic feature in participants with and without a molecular diagnosis was not significantly different (21/24, 87.5% vs 22/27, 81.5%, respectively, p=0.87). There were significantly more PCG participants with a molecular diagnosis who reported an overweight or obese BMI compared to those without a molecular diagnosis (9/22, 40.9% vs 1/23, 4.3%, respectively, p=0.02). Among those with a molecular diagnosis and a BMI indicating overweight or obese, 7/9 (77.8%) had unilateral or bilateral BCVA <6/60. No other systemic feature was significantly different between groups (Appendix B, Table B9).

5.3.2.2 JOAG

Systemic features were reported by 15/17 (88.2%) participants with JOAG. Like PCG, bone fractures were the most common systemic feature reported (6/17, 35.3%). Bone fractures in the JOAG cohort were higher than both cohorts with secondary glaucoma (SG-O: 4/16, 25.0% and SG-S: 1/7, 14.3%) but were not higher than the rate of bone fractures reported by participants with PCG (23/51, 45.1%). Between participants who did or did not report a bone fracture, female sex (3/6, 50.0% vs 6/11, 54.5%, respectively, p=1.0), age at survey completion (median [IQR]: 24.5 years [22.0–28.0] vs 36.3 years [26.8–53.2], respectively, p=0.13) and the presence of unilateral or bilateral BCVA <6/60 (0/6, 0.0% vs 1/11, 9.1%, respectively, p=1.0) were similar.

A mental health issue or mood disorder was equally as commonly reported as a bone fracture (6/17, 35.3%). However, the rate of a mental health issue or mood disorder was lower than that reported by the SG-O cohort (9/18, 50.0%). Compared to other cohorts, the rate of reproductive issues (4/17, 23.5%) and abnormally shaped teeth (3/17, 17.6%) were highest among participants with JOAG (Table 5.2). Reproductive issues included endometriosis (n=2) and polycystic ovary syndrome (n=2).

The prevalence of systemic features amongst participants with JOAG with or without a molecular diagnosis were also analysed for completeness (Appendix B, Table B9). After adjusting for age at last follow-up and sex, there was no significant difference in the overall prevalence of any systemic feature in participants with and without a molecular diagnosis (7/8, 87.5% vs 8/9, 88.9%, respectively, p=0.64; Appendix B, Table B9). Overall musculoskeletal and connective tissue features were significantly more commonly reported in participants with a molecular diagnosis (7/8, 87.5% vs 3/9, 33.3%, p=0.007), but there were no significant differences found between any specific musculoskeletal or connective tissue

feature. No other group of systemic features or specific systemic features were significantly different between groups (Appendix B, Table B9).

5.3.2.3 SG-O

Most participants with SG-O had ARS (21/32, 65.6%) and almost all participants had at least one systemic feature (41/45, 91.1%). Compared to other cohorts, the rate of several systemic features was highest among participants with SG-O (Table 5.2). This included joint abnormalities (10/16, 62.5%), hernias (6/32, 18.8%), missing teeth (11/32, 34.4%), cardiac defects (7/32, 21.9%), hydrocephalus (2/32, 6.3%), learning difficulties (5/32, 15.6%), behavioural disorders (3/17, 17.6%), hearing loss (8/32, 25.0%), redundant periumbilical skin (9/32, 28.1%), a BMI indicative of being overweight or obese (11/23, 47.8%) and a mental health issue or mood disorder (9/18, 50.0%). Participants with SG-O also reported the highest rate of anxiety (7/18, 38.9%) and depression (5/18, 27.8%), of whom 3/7 (42.9%) and 3/5 (60.0%) had unilateral or bilateral BCVA <6/60, respectively. Statistical testing for differences in the prevalence of systemic features between individuals with and without a molecular diagnosis was not performed as there were only two individuals without a molecular diagnosis.

5.3.2.4 SG-S

Seven participants had SG-S. Of these individuals, two participants had NF1 with a heterozygous variant in *NF1*. A further two had a clinical diagnosis of SWS, one had Pierre Robin Sequence and one had a clinical diagnosis of Stickler syndrome. An additional participant had a chromosome 7 deletion (del7q11.22q21.11) and a clinical diagnosis of Williams syndrome. Each participant had systemic features consistent with their respective syndrome.

Compared to other cohorts, the rate of several systemic features was highest among participants with SG-S (Table 5.2). This included skeletal abnormalities (4/7, 57.1%), developmental delay (4/7, 57.1%), skin abnormalities (4/7, 57.1%), and small teeth (3/7, 42.9%). Skeletal abnormalities included short stature (reported by one individual each with NF1, Pierre Robin Sequence and William syndrome) and sphenoid bone dysplasia (reported by one individual with NF1). Developmental delay was reported by both individuals with NF1, the individual with Williams syndrome, and the individual with Stickler syndrome. Skin abnormalities included cafe-au-lait spots, reported by both individuals with NF1, and facial haemangiomas, reported by both individuals with SWS. Small teeth were reported by one individual each with NF1, Pierre Robin Sequence and Williams syndrome. The individual with Pierre Robin Sequence was also the only individual to report having had a cleft palate.

Table 5.2. Systemic features per subtype of childhood glaucoma

Characteristic[†]	PCG	JOAG	SG-O	SG-S	Total
Any systemic feature	43/51 (84.3)	15/17 (88.2)	29/32 (90.6)	7/7 (100.0)	**94/107 (87.9)**
Musculoskeletal and connective tissue	33/51 (64.7)	10/17 (58.8)	19/32 (59.4)	5/7 (71.4)	**67/107 (62.6)**
Skeletal abnormality	9/51 (17.6)	1/17 (5.9)	10/32 (31.3)	4/7 (57.1)	**24/107 (22.4)**
Tall stature	2/46 (4.3)	1/14 (7.1)	4/26 (15.4)	0/6 (0.0)	**7/92 (7.6)**
Short stature	4/46 (8.7)	0/14 (0.0)	3/26 (11.5)	3/6 (50.0)	**10/92 (10.9)**
Other skeletal abnormality	3/51 (5.9)	0/17 (0.0)	4/32 (12.5)	2/7 (28.6)	**9/107 (8.4)**
Cleft lip	0/48 (0.0)	0/17 (0.0)	0/16 (0.0)	0/7 (0.0)	**0/87 (0.0)**
Cleft palate	0/49 (0.0)	0/17 (0.0)	0/16 (0.0)	1/7 (14.3)	**1/87 (1.1)**
Joint abnormality	7/51 (13.7)	2/17 (11.8)	10/16 (62.5)	2/7 (28.6)	**21/91 (23.1)**
Joint hypermobility	3/51 (5.9)	0/17 (0.0)	10/16 (62.5)	1/7 (14.3)	**9/91 (9.9)**
Arthritis	3/51 (5.9)	1/17 (5.9)	4/16 (25.0)	0/7 (0.0)	**8/91 (8.8)**
Other joint abnormality	1/51 (2.0)	1/17 (5.9)	1/16 (6.3)	1/7 (14.3)	**4/91 (4.4)**
Hernia	3/51 (5.9)	1/17 (5.9)	6/32 (18.8)	1/7 (14.3)	**11/107 (10.3)**
Bone fracture	23/51 (45.1)	6/17 (35.3)	4/16 (25.0)	1/7 (14.3)	**34/91 (37.4)**
Age at first bone fracture, years (median, IQR)	16.0 (9.0–30.0)	14.5 (11.0–18)	33.5 (23.5–35.5)	-	**16.5 (10.0–32.0)**
No. of bone fractures (median, IQR)	0 (0–1)	0 (0–1)	0 (0–1)	0 (0–0)	**0 (0–1)**
Genitourinary	7/51 (13.7)	4/17 (23.5)	4/16 (25.0)	1/7 (14.3)	**16/91 (17.6)**
Reproductive	4/51 (7.8)	4/17 (23.5)	2/16 (12.5)	0/7 (0.0)	**10/91 (11.0)**
Female sex	4/26 (15.4)	4/9 (44.4)	2/10 (20.0)	0/4 (00.0)	**10/49 (20.4)**
Male sex	0/25 (0.0)	0/8 (0.0)	0/6 (0.0)	0/3 (0.0)	**0/42 (0.0)**
Renal	4/51 (7.8)	0/17 (0.0)	2/16 (12.5)	1/7 (14.3)	**7/91 (7.7)**
Dental features	15/51 (29.4)	5/17 (29.4)	14/32 (43.8)	4/7 (57.1)	**38/107 (35.5)**
Missing teeth	7/51 (13.7)	3/17 (17.4)	11/32 (34.4)	1/7 (14.3)	**22/107 (20.6)**
Extra teeth	5/51 (9.8)	0/17 (0.0)	0/32 (0.0)	1/7 (14.3)	**6/107 (5.6)**
Small teeth	3/51 (5.9)	0/17 (0.0)	8/32 (25.0)	3/7 (42.9)	**14/107 (13.1)**
Abnormally shaped teeth	5/51 (9.8)	3/17 (17.6)	1/32 (3.1)	1/7 (14.3)	**10/107 (9.3)**
Other dental anomaly	5/51 (9.8)	1/17 (5.9)	6/32 (18.8)	2/8 (25.0)	**14/107 (13.1)**
Cardiovascular	1/51 (2.0)	0/17 (0.0)	8/32 (25.0)	1/7 (14.3)	**10/107 (9.3)**
Cardiac defect	1/51 (2.0)	0/17 (0.0)	7/32 (21.9)	1/7 (14.3)	**9/107 (8.4)**
Stroke or ministroke	0/51 (0.0)	0/17 (0.0)	1/32 (3.1)	0/7 (0.0)	**1/107 (0.9)**
Neurodevelopmental	18/51 (35.3)	7/17 (41.2)	15/32 (46.9)	4/7 (57.1)	**44/107 (41.1)**
Hydrocephalus	0/48 (0.0)	0/17 (0.0)	2/32 (6.3)	0/7 (0.0)	**2/103 (1.9)**
Developmental delay	4/49 (8.2)	1/17 (6.7)	4/18 (22.2)	4/7 (57.1)	**13/89 (14.6)**
Learning difficulty	1/51 (2.0)	0/17 (0.0)	5/32 (15.6)	1/7 (14.3)	**7/107 (6.5)**

Behavioural disorder	0/51 (0.0)	0/17 (0.0)	3/17 (17.6)	1/7 (14.3)	**4/92 (4.3)**
Mental health issue or mood disorder	13/51 (25.5)	6/17 (35.3)	9/18 (50.0)	2/7 (28.6)	**30/93 (32.3)**
Anxiety	11/51 (21.6)	4/17 (23.5)	7/18 (38.9)	2/7 (28.6)	**24/93 (25.8)**
Depression	8/51 (15.7)	2/17 (11.8)	5/18 (27.8)	1/7 (14.3)	**16/93 (17.2)**
Other mental health issue or mood disorder	2/51 (3.9)	1/17 (5.9)	1/18 (5.6)	0/7 (0.0)	**4/93 (4.3)**
Other neurodevelopmental	3/51 (5.9)	1/17 (5.9)	1/32 (3.1)	1/7 (14.3)	**6/107 (5.6)**
Gastrointestinal	2/51 (3.9)	0/17 (0.0)	2/32 (6.3)	0/7 (0.0)	**4/107 (3.7)**
Hearing loss	1/51 (2.0)	3/17 (17.6)	8/32 (25.0)	3/7 (42.9)	**15/107 (14.0)**
Hearing aid, yes	1/51 (2.0)	1/17 (5.9)	2/27 (7.4)	2/7 (28.6)	**6/102 (5.9)**
Age at time of hearing aid, years (median, IQR)	-	-	16.0 (4.0–28.0)	8.6 (0.3–17.0)	**22.5 (4.0-63.0)**
Skin abnormalities	1/51 (2.0)	0/17 (0.0)	1/16 (6.3)	4/7 (57.1)	**6/91 (6.6)**
Diabetes	2/51 (3.9)	0/17 (0.0)	1/16 (6.3)	0/7 (0.0)	**3/91 (3.3)**
Type 1	0/51 (0.0)	0/17 (0.0)	0/16 (0.0)	0/7 (0.0)	**0/91 (0.0)**
Type 2	2/51 (3.9)	0/17 (0.0)	1/16 (6.3)	0/7 (0.0)	**3/91 (3.3)**
BMI overweight/obese	10/45 (22.2)	3/14 (21.4)	11/23 (47.8)	1/6 (16.7)	**25/88 (28.4)**
Cancer	2/51 (3.9)	0/17 (0.0)	0/16 (0.0)	0/7 (0.0)	**2/91 (2.2)**
Sex hormone-related cancer‡	0/51 (0.0)	0/17 (0.0)	0/16 (0.0)	0/7 (0.0)	**0/91 (0.0)**
Other cancer	2/51 (3.9)	0/17 (0.0)	0/16 (0.0)	0/7 (0.0)	**2/91 (2.2)**
Redundant periumbilical skin	2/51 (3.9)	0/17 (0.0)	9/32 (28.1)	0/7 (0.0)	**11/107 (10.3)**
Other systemic feature	3/51 (5.9)	0/17 (0.0)	3/32 (9.4)	3/7 (42.9)	**9/107 (8.4)**

PCG: primary congenital glaucoma; JOAG: juvenile open-angle glaucoma; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; SG-S: secondary glaucoma associated with a non-acquired systemic condition; IQR: interquartile range; BMI: body mass index.
Totals for each variable may not equal the total number of participants due to missing data.
†All values presented as n (%) unless otherwise specified.
‡Includes breast, cervical and prostate cancer

5.3.3 Systemic features in primary and secondary non-acquired childhood glaucoma

The presence of systemic features in participants with primary childhood non-acquired glaucoma (i.e., PCG and JOAG) were compared to those with secondary non-acquired childhood glaucoma (i.e., SG-O and SG-S) as summarised in Table 5.3. This comparison was defined on the premise that individuals with primary glaucoma are not known to have systemic associations, whilst individuals with secondary glaucoma frequently have anomalies in several organs and tissues of neural crest cell origin.[125–127,130,132,192,195] A sub-analysis was further performed in individuals who did or did not have a molecular diagnosis (Table 5.3). For completeness, the analysis was repeated but individuals with SG-S were excluded to remove any potential effect of predominantly systemic conditions (Appendix B, Table B10). As the findings were relatively unchanged, the results amongst all individuals with primary and secondary childhood glaucoma are herein presented.

As per Table 5.3, after adjusting for age at survey completion and participant sex, overall reports of systemic features were similar between participants with primary and secondary glaucoma (58/68, 85.3% vs 36/39, 92.3%, respectively, p=0.19). Musculoskeletal or connective tissue features were the most common group of features reported in either cohort (primary glaucoma: 43/68, 63.2% vs secondary glaucoma: 24/39, 61.5%, p=0.86). Regarding specific musculoskeletal or connective tissue features, participants with secondary disease were significantly more likely to report skeletal abnormalities (14/39, 35.9% vs 10/68, 14.7%, p=0.02). Other skeletal abnormalities were also significantly higher in individuals with secondary disease (6/36, 15.4% vs 3/68, 5.0%, p=0.04) and in participants with secondary disease, these included scoliosis (n=2), pelvic bone dysplasia (n=1), sphenoid bone dysplasia (n=1), pectus excavatum (n=1) and a short torso in association with tall stature (n=1). Participants with secondary glaucoma were significantly more likely to report joint abnormalities (12/23, 52.2% vs 9/68, 13.2%, p<0.001) and had a significantly higher prevalence of joint hypermobility (6/23, 26.1% vs 3/68, 4.4%, p=0.02) and arthritis (4/23, 17.4% vs 4/68, 5.9%, p=0.01). Participants with secondary glaucoma were also significantly more likely to report a history of hernias (7/39, 17.9% vs 4/68, 5.9%, p=0.01). Hernias reported by those with secondary glaucoma included umbilical (n=3), hiatal (n=3) and inguinal (n=1). Conversely, bone fractures were almost twice as common in the primary disease cohort compared to the secondary disease cohort, but with additional adjustment for BCVA, this was not a significant finding (29/68, 42.6% vs 5/23, 21.7%, respectively, p=0.11; Table 5.3).

Dental anomalies were more prevalent among participants with secondary glaucoma compared to those with primary glaucoma, although this did not reach significance (18/39, 46.2% vs 20/68, 29.4%, respectively, p=0.05). However, participants with secondary glaucoma were significantly more likely to report missing teeth (12/39, 30.8% vs 10/68, 14.7%, p=0.02) and small teeth (11/39, 28.2% vs 3/68, 4.4%, p<0.001). Cardiovascular features were significantly more common among participants with secondary glaucoma (9/39, 23.1% vs 1/68, 1.5%, p<0.001) and there was a higher prevalence of cardiac defects (8/39, 20.5% vs 1/68, 1.5%, p=0.001). Among those with secondary glaucoma, cardiac defects included atrial septal defects (n=2), mitral valve disease (n=3), supravalvular aortic stenosis (n=1), tetralogy of Fallot (n=1) and Wolff-Parkinson-White syndrome (n=1).

Neurodevelopmental features were not significantly different between the two cohorts (secondary glaucoma: 19/39, 48.7% vs primary glaucoma: 25/68, 36.8%, p=0.24), although participants with secondary glaucoma were significantly more likely to report having had developmental delays (8/25, 32.0% vs 5/64, 7.8%, p=0.007), learning difficulties (6/39, 15.4% vs 1/68, 1.5%, p=0.01) and behavioural disorders (4/24, 16.7% vs 0/68, 0.0%, p=0.002). Other features that were significantly more common in the secondary glaucoma cohort included hearing loss (11/39, 28.2% vs 4/68, 5.9%, p<0.001), a BMI

classified as overweight or obese (12/29, 41.1% vs 13/59, 22.0%, p=0.02), redundant periumbilical skin (9/39, 23.1% vs 2/68, 2.9%, p<0.001) and skin abnormalities (5/23, 21.7% vs 1/68, 1.5%, p=0.008). Among individuals with secondary glaucoma, skin abnormalities included cafe-au-lait spots associated with NF1 in two individuals each, facial haemangiomas associated with SWS in two individuals each and chronic wounds (impaired skin healing) in one individual. There were no significant differences in reports of any other systemic feature between groups (Table 5.3).

5.3.3.1 Systemic features in primary and secondary non-acquired childhood glaucoma with a molecular diagnosis

As identified in Chapter 3,[386] participants with SG-O and SG-S may be misdiagnosed as PCG or JOAG prior to genetic testing. A sub-analysis was therefore performed on participants who had a molecular diagnosis and a confirmed clinical diagnosis of primary or secondary glaucoma (Table 5.3). The differences in the prevalence of groups of systemic features between cohorts remained similar and are illustrated in Figure 5.1. Only cardiovascular features were significantly more common amongst participants with secondary glaucoma (9/33, 27.3% vs 1/32, 3.1%, p=0.02; Figure 5.1). Significant differences in the prevalence of several specific systemic features also remained after adjusting for age at survey completion and participant sex. These are illustrated in Figure 5.2 and are detailed in Table 5.3. However, participants with secondary glaucoma were no longer significantly more likely to report skeletal abnormalities (p=0.21), hernias (p=0.22), missing teeth (p=0.06), learning difficulties (p=0.16), behavioural disorders (p=0.06) or a BMI indicative of being overweight or obese (p=0.45) than participants with primary glaucoma. Participants with primary glaucoma were additionally found to be significantly more likely to report having abnormally shaped teeth than those with secondary glaucoma (5/32, 15.6% vs 1/33, 3.0%, p=0.046, Figure 5.2). Non-significant differences in other specific systemic features between cohorts with a molecular diagnosis are further provided in Table 5.3.

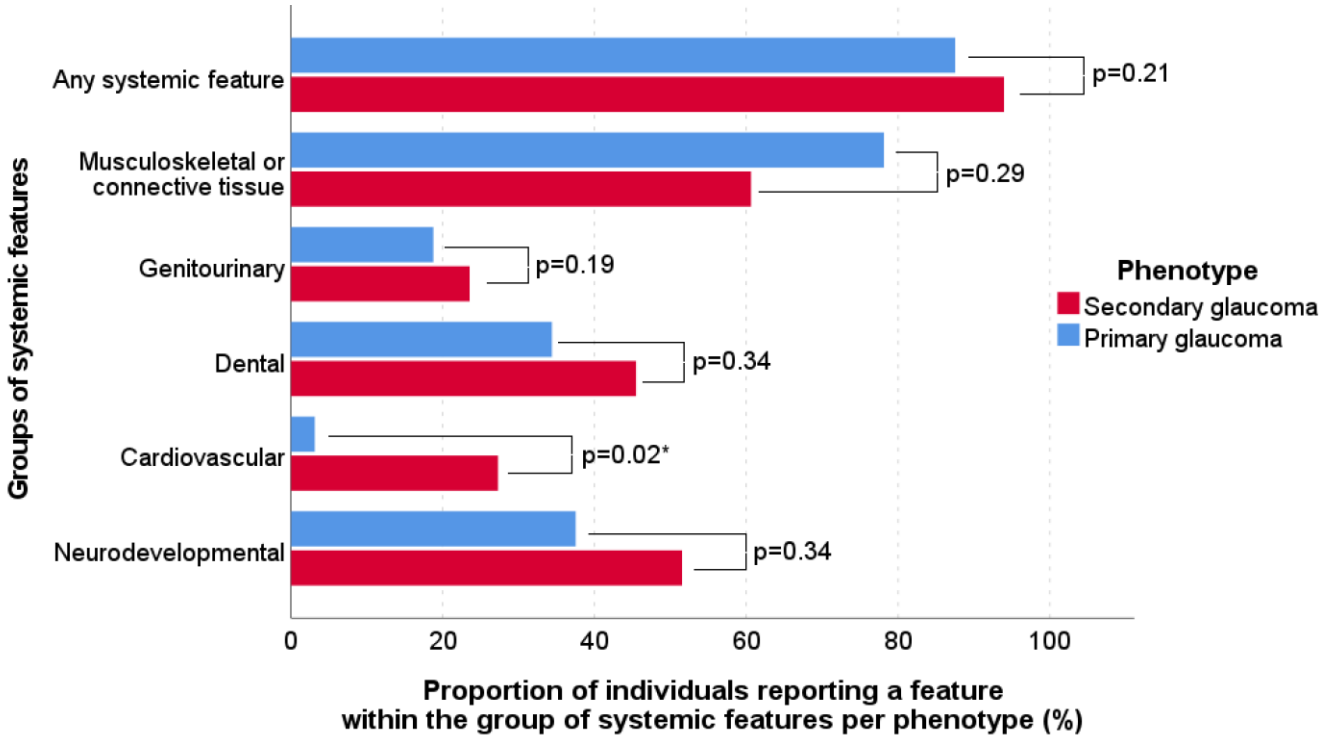

Figure 5.1. The relative proportion of groups of systemic features between participants with primary glaucoma and a molecular diagnosis and secondary glaucoma with a molecular diagnosis

Participants with primary glaucoma included those with PCG and JOAG and secondary glaucoma included those with SG-O and SG-S. Full details of the relative proportion of systemic features per cohort are reported in Table 5.3.

*Indicates statistical significance ($p<0.05$). P values presented were age- and sex-adjusted.

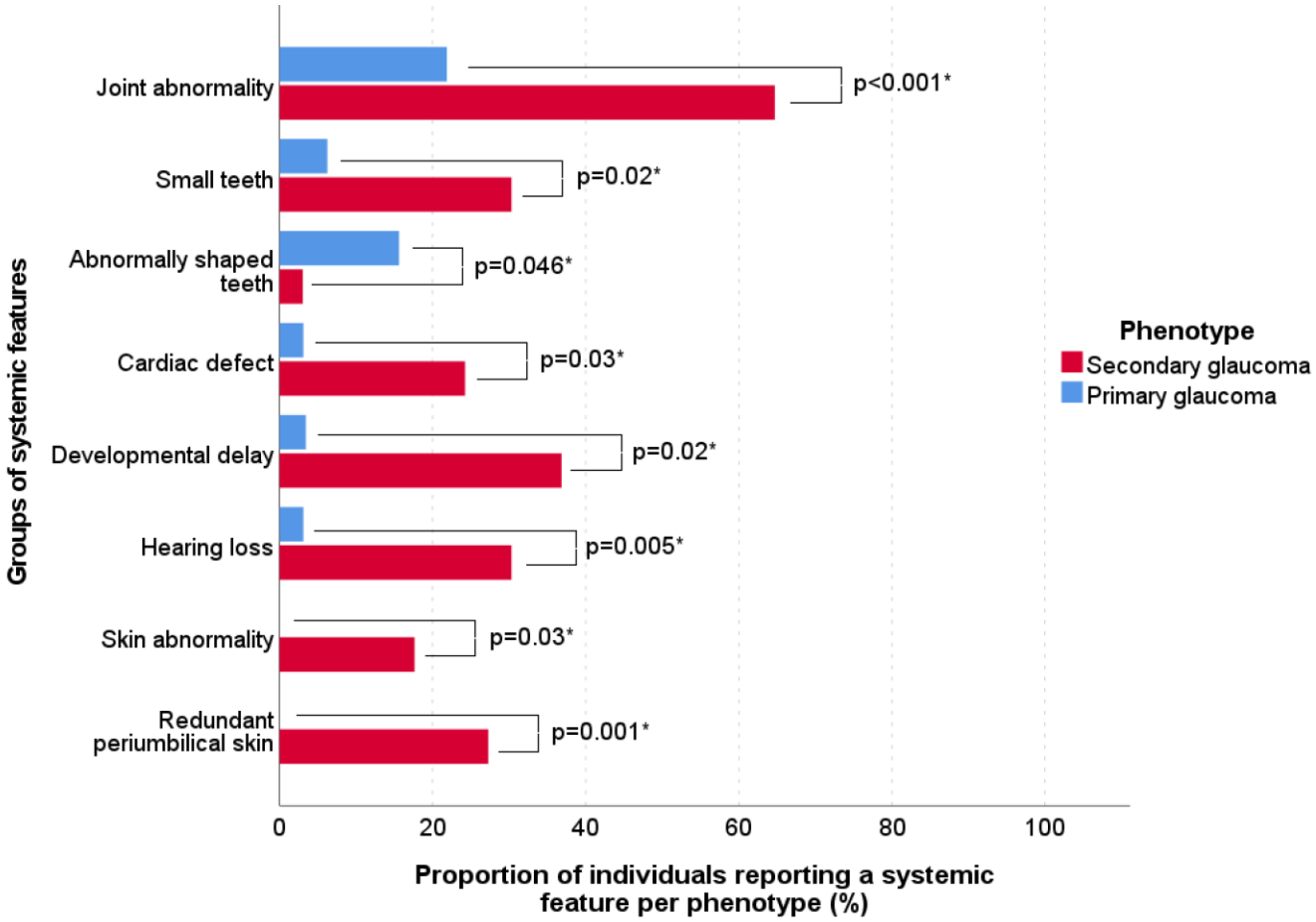

Figure 5.2. Significant differences in the relative proportion of specific systemic features between participants with primary glaucoma and a molecular diagnosis and those with secondary glaucoma and a molecular diagnosis

Participants with primary glaucoma included those with PCG and JOAG and secondary glaucoma included those with SG-O and SG-S. Full details of the relative proportion of systemic features per cohort are reported in Table 5.3.

*Indicates statistical significance (p<0.05). P values presented were age- and sex-adjusted.

5.3.3.2 Systemic features in primary and secondary non-acquired childhood glaucoma without a molecular diagnosis

After correcting for age at survey completion and participant sex, the overall prevalence of any systemic feature among participants with primary or secondary glaucoma without a molecular diagnosis was similar (30/36, 83.3% vs 5/6, 83.3%, respectively, p=0.86). As per Table 5.3, only two systemic features were significantly higher in participants with secondary glaucoma without a molecular diagnosis: skin abnormalities (1/25, 4.0% vs 1/36, 2.8%, p=0.04) and a BMI classified as overweight or obese (2/5, 40.0% vs 2/31, 6.5%, p=0.02).

Table 5.3. Differences in systemic features between individuals with primary non-acquired childhood glaucoma (PCG or JOAG) compared to individuals with secondary non-acquired childhood glaucoma (SG-O or SG-S).

	Combined molecular and non-molecular diagnosis				Molecular diagnosis only				No molecular diagnosis			
Characteristic†	**Primary glaucoma**	**Secondary glaucoma**	**p-value**	**Adjusted p-value‡**	**Primary glaucoma**	**Secondary glaucoma**	**p-value**	**Adjusted p value‡**	**Primary glaucoma**	**Secondary glaucoma**	**p-value**	**Adjusted p-value‡**
Any systemic feature	58/68 (85.3)	36/39 (92.3)	0.37[c]	0.19	28/32 (87.5)	31/33 (93.9)	0.43[c]	0.21	30/36 (83.3)	5/6 (83.3)	1.0[c]	0.86
Musculoskeletal and connective tissue	43/68 (63.2)	24/39 (61.5)	1.0[b]	0.86	25/32 (87.1)	20/33 (60.6)	0.21[b]	0.29	18/36 (50.0)	4/6 (67.7)	0.67[b]	0.32
Skeletal abnormality	10/68 (14.7)	14/39 (35.9)	**0.02[b]**	**0.02**	6/32 (18.8)	12/32 (36.4)	0.19[b]	0.21	4/36 (11.1)	2/6 (33.3)	0.20[b]	0.29
Tall stature	3/60 (5.0)	4/32 (12.5)	0.23[c]	0.31	3/28 (10.7)	4/27 (14.8)	0.71[c]	0.78	0/32 (0.0)	0/5 (0.0)	-	-
Short stature	4/60 (6.7)	6/32 (18.8)	0.09[c]	0.16	2/28 (7.1)	4/27 (14.8)	0.42[c]	0.65	2/32 (6.3)	2/5 (40.0)	0.08[c]	0.12
Other skeletal abnormality	3/68 (5.0)	6/39 (15.4)	0.07[c]	**0.04**	1/32 (3.1)	6/33 (18.2)	0.11[c]	**0.04**	2/36 (5.6)	0/6 (0.0)	1.0[c]	1.0
Cleft lip	0/64 (0.0)	0/23 (0.0)	-	-	0/28 (0.0)	0/17 (0.0)	-	-	0/36 (0.0)	0/6 (0.0)	-	-
Cleft palate	0/65 (0.0)	1/22 (4.5)	0.25[c]	0.21	0/29 (0.0)	0/16 (0.0)	-	-	0/36 (0.0)	1/6 (16.7)	0.14[c]	0.49
Joint abnormality	9/68 (13.2)	12/23 (52.2)	**<0.001[b]**	**<0.001**	7/32 (21.9)	11/17 (64.7)	**0.008[b]**	**<0.001**	2/36 (5.6)	1/6 (16.7)	0.38[b]	0.13
Joint hypermobility	3/68 (4.4)	6/23 (26.1)	**0.007[c]**	**0.02**	2/32 (6.3)	6/17 (35.3)	**0.02[c]**	**0.04**	1/36 (2.8)	0/6 (0.0)	1.0[c]	0.87
Arthritis	4/68 (5.9)	4/23 (17.4)	0.11[c]	**0.01**	3/32 (9.4)	3/17 (17.6)	0.41[c]	0.10	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.11
Other joint abnormality	2/68 (2.9)	2/23 (8.7)	0.26[c]	0.21	2/32 (6.3)	2/17 (11.8)	0.60[c]	0.39	0/36 (0.0)	0/6 (0.0)	-	0.49
Hernia	4/68 (5.9)	7/39 (17.9)	0.09[b]	**0.01**	3/32 (9.4)	6/33 (18.2)	0.48[c]	0.22	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.11
Bone fracture	29/68 (42.6)	5/23 (21.7)	0.12[b]	0.11[1]	15/32 (46.9)	4/17 (23.5)	0.20[b]	0.19[1]	14/36 (38.9)	1/6 (16.7)	0.40[c]	0.77[1]
Age at first bone fracture, years (median, IQR)	16.0 (10.0–28.0)	32.0 (15.0–35.0)	1.0[a]	0.16[1]	16.0 (11.0–30.0)	33.5 (23.5–35.5)	0.30[a]	0.08[1]	16.5 (6.0–23.0)	-	1.0[a]	0.08[1]
No. of bone fractures (median, IQR)	0 (0–1)	0 (0–0)	0.12[a]	0.84[1]	0 (0–1)	0 (0–0)	0.19[d]	0.87[1]	0 (0–1)	0 (0–0)	0.55[a]	0.83[1]
Genitourinary	11/68 (16.2)	5/23 (21.7)	0.54[c]	0.29	6/32 (18.2)	4/17 (23.5)	0.72[c]	0.19	5/36 (13.9)	1/6 (16.7)	1.0[c]	0.96
Reproductive	8/68 (11.8)	2/23 (8.7)	1.0[c]	0.85	4/32 (12.5)	2/17 (11.8)	1.0[c]	0.52	4/36 (11.1)	0/6 (0.0)	1.0[c]	0.38

Female sex	8/35 (22.9)	8/35 (22.9)	0.70[c]	-	4/21 (19.0)	2/10 (20.0)	1.0[c]	-	4/14 (28.6)	0/4 (0.0)	0.52[c]	-
Male sex	0/33 (0.0)	0/9 (0.0)	-	-	0/11 (0.0)	0/7 (0.0)	-	-	0/22 (0.0)	0/2 (0.0)	-	-
Renal	4/68 (5.9)	3/23 (13.0)	0.36[c]	0.14	3/32 (9.4)	2/17 (11.8)	1.0[c]	0.41	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.16
Dental anomalies	20/68 (29.4)	18/39 (46.2)	0.13[b]	0.05	11/32 (34.4)	15/33 (45.5)	0.51[b]	0.34	9/36 (25.0)	3/6 (50.0)	0.33[c]	0.29
Missing teeth	10/68 (14.7)	12/39 (30.8)	0.08[b]	**0.02**	4/32 (12.5)	10/33 (30.3)	0.15[b]	0.06	6/36 (16.7)	2/6 (33.3)	0.32[c]	0.34
Extra teeth	5/68 (7.4)	1/39 (2.6)	0.41[c]	0.42	4/32 (12.5)	0/33 (0.0)	0.05[c]	0.12	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.18
Small teeth	3/68 (4.4)	11/39 (28.2)	**0.001[b]**	**<0.001**	2/32 (6.3)	10/33 (30.3)	**0.03[b]**	**0.02**	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.18
Abnormally shaped teeth	8/68 (11.8)	2/39 (5.1)	0.32[c]	0.29	5/32 (15.6)	1/33 (3.0)	0.11[c]	**0.046**	3/36 (8.3)	1/6 (16.7)	0.47[c]	0.59
Other dental anomaly	6/68 (8.8)	8/39 (20.5)	0.15[b]	0.11	3/32 (9.4)	7/33 (21.2)	0.30[c]	0.20	3/36 (8.3)	1/6 (16.7)	0.47[c]	0.63
Cardiovascular	1/68 (1.5)	9/39 (23.1)	**<0.001[c]**	**<0.001**	1/32 (3.1)	9/33 (27.3)	**0.01[c]**	**0.02**	0/36 (0.0)	0/6 (0.0)	-	-
Cardiac defect	1/68 (1.5)	8/39 (20.5)	**0.001[c]**	**0.001**	1/32 (3.1)	8/33 (24.2)	**0.03[c]**	**0.03**	0/36 (0.0)	0/6 (0.0)	-	-
Stroke or ministroke	0/68 (0.0)	1/39 (2.6)	0.36[c]	0.27	0/32 (0.0)	1/33 (3.0)	1.0[c]	0.59	0/36 (0.0)	0/6 (0.0)	-	-
Neurodevelopmental	25/68 (36.8)	19/39 (48.7)	0.32[b]	0.24	12/32 (37.5)	17/33 (51.5)	0.38[b]	0.34	13/36 (36.1)	2/6 (33.3)	1.0[c]	0.95
Hydrocephalus	0/64 (0.0)	2/39 (5.1)	0.14[c]	0.12	0/28 (0.0)	2/33 (6.1)	0.50[c]	0.50	0/36 (0.0)	0/6 (0.0)	-	-
Developmental delay	5/64 (7.8)	8/25 (32.0)	**0.007[c]**	**0.007**	1/29 (3.4)	7/19 (36.8)	**0.004[c]**	**0.02**	4/35 (11.4)	1/6 (16.7)	0.57[c]	0.36
Learning difficulty	1/68 (1.5)	6/39 (15.4)	**0.009[c]**	**0.01**	1/32 (3.1)	6/33 (18.2)	0.11[c]	0.16	0/36 (0.0)	0/6 (0.0)	-	-
Behavioural disorder	0/68 (0.0)	4/24 (16.7)	**0.004[c]**	**0.002**	0/32 (0.0)	3/18 (16.7)	**0.04[c]**	0.06	0/36 (0.0)	1/6 (16.7)	0.14[c]	0.08
Mental health issue or mood disorder	19/68 (27.9)	11/25 (44.0)	0.22[b]	0.11	11/32 (34.4)	10/19 (52.6)	0.25[c]	0.16	8/36 (22.2)	1/6 (16.7)	1.0[c]	0.92
Anxiety	15/68 (22.1)	9/25 (36.0)	0.27[b]	0.15	10/32 (31.3)	8/19 (42.1)	0.63[b]	0.48	5/36 (13.9)	1/6 (16.7)	1.0[cc]	0.61
Depression	10/68 (14.7)	6/25 (24.0)	0.36[c]	0.15	6/32 (18.8)	5/19 (26.3)	0.73[c]	0.28	4/36 (11.1)	1/6 (16.7)	0.58[c]	0.58
Other mental health issue or mood disorder	3/68 (4.4)	1/25 (4.0)	1.0[c]	0.94	2/32 (6.3)	1/19 (5.3)	1.0[c]	0.94	1/36 (2.8)	0/6 (0.0)	1.0[c]	0.98
Other neurodevelopmental	4/68 (5.9)	2/39 (5.1)	1.0[c]	0.91	2/32 (6.3)	2/33 (6.1)	1.0[c]	0.71	2/36 (5.6)	0/6 (0.0)	1.0[c]	0.94
Gastrointestinal	2/68 (2.9)	2/39 (5.1)	0.51[c]	0.38	1/32 (3.1)	2/33 (6.1)	1.0[c]	0.49	1/36 (2.8)	0/6 (0.0)	1.0[c]	0.97

Hearing loss	4/68 (5.9)	11/39 (28.2)	**0.004[b]**	**<0.001**	1/32 (3.1)	10/33 (30.3)	**0.01[c]**	**0.005**	3/36 (8.3)	1/6 (16.7)	0.47[c]	0.24
Hearing aid, yes	2/68 (2.9)	4/34 (11.8)	0.09[c]	0.05	1/32 (3.1)	3/28 (10.7)	0.33[c]	0.21	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.14
Age at time of hearing aid, years (median, IQR)	65.5 (63.0–68.0)	10.5 (2.1–22.5)	0.40[a]	-	-	4.0 (2.1–16.0)	-	-	-	-	-	-
Skin abnormalities	1/68 (1.5)	5/23 (21.7)	**0.004[c]**	**0.008**	0/32 (0.0)	3/17 (17.6)	**0.04[c]**	**0.03**	1/36 (2.8)	1/25 (4.0)	**0.049[c]**	**0.04**
Diabetes	2/68 (2.9)	1/23 (4.3)	1.0[c]	0.60	2/32 (6.3)	1/17 (5.9)	1.0[c]	0.56	0/36 (0.0)	0/6 (0.0)	-	-
Type 1	0/68 (0.0)	0/23 (0.0)	-	-	0/32 (0.0)	0/17 (0.0)	-	-	0/36 (0.0)	0/6 (0.0)	-	-
Type 2	2/68 (2.9)	1/23 (4.3)	1.0[c]	0.60	2/32 (6.3)	1/17 (5.9)	1.0[c]	0.56	0/36 (0.0)	0/6 (0.0)	-	-
BMI overweight/obese	13/59 (22.0)	12/29 (41.4)	0.10[b]	**0.02**	11/28 (39.3)	10/24 (41.7)	1.0[b]	0.45	2/31 (6.5)	2/5 (40.0)	0.08[b]	**0.02**
Cancer	2/68 (2.9)	0/23 (0.0)	1.0[c]	0.84	1/32 (3.1)	0/17 (0.0)	1.0[c]	0.91	1/36 (2.8)	0/6 (0.0)	1.0[c]	0.55
Sex hormone-related cancer[§]	0/68 (0.0)	0/23 (0.0)	-	-	0/32 (0.0)	0/17 (0.0)	-	-	0/36 (0.0)	0/6 (0.0)	1.0[c]	0.49
Other cancer	2/68 (2.9)	0/23 (0.0)	1.0[c]	0.84	1/32 (3.1)	0/17 (0.0)	1.0[c]	0.91	1/36 (2.8)	0/6 (0.0)	-	-
Redundant periumbilical skin	2/68 (2.9)	9/39 (23.1)	**0.002[c]**	**0.001**	0/32 (0.0)	9/33 (27.3)	**0.002[c]**	**0.001**	2/36 (5.6)	0/6 (0.0)	1.0[c]	0.70
Other systemic feature	3/68 (4.4)	6/39 (15.4)	0.07[c]	0.07	2/32 (6.3)	5/33 (15.2)	0.43[c]	0.44	1/36 (2.8)	1/6 (16.7)	0.27[c]	0.15

IQR: interquartile range; BMI: body mass index
Totals for each variable may not equal the total number of participants due to missing data.
Bold values indicate statistical significance (p<0.05)
[a]Median test, [b]Chi square with continuity correction, [c]Fisher exact test, [d]Mann-Whitney U test
[†]All values presented as n (%) unless otherwise specified.
[‡]All values adjusted for participant age at survey completion and sex.
[§]Includes breast, cervical and prostate cancer
[1]P values have been further adjusted for unilateral or bilateral BCVA <6/60

5.3.4 Systemic features per genetic cohort

Survey responses amongst participants with biallelic pathogenic variants in *CYP1B1* or *CPAMD8*, or heterozygous pathogenic variants in *MYOC, TEK*, *FOXC1, PITX2* or *PAX6* were further analysed to generate hypotheses regarding potential systemic associations with specific molecular diagnoses. This included an analysis of 115/162 (71.0%) total participants with a molecular diagnosis as defined above. The demographic characteristics and the ocular phenotype of each genetic cohort are provided in Table 5.4. The median age amongst all participants was 45.6 years (IQR: 25.0–65.4) and 71/115 (61.7%) were female. Participants with a *TEK* variant were the youngest at the time of survey completion (median: 18.7 years [IQR: 12.9–48.3]) whilst participants with a *MYOC* variant were the oldest cohort at the time of survey completion (median: 68.0 years [IQR: 51.7–74.8]). Participants with biallelic *CYP1B1* variants reported the highest prevalence of unilateral or bilateral BCVA <6/60 (11/15, 73.3%; Table 5.4). The majority of participants had primary disease (67/115, 58.3%) while no participant had SG-S.

The prevalence of specific systemic features was examined within each genetic cohort and are presented in Table 5.5. Prevalence rates within each genetic cohort were also considered with respect to the overall prevalence of the specific systemic feature across all participants with a molecular diagnosis. Figure 5.3 illustrates the prevalence per genetic cohort with respect to the total prevalence of each systemic feature. For brevity, only the most notable findings are detailed below.

Table 5.4. Demographic and ocular phenotypic characteristics per genetic cohort

Characteristic[†]	*CYP1B1*	*TEK*	*MYOC*	*CPAMD8*	*FOXC1*	*PITX2*	*PAX6*	Total
Age at survey completion, years (median, IQR)	37.1 (23.3–52.8)	18.7 (12.9-48.3)	68.0 (51.7–74.8)	23.1 (10.2–26.0)	38.6 (13.8–49.6)	41.2 (25.7–50.6)	32.1 (32.1–56.9)	**45.6 (25.0–65.4)**
Female sex	12/16 (75.0)	7/12 (58.3)	26/38 (68.4)	3/6 (50.0)	14/25 (56.0)	5/13 (38.5)	4/5 (80.0)	**71/115 (61.7)**
European ancestry	12/16 (75.0)	12/12 (100.0)	36/38 (94.7)	6/6 (100.0)	22/25 (88.0)	13/13 (100.0)	5/5 (100.0)	**106/115 (92.2)**
Probands	13/16 (81.3)	8/12 (66.7)	31/38 (81.6)	5/6 (83.3)	15/25 (60.0)	9/13 (69.2)	3/5 (60.0)	**84/115 (73.0)**
Primary disease	15/16 (93.8)	12/12 (100.0)	34/38 (89.5)	0/6 (0.0)	1/25 (4.0)	0/13 (0.0)	0/0 (0.0)	**67/115 (58.3)**
PCG	12/16 (75.0)	11/12 (91.7)	0/38 (0.0)	0/6 (0.0)	0/25 (0.0)	0/13 (0.0)	0/0 (0.0)	**23/115 (20.0)**
JOAG (childhood onset)	2/16 (12.5)	0/12 (0.0)	6/38 (15.8)	0/6 (0.0)	0/25 (0.0)	0/13 (0.0)	0/0 (0.0)	**8/115 (7.0)**
JOAG (early-onset)	0/16 (0.0)	0/12 (0.0)	6/38 (15.8)	0/6 (0.0)	1/25 (4.0)	0/13 (0.0)	0/0 (0.0)	**7/115 (6.1)**
POAG	1/16 (6.3)	0/12 (0.0)	22/38 (57.9)	0/6 (0.0)	0/25 (0.0)	0/13 (0.0)	0/0 (0.0)	**23/115 (20.0)**
OHT	0/16 (0.0)	1/12 (8.3)	0/38 (0.0)	0/6 (0.0)	0/25 (0.0)	0/13 (0.0)	0/0 (0.0)	**1/115 (0.9)**
Secondary disease	1/16 (6.3)	0/12 (0.0)	0/38 (0.0)	5/6 (83.3)	23/25 (92.0)	13/13 (100.0)	5/5 (100.0)	**43/115 (37.4)**
SG-O (childhood onset)	1/16 (6.3)	0/12 (0.0)	0/38 (0.0)	5/6 (83.3)	14/25 (56.0)	7/13 (53.8)	3/5 (60.0)	**30/115 (26.1)**
SG-O (early-onset)	0/16 (0.0)	0/12 (0.0)	0/38 (0.0)	0/6 (0.0)	3/25 (12.0)	2/13 (15.4)	1/5 (20.0)	**6/115 (5.2)**
ASD only	0/16 (0.0)	0/12 (0.0)	0/38 (0.0)	0/6 (0.0)	6/25 (24.0)	4/13 (30.8)	1/5 (20.0)	**11/115 (9.6)**
Unaffected	0/16 (0.0)	0/0 (0.0)	4/38 (10.5)	1/6 (16.7)	1/25 (4.0)	0/13 (0.0)	0/0 (0.0)	**5/115 (4.3)**
Unilateral or bilateral BCVA <6/60	11/15 (73.3)	4/12 (33.3)	1/38 (2.6)	1/6 (16.7)	6/24 (25.0)	4/13 (30.8)	5/5 (100.0)	**32/113 (28.3)**

IQR: interquartile range; PCG: primary congenital glaucoma; JOAG: juvenile open-angle glaucoma; POAG: primary open-angle glaucoma; OHT: ocular hypertension; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; BCVA: best-corrected visual acuity

Totals for each variable may not equal the total number of participants due to missing data.

[†]All values presented as n (%) unless otherwise specified.

5.3.4.1 CYP1B1

Systemic features were reported by 15/16 (93.8%) participants. Participants with biallelic *CYP1B1* variants reported a higher rate of a mental health or mood disorder compared to the overall cohort (9/16, 53.6% vs 27/86, 31.4%, respectively; Figure 5.3). A history of anxiety (7/16, 43.8%) and depression (5/16, 31.3%) were recorded, of whom 4/7 (57.1%) and 4/5 (80.0%) had unilateral or bilateral BCVA <6/60, respectively. Few dental features were also highest in the *CYP1B1* cohort compared to any other single genetic cohort and the overall cohort. These included abnormally shaped teeth (*CYP1B1*: 5/16, 31.3% vs overall: 8/115, 7.0%) and extra teeth (*CYP1B1*: 3/16, 18.8% vs overall: 5/115, 4.3%; Figure 5.3 and Table 5.5). Genitourinary features were reported by 7/16 (43.8%) participants, with reproductive issues being more often reported in the *CYP1B1* cohort than the overall cohort (5/16, 31.3% vs 9/85, 10.6%, respectively; Figure 5.3). All these individuals were female (Table 5.5). One female each reported a uterine prolapse, uterine fibroid, ovarian cysts, polycystic ovary syndrome and having had a miscarriage. Short stature was also measured most frequently in this cohort compared to other genetic cohorts and overall (*CYP1B1*: 3/13, 21.4% vs overall: 7/102, 6.9%; Table 5.5).

5.3.4.2 TEK

Among participants with a *TEK* variant, 10/12 (83.3%) reported at least one systemic feature. A history of bone fractures was highest among participants with *TEK* variants compared to any other single genetic cohort and the overall cohort (*TEK*: 7/12, 58.3% vs overall: 36/84, 42.9%; Figure 5.3 and Table 5.5). The median age at first bone fracture was 16.0 years (IQR: 12.5–41.0 years). Participants who reported a bone fracture were older than respondents who did not report a bone fracture, although this was not statistically significant (median [IQR]: 35.2 years [18.7–56.3] vs 10.8 years [9.4–15.5], respectively, p=0.24). Between those who did or did not report a bone fracture, there was no difference in female sex (4/7, 57.1% vs 3/5, 60%, p=1.0). Participants with a bone fracture were more likely to have unilateral or bilateral BCVA <6/60 than participants who did not report a bone fracture, but this was not statistically significant (4/7, 57.1% vs 0/5, 0.0%, p=0.08). One individual with a *TEK* variant, who had OHT, was also the only individual to report having had a cleft lip.

5.3.4.3 MYOC

A systemic feature was reported by 33/38 (86.8%) participants. Compared to the overall cohort, the *MYOC* cohort reported a higher rate of joint abnormalities (*MYOC*: 21/38, 55.3% vs overall: 36/84, 42.9%; Figure 5.3), bone fractures (*MYOC*: 18/38, 47.4% vs overall: 36/84, 42.9%, Figure 5.3) and arthritis (*MYOC*: 19/38, 50.0% vs overall: 24/84, 28.6%; Table 5.5). In addition, reports of cancer were

higher in participants with *MYOC* variants compared to any other single genetic cohort and the overall cohort (*MYOC*: 6/38, 26.3% vs overall: 14/86, 16.3%; Figure 5.3). Within the *MYOC* cohort, those who reported having had cancer were older than participants who had not had cancer, although this was not statistically significant (median [IQR]: 76.8 years [69.0–83.0] vs 65.3 years [44.9–70.9], respectively, p=0.08). Because participants in the *MYOC* cohort were the oldest compared to the other genetic cohorts (Table 5.5), some of the features reported such as arthritis, bone fractures or cancer may be related to age.

5.3.4.4 CPAMD8

At least one systemic feature was reported by all participants with biallelic *CPAMD8* variants (6/6, 100.0%). One individual had a previous clinical diagnosis of Stickler syndrome and history of retinal detachment. The *CPAMD8* cohort reported the highest rate of skeletal abnormalities amongst all genetic cohorts (3/6, 50.0%; Figure 5.3). This was due to the prevalence of tall stature, which was higher in the *CPAMD8* cohort compared to the overall cohort (2/6, 33.3% vs 8/101, 7.9%, respectively) and any other single genetic cohort (Table 5.5). Compared to other genetic cohorts and the overall cohort, the *CPAMD8* cohort also recorded the highest rate of joint abnormalities (*CPAMD8*: 4/6, 66.7% vs overall: 36/84, 42.9%; Figure 5.3), joint hypermobility (*CPAMD8*: 4/6, 66.7% vs overall: 9/84, 10.7%; Table 5.5) and hearing loss (*CPAMD8*: 2/6, 33.3% vs overall: 21/115, 18.3%; Figure 5.3).

5.3.4.5 FOXC1

Six participants with a heterozygous *FOXC1* variant included in the study completed all survey questions whilst responses from two previously published studies were further included for 19 participants.[130,132] The majority of participants had ARS (23/25, 92.0%) and systemic features were recorded by 19/25 (76.0%) participants. Compared to any other single genetic cohort and the overall cohort, the *FOXC1* cohort reported the highest rate of hydrocephalus (*FOXC1*: 3/25, 12.0% vs overall: 3/111, 2.7%), learning difficulties (*FOXC1*: 6/25, 24.0% vs overall: 10/114, 8.8%) and behavioural disorders (*FOXC1*: 1/7, 14.3% vs overall: 3/85, 3.5%), as illustrated in Figure 5.3. Mental health issues or mood disorders were also higher in the *FOXC1* cohort than the overall cohort (3/6, 50.0% vs 27/86, 31.4%, respectively), with anxiety (3/6, 50.0%) and depression (2/6, 33.3%) being the most common mental health issues. The same participant with unilateral BCVA <6/60 reported having anxiety and depression whilst none had bilateral BCVA <6/60. Cardiovascular features were also highest amongst this cohort compared to other genetic cohorts (10/25, 40.0%; Table 5.5). Cardiac defects were higher in the *FOXC1* cohort compared to other genetic cohorts and the overall cohort (*FOXC1*: 9/25, 36.0% vs overall: 13/115, 11.3%; Figure 5.3) and included atrial septal defects (n=4), mitral valve disease (n=3), pulmonary

stenosis (n=1) and tetralogy of Fallot (n=1). The rate of hearing loss was also higher in the *FOXC1* cohort compared to the overall cohort (8/25, 32.0% vs 21/115, 18.3%, respectively, Figure 5.3 and Table 5.5).

5.3.4.6 PITX2

One participant with a *PITX2* variant completed all survey questions whilst responses from two previously published studies were further included for 12 participants.[130,132] All participants had ARS (13/13, 100.0%) and all reported at least one systemic feature (13/13, 100.0%). Participants with *PITX2* variants reported the highest rate of dental features (13/13, 100.0%; Table 5.5). Compared to other genetic cohorts and the overall cohort, the *PITX2* cohort had the highest rate of missing teeth (*PITX2*: 11/13, 84.6% vs overall: 27/115, 23.5%) and small teeth (*PITX2*: 12/13, 92.3% vs overall: 18/15, 15.7%) as illustrated in Figure 5.3. Several other features were most frequently reported amongst those with a *PITX2* variant compared to other single genetic cohorts and the overall cohort (Figure 5.3; Table 5.5). These included a BMI classified as overweight or obese (*PITX2*: 8/12, 66.7% vs overall: 38/96, 39.6%), redundant periumbilical skin (*PITX2*: 13/13, 100.0% vs overall: 18/115, 15.7%), gastrointestinal features (*PITX2:* 2/13, 15.4% vs overall: 4/115, 3.5%) and hernias (*PITX2*: 6/13, 46.2% vs overall: 12/115, 10.4%). Gastrointestinal features included an imperforate anus (n=1) and anal stenosis (n=1) while the types of hernias reported included umbilical hernias (n=4) and hiatal hernias (n=2). Reports of learning difficulties were also higher in the *PITX2* cohort compared to the overall cohort (2/12, 15.4% vs 10/114, 8.8%, respectively; Figure 5.3 and Table 5.5).

5.3.4.7 PAX6

All participants with a *PAX6* variant had aniridia and at least one systemic feature (5/5, 100.0%). All reported a neurodevelopmental feature (5/5, 100.0%; Table 5.5) with 2/5 (40.0%) reporting developmental delays and 3/5 (60.0%) reporting a history of a mental health or mood disorder. Of the latter, 1/5 (20.0%) reported a history of anxiety and 2/5 (40.0%) had depression. All individuals had bilateral BCVA <6/60. Meanwhile, 2/5 (40.0%) indicated they had type 2 diabetes. The significance of these findings was limited by the small number of participants in this cohort.

Table 5.5. Prevalence of all systemic features per genetic cohort

Characteristic[†]	*CYP1B1*	*TEK*	*MYOC*	*CPAMD8*	*FOXC1*[‡]	*PITX2*[‡]	*PAX6*	Total
Any systemic feature	15/16 (93.8)	10/12 (83.3)	33/38 (86.8)	6/6 (100.0)	19/25 (76.0)	13/13 (100.0)	5/5 (100.0)	**101/115 (87.8)**
Musculoskeletal and connective tissue	12/16 (75.0)	10/12 (83.3)	30/38 (78.9)	5/6 (83.3)	8/25 (32.0)	7/13 (53.8)	3/5 (60.0)	**75/115 (65.2)**
Skeletal abnormality	4/16 (25.0)	2/12 (16.7)	5/38 (13.2)	3/6 (50.0)	6/25 (24.0)	3/13 (23.1)	0/5 (0.0)	**23/115 (20.0)**
Tall stature	0/13 (0.0)	2/11 (18.2)	2/37 (5.4)	2/6 (33.3)	1/16 (6.3)	1/13 (7.7)	0/5 (0.0)	**8/101 (7.9)**
Short stature	3/13 (21.4)	0/11 (0.0)	1/37 (2.7)	0/6 (0.0)	2/16 (12.5)	1/13 (7.7)	0/5 (0.0)	**7/101 (6.9)**
Other skeletal abnormality	1/16 (6.3)	0/12 (0.0)	2/38 (5.3)	2/6 (33.3)	3/25 (12.0)	1/13 (7.7)	0/5 (0.0)	**9/115 (7.8)**
Cleft lip	0/13 (0.0)	1/12 (8.3)	0/37 (0.0)	0/6 (0.0)	0/6 (0.0)	0/1 (0.0)	0/5 (0.0)	**1/80 (1.3)**
Cleft palate	0/13 (0.0)	0/12 (0.0)	0/37 (0.0)	0/6 (0.0)	0/6 (0.0)	1/1 (100.0)	0/5 (0.0)	**1/80 (1.3)**
Joint abnormality	5/16 (31.3)	2/12 (16.7)	21/38 (55.3)	4/6 (66.7)	3/6 (50.0)	0/1 (0.0)	0/5 (0.0)	**36/84 (42.9)**
Joint hypermobility	1/16 (6.3)	2/12 (16.7)	2/38 (5.3)	4/6 (66.7)	0/6 (0.0)	0/1 (0.0)	0/5 (0.0)	**9/84 (10.7)**
Arthritis	2/16 (12.5)	0/12 (0.0)	19/38 (50.0)	0/6 (0.0)	2/6 (33.3)	0/1 (0.0)	1/5 (20.0)	**24/84 (28.6)**
Other joint abnormality	2/16 (12.5)	0/12 (0.0)	0/38 (0.0)	0/6 (0.0)	1/6 (16.7)	0/1 (0.0)	1/5 (20.0)	**4/84 (4.8)**
Hernia	1/16 (6.3)	1/12 (8.3)	3/38 (7.9)	0/6 (0.0)	1/25 (4.0)	6/13 (46.2)	0/5 (0.0)	**12/115 (10.4)**
Bone fracture	7/16 (43.8)	7/12 (58.3)	18/38 (47.4)	0/6 (0.0)	2/6 (33.3)	0/1 (0.0)	2/5 (40.0)	**36/84 (42.9)**
Age at first bone fracture, years (median, IQR)	24.0 (11.5–31.5)	16.0 (12.5–41.0)	23.0 (14.0–32.0)	-	25.5 (15.0–36.0)	-	23.0 (14.0–32.0)	**22.5 (13.0–51.5)**
No. of bone fractures (median, IQR)	0 (0–1)	1 (0–2)	0 (0–1)	0 (0–0)	0 (0–1)	-	0 (0–1)	**0 (0–1)**
Genitourinary	7/16 (43.8)	1/12 (8.3)	3/38 (7.9)	0/6 (0.0)	2/6 (33.3)	2/3 (66.7)	1/5 (20.0)	**16/86 (18.6)**
Reproductive	5/16 (31.3)	0/12 (0.0)	2/38 (5.3)	0/6 (0.0)	0/6 (0.0)	1/2 (50.0)	1/5 (20.0)	**9/85 (10.6)**
Female sex	5/12 (41.7)	0/7 (0.0)	1/26 (3.8)	0/3 (0.0)	0/3 (0.0)	1/1 (100.0)	1/4 (25.0)	**8/56 (14.3)**
Male sex	0/4 (0.0)	0/5 (0.0)	1/12 (8.3)	0/3 (0.0)	0/3 (0.0)	0/1 (0.0)	0/1 (0.0)	**1/29 (3.4)**
Renal	3/16 (18.8)	1/12 (8.3)	1/38 (2.6)	0/6 (0.0)	2/6 (33.3)	1/2 (50.0)	0/5 (0.0)	**8/85 (9.4)**

Dental anomalies	7/16 (43.8)	3/12 (25.0)	12/38 (31.6)	2/6 (33.3)	5/25 (20.0)	13/13 (100.0)	2/5 (40.0)	**44/115 (38.3)**
Missing teeth	2/16 (12.5)	1/12 (8.3)	7/38 (18.4)	2/6 (33.3)	3/25 (12.0)	11/13 (84.6)	1/5 (20.0)	**27/115 (23.5)**
Extra teeth	3/16 (18.8)	1/12 (8.3)	1/38 (2.6)	0/6 (0.0)	0/25 (0.0)	0/13 (0.0)	0/5 (0.0)	**5/115 (4.3)**
Small teeth	1/16 (6.3)	0/12 (0.0)	2/38 (5.3)	0/6 (0.0)	3/25 (12.0)	12/13 (92.3)	0/5 (0.0)	**18/115 (15.7)**
Abnormally shaped teeth	5/16 (31.3)	1/12 (0.0)	1/38 (2.6)	0/6 (0.0)	0/25 (0.0)	1/13 (7.7)	0/5 (0.0)	**8/115 (7.0)**
Other dental anomaly	2/16 (12.5)	1/12 (8.3)	1/38 (2.6)	1/6 (16.7)	1/25 (4.0)	3/13 (23.1)	1/5 (20.0)	**10/115 (8.7)**
Cardiovascular	1/16 (6.3)	1/12 (8.3)	1/38 (2.6)	0/6 (0.0)	10/25 (40.0)	1/13 (7.7)	1/5 (20.0)	**15/115 (13.0)**
Cardiac defect	1/16 (6.3)	1/12 (8.3)	1/38 (2.6)	0/6 (0.0)	9/25 (36.0)	1/13 (7.7)	0/5 (0.0)	**13/115 (11.3)**
Stroke or ministroke	0/16 (0.0)	0/12 (0.0)	0/38 (0.0)	0/6 (0.0)	1/25 (4.0)	0/13 (0.0)	1/5 (20.0)	**2/115 (1.7)**
Neurodevelopmental	9/16 (56.3)	3/12 (25.0)	8/38 (21.1)	1/6 (16.7)	11/25 (44.0)	3/13 (23.1)	5/5 (100.0)	**40/115 (34.8)**
Hydrocephalus	0/13 (0.0)	0/12 (0.0)	0/37 (0.0)	0/6 (0.0)	3/25 (12.0)	0/13 (0.0)	0/5 (0.0)	**3/111 (2.7)**
Developmental delay	1/14 (7.1)	0/12 (0.0)	0/37 (0.0)	0/6 (0.0)	2/8 (25.0)	1/3 (33.3)	2/5 (40.0)	**6/85 (7.1)**
Learning difficulty	1/16 (6.3)	0/12 (0.0)	1/38 (2.6)	0/6 (0.0)	6/25 (24.0)	2/12 (15.4)	0/4 (0.0)	**10/113 (8.8)**
Behavioural disorder	1/16 (6.3)	0/12 (0.0)	1/38 (2.6)	0/6 (0.0)	1/7 (14.3)	0/1 (0.0)	0/5 (0.0)	**3/85 (3.5)**
Mental health issue or mood disorder	9/16 (56.3)	2/12 (16.7)	6/38 (15.8)	1/6 (16.7)	3/6 (50.0)	2/3 (66.7)	3/5 (60.0)	**27/86 (31.4)**
Anxiety	7/16 (43.8)	2/12 (16.7)	6/38 (15.8)	1/6 (16.7)	3/6 (50.0)	2/3 (66.7)	1/5 (20.0)	**22/86 (25.6)**
Depression	5/16 (31.3)	1/12 (8.3)	3/38 (7.9)	1/6 (16.7)	2/6 (33.3)	1/3 (33.3)	2/5 (40.0)	**15/86 (17.4)**
Other mental health issue or mood disorder	3/16 (18.8)	0/12 (0.0)	0/38 (0.0)	0/6 (0.0)	0/6 (0.0)	0/3 (0.0)	0/5 (0.0)	**3/86 (3.5)**
Other neurodevelopmental	1/16 (6.3)	1/12 (8.3)	2/38 (5.3)	0/6 (0.0)	3/25 (12.0)	0/13 (0.0)	0/5 (0.0)	**7/115 (6.1)**
Gastrointestinal	1/16 (6.3)	0/12 (0.0)	0/38 (0.0)	0/6 (0.0)	1/25 (4.0)	2/13 (15.4)	0/5 (0.0)	**4/115 (3.5)**
Hearing loss	0/16 (0.0)	0/12 (0.0)	7/38 (18.4)	2/6 (33.3)	8/25 (32.0)	2/13 (15.4)	2/5 (40.0)	**21/115 (18.3)**
Hearing aid, yes	0/16 (0.0)	0/12 (0.0)	7/38 (18.4)	2/6 (33.3)	1/21 (4.8)	0/11 (0.0)	0/5 (0.0)	**10/109 (9.2)**
Age at time of hearing aid, years (median, IQR)	-	-	68.0 (65.5–73.0)	36.5 (4.0–69.0)	-	-	-	**67.0 (59.0–70.0)**

Skin abnormalities	0/16 (0.0)	0/12 (0.0)	2/38 (5.3)	0/6 (0.0)	1/6 (16.7)	0/1 (0.0)	0/5 (0.0)	**3/84 (3.6)**
Diabetes	1/16 (6.3)	1/12 (8.3)	1/38 (2.6)	0/6 (0.0)	0/6 (0.0)	0/1 (0.0)	2/5 (40.0)	**5/84 (6.0)**
Type 1	0/16 (0.0)	0/12 (0.0)	1/38 (2.6)	0/6 (0.0)	0/6 (0.0)	0/1 (0.0)	0/5 (0.0)	**1/84 (1.2)**
Type 2	1/16 (6.3)	1/12 (8.3)	0/38 (0.0)	0/6 (0.0)	0/6 (0.0)	0/1 (0.0)	2/5 (40.0)	**4/84 (4.8)**
BMI overweight/obese	7/14 (50.0)	3/11 (27.3)	10/37 (27.0)	0/3 (0.0)	7/15 (43.8)	8/12 (66.7)	3/4 (75.0)	**38/96 (39.6)**
Cancer	1/16 (6.3)	1/12 (8.3)	10/38 (26.3)	0/6 (0.0)	1/7 (14.3)	1/2 (50.0)	0/5 (0.0)	**14/86 (16.3)**
Sex hormone-related cancer[§]	0/16 (0.0)	0/12 (0.0)	4/38 (10.5)	0/6 (0.0)	0/7 (0.0)	0/2 (0.0)	0/5 (0.0)	**4/86 (4.7)**
Other cancer	1/16 (6.3)	1/12 (8.3)	6/38 (15.8)	0/6 (0.0)	1/7 (4.0)	1/2 (50.0)	0/5 (0.0)	**10/86 (11.6)**
Redundant periumbilical skin	0/16 (0.0)	0/12 (0.0)	1/38 (2.6)	0/6 (0.0)	3/25 (12.0)	13/13 (100.0)	0/5 (0.0)	**18/115 (15.7)**
Other systemic feature	2/16 (12.5)	1/12 (8.3)	5/38 (13.2)	0/6 (0.0)	3/25 (12.0)	2/13 (15.4)	0/5 (0.0)	**13/115 (11.3)**

IQR: interquartile range; BMI: body mass index

Totals for each variable may not equal the total number of participants due to missing data.

[†]All values presented as n (%) unless otherwise specified.

[‡]Denominators may be low in some systemic features due to inclusion of results from prior study[130,132] and consequent missing data as per Methods.

[§]Includes breast, cervical and prostate cancer

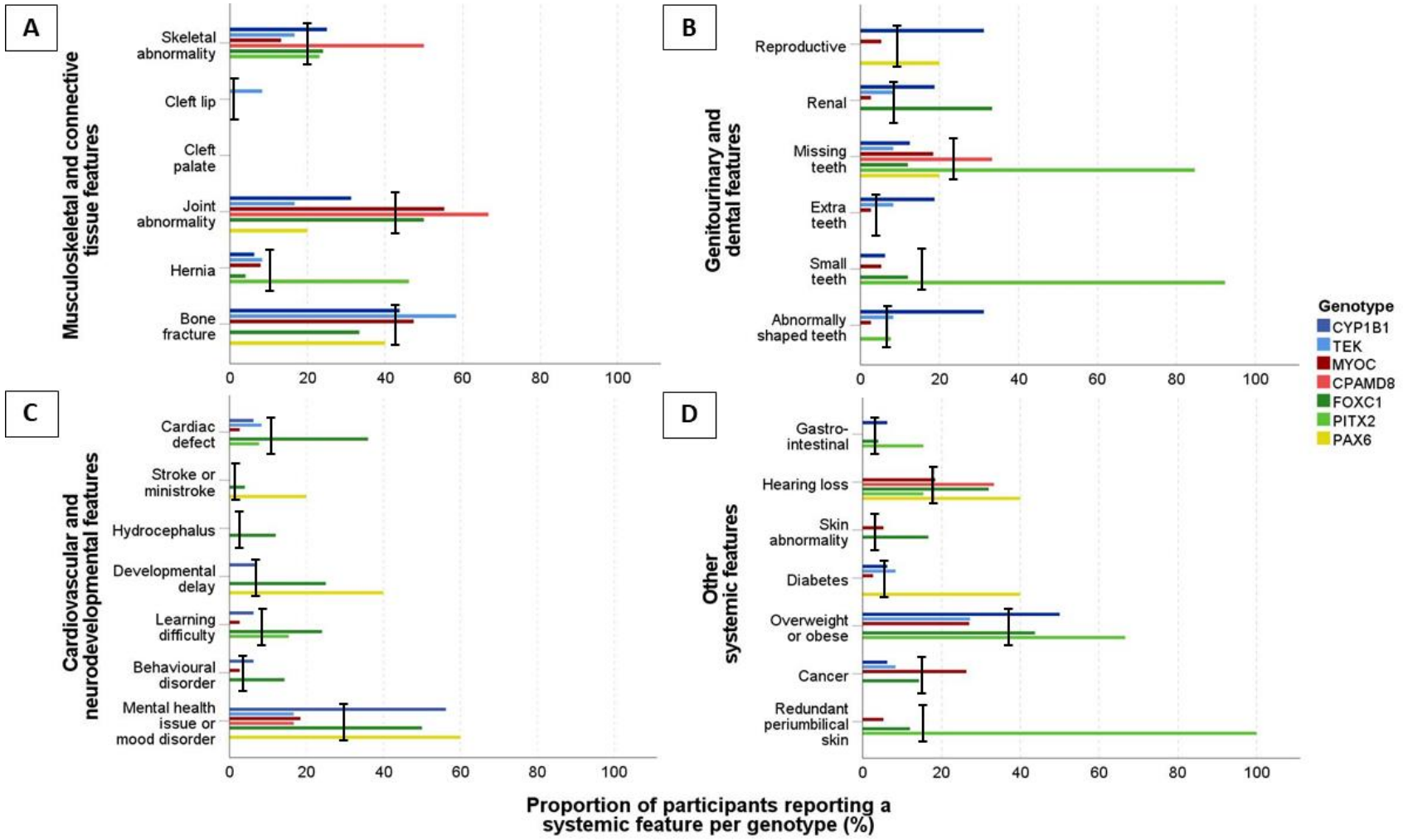

Figure 5.3. The relative frequencies of systemic features per genotype

The relative frequencies of systemic features per genotype are presented with reference to the total prevalence of the systemic feature across all genotypes as indicated by ⊥. Musculoskeletal and connective tissue features (Panel A), genitourinary and dental features (Panel B), cardiovascular and neurodevelopmental features (Panel C) and other systemic features (Panel D) are presented per genotype. If prevalence data for a systemic feature within a genetic cohort was recorded for <5 participants, it was excluded from the figure to avoid misrepresenting data. This included reports of cleft palate, reproductive and renal features, developmental delay, cancer and mental health issues or mood disorders in *PITX2,* and reports of BMI classified as overweight or obese in *PAX6*. These are otherwise reported in Table 5.5.

5.4 Discussion

This study provided an assessment of the relative prevalence of self-reported systemic features in the largest known cohort of individuals with childhood glaucoma of predominantly European ancestry and contributes to a very limited body of literature. Furthermore, it is the first study to systematically investigate these features in a cohort with biallelic *CYP1B1* and *CPAMD8* variants and heterozygous *TEK* and *MYOC* variants and provided an original contribution to knowledge. The exploration of specific systemic features enabled generation of new hypotheses regarding possible pleiotropic functions of genes associated with this rare group of disease and increased awareness of possible systemic associations that require appropriate diagnosis and management. The hypotheses generated from this study should, however, be interpreted with caution due to the exploratory nature of the study and the absence of an adequate control group.

Participants with primary childhood glaucoma (i.e., PCG and JOAG) did not report systemic features that were suggestive of an associated systemic disease phenotype. Overall, bone fractures were relatively high in PCG (45.1%) and JOAG (35.3%) compared to secondary glaucomas including SG-O (25.0%) and SG-S (14.3%), and a large international meta-analysis which reported a history of bone fractures in 26% of adults.[431] However, this finding is more likely to be explained by the visual abilities, and consequent risk profile, of individuals with PCG and JOAG rather than being indicative of an underlying disease association. Adults with glaucoma and vision loss have been reported to have a 67.4% increased risk of a fracture and 58.6% risk of injury compared to normal-sighted adults with glaucoma.[432] Reduced BCVA was also significantly associated with reports of bone fractures in the PCG cohort while bone fractures in the JOAG cohort could be associated with a restricted visual field, which was not analysed in this study. After adjusting for BCVA, along with age at survey completion and participant sex, a history of bone fractures was not significantly different between those with primary disease compared to the secondary disease cohort. Whilst there are many other factors that could explain the higher prevalence of bone fractures that were not considered in this study (e.g., participation in contact sports, calcium intake, sedentary behaviours, other hereditary factors),[433] the findings may suggest that these cohorts have a higher injury-risk profile than other forms of childhood glaucoma due to visual status.

It is unlikely that the prevalence of bone fractures in individuals with primary childhood glaucoma is related to an underlying molecular diagnosis. Bone fractures were highest in individuals with pathogenic *TEK* variants (58.3%), majority of whom had PCG, compared to other single genetic cohorts and the overall prevalence of bone fractures among all participants with a molecular diagnosis (42.9%). However, this finding is difficult to interpret because it was based on a small number of participants and

could be because more than half of these participants recorded one or both eyes to have vision impairment. Interestingly, however, *TEK* has recently been implicated in osteogenesis, bone mineralisation and bone regeneration.[145,146] Although its exact role remains unknown, murine studies have demonstrated that inhibition of *TEK* was found to block osteogenic differentiation and mineralisation of bone marrow stem cells.[145] Conversely, recent genome-wide association studies have not identified variants at the *TEK* loci to be associated with bone marrow density and increased fracture risk.[434–436] The significance of these findings with respect to the higher prevalence of bone fractures observed in this study is therefore uncertain. Future research could evaluate bone mineral density in individuals with *TEK* variants to help ascertain a possible role of *TEK* in osteogenesis and whether a loss-of-function mechanism may result in an increased risk of bone fractures.

Among individuals with primary and secondary disease with a molecular diagnosis, the only systemic feature that was significantly more common in individuals with primary disease was abnormally shaped teeth. This seemed to be driven by the higher prevalence of individuals with biallelic *CYP1B1* variants who had primary childhood glaucoma. The *CYP1B1* cohort reported the highest rate of abnormally shaped teeth (31.3%) compared to all participants with a molecular diagnosis (7.0%). Interestingly, participants with biallelic *CYP1B1* variants also reported the highest rate of extra teeth (18.8%) and short stature (21.4%) compared to other single genetic cohorts. However, the significance of these findings is unknown because other reports of systemic features in individuals with *CYP1B1* are extremely scarce. Five pedigrees with *CYP1B1*-associated Peters anomaly were not found to have systemic features, although the method of assessment of systemic features was not reported.[110] Meanwhile, a 9-month-old infant who was reported to have *CYP1B1*-associated ARS based on ocular findings (iridocorneal adhesions, posterior embryotoxon, anterior iris insertion), was considered to have systemic features including a broad nasal bridge and protruding umbilicus.[119] Whilst a broad nasal bridge and umbilical anomalies are often observed in ARS,[125–132] these features may just be typical of an infant and may therefore not be suggestive of systemic involvement in *CYP1B1*-associated ocular disease.[133,134] Moreover, the exact role of *CYP1B1* in several metabolic pathways is not yet established,[121–124] and currently does not currently support any known systemic associations. Further research is required to establish whether the systemic features observed in this study are part of the *CYP1B1*-associated disease spectrum or are a result of other genetic or environmental factors not measured.

The lack of systemic features reported in the *MYOC* cohort likely further contributed to the low prevalence of systemic features amongst individuals with primary glaucoma and a molecular diagnosis. This is consistent with previous reports that demonstrated that *MYOC* is mostly expressed in the

eye.[437,438] *MYOC*-associated glaucoma is due to a gain-of-function mechanism and systemic features with the same disease pathogenesis have not yet been reported.[174] It is therefore more likely that reports of systemic features in the *MYOC* cohort were due to other factors including environment and older age. This would explain the higher rates of cancer (26.3%) and arthritis (50.0%). Malignant cancers and arthritis have been reported by 6.6% and 49.0% of the general Australian population aged ≥65 years, respectively.[439] The higher prevalence of bone fractures (47.4%) also observed in this cohort could also be associated with visual ability as described above, particularly as *MYOC* is associated with severe visual field loss.[303,304] Collectively, these findings suggest that *MYOC* variants implicated in glaucoma are not associated with systemic features.

There were several systemic features that were significantly higher in participants with secondary childhood glaucoma compared to those with primary childhood glaucoma. Among participants with a molecular diagnosis, there was a significantly higher prevalence of joint abnormalities, small teeth, cardiac defects, developmental delay, hearing loss, skin abnormalities and redundant periumbilical skin. This was not surprising, given that the majority of the secondary glaucoma cohort had *FOXC1*- or *PITX2*-associated ARS. *FOXC1* variants are well-known to be associated with hearing loss, cardiac defects, hydrocephalus, learning difficulties and developmental delays, in keeping with the observations of this study.[125,126,130,132,192,195] Similarly, individuals with *PITX2* variants are frequently reported to have dental features (missing teeth, small teeth), redundant periumbilical skin or umbilical hernias, as observed here.[125,127,130,132,192] The differences in the prevalence rates of systemic features found between those with primary and secondary glaucoma in this study may therefore be due to a recruitment bias toward individuals with ARS-associated glaucoma. However, ARS-associated glaucoma is among the more commonly encountered forms of SG-O.[43,73] Meanwhile, differences in skin abnormalities were driven by individuals with SG-S who had cafe-au-lait spots associated with NF1 and those with facial haemangiomas associated with SWS. Investigation and identification of these systemic features by a paediatrician or geneticist may therefore assist in obtaining an accurate clinical diagnosis of primary or secondary childhood glaucoma and facilitate genetic testing. This may be particularly helpful where an anterior segment examination is challenging due to young age of disease onset with consequent corneal clouding, or where a child is noncompliant with testing.[194] Furthermore, appropriate medical subspecialist referrals can be made for the management of any systemic feature found in any individual.

The findings of this study suggested that *CPAMD8*-associated glaucoma may be related with a connective tissue disorder. This is because this cohort reported the highest rate of joint hypermobility (66.7%), compared to any other single genetic cohort. Similarly, the rate of joint hypermobility was higher than a large meta-analysis which reported a rate of joint hypermobility of 34.1% in children and

adolescents.[440] Tall stature was also highest amongst individuals with biallelic *CPAMD8* variants (33.3%) which otherwise has a general population prevalence of approximately 3% (i.e., above the 97th percentile).[427] The prevalence of hearing loss was also higher compared to the overall cohort (33.3%). Whilst these observations are based on a small number of individuals, systemic features have not been reported in *CPAMD8*-associated ocular disease.[101,111,185–188] *CPAMD8* is also not present in rodent genomes, making it difficult to study the role of the gene and its possible association with connective tissue disease.[185] However, loss-of-function variants in *CPAMD8* result in a disorganised extracellular matrix of the eye, which gives rise to an ocular phenotype including ectopia lentis (36%),[186] retinal detachment (27%)[186] and myopia.[185,186,188] This ocular phenotype is shared with connective tissue diseases including Marfan syndrome (*FBN1*), which may result in ectopia lentis (70–82%), retinal detachment (7%) and myopia.[47,441,442] Marfan syndrome is also associated with systemic features including joint hypermobility (5–89%),[430,443] hearing loss (53%),[444] and tall stature, with a mean height above the average population.[445,446] Meanwhile, individuals with Type 1 and Type 2 Sticklers syndrome (*COL2A, COL11A1)* have a high rate of retinal detachment (42–73%), myopia (84–87%), joint hypermobility (29–55%) and hearing loss (70%).[447–450] This overlapping phenotype may explain why one participant in this study with *CPAMD8* variants, and a history of retinal detachment, was clinically diagnosed with Stickler syndrome. Despite the shared phenotype between *CPAMD8, FBN1 and COL2A1/COL11A1*-associated disease, it is unknown if CPAMD8 interacts with either of these genes or their protein products in the development or maintenance of connective tissues. Furthermore, no study has documented the expression of CPAMD8 proteins in non-ocular elastic tissue including cartilage.[185,189] Further research is required to ascertain the significance of these reports of joint hypermobility, tall stature and hearing loss in individuals with biallelic *CPAMD8* variants.

Connective tissue disorders are often reported in conjunction with childhood glaucoma.[155,253,255,386] These include Stickler syndrome, as observed in this study and Weill-Marchesani syndrome, which can be associated with *LTBP2, ADAMTS10* or *ADAMTS17* variants.[155,253,255] Other systemic conditions reported may include SWS, NF1, and Down syndrome (Chapter 3).[255,386] All of these conditions have systemic features that require specialist management and may pose an anaesthetic risk for when glaucoma surgery or an examination under anaesthetic is required (e.g., increase in intracranial pressure in SWS).[451] Recruitment of individuals with SG-S was low in this study and are therefore underrepresented. As discussed in Chapter 3,[386] this is due to the historical recruitment of the ANZRAG. Nonetheless, it is recommended that children diagnosed with glaucoma undergo appropriate assessment and surveillance of systemic features to exclude possible genetic conditions.

The frequency of mental health issues, in particular anxiety and depression, were the most common neurodevelopmental features across all phenotypic cohorts excluding SG-S. The frequencies of anxiety and depression were at times higher than that of the general Australian population. A recent Australian study, conducted during 2020 and 2021, found that 28.8% of adults aged 16–85 years old had experienced an anxiety disorder whilst 11.2% had a history of depression or depressive episodes.[452] In comparison, the SG-O cohort reported a higher rate of anxiety (38.9%) whilst participants with SG-O (27.8%) and PCG (15.7%) reported higher rates of depression.[452] These findings could be influenced by several glaucoma-related and non-glaucoma related factors not measured in this study. Glaucoma-related factors may include the variable and often severe disease outcomes observed in *CYP1B1*-(Chapter 4), and *FOXC1*-associated glaucoma*,*[193,194] and the potential impact this may have on QoL. Although a history of anxiety or depression were high in these genetic cohorts, a neurodevelopmental pathway for either gene has not been established,[453,454] and there is currently insufficient data to support whether a molecular association may exist. Nevertheless, an individual's ability to complete daily tasks, their financial, mental, and social well-being, and coping strategies should be considered as potential risk factors for the development of anxiety or depression. The impact of a genetic diagnosis on decision-making in family planning may be important, particularly where there is an autosomal dominant mode of inheritance. These factors have not yet been thoroughly investigated in children or adults with childhood glaucoma.[306–312] These findings are a concern because a healthcare professional trained in the provision of psychological support (e.g., psychologist, social worker) has not yet been recommended as a core member in the multidisciplinary management of childhood glaucoma.[8,255] To support their involvement, further investigation of the risk factors for anxiety and depression, and the greater impact of the condition on QoL, is required.

There were two main limitations of this study. Firstly, self-reported data was used to explore the presence and absence of systemic features. This might have led to recall bias, missing data and measurement error, as self-reported diagnoses may not correspond to the symptoms experienced. Self-reports of systemic features may be influenced by health literacy and sociocultural factors such as age, gender or ethnicity that may influence how an individual reports their health. Self-stigmatisation of any one condition may have led some participants to not declare certain features. Secondly, the response rate was relatively low, with 29.8% of surveys completed. This may have introduced self-selection bias, whereby individuals with no systemic features may have been less likely to respond to the survey as they may not have considered it useful to do so, whilst those with systemic features may have been more likely to respond. Non-respondents may have been more concerned about how their health information was handled and opted not to participate. More detailed information about the purpose of the study and how confidentiality was assured may have resulted in a higher proportion of respondents.

Individuals with a higher health literacy and those with a clearer understanding of the English language may have been more likely to respond to the survey. The latter may particularly explain why non-Europeans were less likely to respond. These factors could have been addressed by ensuring that the survey was piloted on participants for readability and understandability and distributed in languages other than the English language. Those who received the survey electronically were more likely to respond compared to those who were sent a postal survey. Electronic surveys may have been easier to complete due to convenience, and accessibility, particularly where an individual with poor visual ability could make use of electronic vision aids (e.g., screen readers). In contrast, greater dexterity may be required to complete a written survey such that older individuals and those with more complex health conditions may not have responded. Whilst every effort is made to ensure individuals' communication preferences are recorded, they may need updating more regularly to improve response rates. These limitations could have influenced prevalence figures and reported systemic features that may be more typical of a younger European population with greater health literacy. Although this was an exploratory study, results should be interpreted with caution. Acquiring clinical reports of all individuals within the ANZRAG from the appropriate physician could ultimately overcome this. However, this was not feasible in the current study as participants were in multiple geographic locations across Australia and may have received care from multiple centres, such that the resources required to source the appropriate details were not available (i.e., time, ethics approval). Nonetheless, the results of the study provide a real-world representation of systemic features that would likely be obtained in a patient history in a clinical ophthalmic setting.

Other study limitations included that prevalence figures may also have been influenced by the inclusion of probands and non-probands in the analyses. It remains possible that there are other heritable confounding factors that were not controlled for. However, systemic features may have varied penetrance within one pedigree such that non-probands were included.[130,192,430] This also assisted with increasing the sample size, which is necessary in the study of a rare disease.[430] Furthermore, as discussed in Chapter 3, those with primary disease and no molecular diagnosis may not truly have primary disease, which may have led to inaccurate reports of systemic features in this cohort. There was also no control cohort. Instead, the overall prevalence of specific systemic features in all participants with a molecular diagnosis and average population references were used where possible to interpret the findings. A suitable control cohort is required in future studies to confirm whether certain systemic features are significantly higher in certain cohorts compared to a normal population. This would also enable analysis of how the age and sex of participants with a molecular diagnosis influenced the results. The survey also predominantly included questions regarding known systemic associations found in molecular diagnoses associated with childhood glaucoma. Subsequently, there may be other systemic

features that are yet to be directly measured and reported. Lastly, the sample sizes per cohort were small. This is inevitable in a rare disease such as childhood glaucoma and future research collaboration is required to affirm the presence of certain features.

In conclusion, this is one of the largest studies to systematically explore the association of systemic features in individuals with childhood glaucoma with respect to their clinical and molecular diagnoses. Identification of systemic features amongst these cohorts is a valuable exercise in determining differential diagnostic features and generating theories regarding possible biological disease pathways in childhood glaucoma. These include the potential of an increased susceptibility to bone fractures in *TEK*-associated glaucoma, connective tissue disease in *CPAMD8*-associated glaucoma, and the inclusion of systemic features in the *CYP1B1*-associated disease spectrum. It is also the first study to document that individuals with SG-O and PCG, specifically those with *CYP1B1*- and *FOXC1*-associated glaucoma, report a higher rate of anxiety and depression. Overall, the findings emphasise the importance of thorough investigation of systemic features in any individual diagnosed with childhood glaucoma and support a multidisciplinary model of care that involves ophthalmologists, paediatricians, clinical geneticists, and mental health professionals. This model will ultimately contribute to better detection and management of possible underlying systemic features, improved genetic diagnostic rates, and better QoL outcomes for individuals affected by childhood glaucoma.

CHAPTER 6 QUALITY OF LIFE IN CHILDREN WITH GLAUCOMA

Published manuscript

The contents of this chapter have been published in a peer-reviewed manuscript of which I am the first author: **Knight LSW,** Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. Quality of life in children with glaucoma: a qualitative interview study in Australia. ***BMJ Open***. 2022;12(7):e062754.

My contributions to the manuscript involved the research conception and design (80%), data collection including interviews with participants (95%), data analysis including identification of themes (100%), interpretation of the data (90%), and drafting the manuscript (100%). All other authors assisted with interpretation of the data and critically revising the manuscript. Emmanuelle Souzeau and Mallika Prem Senthil were further involved in research conception and design (20%), whilst Bronwyn Ridge assisted with participant interviews (5%). Project funding was provided by Emmanuelle Souzeau, Jamie Craig, Mallika Prem Senthil and myself.

The introduction and methods of this manuscript have been edited to fit the structure of this thesis.

6.1 Introduction

The long-term management and treatments, disease sequelae and uncertain visual outcome of childhood glaucoma may pose detrimental social, emotional, and physical impacts on an individual. Individuals may also be impacted by cosmetic concerns associated with buphthalmos and corneal opacification, sensory strabismus, occlusion therapy for amblyopia, or spectacle wear for high myopia. These experiences may contribute to an overall reduced QoL in an individual and may be associated with the notable rate of mental health issues reported in Chapter 5. However, there is a paucity of literature exploring the impact of childhood glaucoma on QoL in children and adults with childhood glaucoma. It is therefore unknown which factors contribute most to QoL and how clinicians can address possible risk factors for mental health issues. This could explain why recommendations for the multidisciplinary care of these individuals is yet to include the provision of psychological support (e.g., psychologist, social worker).[8,255] Further investigation of the impact of the condition on QoL is warranted. This chapter considers the impact of the condition on children.

Previous literature detailing QoL in children with glaucoma is limited to quantitative association studies that utilised non-glaucoma specific PROMs designed to measure the impact of vision impairment on QoL (referred to as VR-QoL)[306–309] or the impact of the condition on overall well-being (referred to as HR-QoL).[309,310] Because the questions asked on these PROMs have not been designed for children with glaucoma, the results of these studies may not be providing an accurate evaluation of QoL in children with glaucoma. These generic PROMs were used because a childhood glaucoma-specific PROM does not exist. Nonetheless, several studies have reported that children with glaucoma who have lower BCVA experienced lower VR-QoL.[306–309] Meanwhile, a younger age has been associated with lower VR-QoL and HR-QoL, although there has been limited investigation as to why this trend was observed.[309,310] It was proposed that children may adapt better to their glaucoma over a longer period of time but exploration of this hypothesis, or whether there may be other social and emotional factors that may explain this finding, were not possible using a quantitative measure. Exploration of reasons for this finding is better suited to more flexible, qualitative inquiry, that enables the ability to generate an in-depth understanding of an individual's experiences.[357]

My original contribution to knowledge was the development of an in-depth insight into disease-specific QoL issues experienced by children with glaucoma using qualitative analysis. Findings from this study support the need for psychosocial support in individuals affected by childhood glaucoma and identified risk factors for the development of mental health issues (Chapter 5). This study will also inform the future development of a childhood glaucoma-specific PROM suitable for children with glaucoma for related QoL research and clinical implementation.

6.2 Methods

6.2.1 Participants

Children were recruited from a large Australasian disease registry (the ANZRAG; Chapter 2) using a non-probability convenience sampling technique. Children were eligible to be interviewed if they currently resided in Australia, were English speaking, had a diagnosis of any subtype of glaucoma in at least one eye as per the CGRN criteria,[4] and were aged between 8 and <18 years. Children aged ≥8 years are more likely to reliably and independently understand questions relating to QoL than children aged <8 years.[455] Children were excluded if they had coexisting ocular disease unrelated to childhood glaucoma or had a hearing or cognitive impairment or other disability impacting on QoL (e.g., intellectual disability) as informed by their referring specialist or parent/guardian (henceforth abbreviated to parent).

Eligible children, and their parent/s, were posted an invitation to be interviewed and asked to return their interest. If both parties expressed interest, an information pack and consent form were sent. An interview was arranged once written informed consent from one parent and assent from the child were provided. If no response was received within two weeks, parents received a follow-up phone call. Children were deemed non-contactable after at least two unsuccessful attempts.

Children's clinical details were obtained from their most recent medical record and included: glaucoma subtype, age at diagnosis, laterality, BCVA (logMAR), IOP, number of surgical interventions, and number of topical antiglaucoma medications currently being used. The International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision),[337] was used to categorise BCVA per eye as described in Chapter 2. Because visual field information was not available for every child, BCVA was used as a measure of disease severity. For analysis, children's ages were grouped into 8 to 12 years and 13 to 17 years, as per the PedsQL version 4.0.[323] Glaucoma onset at ≥4 years was considered juvenile.[4]

Ethical approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/161) and the study adhered to the tenets of the Declaration of Helsinki.

6.2.2 Interviews

As detailed in Chapter 2, a semi-structured interview was used to explore QoL in children. It was developed from a literature review of QoL studies of children with glaucoma and the VR-QoL and HR-QoL PROMs used in each study.[306–310,323–325] The interview guide consisted of questions related to schooling, role performance, interpersonal relationships, medical care and mobility (e.g., *Do you feel*

like other children treat you differently because of your eyes? Can you explain that?). Questions regarding the emotional, social, and psychological consequences of the condition were further asked (e.g., *Do you ever feel sad or angry about your eyes? What cheers you up?* and *what worries or concerns do you have regarding the future?*). Due to ethical considerations, children were not asked whether they had fears related to future disease progression. The complete set of questions is provided in Appendix A, Interview Guide A1.

The semi-structured interviews were offered to be conducted one-on-one via telephone or Cisco WebEx. For this study, most children preferentially selected a telephone interview (n=17), although reasons for this were not investigated. Most of the interviews were conducted by me (n=17) while one was conducted by one co-author (BR; a health counsellor). Participants, and their caregiver, were informed the study was being completed in the context of higher degrees for both interviewers and no child was under the care of either interviewer. Children aged <16 years required a parent chaperone and parents were not to answer questions on their child's behalf. Interviews were audio-recorded and transcribed verbatim. Interview transcripts and overall findings were not returned to children for accuracy or feedback as it was considered burdensome to the child and unethical (i.e., the maturity and comprehension required to understand their contents could not be assured). Instead, at the conclusion of each interview, the child was provided with a verbal summary of their responses for confirmation that they had been interpreted correctly. Interviews continued until thematic saturation was achieved (i.e., the point where no new information was gained from subsequent interviews).[363] Thematic saturation occurred after the fourteenth interview. An additional four interviews with participants already recruited to the study were conducted to confirm data saturation. Recruitment ceased thereafter.

6.2.3 Data analysis

A general inductive approach[365] was used to identify QoL themes as previously described (Chapter 2). Briefly, transcripts were closely read and systematically coded using QSR NVivo 12 during the study recruitment period. Coding checks were frequently and separately performed by three co-authors to ensure credibility of findings (BR, MPS and ES).[365] Major QoL themes, and their sub-themes were determined by grouping codes that contained text with similar or repetitive patterns of meaning in an iterative process.[371] The themes developed were not conceptualised *a priori*. They were dependent upon the use of the general inductive approach, which allows themes that best represent the data obtained to emerge from the data.[365] To enhance the readability and application of the qualitative findings presented, major themes were abbreviated to be consistent with previous terms used in ophthalmic QoL research.[372–374] The prominence of QoL themes was determined by the number of children who raised issues connected to the corresponding theme. As the theme of coping was developed, the Stress and

Coping Model[456] was used to support the categorisation of sub-themes into adaptive and maladaptive coping strategies. This model describes that the coping strategy adopted by an individual is governed by whether the individual first perceives an encounter as a threat to their well-being, and whether the situation is considered changeable. Adaptive coping strategies were further defined as problem-focused (i.e., strategies which actively confront the problem) or emotion-focused (i.e., a strategy which involves regulation or minimisation of negative emotions). Where an individual perceives that the situation is changeable, a problem-focused strategy is more likely used.[456] However, if the situation is perceived as less changeable, an emotion-focused strategy is used.[456] Statistical calculations were performed using SPSS version 27.0 for Windows.

6.3 Results

6.3.1 Participants

Fifty-four eligible children from the ANZRAG were invited to participate and 18 (33%) were interviewed (see Appendix C, Figure C6 for a flow chart depicting the recruitment of participants). The proportion of participants and non-participants with bilateral disease was significantly different (11/18, 61% vs 34/36, 94%, respectively, p=0.004) whilst all other demographic and clinical variables were similar (see Appendix B, Table B11). Reasons for declining to participate were not recorded due to the sensitive nature of the study.

Interviews were conducted between April 2020 and July 2021. The average interview length was 30±14 minutes and the median age of children interviewed was 12.1 years (IQR: 9.7–14.5 years). Glaucoma care was provided by multiple specialists at several centres across Australia. One co-investigator (JEC) was identified as a treating specialist for two participants, but was not involved in participant recruitment, interviewing or data analysis. Demographic and clinical characteristics of the children interviewed are detailed in Table 6.1.

Table 6.1. Demographic and clinical characteristics of children interviewed

Variable			n (%)[†]
Age at glaucoma diagnosis, years (median [range])			0.5 [0–15]
Time since diagnosis, years (median [IQR])			9.8 [7.3–13.6]
Age at interview			
8–12 years			10 (56)
13–17 years			8 (44)
Gender, female			6 (33)
Laterality of glaucoma, bilateral			11 (61)
Self-reported ancestry, European			16 (89)
Subtype of childhood glaucoma			
Primary congenital glaucoma			12 (67)
Glaucoma associated with non-acquired ocular anomalies			
Aniridia			1 (6)
Axenfeld-Rieger syndrome			1 (6)
Glaucoma associated with non-acquired systemic condition			
Sturge-Weber syndrome			1 (6)
Glaucoma associated with an acquired condition			
Idiopathic uveitis[‡]			2 (11)
Glaucoma following cataract surgery			1 (6)
Number of topical antiglaucoma medications currently using			
0			13 (72)
≥1			5 (28)
Intraocular pressure at last ophthalmic appointment, mmHg (median [range])			18 [14–25]
Time since last ophthalmic appointment, months (median [IQR])			3.8 [2.9–7.4]
Number of surgical interventions per child (median [IQR])			2 [2–4]
Time since last ophthalmic surgical intervention, years (median [IQR])			6.7 [1.6–13.6]
Disease complications			
Corneal disease			1 (6)
Cataract			4 (22)
Molecular diagnosis identified			9 (50)
Autosomal recessive inheritance			2 (11)
Autosomal dominant inheritance			7 (39)
Vision category	**BCVA (Snellen)**	**Better Eye BCVA (n, %)**	**Worse Eye BCVA (n, %)**
No vision impairment	≥6/12	15 (83)	8 (44)
Mild vision impairment	<6/12 - ≥6/18	1 (6)	4 (22)

Moderate vision impairment	<6/18 - ≥6/60	1 (6)	2 (11)
Severe vision impairment or blindness	<6/60 - ≥6/120	0 (0)	1 (6)
Blindness	<6/120 - CF	1 (6)	2 (11)
	HM or LP	0 (0)	1 (6)
	NLP	0 (0)	0 (0)

BCVA: Best-corrected visual acuity; CF: count fingers; HM: hand movements; IQR: interquartile range; LP: light perception; NLP: no light perception
†: n (%) presented unless otherwise specified
‡: No underlying systemic disease was diagnosed

6.3.2 Quality of life themes

Seven QoL themes emerged from the data. The total proportion of children experiencing issues per QoL theme and coded segments per theme are shown in Figure 6.1. Additional sub-themes not presented within the results are provided in a mind map (Appendix C, Figure C7).

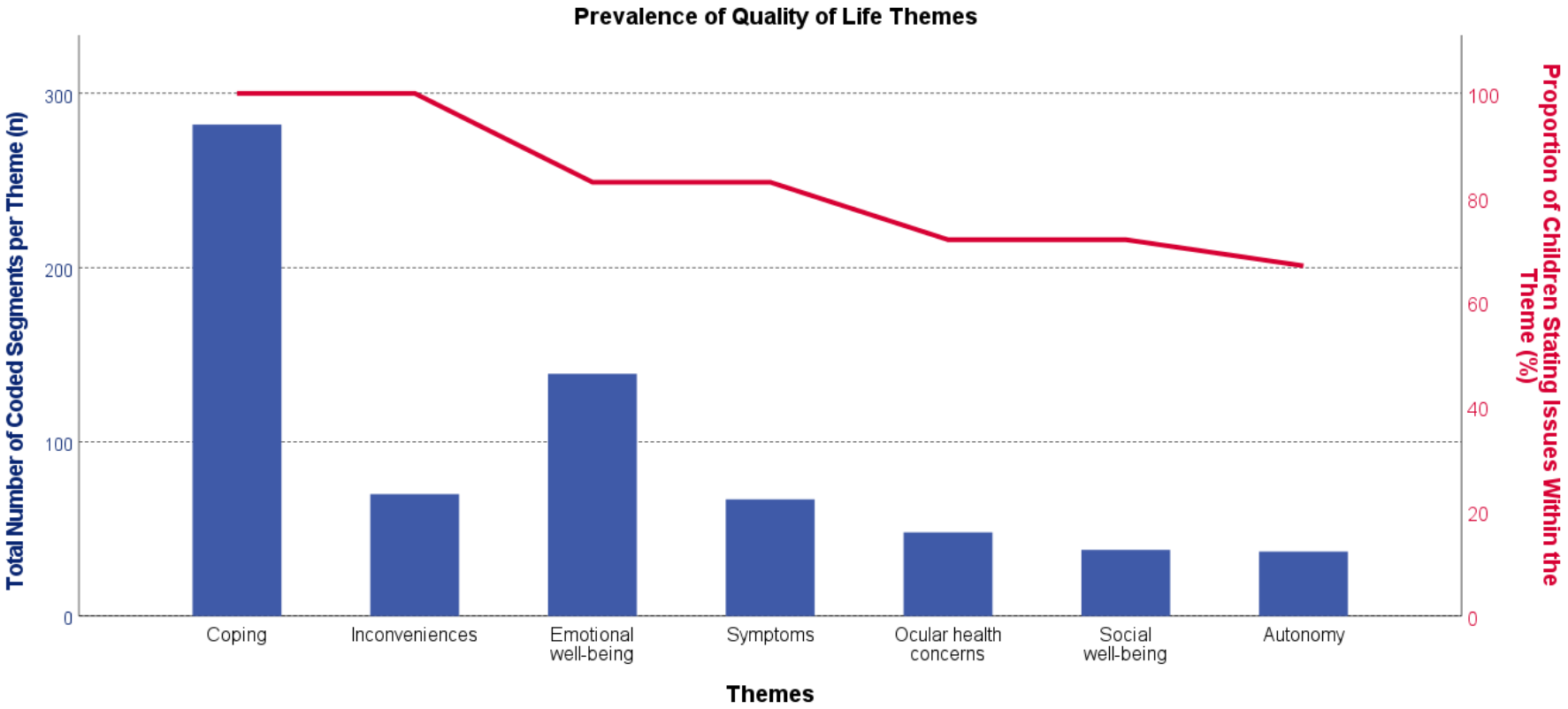

Figure 6.1. Quality of life themes identified in children with glaucoma
This Dual Y Axis Chart demonstrates the total number of codes per theme (blue bar chart) and the proportion of children who discussed an issue within the theme (red line chart).

6.3.2.1 Theme 1: Coping

All children used coping strategies to manage the impacts of their glaucoma (Figure 6.1). All children (18/18, 100%) discussed being resilient, which is an adaptive emotion-focused coping strategy.[456]

> "*I've grown up with it. I've gotten used to it. I just don't pay much attention to it now.*" (Child aged 13–17 years)

Adaptive problem-focused strategies included developing a positive relationship with their ophthalmologist (12/18, 67%), accepting parents' use of positive reinforcement for appointment attendance (9/18, 50%) and seeking and accepting support from family, friends, or schoolteachers (11/18, 61%). The latter coping strategy was more common amongst children aged 13 to 17 years than children aged 8 to 12 years (7/8, 88% vs 4/10, 40%, respectively).

> "*I'm a lot more comfortable with [my ophthalmologist] because he's been doing it with me since basically the first time I went there... we're friends*." (Child aged 8–12 years)

Several children (10/18, 56%) discussed adapting to activity limitations secondary to visual abilities or symptoms, such as photophobia. This was observed in children with bilateral (3/3, 100%) or unilateral BCVA <6/12 (3/7, 43%) and children with no BCVA impairment (4/8, 50%). Adapting to visual limitations was improved with the use of electronic devices in the classroom (e.g., laptop computer) whereby text size and contrast could be manipulated. Adapting to photophobia was usually resolved with sunglasses wear. Consequently, 5/18 (28%) children explicitly stated that their glaucoma did not impact their participation in daily activities.

> "*A lot of [schooling] stuff is on the computers and not written on the board anymore. So yeah, like, I don't really think that I have troubles.*" (Child aged 13–17 years)

Dissociating from one's glaucoma outside of the clinical setting and ignoring its presence was used by 8/18 (44%) children, most of whom did not have bilaterally impaired BCVA (7/8, 88%). This was considered an adaptive strategy in 4/8 (50%), 3/4 (75%) of whom were aged 8 to 12 years, as these children considered themselves unaffected by their glaucoma. Conversely, it was considered maladaptive in 4/8 (50%) children, irrespective of age or gender, because these children avoided asking for vision-related assistance from teachers or were disinterested in possible disease consequences.

> "*I'm just not interested in my eyes much.*" (Child aged 8–12 years)

Actively leaving medical responsibilities and decision-making to their parent/s was discussed by more children aged 13 to 17 years compared to their younger counterparts (5/8, 63% vs 2/10, 20%, respectively). Gender, antiglaucoma medication use, and BCVA did not appear influential.

> "*I'd let Mum ask the questions… I'm more of a listener. Like a bystander… I'll get all the information I want out of Mum.*" (Child aged 13–17 years)

Furthermore, 3/4 (75%) children aged ≥16 years discussed strong feelings of wanting to avoid attending their ophthalmic appointments.

> "*I was just yelling and screaming… I really did not want to go [to my appointment].*" (Child aged 13–17 years)

6.3.2.2 Theme 2: Inconveniences

All children discussed several inconveniences related to their ophthalmic appointments or glaucoma treatment. Clinic waiting time caused boredom for 6/18 (33%) children and 5/18 (28%) discussed negative outcomes related to school absenteeism. These were exacerbated where travelling long distances for ophthalmic review was required. Conversely, 7/18 (39%) reasoned that school absenteeism was a positive experience.

> "*It took us like three hours to get there and to go back... I often had to skip school to go there, and it was often always the fun days*." (Child aged 8–12 years)

Most children (11/18, 61%) discussed the inconvenience of having blurred vision for many hours following pupillary dilatation, whilst 4/18 (22%) considered a visual field test burdensome. Only two children had discussed that their visual impairment was an inconvenience to their daily activities of living. These activities included schoolwork and sporting activities.

> "*I hate getting drops… everything I see is blurry for six or seven hours… They're still the worst thing that could possibly happen.*" (Child aged 13–17 years)

Spectacle wear was considered inconvenient and uncomfortable by 6/18 (33%) children, particularly during sporting activities. Among children who currently used topical antiglaucoma medication, 2/5 (40%) considered them bothersome.

> "*I don't really like wearing [glasses]... because my nose gets sweaty.*" (Child aged 8–12 years)

6.3.2.3 Theme 3: Emotional well-being

Negative emotional experiences were discussed by 15/18 (83%) children. Feeling frustrated (13/18, 72%) or anxious (10/18, 56%) were often experienced in the contexts of requiring pupil dilatation or performing certain clinical tests (e.g., visual field test, IOP test), irrespective of age.

> "*The sight field test… has like things that blink and it's just like heaps of them, and it's like in a way sort of overwhelming*." (Child aged 8–12 years)

Several children (7/18, 39%) of varying ages discussed feeling misunderstood at times by their friends, peers and/or schoolteachers. At times, this led to concealment of their condition.

> "*I like keeping [my glaucoma] a bit of a secret… Because when I try to explain - no one understands and I have to keep explaining, explaining and explaining*." (Child aged 8–12 years)

Feeling self-conscious of their appearance was expressed by 6/18 (33%) children. Reasons included their eye appearance, wearing spectacles or wearing an eye patch for amblyopia therapy. These were not dependent on BCVA, gender or age with the exception that one child, with bilateral BCVA <0.5, expressed feeling self-conscious whilst using their white cane for mobility.

> "*I hate [all the photos] when I'm younger because of the big, shaded glasses and stuff... I'm not a very photogenic person.*" (Child aged 13–17 years)

6.3.2.4 Theme 4: Symptoms

Symptoms related to having childhood glaucoma were discussed by 15/18 (83%) children. The most common symptom raised by children was blurred vision (13/18, 72%). Of these, 3/13 (23%) had bilateral disease with bilateral BCVA <6/12, whilst 4/13 (31%) had unilateral disease, and 7/13 (54%) had no BCVA impairment. It was usually described in the context of reading the classroom board, reading small texts, and playing sports that involve a small ball (e.g., tennis).

> "*If it's small writing and I'm at the back of the class I can't always get it but if it's like medium like to big writing I can see*." (Child aged 13–17 years)

Glare or photophobia (8/18, 44%), reduced peripheral vision (2/18, 11%) and sore eyes (4/18, 22%) were other symptoms discussed by children, irrespective of any clinical or demographic characteristic. Various reasons for sore eyes discussed by children included emotional stress related to having reduced

vision, exertion required to read a book and ingrown eyelashes caused by topical antiglaucoma medications.

> "*I hate the sun… It hurts my eyes… I do stay inside most of my life."* (Child aged 8–12 years)

Meanwhile, reduced contrast sensitivity was discussed by 6/18 (33%) children, all of whom had bilateral disease. Additional symptoms included headaches attributed to photophobia and difficulty adapting to lighting conditions, which were discussed by one child each.

> "*The stronger colours like blue, purple and black I can read but when it goes to like green and all of them other colours like orange I can't, it's harder for me to read what it says*." (Child aged 13–17 years)

6.3.2.5 Theme 5: Ocular health concerns

Several children (13/18, 72%) discussed ocular health concerns which were often experienced as worry or anxiety. Hypersensitivity of objects touching their eye was the most common concern raised (6/18, 33%), particularly by children with bilateral disease (5/6, 83%).

> "*One time my eye was really sore, and I got kind of worried, and kind of scared, but it turned out it was just the ingrown eyelash."* (Child aged 8–12 years)

Concerns for raised IOP (5/18, 28%) and losing vision (4/18, 22%) were additionally discussed. The former was more typical among children aged between 13 and 17 years (4/5, 80%) while losing vision did not appear to be an age-related concern.

> "*When I go to the like appointment, and I get my pressures checked I get nervous of if I'm going to get like a high pressure*." (Child aged 13–17 years)

Requiring future surgery (2/18, 11%), forgetting to use their antiglaucoma medication (2/18, 11%) and changing ophthalmologist (1/18, 6%) caused concerns among fewer children.

> "*I don't want any more surgery. I'm done… it's just really scary*." (Child aged 13–17 years)

6.3.2.6 Theme 6: Social well-being

Having glaucoma caused social issues for 13/18 (72%) children. Schoolyard bullying was raised by 5/18 (28%) children irrespective of age. Bullying was attributed to their visual ability, need to wear spectacles, or need for sunglasses in the schoolyard.

> "*There are some kids at our school that have glasses that get bullied... Those kids have tried to bully me and my friends, so we have to defend ourselves*." (Child aged 8–12 years)

Several children (5/13, 28%), of whom 4/5 (80%) were aged 13 to 17 years, discussed feeling socially isolated by their condition due to its rarity. It was often relieved by a desire to meet another child with glaucoma.

> "*I'm a loner at my school… People are a bit standoffish. I don't think they really know how to approach me*." (Child aged 13–17 years)

Conversely, 6/18 (33%) children, of whom 4/6 (67%) were aged 8 to 12 years, reasoned that they had good social well-being.

> "*[My friends] all know about [my glaucoma] already… They just treat me the same.*" (Child aged 8–12 years)

6.3.2.7 Theme 7: Autonomy

Two-thirds (12/18, 67%) of children discussed issues relating to their autonomy. These were typically discussed by children aged 13 to 17 years compared to those aged 8 to 12 years (7/8, 88% vs 5/10, 50%). The main issue related to autonomy raised by younger children was that they wanted to administer their antiglaucoma medication without parental assistance. These children, however, frequently discussed being forgetful of when to use them.

> "*Most of the time I [put in the eye drops] myself and kept on forgetting.*" (Child aged 8–12 years)

All children aged ≥16 years (4/4, 100%) discussed issues becoming responsible for their own glaucoma care. These included actively engaging with the ophthalmologist and attending appointments without their parents, which were often met with feeling nervous or anxious.

> "*There's definitely questions I would like to ask but - I don't know…. I still get nervous asking."* (Child aged 13–17 years)

Among children aged 13 to 17 years, 4/8 (50%) wanted to know what caused their glaucoma and the risk involved in passing on their glaucoma to their future children.

> "*I'd definitely be interested to find out where I got it from… [but] if my children [have glaucoma], I guess it should be fine*." (Child aged 13–17 years)

The impact of glaucoma on their future career was discussed by 5/18 (28%) children, all of whom had bilateral or unilateral BCVA <0.5. Four (4/5, 80%) were aged 13 to 17 years.

> "*I can't actually join the Army, because of my lack of vision… It just sucks, because now I don't actually have a plan for my life*." (Child aged 13–17 years)

Two children aged 13 to 17 years (2/18, 11%), one of whom had bilateral BCVA <6/12, discussed future issues with obtaining a driver's licence whilst 3/18 (17%) children discussed issues with independently navigating environments due to their sight.

> "*I just think about what it'd be like if I could get a [driver's] licence, when I'm driving on the road… I don't know if some person would pick on me because of the condition that I have*." (Child aged 13–17 years)

6.4 Discussion

To the best of my knowledge, this exploratory interview study is the first qualitative study to explore the QoL issues experienced by children with glaucoma and therefore provides an original contribution to knowledge. Six of the seven themes identified were consistent with those reported in individuals with adult-onset glaucoma.[374,457] The impact of the condition on a child's autonomy was novel and provided a unique perspective of how childhood glaucoma impacts on the transition from childhood to adulthood. Each theme was relevant to all glaucoma subtypes and thus provided a thorough representation of how a child may live with glaucoma.

There are evidently several glaucoma-related non-visual and non-clinical variables that influence a child's QoL. Most notably, this includes how a child copes with their condition. Resilience, adaptation and establishing a positive relationship with the ophthalmologist were among the most common coping strategies identified. Becoming resilient was further identified as a coping strategy in children with cystic fibrosis,[458] spina bifida,[459] and type 1 diabetes.[460] This often assisted in self-management of their

condition, as observed in this study whereby children, particularly those aged 8 to 12 years, expressed a desire to self-manage their antiglaucoma medication. Conversely, older youths with spina bifida,[459] and children with type 1 diabetes,[461] were more likely to disengage in their care over time, possibly due to having increased medical responsibilities and feeling overwhelmed. The same trend may be occurring in this study whereby children aged older than 16 years discussed issues related to disengagement in clinical care.

This possible age-related coping trend regarding disengagement may be underpinned by concurrent QoL issues. In this study, it was observed that a greater proportion of children aged 13–17 years described more disruptions to QoL compared to children aged 8–12 years. These disruptions were particularly related to autonomy (becoming responsible for own care, career choices, driving, family planning), social well-being (social isolation) and ocular health concerns (increasing IOP). The latter may be particularly due to an increased understanding of glaucoma disease itself. Subsequently, these collective issues may contribute to a greater psychosocial impact of glaucoma in older children.

This hypothesis is opposite to findings in previous childhood glaucoma studies which reported lower VR-QoL and HR-QoL in younger children compared to their older counterparts.[309,310] Other characteristics including BCVA, disease laterality, gender and duration since surgery were not found to influence this age-related finding.[310] Consequently, it was hypothesised that an older child may experience better QoL as they may develop a better understanding of their condition and better coping strategies over time.[309,310] This has been referred to as the “response shift”.[310] In contrast, the findings from this study suggest there is an ‘implications shift’ whereby children appeared to be more concerned about limitations their glaucoma may place on their adult life as they enter adolescence. The apparent disparity between findings suggestive of a ‘response shift’ or an ‘implications shift’ may be explained by the studies’ different approaches (i.e., the use of a non-disease specific PROM to measure QoL,[309,310] compared to semi-structured interviews) or the clinical and demographic differences in the cohorts studied, including children’s abilities to respond to QoL-related questions. This age-related hypothesis could further be related to the small number of children interviewed in this study, as determined by thematic saturation, or the influence of age on maturity and the child’s ability to reflect on how childhood glaucoma may influence their lives. It would therefore be useful to further investigate the influence of ageing on QoL in a larger cohort and whether the ‘response shift’ or ‘implications shift’ is more likely to dominate the lived experience. This could be explored in future qualitative studies or quantitative association studies that utilise a childhood glaucoma-specific PROM. Nonetheless, our age-related findings are consistent with observations reported in children aged 14 to 18 years with cystic fibrosis who reported a greater disease-related impact on body image, emotional state and treatment burden

compared to younger children.[327] Adolescents with type 1 diabetes additionally reported issues balancing demands between medical management and non-disease related pressures of being an adolescent.[328] Disease stigmatisation, social isolation, self-image and school absenteeism concerns were otherwise experienced among children of any age with asthma and epilepsy,[462] type 1 diabetes,[460,461] and juvenile idiopathic arthritis.[463] Thus, the issues identified in children with glaucoma align with the greater childhood chronic disease experience and their impact may be exacerbated when a child approaches adulthood.

Clinicians should be aware of possible issues, particularly experienced during adolescence, as they may cumulatively influence the use of maladaptive coping and lead to medical negligence. Such coping behaviours could lead to worse visual outcomes. Adolescents may therefore require additional support to facilitate their transition toward adulthood and medical autonomy. In the clinical setting, this could involve provision of coping skills training, which aims to increase medical competence and the use of positive coping strategies.[464] This training has been successful for children with type 1 diabetes.[464] Ancillary ophthalmic personnel (e.g., orthoptists) may be best suited to facilitate this and future research could evaluate its effectiveness in children with glaucoma. Other support strategies in the clinical setting include development and delivery of educational material for children and their parents which details the medical and psychosocial aspects of their condition that may arise, and development of a healthcare transition plan that is formed with consultation between the child, their family, paediatric healthcare services and adult healthcare services.[465,466] Clinicians are also encouraged to view the child's condition within a wider social context and provide children with an opportunity to discuss concerns.[465,466] Parent-to-child transfer of glaucoma self-management may otherwise begin at any age by providing children with an active voice in their care and increasing their knowledge of their glaucoma, as encouraged in other childhood chronic conditions.[465,466] These processes, however, must be tailored to the child's maturity, visual abilities and emotional state, with consideration to potential parental anxiety over relinquishing control of care to their child.[467]

It is important to recognise that some QoL sub-themes identified in this study appeared to be raised by children irrespective of their clinical characteristics (i.e., BCVA and laterality). Previous research has demonstrated that VR-QoL is negatively associated with BCVA in the better-seeing eye in children with glaucoma.[306–309] Despite this, several studies have been unable to establish whether disease laterality is associated with VR-QoL.[306,307,309] Moreover, self-reported HR-QoL has not been found to be associated with disease laterality.[309,310] This suggests that unilateral disease may still impact QoL even if the child has normal BCVA in their better-seeing eye. The results of this study may offer some insight into these contradictory findings. Firstly, children with bilaterally impaired BCVA used adaptive

technology and did not consider that their participation in daily activities was impacted. The availability and use of such technology may therefore influence how a child responds to QoL-related questions. Secondly, children reported subjective symptoms including glare and reduced contrast sensitivity. These are yet to be measured as variables that may affect QoL in children with glaucoma.[306–310] Glare is a common symptom of childhood glaucoma and may impact participation in outdoor activities including sports. It is therefore possible that the experience of these symptoms has a greater impact on QoL than disease laterality. Lastly, few children in this study subjectively reported that they had reduced BCVA irrespective of objective measurements and laterality. This may further contribute to unexpected or conflicting findings in quantitative association studies. Evidently, the impact of childhood glaucoma on QoL extends beyond a child's clinical characteristics and their subjective experience must be considered in clinical management of the condition.

To guide glaucoma management and enable more accurate investigation of the influence of clinical and demographic variables on QoL, a childhood glaucoma-specific PROM must be developed. Prior research has instead utilised VR-QoL (Impact of Vision Impairment for Children Questionnaire[325])[306–309] and HR-QoL measures (Kidscreen-27 Questionnaire,[324] PedsQL 4.0[323])[309,310] that do not measure disease-specific QoL issues such as those identified in this study (e.g., concern for IOP, feeling misunderstood due to disease rarity). A childhood glaucoma-specific PROM will substantially improve our understanding of the disease impact and inform clinicians and education providers of QoL issues encountered by children. The results of this study will assist with the identification of items for a childhood glaucoma-specific PROM for children. This thesis does not entail the development of a childhood glaucoma-specific PROM suitable for children beyond that described in Chapter 6 as this required a large sample size (n=64–144) that was not considered feasible.[468]

Study limitations include that children were recruited from a national registry and interviewed after receiving parental consent and child assent. Consequently, the child and/or parent may be more willing to participate and may be less impacted by childhood glaucoma than non-respondents and/or their parents. Furthermore, children resided in Australia and the majority were of self-reported European ancestry. Consequently, the findings of this study may only be relevant to cohorts with similar socio-demographics, healthcare, and education systems, and those with similar access to resources supporting visual functioning. Children with disease onset at age 16 or 17 years were unable to be recruited, likely owing to the narrow time frame between reaching adulthood and time required to conceptualise their diagnosis before agreeing to be interviewed. The experience of someone diagnosed at this age is otherwise captured in a consecutive study on QoL in adults with childhood glaucoma (Chapter 7). Furthermore, more children interviewed had unilateral disease compared to non-

respondents, and most children had no vision impairment in their better eye. It is unknown how these characteristics may have influenced results as thematic saturation was reached. Inclusion of additional children with bilateral visual impairment may have resulted in more prominent themes pertaining to visual impairment such as mobility, and deeper exploration of associations between some sub-themes and clinical characteristics. Lastly, the interviews specifically evaluated the impact of glaucoma such that the influence of conditions unique to uveitis, aniridia, SWS and ARS were not included in the analysis. However, it remains possible that the physical manifestations of these conditions have impacted the QoL outcomes of this study.

Despite these limitations, this study provided unique insight into the QoL issues experienced in childhood glaucoma from the perspective of the child. This rare condition may cause a considerable impact upon a child's physical, emotional, and social well-being which is managed with the use of coping strategies. Overall, our findings suggest that older children may experience more QoL issues compared to their younger counterparts and hypothesise that increasing age may be associated with a lower QoL. Healthcare professionals and parents should be mindful of this trend, and social and ophthalmic interventions may be required to support a child as they transition into adulthood and achieve medical autonomy. Future research endeavours should evaluate the most appropriate method to facilitate medical autonomy and subsequently ensure that any individual with childhood glaucoma achieves the best possible long-term visual and quality of life outcomes.

CHAPTER 7 QUALITY OF LIFE IN ADULTS WITH CHILDHOOD GLAUCOMA

Published manuscript

The contents of this chapter have been published in a peer-reviewed manuscript of which I am the first author: **Knight LSW**, Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. Quality of life in adults with childhood glaucoma: an interview study. ***Ophthalmol Glaucoma***. 2022;5(3):325-36.

My contributions to the manuscript involved the research conception and design (80%), data collection including interviews with participants (100%), data analysis including identification of themes (100%), interpretation of the data (90%), and drafting the manuscript (100%). All other authors assisted with interpretation of the data and critically revising the manuscript. Emmanuelle Souzeau and Mallika Prem Senthil were further involved in research conception and design (20%). Project funding was provided by Emmanuelle Souzeau, Jamie Craig, Mallika Prem Senthil and myself.

The introduction and methods of this manuscript have been edited to fit the structure of this thesis.

7.1 Introduction

It was hypothesised in Chapter 6[358] that the psychosocial impact of childhood glaucoma may worsen as an individual ages and may result in neglect of glaucoma care. This trend remains a concern as it could lead to unfavourable disease outcomes. However, little is known about the QoL issues experienced in adults with childhood glaucoma. There are only two quantitative studies that have investigated the QoL of adults with childhood glaucoma, and each has used non-glaucoma specific PROMs to measure HR-QoL, VR-QoL and life satisfaction.[311,312] These PROMs included the WHOQoL-BREF,[330] for measurement of HR-QoL, the NEI-VFQ 25[329] for measurement of VR-QoL and the 5-item Satisfaction with Life Scale,[331] for measurement of life satisfaction. None of these PROMs, however, were designed for adults with childhood glaucoma such that they may not provide an accurate measure of QoL and may result in a possible incomplete understanding of the disease impact. Studies have nonetheless found considerable dissatisfaction with life,[311] and lower VR-QoL and HR-QoL in some adults with childhood glaucoma.[312] It was reported that worse visual field loss was associated with worse VR-QoL,[312] whilst no clinical variable, including BCVA, was associated with HR-QoL or life satisfaction measures.[311] Interestingly, a lower education and rural residence was associated with worse HR-QoL while being unmarried was associated with lower life satisfaction.[311] It is unclear, however, whether these social factors were at all related to the experience of having childhood glaucoma because the use of a PROM, which has a set list of questions, does not lend itself to explore such possibilities. This is better explored using semi-structured interviews, which allow for an in-depth exploration of how childhood glaucoma can impact QoL as per Chapter 6.[357,358]

No studies have evaluated the impact of childhood glaucoma on family planning or explored the use of coping mechanisms in adults with childhood glaucoma. Given that childhood glaucoma is predominantly an inherited disease (Chapter 3),[7,386] it is important to investigate how the condition may impact decision-making in family planning and reproductive options. This would further support our understanding of how the condition may influence QoL and help inform genetic counselling practices on concerns surrounding conception and parenthood in this cohort. Investigation of the use of coping strategies in adults with childhood glaucoma would further support our understanding of the psychosocial impact of the condition.

My original contribution to knowledge was the development of a thorough understanding of the childhood glaucoma-specific QoL issues experienced by adults with childhood glaucoma using qualitative analysis. The issues identified may be relevant for the development of mental health issues identified in Chapter 5 and continue to support that psychological support may be required for individuals

with childhood glaucoma. Findings from this study also informed the development of a childhood glaucoma-specific PROM suitable for adults with the condition (Chapter 9).

7.2 Methods

7.2.1 Participants

A non-probability convenience sampling technique was used to recruit participants from the ANZRAG. This is a technique that describes the selection of a readily accessible cohort for the purpose of the research.[418] The ANZRAG is a large Australasian glaucoma registry designed to identify genes associated with glaucoma, whereby all participants undergo genetic testing.[386] It therefore provided a suitable cohort to evaluate the effect of childhood glaucoma on QoL and family planning. Adults were eligible to be interviewed if they currently resided in Australia, were English speaking, had a diagnosis of any subtype of childhood glaucoma (before age 18 years) in at least one eye as per the CGRN criteria,[4] and were ≥18 years of age at the time of their interview. Participants were excluded if they had coexisting ocular disease unrelated to the spectrum of childhood glaucoma, had a hearing or cognitive impairment, or other disability impacting on QoL (e.g., intellectual disability, motor disorder) as informed by their referring glaucoma specialist or primary caregiver.

Individuals meeting the eligibility criteria were invited to participate in the study by mail and asked to return their interest. Those who expressed interest in being interviewed were sent an information pack and consent form. Once written informed consent was obtained, an appropriate interview time was organised. This initial contact helped develop participant rapport prior to the interview. This was particularly important where an individual was visually impaired and unable to read print material easily. If no reply was received within two weeks, a follow-up phone call was initiated. Participants were deemed non-contactable after a minimum of two unsuccessful attempts.

Clinical details of participants were obtained from their medical records, including glaucoma subtype, BCVA, disease laterality, age at diagnosis and the number of topical antiglaucoma medications being used at the time of the interview. The glaucoma subtype was classified according to the CGRN criteria.[4] Disease onset at 4 years of age or later was considered juvenile.[4] Glaucoma severity was defined as advanced or non-advanced as per Chapter 2.[171,335] To understand the structural and functional implications of an individual's glaucoma severity status, their self-reported ability to drive a personal vehicle was used as it can provide a measure of disability.[469] To operate a motor vehicle in Australia, an individual is required to have ≥110 degrees of the horizontal visual field, no significant central defect within 20 degrees superior or inferior to the midline, and binocular BCVA ≥6/12.[470] Visual field indices were not used as a marker of visual disability because there is yet to be consensus regarding the

relationship between these variables.[471] Furthermore, visual field indices may not be reliable in individuals with BCVA <6/18.[395] BCVA was categorised according to the International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision) as outlined in Chapter 2.[337]

Ethical approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/161) and the study adhered to the tenets of the Declaration of Helsinki.

7.2.2 Interviews

A semi-structured interview guide was developed from a literature review of studies investigating QoL issues in children and adults with childhood glaucoma, the PROMs used in each study, and PROMs used to investigate QoL in adult-onset glaucoma, as described in Chapter 2.[306,307,309–312,359–361] The interview guide consisted of questions related to schooling, employment, role performance, medical care, mobility, interpersonal relationships and family-planning (e.g., *Do you feel that having glaucoma determined what you are doing now? Does/did having glaucoma change or impact your decision to have any children?*). Questions regarding the emotional, social, and psychological consequences of the condition were further asked (e.g., *Because of your glaucoma, do you feel in control of your life?*). The complete set of questions is provided in Appendix A, Interview Guide A2.

I had conducted all semi-structured interviews one-on-one via telephone or Cisco WebEx, subject to participant preference (n=47). For this study, most individuals preferentially selected a telephone interview (n=46), although reasons for this were not investigated. Participants were informed that I was completing a Doctor of Philosophy and no participants were under my care. Participants were asked to be alone during the interview to eliminate external influences of responses. All interviews were audio-recorded and transcribed verbatim. As described in Chapter 2, interviews continued until thematic saturation was achieved, defined as the point where no new information was gained from subsequent interviews.[363] Thematic saturation occurred after the 39th interview. An additional eight interviews with individuals already recruited to the study were conducted to confirm data saturation. Recruitment ceased thereafter. Adult participants were offered the opportunity to review their transcript for accuracy and receive information on counselling services if desired.

7.2.3 Data analysis

Data analysis including coding of transcripts and identification of themes was performed as previously described (Chapters 2 and 6).[358]

7.3 Results

7.3.1 Participants

A total of 130 eligible adult individuals from the ANZRAG were sent an invitation to be contacted about the study. Of these, 47 participants (36%) were interviewed (Figure 7.1). Reasons for declining to participate were not recorded due to the sensitive nature of the study. Participant characteristics are detailed in Table 7.1. There were no significantly different characteristics between the participants recruited and those who could not be contacted or declined participation (Appendix B, Table B12).

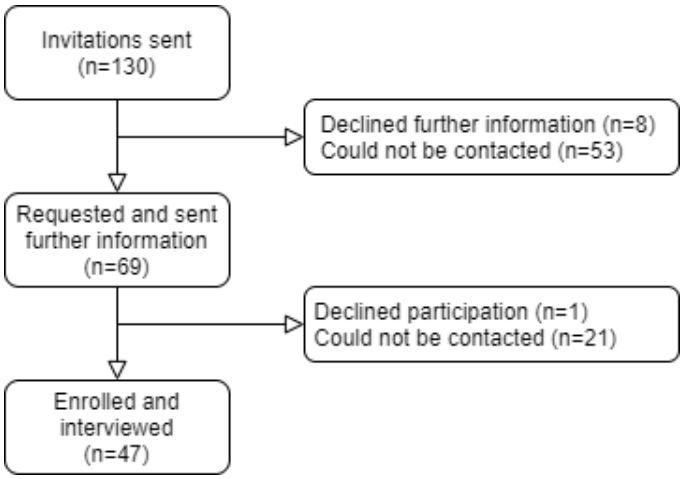

Figure 7.1. Flow chart of participant recruitment for interviews with adults with childhood glaucoma

Interviews were conducted between February 2020 and March 2021. The average interview length was 66±23 minutes and mean participant age was 40.0±15.3 years. The mean time elapsed between the interview and last clinical examination was 4.9±4.15 months. The regularity of participants' appointments was ≤3–monthly (15/47, 32%), 3–≤6-monthly (25/47,53%) and yearly (6/47, 13%). One participant reported that they no longer undergo ophthalmic examinations as they had hand movements vision and consequently did not believe ophthalmic follow-up was necessary. Glaucoma care was provided by multiple specialists at several centres across Australia. One co-investigator (JEC) was identified as a treating specialist for nine participants, but was not involved in participant recruitment, interviewing or data analysis.

Table 7.1. Demographic and clinical characteristics of adults interviewed

Variable	n (%)[†]
Age at glaucoma diagnosis	
<4 years	30 (64)
Years since diagnosis (median, IQR)	34 (23–50)
Age at interview	
18–29 years	14 (30)
30–39 years	9 (19)
40–49 years	10 (21)
≥50 years	14 (30)
Gender, female	26 (55)
Laterality of glaucoma, bilateral	43 (91)
Self-reported ancestry, European	40 (85)
Subtype of childhood glaucoma	
Primary congenital glaucoma	27 (57)
Juvenile open-angle glaucoma	11 (23)
Glaucoma associated with non-acquired ocular anomalies	8 (17)
Axenfeld-Rieger syndrome	4 (9)
Aniridia	3 (6)
Iris coloboma	1 (2)
Glaucoma following cataract surgery	1 (2)
Glaucoma severity status	
Advanced, bilateral	15 (32)
Advanced, unilateral & non-advanced, unilateral	15[a] (32)
Non-advanced, bilateral	17[b] (36)
Self-reported ability to drive a personal vehicle	
Unable to drive	20 (43)
Advanced glaucoma, bilateral	15 (32)
Advanced, unilateral & non-advanced, unilateral	3 (6)
Non-advanced, bilateral	2 (4)
Number of topical antiglaucoma medications currently using	
0	19 (40)
1	16 (34)
2	11 (23)
3	1 (2)
Ocular complications	
Ocular prosthesis	5 (11)

Retinal detachment			4 (9)
Corneal transplant			3 (6)
Genetic results			
Molecular diagnosis identified			27 (57)
Autosomal recessive inheritance			16 (34)
Autosomal dominant inheritance			11 (23)
First degree relative affected by glaucoma, yes			17 (36)
Parenting status, has children			21 (45)
Vision category	**BCVA**	**Better Eye BCVA (n, %)**	**Worse Eye BCVA (n, %)**
No vision impairment	≥6/12	30 (64)	13 (28)
Mild vision impairment	<6/12 - ≥6/18	4 (9)	1 (2)
Moderate vision impairment	<6/18 - ≥6/60	5 (11)	8 (17)
Severe vision impairment	<6/60 - ≥6/120	3 (6)	3 (6)
Blindness	<6/120 - CF	3 (6)	5 (13)
	HM or LP	2 (4)	7 (15)
	NLP	0 (0)	10 (19)

IQR: interquartile range; BCVA: Best-corrected visual acuity; CF: count fingers; HM: hand movements; LP: light perception; NLP: no light perception
†: n (%) presented unless otherwise specified
[a]Includes two unilateral cases with advanced glaucoma in one eye
[b]Includes two unilateral cases with non-advanced glaucoma in one eye

7.3.2 Quality of life themes

Ten QoL themes, and their subthemes, were developed. The total proportion of participants experiencing issues within the QoL theme and coded segments per theme are shown in Table 7.2. A mind map of the themes and subthemes is supplied in Appendix C, Figure C8.

Table 7.2. Quality of life themes identified in adults with childhood glaucoma

Theme Number	Major quality of life theme	Participants n (%)	Number of coded segments
1	Coping: Adaptive and maladaptive coping strategies are used to manage stressors related to childhood glaucoma	47 (100)	1235
2	Emotional wellbeing: Disease rarity, chronicity and sequelae mediates the emotional response	47 (100)	1137
3	Ocular health concern: Disease incurability inflicts several ocular health concerns	46 (98)	406
4	Symptoms: Disease permanence causes unwanted visual and non-visual symptoms	45 (96)	279
5	Family planning: An individual's experience of childhood glaucoma mediates decision-making in family planning	43 (91)	227
6	Inconveniences: Disease chronicity causes several disruptions to daily life	40 (85)	194
7	Social wellbeing: Peer awareness, understanding and acceptance influences the individual's social network	39 (83)	266
8	Activity limitation: Participation in daily life may be limited by disease sequelae	36 (77)	185
9	Economic: Clinical costs and career options may threaten financial security	36 (77)	123
10	Mobility: Disease sequelae may cause mobility issues	21 (45)	72

7.3.2.1 Theme 1: Coping

As per Table 7.2, all participants used coping strategies to mediate the social, emotional, and physical consequences of childhood glaucoma. Positive adaptive coping strategies included emotion-focused strategies, which are used to regulate negative emotions.[456] These included being resilient, which was adopted by 35/47 (74%) participants, while 24/47 (51%) participants expressed acceptance of their eye condition. Physical exercise, meditation, using humour and being determined to remain independent were also frequently adopted. Meanwhile, 3/47 (6%) participants stated that they sought psychological support whilst 40/47 (85%) participants indicated they relied on family, friends, and spouses for emotional support.

> *"We were matter of fact, you did what you had to do and just... got on with life."* (P06)

> *"I think it's probably put my life in a better mindset and vision sort of thing. For myself now and [in] the future."* (P07)

Positive problem-focused adaptive strategies, which are active behaviours that directly eliminate sources of stress,[456] were used. These included adapting to disease limitations and having a positive

relationship with their ophthalmologist, which were used by 37/47 (79%) and 34/47 (72%) participants, respectively. The latter also eased health anxieties.

> *"Having it since I was so young... this is what I've got and this is how I need to act to make the best use of it so I can still function."* (P38)

> *"I love my eye doctor… I've had him forever. I feel so comfortable… and trust him."* (P01)

Maladaptive coping strategies were adopted by approximately half of participants. Avoiding thoughts about their current or future glaucoma status was reported by 22/47 (47%) participants, of whom 15/22 (68%) had no vision impairment in their better eye. Ignoring their glaucoma care, including delaying their appointment and nonadherence to antiglaucoma medication use, was reported by 21/47 (45%) participants, of whom 15/21 (71%) had no vision impairment in their better eye and 17/21 (81%) were reviewed >3 to ≤6 monthly or yearly. Meanwhile, this coping strategy was not dependent on whether an individual was currently using antiglaucoma medication or not (10/19, 53% not using medication vs 11/28, 39% using ≥1 medication). Furthermore, there was a trend for participants aged <40 years to use maladaptive coping techniques more often than their older counterparts. In contrast, the use of positive adaptive strategies increased with age as demonstrated in Figure 7.2.

> *"I try not to think about it too much because I sort of can't see the situation getting better, only really worse."* (P03)

> *"I had [eye drops for glaucoma] but I never stuck to it, I kind of just gave up on it for probably like six months, maybe eight months."* (P29)

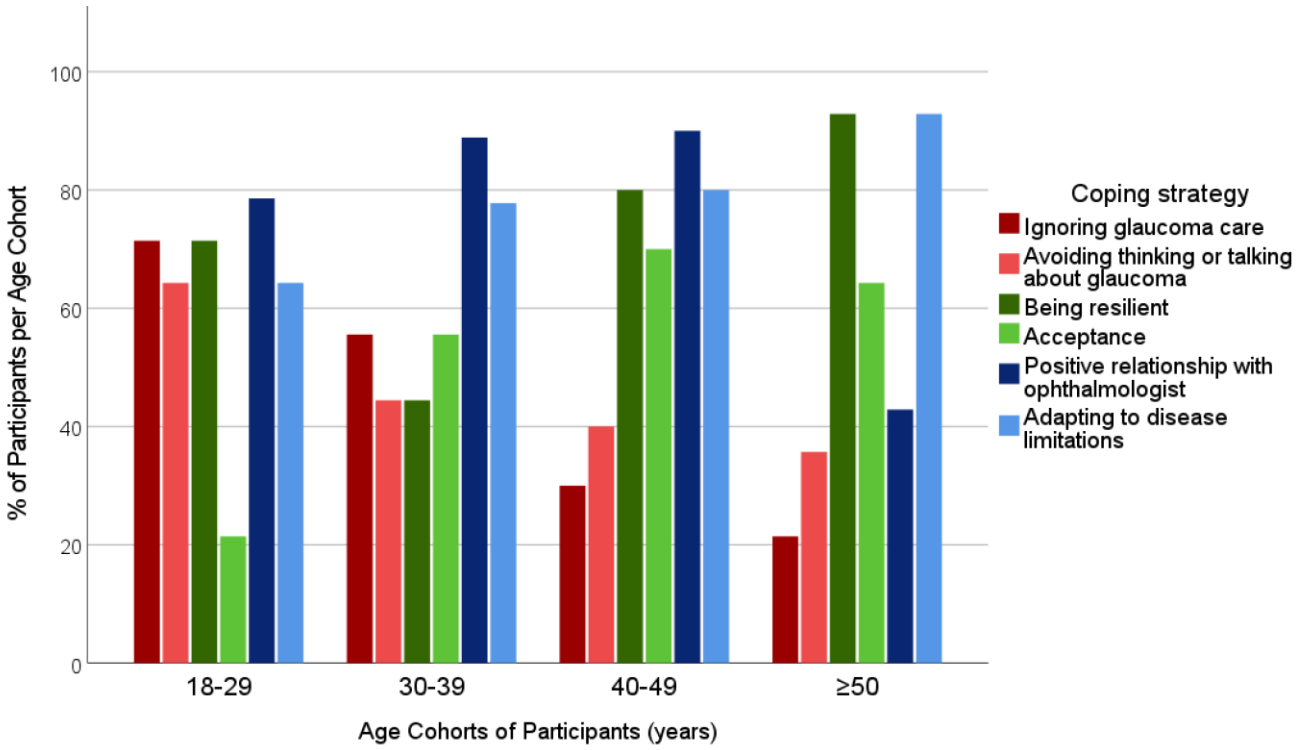

Figure 7.2. Comparison of coping strategies adopted in adults with childhood glaucoma per age group

Cluster bar chart comparing the percentage of participants per age group who made statements regarding the use of maladaptive coping strategies (in shades of red) and adaptive coping strategies that are emotion-focussed (in shades of green) and problem-focussed (in shades of blue). The number of individuals within each age cohort is provided in Table 7.1.

7.3.2.2 Theme 2: Emotional well-being

Having childhood glaucoma resulted in a spectrum of negative emotions in all participants. Most participants (41/47, 87%) expressed feelings of being misunderstood. This was commonly attributed to having a rare disease.

> *"It's not really a common thing for someone so young to experience… You can't really talk to anyone about it because they don't understand what it's all about."* (P03)

Feeling self-conscious (37/47, 79%) was commonly experienced due to the appearance of the eye (29/37, 78%), using vision aids (11/37, 30%) and having poor visual ability (10/37, 27%). Appearance concerns were often attributed to having buphthalmos, sensory strabismus and corneal opacification. Eight participants further described being self-conscious of their pupil size, of which two had ARS. Four participants recalled being self-conscious of their phthisical eye, which was relieved in three individuals who now have a prosthetic eye.

> *"It's just very cloudy and it doesn't look so nice… I probably tend to hide behind dark glasses when I can."* (P22)

Losing vision or having low vision caused 27/47 (57%) participants to feel frustrated due to the associated or perceived limitations of their abilities. Of these individuals, 12/27 (44%) were still able to drive a motor vehicle.

> *"I have a problem with people using blind so flippantly. And calling me blind… It's a triggering word to me."* (P10)

A third of participants (16/47, 34%) experienced regret for several reasons. Most of these individuals were female (11/16, 69%) or were aged ≥40 years (11/16, 69%). Regrets commonly reported included not accepting or understanding their visual limitations earlier, resulting in a physical injury and neglect of their glaucoma care, often resulting in permanent vision loss.

> *"I know it sounds crazy in retrospect, but because it didn't actually change my life, I didn't take it as seriously… [and] I have to live with that for the rest of my life."* (P08)

Negative emotions were overall often mitigated by feeling hopeful for future medical advances to repair optic nerve head damage.

> *"I would hope that it would get better as opposed to worse with all the new medical procedures and medications available."* (P01)

7.3.2.3 Theme 3: Ocular health concerns

Almost all participants (46/47, 98%) experienced concern for their ocular health. Disease-specific concerns such as IOP control were reported by 25/47 (53%) participants.

> *"This last time [when the pressure rose] was very stressful, like I felt sick because I was so scared, because what if the eye drops don't work?"* (P44)

Requiring future glaucoma surgery caused great concern amongst 24/47 (51%) participants irrespective of their past surgical care. Furthermore, 19/30 (63%) individuals with no vision impairment in their better eye, of whom 12/19 (63%) had BCVA <6/12 in their worse eye, often experienced this concern as fear and anxiety.

> *"I think if I would have to have my eye surgery, it would send me off the deep end… I'm really hoping I don't ever have to have that."* (P26)

Many participants discussed concerns about losing their vision (25/47, 53%) or their independence in the future (15/47, 32%). These concerns were expressed by 16/25 (64%) and 12/15 (80%) individuals, respectively, with no vision impairment in their better seeing eye. Of these individuals, 9/16 (56%) and 8/12 (67%) had BCVA <6/12 in their fellow eye, respectively. Age and gender did not otherwise appear to be influential.

> *"I do worry, basically losing vision… and the impact on my family, on my career, on my life, and everything."* (P27)

Other ocular health concerns included the side effects and long-term use of anti-glaucoma medications and developing another eye disease later in life. Notably, 18/47 (38%) participants described being hypersensitive to objects going near their eyes.

> *"I almost put the safety glasses on to go out and move the rubbish bin."* (P31)

Changing ophthalmologists caused anxiety among 20/47 (43%) participants as they were concerned about being treated by someone unfamiliar.

> *"He's the only ophthalmologist that I've ever seen… I'd be apprehensive about going to find another ophthalmologist."* (P19)

7.3.2.4 Theme 4: Symptoms

All participants, except two, reported unwanted visual and non-visual symptoms (45/47, 96%). The most common visual symptoms reported by participants were glare (29/47, 62%), blurred vision (29/47, 62%) and reduced peripheral vision (25/47, 54%). These symptoms were not dependent on disease laterality, BCVA in the better eye, ability to drive a motor vehicle, or glaucoma subtype and were often described alongside having poor depth perception. Symptoms of reduced contrast sensitivity and night vision, however, were exclusive to individuals with bilateral disease but were not dependent on visual status.

> *"My sight is an awful lot worse outside… because of the increasing light sensitivity and glare."* (P12)

Non-visual symptoms typically included soreness and dry eyes, irrespective of anti-glaucoma medication use (14/47, 30%). Ocular pain was frequently recalled to be experienced post-surgery, whilst severe headaches were described during times of IOP spikes.

7.3.2.5 Theme 5: Family planning

Concerns regarding family planning featured highly in the cohort interviewed (43/47, 91%). Thirty-one participants (31/47, 66%) worried about their child inheriting glaucoma because they did not want them to have the same experiences or risk them being visually impaired. Majority of these individuals had vision impairment in one or both eyes (22/31, 71%). Furthermore, this worry was observed in 17/26 (65%) individuals who had not yet had children and 14/21 (67%) individuals who already had children. In addition, 23/30 (77%) individuals without an affected first-degree relative expressed such worry compared to 8/17 (47%) of those with a relative with glaucoma.

> *"I used to have nightmares about it. I actually used to wake up in the middle of the night, thinking I've – he's going to have glaucoma."* (P18)

> *"I have been scared that I'll, you know, pass on the weaker genetics of my eyes and also for a very long time I'm really scared… that I'd go blind before I'd even be able to look my child in the face."* (P47)

Consequently, 28/31 (90%) participants who experienced this worry, of whom 19/28 (68%) were female, indicated they sought (n=22) or would seek (n=6) genetic testing and counselling for peace of mind. Of the 22 who had already sought genetic testing and counselling, 21/22 (95%) were aged >30 years and 17/22 (78%) had children. All individuals who indicated they would seek genetic testing were <30 years of age and did not yet have children. The inheritance pattern did not appear to influence this decision-making process. Five participants considered their reproductive options including using *in vitro* fertilisation or having children through adoption, and three participants decided not to have children.

> *"[Genetic testing] did [give me peace of mind]… I wouldn't want someone to go through like the same things as me, so especially not one of your kids. So it did, it helped."* (P29)

> *"I will never have children because I will either require them to give me assistance or they may be born with the disorder."* (P46)

Nine participants (9/47, 19%) expressed concerns in not being able to fulfil typical parental duties. Issues raised centred on their child's safety and ability to drive their child to school or extracurricular activities. Majority of these individuals were female (8/9, 89%), already had children (7/9, 78%), or had vision impairment in both eyes and were unable to qualify for a driver's licence (5/9, 56%).

> *"I want to have a wife and kids, but... I wouldn't be able to drop them off at school, or pick them up, or run errands for them… [I cannot] contribute in that way."* (P30)

These views were balanced by fewer participants (13/47, 28%), who indicated they did not feel the need to access genetic counselling. These views were not influenced by age, although 8/13 (62%) individuals did not have children and the majority (11/13, 85%) had no visual impairment. This view was often attributed to having knowledge of what glaucomatous signs to look for or being confident that their child's QoL would not be impacted as they were able to cope with their own condition.

> *"I feel that it never stopped me doing anything in my life... If a child has it, we'll deal with it and move from there."* (P06)

7.3.2.6 Theme 6: Inconveniences

Most of the participants (40/47, 85%) stated that they experienced several inconveniences related to their condition. Participants reported being bothered by having to perform routine clinical tests (17/47, 36%), having to schedule an appointment around employment commitments (13/47, 28%), and clinic waiting time (10/47, 21%). The majority of all the individuals who complained of clinical tests (16/17, 94%), appointment scheduling (12/13, 92%), and waiting time (10/10, 100%) were of working age (i.e., <65 years of age).

> *"I'm always rushing to get there because [of] work... You try and finish your job and - and - and you have to run off and have your appointment."* (P41)

Inconveniences related to topical antiglaucoma medication were reported by 14/47 (30%) participants. Fewer participants complained of having to wear high prescription glasses (8/47, 17%) or contact lenses (5/47, 11%) due to their buphthalmos.

> "*If I'm out in the evening, I have to kind of plan out...* "*Oh, I've got to be back at this time so I can put [my drops] in.*" (P25)

Taking longer to perform visual tasks was expressed as an inconvenience by 9/47 (19%) participants. Of these 9 participants, 5/9 (56%) had BCVA <6/12 in their better seeing eye whilst the other 4/9 (44%) self-reported that they were able to operate a motor vehicle. Having to rely on someone else, and using public transport or taxis for general travel, was experienced by half of the individuals who self-reported that they did not meet visual requirements for operating a motor vehicle (10/20, 50%).

> *"How much easier is it to go and be in control of [when you leave an event] and hop into your car as opposed to, "I've got to ring a taxi and I've got to wait for it?"* (P04)

7.3.2.7 Theme 7: Social well-being

Issues pertaining to social well-being were reported by 39/47 (83%) participants. Having a strong desire to hide their condition from their colleagues or peers, because they did not want to appear different, was discussed by 23/47 (49%) participants. Such comments were more frequently made by females compared to males across the cohort (15/26, 58% vs 8/21, 38% respectively).

> *"I don't feel like I need to…. tell everyone, "Oh look, by the way, I can't see".... I will never feel comfortable with it."* (P14)

Seventeen participants (17/47, 36%) recalled experiencing schoolyard bullying during their childhood, which may have had implications for their confidence in adulthood. Notably this was experienced by 7/8 (88%) with SG-O, 9/27 (33%) with PCG and 1/11 (9%) with JOAG. Participants frequently stated they were bullied due to needing to wear glasses, wearing an eye patch for amblyopia therapy, having buphthalmos, having poor vision or using vision aids. Two participants attributed being bullied due to the shape of their pupil: one participant with PCG had iatrogenic corectopia from surgery, whilst the other had pseudopolycoria secondary to ARS. Participants however often expressed that they became resilient in their adulthood due to childhood bullying.

> *"I got used to being called 'four eyes' and that sort of thing.... I think it did — has affected my — with being more shy and — and less confident."* (P28)

Because of the future uncertainties of disease progression, 17/47 (36%) participants expressed difficulty in establishing and maintaining close or intimate relationships. This was often attributed to fear of becoming reliant on someone and was commonly expressed by individuals aged >50 years (10/17, 59%).

> *"I wonder if someone wouldn't be interested in me because they'd be like – oh I'm going to have to take care of her because she's not going to have any eyesight."* (P44)

Receiving inadequate support in the workplace or experiencing workplace discrimination was stated by 18/47 (38%) participants. Conversely, 5/47 (11%) participants discussed good workplace relations, whereas overall, 41/47 (87%) participants stated they had good support from a variety of other established social networks, including close friends, family members and spouses.

> *"Some of the things they said they [did a work assessment on] weren't tested on. I think it was just a way to alleviate me [of my responsibilities] without being held at a legal responsibility."* (P16)

7.3.2.8 Theme 8: Activity limitations

Activity limitations were reported by 36/47 (77%) participants. Sporting activities or exercise was the most common activity that individuals with childhood glaucoma could not participate in to the extent they desired (25/47, 53%). It was more commonly reported by males compared with females (13/21, 62% vs 12/26, 46%, respectively) and those unable to drive a motor vehicle (15/25, 60%), despite almost half (12/25, 48%) of individuals recording normal BCVA. Ball sports and team sporting activities such as Australian rules football and netball were problematic, particularly where the game was played outdoors in bright conditions. Running and cycling were also often made challenging where peripheral vision was reduced.

> *"Anything with a fast-moving ball. Unless it was coming directly at me low enough down in my field of vision, I wouldn't be able to see it coming to catch it."* (P13)

Being unable to drive a motor vehicle was almost as restrictive as participating in sporting activities (20/47, 43%). No individual with bilateral advanced glaucoma (15/15, 100%) held a driver's licence. Conversely, 8/27 (30%) individuals who were able to hold a driver's licence, found driving at night, dusk or dawn, most problematic and consequently did not drive at these times.

> *"The biggest thing in my life is that I wasn't able to drive. If I could have an eye transplant… [it would] probably change my life all the way totally."* (P41)

The ability to read near and distance objects was limited for 10/47 (21%) and 15/47 (32%) participants, respectively. This was typically experienced by individuals with BCVA <6/12 in their better eye. Fourteen participants (14/47, 30%) recalled difficulty in reading the board at school from a distance, which transferred to difficulties in learning and not being able to see a presentation in a workplace or university. In contrast, 15/47 (32%) participants experienced no limitation in performing daily tasks. Of these, 3/15 (20%) were unable to drive a motor vehicle while the remaining 12/15 (80%) had no visual impairment in their better eye.

> *"It takes me longer…. [to find] the one particular critical information in an entire book… A needle in a haystack, that's what it's like." (*P02)

7.3.2.9 Theme 9: Economic

The majority of participants (36/47, 77%) stated they had financial, or employment concerns caused by their glaucoma. The main financial concerns were costs associated with seeing their glaucoma specialist, including the consultation fee and ancillary tests (12/47, 26%), and the cost of glaucoma medication and surgery (9/47, 19%). The former was more commonly expressed by individuals aged

>50 years (8/12, 67%). The financial impact varied depending on whether the participant stated that they were currently receiving welfare payments, had a well-paying occupation, had private health insurance, or were treated in a public hospital, which incurs no cost to Australian residents. Consequently, 12/47 (26%) participants, all of whom were of working age (i.e., <65 years), explicitly stated that they experienced no financial burden.

> *"It's not just clinical. It's also financially really hard as well.... it's been expensive for me and my husband."* (P23)

Several participants experienced employment concerns. Twenty participants (20/47, 43%), of whom 16/20 (80%) were aged <50 years, stated that they were limited in what career they were able to pursue (e.g., pilot, police officer, nurse). Eight of these individuals (8/20, 40%) had no vision impairment in their better eye, although 5/8 (63%) had a vision impairment in their worse eye.

> *"I wanted to be a doctor or vet… but any deterioration [in my vision] and you know, that's what, eight years of study, work placement and internship down the drain."* (P30)

Moreover, several participants (13/47, 28%) were concerned that their ability to perform work tasks would be affected, often resulting in a fear of failing work performance reviews or losing their job.

> *"I was always getting into trouble for missing bits and pieces for that sort of job… I try really hard and I can't see it… and you get picked on for it."* (P13)

7.3.2.10 Theme 10: Mobility

Mobility issues were experienced by 21/47 (45%) participants, all of whom had BCVA <6/12 in their worst eye. Similarly, the majority (6/8, 75%) of individuals with visual acuity <6/60 in their better-seeing eye and the majority of those unable to drive a motor vehicle (16/20, 80%) reported mobility issues. Bumping into objects on one side was stated by 12/47 (26%) participants, of whom 11/12 (92%) had BCVA <6/12 in their worst eye.

> *"If I'm walking down the outside or if someone's coming up on my left side, like I'll usually end up moving myself over a bit too much and running myself into something."* (P47)

Difficulties in using public transport (12/21, 57%), navigating unfamiliar environments (10/21, 48%) or navigating crowded places (7/21, 33%) were also reported amongst those with mobility issues. All mobility issues reported did not appear to be influenced by the participant's age.

"People look at me now even with the cane bobbing along the street or in the shopping centre. I've got focused on what I have to do and the brain gets so tired… sometimes I get myself in a real mess!" (P35)

7.4 Discussion

In this exploratory qualitative research study, the psychosocial impact of childhood glaucoma experienced by adults of predominantly European ancestry was examined. To the best of my knowledge, this is the first study to qualitatively investigate the lived experience of childhood glaucoma in adults and therefore provides an original contribution to knowledge. I performed comprehensive interviews covering all aspects of life for affected individuals. Nine of the ten themes herein identified are consistent with those reported in studies involving adults with adult-onset glaucoma.[374,457] The impact of childhood glaucoma on family planning was a novel finding. Each theme was relevant to all glaucoma subtypes herein described and therefore provided a detailed description of the collective childhood glaucoma experience.

The most prominent theme identified was coping. Majority of the participants adopted positive coping strategies which were problem-focused (i.e.., changing behaviours to mitigate the problem) and emotion-focused (i.e., regulating emotions in response to the problem), as defined by the Stress and Coping Model.[456] These included acceptance, humour and social support, which is consistent with reports of coping strategies in adults with other hereditary ocular diseases, including retinitis pigmentosa[472] and Stargardt's disease.[473] Alternatively, maladaptive avoidance coping strategies were reported by nearly half of the individuals in this study, particularly those aged less than 40 years and those with no vision impairment in their better eye. To my knowledge, no studies have investigated the use of coping strategies in adults with childhood glaucoma, why this age phenomena may occur or the effect it may have on glaucoma progression, and contributes to the finding that adolescents may use maladaptive coping too (Chapter 6).[358] It may be a result of younger individuals not being able to fully grasp the longevity of their glaucoma, having alternate priorities or having negligible activity limitations, as hypothesised by Gupta and colleagues.[332] It could additionally be due to nonacceptance of their condition, as seen in adult survivors of retinoblastoma, a childhood ocular cancer, who have been reported to avoid coping with their emotions using internalisation.[474] The association between the use of avoidance coping and age is nonetheless an important trend to investigate. Denial,[475] and treatment non-adherence,[333] have been found to be associated with worsening visual field mean deviation in individuals with adult-onset glaucoma and binocular vision equal to or better than 6/12. Furthermore, individuals with adult-onset glaucoma aged less than 50 years have been found to be less likely to

adhere to treatment.[333] Younger adults with childhood glaucoma and no vision impairment may therefore be more at risk of treatment nonadherence and consequent disease progression.

There are no known studies which have evaluated interventions which aim to improve treatment nonadherence in adults with childhood glaucoma. In cohorts with adult-onset glaucoma, however, reminder systems including alarms, text messages and phone calls have been successful. Motivational interviewing, problem solving training and patient-focused delivery of educational material to individuals and their caregivers have further been useful.[476] Similarly, the use of alternate topical antiglaucoma medications with less side effects has been considered useful in improving treatment compliance in individuals with adult-onset disease.[477] These strategies may be useful in improving treatment noncompliance in adults with childhood glaucoma and could be trialled. Non-invasive procedures including laser selective trabeculoplasty[478] and minimally invasive glaucoma surgery[479] to control IOP, have been proposed to eliminate issues related to patient non-compliance with topical antiglaucoma medications in adult-onset glaucoma. However, these procedures are not yet commonly used in childhood glaucoma,[273] with very few studies reporting the effectiveness of selective laser trabeculoplasty[480] and minimally invasive glaucoma surgery in childhood glaucoma.[481,482] Despite the paucity of literature available, Horne et al.[483] more generally recommend that clinicians should spend time to understand reasons for non-adherence and how patients judge their need for treatment with consideration to the presence of other circumstantial stressors. The findings from this study support this, particularly where the use of maladaptive coping strategies is suspected.

Most individuals in this study expressed a range of negative emotions. These included feeling misunderstood due to the disease rarity and feeling self-conscious of their eye appearance, use of vision aids and visual ability. These feelings have not yet been evaluated in adults in childhood glaucoma. Feeling misunderstood has been previously reported to contribute to a lower psychosocial well-being and self-image in individuals with adult-onset glaucoma.[359,484] Lower self-image, however, was attributed to a fear of falling likely due to decreased visual ability, and feeling older due to the disease rather than the association between eye appearance and use of vision aids on self-image. Moreover, these emotions may be attributed to a lack of awareness of glaucoma and public health campaigns in the general population. A previous Australian study reported that only one third of people were able to correctly recognise glaucoma as an asymptomatic ocular condition,[485] whilst knowledge of childhood glaucoma was not assessed. Literature assessing awareness of childhood glaucoma, however, is scarce and requires evaluation in an effort to alleviate these unique negative emotions.

Concerns for self-image and being misunderstood often negatively impacted social well-being. Approximately half of participants expressed a fear of being seen as different and being mistreated,

resulting in concealment of their condition in a social or workplace setting. Social embarrassment and workplace discrimination has been reported by individuals with retinitis pigmentosa,[472] and Stargardt's disease,[473] and was largely attributed to one's vision impairment. Participants herein additionally described childhood bullying during schooling years, often owing to their eye appearance or visual ability. Children aged less than 12 years with childhood glaucoma have reported lower psychosocial well-being compared to older children,[309,310] which may be indicative of childhood bullying. Bullying was observed in almost one third of children with glaucoma (Chapter 6).[358] Adult survivors of retinoblastoma similarly have reported schoolyard bullying, due to eye appearance, having a prosthetic eye or their facial appearance following radiation therapy to control their disease.[486] This significantly affected survivors' emotional and physical functioning, and social well-being as an adult.[486] In contrast, a minority of participants in this study discussed a lasting impact of childhood bullying whilst the use of an ocular prosthetic made three individuals less self-conscious in comparison to their phthisical eye. Meanwhile, schoolyard bullying frequently made others consider themselves more resilient, which improved their quality of life as an adult. Developing improved QoL over time is referred to as the 'response shift', a phenomenon commonly observed in chronic illnesses as individuals accommodate to life with their condition.[487] This may explain why some participants did not discuss issues with their social well-being. Nonetheless, the impact of childhood glaucoma on social well-being at various ages warrants further investigation, particularly as childhood experiences may have negative implications for the individual's future.

Almost all participants reported ocular health concerns including fear and anxiety about losing their vision or their independence in the future. This was particularly observed in participants with no vision impairment in their better eye and vision impairment in their fellow eye. Individuals aged over 60 years with adult-onset glaucoma and unilateral, painless vision loss, have similarly been found to experience higher levels of depression, anxiety and hopelessness compared to normal-sighted individuals.[488] These emotions were attributed to worry of future vision loss, in agreement with our observations. Meanwhile, a large cohort study from North Carolina reports anxiety and depression in 17% and 22% of adults aged 18 years and older with glaucoma, respectively, although it was not reported how many individuals had childhood onset disease.[489] Whilst psychiatric manifestations were not formally evaluated in this study, three participants reported accessing psychological support because of their experience with glaucoma. Conversely, it is possible that peer support may mitigate the risk of anxiety and depression in glaucoma as many participants in this study indicated that spouses, friends, and family were their primary support. Research evaluating the presence of anxiety and depression and need for psychological support in this cohort is consequently required and would support findings from Chapter 5.

The effect of childhood glaucoma on family planning is a novel and significant issue which was discussed by the majority of participants. Two thirds of participants expressed concern that their child may inherit the condition, become visually impaired or have the same childhood and adult experiences. This was particularly observed where the adult was visually impaired in one or both eyes. Adults with retinoblastoma,[490] and Stargardt's disease,[473] have similarly been reported to express concern for their child to inherit the condition. Participants in this study additionally experienced anxieties and worries for their own social well-being and ocular health, and these may be transferred to their child or future child. These concerns, however, were experienced less commonly by individuals with an affected first-degree relative. It is possible that these individuals and their families were more familiar with glaucoma and its potential limitations and had routinely practised normalisation of their condition. This practice minimises the disease impact on daily living and is an adaptive practice common in individuals with chronic inherited disease.[491] Nonetheless, clinicians should give attention to and understand these concerns particularly when an individual is planning to have children.

Genetic counselling was sought or desired by the majority of participants who expressed concern for family planning. This observation may be biased by the fact that the cohort was recruited from a genetic registry (ANZRAG). Nonetheless, the substantial proportion of participants exhibiting this behaviour implies that genetic testing and counselling is considered valuable and necessary to achieve peace of mind. Alternatively, the majority of those who did not seek genetic counselling were not visually impaired and consequently did not see a benefit of the service. To my knowledge, this is the first account of this behaviour in adults with childhood glaucoma. Genetic testing for family planning purposes has otherwise been reported to be sought by 65% of individuals with inherited retinal diseases.[492] In survivors of retinoblastoma, 33% sought genetic testing whilst 36% avoided getting pregnant so that pathogenic genetic variants would not be passed on.[490] The latter behaviour was discussed by three adults in this study. Preimplantation genetic diagnosis could be a possible alternative for these individuals to alleviate the risk of passing on a pathogenic variant. Attitudes towards this process was not discussed in this study, however, 52% of individuals with inherited retinal diseases supported the use of preimplantation genetic diagnosis.[492] With consideration to genetic counselling-seeking behaviours in other ocular conditions, these findings warrant further investigation into the attitudes and perceived benefits of genetic testing and counselling in individuals with childhood glaucoma. The results of this study otherwise support that genetic testing and counselling services should be made available and accessible to adults with childhood glaucoma undergoing family planning.

The remaining themes (symptoms, inconveniences, activity limitation, economic and mobility) are similar to other QoL research in individuals with adult-onset glaucoma.[374,457] In a previous study which

interviewed 72 individuals with adult-onset glaucoma, issues with activity limitation, emotional well-being and conveniences were the most common.[374,457] In contrast, activity limitation was not a major theme discussed by our participants. This is likely due to the high average number of years since individuals were diagnosed with their glaucoma in our cohort and consequently participants had many years to adapt to their condition. The advancement and increased availability of adaptive technologies at the time of this study, in addition to the visual and physical capabilities of participants, may further have influenced this finding. This may additionally explain why mobility issues were discussed least by participants. Nonetheless, the issues raised within these themes reached data saturation within the cohort studied. It must however be emphasised that the participants herein reported are younger than the typical adult-onset glaucoma cohort such that these issues are experienced in a different social context. In particular, the inability to fulfil parental duties, pursue and maintain an intimate relationship or certain career trajectory may affect one's QoL to a larger extent than someone with adult-onset glaucoma who has an established family, relationship, or career prior to disease onset. These themes are consistent with previous reports in Stargardt's disease,[473] retinoblastoma,[493] and retinitis pigmentosa.[472] Furthermore, non-participation in sporting or physical activities in otherwise young and healthy individuals with a vision impairment has been associated with lower mental, social and physical well-being.[494] However, this may change in the future with the increasing availability of competitive sports for individuals with a vision impairment at highly competitive levels.

The effect of childhood glaucoma on QoL is not yet accurately captured by current PROMs. Prior research has utilised PROMs or QoL measures that are designed to measure general well-being,[311,312,332] rather than capturing the specific effect of glaucoma. For example, the 26-item WHOQoL-BREF and the 5-item Satisfaction with Life Scale, which has been completed by young adults with childhood glaucoma in India,[311] do not measure issues specific to vision-loss or glaucoma. Furthermore, the NEI-VFQ 25, completed by adults with childhood glaucoma in Iran,[312] may not be the most appropriate tool, as its ability to measure social functioning or mental health is not considered psychometrically sound.[495] It is therefore paramount that a quantitative measure of QoL in individuals with childhood glaucoma is performed using a childhood glaucoma-specific PROM. This will enable accurate investigation of associations between clinical characteristics and QoL scores. Consequently, clinicians would be able to identify at-risk individuals and appropriately refer such individuals to non-ophthalmic services (e.g., psychology or genetic counselling services) where indicated. The development of a childhood glaucoma-specific PROM would also enable cross-cultural investigation of QoL with the assistance of international collaboration. The results of this study assisted with the identification of items, across the 10 QoL issues herein presented, to develop a childhood glaucoma-specific PROM (Chapter 9).

Study limitations include that participants were recruited from a registry and thus may be more willing to participate because they are experiencing a higher QoL than those who did not participate. Nonetheless, the findings were triangulated with previous glaucoma QoL research and identified several areas which have implications for clinical practice. Furthermore, the majority of participants were of self-reported European ancestry and resided in Australia. Findings may therefore only be extrapolated to a population with similar social, cultural, ethical, and religious beliefs and healthcare setting. However, the experiences herein described are representative of the wider Australian population as recruitment was from a national registry. Lastly, QoL issues were explored in more individuals with primary glaucoma compared to secondary forms of glaucoma. It remains possible that individuals with secondary glaucoma have more specific issues that impact on QoL that were not captured in this study (e.g., systemic and dental anomalies in ARS). Nonetheless, the inclusion of individuals with different subtypes of childhood glaucoma provides detailed descriptions of the lived experience of the disease as a whole.

The present study explored the QoL issues experienced by adults with childhood glaucoma. It is the first study to qualitatively assess this construct and contributes to a very limited body of literature. In keeping with the findings from Chapter 6,[358] adolescents and young adults with childhood glaucoma may represent a high-risk group for disease progression and treatment non-adherence due to a higher trend in the use of maladaptive coping strategies. The results emphasise the need for glaucoma PROMs to include assessment of coping strategies to understand patient motivation and treatment behaviour. The results also support the development of a childhood glaucoma-specific QoL PROM to accurately capture the lived experience of this disease in such a cohort.

CHAPTER 8 THE CAREGIVER EXPERIENCE IN CHILDHOOD GLAUCOMA

Published manuscript

The contents of this chapter have been published in a peer-reviewed manuscript of which I am the first author: **Knight LSW,** Ridge B, Staffieri SE, Craig JE, Prem Senthil M, Souzeau E. The caregiver experience in childhood glaucoma: an interview study. ***Ophthalmol Glaucoma***. 2022;5(5):531-43.

My contributions to the manuscript involved the research conception and design (80%), data collection including interviews with participants (85%), data analysis including identification of themes (100%), interpretation of the data (90%), and drafting the manuscript (100%). All other authors assisted with interpretation of the data and critically revising the manuscript. Emmanuelle Souzeau and Mallika Prem Senthil were further involved in research conception and design (20%), whilst Bronwyn Ridge assisted with participant interviews (15%). Project funding was provided by Emmanuelle Souzeau, Jamie Craig, Mallika Prem Senthil and myself.

The introduction and methods of this manuscript have been edited to fit the structure of this thesis.

8.1 Introduction

A diagnosis of childhood glaucoma can be a stressful or traumatic experience for caregivers. This is compounded by the disease's chronicity and uncertain visual prognosis, the requirements of surgical intervention and frequent examinations under anaesthetic, the child's future level of independence, and the likely genetic cause of disease. There are few studies which have investigated the impact of the condition on caregivers.[313–318] Caregivers have reported a high prevalence of depressive symptoms,[313–317] and high caregiver burden whilst caring for a child with childhood glaucoma,[314] but there is a paucity of literature that explores the reasons for these findings. None are yet to evaluate the use of coping strategies in the context of a high caregiver burden or investigate beyond clinical parameters why low emotional and social well-being may be experienced. Furthermore, decision-making around family planning from the perspective of the caregiver, who may be affected with glaucoma themselves, has not yet been investigated. This is critical in the context of an inherited disease.

My original contribution to knowledge was the development of a comprehensive understanding of the psychosocial impact of childhood glaucoma on caregivers and the QoL issues they encounter. Findings from this study further supported the need for psychosocial support in individuals and families affected by childhood glaucoma.

8.2 Methods

8.2.1 Participants

A non-probability convenience sampling technique was adopted to recruit caregivers from the ANZRAG. The ANZRAG additionally recruits family members, including caregivers, to undergo genetic testing to identify genes associated with glaucoma.[386] It therefore provided a suitable cohort to evaluate the effect of childhood glaucoma on QoL and family planning from the perspective of the caregivers. Caregivers residing in Australia were invited to participate if their child had a diagnosis of glaucoma at <18 years (irrespective of the glaucoma subtype), were English speaking and had or are currently having an active role in their child's glaucoma care. Consequently, more than one caregiver per child was accepted into the study. Participants were excluded if they had a disability impacting on their own QoL (e.g., hearing, or cognitive impairment) as informed by their partner or other carer, or their child had coexisting ocular or systemic disease unrelated to the spectrum of childhood glaucoma as informed by the caregiver or child's glaucoma specialist.

Eligible caregivers were invited to participate in the study by mail and asked to register their interest. Upon receipt of interest to be interviewed, caregivers were sent an information pack and consent form.

Once informed written consent was obtained, caregivers were contacted to coordinate an appropriate time to be interviewed. If no reply was received within two weeks, a follow-up phone call was initiated, and caregivers were deemed non-contactable after a minimum of two unsuccessful attempts. Clinical details of caregivers' children were obtained from their medical record at the time of the interview. The glaucoma subtype was classified according to the CGRN classifications.[4] Disease onset at 4 years of age or later was classified as juvenile-onset.[4] Vision impairment was considered to be present if one eye had BCVA <6/12 according to the International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision),[337] as described in Chapter 2. This level of visual acuity is required in at least one eye to be able to operate a motor vehicle in Australia.[470] The self-reported ability of a child to operate a motor vehicle was not used as a measure of visual disability as children must be at least 16 years of age to drive a motor vehicle in Australia.[496] Any analysis of this variable would therefore exclude caregivers of children younger than 16 years of age. Similarly, visual field indices were not used as a marker of visual disability as accurate measurements are typically retrieved in children aged >10 years,[396] and those with BCVA <6/18.[395] Furthermore, the relationship between visual field indices and visual disability is yet to be established.[471] For the purpose of analyses, details of the eldest child with glaucoma were used where more than one child within a family had childhood glaucoma.

Ethical approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/161) and the study adhered to the tenets of the Declaration of Helsinki.

8.2.2 Interviews

To comprehensively investigate the caregivers' lived experience, a semi-structured interview guide consisting of open-ended questions was developed from a literature review of QoL issues experienced by caregivers of a child with childhood glaucoma or vision-impairment secondary to another ocular condition as described in Chapter 2.[313–317,362] The interview guide consisted of questions about the caregiver's experiences during the period of diagnosis and throughout various treatments and ophthalmic examinations (e.g., *How has the course of treatment and examinations impacted you as a caregiver?*). Additional questions about the social, physical, and emotional impact of the condition, with particular reference to their family life, their child's prognosis, their access to support and ability to cope were asked (e.g., *What worries or concerns do you have for your child right now? What helps you cope with your child's current state of health?*). The complete set of questions are provided in Appendix A, Interview Guide A3.

The semi-structured interviews were offered to be conducted one-on-one via telephone or Cisco WebEx. For this study, all caregivers preferentially selected a telephone interview, although reasons for this were not investigated. The majority of interviews were conducted by me (n=30) while five were conducted by co-author (BR; a health counsellor). Participants were informed the study was being completed in the context of higher degrees for both interviewers. No caregivers' children were under the clinical care of either interviewer. Caregivers were encouraged to be alone during the interview to control for any external influences on their responses. All interviews were audio-recorded and transcribed verbatim. As described in Chapter 2, interviews continued until thematic saturation was reached.[363] Thematic saturation occurred at the 32nd interview, and a further three interviews with individuals already recruited to the study were conducted to confirm data saturation. Interviews ceased thereafter. Caregivers were offered the opportunity to review their transcript for accuracy and receive information on counselling services if desired.

8.2.3 Data analysis

Data analysis including coding of transcripts and identification of themes was performed as previously described (Chapters 2, 6 and 7). As per the use of the generalised inductive approach, the themes developed were not conceptualised *a priori*. Instead, themes that best represented the data emerged directly from the data.[365] Independent parallel coding was further performed with one co-author (BR), to ensure that our interpretation of the five interviews not conducted by me were similar. This involved comparing and establishing an agreement upon the codes used for these transcripts.[365]

8.3 Results

8.3.1 Participants

A total of 156 eligible caregivers of an individual with childhood glaucoma from the ANZRAG were sent an invitation to be contacted about the study. A total of 35 (22%) caregivers were interviewed between March and September 2020. The mean interview time was 60±19 minutes. The mean caregiver age was 50.2±13.6 years and 27/35 (77%) were women (i.e., a mother). Seven mother-father dyads were included. Most caregivers (32/35, 91%) had one child with childhood glaucoma whilst 3/35 (9%) had two or more children with the condition. Of the caregivers' eldest child with childhood glaucoma, 17/35 (49%) were female, 10/35 (29%) had bilateral vision impairment, 17/35 (49%) had now reached adulthood and 31/35 (89%) had PCG. Additional caregiver and child characteristics are further detailed in Table 8.1 and Table 8.2, respectively. The exact level of BCVA per child per eye is provided in Appendix B, Table B13.

Table 8.1. Demographic characteristics of caregivers

Variable	n (%)[†]
Caregiver characteristics	
Age at interview	
30–39 years	8 (23)
40–49 years	11 (31)
50–59 years	10 (29)
≥60 years	6 (17)
Median (range) years since child diagnosis, years	12 (0.7–61)
Gender, female	27 (77)
Self-reported ancestry, European	33 (94)
Had childhood glaucoma, yes	4 (11)
Relative (other than child) affected by childhood glaucoma, yes	5 (14)
Genetic results	
Molecular diagnosis identified	14 (40)
Autosomal recessive inheritance established	9 (26)
Autosomal dominant inheritance established	5 (14)
Median (range) number of children	2 (1–6)
Had more than one child, yes	25 (71)
Order of first affected child per caregiver	
First	27 (77)
Middle	2 (6)
Last	6 (17)

[†]Data are presented as no. (%) unless otherwise indicated

Table 8.2. Demographic and clinical characteristics of the caregivers' first child with childhood glaucoma

Variable	n (%)[†]
Characteristics of caregivers' first child with childhood glaucoma	
Gender, female	17 (49)
Current age	
0–3 years	8 (23)
4–17 years	10 (29)
18–39 years	14 (40)
≥40 years	3 (9)
Median (range) age at time of caregiver interview, years	16 (4–62)
Median (range) age at glaucoma diagnosis, years	0.2 (0–17)
Laterality of glaucoma, bilateral	31 (89)
Subtype of childhood glaucoma	
Primary congenital glaucoma	31 (89)
Juvenile open-angle glaucoma	3 (9)
Glaucoma associated with non-acquired ocular anomalies (Aniridia)	1 (3)
Visual impairment[a]	
None in either eye	14 (40)
Unilateral	8 (23)
Bilateral	10 (29)
Too young for formal visual acuity assessment	3 (9)

[†]Data are presented as no. (%) unless otherwise indicated
[a]Visual impairment was defined as <6/12 BCVA.[337] This level of visual acuity is required in at least one eye to be able to operate a motor vehicle in Australia.[470] The exact level of visual acuity per child per eye is provided in Appendix B, Table B13.

8.3.2 Quality of life themes

Six QoL themes and their subthemes emerged from the interview data. This process is outlined in Table 8.3, whereby codes or subthemes that have positive or negative impacts on QoL were grouped into major QoL themes. The proportion of caregivers who expressed issues within the QoL theme, and the total number of coded segments per theme, are illustrated in Figure 8.1.

Table 8.3. The major quality of life themes grouped by sub-themes/codes that have a positive or negative impact on quality of life

Theme Number	Major quality of life theme	Subthemes/codes with positive quality of life impacts	Subthemes/codes with negative quality of life impacts
1	Coping	Social support Normalisation Appreciating child's resilience	Avoiding glaucoma-related thoughts Emotional detachment Blaming health professionals
2	Emotional well-being	Managing fleeting anxiety Feeling hopeful or grateful Feeling proud of child	Feeling anxious or scared Feeling shocked, guilty, or regretful Feeling low or helpless
3	Medical and social support	Medical care becomes routine Positive reinforcement with child Community establishment	Perceived that treatment is hurting child Overprotective of child Fear of schoolyard bullying
4	Social well-being	Relationship teamwork Connecting with other caregivers Sharing experience	Relationship conflict Trouble caring for other children Social isolation
5	Clinical and familial control	Acceptance of disease outcomes Trusting the child to be autonomous Confidence in managing disease	Wanting a cure Attending appointments with adult child Worried about others caring for child
6	Family planning	Gaining knowledge of future risk Confident in detecting condition Planning ophthalmic follow-ups	Worried about future children/grandchildren Not wanting more children Self-blame for genetic results

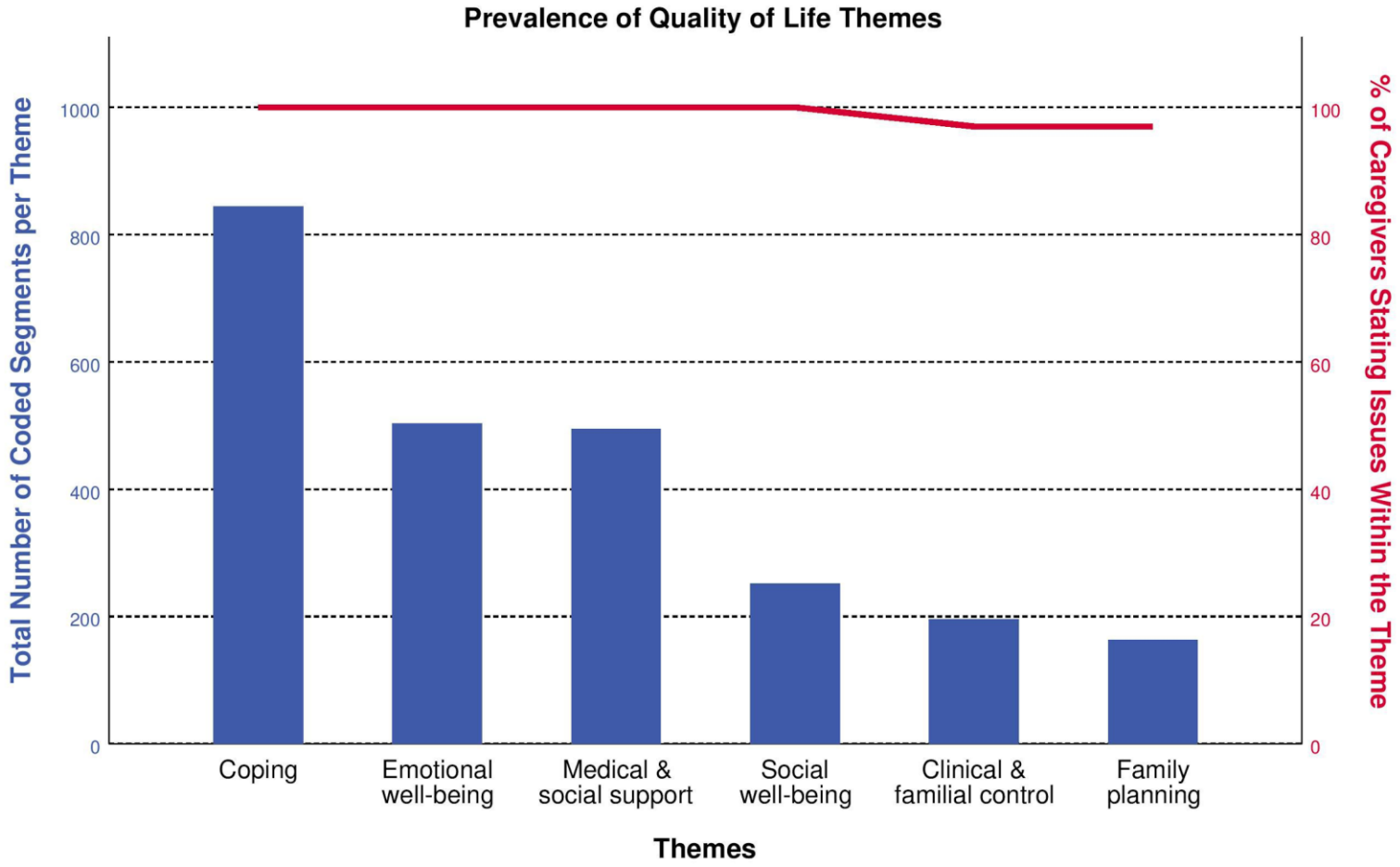

Figure 8.1. Quality of life themes identified in caregivers of individuals with childhood glaucoma
This Dual Y Axis Bar Chart demonstrates the total number of codes per theme (blue bar chart) and the proportion of caregivers who discussed an issue within the theme (red line chart).

8.3.2.1 Theme 1: Coping

To manage the emotional and social challenges of raising a child with childhood glaucoma, several coping strategies were adopted. These included adaptive and maladaptive coping strategies considered to be either problem-focused (i.e., actively confronting the problem) or emotion-focused (i.e., regulating or dampening negative emotions brought on by the stressors).[456]

The most common adaptive problem-focused strategy was seeking and accepting assistance provided by social and professional support systems. This was expressed by almost all caregivers (34/35, 97%). The most valued social support system was the caregivers' spouse or partner (30/35, 86%) (henceforth collectively referred to as "partner"), particularly in the context of their child's appointments, when the child was undergoing surgery or being anaesthetised, and when administering the child's medication. All caregivers within the mother-father dyads expressed the positive value of their partner. The caregivers' parents were also considered highly valuable by 22/35 (63%) caregivers, especially in cases when other children required care or when respite care was required due to feeling sleep deprived. Sleep deprivation was attributed to staying awake due to glaucoma-related anxieties or the child's disrupted sleep pattern post-anaesthetic for 4/35 (11%) caregivers. Healthcare staff (13/35, 37%), vision support services (10/35, 29%) and psychology or counselling services (9/35, 26%), were further considered important support systems.

> "*I think it's always better if the two of you are [at the appointments] to take it in, the information... we were always in it together and well, we are still together so anyhow, 30 years later."* (CG09)

Most caregivers (32/35, 91%) reflected that they normalised their child's glaucoma. This was often adopted so that caregivers could provide their child with equal opportunities to their child's peers. Similarly, caregivers found this process helpful in building their child's independence. Other problem-focused coping strategies included gaining knowledge of childhood glaucoma (16/35, 46%) and modifying their own behaviours to adapt to their child's visual limitations (9/35, 26%).

> "*We've tried to normalise it as much as possible… her whole life doesn't revolve around her vision."* (CG24)

The most often used emotion-focused coping strategy was appreciating the child's resilience and ability to adapt to their condition (31/35, 89%). This was irrespective of the child's current age but was more commonly used in caregivers of a child with a unilateral or bilateral vision impairment compared to caregivers of a child without a vision impairment (17/18, 94% vs 10/14, 71%, respectively). Sixteen

(16/35, 46%) caregivers additionally reflected that witnessing their child's ability to achieve developmental milestones provided an important means of coping.

> "*Her vision impairment was more just part of her rather than anything that ever held her back."* (CG04)

Other common emotion-focused coping strategies included trusting the ophthalmologist to provide optimum care to their child (29/35, 83%) and being grateful that their child's condition had not worsened or that it was limited to their eyes (26/35, 74%).

> *"We completely trust [the ophthalmologist]… he doesn't give us false hope and doesn't tell us what the future looks like, he just tells us the next step."* (CG27)

Accepting their child's condition (24/35, 69%), communicating openly about their experience (15/35, 43%) and relating to other families with a child with vision impairment and/or childhood glaucoma (12/35, 34%) were additionally expressed.

> *"[My ophthalmologist] said to me… I think there's one mum [of a child who also has glaucoma] that would be really, really happy to talk to you… she rang me, and we had the biggest chat and it just made me feel so much better."* (CG33)

Although common, caregivers used maladaptive coping strategies less frequently than adaptive coping strategies, regardless of the time since diagnosis (22/35, 63% vs 35/35, 100%, respectively). The most common strategy was to avoid thinking or talking about their child's glaucoma (10/35, 29%) whereas 4/35 (11%) caregivers explicitly stated that they became emotionally detached from their child when they were undergoing surgery as an infant. Whilst at times protective of feelings of anxiety, detachment often led to social isolation or an inability to bond with their child.

> *"When she was born and got the diagnosis, I kind of shut off from her. It was too painful… I didn't bond with her until she was 4–5 months... It became my job. I was here to medicate this child."* (CG21)

Another common maladaptive strategy was blaming health professionals for not diagnosing or managing the condition earlier (7/35, 20%). This was exclusively described by caregivers of children with unilateral or bilateral vision impairment.

> "*If [the ophthalmologist] had picked it up the first time, would [my child] have better eyesight?... I've still probably got a bit of a scar about that.*" (CG16)

Avoiding current glaucoma-related thoughts with distraction from either work, alcohol or indulging in comfort foods (4/35, 11%), or suppressing thoughts of the future (5/35, 14%) were additionally practised by caregivers.

> "*I don't deal with the future, that's okay, it'll happen when it happens."* (CG02)

8.3.2.2 Theme 2: Emotional well-being

The caregiver experience of childhood glaucoma presented many negative emotional experiences. Almost all caregivers (33/35, 94%) expressed feeling anxious, particularly regarding their child's ocular surgery (19/35, 54%), and requirement for general anaesthetics (14/35, 40%). The latter was exclusively experienced by caregivers of children with PCG, because of the early age of disease onset and requirement for treatment.

> *"I suppose it sort of tugs at your heartstrings, your baby is going to be put to sleep and taken away from you."* (CG09)

Caregivers additionally experienced anxiety and fear regarding their child's current or future vision (17/35, 49%), future ocular health (12/35, 34%), control of IOP (12/35, 34%) and risk of sustaining an ocular injury (11/35, 31%) but these were often expressed as manageable anxieties with the use of coping strategies. If the child had unilateral or bilateral vision impairment, caregivers were more often anxious of their child's vision, future ocular health, and risk of injury whereas anxiety of IOP was independent of vision status.

> "*Our concern [was] if she got hit in the eye [or] if there was a sudden increase in eye pressure... Those sorts of things were and still are the biggest worry."* (CG12)

Most caregivers (24/35, 69%) recalled experiencing shock when their child received the diagnosis as they were unaware that glaucoma could be diagnosed in a child. Shock was followed by feelings of guilt (19/35, 54%) and regret (18/35, 51%), whereas shame was infrequently experienced (2/35, 6%). These feelings were typically associated with a yearning to have a healthy child, not recognising glaucomatous signs sooner or not pushing the healthcare practitioner for a diagnosis sooner. These experiences seemed to be independent of the caregiver's gender, the glaucoma subtype, and the age of diagnosis. Among the mother-father dyads, guilt was expressed by both caregivers in 1/7 (14%) dyad, and only one of two caregivers in 3/7 (43%) dyads.

"*She'd be squinting her eye all the time because she couldn't tolerate light. Well, I just didn't click. Nothing clicked with me because I don't really know anything about ophthalmology… I'd never heard of infantile glaucoma."* (CG10)

Feelings of guilt in mothers were more specifically associated with possibly harming the child *in utero* with medication or alcohol intake (3/27, 11%), or passing on a possible genetic variant (9/27, 33%), despite 5/9 (56%) not having a genetic diagnosis.

"It's just that you feel guilty... that I brought some innocent little victim into the world… Because when you're having a baby, it's all part of you, and you don't want anything to go wrong with it." (CG29)

Frustration was expressed by 18/35 (51%) caregivers, with the emotion commonly associated with the lack of awareness and knowledge of childhood glaucoma from healthcare professionals or peers. Caregivers frequently stated that their child's glaucoma was misdiagnosed as blocked tear ducts.

"I was frustrated that the midwives weren't more accepting of it, because they just couldn't see anything… I was kind of annoyed at myself for not pushing the matter." (CG24)

Twelve (12/35, 34%) caregivers reflected that the first years following diagnosis brought feelings of sadness with 4/35 (11%) female caregivers stating they experienced symptoms of postpartum depression and 3/35 (9%) caregivers describing feeling helpless. Eleven (11/35, 31%) caregivers further described the diagnostic period as traumatic and many recounted the day of diagnosis vividly. Of these 11 caregivers, 9/11 (82%) had their first-born child receive a diagnosis of PCG.

"I remember saying, 'This has got to be the worst day of my life'... I felt very helpless because I couldn't get answers to questions... Would she have any eyesight after all this was over? It was just the whole unknown." (CG14)

Negative feelings were overcome by feeling hopeful of their child's future eye health or that a cure would be discovered, feeling proud of their child's achievements, and feeling grateful for support they have received from medical and social systems.

"*I'm a 'hope person'… My hope for her in the future is to hold her sight".* (CG06)

8.3.2.3 Theme 3: Medical and social support

The caregivers' role of providing support was particularly centred on the medical and social needs of the child. The main medical support tasks considered influential in the caregivers' experience were

instilling antiglaucoma medication (i.e., eye drops; 18/35, 51%), taking the child to multiple appointments (20/35, 57%), and managing post-operative care and post-anaesthetic behaviour changes (12/35, 34%). These duties seemed to be widely shared amongst the mother-father dyads interviewed. However, these duties were often met with stress and anxiety as caregivers reasoned that their child often resisted treatment because they were too young to understand why it was needed or had perceived their child to be in pain. Caregivers otherwise considered these medical duties to be part of a routine.

> "*No one wants to hurt their child - hold them down and pry their eyes open - a baby's not going to cooperate, are they?"* (CG09)

These emotions of stress and anxiety were negated by normalising the condition, bonding with the child, and using positive reinforcement.

> *"I teach him, I'm just there, I just want to be there for him… there's plenty of laughing involved on those days he has procedures… We just try and make it a fun day."* (CG26)

Almost half of the caregivers (14/35, 40%) additionally spoke of feeling overprotective of their child's health irrespective of the age of the child or vision status.

> "*The biggest challenge we have is around outdoor play because she was so light-sensitive for so long… When we're outside, I feel much more protective of her."* (CG25)

Caregivers often discussed the need to advocate for their child's needs to be met within the education system. Caregivers (16/35, 46%) were particularly concerned about their child experiencing schoolyard bullying due to their visual ability or their eye appearance, including buphthalmos and strabismus, and the need to wear sunglasses due to photophobia.

> *"We had really good early intervention… And then when she got a bit older it was sort of that fine line between, you know, making use of that support to… not being - wanting to be singled out as being different."* (CG05)

This led 6/35 (17%) caregivers to establish themselves within a community or a particular school so others would know of and support their child from a young age.

> "*We're not going to stay [in this town]... I feel like kids that grow up with her are much less likely to bully her for her condition… That's something that we've taken into account in our life planning."* (CG11)

8.3.2.4 Theme 4: Social well-being

All caregivers experienced strain on their immediate and extended familial and extrafamilial relationships in various capacities due to childhood glaucoma. Several caregivers (10/35, 29%), 6/10 (60%) of whom were from 3/7 (43%) mother-father dyads, explained that relationship conflicts were commonly experienced around the time of a child's appointment, surgery, or medication. Five (5/35, 14%) caregivers reported separating from their partner, although the degree to which the child's glaucoma impacted on this decision was unable to be determined. Financial concerns regarding costs of glaucoma treatment were otherwise raised by 1/35 (3%) caregiver, but this was not associated with experiencing relationship conflict.

> "*I'm just snapping at [my partner] at least a day or two before the operation. We're just completely on edge and it's just daunting."* (CG27)

Alternatively, 22/35 (63%) caregivers, 8/22 (36%) of whom were from 4/7 (57%) mother-father dyads, reported that they always had good teamwork with their partner when managing aspects of their child's health, including which caregiver took the child to an appointment, who was responsible for preparing the child for surgery or who administered medication. Among the six caregivers from the 3/7 (43%) mother-father dyads who experienced relationship conflict, each discussed that there were additional moments of good teamwork. The time since diagnosis between caregivers who reported undergoing a partner separation and those who reported good teamwork was similar (median [interquartile range]: 16 years [5 - 20 years] vs 14 years [4 - 25 years], respectively).

> *"It was something we had to, you know, show a united front against and support each other."* (CG04)

Of the 25 caregivers who had more than one child, 14/25 (56%) expressed challenges associated with parenting, providing attention to, and bonding with their other children. The three caregivers who had more than one child with glaucoma did not express these challenges.

> *"It affected our [other child]... [They] used to get pushed aside a lot because you know oh 'hang on mummy's just got to do these drops.' It was really, really hard… and it did take its toll on us."* (CG33)

Over half of the caregivers (22/35, 63%) discussed that their extended familial and extrafamilial relationships suffered because their friends or social groups could not understand or relate to their unique experiences. At times, this led to feelings of social isolation. Consequently, more than half (20/35, 57%) of caregivers expressed they wanted advice from other families who have had the same

experience and joined several online social support groups. To reciprocate, 14/20 (70%) of these caregivers stated that they were interested in sharing their experiences with others whilst being mindful of not reading into “worst-case” scenarios.

> *“I think it definitely helps… reading someone else’s story gives you a feeling of um, I guess that you’re not alone.”* (CG25)

8.3.2.5 Theme 5: Clinical and familial control

Disease incurability and child autonomy challenged many caregivers’ (34/35, 97%) sense of control in both the clinical and familial environments. Most caregivers (24/35, 69%) often discussed feeling unable to medically control the disease and had struggled to accept that there was no cure. The impact of these thoughts and emotions was minimised where caregivers had accepted and normalised the clinical course of the condition or had become hopeful that a future cure would be discovered. Not feeling in control and struggling to accept the disease’s chronicity were often experienced by caregivers of a female child (18/24, 75%) and those that expressed feelings of guilt or regret (17/24, 71%) but did not appear to be dependent on the vision status of the child, the caregiver’s age or the number of years elapsed since the diagnosis.

> “*There's no control. I can't, um, fix the problem for her or help her fix it for herself… we wait for potentially ultimately some sort of transplant or cure.*” (CG01)

Relinquishing the role of the primary caregiver as the child developed medical autonomy presented challenges for several caregivers (28/35, 80%). This particularly included trusting the child to develop their own autonomy for their condition (15/35, 43%), balanced by wanting to know what happened at ophthalmic appointments (10/35, 29%). Among these caregivers, most had children aged 18 to 39 years (11/15, 73% and 8/10, 80%, respectively). These experiences caused 8/17 (47%) caregivers of adult children to continue to accompany their child to ophthalmic appointments. Meanwhile, 5/35 (14%) expressed worry for their child’s ability to afford medical care when they reached adulthood (e.g., cost of medication, cost of specialist care in the private healthcare system).

> “*Since he's been an adult and no longer lives at home.... I think he just gets into a headspace of why me, I'm not going to use [eye drops] anymore… I've got to let him do what he needs to do to stay well, but as a mum it - it terrifies me that he won't.*” (CG32)

Meanwhile, 8/18 (44%) caregivers who had children younger than 18 years expressed strong concern for someone other than a family member taking care of their child such as a teacher, friend, or babysitter.

> *"We're getting ready to send her off to day-care. Talking about it would make me feel like the air was being sucked out of me… I do worry that you know, sometimes she'll be uncomfortable, and [the teachers] won't notice."* (CG11)

8.3.2.6 Theme 6: Family planning

Most caregivers (34/35, 97%) discussed the effect of childhood glaucoma on family planning. Of these caregivers, 14/34 (41%) expressed worry that their other children would develop glaucoma. Consequently, 6/35 (17%) caregivers, of whom 4/6 (67%) had their firstborn diagnosed with PCG, decided not to have any more children. These caregivers additionally did not have a molecular diagnosis.

> *"I wanted a big family... [but] I never had any more children… That would have been devastating, to me, to bring any more into the world, like, to have [eye] problems."* (CG29)

Alternatively, 19/35 (54%) caregivers, of whom 6/19 (32%) had a molecular diagnosis for their child, expressed that they were determined to have more children while of childbearing age. This was often attributed to normalising the condition, becoming confident in how to manage childhood glaucoma, knowing what to expect and knowing what disease signs to detect in subsequent children. Of the four caregivers who had childhood glaucoma, three did not express concern for the possibility of their child having glaucoma as they had normalised the condition. Meanwhile, 1/35 (3%) caregiver who had childhood glaucoma opted to use *in vitro* fertilisation and preimplantation genetic diagnosis to ensure that their child would not be affected with childhood glaucoma. Among the mother-father dyads, there were 3/7 (43%) whereby one caregiver discussed having more children whilst their counterpart did not.

> *"Now we know what glaucoma is and how it is working and the results. Obviously, you get onto it early and it's nothing to be afraid of… [Having another child] doesn't have any sort of concern to us."* (CG28)

The time since diagnosis appeared to be associated with the decision to have further children in 12/35 (34%) caregivers who were of childbearing age (i.e., younger than 45 years) at the time of the interview. The 4/12 (33%) caregivers who did not want additional children had a child more recently diagnosed with childhood glaucoma compared with 8/12 (67%) caregivers who did want further children (median [interquartile range]: 19 months [9 months–3 years] vs 3.5 years [3 years–4 years], respectively).

> *"It wasn't until generally in that 15-month mark where I was like… 'We could have another one.' But then that was like 'Oh no but that was too scary.' … And then probably at two*

and a half… you know like we can do this. And if we have another one that's got glaucoma, we know what's going to happen now." (CG21)

To control anxieties related to having another child with glaucoma, 6/35 (17%) caregivers discussed that they had planned for an ophthalmologist or paediatrician to examine their child's eyes immediately or shortly after giving birth.

"When he was born, the paediatrician... showed me and got [his] eyes and wedged them open, and I went, yeah, right okay… I knew straight away that he was fine." (CG06)

Whilst planning for further children, 20/35 (57%) caregivers, 8/20 (40%) of whom were from 4/7 (57%) mother-father dyads, discussed accessing genetic counselling to understand their risk of having another child with glaucoma prior to conception. As per Figure 8.2, caregivers decided to not have further children only where no molecular diagnosis could be established (4/14, 29%).

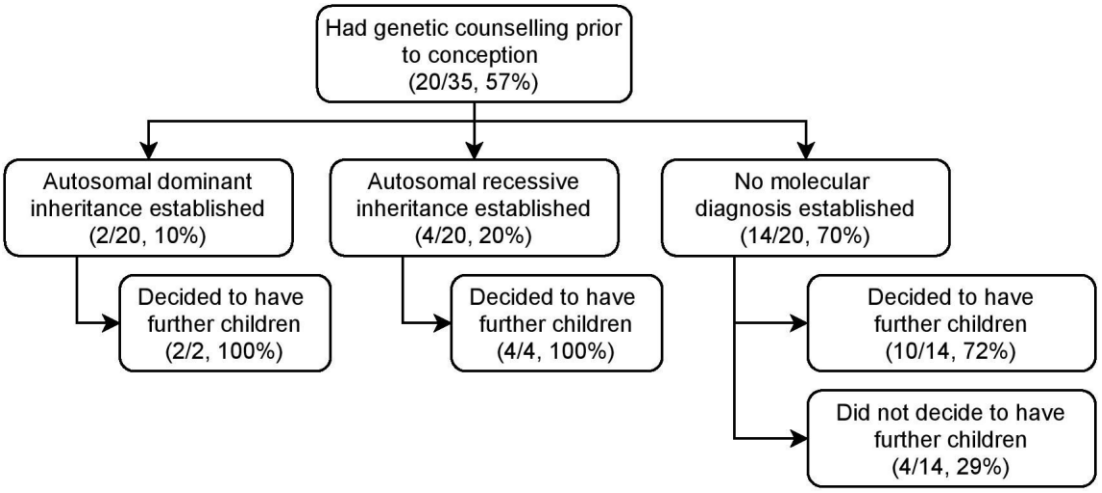

Figure 8.2. The caregivers' decision-making process in family planning
Flow chart depicting the decision-making process among caregivers who sought genetic counselling prior to conception, based on the mode of inheritance established for their child's glaucoma.

Reasons for not accessing genetic counselling at the time of family planning, discussed by 10/35 (29%) caregivers, included not having a family history of the condition, not having access to testing when they were of childbearing age, believing that the genetic result would not impact their family-planning decision or the child had a juvenile diagnosis (i.e., the child was older than 4 years of age at the time of diagnosis). Of these caregivers, 3/10 (30%) decided to have more children regardless. Meanwhile, 6/10 (60%) caregivers wanted to know the origin of their child's glaucoma and sought genetic testing sometime after they had decided not to have any more children. Guilt associated with genetic findings was reported by 2/35 (6%) caregivers.

> *"I'd prefer to know [the genetic risk] because that would make it mean that we can make informed decisions about how we have another child."* (CG25)

The implications of childhood glaucoma had a generational effect, with 16/35 (46%) caregivers worried that glaucoma would develop in their grandchildren. Of these caregivers, 10/16 (63%) discussed that they wanted their child to have genetic counselling prior to conception.

> *"Information is power… if it means we can somehow prevent any future children in the family [from] having it, well great, you know?"* (CG31)

8.4 Discussion

The results of this exploratory qualitative interview study offer a unique, valuable, and complex insight into the psychosocial impact of childhood glaucoma from the perspective of caregivers of predominantly self-reported European ancestry and contribute to an otherwise very limited body of literature. Previous studies have been undertaken in Saudi Arabian,[315] Indian,[313,314,316,317] and Brazilian caregiver populations,[318] which may limit their extrapolation to an Australian cohort due to social and cultural differences. Of the six themes identified, three themes (emotional well-being, medical and social support and social well-being) have broadened our understanding as to why caregivers may experience depressive symptoms, a high caregiver burden, and substantial impact on social well-being, as identified in prior literature.[313–318] Meanwhile, the impact of childhood glaucoma on coping, sense of control and family planning were novel themes. The inclusion of both caregivers within the same mother-father dyad offered valuable and contrasting experiences from their partner (e.g., guilt, family planning) whilst the inclusion of several childhood glaucoma subtypes, and the varied ages of caregivers and their children at the time of the interview, provided a detailed description of the caregiver experience beyond the diagnostic period.

Coping and social support

Like the lived experience of children and adults with childhood glaucoma,[355] the major theme identified was coping. Seeking and accepting social support was identified as one of the most useful resources to manage the disease's emotional and social impacts whilst assuming the caregiver role. Under the stress-buffering hypothesis, social supports are considered to be protective against the effects of a chronic stressor, especially where the support directly provides a solution to the main stressor (e.g., management of childhood glaucoma).[497] The stress-buffering hypothesis further discusses that the resources required to cope with a stressor, such as social support, are only beneficial for those who are suffering adversity that may be detrimental to psychological or physical health.[497] Stress-buffering was

observed in the cohort studied, illustrated by the cohesion of the partner relationship and a shared and practical approach to the child's treatment. Caregivers often discussed that this type of social support assisted with the ability to cope with stressful situations such as the diagnostic period, attending ophthalmic appointments or when their child required treatments or surgeries. This same cohesive relationship and shared responsibility has been observed in parents of children with retinoblastoma.[498] Alternatively, it has been demonstrated in non-ocular paediatric cancer, that when the supportive caregiver's well-being is low, the partner relationship can become strained and primary caregivers can withdraw from co-parenting roles.[499] This may contribute to the relationship conflicts observed in this study, particularly when caregivers reported separation from their partner. The rate of separation herein reported may further be influenced by the number of mother-father dyads interviewed, who all reported positive partner teamwork and relatively equally shared caregiver roles. Separation in childhood disease may otherwise be due to an accumulation of hardships that are related to the core stressor (i.e., childhood glaucoma). This is considered in the Family Stress Process model, which discusses that if a family's available resources cannot meet the compounding demands created by a stressful event, then tension or distress within the family unit occurs.[500] In the context of childhood glaucoma, for example, medical costs, cost of travel to appointments and absenteeism from work may have compounding financial consequences that are difficult to resolve. This could create tension or distress in the partner relationship.[500] Financial stressors, however, were not identified in this study. Relationship conflict has otherwise been observed in caregivers of children with paediatric cancer,[501] and juvenile idiopathic arthritis;[502] two conditions similar to childhood glaucoma in that they are characterised by remitting and relapsing patterns. In previous childhood glaucoma caregiver QoL research, studies have included caregiver cohorts with at least a 90% married status,[313,315–317] which may have prevented any analysis of the impact of partner separation or tension on the caregiver's QoL. Healthcare providers should nonetheless be mindful of caregivers' support systems and future research should acknowledge partner conflict as a variable that may affect caregiver QoL.

Support groups may additionally provide stress-buffering and offset the threat of disease to emotional well-being and social isolation. As identified in this study, support groups, whether face-to-face or online, can offer a sense of connectedness and empowerment.[503] Despite a paucity of literature, similar findings have been observed in other childhood ocular diseases including retinopathy of prematurity,[504] and retinoblastoma.[498,505] Online support groups have additionally been found beneficial for adults with adult-onset glaucoma, and can provide a source of knowledge.[506] Alternatively, online support groups may trigger negative emotions when reading content pertaining to negative outcomes or information overload regarding treatments or procedures.[503] Caregivers in this study acknowledged this as a pitfall of online support groups. Engagement in peer support is otherwise yet to be evaluated as a variable that may

offset feelings of social isolation in caregivers of children with childhood glaucoma.[313–318] Nonetheless, well-moderated peer support groups could be recommended by healthcare providers to supplement professional healthcare.[503,506]

Coping and normalisation

Normalisation was the second most common coping strategy adopted. It played a role in the provision of medical and social support, the caregiver's emotional well-being and sense of control. Normalisation is a dynamic process whereby caregivers aim to achieve a positive balance between providing support to the child, accommodating their needs and maintaining typical family dynamics and role functioning.[507] It is based on how a caregiver conceptualises the impact of a disease on daily functioning and deliberately attempts to shift the focus away from the condition and towards aspects of their lives that are less disrupted.[507] In parents of children with chronic inherited disease, normalisation has been shown to increase parenting competence and confidence in their ability to provide medical and social support to the child.[491] Furthermore, normalisation resulted in fleeting and manageable feelings of parental guilt or inadequacy related to the child's condition.[491] Similarly, in parents of children with visual impairment or blindness, anxiety was reduced where self-esteem was high owing to psychological adjustment of the condition.[508] This phenomenon is observed in this study, whereby caregivers discussed that anxieties related to the condition were manageable. Normalisation additionally promotes child resilience and autonomy, particularly through adjustment to medical procedures and adherence to treatment.[509] Caregiver observation of child resilience in this study cyclically caused caregivers to cope better. This process has been observed in parents of children with congenital heart defects whereby caregivers positively reframed their child's illness and celebrated their child's ability to cope instead of viewing their child as vulnerable.[510] In this study, this process negated the emotional impact of the disease as evidenced by feelings of hope, gratitude and pride in their child's abilities. Caregivers should evidently be supported to achieve normalisation as it has benefits for the child and the caregiver. Mindfulness-based stress reduction programs,[511] problem-solving therapy,[512] and support groups,[513] have been successful for parents of children with chronic disease to achieve normalisation and further studies could evaluate their efficacy in caregivers of children with childhood glaucoma.

Emotional well-being

The path to achieving normalisation is complicated by persistent threats to emotional well-being and the use of maladaptive coping strategies. Caregivers recalled experiencing shock, guilt, regret, frustration and feeling traumatised, particularly at the time of diagnosis and the child's younger years. Such feelings, collectively referred to as existential unease, are experienced as caregivers make sense of or

conceptualise their child's diagnosis, learn how to cope and understand their child's needs.[514] This emotional experience is mirrored in caregivers of children with congenital cataract,[515] and retinoblastoma,[505] with the diagnostic period often described as a feeling of losing control, and riding an "emotional rollercoaster" among a series of stressful events including surgery and medical management.[505] These feelings can cause caregivers to detach from the experience and consequently have difficulty bonding with their child,[498,516] as observed in this study. This additionally led some caregivers to experience postpartum depression. This has similarly been observed in caregivers of children with retinoblastoma,[498] and retinopathy of prematurity.[516] Caregivers of children with PCG have reported a high rate of depressive symptoms,[313,314,316,317] with a recent study suggesting that this may be caused by mourning the loss of the idealisation of their child's birth and parenthood.[318] Low caregiver QoL in childhood glaucoma has otherwise been associated with unemployment, having additional children with glaucoma and caring for a child who is legally blind, which may make the caregiver vulnerable to depressive symptoms.[315] Evidently, psychological evaluation and support for caregivers of children with glaucoma may be indicated, particularly during the diagnostic period.

Changes in a child's health can disrupt the normalisation process and reignite feelings of parental uncertainty, self-doubt and guilt.[491,509] Due to the disease's unpredictability,[11] caregivers in this study often expressed concerns for their child's ocular health, social well-being and their future abilities, irrespective of the child's age. These concerns are shared amongst caregivers of children with congenital cataracts,[517] vision impairment,[518] and retinoblastoma,[498,505] evidencing a collective caregiver experience in childhood eye disease. In this study, self-doubt, anxiety, and stress were particularly amplified where the child resisted the instillation of eye drops. This is similar to a caregiver's anguish in the setting of retinoblastoma and congenital cataract, whereby their child resisted the insertion and removal of their prosthetic eye,[498] or contact lens,[519] respectively. It is further possible that these parental feelings of concern, self-doubt and anxiety throughout the child's upbringing are influencing caregivers' perception of their child's QoL. In childhood glaucoma research, caregivers have consistently under or over-estimated their child's QoL compared to the child themselves.[309,520] This phenomenon has previously been hypothesised to be caused by a child's inability to articulate their experience to their parent,[520] but exploration of the caregiver's QoL and its relationship with their perception of their child's QoL may provide insight into understanding this parent-child disparity.

Child transitioning to adulthood

Disease incurability and a caregiver's devotion to gain control of the disease can cause caregivers to become overprotective and consequently inhibit their child's development of autonomy.[509] Caregivers in this study often reported feeling overprotective of their child and at times, were distrusting of others'

care. Most importantly, caregivers appeared distrusting of their own child's autonomy of their medical condition, including when the child had become an adult. Meanwhile, the caregiver's sense of control over the disease was rarely influenced by financial stressors (e.g., surgical costs). This is likely because children with glaucoma are typically treated in a public hospital due to disease instability and complexity (e.g., requiring multiple consultations, surgeries and anaesthetics).[11] Public healthcare incurs no cost to Australian residents. Conversely, an adult with childhood glaucoma may opt to be treated in a public hospital or receive private healthcare which can be costly (Chapter 7).[355] As a result, some caregivers were concerned for their child's ability to afford ophthalmic care, including medications and private healthcare, when they reached adulthood and became financially independent. This consequently appears to be a critical transition period from parent dependence to child autonomy as younger adults with childhood glaucoma may exhibit poor compliance with medication and appointment attendance and may require financial assistance (Chapter 7).[355]

Difficulties for caregivers to relinquish their control of their child's medical condition have been further detailed in caregivers of adolescents with chronic illness.[521] One of the main difficulties was the child's medication management and parental hesitation in encouraging autonomy so as not to upset their child.[521] This process of "letting go" may further be complicated by a caregiver's experience of chronic sorrow. Chronic sorrow is a periodic mourning or feelings of guilt or grief related to loss.[522] In childhood glaucoma, this sorrow could be reactivated when an adult child receives a poor prognosis regarding vision loss, requires another surgery, or is unable to achieve a certain career objective or other milestone, as seen in caregivers of adults with intellectual disability.[523] Chronic sorrow, in addition to distrust and overprotection, may explain why caregivers still attend appointments with their adult child. Healthcare professionals should be aware of these possibilities and encourage shared parent-child management of the condition where the child and parent are first receptive to the idea.

Decision-making in family planning

The normalisation of childhood glaucoma was seen to impact decision-making in family planning amongst caregivers. In this study, more caregivers were determined to have additional children when they achieved parenting confidence over time compared to those who did not, and this varied within caregiver dyads. Caregivers of children with inherited systemic genetic conditions have previously expressed self-doubt and self-blame and consequently regretted having a child or did not conceive additional children.[491] Whilst guilt and self-blame were observed in this study, no caregivers expressed regret for having a child whilst 17% decided not to have additional children. Although comparative literature in inherited ocular conditions is scarce, 70% of caregivers of children with an inherited retinal disease in China,[524] and 36% of unaffected parents of children with retinoblastoma in the Netherlands,[525]

decided not to have more children. Similarly, 43% of adults who had retinoblastoma,[525] and 6% of adults with childhood glaucoma decided not to have children (Chapter 7).[355] From the caregiver and affected adult perspectives, this low impact of having additional children in the context of childhood glaucoma is possibly due to the disease's non-life threatening nature, treatability and it generally being non-progressive, although disease severity and outcomes can be variable.[11] This is in contrast to retinoblastoma (life-threatening, increased life-time risk of second primary cancers),[526] and inherited retinal diseases such as retinitis pigmentosa, which results in non-treatable progressive vision loss.[527] Caregivers in this study were instead in favour of having their child's eyes checked immediately or shortly after birth whilst one caregiver opted for preimplantation genetic diagnosis. Attitudes towards this type of reproductive option and barriers to its access (e.g., cost, availability) was not discussed in this study but its use is otherwise supported in 52% of individuals with inherited retinal diseases.[492] Nonetheless, normalisation and the often non-threatening nature of childhood glaucoma appear to be important factors in caregivers' family planning decisions.

Genetic counselling was sought by 57% of caregivers to understand their risk of passing on any genetic variants that would cause glaucoma in their child. This may be biased by the fact that caregivers were recruited from a genetic registry (ANZRAG) and the number of mother-father dyads who sought counselling and participated in shared decision-making. Nonetheless, this rate is similar to studies of caregivers of and affected individuals with inherited retinal disease,[492,524] retinoblastoma survivors,[490] and adults with childhood glaucoma (Chapter 7),[355] which report a combined rate of 33% to 60%. Whilst the result did not inherently impact a caregiver's decision to have more children, except where genetic diagnosis was unknown, the information was valued in planning further children and understanding the risk for future generations. For inherited retinal diseases, the main reasons for accessing genetic testing were to plan for future children who may develop the condition and to prepare for novel genetic therapeutic interventions.[524] Genetic results were rarely associated with guilt and self-blame in this cohort, but is a commonly reported theme in caregivers of children with retinoblastoma.[528] Further exploration of the perceived benefit or barriers to genetic testing in childhood glaucoma is warranted. The results of this study otherwise support that caregivers are in favour of seeking genetic counselling and these services should be readily available and accessible when undergoing decision-making for family planning.

Limitations

Study limitations include that caregivers were recruited from a national disease registry which requires consent to genetic testing for research. Consequently, caregivers may have been more willing to participate in this type of research and therefore may represent a subgroup of caregivers who may have

a better experience with childhood glaucoma and/or may be coping better than caregivers who did not participate. Furthermore, caregivers were asked to recall the diagnostic period such that their recounts may lack accuracy. Nonetheless, the depth of responses and developed themes have been triangulated with several ocular and non-ocular childhood diseases. In addition, thematic saturation was reached. Moreover, the cohort studied includes caregivers with infant, adolescent and adult children, and a varied range of time elapsed since diagnosis, such that the lived experience is herein captured across a comprehensive disease timeline. Caregivers were further predominantly of European ancestry and resided in Australia such that the findings may only be extrapolated to populations with similar socio-demographics and healthcare setting. Public healthcare in Australia is provided at no cost and this may explain why most caregivers did not experience a financial burden. The inclusion of mother-father dyads may have further influenced research findings although differences were frequently observed between caregivers of the same dyad. Further research will be required to ascertain if these findings can be applied to other cohorts of European and non-European ancestry and to elucidate the differences between experiences of caregivers within the same dyad. Lastly, we included caregivers of children with any type of childhood glaucoma but were unable to recruit caregivers of children with SG-A, (e.g., uveitic, trauma), SG-S or SG-C. These specific subtypes of childhood glaucoma may result in a different caregiver experience particularly given that these subtypes are preceded by an underlying medical and/or ocular disease that may impose further impacts on a caregiver's lived experience. Nonetheless, our findings broadened our insights into the lived experience of caregivers of individuals with childhood glaucoma.

In conclusion, our findings provide a detailed description of the lived experience of caregivers of individuals with childhood glaucoma. Childhood glaucoma poses a substantial threat to caregivers' social and emotional well-being, sense of control and decision-making in family planning. The impact of this threat is minimised by the use of coping strategies. Caregivers of individuals with childhood glaucoma may require support to achieve normalisation, assistance in accessing peer support and guidance in participating in shared parent-child management. Concurrently, psychotherapeutic interventions and genetic counselling could be offered in a timely manner where appropriate. Further research should evaluate the acceptability and effectiveness of such services, which ultimately aim to promote optimal disease outcomes and QoL for the child and the caregiver(s).

CHAPTER 9 DEVELOPMENT OF THE CGQOL-14: A TOOL THAT MEASURES THE IMPACT OF CHILDHOOD GLAUCOMA ON QUALITY OF LIFE IN ADULTS

9.1 Introduction

As defined by the WHO, QoL is conceptualised as an individual's perception of their position in life with respect to their culture and value systems and is impacted by their physical and psychological states and social relationships.[529] Measurement of QoL should target an individual's physical, emotional and social well-being, and include an assessment of their level of independence and relationship to their environment.[529] There are three types of QoL measures typically used throughout ophthalmic literature. These include HR-QoL, VR-QoL and disease-specific QoL PROMs. The former are a generic measure of health, and are not considered sensitive for measuring matters faced by individuals with a vision-threatening disease.[311,320] Examples of HR-QoL PROMs include the WHOQOL-BREF[330] and the Short-Form Health State Classification.[530] Ophthalmic VR-QoL instruments consider vision-specific impacts on QoL (e.g., NEI-VFQ 25)[329] whilst ophthalmic disease-specific PROMs are considered to provide more insight as to how a specific ocular disease may impact on one's physical, emotional and social well-being (e.g., Macular Disease-dependent QoL).[320–322]

As discussed in Chapters 6[358] and 7,[355] little is known of the disease-specific QoL in children and adults with childhood glaucoma. In the past five years, there has been an increasing trend in the literature to focus on the psychosocial impact of the disease. This has been particularly explored in children,[306–310] with studies concluding that lower BCVA is associated with lower VR-QoL.[306–309] Only one study, in Iran, measured VR-QoL in adults with PCG.[312] The findings from this study, however, are limited: it used the NEI-VFQ 25[312] which has been shown to be an inaccurate measure of VR-QoL, as its psychometric properties suggest that the questions it asks do not accurately align with the concept of VR-QoL.[495] Meanwhile, a study measured HR-QoL in Indian adults with PCG.[311] However, as mentioned, HR-QoL does not provide a sensitive measurement of the lived experience of an ocular disease. One possible reason for the limited research of disease-specific QoL in the adult childhood glaucoma population is that a disease-specific QoL PROM suitable for this population does not exist.

There are several PROMs that measure adult-onset glaucoma-specific QoL. These are either pen-and-paper based or electronic (called item banks). As their name suggests, pen-and-paper based PROMs are designed to be short and are completed by hand. Examples of these include the Glau-QoL 36,[359]

the Symptom Impact Glaucoma,[360] and the Glaucoma Quality of Life-15.[361] Although more commonly used, pen-and-paper based PROMs risk becoming outdated as treatment options and disease outcomes improve.[531] Item banks, delivered by computerised adaptive testing, overcome this, by storing a pool of questions (henceforth referred to as items) that can be updated quickly.[367] The computerised adaptive algorithm then selectively presents the items that provide the most efficient measure of QoL.[532] The introduction of item banks in glaucoma is relatively new with the first having just been validated in 2022 (Glaucoma Quality of Life Item Banks).[532] As identified in Chapter 7,[355] the issues impacting adults with childhood glaucoma are considered different to those impacting individuals with adult-onset disease. Subsequently, these glaucoma-specific QoL PROMs developed for populations with adult-onset glaucoma cannot be readily used for populations with childhood glaucoma. There is a need to address this gap in knowledge and develop a childhood glaucoma-specific QoL PROM.

Existing PROMs which measure QoL in adult-onset glaucoma include items pertaining to all QoL themes identified in Chapter 7 (e.g., activity limitations, emotional well-being, financial concerns) except for coping.[359,361,531] This is likely because measurement of coping and QoL are considered conceptually different. Measurement of QoL should incorporate items that are directly related to issues impacting an individual's physical, emotional and social well-being.[529] Conversely, measurement of coping should incorporate items that are targeted toward how an individual overcomes these QoL issues.[533] This difference has led to previous studies to examine the relationship between QoL and coping using separate measures as the coping strategies used by participants were considered to moderate QoL.[534–536] For example, the use of maladaptive coping strategies are associated with low VR-QoL in individuals with vision impairment,[534] and low HR-QoL in individuals with other chronic diseases such as cancer.[535] However, these studies have relied on generic measures of coping (e.g., Coping Strategy Indicator,[537] Brief Cope Questionnaire[533]). More recently, a disease-specific measure of coping for individuals with inherited retinal diseases had been developed, and evaluated the specific types of coping strategies used by individuals with these conditions.[538] Measurement of the level of an individual's ability to cope with childhood glaucoma using a specifically design coping PROM has the potential to increase our understanding of the coping strategies used and how these may impact on QoL.

There are two methods typically used for the development of PROMs. These are Classical Test Theory and Item Response Theory.[539–541] To develop a psychometrically robust PROM, the use of Item Response Theory is preferred.[495,539,540] There are two main reasons for this. First, items on PROMs are generally scored on an ordinal Likert-type rating scale (e.g., no difficulty = 4, little difficulty = 3, very difficult = 2 and extremely difficult = 1). Classical test theory-developed PROMs are designed to create interval-level measurements of the underlying trait (e.g., visual function, QoL) by simply summing the

raw ordinal scores from the Likert scale.[539,540] This assumes that the differences between the response categories are equal to the amount of the underlying trait being measured (e.g., someone who scores no difficulty [a score of 4] is considered to have twice the amount of visual function compared to someone who scores very difficult [a score of 2]) and is not a true interval-level measurement.[540,541] This is how the Glau-QoL 36, Symptom Impact Glaucoma and Glaucoma Quality of Life-15 were designed.[359–361] Conversely, Item Response Theory uses probabilistic mathematical modelling to convert raw ordinal scores into true interval-level measurements.[540,542] The Rasch model, which adopts the principles of Item Response Theory, is increasingly being used for the development of PROMs across ophthalmic literature,[316,321,531,543] and more recently has been adopted to develop a PROM for caregivers of individuals with childhood glaucoma (CarCQQoL).[316] The Rasch model also tests several other psychometric properties to ensure that all items on a PROM serve to accurately and meaningfully measure the construct that it claims to measure (e.g., disease-specific QoL).[544]

My original contribution to knowledge was the development of a childhood glaucoma-specific QoL PROM suitable for adults using Rasch analysis. This included a collection of items which incorporated the QoL themes identified in Chapter 7.[355] A secondary aim was to develop a separate childhood glaucoma coping PROM.

9.2 Methods

Development of a PROM consists of five distinct phases as adapted from Gothwal et al.[316] These include:

- Phase I: Item generation
- Phase II: Item reduction
- Phase III: Cognitive debriefing
- Phase IV: Pilot testing (includes Rasch analysis); and
- Phase V: Testing validity and reliability.

The PROMs in this study were designed to be pen-and-paper based. This is because development of an item bank, delivered by computerised adaptive testing, typically requires a sample size >250.[468,532,545] This was not feasible in a rare disease like childhood glaucoma.

Ethical approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/161) and the study adhered to the Tenets of the Declaration of Helsinki.

9.2.1 Phase I - Item generation

Item generation involves consultation with the literature and patients themselves.[546] A literature review was first performed to understand the utility and selection of QoL PROMs used in previous childhood glaucoma QoL research in adults. As identified in Chapter 7,[355] prior research had utilised generic VR-QoL and HR-QoL measures because a childhood glaucoma-specific QoL PROM does not exist.[311,312] Whilst these measures were useful in achieving familiarisation of the language required for PROM development, there were no qualitative studies in the literature to advise on item generation for either PROM and semi-structured interviews were required to generate data.

9.2.1.1 Semi-structured interviews

The data obtained from the semi-structured interviews, as described in Chapter 7,[355] were used to generate items. Items were extracted from each of the major QoL themes and their subthemes, for PROM development. Items were kept as close as possible to the original language of the participant statements.

9.2.1.2 Identification of item stem and response category options

To help transform the participant statements into items, they required a stem (i.e., a suitable phrase before the question) and response categories to choose from.[367] Item stems (e.g., *Because of your glaucoma, how much difficulty do you have…*) were determined based on their use in other similar ophthalmic QoL PROMs.[367,374,547,548] Item response categories (e.g., *none, a little, quite a bit, a lot*) were constructed based on available empirical evidence, whereby it is recommended that each item does not have more than four or five response categories.[367]

9.2.2 Phase II - Item reduction

Item reduction involves the process of removing redundant items by binning, winnowing and expert panel review. Binning is a process whereby items are grouped together based on having similar meaning.[549] For example, the items '*anxiety under testing conditions*' and '*anxious about meeting new people*' were binned together under '*feeling anxious*'. Winnowing is the process by which a large number of items are reduced to a set of items that represent the theme being measured.[549] The following predefined criteria was used in the winnowing process to remove items: (1) items that were inconsistent with the definition of the theme being measured, (2) the item had a similar phrasing or meaning with another item, (3) the item was too specific to have universal applicability (i.e, was only mentioned by few interviewees) and (4) the meaning of the item was unclear.[549] At each stage of binning and winnowing, the items were revised by supervisors ES and MPS. ES is a clinical and research genetic

counsellor with extensive experience in research translation while MPS is an expert in PROM development.[538,547] Any issue identified was resolved through discussion.

9.2.3 Phase III - Cognitive debriefing

Cognitive debriefing involves an interview process which aims to determine item appropriateness, understandability and interpretation for the intended target population.[550] Participants who provided verbal consent to be recontacted during Phase I semi-structured interviews (Chapter 7)[355] were recruited to take part in a cognitive interview using a purposive sampling technique. Individuals were recruited to broadly represent the cohort from which the items were developed (e.g., were of varied ages, gender, visual impairment status, employment status). The target number of interviews was 12 to 15, subject to data saturation.[550] Once written informed consent to participate in the cognitive interview was obtained, individuals were sent an electronic version of the PROMs, designed using Qualtrics (Provo, Utah, US), and a date and time was coordinated where I could administer the PROM.

Cognitive interviews were conducted according to standard recommendations.[550] Participants were made aware that the interview was to source their opinion on the wording, appropriateness, diversity and clarity of the item stems, the item themselves, and the response categories. Participants were informed that their exact answers would not be recorded and analysed, but rather their opinions and thoughts would be used to inform the interviewer as to how they would approach answering the question. Field notes were taken throughout the interview. There was no time limit applied and interviewees were encouraged to take breaks or pause the interview where needed. Various probes were used throughout the interview to gain insightful and productive information (e.g., "*What does this word mean to you? Do you have any issues with it? Can you think of a better word?*" and "*Does your answer fit into one of these categories or does there need to be an additional category? Why?"*). Interview reports were completed within 24 hours of the interview and referred to once all interviews were completed and required summarising.

9.2.4 Phase IV - Pilot testing

9.2.4.1 Participants

For this phase, participants were recruited from the ANZRAG and via advertisement through Australian and New Zealand glaucoma and vision-related support organisations and networks, and professional ophthalmology networks. These included Glaucoma Australia, Glaucoma New Zealand, Guide Dogs Australia, Blind Citizens Australia, the Royal Society for the Blind, Beyond Blindness, the Vision Impaired People's List mailing list, Insight Magazine and the Royal Australian and New Zealand College of Ophthalmology communications. The inclusion criteria were that participants had a diagnosis of glaucoma at <18 years of age, were ≥18 years of age at recruitment and did not have a cognitive impairment inhibiting their ability to understand the PROM as informed by the referring ophthalmologist (if recruited via the ANZRAG), their carer or themselves. Participants were either sent an electronic or postal pack subject to their preference. The pack included an invitation letter describing the purpose of the study, a set of demographic and clinical questions and all of the items for development of the two PROMs (QoL and coping; Appendix E). The electronic version was designed and distributed via Qualtrics software. In the invitation letter, participants were offered to complete the items over the phone if preferred. Completion of the items was accepted as consent.

Sociodemographic data collected included name, date of birth, gender, postal code, main language spoken at home, cultural background (including Indigenous status), marital status, highest level of education attained, current employment status and number of children. The postal code was used to determine whether participants' lived in a rural or urban area.[551,552] Clinical data collected included disease laterality, age of diagnosis, ocular comorbidities, use of vision aids, whether the individual seeks public or private healthcare, time elapsed since their last ophthalmic appointment and surgery (if applicable), the number of topical antiglaucoma medications they are currently using, their BCVA and their last known IOP measurement. If the participant was registered with the ANZRAG, BCVA and IOP were cross-referenced with their ANZRAG record or referring consultant. For individuals not enrolled in the ANZRAG, clinical details were collected via self-reporting.

9.2.4.2 Assessing the psychometric properties using Rasch analysis

As mentioned, the Rasch model creates an interval-level measurement. This is done using a probabilistic mathematical model whereby the raw score is conceptualised as the difference between item difficulty relative to the ability of the individuals completing it (i.e., item responses are weighted).[540,541,544] This difference is considered equal to the log-odds ratio of the probability of being able to do the item to the probability of not being able to do the item.[541] This creates a new linear

continuous measure of QoL, instead of using simple summation of raw scores. Values on this new scale are referred to as logits.[541]

Rasch analysis ensures that all items are productive for measuring the intended construct (i.e., childhood glaucoma-specific QoL or coping). When a PROM successfully measures only one construct, it is considered unidimensional.[541] To create a functional, unidimensional PROM utilising the Rasch model, a set of prerequisites must be met.[553] These include an ordered category threshold order, adequate measurement precision and targeting, unidimensionality and limited differential item functioning. These are described below. To have 95% confidence that the calibrations for the PROMs are stable within 0.5 logit from its modelled standard error, a sample size between 64 to 144 is required.[468]

Items are scored such that the more positive their score, the higher the individuals' QoL.[316] For example, response options pertaining to difficulty along the scale of '*none'* to '*unable to do because of my vision'* are scored such that '*None*' = 5, '*A little*' = 4, '*Quite a bit*' = 3, '*A lot*' = 2 and '*Unable to do because of my vision*' = 1. Responses were recorded as missing where an individual recorded '*this is not relevant to me, or I do not do this'* or *'I do not wish to answer'.* Childhood glaucoma QoL items and coping items underwent separate Rasch analysis with the intent to create two separate PROMs.

9.2.4.2.1 Category threshold order

The first step of Rasch analysis involved assessment of the response category threshold order.[495] This was performed using the Andrich rating scale model using joint maximum-likelihood estimation for each group of questions with the same response structure.[554] The Andrich rating model tested whether the response categories (or options) were chosen in a logical order as they were intended, with respect to the increasing difficulty of the response categories. For example, the response categories along the scale of '*none'* to '*unable to do because of my vision'* (as outlined above) are intended to follow a hierarchical increase in difficulty of the item. A threshold represents the transition between two sequential categories in the scale, where the probability of either of them being selected is equal.[316,495] Ordered thresholds are graphically depicted whereby each curve has a distinct peak after intersecting with the previous curve, and the thresholds are hierarchically arranged (e.g., a threshold occurs between none and a little, rather than none and a lot).[543] An example of disordered and ordered categories are provided in Figure 9.1. Disordering of thresholds may occur in several instances. These include where the category is underutilised, the meaning of the item is ambiguous, or there are too many categories such that participants are unable to distinguish the difference between them.[543,555]

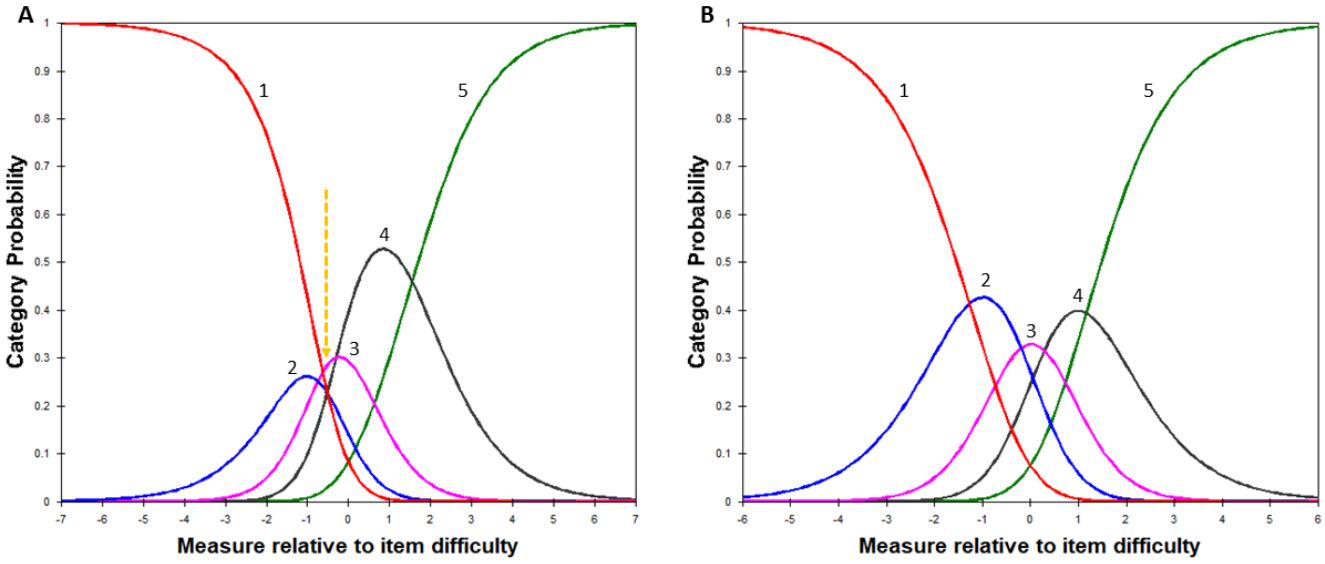

Figure 9.1. Example of disordered and ordered category thresholds
Panel A demonstrates that categories are disordered, and Panel B represents ordered thresholds. In both panels, the red line represents response option 1, e.g., 'always'; blue line represents response option 2, e.g., 'very often'; pink line is response option 3, e.g., 'quite often'; black line is response option 4, e.g., 'occasionally' and green line is response option 5, e.g., 'never'. The *x*-axis refers to the measure of QoL whereby more positive integers measure a higher QoL relative to the item difficulty. The probability of the category being selected is measured along the *y-axis*. In Panel A, the dotted orange arrow represents where category disordering has occurred. The first intersection of the category probability curves occurs where the red line (option 1; always) intersects with the pink line (option 3; quite often). This violates the hierarchical order of response options. Panel B indicates ordered category thresholds whereby the intersections occur hierarchically in the order of 1–2, 2–3, 3–4 and 4–5.

9.2.4.2.2 Measurement precision

Measurement precision was determined by the person separation index (PSI).[556] It refers to the PROM's ability to distinguish between the levels of participants' abilities based on their scores (e.g., high or low QoL).[556] It is measured by dividing the observed variance in the person measures (or QoL scores) across the sample by the average measurement error.[556] A PSI value of ≥2.00 was considered acceptable.[546] A PSI of ≥2.00 indicates that the PROM can distinguish between three levels of participants' abilities (e.g., high, moderate or low QoL) whilst a PSI of ≥3.00 indicates that four levels can be distinguished (e.g., very high, high, moderate or low).[556] A low PSI may occur due to a sample having similar ability, the test being too short or there are too few category responses resulting in individuals measuring similar scores. Conversely, a higher PSI may be achieved with a wider sample ability range, a longer test, and more response categories, as individuals will more likely score differently to one another.[557]

9.2.4.2.3 Unidimensionality

Unidimensionality was determined by the fit statistics and the principal components analysis (PCA) of the residuals.[558] Fit statistics were resolved before examining the PCA.[559,560]

The fit (including infit and outfit statistics) statistics demonstrate how well the items fit with the expectation of the Rasch model and are indicated by the mean square standardised residual (MNSQ). Item infit considers the difference between the observed and expected responses for items that have a level of difficulty close to the level of the ability of the respondent.[561] Alternatively, outfit statistics consider these differences for items that have a level of difficulty far from the respondent's ability.[321,561] The infit statistic is considered more informative because it is less sensitive to outliers. An infit and outfit MNSQ value between 0.7 to 1.3 was considered acceptable.[546] A fit MNSQ >1.3 indicated unacceptable levels of measurement noise whilst items with fit MNSQ <0.7 were considered redundant and were removed. Accordingly, item infit and outfit were used to guide item reduction, in addition to further item characteristics. The following guidelines, as defined by Pesudovs et al.[548] and modified by Khadka et al.[546] were used in order of priority to guide item reduction:

1. Items with infit MNSQ <0.7 or >1.3
2. Items with outfit MNSQ <0.7 or >1.3
3. Items with a high proportion of missing data (>50%), as large portions of missing data imply that either the question is ambiguous or is not applicable to a substantive number of respondents.
4. Items with a ceiling effect, defined by the presence of >50% of responses in the end-response category; and
5. Skew and kurtosis <-2.00 or >+2.00

Items were removed one at a time as each time an item was removed, the infit and outfit statistics changed. This process continued until all items showed good fit.[321]

The PCA indicates if the PROM measures a single construct (e.g., childhood glaucoma-specific QoL or coping) or whether the instrument is multidimensional (i.e., items group together to form separate measures of activity limitation and symptoms rather than join to form a unified measure of childhood glaucoma-specific QoL). It is indicated by two parameters: the proportion of raw variance explained by the measure and the eigenvalue of the unexplained variance in the first contrast.[546] The amount of raw variance is ideally >60% although a level of >50% is considered acceptable.[546,547,562] This is provided that the eigenvalue of the first contrast is <2.0 because a value ≥2.0 means that two items are measuring a separate construct.[546] The thresholds used in this study to determine if the PROM measured a single construct were an amount of raw variance >50% and an eigenvalue of the first contrast <2.0. If the

eigenvalue was ≥2.0, a loading of ≥0.4 was used to identify which items were responsible for forming a separate construct.[495]

9.2.4.2.4 Targeting

Targeting is the term used to describe whether the difficulty of the items in the PROM appropriately match the abilities of the population sampled, or whether they are too easy or too difficult.[495] It is determined by the difference in the mean of the item difficulty and person ability. A person and item mean difference ≤1.0 logits were considered good whilst a score of 0 indicated perfect targeting.[546]

9.2.4.2.5 Re-addition of items

Because of the volatility of Rasch analysis, constructive items could be removed in the earlier stages (i.e., misfitting items, unidimensionality). Subsequently, items deemed important with consideration to the qualitative interview data (Phase I) could be readded or changed if they resulted in optimisation of the PROM.[321,495]

9.2.4.2.6 Differential item functioning

Differential item functioning (DIF) measures whether people within a certain subgroup in the sample, with comparable levels of ability, perform better or worse on an item compared to another group.[321,557] These groups are best defined *a priori*.[316] DIF variables for participant age (split based on the median age of interview participants in Phase I; <40 years vs ≥40 years) and gender (male versus female) were assessed. The mode of item administration (self-administered vs interviewer-administered), and main language spoken at home (English or other) were further analysed for DIF to assess for item interpretability. An item was determined to have DIF if the mean difference in person measures between groups was >1.0 logit and there was statistical significance (i.e., a corresponding p value of <0.05).[538,557] The Rasch-Welch t test method was used to determine if the DIF contrast was significant.[563] If DIF was found, an item was considered for deletion if it was not considered clinically meaningful and removal of the item improved the aforementioned characteristics in the Rasch model.[316,547]

9.2.5 Phase V - Validity and reliability

There are several parameters that require testing after pilot testing and before clinical implementation.[546] These include:

1. Test-retest reliability, which tests the stability of repeated measures and how much the scores are free from random error.[564] The time period between repeated measures should be long

enough to prevent any recall of responses but short enough so that participants' condition has unlikely changed.[564] One to two weeks between measures is considered appropriate.[564]

2. Responsiveness, which tests the ability of the PROM to detect change in the construct (i.e., QoL or coping) over a long period of time.[546]
3. Concurrent validity, which tests if PROM scores correlate with the accepted 'gold standard' measure of QoL at the time or another clinical measure (e.g., BCVA, visual field mean deviation).[546]
4. Convergent and divergent validity, which test to what degree PROM scores correlate with existing PROMs that measure similar constructs and dissimilar constructs, respectively;[546] and
5. Known group validity, which tests whether specific groups score differently to one another based on accepted criteria (e.g., *do participants with worse disease score better than those with less severe disease?*).[546]

Due to time constraints, Phase V was not completed during this thesis.

9.2.6 Statistical analyses

All participant socio-demographic and clinical characteristics were analysed using SPSS version 27.0 for Windows. Rasch analysis was performed using Winsteps software, version 5.2.2.0 (Chicago, IL, USA) using the Andrich rating scale for each group of items with the same item stems and item response categories. The chi-square test with continuity correction or Fisher exact test were used for categorical variables and the Mann-Whitney U test or median test were applied to non-parametric continuous variables where appropriate.

9.3 Results

9.3.1 Phase I - Item generation

9.3.1.1 Semi-structured interviews

As per Chapter 7,[355] a total of 47 semi-structured interviews were conducted with adults with childhood glaucoma. The mean participant age was 40.0±15.3 years, 55% were female and 19% had bilateral BCVA <6/60. There were no significantly different clinical or demographic characteristics between participants recruited for the interviews and those who could not be contacted or declined participation (Appendix B, Table B12). There was a range of glaucoma subtypes represented amongst those interviewed. These included PCG (55%), JOAG (23%), SG-O (17%) and SG-C (2%). The major themes developed, in order, included coping, emotional well-being, ocular health concerns, symptoms, family planning, inconveniences, social well-being, activity limitation, economic and mobility.

For the childhood glaucoma-specific QoL PROM, a total of 581 items were generated from the interviews. The theme with the most items was emotional well-being (n=193 items). Other themes and the number of items included ocular health concerns (n=94 items), family planning (n=54 items), activity limitation (n=45 items), economic (n=33 items), symptoms (n=31 symptoms; 93 items due to symptom frequency [n=31 items], symptom severity [n=31 items] and how much of a problem the symptom is [n=31 items]), social wellbeing (n=28 items), convenience (n=28 items) and mobility (n=13 items). For the purpose of PROM development and brevity, the themes of ocular health concerns and family planning were combined to form the broader theme of health concerns (n=148 items). The coping PROM had 186 items generated from the theme of coping. Examples of item generation from participant quotes are provided in Table 9.1.

Table 9.1. Examples of items generated from participant quotes

QoL Theme	Participant quote	Item developed
Emotional well-being	“I was not expecting [my pressures to go up]... I hadn’t had any changes for so long... I felt sick because I was so scared.” (P44)	Feel scared of eye pressure
Health concern	“I do have worries where I'm like "Are my eyes going to get real bad?” … Is drive - like “Am I going to still be able to drive?"... because it - it means I can - I - it means I'm as independent sort of as everyone else or I can do all the things I want to do.” (P10)	Losing independence
Symptom	“Like for example if I’m out and… the only seat available at a table in a café is like facing the sun, I know that’s going to bother me.” (P25)	Trouble with glare
Inconveniences	“[The appointment] comes around quickly. Umm so, oh look it’s a pain…I always try and get an early appointment so I can get in and out.” (P26)	The frequency of your eye appointments
Social well-being	“Sometimes it plays in my mind it’s like oh I wonder if someone wouldn’t be interested in me because they’d be like oh I’m going to have to take care of her because she’s not going to have any eyesight.” (P44)	Trouble establishing and maintaining close relationships
Activity limitation	“I can’t read a menu at a fast food place, the ones that are up on the wall, you know, behind the counter.” (P30)	Reading things from a distance
Economic	“I was working in a furniture factory where you had to sand the furniture before – it was painted... And of course I can’t see that… So I was always getting into trouble for missing bits and pieces for that sort of job.” (P13)	Ability to do work tasks being impacted by your glaucoma
Mobility	“Like um you know, festivals or going to things like that and trying to find a friend again is near impossible for me. So I'm like "Don't leave me." Or like "I need you to stay with me." (P10)	Navigating crowded places
Coping	“Having it since I was so young… my brain has learnt, “Oh, this is what I’ve got and this is how I need to act to make the best use of it so I can still function.” (P38)	Finding ways to adapt

9.3.1.2 Identification of item stem and response category options

Item stems, and their respective response categories, per theme or group of themes (referred to as Category Response Types A–G for brevity) are summarised in Table 9.2. Each of these were generated from empirical evidence.[367,374,543,547,548,565,566] The theme 'symptoms' required measurement of three constructs: frequency, severity and bothersome (analogous with how much of a problem is the symptom?).[565] Each of these constructs required a different item stem and response categories (Types A–C, Table 9.2). The themes of activity limitation, mobility, and social well-being shared the same group of response categories on a 5-point Likert scale (Type D; Table 9.2) as they all related to an individual's difficulty with a task.[367,543,547] The phrasing of the response categories along the Likert scale was selected based on the review by Khadka et al.,[543] who identified that such categories were able to achieve a good range of responses. The response categories were similar for inconvenience-based items, but '*unable to do because of my vision*' was rephrased to '*an extreme amount*' (Type E, Table 9.2), as logically it did not make sense to use the former.[374] The themes of economic and health concerns were grouped to share a different 5-point Likert scale as they related to an individual's concern (Type F, Table 9.2). The response categories along this scale have previously been proven to be ordered,[547] meaning that participants could accurately discriminate between the response categories.[543] Response categories of '*this is not relevant to me or I do not do this'* or '*this is not relevant to me'* (i.e., not applicable) and '*I do not wish to answer*' were further added as necessary (Type D, E and F; Table 9.2).

For themes including emotional well-being and coping, a time-based 5-point Likert scale was used (Type G, Table 9.2). The range and evenness of the response categories on this scale have been shown to be relatively effective for use in the NEI-VFQ 25.[543] These response categories were further used in the Kessler-10, a commonly used tool to measure psychological distress, where five responses performed better than four.[566] The response category, '*I do not wish to answer*' was added.

Table 9.2. Item stems and response categories per QoL theme as determined by empirical evidence

QoL theme/s	Item stem (Because of your glaucoma and its treatment…)	Types of response category	Response categories
Symptoms - Frequency	How often do you experience…?	A	Never, occasionally, quite often and very often
Symptoms - Severity	How severe is…?	B	Not at all, mild, moderate, and severe
Symptoms - Problem/Bother	How much of a problem is…?	C	Not at all, a little, quite a bit and a lot
Activity limitation, mobility, social well-being	How much difficulty do you have…?	D	None, a little, quite a bit, a lot, and unable to do because of my vision†
Inconveniences	How much trouble is…?	E	None, a little, quite a bit, a lot, and an extreme amount†
Health concerns, economic	How concerned are you about…?	F	Not at all, a little bit, moderately, a lot and extremely‡
Emotional well-being	During the past month, how often did you feel…?	G	None of the time, a little of the time, some of the time, most of the time and all the time§
Coping	How often do you…?		

Empirical evidence consulted in the construction of this table.[367,374,543,547,548,565,566]
†Additional response categories included: '*This is not relevant to me or I do not do this'* and *'I do not wish to answer'*
‡Additional response categories included: '*This is not relevant to me'* and '*I do not wish to answer'*
§Additional response category included: '*I do not wish to answer*'

9.3.2 Phase II - Item reduction

To reduce the number of items for the PROMs, several items underwent binning, winnowing and expert panel review. Binning consisted of grouping items with similar meaning. Table 9.3 provides examples of the binning process for items for the childhood glaucoma-specific QoL PROM.

Table 9.3. Examples of item binning in the first phase for items for the childhood glaucoma-specific QoL PROM

Item/s	QoL theme	Item bin created
Difficulty with fishing Difficulty woodworking Difficulty with photography Difficulty gardening	Activity limitation	Difficulty doing leisure activities/hobbies (e.g., fishing/gardening)
Fear of going blind Fear of losing career Fear of hurting someone	Emotional well-being	Feeling scared
Not being able to drive self or children Getting transport assistance	Inconveniences	Relying on others to drive you to places
Wanting acceptance when meeting new people Considered self to be introverted due to condition Lacked social confidence	Social well-being	Meeting new people

After binning was complete, items underwent winnowing, a process by which items were removed based on their redundancy, specificity, and understandability.[549] For example, '*being concerned of having a surgical complication*' was considered redundant under the item of '*developing a different eye disease or condition*' and '*feeling squeamish about a surgical procedure*' was removed because it was stated by one participant only. All items related to COVID-19 and its potential impact on glaucoma outcomes or treatment were removed, as this was contextual to the time in which the PROMs were designed and would unlikely be relevant in future evaluation of QoL.

After the first binning and winnowing process, the number of items for the childhood glaucoma-specific QoL PROM were reduced from 581 to 168 and the number of items for the coping PROM were reduced from 186 to 28. Items for the QoL PROM and Coping PROM underwent a second round of binning and winnowing as outlined in Table 9.4 and Table 9.5, respectively. The resulting number of items were reduced to 130 and 20, for the QoL PROM and Coping PROM, respectively.

Table 9.4. Results of the second round of item reduction for the childhood glaucoma-specific QoL PROM

QoL theme	Items after Round 1 of item reduction (n)	Items considered for binning or deletion	Reason for deletion	Items after Round 2 of item reduction (n)
Symptoms	54 (i.e., 18 symptoms with frequency, severity, problem of each symptom)	1. Difficulty adjusting or changing focus 2. Poor balance or coordination 3. Distorted vision 4. Double vision 5. Eye pain	1. Unclear meaning 2. Redundant under mobility and activity limitation items (e.g., participating in sporting activities) 3. Unclear meaning 4. Not consistent with glaucoma symptoms 5. Redundant under 'sore or uncomfortable eyes'	36 (i.e., 13 symptoms with frequency, severity, problem of each symptom)
Activity limitations	14	1. Playing ball sports 2. Participating in adventurous sports 3. Difficulty reading text on mobile phone 4. Seeing what happens at a sporting event	1 & 2. Redundant under 'Playing sports or exercising' 3. Redundant under 'difficulty reading small text' 4. Too specific	10
Mobility	6	1. Bumping into things on your side	1. Redundant under all other mobility items	5
Social well-being	14	1. Telling people about your glaucoma 2. With family members making an issue of your eye problem	1. Considered to be a coping strategy 2. Redundant under 'feeling frustrated' and 'feeling misunderstood' (emotional well-being)	12
Inconveniences	17	1. Having to undergo a visual field test 2. Having to wear glasses while playing sport or exercising 3. Having to take time to recover from surgery 4. Having to get government transport assistance 5. Wearing contact lenses	1. Redundant under 'having to undergo routine eye tests at every glaucoma appointment' 2. Redundant under 'having to wear glasses' 3. Redundant under 'needing future surgery' (health concerns) 4. Redundant under 'getting help and support from government or social welfare' (social well-being) 5. Too specific	12
Economic concerns	9	1. The cost of genetic counselling and family planning	1. Too specific	8
Health concerns	16	1. Your glaucoma getting worse 2. Having side effects from your medication	1. Redundant under 'glaucoma affecting your better eye' and 'losing vision' 2. Redundant under 'being on long-term medication'	14
Emotional well-being	38	1. Feel tired or exhausted 2. Feel jealous 3. Feel disengaged 4. Feel shocked 5. Feel awkward	1. Redundant under 'exhaustion or tiredness' (symptoms) 2. Unclear meaning 3. Considered to be a coping strategy 4. Too specific (referred to diagnostic period) 5. Redundant under 'feel self-conscious' (emotional well-being)	33
				Total: 130

Table 9.5. Results of the second round of item reduction for the childhood glaucoma-specific coping PROM

No. of items after Round 1 of item reduction	Items considered for binning or deletion	Reason for deletion	No. of items after Round 2 of item reduction
28	1. Blaming someone else for your eye condition 2. By not letting glaucoma stop me from doing what I want to do 3. Asking for help when you need it 4. Being pragmatic about your condition 5. Living in the moment 6. Preparing for the worst 7. Learning as much as I can about my glaucoma 8. Using religion	1. Redundant under 'acceptance' 2. Redundant under 'trying to be independent' 3. Redundant under 'getting professional support' and 'peer support' 4. Redundant under 'acceptance' 5. Unclear 6. Redundant under 'acceptance' 7. Unclear 8. Too specific	20

A third round of binning and winnowing was undertaken for all items and a further 17 items were removed for the QoL PROM. The resultant pilot QoL questionnaire had 113 items from the corresponding themes: symptoms (n=11 symptoms; 33 items due to frequency [11 items], severity [11 items] and problem of symptom [11 items]), activity limitation (n=10), mobility (n=5), social wellbeing (n=12), inconveniences (n=12), economic (n=8), health concerns (n=14) and emotional well-being (n=19). The coping PROM did not have any additional items removed in the third round (n=20).

9.3.3 Phase III - Cognitive debriefing

Twelve individuals consented to participate in a cognitive interview to evaluate the contents for either PROM. The average cognitive interview was 146±56 minutes and data saturation was achieved. Their characteristics provided a representation of the participants who were interviewed in Phase I (Appendix B, Table B14). There were an equal number of females and males (6/12, 50%), and the mean age of participants was 40.5±12.6 years (range: 20–60). Two thirds of participants were diagnosed with PCG (8/12, 67%), 2/12 (17%) had JOAG and 2/12 (17%) had SG-O. Of these individuals, 5/12 (42%) had bilaterally impaired BCVA (i.e., BCVA <6/12 in each eye),[337] 4/12 (33%) had unilateral vision impairment (i.e., BCVA <6/12 in one eye),[337] and 7/12 (58%) were unable to drive. Topical antiglaucoma medications were being used by 7/12 (58%). Other participant characteristics included their marital status (never married: 4/12, 33%), employment status (employed: 11/12, 93%), whether they had children or not (had children: 9/12, 67%) and whether they were receiving healthcare in the public or private system (private healthcare: 7/12, 58%).

The electronic format for completion of the items for each PROM was considered accessible by all individuals. Those who used screen-reading devices, due to the vision impairment, reported that Qualtrics software was compatible with their device. The number of items was considered to be appropriate, and each were relevant to their experiences. However, several items required rewording,

separation into two separate items or required examples. Examples of these item changes for the QoL PROM are provided in Table 9.6.

Table 9.6. Examples of item changes after cognitive interviews for the childhood glaucoma-specific QoL PROM

QoL theme	Item	Change required	Final accepted item
Symptoms	Difficulty distinguishing contrast	The term contrast was not easily understood. Rephrasing and examples were required.	Difficulty seeing objects or reading text with a similar colour to its background (e.g., reading black text on grey paper vs reading text on white paper)
	Difficulty adapting to light and dark conditions	Participants did not like the term adapting.	Difficulty adjusting to light and dark conditions
Activity limitations	Playing sports or exercising	Playing sports was considered a hobby.	Doing daily exercise
	Watching movies (including 3D movies)	3D movies were considered irrelevant. Participants considered seeing a play at the theatre to be of the same difficulty as watching a movie at the cinema	Watching a film at the cinema or seeing a play at the theatre
	Watching TV	Participants considered that there are several methods to 'watch TV' depending on their visual ability	Watching a TV programme or movie on your preferred electronic device (e.g., TV, laptop, tablet)
	Doing the household chores (e.g., cleaning or cooking)	Participants considered that these were two different questions, resulting in a split item	1. Doing the household cleaning 2. Cooking and preparing meals
Social well-being	With people bullying you or treating you poorly	The wording was considered to imply that schoolyard bullying had occurred	With people treating you unfairly
	Getting help and support from your family and friends	Participants considered these were two different questions, resulting in a split item	1. Getting help and support from your family 2. Getting help and support from your friends
	Getting help and support from government or social welfare	The term social welfare was not favoured	Getting help and support from government or social services
Convenience	The frequency of your eye appointments	The wording was considered confusing	How often you need to go to an eye appointment
	Making things larger to read or see clearly	The wording was considered discriminatory to individuals with vision impairment	Making text in an accessible format (e.g., making it larger to read, converting text to speech)

Several cognitive interviewees requested that certain items be added. Each time a new item was proposed to be added it was subjected to feedback from the consecutive interviewees prior to adding it to the final item set. The items added under their respective themes are as follows:

1. Activity limitations: '*finding something in a cluttered space*'
2. Mobility: '*crossing the road*', '*going up or down stairs*', and '*finding landmarks*'
3. Social well-being: '*taking care of your pet/s*'
4. Convenience: '*wearing contact lenses*' (despite its removal in Round 2 of item reduction)
5. Economic: '*losing your source of income*'
6. Health concerns: '*your overall appearance (e.g., applying make-up, shaving, dressing yourself)*' and '*maintaining good personal hygiene (e.g., bathing, cutting your nails)*'

Participants further identified items that could be removed. Seven emotional well-being items were considered redundant. These included feeling: '*inadequate or incapable of doing something*', '*worried*', '*helpless*', '*confused*', '*like giving up*', '*overwhelmed*' and '*like I have lost my confidence*'. The item '*Interacting with someone with a similar eye condition or visual impairment*' (social well-being) was identified as a discriminatory item as individuals considered that they would not have difficulty interacting with someone based on their visual status. Symptoms of dry eye, and exhaustion and tiredness were further removed as their meaning was not clear. One coping item, '*try to get on with your life*' was removed as it is considered redundant under the item '*try to have a positive outlook on life*'.

Few changes were made to the item stems and item response categories as listed in Table 9.2. The item stem pertaining to symptom problem/bother was changed to "*How much of an impact is/are the…"* and the item stem for inconveniences was changed to "*How inconvenient is…?*". Type A response categories, which related to symptom frequency, required the addition of '*always*'. In Type F response categories (for concern-based items), the category of '*a little bit'* was changed to '*a little'*. For Type G response categories (for emotional well-being and coping items), the phrase '*none of the time'* was changed to '*never'* and *'some of the time'* was changed to '*sometimes*'.

The final number of items intended for the pilot childhood glaucoma-specific PROM was 112, and the pilot coping PROM consisted of 19 items. The final set of items are provided in Appendix B, Table B15. To assist with understanding the results of Rasch analysis, each item for the pilot PROMs was allocated a number as per Appendix B, Table B15.

9.3.4 Phase IV - Pilot testing (Rasch analysis)

9.3.4.1 Participants

The items for the pilot PROMs were distributed to 156 adults with childhood glaucoma registered with the ANZRAG. Of these, 93/156 (59.6%) completed the items. Rates of completion among those distributed via post was significantly lower than individuals who received them electronically (18/55, 32.7% vs 75/101, 74.3%, respectively, p<0.001). Individuals who completed the items were older compared to nonrespondents, although this finding did not reach statistical significance (median: 43.6 years [range: 18.5–75.4] vs median: 29.6 years [range: 18.1–85.0], respectively, p=0.05). There was no difference in the proportion of individuals with bilateral BCVA <6/60 who did or did not complete the items (15/93, 16.1% vs 9/62, 14.5%, respectively, p=0.96). The rate of completion per gender was not significantly different (females completed: 47/76, 61.8% vs males completed: 45/79, 57.0%, p=0.65). An additional 9 individuals, not registered within the ANZRAG, completed the items, totalling 102 responses.

The socio-demographic and clinical characteristics of participants are provided in Table 9.7 and Table 9.8, respectively. The median age among those who completed the items was 41.1 years (range: 18.5–75.4) and 53/102 (52.0%) were female. One respondent indicated that they identified as non-binary (1/102, 1.0%). The majority of participants resided in a major city or urban area (82/102, 80.4%). The most common glaucoma subtype among respondents was PCG (49/102, 48.0%) and 91/102 (89.2%) had bilateral disease. The time elapsed since participants' last ophthalmic appointment were ≤3-monthly (47/102, 46.1%), 3–≤6-monthly (17/102, 17.2%), 6–≤12-monthly (18/102, 18.2%) or ≥12-monthly (17/102, 17.2%).

Table 9.7. Socio-demographic characteristics of participants who completed the pilot PROMs

Socio-demographic characteristic	**n (%)[†]**
Participant age, years (median [range])	41.1 (18.5–75.4)
Gender, female	53 (52.0)
European ancestry	78 (78.0)
Main language spoken at home, English	91 (89.2)
Married or de-facto	54 (52.9)
Currently employed	66 (64.7)
Currently receive income support payments	13 (12.7)
Has children	51 (50.0)
Mode of healthcare	
Private	60 (58.8)
Public	22 (21.6)
Both public and private	18 (17.6)
No longer receives ophthalmic care	2 (2.0)

[†]Data are presented as no. (%) unless otherwise indicated

Table 9.8. Clinical characteristics of participants who completed the pilot PROMs

Clinical characteristic	n (%)
Subtype of childhood glaucoma	
PCG	47 (46.1)
JOAG	30 (29.4)
SG-A	
Trauma	2 (2.0)
Maternal rubella	1 (1.0)
SG-O	
Axenfeld-Rieger syndrome	7 (6.9)
Aniridia	5 (4.9)
Unspecified anterior segment dysgenesis	4 (3.9)
Peters anomaly	1 (1.0)
SG-S	
Weill-Marchesani syndrome	1 (1.0)
Sturge Weber syndrome	1 (1.0)
SG-C	3 (2.9)
Laterality of glaucoma, bilateral	91 (89.2)
Level of bilateral vision impairment†	
None	63 (61.8)
Mild	6 (5.9)
Moderate	13 (12.7)
Severe	20 (19.6)
Ocular comorbidity	
Retinal detachment	16 (15.7)
Corneal disease	16 (15.7)
Ocular prosthesis	11 (10.8)
Cataract	33 (32.4)
Currently using topical antiglaucoma medication, yes	63 (63.0)
Uses a vision aid or assistive technology	26 (25.5)

PCG: primary congenital glaucoma; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; JOAG: juvenile open-angle glaucoma; SG-A: secondary glaucoma associated with an acquired condition; SG-C: secondary glaucoma following cataract surgery
†Vision categories determined by BCVA as per Methods (Chapter 2)[337]
‡Included 34/63 (54.0%) individuals with unilateral impaired BCVA

9.3.4.2 Rasch analysis of the pilot childhood glaucoma-specific QoL PROM

The psychometric properties of the items for the pilot childhood glaucoma-specific QoL PROM were tested using Rasch analysis. All items were analysed together, as separate analyses of items per theme did not result in Rasch-acceptable measurement subscales (Appendix B, Table B16). Overall, the Rasch analysis of the 112 item PROM showed acceptable PSI (5.47) and targeting (0.81). However, several item response categories were disordered, and 47 items had infit and/or outfit values <0.7 and >1.3 indicating that they did not fit the model. In addition, the PROM showed multidimensionality, with the eigenvalue of the first contrast measuring >2.0 (14.5) and amount of raw variance measuring 46.7%. Several changes were made to meet the requirements of the Rasch model.

9.3.4.2.1 Category threshold assessment

The category response thresholds for each category response type (i.e., Type A–F; Table 9.2) were first addressed. Type A category responses, which corresponded to items regarding symptom frequency, were found to be disordered as demonstrated by the failure of the curves to intersect in a hierarchical order on the category probability curve (Figure 9.2A). The response categories '*very often*' and '*quite often*' were underutilised likely owing to participants being unable to distinguish the difference between these categories. To correct this, the response category '*very often*' was combined with '*always*' to make the category of '*very often or always*'. However, the thresholds remained disordered (Figure 9.2B). To correct this, the category '*quite often*' was collapsed with '*occasionally*' to make the category '*occasionally or quite often*' and the thresholds became ordered (Figure 9.2C).

Type B (symptom severity) and Type C (problem of symptom) category responses were ordered hierarchically. However, to maintain consistency of having three response categories for symptoms, as done for symptom frequency, collapsing was performed. When collapsing the Type B category responses, '*moderate*' and '*severe*', the PSI improved to 5.48 and targeting improved 0.77. Consequently, this change was accepted as it improved the Rasch model. This generated new response categories including '*none'*, '*mild'* and '*moderate to severe'*. For Type C responses, the category responses '*quite a bit*' and '*a lot*' were collapsed to form the category responses: *'not at all*', *'a little'*, and '*a lot*'. This resulted in improved targeting of 0.73 while PSI remained at 5.48.

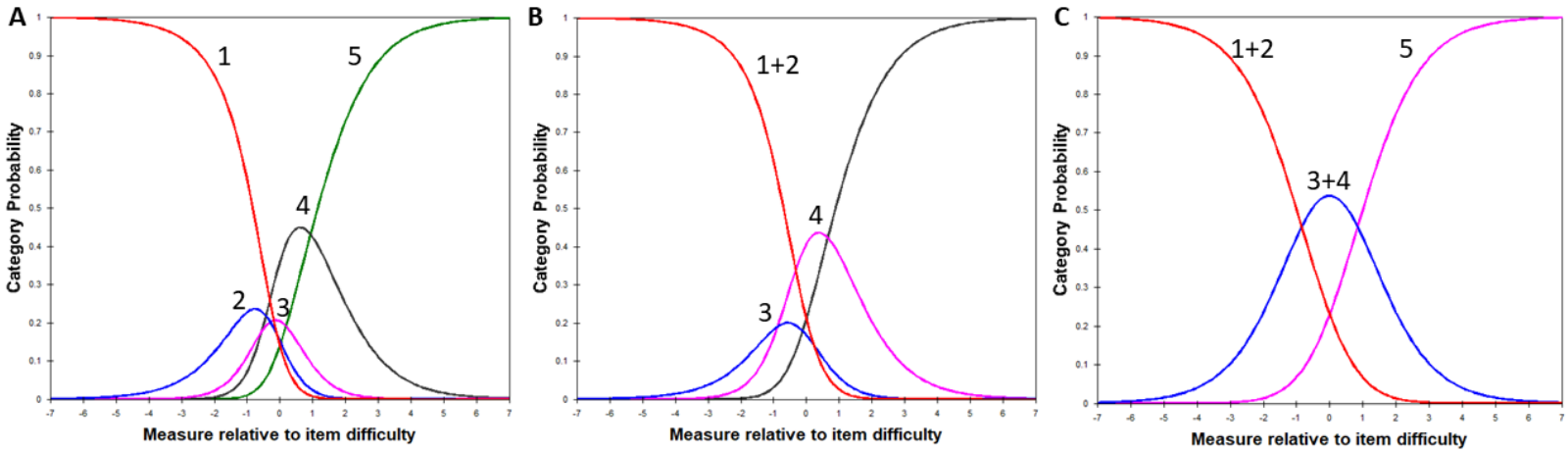

Figure 9.2. Ordering of Type A response categories

The Rasch model category probability curves for all items with Type A response categories (i.e., symptoms frequency) showing the probability that an individual with a particular QoL will select one of the categories. Panel A demonstrates that categories were disordered. In Panel A, the red line represents 1, 'always'; blue line represents 2, 'very often'; pink line is 3, 'quite often'; black line is 4, 'occasionally' and green line is 5, 'never'. Panel B continued to demonstrate disordered categories after collapsing categories 1 and 2. Panel C demonstrated ordered thresholds after collapsing category 1 with category 2 and collapsing category 3 with category 4.

Type D and G response categories were not ordered, and a three-option response category scale was required for each response category (Figure 9.3). For Type D (i.e., difficulty-based items), the categories '*a little*','*quite a bit*' and '*a lot'* were underutilised (Figure 9.3A). The former two categories were collapsed while '*a lot*' and *'unable to do because of my vision*' were collapsed to achieve ordered response thresholds (Figure 9.3B). The new category responses became: '*none'*, '*a little or quite a bit'*, and *'a lot'*. Type G (i.e., frequency of emotions) response categories were also disordered (Figure 9.3C). To correct this, response categories '*a little of the time'* and '*sometimes'* were collapsed and '*most of the time*' and '*all the time*' were collapsed (Figure 9.3D). The new category responses became: '*never*', '*sometimes'* and *'most of the time'*. The PSI improved to 5.50 and targeting remained at 0.73, indicating that the Rasch model accepted the changes.

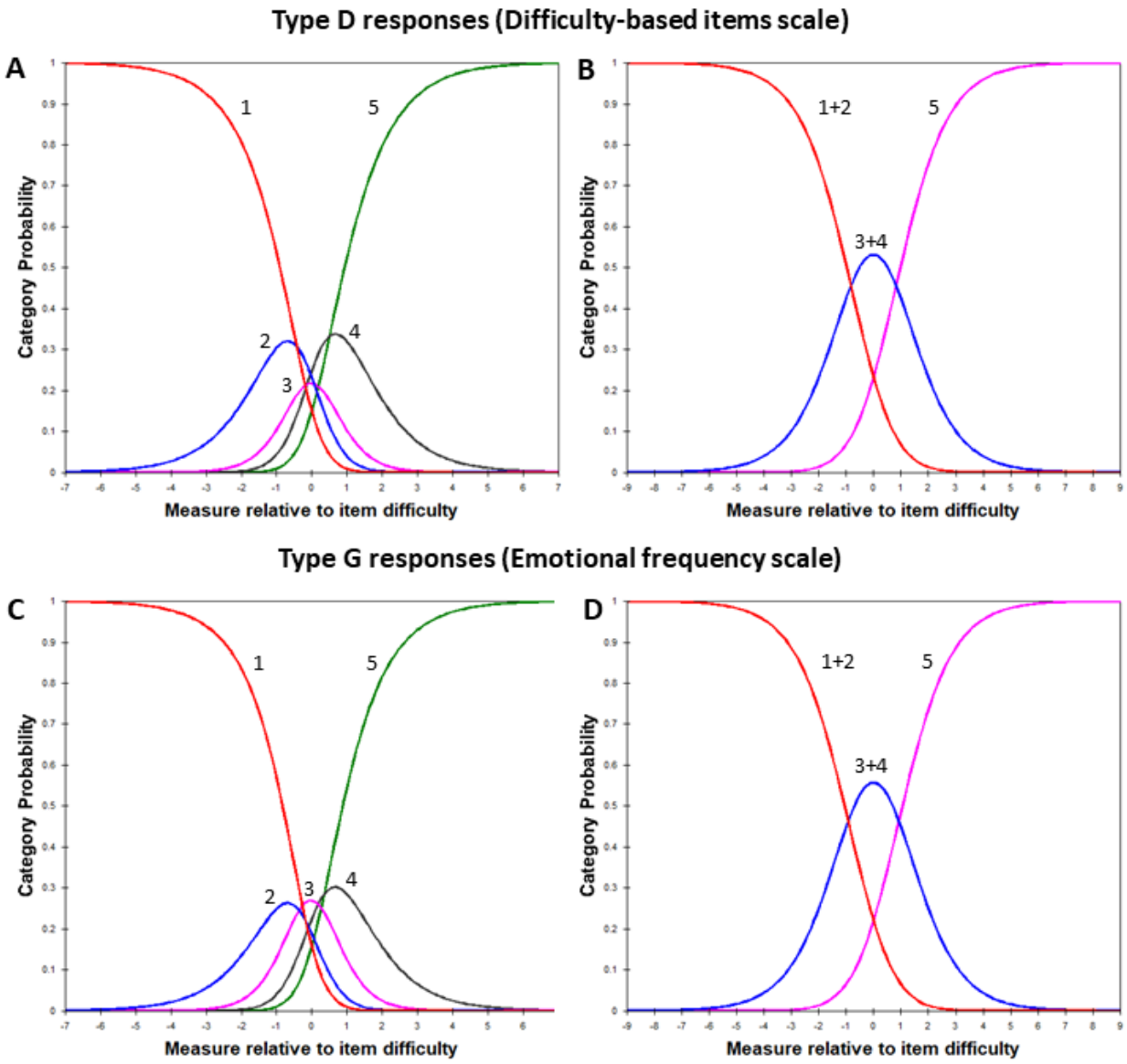

Figure 9.3. Reordering of Type D and G response categories

The Rasch model category probability curves for all items with Type D (i.e., difficulty-based items for themes of activity limitation, mobility and social well-being) and Type G response categories (i.e., frequency of emotions) showing the probability that an individual with a particular QoL will select one of the categories. Panel A (Type D) and C (Type G) demonstrate that categories were disordered. In Panel A, the red line represents 1, 'unable to do because of my vision'; blue line represents 2, 'a lot'; pink line is 3, 'quite a bit'; black line is 4, 'a little' and green line is 5, 'none'. Panel B demonstrated collapsing of Type D response categories 1 and 2, and 3 and 4, to achieve ordered responses. In Panel C, the red line represents 1, 'all the time'; blue line represents 2, 'most of the time'; pink line is 3, 'sometimes'; black line is 4, 'a little of the time' and green line is 5, 'never'. Panel D demonstrated collapsing of Type G response categories 1 and 2, and 3 and 4 to achieve ordered responses.

Type E (i.e., convenience-based items) and Type F (i.e., concern-based items) category responses were ordered hierarchically. However, because a three-option response category scale optimised the Rasch model for the preceding categories, a three-option response category scale was trialled for Type E and F. For Type E, response categories '*a little*' and '*quite a bit*' were collapsed to create the category, '*a little or quite a bit'*, while *'a lot*' and *'an extreme amount*' were collapsed to form the category '*a lot*'. For Type F, the transformed category rating scale included '*not at all'*, '*a little to a moderate amount'* and *'a lot'*. These changes again improved the Rasch model. The PSI improved to 6.32 and targeting improved to 0.69. A consistent three-option response category scale across all questions was considered to improve readability of the items and reduce respondent burden.

9.3.4.2.2 Addressing item misfit and multidimensionality

After addressing the disordered thresholds, 32 items continued to have misfitting statistics (i.e., had infit or outfit MNSQ <0.7 or >1.3). To address this, the infit of the items was first considered, where items measuring an infit MNSQ <0.7 or >1.3 were removed one at a time. Each time an item was removed, the infit statistics changed. A total of 55 items were deleted (items 3, 5, 6, 8, 9, 12, 13, 15, 16–18, 21, 24–27, 35, 45, 47, 57, 61–64, 66, 68–70, 74–78, 81, 84–96, 98–101, 107–109, 112; Appendix B, Table B15) to achieve infit statistics ≥0.7–≤1.3. Outfit statistics were then considered whereby items were deleted due to outfit MNSQ <0.7 or >1.3. After deleting six items with poor outfit (items 102, 111, 36, 51, 59, 56; Appendix B, Table B15), item 58 had poor infit statistics and was deleted. A further five items were deleted due to poor outfit statistics (items 33, 41, 42, 44 and 52; Appendix B, Table B15). Thereafter, the pilot QoL PROM was reduced to 45 items. PSI continued to measure well, scoring 4.03 whilst targeting remained acceptable with a value of 0.92. The PROM however, remained multidimensional, with the eigenvalue of the first contrast measuring 4.8.

No remaining item had missing data >50%. A further nine items were deleted because they demonstrated a ceiling effect (i.e., >50% in the end response category; items 28, 48, 50, 53, 55, 60 71, 79, 105 and 106; Appendix B, Table B15). This resulted in unacceptable infit or outfit MNSQ for six items (items 20, 32, 49, 82, 97 and 103; Appendix B, Table B15). These items were removed. No remaining items had skew or kurtosis. These changes resulted in improved targeting of 0.54 whilst PSI decreased to 3.49.

The items continued to lack unidimensionality. Three separate subscales were evidenced by the eigenvalue of the first contrast being 3.6, the eigenvalue of the second contrast was 2.9 and the third contrast measured an eigenvalue of 2.6. Items in the first contrast were all symptoms related to luminance and ability to see in the dark and therefore formed its own subscale (items 4, 14, 22 and 23;

Appendix B, Table B15). The second contrast formed a subscale related to level of visual acuity (items 1, 2, 10 and 19; Appendix B, Table B15) and the third contrast resembled a subscale of recognition (items 30 and 38; Appendix B, Table B15). These items were all removed, followed by a further four items demonstrating unacceptable outfit MNSQ (items 7, 34, 65 and 67; Appendix B, Table B15). After this, the PCA demonstrated unidimensionality with the raw variance explained by the measures being 55.4% and the eigenvalue of the first contrast measuring 1.97. The PSI measured 2.71 and targeting was 0.88.

The remaining 15 items were reviewed for suitability and applicability before assessing DIF. The item pertaining to losing your job (item 83) was changed for the item describing one's ability to do work tasks (item 82) due to the phrasing preference of the expert panel review. This improved the raw variance explained by the measure to 56.8% and the eigenvalue of the first contrast measured 1.96. The PSI improved to 2.79 and targeting improved to 0.85. No further items deemed important from Phase I were able to be added without detriment to the Rasch model.

There was no DIF reported between groups based on their gender. However, individuals aged <40 years found it more difficult to answer the item, '*feeling frustrated*' (item 104; Appendix B, Table B15) compared to older individuals (DIF contrast: 1.11, p=0.01). Individuals who completed the items on their own (i.e., self-administered) found the item pertaining to the severity of their difficulty with contrast (item 11; Appendix B, Table B15) more difficult than those who completed the items via interviewer-administration (DIF contrast: 1.65, p=0.01). Alternatively, those who completed the items via interviewer-administration found the items pertaining to difficulty driving during the day (item 31 [Appendix B, Table B15], DIF contrast: 2.31, p=0.01), difficulty navigating crowded places (item 40 [Appendix B, Table B15], DIF contrast: 1.57, p=0.03) and concern for their ability to do work tasks (item 82 [Appendix B, Table B15], DIF contrast 1.26, p=0.046) more difficult. Item 11 was deleted due to likely difficulty in its interpretation whilst the other items demonstrating DIF remained as their deletion was detrimental to all Rasch parameters. Furthermore, it was deemed that the identified DIF was due to the small sample size or a reflection of the ability of the individual. Amongst those who opted for interviewer-administered items, 7/13 (53.8%) had BCVA <6/60 whilst 13/89 (14.6%) of those who completed the items on their own had BCVA <6/60 (p=0.003).

After a total of 97 iterations, a final version of the Childhood Glaucoma QoL 14-item PROM (CGQoL-14) was developed. It measured a PSI of 2.71 meaning it could distinguish at least three groups of person ability (high, moderate and low QoL). It was unidimensional, with a raw variance of the measures

of 56.8% and an eigenvalue of the first contrast of 1.92. All items had acceptable infit and outfit statistics (Table 9.9).

Table 9.9. The final set of items in the CGQoL-14

QoL theme	Old item number	Revised item number	Items	Infit MNSQ	Outfit MNSQ
Activity limitations	29	1	Reading things from a distance (e.g., road signs, street signs, train station times)	0.99	0.87
	31	2	Driving during the day	1.02	0.90
	37	3	Pursuing your hobby (e.g., playing sports, gardening)	1.06	1.09
	39	4	Finding something in a cluttered space	0.90	0.83
Mobility	40	5	Navigating crowded places	0.78	0.70
	43	6	Noticing objects or people on your side	1.20	1.27
	46	7	Getting around on sunny days or in bright conditions	1.04	1.13
Social well-being	54	8	Attending events or social gatherings	0.87	1.00
Inconveniences	72	9	Taking longer to perform a task	0.78	0.74
	73	10	Relying on public transport or taxis to get places	0.96	0.83
Economic	80	11	The cost of assisted travel	1.25	1.03
	82	12	Your ability to do work tasks being impacted by your glaucoma	0.89	0.99
Emotional well-being	104	13	Feel frustrated	1.09	1.05
	110	14	Feel self-conscious	1.20	1.13

In Figure 9.4, the distribution of the item difficulty of the final set of items on the CGQoL-14 is illustrated in comparison to the distribution of person ability. The items were well-targeted, meaning that the average item difficulty corresponded to the average person ability/QoL. This was demonstrated by a small difference between the person mean and the item mean, measuring 0.93 (or ≤1.0). Few items had the same level of difficulty as indicated by those being on the same line of the map. However, the removal of any of these was not considered necessary as they were deemed relevant to QoL (Phase I interviews)[355] and the CGQoL-14 was already relatively short.

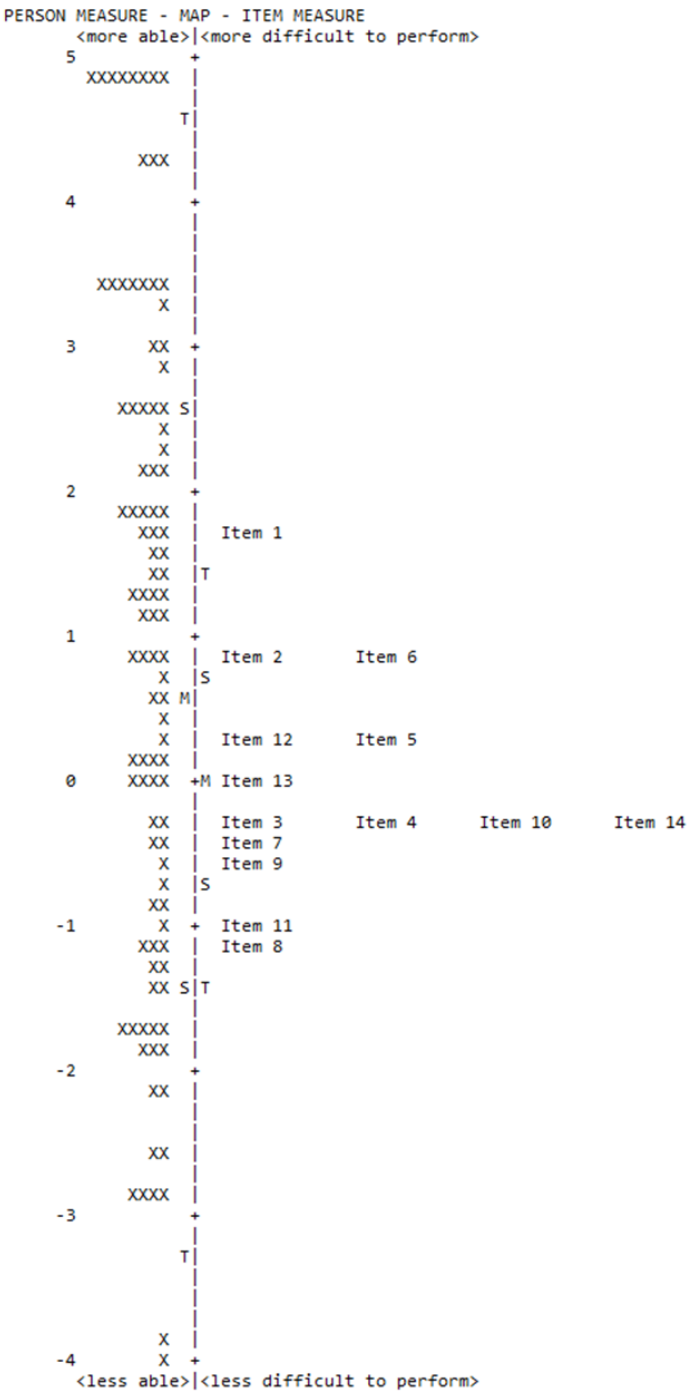

Figure 9.4. The person-item map for the CGQoL-14

The dashed vertical line separates the person and item measures. The person measures are to the left of the vertical dashed line with each X representing one participant. Participants with higher ability (or higher QoL) are located toward the top of the map. The item measures are on to the right of the vertical dashed line. The items with higher difficulty are located toward the top of the map. The most difficult item was Item 1 (Reading things from a distance). The easiest item was Item 8 (Attending social gatherings or events). The corresponding items per item number are found in Table 9.9. The scale units (-4 to 5) are in logits.

M, mean; S, 1 standard deviation from the mean; T, 2 standard deviations from the mean.

9.3.4.3 Rasch analysis of the pilot Coping PROM

Reverse scoring was first applied for several coping items (items 113, 114, 115, 117, 119, 123–131; Appendix B, Table B15) due to use of positive phrasing of the item. This meant that lower scores measured a lower ability to cope.

The items on the pilot coping PROM did not exhibit acceptable Rasch parameters. Category thresholds were disordered, PSI was 1.82 and the PCA indicated multidimensionality, with an eigenvalue of the first contrast measuring 3.2. To achieve ordered category thresholds, response options '*never'* and '*a little of the time'* were collapsed, and the response option *'sometimes'* was collapsed with '*most of the time'*. A total of 12 items were removed due to unacceptable infit and outfit MNSQ (items 113, 115, 118–122 and 127; Appendix B, Table B15) and ceiling effects (items 123–125 and 130; Appendix B, Table B15). The resultant PSI was 1.31, meaning that the items on the coping PROM could only distinguish between two levels of ability (i.e., those who were coping and those who were not coping). The amount of raw variance explained by the measures was 37.8% despite the eigenvalue of the first construct measuring 1.7. A childhood glaucoma-specific coping PROM was therefore not successfully developed.

9.3.4.4 Rasch analysis of the combined childhood glaucoma-specific QoL PROM and Coping PROM

To demonstrate whether a combined childhood glaucoma-specific QoL and Coping PROM was possible, Rasch analysis was repeated on all items on either pilot PROM. Overall, the Rasch analysis of the 131 items showed acceptable PSI (2.93) and targeting (0.62). However, several item response categories were disordered, and 56 items had infit or outfit values <0.7 and >1.3 indicating that they did not fit the model. In addition, the PROM showed multidimensionality, with the eigenvalue of the first contrast measuring >2.0 (11.4) and amount of raw variance measuring 68.4%.

After changes to the category thresholds were addressed as outlined above, the eigenvalue of the first contrast measured 11.1 and 38 items were misfitting. Items with infit MNSQ <0.7 or >1.3 were removed one at a time followed by items with outfit MNSQ <0.7 or >1.3. A total of 84 items, which included all items related to coping, were removed (items 4, 9, 18, 20, 25, 27, 28, 31–34, 41, 50, 52–64, 67–71, 73–85, 88–97, 99–102, 105–131; Appendix B, Table B15). After this, the PCA demonstrated multidimensionality with the raw variance explained by the measures being 55.3% and the eigenvalue of the first contrast measuring 3.9. Further iterations to the Rasch model could not rectify the issue of multidimensionality. This investigation supported that coping items were not conducive to the measurement of QoL in adults with childhood glaucoma and measurement of QoL and coping should be considered separately.

9.4 Discussion

This study highlights my original contribution to knowledge with the design, development, and psychometric assessment of the first childhood glaucoma-specific QoL PROM for adults with childhood glaucoma: the Childhood Glaucoma QoL 14-item (CGQoL-14). Using Rasch analysis, it has proven to be unidimensional and psychometrically robust, with acceptable targeting, person separation, item fit statistics, and well-functioning rating scales. The final version of the CGQoL-14 was considered relatively easy to complete with a low respondent burden, with 14 questions and three response categories per response scale.

There is a paucity of literature investigating the QoL of adults with childhood glaucoma. A recent study conducted in Iran investigated VR-QoL in 23 adults with PCG,[312] using the NEI-VFQ 25. However, the NEI-VFQ 25 has been demonstrated to have disordered thresholds, poor targeting, several misfitting items, and multidimensionality.[495] It is therefore unclear whether VR-QoL or another undefined construct was measured in the PCG population.[312] A later study in an Indian adult population[311] used generic instruments to instead measure HR-QoL and life satisfaction including the WHOQOL-BREF[330] and the Satisfaction with Life Scale,[331] respectively. These instruments were not designed for use in adults with childhood glaucoma, such that the items included in these PROMs are not relevant to the condition (i.e., content validity is not achieved).[546] This might explain why the study did not find any correlation between QoL scores and treatment or clinical parameters.[311] The findings may therefore not be representative of childhood glaucoma, particularly as topical antiglaucoma medication use and impaired BCVA were considered to have important QoL impacts in childhood glaucoma as per Chapter 7.[355] Despite these research limitations, previous studies have drawn valuable attention to the childhood glaucoma community and their findings are useful for the exploration of the impact of the condition on QoL. These gaps in knowledge highlight the importance of developing a suitable PROM for adults with childhood glaucoma, to enable accurate measurement of QoL and draw potential associations between QoL and demographic and clinical characteristics.

The development of a childhood glaucoma-specific QoL PROM had not been attempted before this study. There are likely several reasons for this. Firstly, childhood glaucoma is a rare condition and adequate population sample sizes are not readily available. Secondly, participation in QoL research requires willing participants such that the ability to achieve an adequate sample size for psychometric assessment can be a challenge. Finally, childhood glaucoma is an extremely clinically heterogeneous disease with vastly different visual, surgical and treatment outcomes.[11,23,87,88,91,301,302] PROM items should therefore be developed with and for a cohort with varied characteristics to ensure that it is

relevant to individuals across the entire disease-spectrum. These challenges were overcome with the availability of the ANZRAG,[335] which provided access to a large cohort of adults who were willing to participate in this type of clinical research. The cohort in this study featured individuals with varying socio-demographic and clinical characteristics which ultimately provided a wide representation of individuals with childhood glaucoma. Most importantly, the cohort studied included individuals with several subtypes of the condition, meaning that the developed instrument is projected to be useful in measuring QoL across the entire childhood glaucoma-disease spectrum. The combination of these factors has inevitably assisted with the development of the world's first childhood glaucoma-specific PROM that measures QoL.

In addition to these factors, the early phases of the development of the CGQoL-14 contributed to its successful development. This included the use of semi-structured interviews with affected individuals to obtain data for item generation relevant to the condition (Phase I). The primary benefit of semi-structured interviews is that they posit the research participants as the 'experts' of living with the condition.[316] This resulted in a comprehensive understanding of how this cohort conceptualises QoL.[316] This was a critical component for PROM development as it ensured content validity (i.e., ensured the items were relevant to the cohort).[311,567] Furthermore, the semi-structured and cognitive interviews during Phases I and III enabled insight into the language used by adults with childhood glaucoma. This ensured that the phraseology of the items, the item stem and response categories were directly understood by, and were relevant to, the cohort of interest.[316] Finally, the varied visual and non-visual traits of those who underwent a cognitive interview allowed for a comprehensive evaluation of the questionnaire prior to piloting. This highlights the benefits and the need for patient engagement in the development of accurate PROMs.

Content validity was demonstrated in the final 14 items as they represented several of the QoL themes identified in Chapter 7.[355] The themes that were represented included social and emotional well-being, activity limitations, economic, inconveniences and mobility. The themes of symptoms and health concerns were not directly measured by any one item. Instead, these themes may be considered by participants to be captured in other items. For example, the item pertaining to mobility in sunny or bright conditions may be influenced by one's experience with the symptom of glare. Similarly, one's concern for their ability to complete work tasks may be underpinned by their concerns for their glaucoma worsening and causing vision loss, as considered in Chapter 7.[355] The possibility that one item represents more than one theme was addressed during the development of the Quality of Life Impact of Refractive Correction Questionnaire.[548] The creators of the this questionnaire discussed that clinicians may overemphasise an individual's experience of a symptom rather than the impact it may have.[548]

Consequently, questions directed at symptom frequency, severity and impact may be redundant and captured elsewhere in the PROM.[548] This appears to have occurred in the development of this PROM. Nonetheless, content validity was achieved.

The remaining psychometric properties of the CGQoL-14 were assessed using Rasch analysis. This is considered a critical component for PROM development and has been used in the creation of many ophthalmic-disease specific PROMs.[316,547,562,563] The initial 112 item childhood glaucoma-specific QoL PROM showed poor compliance with Rasch parameters, including disordered thresholds, item misfit and multidimensionality. Disordered thresholds are resolved by collapsing categories and is a common technique performed throughout PROM development.[316,547,562,563] It was apparent that participants in this study struggled with distinguishing differences between response categories due to either the phrasing used or because the response options were too similar. This was resolved by collapsing the response scales to have three category response options instead of five. Three response categories have been suitable in the development of the CarCGQoL[316] and the Quality of Life Impact of Refractive Correction Questionnaire,[548] suggesting that fewer options are often considered potentially less confusing for participants and more productive for measurement. Uniformity of response categories across all items may have also assisted participants with completion of the survey and resulted in less disordered category thresholds. Furthermore, strict item misfit criteria, as recommended by formal Rasch guidelines,[546] identified a total of 87 misfitting items that were not productive for measurement and required removal. Targeting was acceptable although few items were found to have the same level of difficulty. This suggests that the items could have been removed, but doing so could cause loss of valuable information, as discussed by the developers of the Impact of Vision Impairment Questionnaire.[568] For example, if an individual's experience with feeling self-conscious was not measured, then appropriate management of their emotional well-being may not be indicated. These items were therefore not deleted. Finally, multidimensionality was restored by removing items that grouped together to form their own construct. As a result, each item on the CGQoL-14 accurately contributed to a measurement of childhood glaucoma-specific QoL.

Optimally functioning PROMs require a total absence of DIF,[546] and this could not be achieved in the development of the CGQoL-14. DIF is sample size dependent, and its presence does not automatically render the item biased.[547] In this study, the item pertaining to frustration exhibited DIF based on the age of the respondents. Frustration was among the most common emotions experienced by individuals in the semi-structured interviews (Phase I; Chapter 7)[355] so it was deemed important and not deleted. Moreover, the DIF suggested that younger adults experienced more frustration with their glaucoma. This may be a reflection of how glaucoma impacts this cohort in their current life stage or may be a result of

the use of maladaptive coping mechanisms, which were more common in individuals aged <40 years (Chapter 7).[355] Three additional items related to visual ability (driving, navigation and ability to work) were more difficult for individuals who completed an interviewer-administered questionnaire by phone. This was not surprising, given that most participants who opted to have the items interviewer-administered had BCVA <6/60 and may therefore score poorly on these visually demanding items. The bias found was unlikely due to having the items interview-administered and rather due to another variable (i.e., BCVA). These items were retained as they were deemed important disease-related factors that influence QoL as identified in the Phase I interviews (Chapter 7).[355] The only item deleted based on DIF pertained to contrast. This item was found more difficult for individuals who completed the PROM on their own. This is likely because the question's phrasing was considered confusing or unclear and required an explanation of its meaning in an interviewer-administered setting. The item was previously identified as problematic in Phase III cognitive interviews by several participants and was removed.

Our ability to understand the differences in QoL is supported by previous findings of coping strategies commonly used in adults in childhood glaucoma (Chapter 7).[355] These were useful in designing a pilot childhood glaucoma-specific coping PROM. In this study, however, the coping PROM failed to demonstrate adequate Rasch properties. The PSI could only determine between two strata of ability: if an individual was coping or not coping. This could have occurred because the number of items was too little (n=19).[557] Acceptable PSI was achieved in a coping PROM designed for individuals with inherited retinal disease.[538] This PROM had 30 items in contrast to the 19 included here.[538] Additional items could be added to the childhood glaucoma-specific coping PROM but this would require repeat pilot testing. However, the number of items tested does not necessarily determine whether acceptable PSI will be achieved. Acceptable PSI measures have occurred in studies which have tested less than 20 items.[532,547] Meanwhile, low PSI could have occurred due to the cohort studied having a similar coping ability such that the Rasch model could not determine enough variation between each participant's responses to coping-related items.[557] This may have inherently been caused by a recruitment bias whereby those who were willing to participate were more likely to be coping better with their glaucoma than those who did want to participate. Participants may have been reluctant to admit that they engaged in maladaptive coping techniques (e.g., ignoring glaucoma care or using unhealthy activities for distraction) due to an underlying fear of being seen as inferior to those who are coping well. Nonetheless, future studies will be required to develop and validate a childhood glaucoma-specific coping PROM in adults with childhood glaucoma.

A main limitation of this study is that test-retest reliability, responsiveness, concurrent validity, convergent validity, and divergent validity (Phase V) are yet to be tested. This is required before the

CGQoL-14 is used more widely in clinical or research settings and will be tested at a later stage. The study was also conducted in a population of predominantly European ancestry. Consequently, the CGQoL-14 may only be applicable to a population with a similar cultural background or use of the English language. Cross-cultural validation is required to ascertain its appropriateness for use in other populations. The cohort studied otherwise provided a broad representation of individuals with childhood glaucoma with respect to other socio-demographic and clinical characteristics, including varied BCVA status and glaucoma subtypes. Furthermore, the CGQoL-14 was unable to demonstrate adequate subscales which represent certain aspects of QoL (e.g., emotional well-being). This has similarly not been achieved in other popular PROMs including the Impact of Vision Impairment Questionnaire[568] and Quality of Life Impact of Refractive Correction Questionnaire.[548] This is likely because the CGQoL-14 was designed for various subtypes of the disease such that all items within a subscale may not be relevant to each subtype. Developing a PROM specific to one subtype of childhood glaucoma would be too cumbersome as several PROMs would be needed for accurate measurement per disease subtype and would be hindered by the rarity of some disease subtypes. The CGQoL-14 also met all Rasch psychometric properties, apart from DIF which was present for a few items. Retention of these items was justified with respect to Phase I semi-structured interviews (Chapter 7).[355] Three category response options were also required to satisfy the Rasch model and may reduce the discriminatory ability of the PROM amongst individuals with milder forms of disease. Lastly, clinical details of individuals not registered within the ANZRAG were self-reported, resulting in the possibility of some bias. However, the cohort of respondents not from the ANZRAG was small and was unlikely to substantially influence results.

In conclusion, the CGQoL-14 is a novel instrument suitable for the assessment of QoL in adults with childhood glaucoma. Unlike the childhood glaucoma-specific coping PROM, the CGQoL-14 showed psychometrically sound properties using Rasch analysis. Future research should assess the clinical and research utility of the CGQoL-14 for distinguishing differences in QoL amongst individuals with various subtypes of childhood glaucoma and genetic diagnoses. Future implementation of the CGQoL-14 may assist our understanding and measurement of the impact of childhood glaucoma, identify at-risk individuals earlier and encourage a much-needed dialogue between clinician and patient to ensure that individuals with childhood glaucoma achieve the best possible QoL.

CHAPTER 10 DISCUSSION AND CONCLUSION

"*Children are the most precious resource of families. Children represent the families' future and their hopes. A blind child is a tragedy… A child whose blindness could have been prevented or cured is an even greater disaster."*[16]

Reducing avoidable blindness and visual impairment in children was a key priority of the global WHO initiative Vision 2020.[16] This was started in 1999. At that time, it was estimated that there were 1.4 million blind children worldwide. This was projected to increase to approximately two million by 2020.[16] Glaucoma was identified as one of the top four leading causes of avoidable blindness in children. In high income regions, glaucoma contributed to 2% of avoidable childhood blindness overall, and up to 6% in low and middle income countries.[16] Research into prevention of blindness from conditions including corneal disease, childhood cataract, retinopathy of prematurity and low vision was determined by the WHO to be a higher priority than research into preventing blindness from childhood glaucoma. Research areas broadly included the characterisation of the disease and their aetiologies, the clinical outcomes, and their impact on QoL.[16] These conditions were prioritised over childhood glaucoma because they were associated with a higher prevalence of severe visual impairment and blindness at the time.[16] In 2012, however, blindness from childhood glaucoma increased.[5] It was estimated that childhood glaucoma caused 3%–4% of childhood vision impairment or blindness in the United States and Europe and up to 7–11% in South-East Asian, African, Eastern Mediterranean and Western Pacific regions.[5]

Despite the rate of visual impairment and blindness in childhood glaucoma, there are no high-quality evidence-based clinical practice guidelines for management of the condition.[13] It has recently been proposed that multidisciplinary involvement from ophthalmologists, clinical geneticists, genetic counsellors and paediatricians are required.[8,255] This is unlike the clinical practice guidelines in the management of congenital cataract, which directly recommend close collaboration between ophthalmologists, geneticists, genetic counsellors, paediatricians, orthoptists, clinical scientists, research experts and other medical subspecialities where systemic features are present.[569] This disparity may be in part due to the fact that research pertaining to congenital cataract, in addition to other ocular conditions, were prioritised over childhood glaucoma in the Vision 2020 initiative.[16] In addition, other factors have likely contributed to the lack of clinical practice guidelines for childhood glaucoma, including low prevalence; limited availability of genetic testing; poor characterisation of the disease, its genetic aetiologies, clinical phenotypes and outcomes, and the benefits of genetic testing and counselling; and the impact of childhood glaucoma on QoL.

The work presented in this thesis addresses these gaps in knowledge to work toward providing an evidence-base for a multidisciplinary model of care for childhood glaucoma. This was performed by providing an original contribution to the delineation of the phenotypic spectrum associated with known childhood glaucoma genes by investigating their ocular and systemic features, detailing the clinical outcomes in the two most common genes implicated in the disease, and providing an in-depth exploration of the impact of the condition on QoL from the perspectives of children and adults with childhood glaucoma, and their caregivers.

10.1 Integrating genetic testing in childhood glaucoma

It has been suggested that a successful clinical approach to childhood glaucoma should integrate genetic testing for all non-acquired glaucomas (i.e., excluding acquired glaucomas such as traumatic and uveitic glaucoma for which there is no supporting evidence for an underlying genetic cause).[8,293] Genetic testing can involve single gene sequencing, gene panel sequencing, whole exome or whole genome sequencing.[570] Single gene sequencing may be applied where a specific gene is suspected to be the most likely cause of disease, whilst gene panel sequencing is performed where multiple genes could be implicated in the disease phenotype.[570] Whole exome or genome sequencing capture the broadest amount of genomic information, and can be used to investigate exonic variants, structural and copy number variants (deletions or duplications), and deep intronic variants across all genes, a subset of which can be investigated in so-called 'virtual' gene panels.[570,571] Genetic testing has long been advocated for in childhood glaucoma.[289,290,572]

The choice of which genetic test to perform may depend on the phenotype. Single gene sequencing for *PAX6* in aniridia-associated glaucoma,[221] or single gene sequencing for *FOXC1* or *PITX2* in ARS-associated glaucoma,[125,126,192] are frequently done as these genes are most likely implicated in their respective diseases. However, variants in these genes are not discovered in all disease cases, with *PAX6* variants attributed to approximately 90% of aniridia cases,[221] and variants in *FOXC1* or *PITX2* accounting for 40–71% of ARS.[125,126,192] Single gene sequencing for *CYP1B1* variants has also been performed in PCG.[289] This is particularly useful in Middle Eastern populations, where biallelic *CYP1B1* variants have been attributed to approximately 75–96% of PCG cases.[100–102] Conversely, single gene sequencing for *CYP1B1* in a European population with PCG may have a diagnostic yield as low as 15–22%,[96,97] owing to the genetic heterogeneity of PCG, as demonstrated in Chapter 3.[386] Because of the genetic heterogeneity of PCG, gene panel sequencing has since been recommended over single gene sequencing in individuals diagnosed with PCG.[290]

There is also a strong case to be made for use of panel sequencing across all subtypes of childhood glaucoma. This is because there is high genetic heterogeneity within each subtype of disease, phenotypic heterogeneity for most genes, and several of the genes implicated in childhood glaucoma have variable expressivity and age-related penetrance as demonstrated in Chapters 3 and 4 (e.g., variants in *CYP1B1* can result in PCG, JOAG, POAG or SG-O).[61,95,103–106,386] Gene panel sequencing can also be useful in clinical settings where it is challenging to obtain phenotypic information required for single gene sequencing. This may occur where an individual has early disease onset with corneal clouding or corneal scarring which prevents an accurate assessment for ASD. A child's age or clinician's experience may prevent accurate gonioscopy. These have been offered as possible reasons for misdiagnosis in individuals with early-onset SG-O secondary to variants in *CPAMD8* and *FOXC1* that mimics a PCG-like presentation.[186,194] Understanding the overlapping phenotypic variability is discussed in more detail below with respect to the benefits of genetic testing.

The development of a gene panel for childhood glaucoma can be guided by the results of this thesis. This thesis detailed one of the first, and the largest study to examine the genetic heterogeneity across the entire childhood glaucoma spectrum with respect to uniform diagnostic classifications; the CGRN classifications.[4] Because genes implicated in childhood glaucoma exhibit strong age-related penetrance and variable expressivity, this thesis further included those with early-onset disease (defined as a diagnosis between the ages of 18 and 40 years; Chapter 3).[386] A total of 18 genes implicated in glaucoma diagnosed before 40 years of age were reported. The use of a gene panel in all subtypes of childhood glaucoma has since been considered by two small European registry-based genetic studies.[113,291] These studies each curated their own list of genes associated with childhood glaucoma as determined from the literature. Across the two studies, a total of eight genes were found to be implicated in childhood glaucoma. Variants in genes reported that were not detected in this thesis included: *SOX11* (Coffin-Siris syndrome), *GJA8* (sclerocornea), and *FYCO1* and *CRYBB3* (congenital cataract/SG-C).[113] A *CHRDL1* variant was further reported in one individual with megalocornea without glaucoma.[113] These genes could be added to a gene panel. Other genes not identified in this thesis that could be added to a gene panel for childhood glaucoma could include *EFEMP1,* which is implicated in JOAG,[93,175,177] and *COL4A1*, *FOXE3, PITX3, B3GLCT* and *PXDN* which may be implicated in ASD or SG-O.[94,573] Other genes associated with congenital cataract and consequent SG-C (e.g., *CRYBB2, CRYBA1*) may be further included or a separate gene panel could be developed.[113,574] This list is by no means exhaustive and any gene panel list for childhood glaucoma will need to be updated as new genes are discovered. If a childhood glaucoma-only gene panel were to be developed, however, *TBK1* and *OPTN* may be removed from the panel as these were exclusive to individuals with early-onset NTG; a phenotype not typically seen in children.[338,376] Early-onset glaucoma gene sequencing panels have

already been developed by several clinical testing laboratories: the Blueprint Genetics panel includes 19 genes,[575] the Prevention Genetics panel includes 23 genes,[576] the Invitae Corporation panel includes 27 genes,[577] the Clinical Biochemical Genetics Diagnostic Laboratory panel includes 37 genes,[578] the Fulgent Genetics panel includes 57 genes,[579] and a congenital glaucoma sequencing panel containing 21 genes has been developed by Victorian Clinical Genetics Services.[580] In comparison with the results of this thesis (Chapter 3),[386] neither panel includes *ANGPT1, TMEM98* or *SLC4A11*. Initiatives that provide evidence-based recommendations on the association between genes and disease such as the ClinGen gene curation expert panels,[581] and PanelApp,[582] will be useful resources for the development of gene panels for early-onset glaucoma.

This thesis provided the first overall success rate of achieving a molecular diagnosis in probands with childhood glaucoma of predominantly European ancestry: 37.6% (Chapter 3).[386] Success rates of achieving a molecular diagnosis in specific childhood glaucoma subtypes, according to the CGRN classifications, were also provided and included: PCG (30.4%), JOAG (30.8%) and SG-O (71.1%) prior to reclassifications. These are useful statistics that may be quoted when providing genetic counselling and may provide an estimation of the success rate of a childhood glaucoma gene panel. These findings, however, should only be applied in the context of populations with a similar ancestral landscape. Additional screening for genes with the use of a comprehensive gene panel is required to determine the diagnostic yield in other populations. Overall, the diagnostic yield in this thesis was relatively low compared to other ocular genetic conditions. Inherited retinal diseases have a molecular diagnostic rate of 66–74%,[583,584] while congenital cataract has a diagnostic yield of 75%–80%.[574,585,586] There is reason to believe that this rate will continue to improve, as more individuals with childhood glaucoma are sequenced by whole exome or whole genome sequencing, or other emerging technologies to improve the detection of new disease genes, and deep intronic variants, copy number variants and structural variants in known genes.[194] Similarly, improved recognition of individuals with mild syndromic forms of childhood glaucoma, or those yet to develop systemic features associated with a syndrome, may improve screening for relevant genes. Ongoing research and international collaborative efforts with multidisciplinary teams of specialist and research clinicians, laboratory scientists, bioinformaticians and clinical geneticists is required to investigate other genetic causes of childhood glaucoma and ultimately improve the diagnostic yield.

10.2 Benefits of genetic testing in childhood glaucoma

The benefits of genetic testing in childhood glaucoma have been demonstrated throughout this thesis. Firstly, genetic testing can aid in achieving the right clinical diagnosis, result in more comprehensive

ocular phenotyping of disease and understanding of the phenotypic spectrum of specific genes (Chapter 3).[386] Secondly, it can result in better prognostication of disease outcomes (Chapter 4) and identify individuals who may benefit from future targeted gene therapies. Thirdly, genetic testing can identify the need for multisystemic management and generate new hypotheses of genotype/phenotype correlations (Chapter 5). Finally, genetic testing and counselling can result in improved decision-making in family planning (Chapters 7 and 8)[354,355] and can enable early detection of disease in at-risk family members.

10.2.1 Aiding clinical diagnosis

As identified in Chapter 3,[386] genetic testing can assist in refining clinical diagnoses. In this thesis, this was best demonstrated through the finding that 10.4% of probands had a clinical reclassification of their glaucoma subtype following clinical re-examination after a molecular diagnosis (Chapter 3).[386] This finding was largely attributed to heterozygous variants in *FOXC1* and biallelic variants in *CPAMD8* which often caused glaucomatous disease with onset within the same period as PCG (i.e., disease onset <3 years) and therefore resulted in a similar disease presentation (e.g., buphthalmos, corneal clouding and Haab striae). After receiving a molecular diagnosis, these individuals were re-examined and found to have SG-O with subtle ocular or systemic ASD features (ARS [*FOXC1*] or unclassified ASD [*CPAMD8*]).[386] Genetic testing also resulted in a clinical reclassification of SG-S in an individual with Knobloch syndrome (*COL18A1*) and in an individual with Stickler syndrome (*COL2A1*) who were initially diagnosed as having PCG and JOAG, respectively.[386] The individual with Knobloch syndrome had a history of retinal detachment and brain MRI showed an osseous defect in the occipital bone and herniation into the dural venous sinus. The individual with Stickler syndrome had a history of retinal detachment and joint problems, consistent with the syndrome.

There have been other reports of clinical misclassifications of early-onset forms of glaucoma throughout the literature. Two individuals with JOAG have been found to have heterozygous *COL1A1* variants, which are typically associated with osteogenesis imperfecta.[587,588] One individual had blue sclera whilst the other exhibited skeletal changes.[587,588] Two individuals diagnosed with PCG were found to have pathogenic *COL1A1* variants, although at the age of the study (15 years and 25 years) were yet to exhibit ocular or systemic features of osteogenesis imperfecta.[588] It is possible that the age at genetic testing precluded the onset of systemic disease.[588] Another individual with a heterozygous *FOXC1* variant had been misdiagnosed as PCG. The individual was later reported to have subtle facial dysmorphism and subtle ASD (posterior embryotoxon, anterior iris insertion) deemed to be consistent with ARS.[589] Other systemic features were absent at age 27 years.[589]

Reports of clinical reclassifications support the use of gene panel sequencing in childhood glaucoma. For example, gene panel sequencing for childhood glaucoma does not require an assessment for ASD to be made prior to genetic testing. This overcomes the challenges associated with detecting subtle features of ASD in either an eye with corneal clouding or scarring, or a young or uncooperative child.[186,194] Gene panel sequencing would also be able to detect a variant in a gene typically associated with ASD, even if ASD is not present (e.g., detection of *FOXC1* variants in JOAG).[386] The use of a gene panel does not need to rely on appropriate investigation for the presence or absence of systemic features at the time of glaucoma diagnosis, particularly as some systemic features may only be recognised at a later age (e.g., short stature, hearing loss, intellectual disability or developmental delay in *FOXC1*).[125,126,130,132,195] Identification of the respective genetic variant implicated in an individual's glaucoma diagnosis through gene panel sequencing can therefore confirm or refine clinical diagnosis irrespective of the presenting phenotype.

10.2.2 Understanding the overlapping ocular phenotypic variability

Genetic testing can further our understanding of the phenotypic disease spectrum of a single gene. The findings of this thesis continued to demonstrate that there was substantial phenotypic heterogeneity within a single genetic cohort. This was achieved by providing an original analysis of the contribution of genes to the phenotypic classifications as determined by the CGRN in the largest known cohort of predominantly European ancestry,[4] as per Chapter 3, and reporting the characteristics in one of the largest cohorts of individuals of predominantly European ancestry with biallelic *CYP1B1* variants and heterozygous *TEK* variants (Chapter 4).

The phenotypic spectrum amongst individuals with biallelic *CYP1B1* variants was detailed in this thesis. Biallelic variants in *CYP1B1* contributed to 15.6% of all PCG probands (Chapter 3).[386] PCG was the most common phenotype amongst all individuals with biallelic *CYP1B1* variants (66.7% of the cohort with glaucoma; Chapter 4). This was not surprising given that biallelic *CYP1B1* variants are the major cause of PCG in probands of predominantly European ancestry, with a prevalence of 15–22%.[96,97] Biallelic *CYP1B1* variants also contributed to 3.2% of all JOAG probands diagnosed prior to 40 years of age (8/252; Chapter 3).[386] This is equivalent to a previous study of a population of Han Chinese ancestry, which reported a contribution of biallelic *CYP1B1* variants in JOAG of 3.3% (2/61).[105] The prevalence rate of *CYP1B1*-associated JOAG in the latter study, however, may have been influenced by the use of a younger age cut-off of 35 years for JOAG diagnosis was used and the cohort was much smaller.[105] Other studies reported that biallelic *CYP1B1* variants accounted for 1.7–1.9% of JOAG diagnosed at <40 years amongst cohorts of predominantly European ancestry.[61,107] The contribution of biallelic *CYP1B1* variants to the SG-O phenotype in a large population remains to be determined. Individuals

with this phenotype were not found at the time of the study in Chapter 3.[386] This thesis also reported one individual with *CYP1B1*-associated PACG and one case of *CYP1B1*-associated Peters anomaly with childhood glaucoma, which contributed to a very limited body of literature (Chapter 4). Individuals with PACG and *CYP1B1* variants have seldom been reported.[590] Peters anomaly is rarely associated with biallelic *CYP1B1* variants, with a limited number of known cases reported at the time of writing.[108–115] *CYP1B1*-associated ARS with childhood glaucoma has also been reported in few individuals with ARS-associated childhood glaucoma,[118,119] although none were observed in the participants in this thesis. Finally, the ocular phenotypic spectrum of *CYP1B1*-associated disease includes POAG. Two individuals with *CYP1B1*-associated POAG reported in this thesis (Chapter 4) were added to the very limited number of individuals with this phenotype in the literature.[104,591]

Heterozygous loss-of-function *TEK* variants were most commonly associated with PCG (75.0% of the *TEK* cohort with glaucoma, Chapter 4), and were implicated in 5.9% of PCG diagnoses in probands (8/135; Chapter 3).[386] This is in agreement with a large multiethnic study which reported *TEK* loss-of-function variants in 5.3% (10/189) of PCG probands (some of which were included in this thesis).[26] A German study reported that *TEK* variants accounted for 10% of PCG cases, although this prevalence rate was calculated from a small cohort of 10 individuals with PCG (i.e., only one individual with *TEK*-associated PCG was reported).[113] In a Han Chinese cohort, *TEK* was reported in 5.5% (11/200) of PCG cases.[138] However, seven of the 11 individuals had *TEK* variants that were either gain-of-function or benign, resulting in a decreased prevalence of 2.0% (4/200) when these were excluded. This thesis further contributed one case of JOAG and POAG in two individuals to the literature (Chapter 4). *TEK*-associated JOAG and POAG have been reported in just two other individuals each.[26,139] Although there are relatively few cases of *TEK*-associated glaucoma reported worldwide, SG-O does not appear to be part of the disease spectrum (Chapter 4).[26,113,138,139] This finding supports the notion that the ANGPT1/2-TEK pathway is not involved in the development of ocular structures outside of the conventional aqueous humour outflow pathway.[26,141]

Phenotypic variability amongst genes associated with secondary forms of childhood glaucoma is well known. In this thesis, individuals with *FOXC1* variants predominantly had ARS, although one individual with JOAG was reported (Chapter 3).[386] The latter cases add to very few previous reports of *FOXC1*-associated JOAG.[200] The overall mean age of glaucoma diagnosis has been reported to be 6±13 years [range 0–37 years],[130] with an early age of onset mimicking a presentation of PCG as previously discussed. There were no cases of *FOXC1*-associated PCG reported in this thesis although one individual had PCG with hearing loss and a congenital heart defect without ocular features and was reclassified as ARS based on the systemic features.[386] Heterozygous *FOXC1* variants have previously

been suggested to cause PCG,[200,205] Peters anomaly with and without SG-O in childhood,[111,112,196,197] and aniridic glaucoma,[197–204] in a limited number of individuals. In contrast, *PITX2*-associated glaucoma has a later mean age of glaucoma diagnosis (18±10.6 years [range: 1–48 years]):[130] consistent with this, the PCG-like phenotype was not observed in our cohort (Chapter 3).[386] All individuals with a *PITX2* variant reported in this thesis exhibited an ARS phenotype with the exception of one individual who had Peters anomaly and SG-O.[386] The latter is a rare phenomenon, with *PITX2*-associated Peters anomaly with and without congenital onset of glaucoma having been reported in only a few individuals.[112,126,206–208] Finally, unclassified ASD appears to be the most common phenotype amongst individuals with *CPAMD8* variants with an early mean age of glaucoma diagnosis (9.22±14.89 years [range: 0–35]).[186] This thesis reiterated that a misdiagnosis of SG-O may occur in those with biallelic *CPAMD8* variants diagnosed with PCG or JOAG (Chapter 3).[186,386] One individual reported in this thesis, however, did have a phenotype of PCG without any features of ASD.[386] Others diagnosed with *CPAMD8*-associated PCG throughout the literature have often been reported to have concurrent unclassified ASD or ectopia lentis.[101,186] Clinicians should be mindful of these varied presentations within each of these genetic cohorts when determining the clinical subtype of disease.

There is marked phenotypic heterogeneity amongst genes associated with childhood glaucoma which results in a broad phenotypic spectrum and overlap between CGRN classifications. Although each gene is more commonly associated with one CGRN classification, several genes can be associated with both primary and secondary forms of the disease (e.g., *CYP1B1*, *FOXC1* and *CPAMD8*). Genes associated with childhood glaucoma can also exhibit primary or secondary disease with varied age-related glaucoma penetrance (e.g., *TEK*). Additional studies are needed to continue to expand the phenotypic spectrum of these genes as this will continue to guide genetic testing practices and clinical management of childhood glaucoma.[8]

10.2.3 Prognostication of ophthalmic clinical outcomes and precision medicine

Accurate interpretation of genetic results, with possible clinical reclassification of glaucoma subtype, has the potential to assist with the management of childhood glaucoma through improved treatment and management plans that have the potential to reduce the risk of vision loss.[289] Work included in this thesis has defined the natural history of *CYP1B1*- and *TEK*-associated glaucoma (Chapter 4). The high rate of *CYP1B1*-associated PCG and *TEK*-associated PCG described in this thesis (Chapter 3) and amongst other cohort studies, justified these genetic cohorts as ideal starting points for clinical outcome studies.[26,96,97,101,113,138,139,291,386]

Previous literature analysing the clinical outcomes of *CYP1B1*- and *TEK*-associated glaucoma is limited. With regard to *CYP1B1*-associated glaucoma, several studies have analysed outcome data with the inclusion of individuals with heterozygous *CYP1B1* variants.[300,305,389] This fundamentally does not provide a clear indication of the severity of *CYP1B1*-associated disease, as it is an autosomal recessive disease requiring the presence of biallelic pathogenic variants.[95,101,102] Parents of individuals with biallelic *CYP1B1* variants and who are carriers are usually not affected, except in situations of pseudodominance in consanguineous kindreds. *CYP1B1* heterozygotes have also not been observed to have disease in various population groups, consistent with a high carrier frequency of certain variants among Middle Eastern populations, including the p.R368H and p.G61E variants.[100,101,592] There are reports of outcome data in individuals with biallelic *CYP1B1* variants, although the significance of their findings are restricted by sample sizes, and statistical adjustments were not made to account for the differing ages at follow-up between participants with and without biallelic *CYP1B1* variants and the inclusion of both eyes from one individual.[298,299,387,388] These factors limited the significance of these findings whilst highlighting the challenges associated with studying the outcomes of a rare disease. Determination of the clinical outcomes in *TEK*-associated glaucoma has also been challenged by the limited number of individuals described with heterozygous *TEK* variants, largely owing to its relatively recent discovery in several cohorts.[26,113,138,139,593] One study had attempted to compare the clinical characteristics between *CYP1B1*-PCG and *TEK*-PCG cohorts, however, as mentioned earlier, this study included individuals with gain-of-function and benign *TEK* variants.[138]

This thesis addressed the limitations of prior literature and sought to compare the clinical severity of individuals with *CYP1B1*-associated glaucoma against individuals with *TEK*-associated glaucoma with appropriate statistical adjustments for age at follow-up. More specifically, clinical outcomes in one of the world's largest cohorts with *CYP1B1*-PCG (n=28) and *TEK*-PCG (n=18) were compared (Chapter 4). The comparative group of *TEK* was chosen as it was identified as the second most common cause of PCG in the studied population (Chapter 3).[386] The findings from Chapter 4 demonstrated that *TEK*-PCG had significantly higher rates of unilateral disease, and were more likely to report better BCVA at follow-up compared to those with *CYP1B1*-PCG. Amongst those with *TEK*-PCG, a significantly lower number of incisional glaucoma drainage surgeries, advanced glaucoma procedures and topical antiglaucoma medications required to control the disease compared to those with *CYP1B1*-PCG. My findings supported that *TEK*-PCG causes less severe disease compared to *CYP1B1*-PCG (Chapter 4). Conclusions regarding clinical outcomes in JOAG and POAG cohorts were not able to be drawn owing to their small sample size but exploration in future studies is warranted.

It is important to recognise that individuals with *TEK*-PCG did not always have favourable clinical outcomes. In this thesis, 67% of individuals had bilateral disease, 10% required enucleation and 23% had severe vision impairment. There are many factors that could explain this finding including but not limited to, delay in diagnosis, treatment options available at the time of diagnosis, noncompliance with management regimes, comorbid ocular disease, surgical complications, or other environmental and genetic factors. Other genetic factors may include rare and common glaucoma risk variants within the ANGPT1/2-TEK pathway (e.g., rare *ANGPT1* variants associated with PCG,[141] rare *SVEP1* variants possibly associated with *TEK* expression,[139] common *ANGPT1* variants associated with IOP,[412] or common variants in *SVEP1* or *ANGPT2* associated with POAG risk)[413] or beyond it (e.g., multi-trait analysis of genome-wide association studies polygenic risk scores).[594] It is also possible that there are deep intronic or other *TEK* variants not captured by short-read whole exome or genome sequencing, or other variants outside of the ANGPT1/2-TEK pathway, that influence disease expressivity and penetrance. Understanding what modifying factors are involved in *TEK*-PCG severity requires further research.

The relative clinical outcomes and prognostication of *CYP1B1*-PCG and *TEK*-PCG supports the use of genetic testing in childhood glaucoma. For example, if biallelic and pathogenic *CYP1B1* variants are found in a newly diagnosed childhood glaucoma case, clinicians may opt to increase surveillance for disease progression and treat a child's glaucoma more aggressively with additional topical medications or repeat glaucoma surgeries to maximise potential visual function. Conversely, if heterozygous *TEK* variants are found, standard angle procedures to increase conventional aqueous humour outflow by incising the trabecular meshwork (i.e., goniotomy)[275] may not be as effective due to hypoplasia of Schlemm's canal.[26,139] In this case, larger incisions into the Schlemm's canal may be required (e.g., a circumferential trabeculotomy) or indeed if Schlemm's canal is absent, development of a secondary outflow pathway (i.e., trabeculectomy or glaucoma drainage device) may be more useful in reducing IOP.[595] The ANGPT1/2-TEK pathway has also become a therapeutic target for the development of a topical antihypertensive medication that activates this pathway by increasing the Schlemm's canal filtration area and increasing outflow facility.[416] Topical administration of this medication, in conjunction with latanoprost, was demonstrated to be more effective in reducing IOP in adults with POAG or OHT compared to latanoprost alone.[417] Topical administration of the same drug in rabbits and mice also demonstrated a significant reduction in IOP.[416] If these treatments are found to effectively reduce IOP and halt glaucoma progression, it would be essential to use genetic testing to identify individuals with *TEK*-associated glaucoma who may benefit from this therapy.

The prognostication of glaucoma disease associated with other genetic variants, including *MYOC*, further supports genetic testing in childhood glaucoma. *MYOC* is the most common gene associated with JOAG diagnosed up to age 40 years, as demonstrated in Chapter 3 and other studies (8–36%),[165,166,386] and *MYOC* variants are associated with an earlier age at glaucoma diagnosis, development of more severe visual field loss, and a higher maximum recorded IOP (Chapter 3).[303,304,386] Those with *MYOC* variants also require more glaucoma filtration surgeries compared to individuals without *MYOC* variants.[303,304] Similar to *CYP1B1*-associated glaucoma, this may result in closer surveillance for disease progression and more aggressive treatments. There are several treatments being developed to target the protein misfolding seen in *MYOC* disease. Murine studies have demonstrated that topical administration of a chemical chaperone, that limits myocilin misfolding, resulted in clearing of mutant MYOC and reduction of IOP.[596,597] Stimulation of autophagic degradation of MYOC through administration of topical drugs has also resulted in reduction of IOP in a murine model.[598] Finally, the use of genome editing with clustered regularly interspaced short palindromic repeats (i.e., CRISPR) technology to eliminate the gain-of-function alleles in *MYOC* glaucoma successfully reduced IOP and prevented further glaucomatous damage in mice.[599] Whilst these candidate treatments are only in early preclinical development, genetic testing can help to identify individuals suitable for human clinical trials.

Whilst there are currently no targeted gene therapies for individuals with *FOXC1* or *PITX2* variants, genetic testing can assist with disease prognostication of the ocular phenotype in these individuals. Individuals with *PITX2*-associated glaucoma are more likely to report vision impairment (i.e., <6/12) than individuals with *FOXC1*-associated glaucoma.[195] In a study conducted by the ANZRAG group, the prevalence of BCVA <6/12 in the better eye was more common among individuals with *PITX2* variants compared to those with *FOXC1* variants (26% vs 7%, respectively).[130] A higher proportion of individuals with *PITX2* required glaucoma surgery to control IOP (65% vs 41%).[130] This implies that individuals with *PITX2* variants require closer surveillance and may require more aggressive glaucoma treatment. However, the clinical outcomes are highly variable between these cohorts and the disease course is complex.[130,193,195] Research peripheral to this thesis which I co-authored further demonstrated that approximately one third of the *FOXC1* and *PITX2* cohorts develop corneal decompensation and may require penetrating keratoplasty.[193] Glaucoma progression and corneal complications should be monitored closely in both cohorts.

The characterisation and prognostication of glaucoma in these genetic cohorts, along with advancements in precision medicine, highlight the potential benefits of genetic testing in childhood glaucoma. Having a better understanding of the disease phenotype, clinical course and their likely

outcomes can support clinicians in the management of disease and patient counselling. The identification of a molecular diagnosis with respect to disease pathogenesis and emerging medical therapies may also guide clinicians in their choice of medical and surgical treatment. My future research in this field will continue to characterise clinical outcomes in individuals with a molecular diagnosis associated with childhood glaucoma and aim to understand specifically how genetic testing may influence the clinical management of disease from the perspective of treating glaucoma specialists. This will further highlight the benefits of genetic testing and support its use in childhood glaucoma.

10.2.4 Identification and management of systemic features

Referral to a clinical geneticist or a paediatrician for investigation of systemic features upon diagnosis is recommended in the care of childhood glaucoma irrespective of whether genetic testing has been done.[8,255,293] This is because there are many syndromes associated with secondary glaucoma that may require prompt management (e.g., ARS, SWS, NF1; Chapter 5). Investigation of systemic features can also complement genetic testing protocols and provide information regarding which gene is most likely implicated in the disease or support the genetic results identified. However, there are limited formalised protocols and recommendations regarding the investigation of specific systemic features in childhood glaucoma, except for ultrasound surveillance for Wilms tumour in sporadic aniridia (i.e., screening for likelihood of *WT1* deletion).[8,255,293] Genetic testing and careful longitudinal phenotyping of childhood glaucoma cases can help support clinicians in organising appropriate referrals for the assessment and management of potential systemic features, whilst increasing our understanding of the phenotypic spectrum and natural history of genes associated with childhood glaucoma.[293]

One of the major benefits of genetic testing in childhood glaucoma, in the context of systemic disease, is demonstrated through the detection of pathogenic variants associated with ARS (i.e., *FOXC1* or *PITX2*). As discussed throughout this thesis, genetic testing is particularly useful in circumstances where an individual presents with a PCG-like or JOAG-like phenotype with no distinct systemic features, and is later found to have a pathogenic *FOXC1* variant (Chapter 3).[386] This can lead to referrals for investigation and management of systemic features observed in *FOXC1*-associated disease, including hearing loss and cardiac defects.[125,126,130,132,192,195] Genetic testing is also useful even where a clinical diagnosis of ARS has already been made. This is because there are distinct differences in systemic features between *FOXC1*-associated ARS and *PITX2*-associated ARS that require overlapping and separate management plans. As recently reported by Reis and colleagues,[192] the care of *PITX2*-associated ARS may require management of umbilical hernias and monitoring for dental, growth, and gastrointestinal symptoms. Conversely, it has been recommended that *FOXC1*-associated ARS management requires assessment for congenital heart defects and regular monitoring for hearing loss,

dental anomalies and skeletal anomalies including scoliosis, hip dysplasia and joint hypermobility. This was determined on the basis of several reports that dental anomalies (small teeth and missing teeth), gastrointestinal anomalies (Meckel diverticulum, anal stenosis) and umbilical hernias are more common in *PITX2*, whilst hearing loss, skeletal abnormalities, dental anomalies (dental crowding and enamel hypoplasia) and cardiac defects are more common in individuals with *FOXC1* variants.[125,126,130,132,192,195] These were similarly observed in this thesis (Chapter 5). Genitourinary features may also be more common in *PITX2*-associated ARS, whilst learning difficulties and developmental delay may be a phenotype more commonly seen in *FOXC1*, in keeping with the results of this thesis (Chapter 5) and other reports.[125,126,130,132,192,195] These features should be managed appropriately. Additional investigation and reporting of these features are however required to confirm whether they should be routinely monitored for in this cohort.[192]

The need for medical subspecialist input in individuals identified to have pathogenic variants in several more common genes associated with childhood glaucoma (i.e., *CYP1B1, TEK, MYOC, CPAMD8,* and *PAX6*; Chapter 3)[386] remains inconclusive. This is because there are very few reports of whether systemic features may occur in these genetic cohorts, owing to the rarity of these molecular diagnoses, limited availability of genetic testing and consequent lack of large cohort studies. To address this gap in knowledge, this thesis provided the first systematic investigation of possible systemic features in these genetic cohorts and thus provided an original contribution to knowledge (Chapter 5). Although the inquiry was exploratory in nature and lacked an adequate control cohort, new hypotheses regarding possible gene-associated systemic features were generated.

Most notably, the results of this thesis provided the first report of the systemic features in *CPAMD8*-associated disease,[185–188] which collectively suggested that biallelic loss-of-function *CPAMD8* variants were associated with a connective tissue disease phenotype (Chapter 5). This was supported by findings that the *CPAMD8* cohort recorded the highest rate of joint hypermobility (66.7%) and tall stature (33.3%) compared to any other cohort. Hearing loss was frequently reported (33.3%). Joint hypermobility and hearing loss are common traits in connective tissue disorders including Marfan syndrome and Stickler syndrome,[430,443,444,448,449] whilst tall stature can additionally be observed in Marfan syndrome.[445,446] These connective tissue disorders share similar ocular disease complications with *CPAMD8*-associated disease including retinal detachment and myopia.[47,185,186,188,441,442,447–450] Ectopia lentis is common to *CPAMD8* and Marfan syndrome,[47,101,185,186,188,441,442] in addition to Weill-Marchesani syndrome; another connective tissue disease.[155,253] It is unknown, however, whether CPAMD8 interacts with any of these connective tissue disorder genes or their gene products. This is particularly difficult to address given the absence of *CPAMD8* from rodent model organism genomes.[185] Larger cohorts and

more detailed examinations of individuals with *CPAMD8*-associated disease are needed to support this finding, which may then influence whether individuals with *CPAMD8*-associated disease require growth monitoring by their paediatrician or management from an audiologist for hearing loss.

The findings of systemic features in *TEK*-associated were less convincing of an associated systemic phenotype. In this thesis, it was reported that bone fractures were highest amongst individuals with a heterozygous loss-of-function *TEK* variant (58.3%; Chapter 5) compared to all other childhood glaucoma and molecular cohorts (0–47.4%). This may have been a result of more than half of these participants recording vision impairment in one or both eyes and/or other factors not measured in this study, rather than an underlying genetic association. The ANGPT1/2-TEK pathway is involved in osteogenesis, bone mineralisation and bone regeneration,[145,146] and murine studies have demonstrated that inhibition of *TEK* function blocked osteogenic differentiation and mineralisation of bone marrow stem cells.[145] However, further research is required to elucidate what effect heterozygous *TEK* loss-of-function variants may have on bone integrity and whether this is related to an increased fracture risk. The ANGPT1/TEK pathway is also involved in lymphangiogenesis, haematopoiesis and the development of heart endocardium.[140,142,143] Only one individual with loss-of-function *TEK* variants in this thesis reported a heart defect (congenital ventricular septal defect) whilst none reported lymphatic defects (Chapter 5). Cardiovascular issues including heart murmur and blood clots were reported in three individuals with a loss-of-function *TEK* variant from the same pedigree.[139] However, these individuals also harboured a rare *SVEP1* variant, and *SVEP1* is similarly involved in vascular regulation.[600,601] It is therefore unclear if *TEK* loss-of-function is associated with cardiac defects. Conversely, cutaneo-mucosal and other venous malformations are known to occur with gain-of-function *TEK* variants, but this disease mechanism is not associated with glaucoma.[26,144] Additional reports of systemic features in individuals with *TEK*-associated glaucoma are needed to determine if management of possible systemic disease is necessary.

Further work is required to determine if the spectrum of *CYP1B1*-associated glaucoma warrants medical subspecialist management. This thesis provided the first account of certain systemic features in this cohort (Chapter 5). Compared to other genetic cohorts, individuals with biallelic loss-of-function *CYP1B1* variants reported the highest prevalence of abnormally shaped teeth (31.3%), extra teeth (18.8%) and short stature (21.4%). The significance of these findings remains unknown. Our understanding of the role of *CYP1B1* is limited and has not been implicated in dental or skeletal development.[121–124] There is a paucity of other studies that have detailed the systemic findings in individuals with C*YP1B1*-associated glaucoma,[110,119] and only one had reported relatively normal findings of a broad nasal bridge and protruding umbilicus in an infant.[119] It is therefore unclear if the systemic features observed in the

CYP1B1 cohort are part of an associated disease spectrum or a result of other genetic or environmental factors. This is in contrast to *MYOC*-associated disease whereby the consequences of loss-of-function *MYOC* variants are considered to be restricted to ocular disease.[437,438] This was supported by the findings of this thesis which suggested that the most common features (cancer, arthritis, bone fractures) were more likely associated with age than an underlying gene function (Chapter 5).

Medical subspecialist input may be required for individuals diagnosed with *PAX6*-associated disease. There are a growing number of reports of metabolic disease including diabetes mellitus and obesity in individuals with pathogenic *PAX6* variants.[223,234–236] It has been proposed that the prevalence of these conditions is related to a role of *PAX6* in pancreatic development and insulin resistance.[231,232] A further two individuals with diabetes mellitus, and three individuals a BMI indicative of being overweight or obese, who had pathogenic *PAX6* variants were reported in this thesis (Chapter 5). A study of 86 individuals with *PAX6*-associated aniridia observed an overall prevalence of Type 2 diabetes and obesity of 12.8% and 23.3%, respectively.[223] However, these conditions are relatively common in the general population and have a multifactorial aetiology. Type 2 diabetes has a prevalence of 5.8% in Australian population adults aged ≥18 years,[602] while 67.0% of Australians aged ≥18 years and 24.9% of children have been reported to have a BMI indicative of being overweight or obese.[603] Obesity and chronic conditions including diabetes are also associated with sedentary behaviours, and sedentary behaviours are more common in individuals with vision impairment compared to those with no vision impairment.[604] The poor visual outcomes often observed in aniridia (mean: 1.0 logMAR or equivalent Snellen measurement of 6/60),[223] may therefore be implicated in the rate of obesity and diabetes in *PAX6*-associated disease. Nonetheless, it has been recommended that clinicians should closely monitor for these conditions in individuals with *PAX6*-associated disease and initiate medical or lifestyle interventions where appropriate.[223]

Continuing to expand the systemic phenotype of these molecular diagnoses has several benefits. As mentioned earlier, detection of systemic features can assist genetic testing protocols. This could result in an improved molecular diagnostic yield for childhood glaucoma and enable the delivery of personalised medicine and better health outcomes. It can lead to the development of management protocols for systemic features within genetic cohorts and childhood glaucoma overall. Management protocols have recently been spearheaded by the works of Reis and colleagues for individuals diagnosed with pathogenic *FOXC1* and *PITX2* variants and are supported by the works of this thesis (Chapter 5). Future research should continue to systematically investigate the systemic features reported throughout this thesis (Chapter 5) and conduct appropriate objective measurements. This should include appropriate assessment from clinical geneticists and other trained specialists using

validated instruments where necessary (e.g., Beighton score for joint hypermobility,[605] and dual-energy X-ray absorptiometry for bone mineral density[606]). Such analysis will contribute to understanding the pleiotropic effects of the genes implicated in childhood glaucoma and support investigative and management guidelines across other genetic cohorts.

10.2.5 Assisting with family planning and testing

Genetic testing in childhood glaucoma is considered to be beneficial within the familial setting.[8,289] The identification of the causative gene and the establishment of the mode of inheritance can assist with informed decision-making in family planning.[8,289] However, family planning decisions in childhood glaucoma, from the perspectives of individuals with childhood glaucoma and their caregivers, has not yet been reported. Whilst these concepts were not directly evaluated in this thesis, a novel exploration of the impact of childhood glaucoma on family planning from the perspectives of adults with childhood glaucoma (Chapter 7; theme 5),[355] and caregivers of individuals with childhood glaucoma (Chapter 8; theme 6),[354] highlighted the importance of genetic testing and counselling.

It was demonstrated throughout this thesis that genetic testing and counselling in the context of childhood glaucoma is valued and has several benefits. Whilst this observation may be biased by the fact that the cohort was recruited from a genetic registry (ANZRAG), a total of 60% of adults and 57% of caregivers indicated that they had or would seek genetic counselling. This was because they perceived that genetic testing would assist with their understanding of the risk of future offspring having glaucoma and help to achieve peace of mind (Chapter 7 and 8).[354,355] The uptake of genetic testing in adults with inherited retinal disease or retinoblastoma, and caregivers of individuals with inherited retinal disease has been reported to be 33–65%.[490,492,524] Similar motivations for and benefits of genetic testing were observed, with those impacted by inherited retinal diseases additionally citing that they could prepare for novel genetic therapies (e.g., *Luxturna* gene therapy in Leber congenital amaurosis).[492,524,607] This was not stated by adults with childhood glaucoma or their caregivers in this thesis,[354,355] likely because genetic therapies do not yet exist for childhood glaucoma. A further 29% of all caregivers interviewed wanted their child, who had glaucoma, to seek genetic counselling to provide assurance as to whether future generations would be impacted by childhood glaucoma. Children as young 13 to 17 years of age with glaucoma expressed that they wanted to seek genetic counselling, with one child citing that this would help explain the origin of their glaucoma. Other reasons for seeking genetic counselling were not investigated in detail in children due to ethical reasons (Chapter 6; theme 7).[358] Overall, these findings collectively supported that individuals impacted by childhood glaucoma should be referred to genetic testing and counselling services.

The importance of genetic counselling in helping individuals with childhood glaucoma or their caregivers to make family planning decisions is not well documented. Although the provision of genetic counselling and impact of the condition on the decision of having children or not was not directly explored in this thesis, some participants did discuss it (Chapter 7 and 8).[354,355] Amongst adults with childhood glaucoma who sought genetic counselling, five expressed that they would have children via other means (e.g., *in vitro* fertilisation or adoption) whilst three decided not to have any children. Similarly, four caregivers who sought genetic counselling did not want additional children. In contrast, 17 adults and 14 caregivers who sought genetic counselling decided to have children anyway. Interestingly, the inheritance pattern did not appear to influence an adult's decision-making process, suggesting that some adults may not want to risk their offspring having glaucoma at all due to other determinants. This could be related to the finding that 66% of adults expressed that they did not want their child to develop vision impairment or have the same experiences of hardships related to their glaucoma diagnosis (e.g., detriment to social well-being, unable to drive a car; Chapter 7).[355] This worry was experienced by more individuals without an affected first-degree relative and was interpreted as a possible influence of not having normalised the condition. It could also be unrelated to the presence of a family history or the recurrence risk and include worries regarding the inability to fulfil the role of being a parent due to their vision status. Meanwhile, caregivers expressed that they did not want additional children only where a molecular diagnosis could not be established. The reason for this finding could be related to the lack of exact recurrence risk, the lack of reproductive options available, the time since their first child was diagnosed with glaucoma or whether normalisation had been achieved. It could also reflect an underlying experience of emotional turmoil or distress because these caregivers did not have an explanation for their child's diagnosis. Although not systematically assessed, other possible emotional consequences of genetic testing such as guilt were seldom observed amongst caregivers (6%; Chapter 8).[354] Further exploration on the impact of the provision of genetic counselling in childhood glaucoma, access to reproductive options and emotional well-being is needed.

Genetic testing and counselling is already recommended within the clinical settings of congenital cataract,[569,574] retinoblastoma,[525] inherited retinal diseases and broader ocular genetic disease.[608,609] It should therefore become part of the clinical practice guidelines for all chronic childhood ocular genetic disease including childhood glaucoma. However, there is also limited research available which explores the impact of these conditions on family planning. One study reported that 13% of parents of children with cataracts worried about the inheritance pattern of the disease but its impact on family planning decisions was not explored.[517] Given that childhood glaucoma is similar to childhood cataract in many ways (i.e., is a relatively rare clinical entity, has syndromic and non-syndromic presentations, poses a threat to visual acuity),[569,610] it would be of interest in future studies to compare the impact of childhood

cataract on family planning and the uptake of genetic counselling with childhood glaucoma. In inherited retinal disease and retinoblastoma, genetic testing has been associated with impacting family planning decisions, with 36%–70% of adults with the condition and caregivers deciding not to have further children.[524,525] This is higher than the rate of adults with childhood glaucoma and caregivers who did not decide to have further children, as per the results of this thesis (6%–17%; Chapters 7 and 8).[354,355] This difference may be because retinoblastoma is life-threatening,[526] and inherited retinal diseases are generally non-treatable,[527] whilst childhood glaucoma is not life-threatening and prompt treatment can usually prevent further vision loss.[11] The lower rate of individuals and caregivers who did not decide to have further children because of childhood glaucoma may also be due to the nature of the study. Individuals who did not decide to have further children may not have decided to participate in the study or disclose their reproductive decisions. Nonetheless, future research into family planning practices in childhood glaucoma and wider ocular genetic diseases is warranted.

Finally, a benefit of genetic testing in the familial setting is to provide a risk estimate for the development of glaucoma to asymptomatic family members. Predictive testing in *MYOC*-associated JOAG and POAG has been demonstrated to be well-accepted by families,[168,611,612] and can result in better clinical outcomes through earlier identification of disease.[613] However, the use of genetic testing to identify at-risk individuals in families with other genes associated with childhood glaucoma has not been evaluated. Whilst the testing of unaffected family members was not considered in this thesis, the results demonstrated that pathogenic *CYP1B1* and *TEK* variants had variable penetrance and age-related expressivity (Chapter 4). Although these are not novel findings, they contributed to a limited body of literature which describes individuals with *CYP1B1*-associated JOAG and POAG,[103,104] and *TEK*-associated JOAG and POAG.[26,139] The results of this thesis continued to demonstrate that pathogenic *FOXC1* variants are associated with an earlier age of onset of glaucomatous disease compared pathogenic *PITX2* variants (Chapter 3).[130,192,386] If family members are found to have pathogenic variants in these genes, they could benefit from close monitoring, earlier detection of possible glaucomatous disease and better clinical outcomes. Community optometrists may be best placed to undertake these examinations. The use of predictive genetic testing, screening protocols, and the clinical outcomes in these genetic cohorts should be considered in future research. The acceptability of and barriers to predictive genetic testing, and the possibility of any psychosocial impacts of predictive testing should also be explored.

Individuals impacted by childhood glaucoma can benefit from genetic testing and counselling within the familial setting. It can assist with understanding the cause of the condition, assist with decision-making in family planning and can help identify at-risk family members. As discussed above, genetic testing and

counselling also have the potential to help families better understand the disease prognosis, improve the identification and management of ocular and systemic complications of the disease, and identify individuals suitable for future clinical trials involving new targeted gene therapies. These benefits, along with the findings from this support, support the integration of genetic testing and counselling into the clinical practice guidelines for childhood glaucoma.

10.3 Integrating psychosocial support for patients and caregivers

The management of childhood glaucoma should incorporate models of care that address the psychosocial impacts of the disease across the entire age spectrum. This is because the condition is chronic, surgeries to control IOP cannot be guaranteed to be successful for one's entire lifetime and individuals typically have a normal life expectancy.[11,272,311] However, there are no evidence-based clinical practice guidelines available which describe the multidisciplinary management required to mitigate the impact childhood glaucoma may have on QoL.[8,255] This is likely because our understanding of the impact of childhood glaucoma on QoL is limited. Few studies have reported QoL in children[306–310] and adults[311,312] with childhood glaucoma, although none had used childhood glaucoma disease-specific quantitative measures of QoL. Their findings may therefore be limited as the QoL measures used may not be asking questions that are pertinent to the childhood glaucoma experience. In contrast, disease-specific quantitative measures have largely been used in reports of the impact of childhood glaucoma in caregivers, but there is still little understanding of the possible factors associated with poorer QoL in this cohort (e.g., use of coping mechanisms).[313–318] In agreement with the World Glaucoma Association Consensus on Childhood Glaucoma, further research was required to understand the psychosocial impact of childhood glaucoma.[12] This type of inquiry is better suited to a qualitative study design using semi-structured in-depth interviews.[357] This thesis addressed these limitations of prior literature by qualitatively exploring the impact of childhood glaucoma from three unique perspectives: the child (Chapter 6),[358] the adult (Chapter 7),[355] and the caregiver (Chapter 8).[354] The results of my research provided a detailed and unique contribution to knowledge of the impact of childhood glaucoma and will serve to inform a multidisciplinary approach required to address the psychosocial impacts of childhood glaucoma. This will ultimately provide those affected with the condition with the best chance at controlling psychosocial outcomes and achieve an optimal QoL.

10.3.1 Support for children and adults with childhood glaucoma

The concurrent investigation of QoL in children and adults in this thesis provided several key insights needed to develop appropriate support models of care. It emphasised that a long-term perspective is needed in the treatment of childhood glaucoma. This is because childhood glaucoma may impact on

QoL at any time across the age-continuum. In particular, the findings of this thesis identified the novel use of maladaptive coping mechanisms used in children and adults with childhood glaucoma (Chapters 6 and 7).[355,358] A deep exploration of the patterns of behaviour and issues that may be associated with the use of maladaptive coping mechanisms and decreased QoL was provided. These findings can inform the development of targeted health strategies to be delivered at the appropriate time.

Maladaptive coping strategies included treatment nonadherence and clinical nonattendance. Interestingly, these were particularly observed amongst children aged ≥16 years (Chapter 6),[358] and young adults aged 18 to <40 years (Chapter 7).[355] This is an important trend to investigate because denial,[475] and treatment non-adherence,[333] have been associated with worsening visual field mean deviation in individuals with glaucoma diagnosed after age 18 years. It could also lead to feelings of regret later in adulthood, as observed in this thesis (Chapter 7).[355] It has been proposed that the use of maladaptive coping in this younger cohort may be a result of having alternate priorities, having negligible activity limitations, or not being able to grasp the chronicity of the condition.[332] Other reasons could revolve around the transition of care from child to adult ophthalmic services, navigation of a different healthcare setting without assistance of a parent or guardian, financial concerns and establishing rapport with an unfamiliar ophthalmologist. These have been considered as barriers to accessing care by adolescents with vision impairment or blindness.[614] The choice of whether to use adaptive or maladaptive coping has been theorised to be related to one's perception of their ability to control the source of the stress.[615] It is possible that the use of maladaptive coping mechanisms reported in the context of childhood may be because an individual determines that their glaucoma cannot be controlled or other factors related to their glaucoma diagnosis cannot be controlled or improved (e.g., ability to drive, social isolation, career choices). In adults with POAG, treatment non-compliance has been associated with not being married, a complicated medication schedule, difficulties with drop instillation, forgetfulness, and symptoms of depression.[333,616,617] Ongoing investigation of the reasons for the use of maladaptive coping strategies in childhood glaucoma, and the consequence of these on clinical outcomes, is required to support clinical care models.

Interventions, programs, models of care and glaucoma treatments which are used to support an increase in treatment compliance in childhood glaucoma have not yet been evaluated. Various interventions have been trialled in adults with glaucoma with relative success,[476] and could be trialled for use in children and adults with childhood glaucoma. These have included various reminder systems including alarms and reminder texts or phone calls, and behavioural change programs including motivational interviewing, problem solving training, and educational programs.[476] Behavioural change programs serve to increase an individual's ability to control a situation and find a solution.[476] Coping

skills training could also be adopted to increase medical competence and the use of positive coping strategies but these are yet to be used in glaucoma care (Chapter 6).[358,464] As discussed in Chapter 6,[358] ancillary ophthalmic personnel such as an orthoptist could be best placed to facilitate these intervention strategies. A social worker could also deliver effective intervention strategies. Social worker-led interventions in adults with glaucoma have resulted in increased resolution of barriers to glaucoma care, including emotional distress, poor medication adherence and poor follow-up adherence.[618] The inclusion of either professional's expertise could therefore serve a valuable role in the multidisciplinary management of children and adults with glaucoma and serve to improve compliance rates. Finally, resolution of issues related to compliance with topical antiglaucoma medications may be achieved with non-invasive glaucoma surgeries. These include selective laser trabeculoplasty and minimally invasive glaucoma surgery which have been shown to be as effective as topical antiglaucoma medications in controlling IOP in cohorts with adult-onset glaucoma.[478,479] However, these procedures are not yet commonly used in childhood glaucoma,[273] due to the scarce literature reporting the effectiveness of selective laser trabeculoplasty[480] and minimally invasive glaucoma surgery in cohorts with types of childhood glaucoma.[481,482] Overall, future research is required to evaluate the implementation and impact of these medical and non-medical methods of improving compliance in childhood glaucoma.

Additional strategies to increase treatment compliance and clinical nonattendance within the paediatric setting can adopt the general guidelines for the management of childhood chronic conditions. A consensus statement regarding the care of children with chronic childhood conditions recognised that young individuals required a family-centred, compassionate and comprehensive approach to their treatment to facilitate medical autonomy and assist with the transition of healthcare from paediatric to adult services.[619] To achieve this, it was recommended that there is one healthcare professional who acts as a healthcare transition case manager, and begins a plan for healthcare transition by around 14 years of age. This plan is reviewed annually in collaboration with the individual and their family.[619] In the ophthalmic setting, this role could again be performed by an orthoptist or social worker. Successful implementation of a healthcare transition plan could alleviate the anxieties related to developing medical autonomy and navigating a different healthcare setting (Chapter 6).[358,614]

Individuals with childhood glaucoma may further benefit from psychological support and intervention to support adherence to glaucoma care and achieve an optimal QoL. A notable self-reported rate of depression was observed amongst individuals with childhood glaucoma throughout this thesis (17.2%; Chapter 5). This is comparable to the rate of depression that was reported amongst adults with glaucoma onset at age ≥18 years (10.9–22.0%),[333,489,620] and is higher than the rate of depression amongst the general Australian population aged 16–85 years (11.2%).[452] Although there are many

ocular and non-ocular factors that may associated with the development of depression, the higher rate of depression observed in childhood glaucoma may be due to the ongoing threat of the condition to emotional and social well-being. Concerns and anxieties related to ocular health, employment, income, and ability to perform parental duties, in addition to the impact that the condition may have on daily activities (e.g., inability to drive a motor vehicle, inability to participate in sports), may increase the risk of developing depression (Chapters 6 and 7).[355,358] Among adults with glaucoma diagnosed at ≥18 years of age, activity limitations and having anxiety related to losing vision have been identified as significant predictors for depression, while clinical parameters including BCVA, age, sex, visual field defects and topical medication use were not.[620] Referral to an appropriate mental health counsellor, psychologist or psychiatrist may be required to assist with managing mental health issues associated with a diagnosis of childhood glaucoma.

Ophthalmic healthcare professionals are well positioned to facilitate referrals to external services including low vision support networks or psychology-based healthcare. This is because individuals with childhood glaucoma often make frequent contact with ophthalmic healthcare professionals as they require regular and long-term care. However, it is well known that referral to services supporting those with low vision by glaucoma specialists has been hindered by the time pressures associated with clinical testing.[621] Glaucoma specialists have also reported that referrals were not often made because patients did not disclose activity limitations associated with their condition or were unaware of the type of services available.[621] These issues may be overcome with the use of designated ancillary ophthalmic staff who are responsible for identifying patient's needs and facilitating referrals. Preferred practice guidelines in glaucoma care which recommend referral to low vision and social services for those with vision impairment or blindness have also been developed.[622] Increased awareness of issues impacting QoL and the benefits associated with referral to external services may also be beneficial.[621] Awareness of these issues were raised during the time of this thesis via numerous ophthalmic conference presentations and online media releases (as detailed in the Thesis Outcomes). Consistent patient advocacy and implementation of public policies may subsequently facilitate referrals to external services and support the well-being of those with childhood glaucoma.

10.3.2 Support for caregivers of children with glaucoma

Caregivers have long been referred to as the 'hidden patient', as they attend appointments with their child without having their own concerns and well-being addressed.[623,624] It has been established that caregivers of children with childhood glaucoma may experience a high caregiver burden,[314] and high rates of depressive symptoms.[313–317] However, there has been a lack of research to understand the reasons or how this may be alleviated within a multidisciplinary model of care. Previous literature has

largely relied on quantitative measures, in the form of PROMs, to explore caregiver QoL.[313–318] The use of PROMs, which have a set list of questions, do not lend themselves to develop a deeper understanding of the caregiver experience in childhood glaucoma.[357] The experiences of the hidden patient in childhood glaucoma were thoroughly detailed in this thesis and provided an original contribution to knowledge (Chapter 8).[354] Most notably, a novel description of how caregivers cope with their child having glaucoma during the diagnostic period and beyond was provided. This emphasised the need for emotional and social support and discussed the importance of achieving normalisation and self-efficacy. This description can be used to support how family-centred care in the setting of childhood glaucoma could be delivered and what targeted interventions are most likely to be effective.

Validated healthcare interventions that promote caregiver well-being, normalisation and self-efficacy have not yet been developed for or trialled in the context of childhood glaucoma. This is problematic because normalisation and parent self-efficacy are needed to promote caregiver well-being and increase child autonomy and resilience.[509] This may instead be achieved with various programs and interventions that have been demonstrated to be successful in other childhood ocular conditions. An interactive 8-week education program which incorporated disease-specific aetiological and management information, parent testimonials and informal peer support significantly reduced stress in parents of children with congenital cataract compared to parents who did not participate in the program.[625] Life skills training, which incorporates teaching self-awareness, stress management and problem solving techniques, empathy and communication skills, could also be successful in childhood glaucoma.[626] This type of training significantly decreased parenting stress in a cohort of mothers of a child with vision impairment compared to mothers who did not have the training.[626] In non-ocular chronic childhood disease, successful development of normalisation has been supported by mindfulness-based stress reduction programs,[511] problem-solving therapy,[512] and support groups.[513] In the context of childhood glaucoma, successful implementation of education-based programs and support groups could be facilitated by an orthoptist or ophthalmologist. A national web-based support group for families impacted by childhood glaucoma is currently being coordinated by an orthoptist at Glaucoma Australia, a national charity organisation which supports individuals diagnosed with glaucoma.[627] The benefit of this web-based support group could be explored in future studies, particularly as participation in online support groups have significantly reduced anxiety and depression in caregivers of children with cancer.[628] Conversely, behavioural change interventions would require an appropriately qualified clinician such as a social worker or psychologist. These strategies could also be trialled in future research that aims to alleviate the caregiver burden.

Normalisation and emotional support for caregivers can be delivered without formalised healthcare interventions. When determining the needs of the caregiver in any condition, it has been recommended that clinicians enquire about caregiver well-being, discuss respite plans and provide education.[624] In the context of childhood glaucoma, caregiver well-being may vary depending on whether a caregiver is within the diagnostic period and experiencing existential unease, has adopted positive or negative coping mechanisms or is experiencing chronic sorrow (Chapter 8).[354] Clinicians should be mindful of these possibilities and manage with appropriate involvement of a social worker or encouragement of the caregiver to seek care from their own physician.[624] Respite may be provided by the caregiver's spouse or parents (Chapter 8).[354] This was considered to reduce the impact of a chronic stressor (i.e., caring for a child with glaucoma) under the stress-buffering hypothesis.[497] Clinicians should be mindful, however, that some caregivers may be experiencing partner conflict associated with the stress of caring for a child with glaucoma or be reluctant to allow someone other than a family member to care for their child (Chapter 8).[354] Respite may also be provided through participation in family-oriented camps, as seen in other paediatric chronic diseases such as spina bifida[629] and diabetes.[630] These camps additionally promoted social support and self-efficacy in disease management for caregivers and their children.[629,630] Whilst a camp for childhood glaucoma does not yet exist, support for disease management in this setting may particularly help diffuse caregiver anxiety or anguish when instilling topical antiglaucoma medications. This was experienced because caregivers perceived their child to be in pain (Chapter 8).[354] Education of how to perform this safely alongside the distribution of information pamphlets or other communications that are written at a suitable reading level could also be considered.

The facilitation of caregiver support by clinicians may be met with some challenges. Within the wider vision impairment community, clinicians have been reported to be often unaware of the emotional support required for caregivers, considered care of the caregiver to be outside of the scope of their role, or were unable to direct caregivers to appropriate support services.[631] Solutions to this problem may include raising awareness of the need for caregiver support in childhood glaucoma.[631] Several online media releases, support group talks and ophthalmic conference presentations were conducted during the time of this thesis to achieve this (as detailed in the Thesis Outcomes). Streamlined caregiver information packs with appropriate referral pathways and resources (e.g., online support groups) may also be developed.[631] Rahi and colleagues[632] have advocated for the use of a 'key worker' in the care of families where a child has been newly diagnosed with vision impairment. Their role, which sounds analogous to a social worker, was to follow patients and their families throughout their clinical assessments, debrief with the family about the results and facilitate educational, emotional, social and peer support. This worker could facilitate referrals for caregivers to the appropriate psychological or counselling service if, for example, postpartum depression or spousal tension were suspected (Chapter

8).[354] Overall, this worker was well accepted to be beneficial amongst families, and their role has been integrated into paediatric ophthalmology department of a large tertiary hospital in the United Kingdom.[632] Ongoing efforts to ensure the facilitation of caregiver support through research, advocacy and health policy should be made to support their well-being.

10.4 Multidisciplinary healthcare models in childhood glaucoma

A multidisciplinary model of healthcare integrating the services offered by several healthcare professionals, research personnel and informal social supports could be adopted in childhood glaucoma. These services and respective personnel have been summarised in Figure 10.1. Similar to models of care in retinoblastoma,[633] a multidisciplinary model of childhood glaucoma care may first involve the design of a childhood glaucoma-specific ophthalmology outpatient clinic which comprises ophthalmologists and geneticists. Flinders Medical Centre in Australia, for example, has designed such a clinical model which incorporates ophthalmologists and orthoptists. A genetic counsellor, who liaises between patients and genetic research scientists (the ANZRAG) is also available as required. Although this is yet to be formally evaluated, it has the potential to result in increased patient satisfaction. In a retinoblastoma-specific clinic, increased patient satisfaction has been primarily attributed to increased patient access to specialised clinicians who are familiar with retinoblastoma disease and its genetic profile.[633] Meanwhile, integration of other personnel such as paediatricians, psychologists, social workers and low vision rehabilitation specialists may be achieved through regular multidisciplinary team meetings. These are adopted widely in the setting of childhood cancer and have contributed to more accurate diagnoses, earlier initiation of treatment and better health outcomes.[634] A multidisciplinary team meeting in childhood glaucoma may particularly assist in earlier detection of noncompliant patients with consequent planned interventions. Social workers may also be integrated into the clinical setting to provide direct social support for patients and caregivers as previously discussed.[632] Overall, however, facilitation of these models of multidisciplinary healthcare will depend on the staffing and financial resources available within any healthcare setting. The results of this thesis support the implementation of a multidisciplinary approach to childhood glaucoma care.

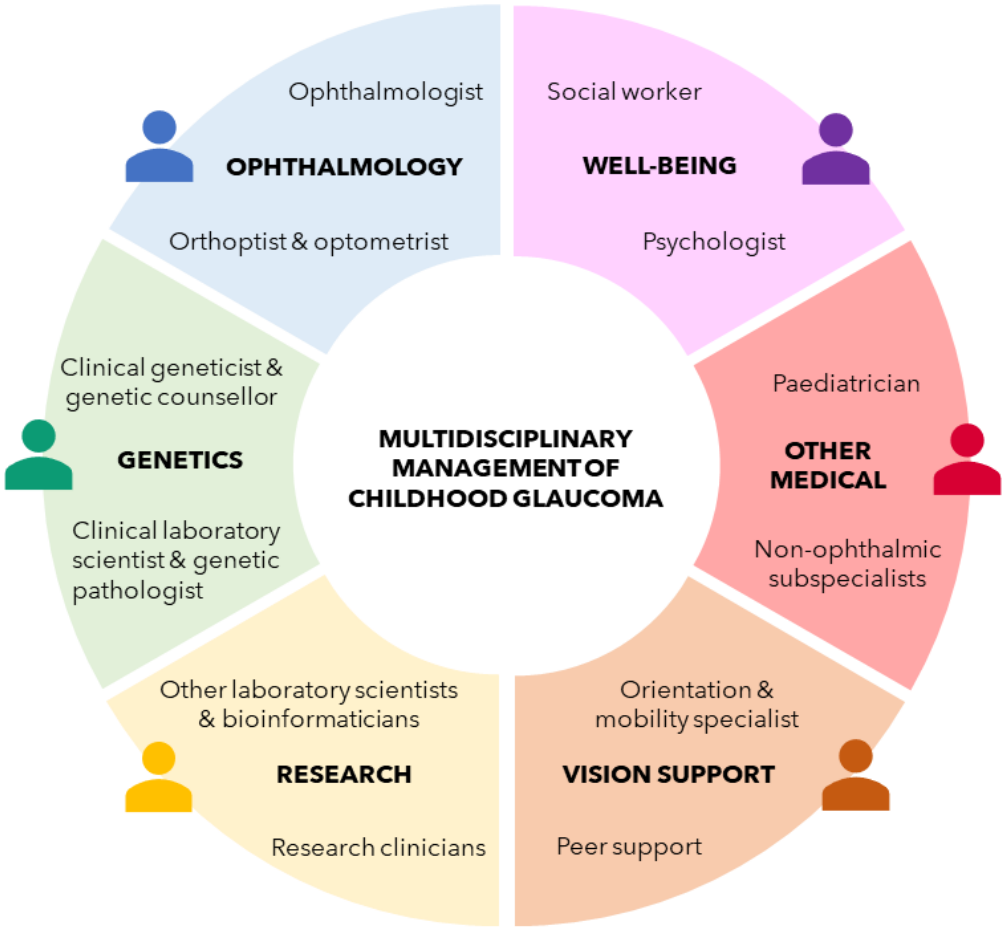

Figure 10.1. Multidisciplinary management of childhood glaucoma

10.5 Measuring the success of healthcare interventions

The implementation of any model of healthcare or specific health intervention requires appropriate evaluation.[319] The choice of measurement depends on what the intervention is targeting. For example, an intervention that aims to increase the level of caregiver QoL should use an appropriate measure of caregiver QoL in childhood glaucoma. The CarCGQoL is an example of a childhood glaucoma disease-specific PROM that serves to evaluate caregiver QoL.[316] If an intervention is designed to improve QoL in children or adults with childhood glaucoma, then a disease-specific measure of QoL in these cohorts should be used. However, as discussed throughout Chapters 6,[358] 7,[355] and 9, there was no childhood glaucoma-specific PROM that served to accurately measure QoL in children or adults with the condition.

This thesis addressed this gap in knowledge and aimed to develop a childhood glaucoma-specific PROM for children and adults with childhood glaucoma. Phase I of PROM development (item generation),[316] was successfully achieved using semi-structured interviews with children and adults with

childhood glaucoma, as described throughout Chapters 6[358] and 7.[355] However, due to time constraints, the feasibility of the project, and the sample size required to validate a PROM,[468] phases II-IV of PROM development (item reduction, cognitive debriefing, pilot testing with Rasch analysis)[316] were only pursued for the adult cohort. My original contribution to knowledge included the successful development of a novel instrument that provides an accurate measure for childhood glaucoma-specific QoL in adults: the CGQoL-14 (Chapter 9). In my future research, I aim to complete the development of a childhood glaucoma-specific QoL PROM suitable for children with glaucoma using an appropriate sample size (n=64–144).[468] Development of a PROM suitable for children will also need to consider the use of age-appropriate language and include items that are relevant to children's experiences of disease.[635–637] Similar to the development of PROMs that measure QoL in children with various eye conditions,[635,636] and children with vision impairment,[637] a separate PROM may be required for children aged 8–12 years and those aged 13–17 years. This is in keeping with the findings of Chapter 6,[358] whereby the disease experience may shift as a child enters adolescence. Furthermore, the minimum age threshold of obtaining reliable self-reports of QoL is considered to be 8 years of age.[455]

There are several other benefits to implementing disease-specific measures of QoL into clinical practice. A disease-specific QoL instrument such as the CGQoL-14 and CarCGQoL can be used to complement diagnostic information in a clinical setting, facilitate discussion around psychosocial well-being, aid clinicians in delivering appropriately informed patient-centred care and shared-decision making, and identify individuals who may benefit from a referral to other services.[638] As discussed by Gothwal and colleagues,[316] items with lower scores can be used to identify individual-specific issues. An individual who scores poorly on mobility-based items may benefit from referral to an orientation and mobility specialist. Individuals who score poorly on the emotional-based items may benefit from patient counselling or referral to psychology. Referral rates of individuals to such services have recently been identified to be relatively poor amongst glaucoma specialists and a tool such as the CGQoL-14 may help improve this.[621] The CGQoL-14 and CarCGQoL can also be used in future research to accurately measure QoL in individuals with childhood glaucoma. This may be important in determining differences in QoL based on the glaucoma subtype and molecular diagnoses across the entire childhood glaucoma spectrum. This has not yet been investigated and would complement the findings of Chapter 5, whereby individuals with biallelic *CYP1B1* variants or a *FOXC1* variant reported higher rates of anxiety and depression compared to other genetic cohorts. Distinguishing differences in QoL amongst individuals impacted by certain glaucoma subtypes or molecular diagnoses may result in earlier initiation of vision rehabilitation or counselling services in clinical settings for at-risk individuals. Differences in QoL between certain genetic groups may also provide evidence to support government-funded genetic testing for childhood glaucoma and assist in counselling individuals regarding their family planning

concerns and options. The joint distribution of these childhood glaucoma-specific QoL PROMs could therefore support a holistic and measurable approach to managing the impacts of the condition.

The implementation of the CGQoL-14 in clinical practice may be met with several challenges. These may include the availability of clinical personnel to administer the PROM, the time required to complete, interpret and discuss the result with the patient, and the patient's ability to self-report (e.g., the need for staff to administer the PROM for individuals with a vision-impairment).[639] However, the CGQoL-14 is considered to have a low administrator and respondent burden, as it has only 14 items with three response categories each. This is unlike other glaucoma-specific QoL PROMs, albeit designed for those with adult-onset glaucoma, such as the Glau-QoL 36 which has 36 items with four or five response categories.[359] The use of item banks, delivered by computerised adaptive testing, may further reduce the burden associated with testing QoL. This is because testing involves selective presentation of items that provide the most efficient measure of QoL, rather than the completion of all items.[532] The use of computerised adaptive testing in a rare condition such as childhood glaucoma, however, is not considered feasible as validation of such an instrument requires a sample size >250.[468,532,545] Nonetheless, there is increasing encouragement for the use of PROMs in ophthalmic practice as evidenced by the plethora of vision-specific and disease-specific QoL PROMs that have been developed over recent years.[640] This is because clinicians can use them to assess the impacts of disease in a way that resonates with patients, rather than relying solely on objective clinical measures of disease severity such as visual acuity.[641] General guidelines which consider the selection of the most appropriate PROM to use and the resources required to implement them have further been developed to support their clinical use.[642] The CGQoL-14, however, remains to be the first tool developed to specifically measure QoL in adults with childhood glaucoma. Evaluation of the clinical utility of the CGQoL-14 in future research will further support its use in ophthalmic healthcare settings.

10.6 Conclusions

Childhood glaucoma describes a heterogeneous group of chronic vision-threatening disorders that can lead to irreversible vision loss and a considerable impact on QoL. Our understanding of the genetic heterogeneity of the condition is advancing rapidly with the increased availability of genetic testing.[7,573] However, there remains a gap in knowledge regarding the ocular and systemic phenotypic heterogeneity, the impact of the condition on family planning, and more broadly, quality of life. This thesis provided evidence to support a clinical approach to childhood glaucoma from a holistic perspective which encompassed investigation of the genetic, phenotypic (including ocular and non-ocular) and quality of life outcomes of this rare condition. My original contribution to knowledge included

an investigation of the genotypic and phenotypic heterogeneity of childhood glaucoma in the largest reported population of predominantly European ancestry, an analysis of the clinical outcomes of the two most common genes implicated in PCG, and an exploratory analysis of the systemic associations of childhood glaucoma. In addition, my thesis provided an original and in-depth analysis of the impact of the disease from the perspectives of the child, adult, and caregiver, and resulted in the successful development of the first childhood glaucoma-specific PROM suitable for an adult cohort. This translational research has led to recommendations for a family-centred, multidisciplinary approach to childhood glaucoma care, summarised in Figure 10.1, which aims to ensure that any individual impacted by this condition achieves the best possible clinical outcomes and optimum quality of life.

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APPENDIX A: INTERVIEW GUIDES

Interview Guide A1. Semi-structured interview guide for children with glaucoma

Period of diagnosis/Emotional

What is it like growing up with glaucoma?

School and Cognitive Functioning

What is school like for you?

Do you think your eyes make some things harder to learn? (like maths, science or geography?)

Do you find it challenging to read your books or papers at school?

How do you find reading the board or laptop in your classroom?

Are you confident to ask for help at school?

How do you feel about the help that you get?

Do you keep up with other children in the classroom or do things take longer for you to finish? Can you tell me why?

Do you feel like your teachers and other children at school understand your eyes?

What do you like to do at playtime or recess? Do you do the same as your friends? Is it because of your eyes?

Can you find your friends easily in the playground? Why not?

Do you think you will finish high school? Why/why not?

Do you think that your glaucoma will determine what you do in the future for work or study?

Are you worried about it?

Relationships

Because of your glaucoma, do you find it easy to make friends?

Do you get along with your brothers and sisters? Do you think that's because of your eyes?

Do you feel that your family and friends understand your eye problem? Why/why not?

Does having glaucoma make you feel different to your friends or brothers or sisters? Why/why not?

Do you feel like other children treat you differently because of your eyes? Can you explain that?

Do you tell your friends about your eyes? Why/why not?

Do your family and friends need to help you do some things? Like what?

Do they give you enough help?

(*For older children if appropriate*) Have you ever been worried if your children will have glaucoma too?

Role Performance and Leisure

Has your eye problem made it hard to do some activities such as sports, playing on the playground, going to the movies, or playing video games?

How does that make you feel?

What do you do when you find something hard to do?

Psychological

Do you worry about your eyes? Why/why not?

Do you ever feel sad or angry about your eyes? What cheers you up?

(*For older children if appropriate*) What worries, or concerns do you have regarding the future?

Treatment/Medical Care

How does going to the eye doctor make you feel? Do you miss out on things because you have to go?

Prompting questions: Do you get nervous before you go? Why? (e.g., reading the vision chart, pressure test, needing eye drops, doing a visual field test, waiting a long time)

Do you feel like your eye doctor helps you? Do you ask questions?

How does putting in eye drops every day make you feel (if applicable)?

Mobility/Autonomy

How do you get to school? Can you catch the bus to school by yourself?

Do you find it hard to cross the road, or go up and down stairs, riding a bike?

Do you feel that you bump into things a lot? When does it happen or what sort of things do you bump into?

Are you worried about driving a car when you're older?

Low Vision Aids

Do you use any special computers or iPads to make things bigger?

Do you like using them?

Does using them make you feel different?

Interview Guide A2. Semi-structured interview guide for adults with childhood glaucoma

Period of diagnosis

Do you remember what it was like growing up with glaucoma? What was it like for you personally?

Schooling and Cognitive Functioning (if currently at high school or university)

Do you think your eyes make some things harder to learn at school/university?

Do you find it challenging to read your books, papers, the board or laptop?

Are you confident to ask for help? Do you feel like you get enough help?

Do you keep up with other students in the classroom or do things take longer for you to finish?

Do you feel like your teachers and other students at school understand your eyes?

Do you think you will finish high school or university? Why/why not?

School, Work and Cognitive Functioning (Schooling questions asked in retrospect)

When you were a child, do you think your glaucoma affected your schooling?

Do you remember being a confident child?

Do you feel that having glaucoma determined what you are doing now?

Do you think that your glaucoma will determine what you do in the future for work or study?

Are you worried about your future work or study?

Relationships

Did having glaucoma make you feel different to the other children? Has it changed over time?

Thinking back to when you were a child, do you think your family life was impacted by your glaucoma?

Has your family life changed now that you are an adult?

Thinking back to when you were younger, did having glaucoma affect your romantic relationships?

Thinking to now, does having glaucoma affect your romantic relationships?

Does/did having glaucoma change or impact your decision to have any children?

Have you ever been worried if your child/ren will have glaucoma too?

Were you ever made aware of the risks of having a child with glaucoma? Who informed you? Was the information enough?

Role performance and leisure

Has your glaucoma ever stopped you from doing something you wanted to do? (if not vision, then doctor follow up appointments, treatment adherence etc.)

Do you experience problems performing any new tasks because of your glaucoma?

What do you do when you find something hard to do?

Psychological

Because of your glaucoma, do you feel in control of your life?

What is your understanding of your glaucoma for the future?

What worries or concerns do you have regarding the future? What about your independence?

Treatment/medical care

How do you feel when you go to the eye doctor?

Prompting questions: Do you get nervous before you go? Why? (e.g. reading the vision chart, pressure test, needing eye drops, doing a visual field test, waiting a long time)

Can you remember going to the eye doctor when you were younger? What was it like?

Do you feel like you get the chance to ask questions when you go to the eye doctor?

Do you feel supported and understood by your eye health team? Can you tell us how you could be supported better in the past? What about now?

How does your glaucoma and its treatment affect you financially?

Mobility/autonomy

Do you feel like you can get around independently and confidently? If not, how do you feel asking for help from others to get around?

Do you have a driver's license (or used to have one) and if so, are you worried about it or driving in general?

How do you feel about using public transport?

Physical/emotional

Thinking back to when you were a child, how did your glaucoma affect you physically? Did you feel different at the time? Do you feel different now?

Thinking back again to when you were a child, how did your glaucoma affect you emotionally? Do you feel different now?

Low vision aids

Do you use any special computers or iPads to make things larger to see?

How do you feel about using them?

Does using them make you feel different?

Interview Guide A3. Semi-structured interview guide for caregivers of children with childhood glaucoma

Period of diagnosis

Can you describe your thoughts and feelings at the time of your child's diagnosis? What was it like for you personally?

What were your concerns or worries?

How was your life impacted by this experience?

What support did you experience at the time?

Treatment – including surgery, EUA and medications

How has the course of treatment and examinations impacted you as a caregiver?

How do you feel when you have to take your child to their eye appointment?

Prompting questions:

1. Do you feel like the eye doctor understands your worries?
2. Do you get the opportunity to ask questions?
3. Do you feel supported and understood by your child's eye health team?

How does/did having a child with glaucoma and its treatment affect you financially?

Family life

How has your family life been impacted by your experience and journey?

Do you feel that you have good family support?

How did/does having a child with glaucoma affect your relationship with: the child's other parent? Your other children? Your partner/husband/wife…?

How did/does having a child with glaucoma change or impact your decision to have any further children?

Were you ever made aware of the risks of having another child with glaucoma? Who informed you? Was the information enough?

Prognosis of vision

What worries or concerns do you have for your child right now?

How do you think they are going at school/work/university?

What is your understanding of your child's prognosis for the future?

What worries or concerns do you have regarding the future?

Social

What helps you cope with your child's current state of health?

How could this be improved?

How has having a child with glaucoma affected your social life?

Do you feel like other parents understand what you have or are going through?

Physical/Emotional

Thinking back to when your child was first diagnosed and the months after that, how did your role as your child's caregiver affect you physically? Do you feel different now?

Thinking back again to those first few months, how did your role as your child's caregiver affect you emotionally? Do you feel different now?

Retrospective need for social support

Looking back, what support options may have been beneficial for you in the past?

Prospective need for social support

Looking forward, what support options may be beneficial for you/for other parent?

APPENDIX B: SUPPLEMENTARY TABLES

Table B1. Clinical subtypes of glaucoma according to the Childhood Glaucoma Research Network Criteria prior to genetic testing

	Childhood					Early-onset				
Diagnosis	**Cases n (%)**	**Eyes n (%)**	**Male n (%)**	**Highest IOP (mmHg)**	**Age diagnosed (years)**	**Cases n (%)**	**Eyes n (%)**	**Male n (%)**	**Highest IOP (mmHg)***	**Age diagnosed (years)***
Primary congenital glaucoma	**167 (57.6)**	**303 (56.8)**	**99/167 (59.3)**	**30 (24–40)**	**0.25 (0–0.6)**	**-**	**-**	**-**	**-**	**-**
Neonatal (age <1 month)	64 (38.3)	119 (39.3)	33/64 (51.6)	30 (25–40)	0 (0–0)	-	-	-	-	-
Infantile (age 1-24 months)	89 (53.3)	160 (52.8)	56/89 (62.9)	30 (23–40)	0.4 (0.3–0.7)	-	-	-	-	-
Late (age >24 months)	8 (4.8)	14 (4.6)	4/8 (50.0)	38 (30–45)	3.5 (3-4)	-	-	-	-	-
Unknown age of onset	3 (1.8)	4 (1.3)	3/3 (100.0)	22 (n/a)	n/a	-	-	-	-	-
Spontaneously arrested PCG	3 (1.8)	6 (2.0)	3/3 (100.0)	35 (27–44)	3 (1–5)	-	-	-	-	-
Juvenile open-angle glaucoma	**56 (19.3)**	**109 (20.5)**	**28/56 (50.0)**	**40 (27–46)**	**14 (12–16)**	**271 (73.2)**	**513 (74.8)**	**147/271 (54.2)**	**29 (23–38)**	**34 (29–37)**
High-tension glaucoma (HTG)	45 (80.4)	87 (79.8)	20/45 (44.4)	40 (31–47)	14 (12–16)	213 (78.6)	407 (79.3)	118/213 (55.4)	32 (26–40)	34 (28–36)
Normal-tension glaucoma (NTG)	-	-	-	-	-	22 (8.1)	40 (7.8)	6/22 (27.3)	15 (14–17)	35 (30–38)
Unknown HTG or NTG	11 (19.6)	22 (20.2)	8/11 (72.7)	18 (16–20)	14 (11–16)	36 (13.3)	66 (12.9)	23/36 (63.9)	18 (16–20)	35 (30–37)
Glaucoma associated with acquired conditions	**3 (1.0)**	**5 (0.9)**	**2/3 (66.7)**	**48 (46–49)**	**6 (5–6)**	**49 (13.2)**	**82 (12.0)**	**36/49 (73.5)**	**36 (30–48)**	**32 (30–37)**
Uveitis	3 (100.0)	5 (100.0)	2/3 (66.7)	48 (46–49)	6 (5–6)	4 (8.2)	5 (6.1)	4/4 (100.0)	34 (25–43)	37 (35–39)
Trauma	-	-	-	-	-	1 (2.0)	1 (1.2)	1/1 (100.0)	38 (n/a)	18 (n/a)
Steroid induced	-	-	-	-	-	13 (26.5)	21 (25.6)	9/13 (69.2)	38 (35–48)	30 (26–31)
Posner-Schlossman syndrome	-	-	-	-	-	1 (2.0)	2 (2.4)	1/1 (100.0)	60 (n/a)	20 (n/a)
Rubeotic glaucoma (secondary to central retinal vein occlusion)	-	-	-	-	-	1 (2.0)	1 (1.2)	0/1 (0.0)	62 (n/a)	37 (n/a)
Pigmentary glaucoma	-	-	-	-	-	24 (49.0)	43 (52.4)	19/24 (79.2)	36 (29–42)	33.5 (30–37)
Pseudoexfoliation syndrome	-	-	-	-	-	5 (10.2)	9 (11.0)	2/5 (40.0)	30 (28–32)	30 (30–30)

Glaucoma associated with non-acquired ocular anomalies	**49 (16.9)**	**93 (17.4)**	**28/49 (57.1)**	**35 (27–45)**	**3 (0.2–8)**	**44 (11.9)**	**79 (11.5)**	**22/44 (50.0)**	**39 (28–45)**	**31 (25–35)**
Axenfeld-Rieger spectrum	28 (57.1)	54 (58.1)	17/28 (60.7)	32 (22–45)	3 (0.6–8)	14 (31.8)	27 (34.2)	5/14 (35.7)	35 (28–48)	25 (21–28)
Aniridia	6 (12.2)	11 (11.8)	4/6 (66.7)	44 (38–50)	7.5 (0–11)	1 (2.3)	2 (2.5)	0/1 (0.0)	40 (n/a)	31 (n/a)
Iris hypoplasia	1 (2.0)	2 (2.2)	0/1 (0.0)	40 (n/a)	0.0 (n/a)	1 (2.3)	2 (2.5)	0/1 (0.0)	39 (n/a)	38 (n/a)
Unclassified anterior segment dysgenesis	8 (16.3)	16 (17.2)	6/8 (75.0)	32 (29–41)	8 (3–12)	8 (18.2)	15 (19.0)	5/8 (62.5)	35 (27.5–43)	34 (30–35)
Ectropion uveae	2 (4.1)	3 (3.2)	0/2 (0.0)	30 (n/a)	6 (0–12)	-	-	-	-	-
Microspherophakia	1 (2.0)	2 (2.2)	0/1 (0.0)	46 (n/a)	1 (n/a)	-	-	-	-	-
Peters' anomaly	1 (2.0)	1 (1.1)	0/1 (0.0)	27 (n/a)	0.0 (n/a)	-	-	-	-	-
Familial exudative vitreoretinopathy	1 (2.0)	2 (2.2)	1/1 (100.0)	48 (n/a)	1 (n/a)	-	-	-	-	-
Congenital hereditary endothelial dystrophy	1 (2.0)	2 (2.2)	0/1 (0.0)	41 (n/a)	0.2 (n/a)	-	--	-	-	-
Nanophthalmos	-	-	-	-	-	2 (4.5)	4 (5.1)	1/2 (50.0)	41 (40–42)	26 (21–31)
Primary angle closure glaucoma	-	-	-	-	-	18 (40.9)	29 (36.7)	11/18 (61.1)	41 (28–48)	33 (28–36)
Glaucoma associated with non-acquired systemic disease	**6 (2.1)**	**7 (1.3)**	**2/6 (33.3)**	**31 (30–38)**	**0 (0–4)**	**5 (1.4)**	**10 (1.5)**	**0/5 (0.0)**	**35 (29–47)**	**23 (21–30)**
Neurofibromatosis Type 1	2 (33.3)	3 (42.9)	0/2 (0.0)	35 (32–38)	0 (0–0)	-	-	-	-	-
Sturge Weber syndrome	4 (66.7)	4 (57.1)	2/4 (50.0)	30 (22–35)	2 (0–5)	1 (20.0)	2 (20.0)	0/1 (0.0)	28 (n/a)	23 (n/a)
Weill-Marchesani syndrome	-	-	-	-	-	1 (20.0)	2 (20.0)	0/1 (0.0)	23 (n/a)	18 (n/a)
Nail Patella syndrome	-	-	-	-	-	2 (40.0)	4 (40.0)	0/2 (0.0)	45 (29–60)	30 (30–30)
Stickler syndrome	-	-	-	-	-	1 (20.0)	2 (20.0)	0/1 (0.0)	35 (n/a)	21 (n/a)
Glaucoma following cataract surgery	**5 (1.7)**	**8 (1.5)**	**3/5 (60.0)**	**37 (22–49)**	**11 (0–15)**	**1 (0.3)**	**2 (0.3)**	**0/1 (0.0)**	**23 (n/a)**	**20 (n/a)**
Unclassified glaucoma	**4 (1.4)**	**8 (1.5)**	**1/4 (25.0)**	**40 (n/a)**	**4 (3–6)**	**-**	**-**	**-**	**-**	**-**
Total	**290 (100.0)**	**533 (100.0)**	**163/288 (56.2)**	**32 (25–40)**	**0.6 (0–7)**	**370 (100.0)**	**686 (100.0)**	**205/370 (55.4)**	**30 (24–40)**	**33 (28–36)**

PCG: primary congenital glaucoma, HTG: high-tension glaucoma, NTG: normal-tension glaucoma
*Highest recorded intraocular pressure (IOP) and age at diagnosis (years) are presented as median (IQR).

Table B2. Frequency of molecular diagnoses per clinical subtype of glaucoma according to the Childhood Glaucoma Research Network in probands only

Clinical diagnosis according to the CGRN classification	Total tested n (%)	Probands tested n (%)	Probands with molecular diagnosis n (%)	Genetic association reported									
				CYP1B1 n (%)	*MYOC* n (%)	*LTBP2* n (%)	*CPAMD8* n (%)	*FOXC1* n (%)	*PITX2* n (%)	*PAX6* n (%)	*OPTN* n (%)	*TBK1* n (%)	Other n (%)
PCG	**154/167 (92.2)**	**135/148 (91.2)**	**41/135 (30.4)**	**21 (15.6)**	**-**	**-**	**5* (3.7)**	**5* (3.7)**	**-**	**-**	**-**	**-**	***COL18A1* (n=1, 0.7%)* *ANGPT1* (n=1, 0.7%) *TEK* (n=8, 5.9%)**
JOAG	**283/327 (86.5)**	**252/295 (85.4)**	**39/252 (15.5)**	**8 (3.2)**	**24 (9.5)**	**-**	**1* (0.4)**	**2* (0.8)**	**-**	**-**	**1 (0.4)**	**2 (0.8)**	**1 (0.4)**
Childhood	49/56 (87.5)	39/45 (86.7)	12/39 (30.8)	5 (12.8)	6 (15.4)	-	-	1* (2.6)	-	-	-	-	-
Early-onset	234/271 (86.3)	213/250 (85.2)	27/213 (12.7)	3 (1.4)	18 (8.5)	-	1* (0.5)	1 (0.5)	-	-	1 (0.5)	2 (0.9)	*COL2A1* (n=1, 0.5)*
Acquired conditions	38/52 (73.1)	38/53 (73.1)	0/38 (0.0)	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Childhood	0/3 (0.0)	0/3 (0.0)	-	-	-	-	-	-	-	-	-	-	-
Early-onset	38/49 (77.6)	38/49 (77.6)	0/38 (0.0)	-	-	-	-	-	-	-	-	-	-
Non-acquired ocular anomalies	**80/93 (86.0)**	**69/81 (85.2)**	**39/69 (56.5)**	**-**	**-**	**2 (2.9)**	**1 (1.4)**	**14 (20.3)**	**12 (17.4)**	**7 (10.1)**	**-**	**-**	**3 (4.4)**
Childhood	45/49 (91.8)	38/41 (92.7)	27/38 (71.1)	-	-	2 (5.3)	-	12 (31.6)	6 (15.8)	6 (15.8)	-	-	*SLC4A11* (n=1, 2.6%)
Early-onset	35/44 (79.5)	31/40 (77.5)	12/31 (38.7)	-	-	-	1 (3.2)	2 (6.5)	6 (19.4)	1 (3.2)	-	-	*TMEM98* (n=2, 6.5%)
Non-acquired systemic disease	**8/11 (72.7)**	**7/10 (70.0)**	**5/7 (71.4)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**5 (71.4)**
Childhood	4/6 (66.7)	4/6 (66.7)	2/4 (50.0)	-	-	-	-	-	-	-	-	-	*NF1* (n=2, 50.0%)
Early-onset	4/5 (80.0)	3/4 (75.0)	3/3 (100.0)	-	-	-	-	-	-	-	-	-	*ADAMTS17* (n=1, 33.3%) *LMX1B* (n=1, 33.3%) *COL2A1* (n=1, 33.3%)
Following cataract surgery	**4/6 (66.7)**	**4/6 (66.7)**	**0/4 (0.0)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Childhood	4/5 (80.0)	4/5 (80.0)	0/4 (0.0)	-	-	-	-	-	-	-	-	-	-
Early-onset	0/1 (0.0)	0/1 (0.0)	-	-	-	-	-	-	-	-	-	-	-
Unclassified (Childhood only)	**3/4 (75.0)**	**1/2 (50.0)**	**1/1 (100.0)**	**-**	**-**	**1 (100.0)**	**-**	**-**	**-**	**-**	**-**	**-**	**-**
Overall	**570/658 (86.6)**	**506/594 (85.2)**	**125/506 (24.7)**	**29 (5.7)**	**24 (4.7)**	**3 (0.6)**	**7 (1.4)**	**21 (4.2)**	**12 (2.4)**	**7 (1.4)**	**1 (0.2)**	**2 (0.4)**	**19 (3.8)**

CGRN: Childhood Glaucoma Research Network; PCG: primary congenital glaucoma, JOAG: juvenile open-angle glaucoma

*CGRN Classification changed post-genetic diagnosis in individuals carrying the variant/s

Table B3. *TEK* variants reported

Family ID	Pedigree ID	Participant ID	Chromosome position (NC_000009.11)	Exon	cDNA (NM_000459.5)	Protein alteration (NP_000450.2)	Variant type	gnomAD allele frequency	gnomAD allele frequency (matched ancestry)*	CADD score	Phenotype
1	1-II-1	PCG027	27204931dup	14	c.2232dup	p.Lys745Glufs*76	Frameshift	nil	nil	-	PCG
2	2-II-1	PCG066.0	27172747T>C	5	c.760+2T>C	-	Splice donor	nil	nil	32	PCG
2	2-I-2	PCG066.1	27172747T>C	5	c.760+2T>C	-	Splice donor	nil	nil	32	Unaffected
3	3-II-1	PCG092.0	27157924C>T	2	c.148C>T	p.Arg50Cys	Missense	8/251328 (0.00003183)	8/113634 (0.00007040)	22.7	PCG
3	3-I-1	PCG092.2	27157924C>T	2	c.148C>T	p.Arg50Cys	Missense	8/251328 (0.00003183)	8/113634 (0.00007040)	22.7	Unaffected
4	4-II-1	PCG100.0	27228305del	22	c.3300+2delT	-	Splice donor	nil	nil	-	PCG
4	4-I-2	PCG100.1	27228305del	22	c.3300+2delT	-	Splice donor	nil	nil	-	Unaffected
4	4-II-2	PCG100.2	27228305del	22	c.3300+2delT	-	Splice donor	nil	nil	-	Unaffected
4	4-II-3	PCG100.4	27228305del	22	c.3300+2delT	-	Splice donor	nil	nil	-	Unaffected
5	5-II-1	PCG122.0	27213567G>A	18	c.2963G>A	p.Gly988Asp	Missense	1/251280 (0.000003980)	1/113606 (0.000008802)	29.3	PCG
5	5-I-1	PCG122.2	27213567G>A	18	c.2963G>A	p.Gly988Asp	Missense	1/251280 (0.000003980)	1/113606 (0.000008802)	29.3	Unaffected
6	6-II-1	PCG135.0	27212730C>G	17	c.2712C>G	p.Tyr904*	Nonsense	nil	nil	35	PCG
6	6-I-1	PCG135.2	27212730C>G	17	c.2712C>G	p.Tyr904*	Nonsense	nil	nil	35	Unaffected
7	7-II-1	PCG148.0	27218815G>C	20	c.3103G>C	p.Gly1035Arg	Missense	nil	nil	35	PCG
7	7-I-1	PCG148.2	27218815G>C	20	c.3103G>C	p.Gly1035Arg	Missense	nil	nil	35	Unaffected
8	8-II-1	PCG153.0	27183545_27183558del	8	c.1119_1132del	p.Gly374Tyrfs*2	Frameshift	nil	nil	-	PCG
8	8-I-1	PCG153.2	27183545_27183558del	8	c.1119_1132del	p.Gly374Tyrfs*2	Frameshift	nil	nil	-	Unaffected
9	9-II-1	PCG160.0	27180258G>A	7	c.922G>A	p.Gly308Arg	Missense	2/251220 (0.000007961)	2/113564 (0.00001761)	28.2	PCG
9	9-I-1	PCG160.2	27180258G>A	7	c.922G>A	p.Gly308Arg	Missense	2/251220 (0.000007961)	2/113564 (0.00001761)	28.2	Unaffected
10	10-II-1	PCG179	27220069G>C	21	c.3126G>C	p.Met1042Ile	Missense	nil	nil	24.4	PCG
11	11-II-1	PCG189.0	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	PCG

11	11-III-1	PCG189.1	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	OHT
11	11-III-2	PCG189.2	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	Unaffected
11	11-II-3	PCG189.4	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	OHT
11	11-III-4	PCG189.5	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	OHT
11	11-I-1	PCG189.7	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	Unaffected
11	11-II-2	PCG189.8	27109589A>T	1	c.1A>T	p.Met1?	Start loss	nil	nil	21.3	OHT
12	12-II-1	PCG190.0	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	PCG
12	12-II-2	PCG190.1	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	PCG
12	12-I-2	PCG190.2	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	Unaffected
12	12-III-1	PCG190.4	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	PCG
12	12-III-2	PCG190.5	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	PCG
12	12-III-3	PCG190.6	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	PCG
12	12-II-3	PCG190.11	27197410_27197411del	12	c.1722_1723del	p.Phe574Leufs*3	Frameshift	nil	nil	-	Unaffected
13	13-II-1	PCG196.0	27197521C>A	12	c.1833C>A	p.Tyr611*	Nonsense	nil	nil	34	PCG
13	13-I-2	PCG196.1	27197521C>A	12	c.1833C>A	p.Tyr611*	Nonsense	nil	nil	34	Unaffected
14	14-II-1	AG0700	27157923del	2	c.147del	p.Trp49Cysfs*9	Frameshift	nil	nil	-	POAG
15	15-II-2	AG1392	27192558C>T	11	c.1561C>T	p.Arg521Cys	Missense	1/251016 (0.000003984)	0/113384 (0.0)	27.9	POAG
16	16-II-1	AG1490	27157907G>A	2	c.131G>A	p.Cys44Tyr	Missense	nil	nil	27.6	POAG
17	17-II-1	AG2924	27157934A>T	2	c.158A>T	p.Glu53Val	Missense	3/251386 (0.00001193)	3/113680 (0.00002639)	25.1	PCG
18	18-II-1	GFMC0098	27209197T>C	16	c.2654T>C	p.Ile885Thr	Missense	nil	nil	28.7	JOAG
19	19-II-1	GFMC0426	27220142G>A	21	c.3199G>A	p.Val1067Met	Missense	1/251120 (0.000003982)	1/113484 (0.000008812)	32	POAG
20	20-II-1	GFMC0625	27169625G>A	4	c.626G>A	p.Arg209Gln	Missense	nil	nil	29.6	POAG

gnomAD: Genome Aggregation Database; CADD: Combined Annotation-Dependent Depletion; PCG: primary congenital glaucoma; OHT: ocular hypertension; POAG: primary open-angle glaucoma; JOAG: juvenile open-angle glaucoma

*gnomAD allele frequency (matched ancestry) values are determined based on participants' self-report Continental ancestry rather than genomic data.

Table B4. *CYP1B1* variants reported

Family ID	Participant ID	Pedigree ID	Hom/ Het	Chromosome position (NC_000002.11)	Exon	cDNA (NM_000104.4)	Protein alteration (NP_000095.2)	Variant type	gnomAD allele frequency	gnomAD allele frequency (matched ancestry)*	CADD Score	Phenotype
21	PCG001	21-II-2	Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	PCG
			Het	38298290_38298299dup	3	c.1200_1209dup	p.Thr404SerfsTer30	Frameshift	60/282448 (0.0002124)	30/128874 (0.0002328)	-	
22	PCG003	22-II-1	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	PCG
			Het	38298071A>G	3	c.1426T>C	p.Ser476Pro	Missense	nil	nil	24.5	
23	PCG040.0	23-I-1	Hom	38298299G>A	3	c.1198C>T	p.Pro400Ser	Missense	3/250896 (0.00001196)	2/30610 (0.00006534)	23.3	PCG
23	PCG040.4	23-III-1	Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	924/30444 (0.03035)	26.9	PCG
			Het	38298299G>A	3	c.1198C>T	p.Pro400Ser	Missense	3/250896 (0.00001196)	2/30610 (0.00006534)	23.3	
24	PCG042.0	24-III-1	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	PCG
			Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	
24	PCG042.1	24-III-2	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	OHT
			Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	
24	PCG042.2	24-I-2	Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	PCG
			Het	38298421_38298433del	3	c.1064_1076del	p.Arg355HisfsTer69	Frameshift	63/278058 (0.0002266)	46/126086 (0.0003648)	-	
25	PCG067	25-II-1	Het	38298338C>T	3	c.1159G>A	p.Glu387Lys	Missense	77/280602 (0.0002744)	58/127616 (0.0004545)	32	PCG
			Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	
26	PCG070.0	26-II-1	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	PCG
			Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	
26	PCG070.2	26-II-2	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	POAG
			Het	38298166C>T	3	c.1331G>A	p.Arg444Gln	Missense	4/282844 (0.00001414)	4/129174 (0.00003097)	26.1	
27	PCG074.0	27-II-1	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	PCG
			Het	38298421_38298433del	3	c.1064_1076del	p.Arg355HisfsTer69	Frameshift	63/278058 (0.0002266)	46/126086 (0.0003648)	-	
27	PCG074.1	27-II-2	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	PCG
			Het	38298421_38298433del	3	c.1064_1076del	p.Arg355HisfsTer69	Frameshift	63/278058 (0.0002266)	46/126086 (0.0003648)	-	

28	PCG077	28-II-1	Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	38/7162 (0.005306)	26.9	PCG
			Het	38301998del	2	c.535del	p.Ala179ArgfsTer18	Frameshift	9/187618 (0.00004797)	0/5464 (0.000)	-	
29	PCG079	29-II-2	Hom	38298092G>A	3	c.1405C>T	p.Arg469Trp	Missense	12/251470 (0.00004772)	0/6138 (0.000)	25.9	PCG
30	PCG087.0	30-II-2	Hom	38302350C>T	2	c.182G>A	p.Gly61Glu	Missense	67/229534 (0.0002919)	9/6226 (0.001446)	23.6	PCG
30	PCG087.2	30-I-2	Hom	38302350C>T	2	c.182G>A	p.Gly61Glu	Missense	67/229534 (0.0002919)	9/6226 (0.001446)	23.6	JOAG
30	PCG087.3	30-II-1	Hom	38302350C>T	2	c.182G>A	p.Gly61Glu	Missense	67/229534 (0.0002919)	9/6226 (0.001446)	23.6	JOAG
30	PCG087.4	30-II-3	Hom	38302350C>T	2	c.182G>A	p.Gly61Glu	Missense	67/229534 (0.0002919)	9/6226 (0.001446)	23.6	PCG
31	PCG088	31-II-1	Hom	38298092G>A	3	c.1405C>T	p.Arg469Trp	Missense	12/251470 (0.00004772)	8/113748 (0.00007033)	25.9	PCG
32	PCG099.0	32-II-1	Hom	38298187G>A	3	c.1310C>T	p.Pro437Leu	Missense	6/282822 (0.00002121)	1/129162 (0.000007742)	28.1	JOAG
32	PCG099.1	32-II-2	Hom	38298187G>A	3	c.1310C>T	p.Pro437Leu	Missense	6/282822 (0.00002121)	1/129162 (0.000007742)	28.1	JOAG
33	PCG114	33-II-3	Het	38298338C>T	3	c.1159G>A	p.Glu387Lys	Missense	77/280602 (0.0002744)	58/127616 (0.0004545)	32	PCG
			Het	38298290_38298299dup	3	c.1200_1209dup	p.Thr404SerfsTer30	Frameshift	60/282448 (0.0002124)	30/128874 (0.0002328)	-	
34	PCG121.0	34-II-4	Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	188/126236 (0.001489)	26.9	PCG
			Het	38297958_38297963del	3	c.1536_1541del	p.Pro513_Lys514del	Indel	3/251452 (0.00001193)	2/113760 (0.00001758)	-	
34	PCG121.1	34-II-2	Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	188/126236 (0.001489)	26.9	PCG
			Het	38297958_38297963del	3	c.1536_1541del	p.Pro513_Lys514del	Indel	3/251452 (0.00001193)	2/113760 (0.00001758)	-	
34	PCG121.4	34-II-3	Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	188/126236 (0.001489)	26.9	PCG
			Het	38297958_38297963del	3	c.1536_1541del	p.Pro513_Lys514del	Indel	3/251452 (0.00001193)	2/113760 (0.00001758)	-	
35	PCG129.0	35-II-1	Hom	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	924/30444 (0.03035)	26.9	PCG
35	PCG129.2	35-I-1	Hom	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	924/30444 (0.03035)	26.9	Unaffected
36	PCG132	36-II-1	Het	38298338C>T	3	c.1159G>A	p.Glu387Lys	Missense	77/280602 (0.0002744)	58/127616 (0.0004545)	32	PCG
			Het	38301669dup	2	c.868dup	p.Arg290ProfsTer37	Frameshift	7/264324 (0.00002648)	5/119150 (0.00004196)	-	
37	PCG152	37-II-2	Hom	38239356-38358664del	1-3	c.(?_-403)_(*1_?)del	-	Deletion	nil	nil	-	PCG
38	PCG156	38-II-1	Het	38298290_38298299dup	3	c.1200_1209dup	p.Thr404SerfsTer30	Frameshift	60/282448 (0.0002124)	30/128874 (0.0002328)	-	PCG
			Het	38298069_38298095dup	3	c.1403_1429dup	p.Arg468_Ser476dup	Indel	15/282876 (0.00005303)	14/129178 (0.0001084)	-	

39	PCG177	39-II-1	Het	38298421_38298433del	3	c.1064_1076del	p.Arg355HisfsTer69	Frameshift	63/278058 (0.0002266)	46/126086 (0.0003648)	-	PCG
			Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	188/126236 (0.001489)	26.9	
40	PCG195	40-II-2	Het	38302215G>T	2	c.317C>A	p.Ala106Asp	Missense	4/196722 (0.00002033)	4/87408 (0.0004576)	25.8	PCG
			Het	38301998del	2	c.535del	p.Ala179ArgfsTer18	Frameshift	9/187618 (0.0004797)	3/74416 (0.00004031)	-	
41	PCG207	41-II-1	Hom	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	924/30444 (0.03035)	26.9	PCG
42	PCG220	42-II-1	Hom	38298421_38298433del	3	c.1064_1076del	p.Arg355HisfsTer69	Frameshift	63/278058 (0.0002266)	3/7162 (0.0004189)	-	PCG
43	AG0180	43-II-1	Het	38301998del	2	c.535del	p.Ala179ArgfsTer18	Frameshift	9/187618 (0.0004797)	3/74416 (0.00004031)	-	JOAG
			Het	38298338C>T	3	c.1159G>A	p.Glu387Lys	Missense	77/280602 (0.0002744)	58/127616 (0.0004545)	32	
44	AG1751	44-II-1	Hom	38301669dup	2	c.868dup	p.Arg290ProfsTer37	Frameshift	7/264324 (0.00002648)	5/119150 (0.00004196)	-	JOAG
45	GFMC1912	45-III-1	Hom	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	38/7162 (0.005306)	26.9	JOAG
45	GFMC1912.2	45-II-3	Hom	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	38/7162 (0.005306)	26.9	PACG
46	AG1791	46-II-1	Hom	38301822G>T	2	c.710C>A	p.Ala237Glu	Missense	-	-	29.9	JOAG
47	GFMC0602	47-II-1	Het	38302226_38302255delinsCC	2	c.277_306delinsGG	p.Pro93GlyfsTer50	Frameshift	-	-	-	JOAG
			Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	188/126236 (0.001489)	26.9	
48	GFMC1026	48-II-1	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	JOAG
			Het	38298394C>T	3	c.1103G>A	p.Arg368His	Missense	1468/278430 (0.005272)	188/126236 (0.001489)	26.9	
49	ASD222	49-II-1	Het	38302361C>T	2	c.171G>A	p.Trp57Ter	Nonsense	42/233224 (0.0001801)	41/106368 (0.0003855)	37	PA
			Het	38298290_38298299dup	3	c.1200_1209dup	p.Thr404SerfsTer30	Frameshift	60/282448 (0.0002124)	30/128874 (0.0002328)	-	
50	GFMC1029	50-II-1	Het	38302350C>T	2	c.182G>A	p.Gly61Glu	Missense	67/229534 (0.0002919)	9/6226 (0.001446)	23.6	JOAG
			Het	38298092G>A	3	c.1405C>T	p.Arg469Trp	Missense	12/251470 (0.00004772)	0/6138 (0.000)	25.9	
51	AG3039	51-II-2	Hom	38298328C>T	3	c.1169G>A	p.Arg390His	Missense	10/281034 (0.00003558)	0/7188 (0.000)	32	PCG

Hom: homozygous; Het: heterozygous; gnomAD: Genome Aggregation Database; CADD: Combined Annotation-Dependent Depletion; PCG: primary congenital glaucoma; OHT: ocular hypertension; POAG: primary open angle glaucoma; JOAG: juvenile open-angle glaucoma; PACG: primary angle closure glaucoma; PA: Peters anomaly

*gnomAD allele frequency (matched ancestry) values are determined based on participants' self-reported Continental ancestry rather than genomic data.

Table B5. Reasons for not being able to obtain reliable Humphrey Visual Field testing (per eye) in participants aged >10 years

Reason for being unable to obtain reliable visual field test data	***CYP1B1*** **(n, %)**	***TEK*** **(n, %)**
BCVA <0.50 logMAR	35 (74.5)	6 (54.5)
Prosthetic eye	4 (8.5)	3 (27.3)
Nystagmus	2 (4.3)	0 (0.0)
Anxiety	2 (4.3)	0 (0.0)
Not performed for unknown reason	4 (8.5)	2 (18.2)
Total	47 (100.0)	11 (100.0)

Table B6. Comparison of clinical characteristics of eyes with *CYP1B1*-associated glaucoma and *TEK*-associated glaucoma in probands only

Clinical characteristic	*CYP1B1*	*TEK*	p-value	Adjusted for age at last examination
Sex, female	19/31 (61.3)	7/20 (35.0)	0.12[a]	-
Bilateral disease	31/31 (100.0)	17/20 (85.0)	0.05[b]	-
Age at diagnosis (years)*	0.1 (0–32)	0.5 (0–70)	0.14[c]	-
Age at last examination (years)*	32.3 (0.2–68.0)	48.0 (1.6–89.0)	0.09[c]	-
IOP at last examination (mmHg)	18 (14–22)	17 (12–21)	0.21[d]	0.48
IOP at diagnosis (mmHg)[†]	38 (28–40)	30 (24–37)	0.29[d]	-
Maximum-recorded IOP (mmHg)	40 (31–46)	29 (22–33)	**<0.001[d]**	**0.01**
BCVA (logMAR)	0.9 (0.3–2.1)	0.3 (0.0–0.6)	0.05[d]	**0.02**
BCVA <6/60[‡]	25/60 (41.7)	6/35 (17.1)	**0.048[d]**	**0.03**
Unable to obtain reliable visual field data among participants aged >10 years	41/53 (77.4)	10/28 (35.7)	**0.007[d]**	0.07
HVF mean deviation (decibels)	-3.36 (-4.69 – -0.36)	-1.80 (-6.39–0.50)	0.73[d]	0.72
Spherical equivalent (dioptres)	-2.5 (-7.25– -0.50)	-1.50 (-3.50–0.0)	0.09[d]	0.06
CCT (µm)	608 (556–665)	552 (532–572)	0.02[d]	0.16
Treatment characteristic per eye				
Had a glaucoma procedure	57/62 (91.9)	30/37 (81.1)	0.59[d]	0.84
Number of glaucoma procedures*	3 (0–31)	1 (0–16)	**0.03[d]**	0.30
Number of incisional glaucoma surgeries*	2 (0–7)	1 (0–5)	**0.03[d]**	0.25
Number of advanced surgical procedures*	2 (0–8)	1 (0–6)	**0.02[d]**	0.18
Glaucoma drainage device implanted	21/62 (33.9)	4/37 (10.8)	0.60[d]	0.70
Number of topical anti-glaucoma medications at last review	1 (1–2)	0 (0–2)	**0.01[d]**	**<0.001**
Complications[§]				
Enucleation, evisceration or phthisis bulbi	8/62 (12.9)	2/37 (5.4)	0.30[d]	**0.02**
Cataract	23/54 (42.6)	18/35 (51.4)	0.65[d]	0.27
Corneal disease	12/54 (22.2)	5/35 (14.3)	0.51[a†]	0.72

IOP: intraocular pressure; BCVA: best-corrected visual acuity, HVF: Humphrey Visual Field; CCT: central corneal thickness. Nonparametric continuous variables are presented as median (IQR) unless otherwise indicated (*).

*Data presented as a range. Bold values indicate statistical significance (p<0.05).

[a]Chi-square test with continuity correction, [b]Fisher exact test, [c]Mood's median test, [d]Linear mixed effect regression adjusting for the inclusion of two eyes of one individual,

[†]IOP at diagnosis was only available for 14 eyes with *CYP1B1*-associated glaucoma and 15 eyes with *TEK*-associated glaucoma.

[‡]LogMAR visual acuity testing was not possible in two eyes from an individual with *CYP1B1*-associated glaucoma as the eyes belonged to an infant. BCVA in two eyes with *TEK*-associated glaucoma were affected by age-related macular degeneration and were therefore excluded from this analysis.

[§]Enucleated eyes were excluded from analysis of cataract and corneal disease

[†]The variance explained by the random effect of the inclusion of both eyes from the same individual was incompatible with the linear mixed effect regression model

Table B7. Comparison of clinical characteristics per PCG-eye per gene in probands only

Clinical characteristic	*CYP1B1*-PCG	*TEK*-PCG	p-value	Adjusted for age at last examination
Sex, female	13/22 (59.1)	5/14 (35.7)	0.31[a]	-
Bilateral disease	22/22 (100.0)	11/14 (78.6)	0.05[b]	-
Age at diagnosis (months)*	0 (0–60)	3.2 (0–30)	**0.03[c]**	-
Age at last examination (years)*	28.2 (0.17–68)	40.4 (1.6–82.5)	0.73[c]	-
IOP at last examination (mmHg)	17 (13–21)	17 (13–21)	0.76[d]	0.98
IOP at diagnosis (mmHg)[‡]	30 (28–40)	33 (30–41)	0.54[d]	-
Maximum-recorded IOP (mmHg)	40 (31–47)	30 (24–38)	**0.01**[d]	**0.02**
BCVA (logMAR)	1.2 (0.6–2.7)	0.4 (0.0–0.8)	0.05[d]	**0.01**
BCVA <6/60[§]	22/42 (52.4)	6/25 (24.0)	0.05[d]	**0.01**
Unable to obtain reliable visual field data among participants aged >10 years	32/36 (88.9)	9/18 (50.0)	**0.003**[d]	**0.01**
HVF mean deviation (decibels)	-2.44 (-3.78 – -1.15)	-0.61 (-6.09–0.19)	0.60[d]	0.95
Spherical equivalent (dioptres)	-3.0 (-7.75 – -0.50)	-1.25 (-3.00–0.5)	0.06[d]	0.07
CCT (µm)	597 (549–694)	570 (539–580)	**0.17**[d]	0.27
Treatment characteristic per eye				
Had glaucoma procedure	43/44 (97.7)	24/25 (96.0)	0.68[d]	0.69
Number of drainage procedures*	5 (1–31)	2 (0–16)	**0.02[d]**	0.08
Number of incisional glaucoma surgeries*	3 (1–7)	1 (0–5)	**0.02[d]**	0.09
Number of advanced glaucoma procedures*	3 (1–8)	1 (0–6)	**0.02[d]**	**0.047**
Glaucoma drainage device implanted	17/44 (38.6)	4/25 (16.0)	0.62[d]	0.30
Number of topical anti-glaucoma medications at last review	1 (1–2)	0 (0–2)	**0.04[d]**	**0.006**
Complications[ŕ]				
Enucleation, evisceration or phthisis bulbi	8/44 (18.2)	2/25 (8.0)	0.27[d]	**0.047**
Cataract	19/36 (52.8)	10/23 (43.5)	0.45[d]	0.19
Corneal disease	9/36 (25.0)	4/23 (17.4)	0.89[d]	0.77

IOP: intraocular pressure; BCVA: best-corrected visual acuity, HVF: Humphrey Visual Field; CCT: central corneal thickness
Nonparametric continuous variables are presented as median (IQR) unless otherwise indicated (*).
*Data presented as a range. Bold values indicate statistical significance (p<0.05).
[a]Chi-square test with continuity correction, [b]Fisher exact test, [c]Mood's median test, [d]Linear mixed effect regression adjusting for the inclusion of two eyes of one individual.
[†]IOP at diagnosis was only available for 4 eyes with *CYP1B1*-PCG and 10 eyes with *TEK*-PCG.
[‡]LogMAR visual acuity testing was not possible in two eyes from an individual with *CYP1B1*-associated glaucoma as the eyes belonged to an infant. BCVA in two eyes with *TEK*-associated glaucoma were affected by age-related macular degeneration and were therefore excluded from this analysis.
[§]Enucleated eyes were excluded from analysis of cataract and corneal disease
[ŕ]The variance explained by the random effect of the inclusion of both eyes from the same individual was incompatible with the linear mixed effect regression model

Table B8. Demographic and clinical characteristics of participants with *CYP1B1*-associated glaucoma without the c.1103G>A (p.R368H) variant compared to *TEK*-associated glaucoma

Demographic characteristic	*CYP1B1* (n, %)	*TEK* (n, %)	p-value	Adjusted for age at last examination
Sex among all participants (F:M ratio; % female)	20:11 (64.5)	16:27 (37.2)	**0.04[a]**	**-**
Total participants with glaucoma	30/31 (96.8)	24/43 (55.8)	**0.003[b]**	**0.004**
Sex among participants with glaucoma (F:M ratio; % female)	20:10 (66.7)	8:16 (33.3)	**0.03[a]**	-
Self-reported ancestry (European)†	16/22 (72.7)	18/20 (90.0)	0.24[c]	-
Family history of glaucoma†	11/22 (50.0)	10/20 (50.0)	1.0[a]	-
Family history of PCG†	7/22 (31.8)	1/20 (5.0)	**0.047[c]**	-
Clinical characteristic				
Bilateral disease	30/30 (100.0)	18/24 (75.0)	**0.005[c‡]**	-
Age at diagnosis (years)*	0.2 (0.0–46.0)	0.3 (0–70)	0.14[b]	-
Age at last examination (years)*	35.5 (6.5–74.8)	46.4 (1.6–89.0)	0.27[d]	-
IOP at last examination (mmHg)	17 (12–21)	18 (14–2)	0.52[b]	0.69
IOP at diagnosis (mmHg)§	38 (30–40)	30 (23–37)	0.35[b]	-
Maximum-recorded IOP (mmHg)	38 (30–47)	30 (22–37)	**0.01[b]**	**0.03**
BCVA (logMAR)	0.90 (0.30–2.7)	0.2 (0.0–0.60)	**0.02[b]**	**0.01**
BCVA <20/200	25/54 (46.3)	7/40 (17.5)	**0.04[b]**	**0.03**
Unable to obtain reliable visual field data among participants aged >10 years	39/52 (75.0)	11/32 (34.4)	**0.005[b]**	**0.02**
HVF mean deviation (decibels)	-1.72 (-3.48–0.0)	-1.74 (-6.07–0.12)	0.83[b]	0.72
Spherical equivalent (dioptres)	-2.5 (-6.75–-0.50)	-1.00 (-3.25–0.0)	0.16[b]	0.14
CCT (µm)	621 (580–678)	548 (525–570)	**0.008[b]**	**0.03**
Treatment characteristic per eye				
Had glaucoma procedure	50/54 (92.6)	35/42 (83.0)	0.67[b]	0.79
Number of glaucoma procedures*	3 (0–31)	1 (0–16)	**0.03[b]**	0.12
Number of incisional glaucoma surgeries*	2 (0–7)	1 (0–5)	**0.04[b]**	0.08
Number of advanced glaucoma procedures*	2 (0–8)	1 (0–6)	**0.02[b]**	**0.04**
Glaucoma drainage device implanted	16/54 (29.6)	4/42 (9.5)	0.64[b]	0.62
Number of topical anti-glaucoma medications at last review	1 (1–2)	0 (0–1)	**0.005[b]**	**0.001**
Complications†				
Enucleation or evisceration	8/54 (14.8)	3/42 (7.1)	0.31[b]	0.09
Cataract	19/46 (41.3)	19/39 (48.7)	0.77[b]	0.82
Corneal disease	15/46 (32.6)	5/39 (12.8)	0.56[b]	-

PCG: primary congenital glaucoma; IOP: intraocular pressure; BCVA: best-corrected visual acuity; HVF: Humphrey Visual Field; CCT: central corneal thickness.

Nonparametric continuous variables are presented as median (IQR) unless otherwise indicated (*).

*Data presented as a range. Bold values indicate statistical significance (p<0.05).

Parametric continuous variables are presented as mean (standard deviation).
[a]Chi-square test with continuity correction, [b]Linear mixed effect regression adjusting for the inclusion of two eyes of one individual and the inclusion of multiple individuals from the same families, [c]Fisher exact test, [d]Mood's median test
[†]Values calculated for probands only
[‡]The variance explained by the random effect of family relatedness in the model was incompatible with the linear mixed effect regression model.
[§]IOP at diagnosis was only available for 8 eyes with *CYP1B1*-associated glaucoma and 16 eyes with *TEK*-associated glaucoma.
[ǂ]Enucleated eyes were excluded from analysis of cataract and corneal disease

Table B9. Differences in demographic and systemic features in participants with PCG and JOAG with and without a molecular diagnosis

	Primary congenital glaucoma				Juvenile open-angle glaucoma			
Characteristic†	**Molecular diagnosis**	**No molecular diagnosis**	**p-value**	**Adjusted p-value‡**	**Molecular diagnosis**	**No molecular diagnosis**	**p-value**	**Adjusted p-value‡**
Any systemic feature	21/24 (87.5)	22/27 (81.5)	0.71[c]	0.87	7/8 (87.5)	8/9 (88.9)	1.0[c]	0.64
Musculoskeletal and connective tissue	18/24 (75.0)	15/27 (55.6)	0.25[b]	0.24	7/8 (87.5)	3/9 (33.3)	0.05[c]	**0.007**
Skeletal abnormality	5/24 (20.8)	4/27 (14.8)	0.72[c]	0.50	1/8 (12.5)	0/9 (0.0)	0.47[c]	0.38
Tall stature	2/22 (9.1)	0/24 (0.0)	0.22[c]	0.08	1/6 (16.7)	0/8 (0.0)	0.43[c]	0.37
Short stature	2/22 (9.1)	2/24 (8.3)	1.0[c]	0.62	0/6 (0.0)	0/8 (0.0)	-	-
Other skeletal abnormality	1/24 (4.2)	2/27 (7.4)	1.0[c]	0.34	0/8 (0.0)	0/9 (0.0)	-	-
Cleft lip	0/21 (0.0)	0/27 (0.0)	-	-	0/7 (0.0)	0/9 (0.0)	-	-
Cleft palate	0/22 (0.0)	0/27 (0.0)	-	-	0/7 (0.0)	0/9 (0.0)	-	-
Joint abnormality	5/24 (20.8)	2/27 (7.4)	0.23[c]	0.42	2/8 (25.0)	0/9 (0.0)	0.21[c]	0.27
Joint hypermobility	2/24 (8.3)	1/27 (3.7)	0.60[c]	0.48	0/8 (0.0)	0/9 (0.0)	-	-
Arthritis	2/24 (8.3)	1/27 (3.7)	0.60[c]	0.95	1/8 (12.5)	0/9 (0.0)	0.47[c]	0.72
Other joint abnormality	1/24 (4.2)	0/27 (0.0)	0.47[c]	0.65	1/8 (12.5)	0/9 (0.0)	0.47[c]	0.40
Hernia	2/24 (8.3)	1/27 (3.7)	0.60[c]	0.87	1/8 (12.5)	0/9 (0.0)	0.47[c]	0.52
Bone fracture	12/24 (50.0)	11/28 (40.7)	0.70[b]	0.60[1]	3/8 (37.5)	3/9 (33.3)	1.0[c]	0.47[1]
Age at first bone fracture, years (median, IQR)	20.0 (11.0–41.0)	16.0 (5.5–25.5)	1.0[a]	0.67[1]	12.0 (11.5–18.5)	17.0 (11.5–17.5)	1.0[a]	0.76[2]
No. of bone fractures (median, IQR)	1 (1–3)	1 (1-2)	0.41[d]	0.30[1]	0 (0-1)	0 (0-1)	1.0[d]	0.86[1]
Genitourinary	5/24 (20.8)	2/27 (7.4)	0.23[c]	0.49	1/8 (12.5)	3/9 (33.3)	0.58[c]	0.16
Reproductive	3/24 (12.5)	1/27 (3.7)	0.33[c]	1.0	1/8 (12.5)	3/9 (33.3)	0.58[c]	0.16
Female sex	3/16 (18.8)	1/10 (10.0)	1.0[c]	-	1/5 (20.0)	3/4 (75.0)	0.21[c]	-
Male sex	0/8 (0.0)	0/17 (0.0)	-	-	0/3 (0.0)	0/5 (0.0)	-	-
Renal	3/24 (12.5)	1/27 (3.7)	0.33[c]	0.32	0/8 (0.0)	0/9 (0.0)	-	-
Dental anomalies	9/24 (37.5)	6/27 (22.2)	0.38[b]	0.54	2/8 (25.0)	3/9 (33.3)	1.0[c]	0.86
Missing teeth	3/24 (12.5)	4/27 (14.8)	1.0[c]	0.65	1/8 (12.5)	2/9 (22.2)	1.0[c]	0.46
Extra teeth	4/24 (16.7)	1/27 (3.7)	0.18[c]	0.34	0/8 (0.0)	0/9 (0.0)	-	-
Small teeth	2/24 (8.3)	1/27 (3.7)	0.60[c]	0.74	0/8 (0.0)	0/9 (0.0)	-	-
Abnormally shaped teeth	4/24 (16.7)	1/27 (3.7)	0.18[c]	0.20	1/8 (12.5)	2/9 (22.2)	1.0[c]	0.91
Other dental anomaly	3/24 (12.5)	2/27 (7.4)	0.66[c]	0.89	0/8 (0.0)	1/9 (11.1)	1.0[c]	0.80

Cardiovascular	1/24 (4.2)	0/27 (0.0)	0.47[c]	0.75	0/8 (0.0)	0/9 (0.0)	-	-
Cardiac defect	1/24 (4.2)	0/27 (0.0)	0.47[c]	0.75	0/8 (0.0)	0/9 (0.0)	-	-
Stroke or ministroke	0/24 (0.0)	0/27 (0.0)	-	-	0/8 (0.0)	0/9 (0.0)	-	-
Neurodevelopmental	9/24 (37.5)	9/27 (33.3)	0.99[b]	0.89	3/8 (37.5)	4/9 (44.4)	1.0[b]	0.91
Hydrocephalus	0/21 (0.0)	0/27 (0.0)	-	-	0/8 (0.0)	0/9 (0.0)	-	-
Developmental delay	1/23 (4.3)	3/26 (11.5)	0.61[c]	0.90	0/6 (0.0)	1/8 (11.1)	1.0[c]	1.0
Learning difficulty	1/24 (4.2)	0/27 (0.0)	0.47[c]	0.27	0/8 (0.0)	0/9 (0.0)	-	-
Behavioural disorder	0/24 (0.0)	0/27 (0.0)	-	-	0/8 (0.0)	0/9 (0.0)	-	-
Mental health issue or mood disorder	8/24 (33.3)	5/27 (18.5)	0.37[b]	0.55	3/8 (37.5)	3/9 (33.3)	1.0[c]	0.70
Anxiety	7/24 (29.2)	4/27 (14.8)	0.37[b]	0.55	3/8 (37.5)	1/9 (11.1)	0.29[c]	0.08
Depression	5/24 (20.8)	3/27 (11.1)	0.45[c]	0.76	1/8 (12.5)	1/9 (11.1)	1.0[c]	0.84
Other mental health issue or mood disorder	2/24 (8.3)	0/27 (0.0)	0.22[c]	0.24	0/8 (0.0)	1/9 (11.1)	1.0[c]	0.50
Other neurodevelopmental	2/24 (8.3)	1/27 (3.7)	0.60[c]	0.43	0/8 (0.0)	1/9 (11.1)	1.0[c]	0.50
Gastrointestinal	1/24 (4.2)	1/27 (3.7)	1.0[c]	0.38	0/8 (0.0)	0/9 (0.0)	-	-
Hearing loss	0/24 (0.0)	1/27 (3.7)	1.0[c]	0.60	1/8 (12.5)	2/9 (22.2)	1.0[c]	0.69
Hearing aid, yes	0/24 (0.0)	1/27 (3.7)	1.0[c]	0.60	1/8 (12.5)	0/9 (0.0)	0.47[c]	0.72
Age at time of hearing aid, years (median, IQR)	-	-	-	-	-	-	-	-
Skin abnormalities	0/24 (0.0)	1/27 (3.7)	1.0[c]	0.69	0/8 (0.0)	0/9 (0.0)	-	-
Diabetes	2/24 (8.3)	0/27 (0.0)	0.22[c]	0.50	0/8 (0.0)	0/9 (0.0)	-	-
Type 1	0/24 (0.0)	0/27 (0.0)	-	-	0/8 (0.0)	0/9 (0.0)	-	-
Type 2	2/24 (8.3)	0/27 (0.0)	0.22[c]	0.50	0/8 (0.0)	0/9 (0.0)	-	-
BMI overweight/obese	9/22 (40.9)	1/23 (4.3)	**0.004[c]**	**0.02**	2/6 (33.3)	1/8 (12.5)	0.54[c]	0.35
Cancer	1/24 (4.2)	1/27 (3.7)	1.0[c]	0.95	0/8 (0.0)	0/9 (0.0)	-	-
Sex hormone-related cancer[§]	0/24 (0.0)	0/27 (0.0)	-	-	0/8 (0.0)	0/9 (0.0)	-	-
Other cancer	1/24 (4.2)	1/27 (3.7)	1.0[c]	0.95	0/8 (0.0)	0/9 (0.0)	-	-
Redundant periumbilical skin	0/24 (0.0)	2/27 (7.4)	0.49[c]	0.54	0/8 (0.0)	0/9 (0.0)	-	-
Other systemic feature	2/24 (8.3)	1/27 (3.7)	0.60[c]	0.44	0/8 (0.0)	0/9 (0.0)	-	-

IQR: interquartile range; BMI: body mass index
Bold values indicate statistical significance (p<0.05)
[a]Median test, [b]Chi square with continuity correction, [c]Fisher exact test, [d]Mann-Whitney U test
[†]All values presented as n (%) unless otherwise specified.
[‡]All values adjusted for participant age at survey completion and sex.
[§]Includes breast, cervical and prostate cancer
[1]P values have been further adjusted for unilateral or bilateral BCVA <6/60
[2]Additional correction for unilateral or bilateral BCVA <6/60 was not possible as all individuals who reported a bone fracture did not have unilateral or bilateral BCVA <6/60

Table B10. Differences in systemic features between individuals with primary non-acquired childhood glaucoma (PCG or JOAG) compared to individuals with SG-O only

	Combined molecular and non-molecular diagnosis				Molecular diagnosis only				No molecular diagnosis[†]	
Characteristic[‡]	**Primary glaucoma**	**Secondary glaucoma**	**p-value**	**Adjusted p-value[§]**	**Primary glaucoma**	**Secondary glaucoma**	**p-value**	**Adjusted p value[§]**	**Primary glaucoma**	**Secondary glaucoma**
Total no. of participants	68	32	-	-	32	30	-	-	36	2
Age at survey completion, years (median, IQR)	28.5 (16.6–46.9)	25.8 (11.3–40.1)	0.83[a]	-	35.0 (20.6–50.7)	25.8 (12.5–39.0)	0.20[a]	-	24.4 (10.5–43.8)	34.2 (8.9–59.4)
Female sex	35/68 (51.5)	16/16 (50.0)	1.0[b]	-	21/32 (65.6)	14/30 (46.7)	0.21[b]	-	14/36 (38.9)	2/2 (100.0)
Any systemic feature	58/68 (85.3)	29/32 (90.6)	0.54[c]	0.44	28/32 (87.5)	28/30 (93.3)	0.67[c]	0.31	30/36 (83.3)	1/2 (50.0)
Musculoskeletal and connective tissue	43/68 (63.2)	19/32 (59.4)	0.88[b]	0.78	25/32 (87.1)	18/30 (60.0)	0.20[b]	0.22	18/36 (50.0)	1/2 (50.0)
Skeletal abnormality	10/68 (14.7)	10/32 (31.3)	0.10[b]	0.06	6/32 (18.8)	10/30 (33.3)	0.31[b]	0.28	4/36 (11.1)	0/2 (0.0)
Tall stature	3/60 (5.0)	4/26 (15.4)	0.19[c]	0.14	3/28 (10.7)	4/24 (16.7)	0.69[c]	0.74	0/32 (0.0)	0/2 (0.0)
Short stature	4/60 (6.7)	3/26 (11.5)	0.43[c]	0.47	2/28 (7.1)	3/24 (12.5)	0.65[c]	0.74	2/32 (6.3)	0/2 (0.0)
Other skeletal abnormality	3/68 (5.0)	4/32 (12.5)	0.21[c]	0.11	1/32 (3.1)	4/30 (13.3)	0.19[c]	0.08	2/36 (5.6)	0/2 (0.0)
Cleft lip	0/64 (0.0)	0/16 (0.0)	-	-	0/28 (0.0)	0/14 (0.0)	-	-	0/36 (0.0)	0/2 (0.0)
Cleft palate	0/65 (0.0)	0/15 (0.0)	-	-	0/29 (0.0)	0/13 (0.0)	-	-	0/36 (0.0)	0/2 (0.0)
Joint abnormality	9/68 (13.2)	10/16 (62.5)	**<0.001[c]**	**<0.001**	7/32 (21.9)	9/14 (64.3)	**0.008[c]**	**0.001**	2/36 (5.6)	1/2 (50.0)
Joint hypermobility	3/68 (4.4)	5/16 (31.3)	**0.005[c]**	**0.006**	2/32 (6.3)	5/14 (35.7)	**0.02[c]**	**0.02**	1/36 (2.8)	0/2 (0.0)
Arthritis	4/68 (5.9)	4/16 (25.0)	**0.04[c]**	**0.01**	3/32 (9.4)	3/14 (21.4)	0.35[c]	0.10	1/36 (2.8)	1/2 (50.0)
Other joint abnormality	2/68 (2.9)	1/16 (6.3)	0.47[c]	0.47	2/32 (6.3)	1/14 (7.1)	1.0[c]	0.61	0/36 (0.0)	0/2 (0.0)
Hernia	4/68 (5.9)	6/32 (18.8)	0.07[c]	**0.02**	3/32 (9.4)	5/30 (16.7)	0.47[c]	0.28	1/36 (2.8)	1/2 (50.0)
Bone fracture	29/68 (42.6)	4/16 (25.0)	0.31[b]	0.20[1]	15/32 (46.9)	4/14 (28.6)	0.40[b]	0.28[1]	14/36 (38.9)	0/2 (0.0)
Age at first bone fracture, years (median, IQR)	16.0 (10.0–28.0)	33.5 (23.5–35.5)	0.55[a]	0.18[1]	16.0 (11.0–30.0)	33.5 (23.5–35.5)	0.30[a]	0.12[1]	16.5 (6.0–23.0)	-

No. of bone fractures (median, IQR)	0 (0–1)	0 (0–1)	0.31[a]	0.32[2]	0 (0–1)	0 (0–1)	0.40[d]	0.95[2]	0 (0–1)	0 (0–0)
Genitourinary	11/68 (16.2)	4/16 (25.0)	0.47[c]	0.39	6/32 (18.2)	4/14 (28.6)	0.47[c]	0.17	5/36 (13.9)	0/2 (0.0)
Reproductive	8/68 (11.8)	2/16 (12.5)	1.0[c]	0.98	4/32 (12.5)	2/14 (14.3)	1.0[c]	0.48	4/36 (11.1)	0/6 (0.0)
Female sex	8/35 (22.9)	2/10 (20.0)	1.0[c]	-	4/21 (19.0)	2/8 (25.0)	1.0[c]	-	4/14 (28.6)	0/2 (0.0)
Male sex	0/33 (0.0)	0/6 (0.0)	-	-	0/11 (0.0)	0/6 (0.0)	-	-	0/22 (0.0)	0/0 (0.0)
Renal	4/68 (5.9)	2/16 (12.5)	0.32[c]	0.29	3/32 (9.4)	2/14 (14.3)	0.63[c]	0.48	1/36 (2.8)	0/2 (0.0)
Dental anomalies	20/68 (29.4)	14/32 (43.8)	0.24[b]	0.13	11/32 (34.4)	13/30 (43.3)	0.64[b]	0.44	9/36 (25.0)	1/2 (50.0)
Missing teeth	10/68 (14.7)	11/32 (34.4)	**0.047[b]**	**0.02**	4/32 (12.5)	10/30 (33.3)	0.10[b]	**0.049**	6/36 (16.7)	1/2 (50.0)
Extra teeth	5/68 (7.4)	0/32 (0.0)	0.17[c]	0.16	4/32 (12.5)	0/30 (0.0)	0.11[c]	0.13	1/36 (2.8)	0/2 (0.0)
Small teeth	3/68 (4.4)	8/32 (25.0)	**0.004[c]**	**0.002**	2/32 (6.3)	8/30 (26.7)	**0.04[c]**	**0.04**	1/36 (2.8)	0/2 (0.0)
Abnormally shaped teeth	8/68 (11.8)	1/32 (3.1)	0.27[c]	0.19	5/32 (15.6)	1/30 (3.3)	0.20[c]	0.06	3/36 (8.3)	0/2 (0.0)
Other dental anomaly	6/68 (8.8)	6/32 (18.8)	0.19[c]	0.16	3/32 (9.4)	6/30 (20.0)	0.29[c]	0.23	3/36 (8.3)	0/2 (0.0)
Cardiovascular	1/68 (1.5)	8/32 (25.0)	**<0.001[c]**	**<0.001**	1/32 (3.1)	8/30 (26.7)	**0.01[c]**	**0.02**	0/36 (0.0)	0/2 (0.0)
Cardiac defect	1/68 (1.5)	7/32 (21.9)	**0.001[c]**	**0.001**	1/32 (3.1)	7/30 (23.3)	**0.02[c]**	**0.04**	0/36 (0.0)	0/2 (0.0)
Stroke or ministroke	0/68 (0.0)	1/32 (3.1)	0.32[c]	0.24	0/32 (0.0)	1/30 (3.3)	0.48[c]	0.58	0/36 (0.0)	0/2 (0.0)
Neurodevelopmental	25/68 (36.8)	15/32 (46.9)	0.46[b]	0.33	12/32 (37.5)	14/30 (46.7)	0.63[b]	0.48	13/36 (36.1)	1/2 (50.0)
Hydrocephalus	0/64 (0.0)	2/32 (6.3)	0.11[c]	0.09	0/28 (0.0)	2/30 (6.7)	0.49[c]	0.48	0/36 (0.0)	0/2 (0.0)
Developmental delay	5/64 (7.8)	4/18 (22.2)	0.10[c]	0.07	1/29 (3.4)	4/16 (25.0)	**0.047[c]**	0.11	4/35 (11.4)	0/2 (0.0)
Learning difficulty	1/68 (1.5)	5/32 (15.6)	**0.01[c]**	**0.01**	1/32 (3.1)	5/30 (16.7)	0.10[c]	0.18	0/36 (0.0)	0/2 (0.0)
Behavioural disorder	0/68 (0.0)	3/17 (17.6)	**0.007[c]**	**0.004**	0/32 (0.0)	2/15 (13.3)	0.10[c]	0.09	0/36 (0.0)	1/2 (50.0)
Mental health issue or mood disorder	19/68 (27.9)	9/18 (50.0)	0.09[b]	0.08	11/32 (34.4)	9/16 (56.3)	0.26[c]	0.12	8/36 (22.2)	0/2 (0.0)
Anxiety	15/68 (22.1)	7/18 (38.9)	0.22[c]	0.16	10/32 (31.3)	7/16 (43.8)	0.59[b]	0.41	5/36 (13.9)	0/2 (0.0)
Depression	10/68 (14.7)	5/18 (27.8)	0.29[c]	0.18	6/32 (18.8)	5/16 (31.3)	0.47[c]	0.22	4/36 (11.1)	0/2 (0.0)

Other mental health issue or mood disorder	3/68 (4.4)	1/18 (5.6)	1.0[c]	0.77	2/32 (6.3)	1/16 (6.3)	1.0[c]	0.80	1/36 (2.8)	0/2 (0.0)
Other neurodevelopmental	4/68 (5.9)	1/32 (3.1)	1.0[c]	0.66	2/32 (6.3)	1/30 (3.3)	1.0[c]	0.49	2/36 (5.6)	0/2 (0.0)
Gastrointestinal	2/68 (2.9)	2/32 (6.3)	0.59[c]	0.35	1/32 (3.1)	2/30 (6.7)	1.0[c]	0.48	1/36 (2.8)	0/2 (0.0)
Hearing loss	4/68 (5.9)	8/32 (25.0)	**0.02[c]**	**0.004**	1/32 (3.1)	8/30 (26.7)	**0.01[c]**	**0.01**	3/36 (8.3)	0/2 (0.0)
Hearing aid, yes	2/68 (2.9)	2/27 (7.4)	0.32[c]	0.17	1/32 (3.1)	2/25 (8.0)	0.58[c]	0.30	1/36 (2.8)	0/2 (0.0)
Age at time of hearing aid, years (median, IQR)	65.5 (63.0–68.0)	16.0 (4.0–28.0)	0.33[a]	**-**	-	16.0 (4.0–28.0)	-	-	-	-
Skin abnormalities	1/68 (1.5)	1/16 (6.3)	0.35[c]	0.24	0/32 (0.0)	1/14 (7.1)	0.30[c]	0.13	1/36 (2.8)	0/2 (0.0)
Diabetes	2/68 (2.9)	1/16 (6.3)	0.47[c]	0.60	2/32 (6.3)	1/14 (7.1)	1.0[c]	0.56	0/36 (0.0)	0/2 (0.0)
Type 1	0/68 (0.0)	0/16 (0.0)	-	-	0/32 (0.0)	0/14 (0.0)	-	-	0/36 (0.0)	0/2 (0.0)
Type 2	2/68 (2.9)	1/16 (6.3)	0.47[c]	0.60	2/32 (6.3)	1/14 (7.1)	1.0[c]	0.56	0/36 (0.0)	0/2 (0.0)
BMI overweight/obese	13/59 (22.0)	11/23 (57.8)	**0.04[b]**	**0.02**	11/28 (39.3)	10/21 (47.6)	0.77[b]	0.35	2/31 (6.5)	1/2 (50.0)
Cancer	2/68 (2.9)	0/16 (0.0)	1.0[c]	0.88	1/32 (3.1)	0/14 (0.0)	1.0[c]	0.94	1/36 (2.8)	0/2 (0.0)
Sex hormone-related cancer[¶]	0/68 (0.0)	0/16 (0.0)	-	-	0/32 (0.0)	0/14 (0.0)	-	-	0/36 (0.0)	0/2 (0.0)
Other cancer	2/68 (2.9)	0/16 (0.0)	1.0[c]	0.88	1/32 (3.1)	0/14 (0.0)	1.0[c]	0.94	1/36 (2.8)	0/2 (0.0)
Redundant periumbilical skin	2/68 (2.9)	9/32 (28.1)	**<0.001[c]**	**0.001**	0/32 (0.0)	9/30 (30.0)	**<0.001[c]**	**0.001**	2/36 (5.6)	0/2 (0.0)
Other systemic feature	3/68 (4.4)	3/32 (9.4)	0.38[c]	0.32	2/32 (6.3)	3/30 (10.0)	0.67[c]	0.75	1/36 (2.8)	0/2 (0.0)

IQR: interquartile range; BMI: body mass index
Bold values indicate statistical significance (p<0.05)
[a]Median test, [b]Chi square with Yates continuity correction, [c]Fisher exact test, [d]Mann-Whitney U test
[†]Statistical testing was not performed due to the small number of participants with SG-only without a molecular diagnosis (n=2)
[‡]Values presented as n (%) unless otherwise specified.
[§]All values adjusted for participant age at survey completion and sex.
[¶]Includes breast, cervical and prostate cancer
[1]P values have been further adjusted for unilateral or bilateral BCVA <6/60

Table B11. Characteristics of children who were interviewed compared to individuals who could not be contacted or declined participation

Characteristic	Individuals enrolled and interviewed, n (%)† (n=18)	Could not be contacted or declined participation, (n, %)† (n=36)	p-value
Current age, years (median [IQR])	12.1 (9.7–14.5)	14.2 (11.4–16.0)	0.14[a]
Current age, ≥13 years	8 (44)	21 (58)	0.50[b]
Years at diagnosis (median [IQR])	0.5 (0.2–4.0)	0.5 (0.0–4.8)	0.89[a]
Age at diagnosis, ≥4 years	5 (28)	10 (28)	1.00[b]
Years since diagnosis (median [IQR])	9.8 (7.3–13.6)	11.2 (8.5–13.7)	0.72[a]
Gender, female	6 (33)	17 (47)	0.50[b]
Laterality of glaucoma, bilateral	11 (61)	34 (94)	**0.004**[c]
Self-reported ancestry, European	16 (89)	21 (60)*	0.06[b]
Glaucoma subtype, primary**	12 (67)	28 (78)	0.51[c]
BCVA better eye, impaired (<6/12)	3 (17)	6 (17)	1.00[c]
Molecular diagnosis identified	9 (50)	9 (25)	0.13[b]
Family history, first degree	4 (22)	17 (49)*	0.12[b]

IQR: interquartile range; BCVA: best-corrected visual acuity
Bold values indicate statistical significance (p<0.05)
†Values presented as n (%) presented unless otherwise specified
[a]Mann-Whitney U test, [b]Chi-square test with Yates' correction for continuity, [c]Fisher exact test
*Data missing for one individual (n=1)
**Primary glaucoma includes primary congenital glaucoma and juvenile open-angle glaucoma

Table B12. Characteristics of adults with childhood glaucoma who enrolled and were interviewed compared to those who could not be contacted or declined participation

Characteristic	Individuals enrolled and interviewed, n (%)† (n=47)	Could not be contacted or declined participation, (n, %)† (n=83)	p-value
Current age, years (mean [SD])	40.0±15.3	40.2±16.9	0.75[a]
Age at diagnosis, <4 years	30 (64)	43 (52)	0.25[b]
Years since diagnosis (median [IQR])	34 (23–50)	31 (20–48)	0.46[a]
Gender, female	26 (55)	34 (41)	0.16[b]
Laterality of glaucoma, bilateral	43 (92)	78 (94)	0.86[b]
Self-reported ancestry, European	40 (85)	67 (81)	0.51[b]
Glaucoma subtype, primary*	38 (81)	68 (82)	1.0[b]
Glaucoma severity of the better eye, advanced	15 (32)	21 (25)	0.55[b]
Bilateral BCVA <6/60	9 (19)	11 (13)	0.52[b]
Molecular diagnosis identified	27 (57)	34 (41)	0.10[b]
Family history, first degree	17 (36)	43 (52)	0.13[b]

SD: standard deviation; IQR: interquartile range
†Values presented as n (%) presented unless otherwise specified
[a]Mann-Whitney U test, [b]Chi-square test with Yates' correction for continuity
*Primary glaucoma includes primary congenital glaucoma and juvenile open-angle glaucoma

Table B13. Best-corrected visual acuity per caregivers' first child with childhood glaucoma per eye

Vision category	BCVA	Better Eye BCVA n (%)	Worse Eye BCVA n (%)
No vision impairment	≥6/12	22 (63)	14 (40)
Mild vision impairment	<6/12 – ≥6/18	5 (14)	5 (14)
Moderate vision impairment	<6/18 – ≥6/60	4 (11)	4 (11)
Severe vision impairment or blindness	<6/60 – ≥6/120	0 (0)	4 (11)
Blindness	<6/120 – CF	1 (3)	2 (6)
	HM or LP	0 (0)	1 (3)
	NLP	0 (0)	2 (6)
Unable to be formally assessed due to young age	n/a	3 (9)	3 (9)

BCVA: Best-corrected visual acuity; CF: count fingers; HM: hand movements; LP: light perception; NLP: no light perception; n/a: not applicable

Table B14. Cognitive interviewee characteristics

Cognitive interviewee	Interview time (minutes)	Gender	Age (years)	Glaucoma subtype	Impaired BCVA	Able to drive motor vehicle	Current medications	Marital status	Employment status	Has children	Receives public or private healthcare
#1	137	M	31	SG-O (Aniridia)	BE	No	1	Married	Employed	Yes	Public
#2	124	F	60	PCG	BE	No	0	Married	Unemployed	Yes	Private
#3	175	M	32	SG-O (ARS)	BE	No	0	Never married	Employed	No	Public
#4	181	F	34	PCG	BE	No	0	De facto	Employed	Yes	Public
#5	170	M	57	PCG	BE	No	2	De facto	Employed	No	Private
#6	185	F	47	PCG	RE	Yes	2	Divorced	Employed	Yes	Private
#7	114	M	20	PCG	RE	Yes	1	Never married	Employed	No	Public
#8	138	F	50	PCG	LE	Yes	0	Married	Employed	Yes	Private
#9	175	F	52	JOAG	-	No	1	Married	Employed	Yes	Private
#10	228	M	28	JOAG	-	No	0	Never married	Employed (and a student)	No	Private
#11	52	F	34	PCG	-	Yes	1	Never married	Employed	Yes	Public
#12	70	M	41	PCG	LE (prosthetic)	Yes	2	Married	Employed	Yes	Private

BCVA: best-corrected visual acuity; M: male; SG-O: secondary glaucoma associated with a non-acquired ocular anomaly; BE: both eyes; F: female; PCG: primary congenital glaucoma; ARS: Axenfeld-Rieger syndrome; RE: right eye; LE; left eye; JOAG: juvenile open-angle glaucoma

Table B15. Items in the childhood glaucoma QoL PROM with corresponding number values (items 1–112) and items in the Coping PROM (items 113–131)

No	Item	No	Item	No	Item
-	**(Symptoms)**	-	**(Activity limitations)**	53	Maintaining your current romantic relationships
1	Blurred vision (F)	28	Doing daily exercise	54	Attending events or social gatherings
2	Contrast (F)	29	Reading things from a distance	55	With people treating you unfairly
3	Difficulty with depth perception (F)	30	Reading things up close	56	Taking care of your family
4	Difficulty adjusting to light and dark conditions (F)	31	Driving during the day	57	Taking care of your pet/s
5	Difficulty seeing at night (F)	32	Driving at night	58	Getting help and support from your family
6	Trouble with glare (F)	33	Watching a film or cinema or seeing a play at the theatre	59	Getting help and support from your friends
7	Uncomfortable or sore eyes (F)	34	Watching a TV programme or movie on your preferred electronic device	60	Getting help and support from your workplace or place of study
8	Eye strain (F)	35	Doing the household cleaning	61	Getting help and support from government or social services
9	Headaches (F)	36	Cooking and preparing meals	-	**(Inconveniences)**
10	Blurred vision (S)	37	Pursuing your hobby	62	The amount of time you have to spend at eye appointments
11	Contrast (S)	38	Recognising people's face	63	How often you need to go to an eye appointment
12	Difficulty with depth perception (S)	39	Finding something in a cluttered space	64	Scheduling an appointment
13	Difficulty adjusting to light and dark conditions (S)	-	**(Mobility)**	65	Getting to and from eye appointments
14	Difficulty seeing at night (S)	40	Navigating crowded places	66	Undergoing the same eye tests at a glaucoma appointment (e.g., visual field test, vision test)
15	Trouble with glare (S)	41	Moving around in unfamiliar environments	67	Wearing glasses
16	Uncomfortable or sore eyes (S)	42	Finding landmarks	68	Wearing contact lenses
17	Eye strain (S)	43	Noticing objects or people on your side	69	Wearing sunglasses
18	Headaches (S)	44	Using public transport	70	Using eye drops
19	Blurred vision (I)	45	Getting around at night	71	Making text in an accessible format (e.g., making it larger to read or converting text to speech)
20	Contrast (I)	46	Getting around on sunny days or in bright conditions	72	Taking longer to perform a task
21	Difficulty with depth perception (I)	47	Crossing the road	73	Relying on public transport or taxis to get places
22	Difficulty adjusting to light and dark conditions (I)	48	Going up or down stairs, steps or street curbs	74	Getting approvals to keep your driver's licence
23	Difficulty seeing at night (I)	-	**(Social well-being)**	-	**(Economic)**
24	Trouble with glare (I)	49	Meeting new people	75	The cost associated with seeing your eye specialist
25	Uncomfortable or sore eyes (I)	50	Making friends	76	The cost of your glaucoma medication (e.g., eye drops)
26	Eye strain (I)	51	Interacting socially with people you already know	77	The cost of your glaucoma surgery, laser surgery or prosthetic eye/s
27	Headaches (I)	52	Maintaining your friendships	78	The cost of your glasses

79	The cost of vision aids (e.g., magnifier, CCTV)	**97**	Your personal safety (e.g., having an accident, tripping over)	**114**	Allow yourself to express what you are feeling (e.g., grief, frustration, sadness)
80	The cost of assisted travel (e.g., taxi or rideshare)	**98**	Losing your driver's license	**115**	Compare your situation to others
81	What career or job you can do (e.g., jobs that require a driver's license or visually demanding jobs)	**99**	Losing your independence	**116**	Learn from or relate to someone else with a similar eye condition or vision impairment
82	Your ability to do work tasks being impacted by your glaucoma	**100**	Passing on your glaucoma to your child/potential child	**117**	Be open with people about your glaucoma
83	Losing your job or work duties	**-**	**(Emotional well-being)**	**118**	Try not to think about your glaucoma
84	Losing your source of income	**101**	Down or low	**119**	Do activities that may be considered healthy to take your mind off your condition (e.g., exercise, meditation, writing)
-	**(Health concerns)**	**102**	Scared	**120**	Do activities that may be considered unhealthy to take your mind off your condition (e.g., alcohol or drug use, eating comfort foods)
85	The control of your eye pressure	**103**	Disadvantaged	**121**	Ignore your glaucoma treatment (e.g., eye drops)
86	Losing your vision	**104**	Frustrated	**122**	Avoid going to your eye appointments
87	Your glaucoma getting worse or glaucoma affecting your better eye	**105**	Misunderstood	**123**	Have faith or trust in your ophthalmologist or treatment
88	Developing a different eye disease or condition (e.g., cataracts)	**106**	Like a burden	**124**	Have a good relationship with your ophthalmologist
89	Changing eye doctor	**107**	Isolated or alone	**125**	Get professional support for your mental health (e.g., psychologist, social worker)
90	Using your glaucoma medication correctly	**108**	Regretful about your eye care in the past	**126**	Get support from friends, family, support group or personal carer
91	Being on long-term medication	**109**	Suicidal	**127**	Try to have a positive outlook on life
92	Needing future eye surgery	**110**	Self-conscious	**128**	Use humour or make light of a situation
93	Something damaging or touching your eye/s (e.g., an injury, corneal scratch)	**111**	Anxious or stressed	**129**	Try to find ways to adapt to your eye condition or vision loss (e.g., using vision aids, relying on your memory)
94	The appearance of your eye	**112**	Like asking yourself, "Why me?"	**130**	Try to maintain your independence
95	Your overall appearance (e.g., applying make-up, shaving, dressing yourself)	**-**	**(Coping)**	**131**	Volunteer or help someone else
96	Maintaining good personal hygiene (e.g., bathing, cutting your nails)	**113**	Accept that you have glaucoma		

(F): symptom frequency; (S): symptom severity; (I): symptom impact

Table B16. Results of the Rasch analysis for items within each subscale/theme of the childhood glaucoma-specific QoL PROM

	Symptoms		Activity limitations		Mobility		Social well-being		Inconveniences		Economic		Health concerns		Emotional well-being	
	Pre-Rasch	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**	**Pre-Rasch**	**Post-Rasch**
Number of items	27	6	12	4	9	3	13	4	13	6	10	4	13	6	9	7
Ordered thresholds (Yes/No)	**No**	Yes	**No**	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	**No**	Yes
Person separation index	2.99	2.74	2.54	**1.61**	2.44	2.44	**1.38**	**1.83**	**1.86**	**1.75**	**1.47**	**1.38**	2.24	**1.73**	**1.81**	**1.62**
Targeting	0.66	0.34	**1.42**	**0.58**	**2.34**	**4.65**	**3.77**	**6.34**	**1.45**	**2.07**	**1.13**	**1.63**	0.27	0.21	**2.45**	**1.86**
Raw variance explained by the measures (%)	**47.1**	62.9	72.3	**49.8**	71.0	84.2	52.9	75.6	**44.5**	56.6	51.3	57.9	50.2	58.1	64.7	56.4
Eigenvalue of the first contrast	**5.7**	**2.3**	**2.5**	**1.6**	**2.2**	1.5	**2.7**	1.7	**2.8**	1.7	**2.8**	1.4	**2.7**	1.7	**2.1**	1.8
Number of misfitting items	**6**	0	**4**	0	**6**	0	**7**	0	**2**	0	**1**	0	**6**	0	**6**	0
Differential item functioning present (Yes/No)	No	No	**Yes**	No	No	No	**Yes**	No	No	No	No	No	No	No	No	No
Meets Rasch parameters after addressing above errors (Yes/No)	No		No		No		No		No		No		No		No	

Bold values indicate errors with the Rasch model.

APPENDIX C: SUPPLEMENTARY FIGURES

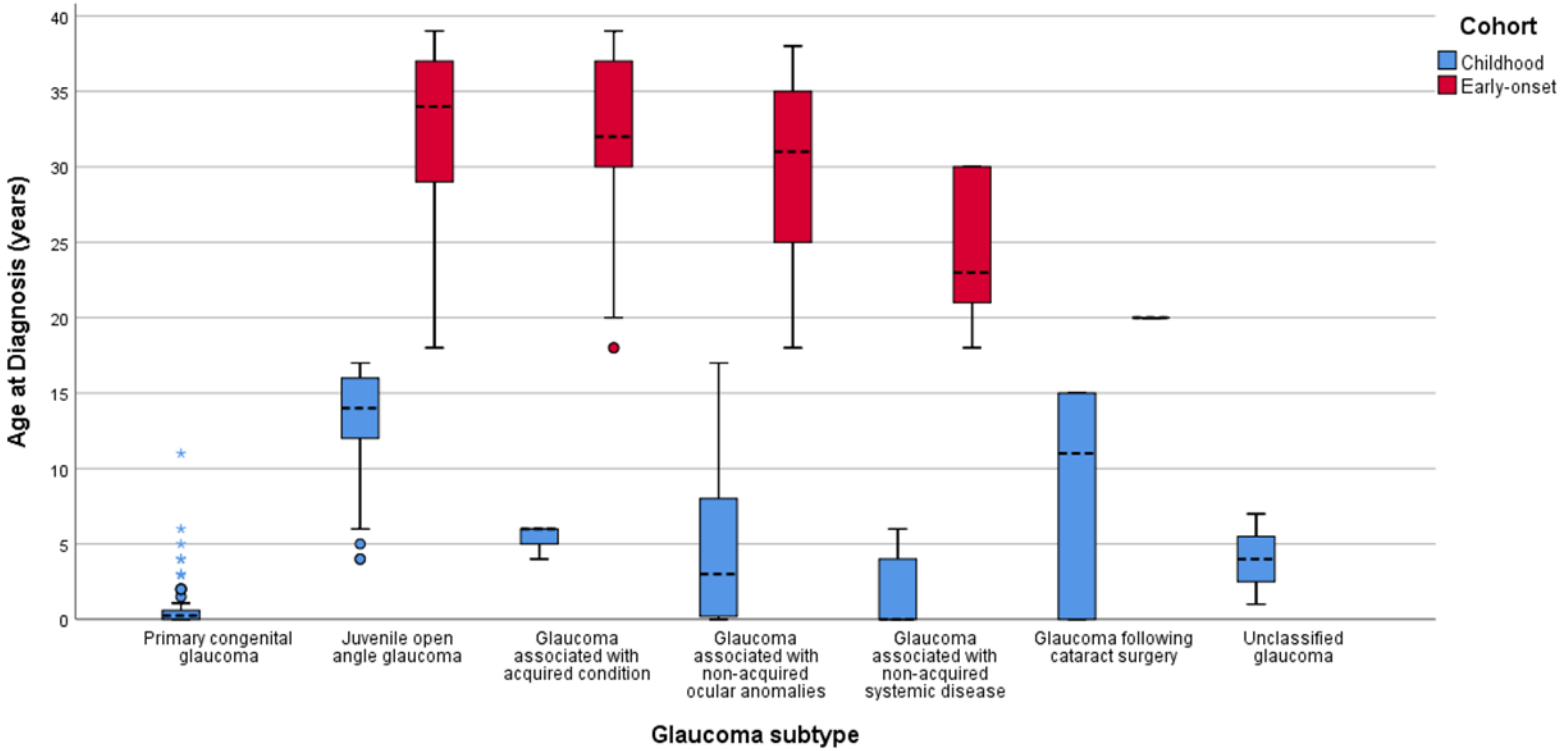


Figure C1. Age at diagnosis in childhood and early-onset glaucoma cohorts
Box and whisker plot for the age at diagnosis (years) per glaucoma subtype per cohort.
Key: - - - median, ⌶ non-outlier range, ■ ■ interquartile range (25%-75%), ∘ outliers, ✶ extremes. Outliers are cases that have values between 1.5 and 3 times the interquartile range and extreme values are cases with values more than 3 times the interquartile range. Extreme values here include individuals with late-onset or late-diagnosis of PCG and the individual with Knobloch syndrome (diagnosed age 11 years).

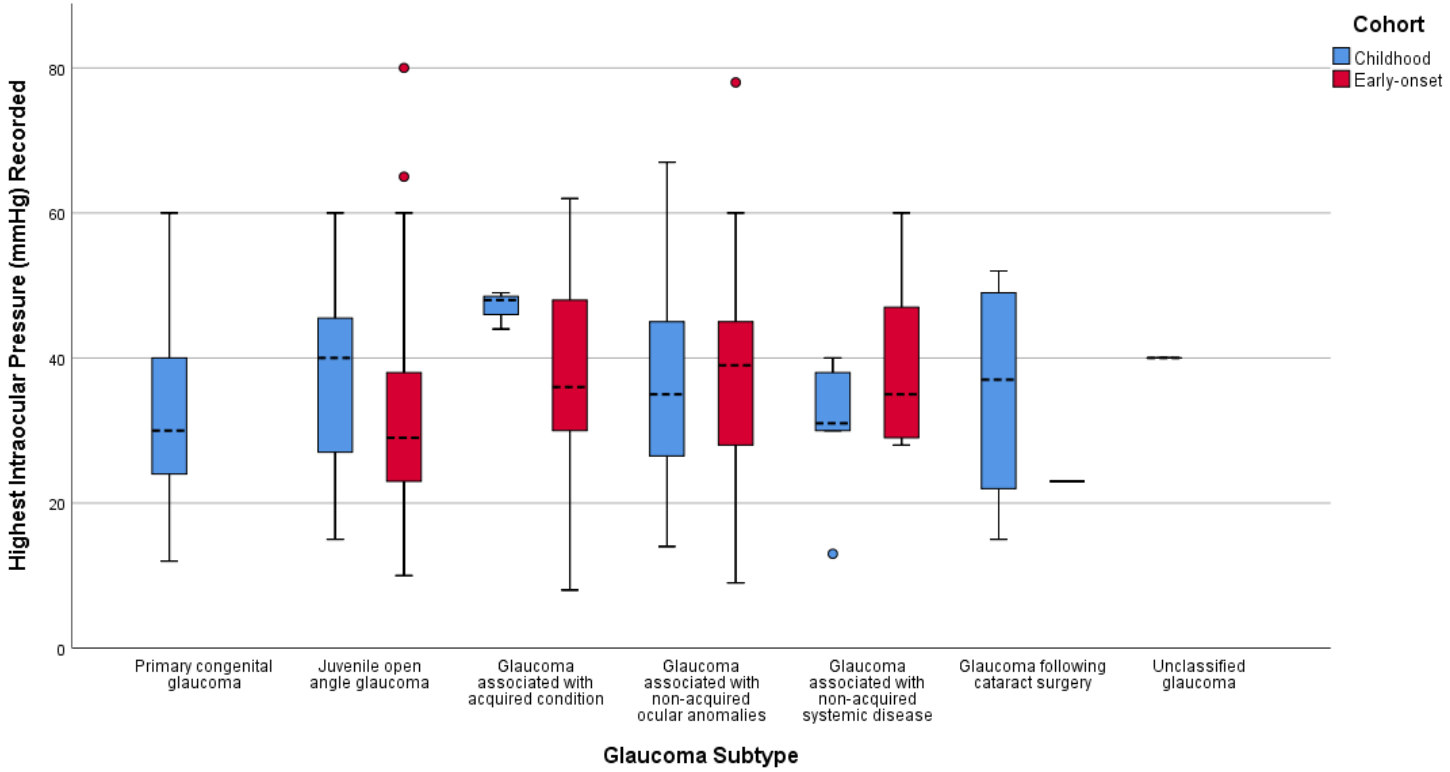


Figure C2. Highest intraocular pressure (mmHg) recorded in childhood and early-onset cohorts

Box and whisker plot for the highest intraocular pressure (mmHg) per glaucoma subtype per cohort.

Key: - - - median, ⌶ non-outlier range, ■ ■ interquartile range (25%-75%), ∘ outliers. Outliers are cases that have values between 1.5 and 3 times the interquartile range.

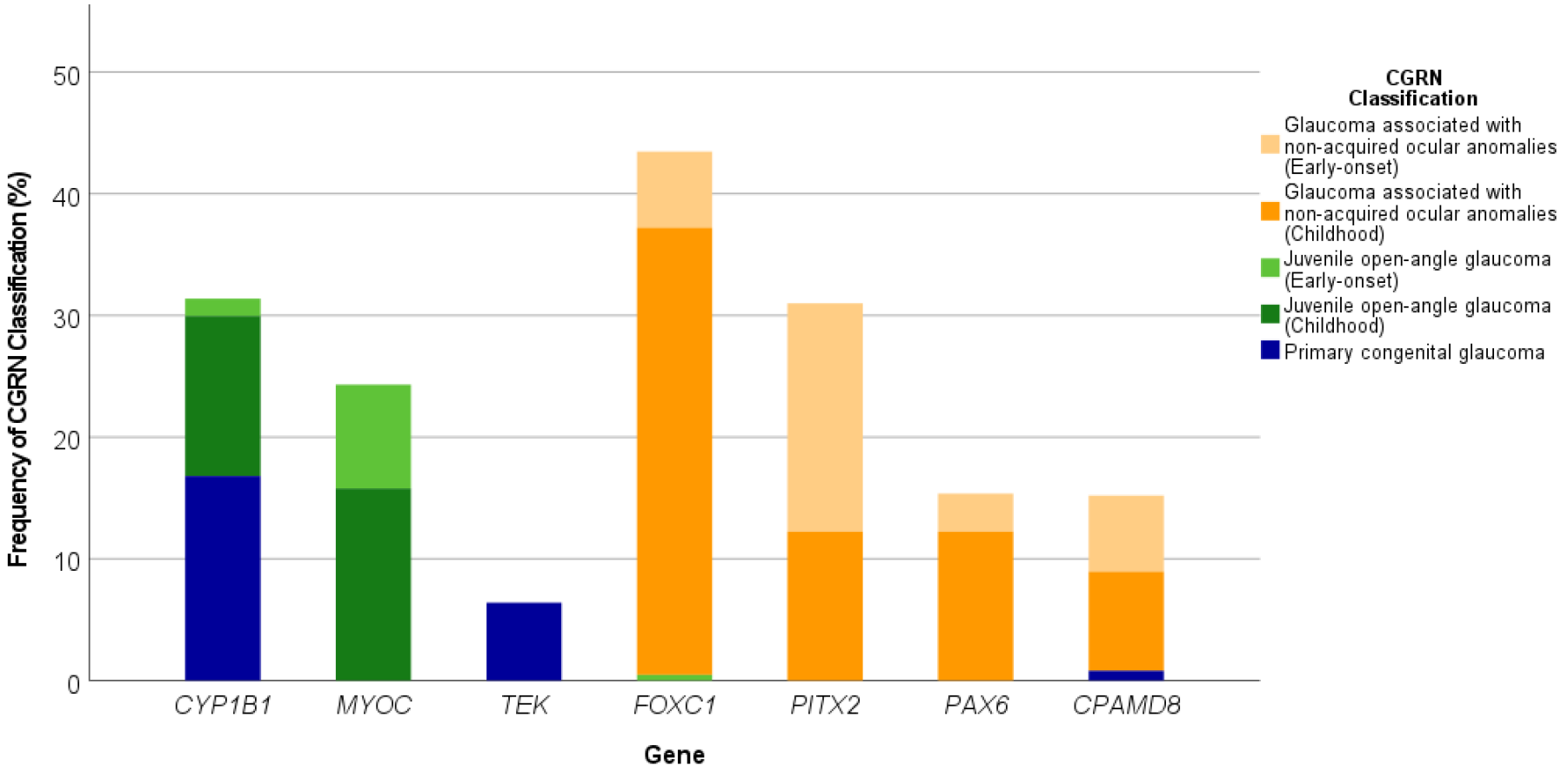


Figure C3. Frequencies of CGRN classification in tested probands stratified by the molecular diagnosis (after reclassification post-genetic diagnosis)

The genes reported in the figure include those where >3 probands reported variants in that gene. The genes reported were not found in any individual with the classification of glaucoma associated with acquired conditions, glaucoma associated with non-acquired systemic disease, glaucoma following cataract surgery and unclassified glaucoma classifications.

CGRN: Childhood Glaucoma Research Network

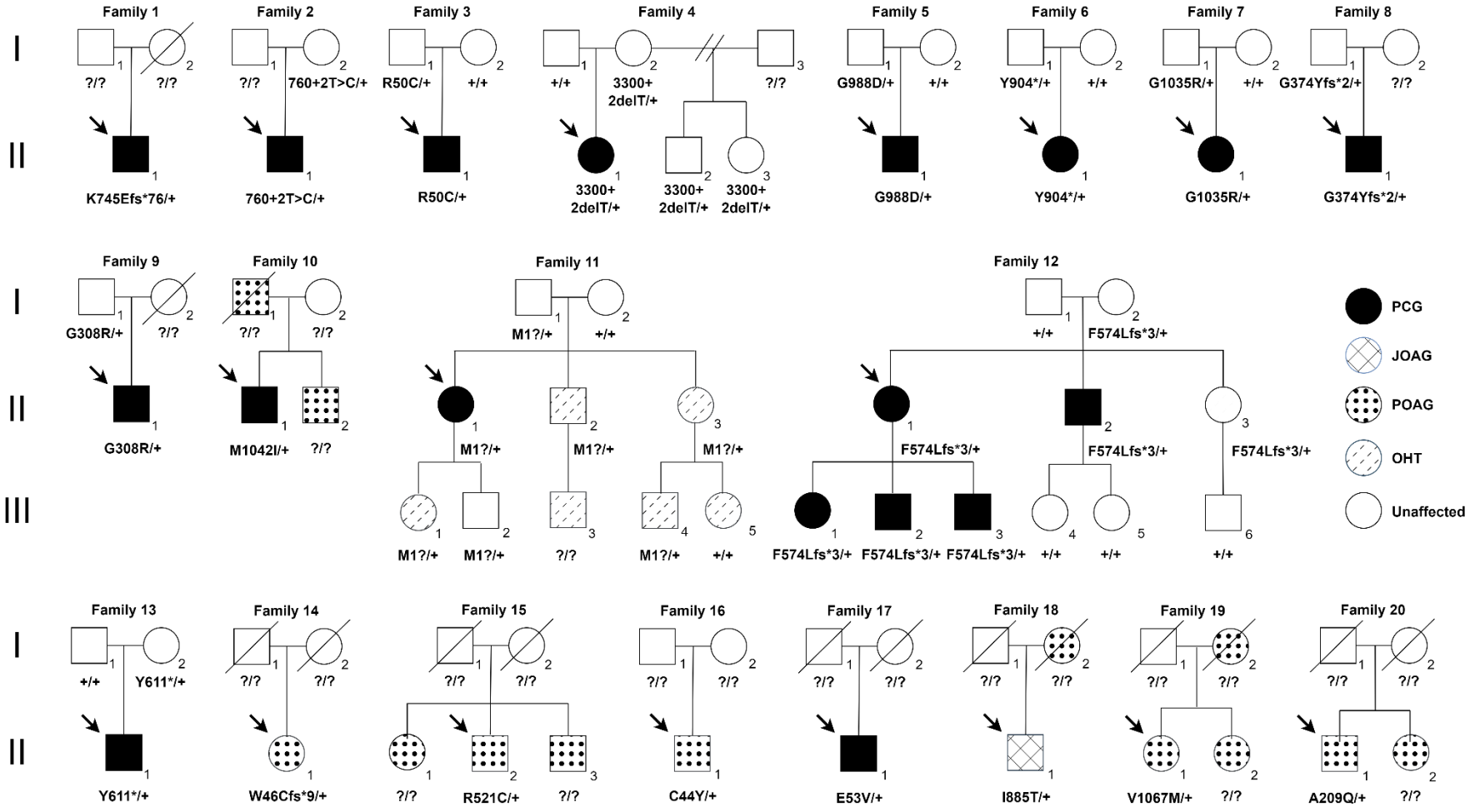
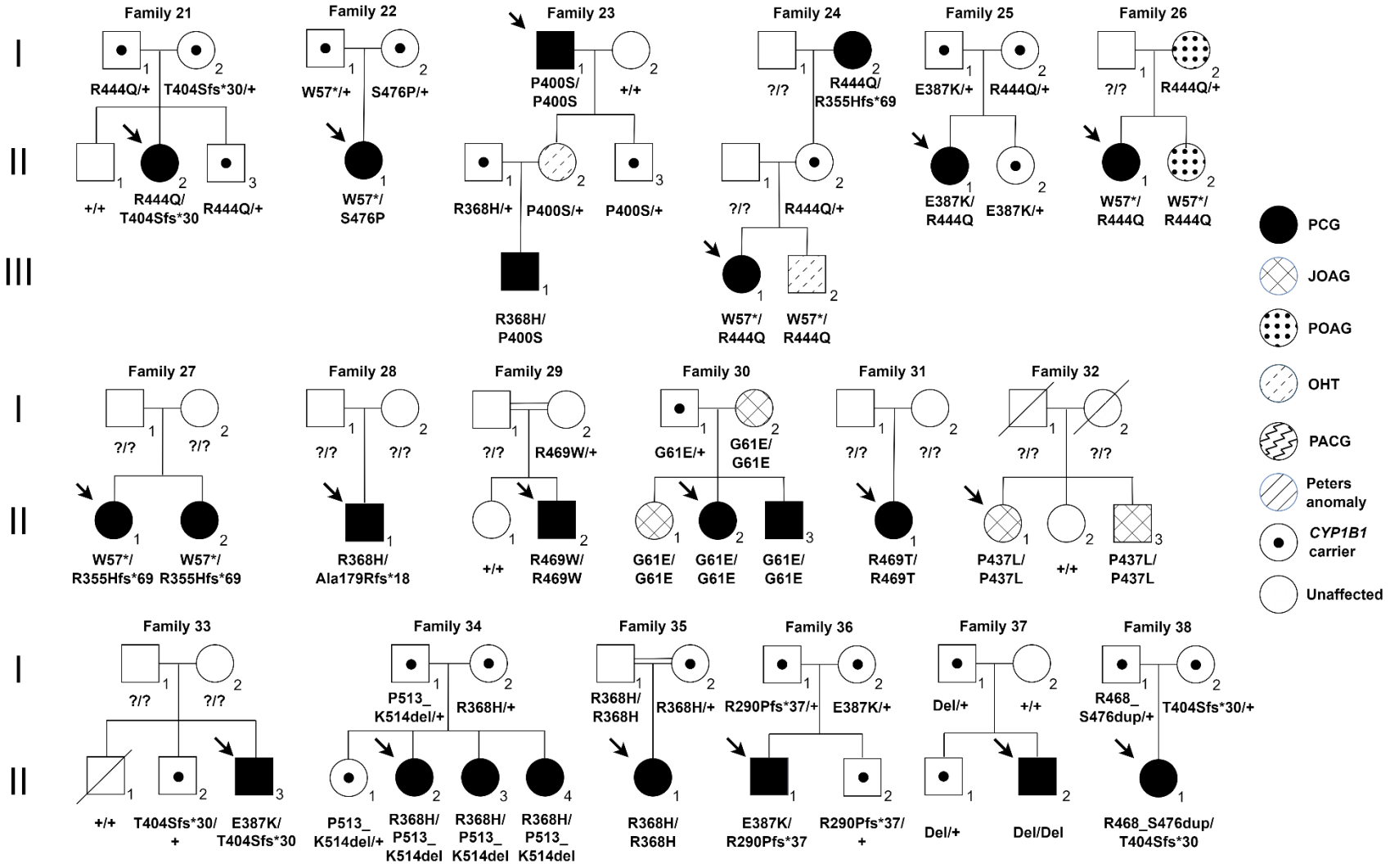


Figure C4. Pedigree structures and *TEK* variants reported in 20 families

The specific *TEK* variant per family is listed under each pedigree. Affected individuals are indicated by the shaded and patterned symbols. Probands are denoted by the arrows. White symbols do not exclude a diagnosis of later-onset disease at the time of this study.

+: wild-type allele; PCG: primary congenital glaucoma; JOAG: juvenile open angle glaucoma; POAG: primary open angle glaucoma; OHT: ocular hypertension


I
II
III
Family 21
R444Q/+
T404Sfs*30/+
+/+
R444Q/
T404Sfs*30
R444Q/+
Family 22
W57*/+
S476P/+
W57*/
S476P
Family 23
P400S/
P400S
+/+
R368H/+
P400S/+
P400S/+
R368H/
P400S
Family 24
?/?
R444Q/
R355Hfs*69
?/?
R444Q/+
W57*/
R444Q
W57*/
R444Q
Family 25
E387K/+
R444Q/+
E387K/
R444Q
E387K/+
Family 26
?/?
R444Q/+
W57*/
R444Q
W57*/
R444Q
PCG
JOAG
POAG
OHT
PACG
Peters
anomaly
CYP1B1
carrier
Unaffected
Family 27
?/?
?/?
W57*/
R355Hfs*69
W57*/
R355Hfs*69
Family 28
?/?
?/?
R368H/
Ala179Rfs*18
Family 29
?/?
R469W/+
+/+
R469W/
R469W
Family 30
G61E/+
G61E/
G61E
G61E/
G61E
G61E/
G61E
G61E/
G61E
Family 31
?/?
?/?
R469T/
R469T
Family 32
?/?
?/?
P437L/
P437L
+/+
P437L/
P437L
Family 33
?/?
?/?
+/+
T404Sfs*30/
+
E387K/
T404Sfs*30
Family 34
P513_
K514del/+
R368H/+
P513_
K514del/+
R368H/
P513_
K514del
R368H/
P513_
K514del
R368H/
P513_
K514del
Family 35
R368H/
R368H
R368H/+
R368H/
R368H
Family 36
R290Pfs*37/+
E387K/+
E387K/
R290Pfs*37
R290Pfs*37/
+
Family 37
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T404Sfs*30/+
R468_S476dup/
T404Sfs*30

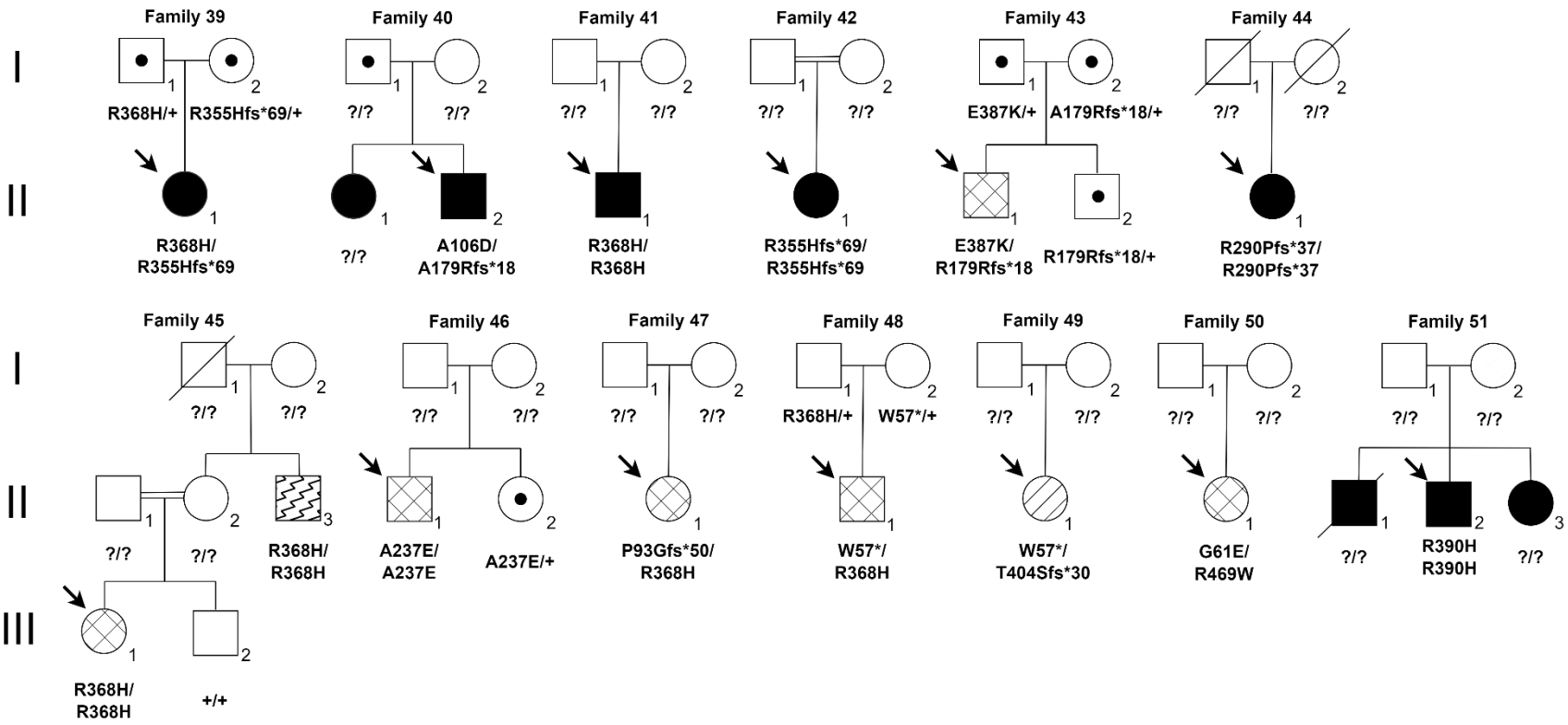

Figure C5. Pedigree structures and CYP1B1 variants reported in 31 families

The specific *CYP1B1* variants per family are listed under each pedigree. Affected individuals are indicated by the shaded and patterned symbols. Probands are denoted by the arrows. White symbols do not exclude a diagnosis of later-onset disease at the time of this study.

+: wild-type allele; PCG: primary congenital glaucoma; JOAG: juvenile open angle glaucoma; POAG: primary open angle glaucoma; OHT: ocular hypertension

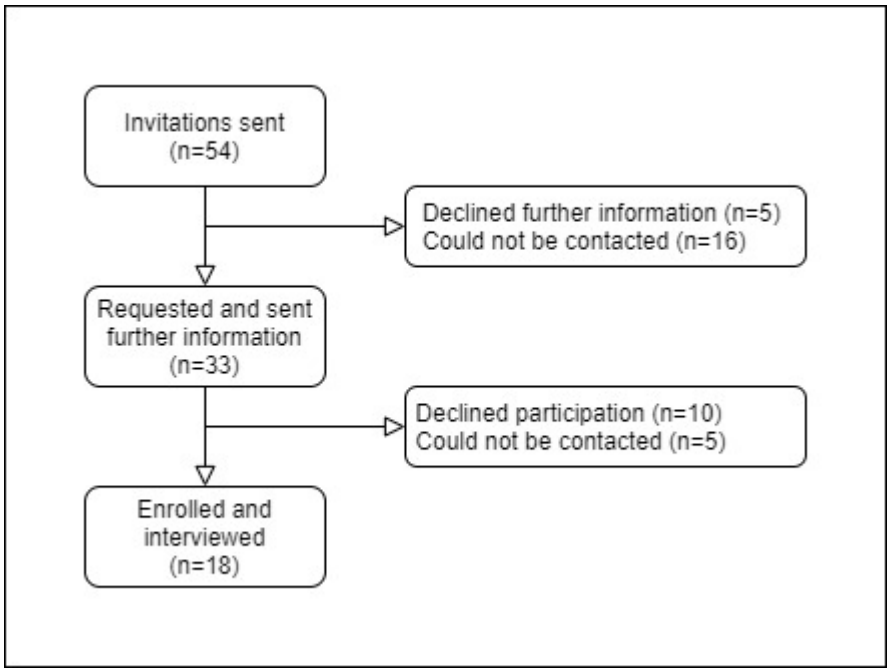

Figure C6. The recruitment of children with glaucoma for interviewing

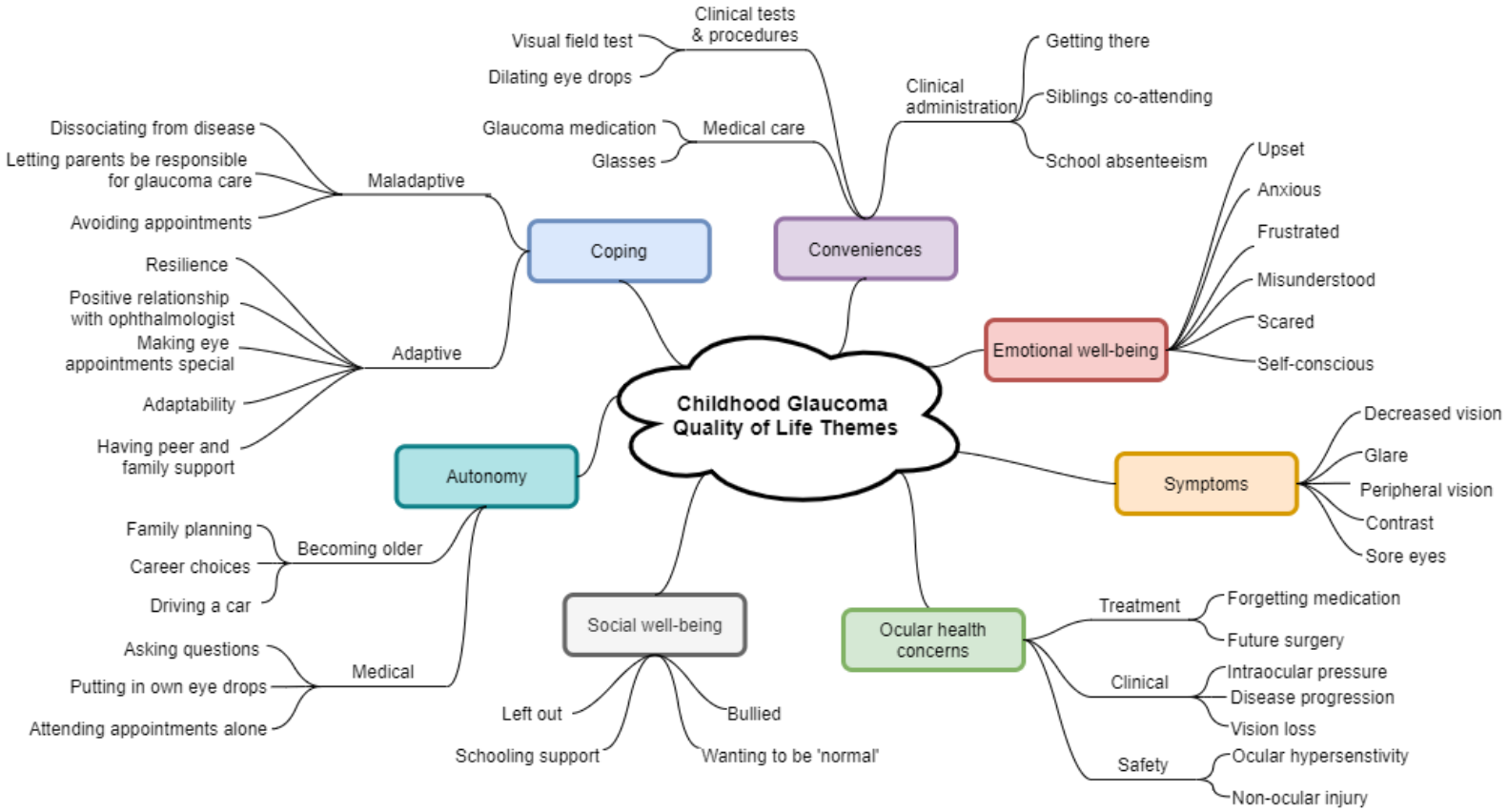

Figure C7. Mind map which illustrates the development of themes and subthemes in children with glaucoma

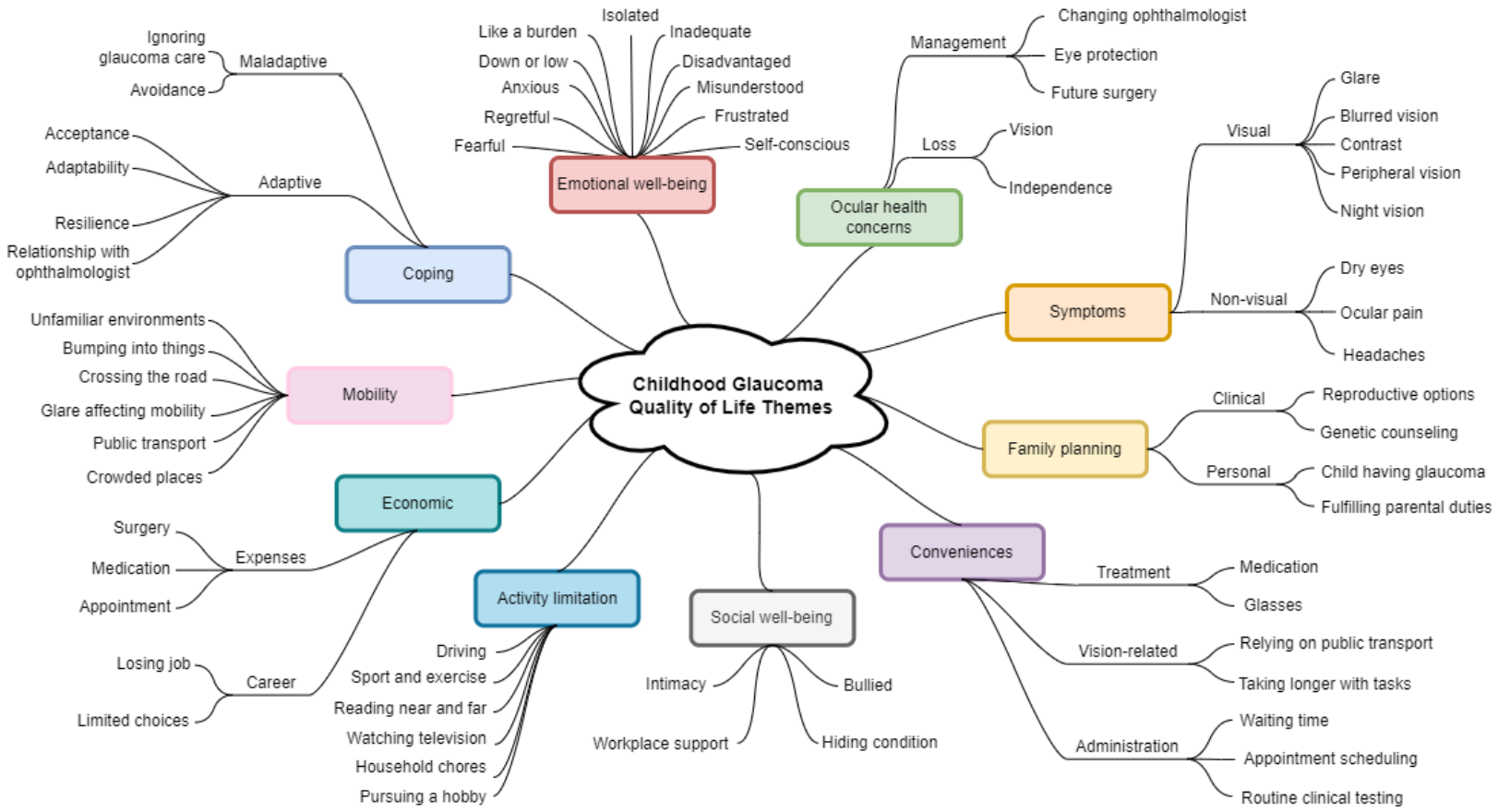

Figure C8. Mind map which illustrates the development of themes and subthemes in adults with childhood glaucoma

APPENDIX D: CHILDHOOD GLAUCOMA HEALTH SURVEYS

Health Survey D1. Childhood Glaucoma General Health Questionnaire

Today's Date: _____

If you do not wish to answer any question, you are welcome to skip it.

Please answer the following questions about you and your general health:

1a. What is your current height: _____ 1b. Weight: _____

2. What is your mother's cultural background? _____

3. What is your father's cultural background? _____

4. Have you been diagnosed with glaucoma? Yes / No

5. What age were you diagnosed with glaucoma and in which eye? _____

6a. Are you currently using any eye drops for glaucoma? Yes / No

6b. If yes, please list the names of these eye drops and how many times a day they are needed:

_____

_____

7a. Have you ever had any surgeries on your eyes? Yes / No

7b. If yes, please specify what type of surgery, which eye and the year it was done (if known):

_____

_____

_____

8a. Have you ever had any eye exams or tests that needed a general anaesthetic? (i.e. needed to be put to sleep) Yes / No

8b. If yes, please specify how many you had and the year these were done (if known):

_____

_____

_____

9a. Have you ever had any surgeries that were not for your eyes? Yes / No

9b. If yes, please specify what surgery and year it was done:

_____

10a. Are you currently taking any medications? Yes / No

10b. If yes, please list the names of these medications:

_____

_____

_____

11a. Have you ever been told you have a genetic condition or syndrome? Yes / No

11b. If yes, please specify the name of this condition or syndrome:

_____

12a. Have you ever been tested for a genetic condition or syndrome? Yes / No / Don't Know

12b. If yes, please specify the name of the condition or syndrome that you were tested for:

_____

Please answer the following questions about your general growth and development:

13. When you were born, were you: Premature (born less than 37 weeks) / At Term (born 38-42 weeks)
(please circle) Overdue (born later than 42 weeks) / Don't Know

14. How many weeks were you born from your due date? (if known) _____

15. How much did you weigh at birth? (if known) _____

16a. Do you, or did you ever have, a developmental delay? Yes / No / Don't Know
(e.g. learned to walk at a late age, speech delay, motor delay)

16b. If yes, please specify the type of developmental delay: _____

_____

17. Have you been ever diagnosed with a learning difficulty? Yes / No / Don't Know

18. Have you ever had hydrocephalus? Yes / No / Don't Know
(Fluid build-up in the brain, usually at birth or childhood)

19. Did you ever have a cleft lip? Yes / No / Don't Know
(A congenital split in the lip, i.e. found at birth)

20. Did you ever have a cleft palate? Yes / No / Don't Know
(A congenital opening in the roof of the mouth, i.e. found at birth)

21a. Have you ever broken or fractured a bone? Yes / No

21b. If yes, which bone and at what age did it happen: _____

_____

22a. Do you have any skeletal or bony abnormalities? Yes / No
(e.g. short or long fingers or toes, abnormal rib cage, scoliosis)

22b. If yes, please describe these as best you can: _____

_____

23a. Do you have any joint abnormalities? Yes / No
(e.g. hypermobile, double-jointed, stiff joints, arthritis):

23b. If yes, please describe these as best you can: _____

_____

Please answer the following specific questions about your health.

Do you or did you ever have:

24. Missing teeth Yes / No

25. Extra teeth Yes / No

26. Small teeth Yes / No

27. Abnormally shaped teeth Yes / No

28a. Other dental or oral/mouth problems: Yes / No

28b. If yes, please describe these as best you can: _____

29a. Hearing loss Yes / No

29b. If yes, is it in the left or right ear, or both? _____

30a. Do you have a hearing aid? Yes / No

30b. If yes, how old were you when you got a hearing aid? _____

31a. Heart defects or problems Yes / No

31b. If yes, please specify: _____

32. A stroke or ministroke Yes / No

33a. Gut or stomach problems Yes / No

33b. If yes, please specify: _____

33a. Kidney problems Yes / No

33b. If yes, please specify: _____

Do you or did you ever have:

34a. Reproductive or genital problems Yes / No

34b. If yes, please specify: _____

35. Extra skin on belly button (an “outie”) Yes / No

36a. Hernia Yes / No

36b. If yes, where is this hernia? _____

37a. Any unusual skin lesions, scars, bumps, spots or birthmarks (this does not include moles or freckles) Yes / No

37b. If yes, please specify the appearance and location of these as best you can: _____

_____

38a. Behavioural problems (e.g. ADHD, Autism Spectrum Disorder) Yes / No

38b. If yes, please specify: _____

39a. Mood disorder or mental health issues (e.g. depression, anxiety) Yes / No

39b. If yes, please specify: _____

40. Any diabetes Type 1 / Type 2 / No

41a. Any cancers Yes / No

41b. If yes, please specify what type of cancer and what year you were diagnosed: _____

_____

And lastly…

42. Do you have any other health problems or further comments that we have not asked about?

_____

_____

43. Are you happy for us to contact you to clarify any answers you have provided? Yes / No

What is your best contact phone number and/or email address?

Phone: _____

Email: _____

Thank you for completing this survey. Your answers are kept confidential.

Health Survey D2. Childhood Glaucoma General Health Questionnaire (Modified)

Today's Date: _____

If you do not wish to answer any question, you are welcome to skip it.

Please answer the following questions about you and your general health:

1. What is your mother's cultural background? _____

2. What is your father's cultural background? _____

3. Have you been diagnosed with glaucoma? Yes / No

4. What age were you diagnosed with glaucoma and in which eye? _____

5a. Are you currently using any eye drops for glaucoma? Yes / No

5b. If yes, please list the names of these eye drops and how many times a day they are needed:

_____

_____

6a. Have you ever had any surgeries on your eyes? Yes / No

6b. If yes, please specify what type of surgery, which eye and the year it was done (if known):

_____

_____

_____

_____

7a. Have you ever had any eye exams or tests that needed a general anaesthetic? (i.e. needed to be put to sleep) Yes / No

7b. If yes, please specify how many you had and the year these were done (if known):

_____

_____

_____

8a. Have you ever had any surgeries that were not for your eyes? Yes / No

8b. If yes, please specify what type of surgery and the year it was done: _____

_____

_____

9a. Are you currently taking any medications? Yes / No

9b. If yes, please list:

_____

_____

_____

Please answer the following questions about your general growth and development:

10. When you were born, were you: Premature (born less than 37 weeks) / At Term (born 38-42 weeks)
(please circle) Overdue (born later than 42 weeks) / Don't Know

11. How many weeks were you born from the due date? (if known) _____

12. How much did you weigh at birth? (if known) _____

13a. Do you, or did you ever have, a developmental delay? Yes / No / Don't Know
(e.g. learned to walk at a late age, speech delay, motor delay)

13b. If yes, please specify the type of developmental delay: _____

_____

14. Did you ever have a cleft lip? Yes / No / Don't Know
(A congenital split in the lip, i.e. found at birth)

15. Did you ever have a cleft palate? Yes / No / Don't Know
(A congenital opening in the roof of the mouth, i.e. found at birth)

16a. Have you ever broken or fractured a bone? Yes / No

16b. If yes, which bone and at what age did it happen: _____

_____

17a. Do you have any skeletal or bony abnormalities? Yes / No
(e.g. short or long fingers or toes, abnormal rib cage, scoliosis)

17b. If yes, please describe these as best you can: _____

_____

18a. Do you have any joint abnormalities? Yes / No
(e.g. hypermobile, double-jointed, stiff joints, arthritis):

18b. If yes, please describe these as best you can: _____

_____

Do you or did you ever have:

19a. Hearing loss Yes / No

19b. If yes, is it in the left or right ear, or both? _____

20a. Do you have a hearing aid? Yes / No

20b. If yes, how old were you when you got a hearing aid? _____

21a. Kidney problems Yes / No

21b. If yes, please specify: _____

22a. Reproductive or genital problems Yes / No

22b. If yes, please specify: _____

23a. Any unusual skin lesions, scars, bumps, spots or birthmarks (this does not include moles or freckles) Yes / No

23b. If yes, please specify the location and appearance (as best you can): _____

_____

24a. Behavioural problems (e.g. ADHD, Autism Spectrum Disorder) Yes / No

24b. If yes, please specify: _____

25a. Mood disorder or mental health issues (e.g. depression, anxiety) Yes / No

25b. If yes, please specify: _____

26. Any diabetes Type 1 / Type 2 / No

27a. Any cancers Yes / No

27b. If yes, please specify what type of cancer and what year you were diagnosed: _____

_____

And lastly…

28. Do you have any other health problems or further comments that we have not asked about?

_____

29. Are you happy for us to contact you to clarify any answers you have provided? Yes / No

What is your best contact phone number and/or email address?

Phone: _____ Email: _____

Thank you for completing this survey. Your answers are kept confidential.

APPENDIX E: CHILDHOOD GLAUCOMA PILOT PATIENT-REPORTED OUTCOME MEASURE

Background Questionnaire

Before we ask you directly about your experiences with childhood glaucoma, we would like to get to know you a bit better. Please complete the following questions that ask some general questions about yourself.

What is the time that you started this questionnaire? _____

Your name: _____ **Date of Birth:** __ __ / __ __ / __ __ __ __

Gender: _____ **Postal code:** _____

Main language spoken at home (please circle): English / Other (*specify)* _____

What is your cultural background? _____

Are you of Aboriginal and/or Torres Strait Islander origin (please circle)? Yes / No

Marital status (please circle): Never married / De-facto / Married / Divorced / Separated / Widowed

Highest level of education:	Primary school:	completed / not completed
(Please circle)	High school:	completed / not completed
	Trade school / TAFE:	completed / not completed
	University, undergraduate:	completed / not completed
	University, postgraduate:	completed / not completed

Current employment status: Working / Student / Volunteer work / Family or home duties
(Please circle all that apply) Unemployed / Retired / I receive income support payments

How many children do you have? _____

Which eye/s has childhood glaucoma (please circle): Right eye / Left eye / Both eyes

What age were you diagnosed with childhood glaucoma? _____

Do you have other eye conditions? None / Corneal disease / Retinal detachment / Prosthetic eye
(Please circle all that apply) Cataract / Other (*please specify)* _____

Do you use any vision aids? Yes / No

If yes, what vision aid/s do you use? _____

Do you get eye care in a public hospital or go to a private clinic (please circle)? Public / Private / Both

How long ago was your last eye appointment (e.g., days, weeks, months, or years)? _____

How long ago was your last eye surgery (e.g., days, weeks, months, or years)? _____

How many glaucoma medications are you currently using? _____

What is your current visual acuity (if known)? Right eye _____ Left eye _____

What was your last intraocular pressure reading (if known)? Right eye _____ Left eye _____

(Theme: Symptoms) **Please tick the box that matches the response that best describes your experience**															
Because of your glaucoma and its treatment, how often do you experience?	Never	Occasionally	Quite often	Very often	Always	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of an impact is/are the…?**	Not at all	A little	Quite a bit	A lot
Blurred vision	☐	☐	☐	☐	☐	Blurred vision	☐	☐	☐	☐	Blurred vision	☐	☐	☐	☐
Difficulty seeing objects or reading text with a similar colour to its background (e.g., reading black text on grey paper vs black text on white paper)	☐	☐	☐	☐	☐	Difficulty seeing objects or reading text with a similar colour to its background (e.g., reading black text on grey paper vs black text on white paper)	☐	☐	☐	☐	Difficulty seeing objects or reading text with a similar colour to its background (e.g., reading black text on grey paper vs black text on white paper)	☐	☐	☐	☐
Difficulty with depth perception (e.g., judging distances)	☐	☐	☐	☐	☐	Difficulty with depth perception (e.g., judging distances)	☐	☐	☐	☐	Difficulty with depth perception (e.g., judging distances)	☐	☐	☐	☐
Difficulty adjusting to light and dark conditions	☐	☐	☐	☐	☐	Difficulty adjusting to light and dark conditions	☐	☐	☐	☐	Difficulty adjusting to light and dark conditions	☐	☐	☐	☐
Difficulty seeing at night	☐	☐	☐	☐	☐	Difficulty seeing at night	☐	☐	☐	☐	Difficulty seeing at night	☐	☐	☐	☐

Because of your glaucoma and its treatment, how often do you experience?	Never	Occasionally	Quite often	Very often	Always	**How severe is/are the…?**	Not at all	Mild	Moderate	Severe	**How much of an impact is/are the…?**	Not at all	A little	Quite a bit	A lot
Trouble with glare	☐	☐	☐	☐	☐	Trouble with glare	☐	☐	☐	☐	Trouble with glare	☐	☐	☐	☐
Uncomfortable or sore eyes	☐	☐	☐	☐	☐	Uncomfortable or sore eyes	☐	☐	☐	☐	Uncomfortable or sore eyes	☐	☐	☐	☐
Eye strain	☐	☐	☐	☐	☐	Eye strain	☐	☐	☐	☐	Eye strain	☐	☐	☐	☐
Headaches	☐	☐	☐	☐	☐	Headaches	☐	☐	☐	☐	Headaches	☐	☐	☐	☐

(Theme: Activity limitations) **Please tick the box that matches the response that best describes your experience**							
Because of your glaucoma and its treatment, how much difficulty do you have…?	**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me/ don't do the task**	**Don't wish to answer**
Doing daily exercise	☐	☐	☐	☐	☐	☐	☐
Reading things from a distance (e.g., road signs, street signs, train station times)	☐	☐	☐	☐	☐	☐	☐
Reading things up close (e.g., a book, a menu)	☐	☐	☐	☐	☐	☐	☐
Driving during the day	☐	☐	☐	☐	☐	☐	☐
Driving at night	☐	☐	☐	☐	☐	☐	☐
Watching a film at the cinema or seeing a play at the theatre	☐	☐	☐	☐	☐	☐	☐
Watching a TV programme or movie on your preferred electronic device (e.g., TV, laptop, tablet)	☐	☐	☐	☐	☐	☐	☐
Doing the household cleaning	☐	☐	☐	☐	☐	☐	☐
Cooking and preparing meals	☐	☐	☐	☐	☐	☐	☐
Pursuing your hobby (e.g., playing sports, gardening)	☐	☐	☐	☐	☐	☐	☐
Recognising people's faces	☐	☐	☐	☐	☐	☐	☐
Finding something in a cluttered space	☐	☐	☐	☐	☐	☐	☐

(Theme: Mobility) **Please tick the box that matches the response that best describes your experience**							
Because of your glaucoma and its treatment, how much difficulty do you have…?	**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This task is not relevant to me/ don't do the task**	**Don't wish to answer**
Navigating crowded places	☐	☐	☐	☐	☐	☐	☐
Moving around in unfamiliar environments	☐	☐	☐	☐	☐	☐	☐
Finding landmarks (e.g., specific shops or addresses)	☐	☐	☐	☐	☐	☐	☐
Noticing objects or people on your side	☐	☐	☐	☐	☐	☐	☐
Using public transport	☐	☐	☐	☐	☐	☐	☐
Getting around at night	☐	☐	☐	☐	☐	☐	☐
Getting around on sunny days or in bright conditions	☐	☐	☐	☐	☐	☐	☐
Crossing the road	☐	☐	☐	☐	☐	☐	☐
Going up or down stairs, steps, or street curbs	☐	☐	☐	☐	☐	☐	☐

(Theme: Social well-being) **Please tick the box that matches the response that best describes your experience**							
Because of your glaucoma and its treatment, how much difficulty do you have…?	**None**	**A little**	**Quite a bit**	**A lot**	**Unable to do because of my vision**	**This issue is not relevant to me/don't do the task**	**Don't wish to answer**
Meeting new people	☐	☐	☐	☐	☐	☐	☐
Making friends	☐	☐	☐	☐	☐	☐	☐
Interacting socially with people you already know	☐	☐	☐	☐	☐	☐	☐
Maintaining your friendships	☐	☐	☐	☐	☐	☐	☐
Maintaining your current romantic relationship (e.g., married, partnered, or dating)	☐	☐	☐	☐	☐	☐	☐
Attending events or social gatherings	☐	☐	☐	☐	☐	☐	☐
With people treating you unfairly	☐	☐	☐	☐	☐	☐	☐
Taking care of your family	☐	☐	☐	☐	☐	☐	☐
Taking care of your pet/s	☐	☐	☐	☐	☐	☐	☐
Getting help and support from your family	☐	☐	☐	☐	☐	☐	☐
Getting help and support from your friends	☐	☐	☐	☐	☐	☐	☐
Getting help and support from your workplace or place of study (e.g., university)	☐	☐	☐	☐	☐	☐	☐
Getting help and support from government or social services (e.g., NDIS, Centrelink)	☐	☐	☐	☐	☐	☐	☐

(Theme: Inconveniences) Please tick the box that matches the response that best describes your experience							
Because of your glaucoma and its treatment, how inconvenient is…?	**None**	**A little**	**Quite a bit**	**A lot**	**An extreme amount**	**This task is not relevant to me/ don't do the task**	**Don't wish to answer**
The amount of time you have to spend at eye appointments	☐	☐	☐	☐	☐	☐	☐
How often you need to go to an eye appointment	☐	☐	☐	☐	☐	☐	☐
Scheduling an appointment	☐	☐	☐	☐	☐	☐	☐
Getting to and from eye appointments	☐	☐	☐	☐	☐	☐	☐
Undergoing the same eye tests at a glaucoma appointment (e.g., visual field test, vision test)	☐	☐	☐	☐	☐	☐	☐
Wearing glasses	☐	☐	☐	☐	☐	☐	☐
Wearing contact lenses	☐	☐	☐	☐	☐	☐	☐
Wearing sunglasses	☐	☐	☐	☐	☐	☐	☐
Using eye drops	☐	☐	☐	☐	☐	☐	☐
Making text in an accessible format (e.g., making it larger to read or converting text to speech)	☐	☐	☐	☐	☐	☐	☐
Taking longer to perform a task	☐	☐	☐	☐	☐	☐	☐
Relying on public transport or taxis to get places	☐	☐	☐	☐	☐	☐	☐
Getting approvals to keep your driver's license	☐	☐	☐	☐	☐	☐	☐

(Theme: Economic) **Please tick the box that matches the response that best describes your experience**							
Because of your glaucoma and its treatment, how concerned are you about…?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**	**This issue is not relevant to me**	**Don't wish to answer**
The cost associated with seeing your eye specialist	☐	☐	☐	☐	☐	☐	☐
The cost of your glaucoma medication (e.g., eye drops)	☐	☐	☐	☐	☐	☐	☐
The cost of your glaucoma surgery, laser surgery or prosthetic eye/s	☐	☐	☐	☐	☐	☐	☐
The cost of your glasses	☐	☐	☐	☐	☐	☐	☐
The cost of vision aids (e.g., magnifier, CCTV)	☐	☐	☐	☐	☐	☐	☐
The cost of assisted travel (e.g., taxi or rideshare)	☐	☐	☐	☐	☐	☐	☐
What career or job you can do (e.g., jobs that require a driver's license or visually demanding jobs)	☐	☐	☐	☐	☐	☐	☐
Your ability to do work tasks being impacted by your glaucoma	☐	☐	☐	☐	☐	☐	☐
Losing your job or work duties	☐	☐	☐	☐	☐	☐	☐
Losing your source of income	☐	☐	☐	☐	☐	☐	☐

(Theme: Health concerns) **Please tick the box that matches the response that best describes your experience**							
Because of your glaucoma and its treatment, how concerned are you about…?	**Not at all**	**A little**	**Moderately**	**A lot**	**Extremely**	**This issue is not relevant to me**	**Don't wish to answer**
The control of your eye pressure	☐	☐	☐	☐	☐	☐	☐
Losing your vision	☐	☐	☐	☐	☐	☐	☐
Your glaucoma getting worse or glaucoma affecting your better eye	☐	☐	☐	☐	☐	☐	☐
Developing a different eye disease or condition (e.g., cataracts)	☐	☐	☐	☐	☐	☐	☐
Changing eye doctor	☐	☐	☐	☐	☐	☐	☐
Using your glaucoma medication correctly	☐	☐	☐	☐	☐	☐	☐
Being on long-term medication	☐	☐	☐	☐	☐	☐	☐
Needing future eye surgery	☐	☐	☐	☐	☐	☐	☐
Something damaging or touching your eye/s (e.g., an injury, corneal scratch)	☐	☐	☐	☐	☐	☐	☐
The appearance of your eye	☐	☐	☐	☐	☐	☐	☐
Your overall appearance (e.g., applying make-up, shaving, dressing yourself)	☐	☐	☐	☐	☐	☐	☐
Maintaining good personal hygiene (e.g., bathing, cutting your nails)	☐	☐	☐	☐	☐	☐	☐
Your personal safety (e.g., having an accident, tripping over)	☐	☐	☐	☐	☐	☐	☐
Losing your driver's license	☐	☐	☐	☐	☐	☐	☐
Losing your independence	☐	☐	☐	☐	☐	☐	☐
Passing on your glaucoma to your child/potential child	☐	☐	☐	☐	☐	☐	☐

(Theme: Emotional well-being) **Please tick the box that matches the response that best describes your experience**						
Because of your glaucoma and its treatment, during the past month, how often did you feel…?	**Never**	**A little of the time**	**Sometimes**	**Most of the time**	**All the time**	**Don't wish to answer**
Down or low	☐	☐	☐	☐	☐	☐
Scared	☐	☐	☐	☐	☐	☐
Disadvantaged	☐	☐	☐	☐	☐	☐
Frustrated	☐	☐	☐	☐	☐	☐
Misunderstood	☐	☐	☐	☐	☐	☐
Like a burden	☐	☐	☐	☐	☐	☐
Isolated or alone	☐	☐	☐	☐	☐	☐
Regretful about your eye care in the past	☐	☐	☐	☐	☐	☐
Suicidal	☐	☐	☐	☐	☐	☐
Self-conscious	☐	☐	☐	☐	☐	☐
Anxious or stressed	☐	☐	☐	☐	☐	☐
Like asking yourself, "Why me?"	☐	☐	☐	☐	☐	☐

(Theme: Coping) Please tick the box that matches the response that best describes your experience						
To cope with or manage your glaucoma and its treatment, how often do you….?	**Never**	**A little of the time**	**Sometimes**	**Most of the time**	**All the time**	**Don't wish to answer**
Accept that you have glaucoma	☐	☐	☐	☐	☐	☐
Allow yourself to express what you are feeling (e.g., grief, frustration, sadness)	☐	☐	☐	☐	☐	☐
Compare your situation to others	☐	☐	☐	☐	☐	☐
Learn from or relate to someone else with a similar eye condition or vision impairment	☐	☐	☐	☐	☐	☐
Be open with people about your glaucoma	☐	☐	☐	☐	☐	☐
Try not to think about your glaucoma	☐	☐	☐	☐	☐	☐
Do activities that may be considered healthy to take your mind off your condition (e.g., exercise, meditation, writing)	☐	☐	☐	☐	☐	☐
Do activities that may be considered unhealthy to take your mind off your condition (e.g., alcohol or drug use, eating comfort foods)	☐	☐	☐	☐	☐	☐
Ignore your glaucoma treatment (e.g., eye drops)	☐	☐	☐	☐	☐	☐
Avoid going to your eye appointments	☐	☐	☐	☐	☐	☐
Have faith or trust in your ophthalmologist or treatment	☐	☐	☐	☐	☐	☐
Have a good relationship with your ophthalmologist	☐	☐	☐	☐	☐	☐
Get professional support for your mental health (e.g., psychologist, social worker)	☐	☐	☐	☐	☐	☐
Get support from friends, family, support group or personal carer	☐	☐	☐	☐	☐	☐
Try to have a positive outlook on life	☐	☐	☐	☐	☐	☐
Use humour or make light of a situation	☐	☐	☐	☐	☐	☐
Try to find ways to adapt to your eye condition or vision loss (e.g., using vision aids, relying on your memory)	☐	☐	☐	☐	☐	☐
Try to maintain your independence	☐	☐	☐	☐	☐	☐
Volunteer or help someone else	☐	☐	☐	☐	☐	☐

And lastly,

What is the time that you finished the questionnaire? _____

Are you happy if we contact you to clarify any answers that you have provided? Yes / No

If yes, what are your best contact details?

Phone: _____

Email: _____

Preferred day and time to receive a phone call: _____

Thank you very much for your time.

APPENDIX F: FIRST AUTHORED PUBLICATIONS

Publication F1. Childhood and early onset glaucoma classification and genetic profile in a large Australasian disease registry

AMERICAN ACADEMY OF OPHTHALMOLOGY®

Childhood and Early Onset Glaucoma Classification and Genetic Profile in a Large Australasian Disease Registry

Lachlan S.W. Knight, BHSc, MOrth,[1] Jonathan B. Ruddle, FRANZCO,[2,3,4] Deepa A. Taranath, MS, FRANZCO,[1] Ivan Goldberg, FRANZCO,[5] James E.H. Smith, FRANZCO,[5,6,7] Glen Gole, MD, FRANZCO,[8] Mark Y. Chiang, MPhil, FRANZCO,[9] Faren Willett, BSc, MOrth,[9] Guy D'Mellow, FRANZCO,[10] James Breen, PhD,[11,12,13] Ayub Qassim, MBBS,[1] Sean Mullany, MD,[1] James E. Elder, FRANZCO,[2,14] Andrea L. Vincent, MD, FRANZCO,[15,16] Sandra E. Staffieri, PhD,[2,4] Lisa S. Kearns, BOrth, OphthalSci,[4] David A. Mackey, MD, FRANZCO,[3,4,17,18] Susie Luu, FRANZCO,[1] Owen M. Siggs, MD, DPhil,[1,*] Emmanuelle Souzeau, PhD,[1,*] Jamie E. Craig, FRANZCO, DPhil[1,*]

Purpose: To report the relative frequencies of childhood and early onset glaucoma subtypes and their genetic findings in a large single cohort.

Design: Retrospective clinical and molecular study.

Participants: All individuals with childhood glaucoma (diagnosed 0 to <18 years) and early onset glaucoma (diagnosed 18 to <40 years) referred to a national disease registry.

Methods: We retrospectively reviewed the referrals of all individuals with glaucoma diagnosed at <40 years of age recruited to the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG). Subtypes of glaucoma were determined using the Childhood Glaucoma Research Network (CGRN) classification system. DNA extracted from blood or saliva samples underwent sequencing of genes associated with glaucoma.

Main Outcome Measures: The phenotype and genotype distribution of glaucoma diagnosed at <40 years of age.

Results: A total of 290 individuals (533 eyes) with childhood glaucoma and 370 individuals (686 eyes) with early onset glaucoma were referred to the ANZRAG. Primary glaucoma was the most prevalent condition in both cohorts. In the childhood cohort, 57.6% of individuals (167/290, 303 eyes) had primary congenital glaucoma (PCG), and 19.3% (56/290, 109 eyes) had juvenile open-angle glaucoma. Juvenile open-angle glaucoma constituted 73.2% of the early onset glaucoma cohort (271/370, 513 eyes). Genetic testing in probands resulted in a diagnostic yield of 24.7% (125/506) and a reclassification of glaucoma subtype in 10.4% of probands (13/125). The highest molecular diagnostic rate was achieved in probands with glaucoma associated with non-acquired ocular anomalies (56.5%). Biallelic variants in *CYP1B1* (n = 29, 23.2%) and heterozygous variants in *MYOC* (n = 24, 19.2%) and *FOXC1* (n = 21, 16.8%) were most commonly reported among probands with a molecular diagnosis. Biallelic *CYP1B1* variants were reported in twice as many female individuals as male individuals with PCG (66.7% vs. 33.3%, $P = 0.02$).

Conclusions: We report on the largest cohort of individuals with childhood and early onset glaucoma from Australasia using the CGRN classification. Primary glaucoma was most prevalent. Genetic diagnoses ascertained in 24.7% of probands supported clinical diagnoses and genetic counseling. International collaborative efforts are required to identify further genes because the majority of individuals still lack a clear molecular diagnosis. *Ophthalmology 2021;128:1549-1560* © *2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

The term "early onset glaucoma" encompasses a heterogeneous group of vision-threatening optic neuropathies with onset before age 40 years.[1] Childhood glaucoma represents a subcategory of early onset glaucoma defined as disease onset at <18 years of age.[2] The different subtypes of childhood glaucoma have been described using various definitions and classification systems that lacked consensus. To address this issue, the Childhood Glaucoma Research Network (CGRN) recently developed a classification system describing the subtypes of childhood glaucoma that has been adopted by the World Glaucoma Association and the American Board of Ophthalmology.[2]

In accordance with the CGRN classification, primary glaucoma includes primary congenital glaucoma (PCG) and

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juvenile open-angle glaucoma (JOAG), whereas secondary glaucomas are subcategorized depending on their underlying pathology. These secondary glaucomas include glaucoma associated with nonacquired ocular anomalies (e.g., Axenfeld-Rieger spectrum [ARS], iris hypoplasia), glaucoma associated with nonacquired systemic disease (e.g., connective tissue disorders), and glaucoma associated with acquired conditions (e.g., uveitis, trauma, or intraocular surgery). Glaucoma after cataract surgery falls under a separate classification.[2]

Likewise, classification systems exist for later adult-onset glaucoma (disease onset >40 years) with subtypes defined as primary open-angle glaucoma, primary angle-closure glaucoma, and, more broadly, glaucoma secondary to other pathology. However, there is no formalized system for glaucoma diagnosis in individuals diagnosed between the ages of 18 and <40 years, henceforth referred to as "early onset glaucoma." This inhibits the understanding of disease patterns in this age group, which is of particular relevance given this cohort is of working age, and may experience more significant visual disability and impact on quality of life compared with those with later adult-onset disease.[3]

Childhood and early onset glaucoma are typically caused by variants in genes with a Mendelian pattern of inheritance.[1] The most common genes implicated are *CYP1B1, LTBP2,* and *TEK* for PCG; *MYOC*, *TBK1,* and *OPTN* for JOAG; and *FOXC1, PITX2, PAX6,* and *CPAMD8* for glaucoma associated with nonacquired ocular anomalies.[1,4] Variants in these genes are usually associated with strong penetrance but variable expressivity, which contributes to a broad phenotypic spectrum and overlap between clinical entities. For example, biallelic *CYP1B1* variants have been associated with PCG, JOAG, and glaucoma associated with nonacquired ocular anomalies.[4] The genetic heterogeneity of childhood and early onset glaucoma coupled with the difficulty of accurately establishing clinical diagnoses in young individuals highlights the importance of genetic testing in childhood and early onset glaucoma.[5]

To the best of our knowledge, the genetic findings of the phenotypes described by the CGRN have not been reported in a large cohort of childhood and early onset glaucoma. In this study, we applied the CGRN classification to the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) childhood and early onset glaucoma cohort. We report the genetic results and diagnostic yield for childhood and early onset glaucoma and each glaucoma subtype in a large population.

Methods

Participants

Ethics approval was obtained through the Southern Adelaide Clinical Human Research Ethics Committee. The study adhered to the revised Declaration of Helsinki (2013) and the National Health and Medical Research Council statement of ethical conduct in research involving humans (2018). Participants included in this study were sourced from the ANZRAG as previously described.[6] In brief, participants were referred to the registry by their ophthalmologist or via self-referral pathways. Clinical details were obtained from participants' glaucoma specialists. Maximum intraocular pressure (IOP) and age at glaucoma diagnosis were recorded for each individual by the referring clinician. Registry staff ensured consistent data recording and requested information from the specialist or reviewed case notes to complete any missing records where possible. Participants, or their parent or guardian, provided informed written consent. Participants then provided a blood or saliva sample for DNA extraction. Participants, or their parent or guardian, were also specifically asked to self-report their continental ancestry (i.e., European, including European Australian and European New Zealander, or non-European, including Asian, Middle Eastern, African, South or Central American, and Oceanian) and any known family history of any subtype of glaucoma, defined as the presence of a fourth-degree or closer relative affected by glaucoma.

All participants who were referred to the registry since its establishment in 2007 to October 2020 and who had a clinical diagnosis of glaucoma between the ages of 0 and <40 years were included. Individuals with a diagnosis of glaucoma between the ages of 0 to <18 years were assigned a diagnosis of childhood glaucoma, and those diagnosed between age 18 to <40 years were considered to have early onset glaucoma. Glaucoma suspects were not included. Participants in either cohort were subsequently assigned 1 of the following 6 CGRN classifications:[2]

I. Primary Glaucoma:

1. PCG, further classified as neonatal onset (0−1 month of age), infantile onset (1−24 months of age), late onset or late recognition of disease (>2 years of age), or spontaneously arrested PCG. Spontaneously arrested PCG was diagnosed in the presence of buphthalmos and Haab striae, with normal IOP, normal-appearing optic discs, and no corneal edema.[7]
2. JOAG, defined as a diagnosis of open-angle glaucoma between age 4 to <40 years of age, not exhibiting features of PCG (i.e., buphthalmos, Haab striae). Individuals were further reported to have normal-tension glaucoma (NTG, described as maximum recorded IOP ≤ 21 mmHg) or high-tension glaucoma (HTG, maximum recorded IOP > 21 mmHg) in the affected eye/s, where possible.

II. Secondary Glaucoma:

1. Glaucoma associated with acquired conditions (in which glaucoma is secondary to a condition that is not present at birth).
2. Glaucoma associated with nonacquired ocular anomalies (in which glaucoma is secondary to a nonacquired condition that is predominantly ocular).
3. Glaucoma associated with nonacquired systemic disease (in which glaucoma develops in the presence of a disease that is predominantly systemic, with or without ocular manifestations).
4. Glaucoma following cataract surgery (in which cataract surgery precedes glaucoma onset regardless of any coexisting ocular or systemic abnormality).

An "Unclassified" category was additionally assigned to individuals for circumstances in which it could not be determined if their glaucoma was primary or secondary due to an insufficient view of the ocular structures or unavailable medical records.

As per the CGRN classification, individuals were classified as having glaucoma associated with nonacquired ocular anomalies, even in the presence of systemic disease, if the disorder was predominantly ocular. This includes individuals with Peters' anomaly or ARS.[2] Individuals with only posterior embryotoxon and no

systemic features were not considered to have ARS as per the 9th Consensus Report of the World Glaucoma Association.[8] When an individual had anterior segment dysgenesis (ASD) that did not fit a specific phenotype, we used the term "unclassified ASD" as recommended by Idrees et al.[9] Individuals with primary angle-closure glaucoma were classified as having glaucoma associated with nonacquired ocular anomalies because this entity is caused by anatomic disorders of the iris, lens, and retrolenticular structures.[10]

Genetic Testing

Targeted genetic testing and exome or genome sequencing were performed on collected samples as they were received, such that the most recent samples are yet to be tested. Venous blood specimens were collected into EDTA tubes, and DNA was extracted by a QIAcube automated system using QIAamp DNA Blood Mini kit (Qiagen). Saliva specimens were collected into an Oragene DNA Self-Collection kit (DNA Genotek Inc.). DNA was isolated as per manufacturer's instructions. Targeted genetic testing was based on the clinical diagnosis (e.g., *CYP1B1* sequencing for PCG, *MYOC* sequencing for JOAG, *FOXC1*/*PITX2* sequencing and copy number variant analysis for ARS). Additionally, some cohorts previously had targeted genetic testing for specific genes (e.g., 160 individuals with JOAG had *CYP1B1* sequencing,[11] and 86 individuals with JOAG and NTG had *TBK1* copy number variant analysis and *OPTN* sequencing for p.E50K).[12] Exome or genome sequencing was performed as previously described[13] on individuals who did not have a molecular diagnosis via targeted genetic testing. Unlike targeted genetic testing, there were no minimum gene-based coverage thresholds applied to exome and genome sequencing data. Genetic results were validated through the National Association of Testing Authorities–accredited laboratories of SA Pathology at Flinders Medical Centre. A majority of the molecular diagnoses presented have been published and are appropriately identified in the "Results."[11-20]

Statistical Analysis

All calculations were performed using SPSS version 27.0 for Windows (IBM/SPSS Inc.). Data normality was assessed using the Shapiro–Wilk test. Continuous variables were expressed as median (interquartile range). Categorical data were expressed as counts and percentages. Statistical analyses of European ancestry and family history were performed on probands only to provide a more accurate representation of the data among families. The chi-square test with Yates' correction for continuity or Fisher exact test was used for categorical variables as appropriate. Standardized adjusted residuals were used during post hoc analyses to interpret any statistical significance. Gender distribution was assessed using a binomial test with the exact Clopper-Pearson 95% confidence interval (CI), in which the probability of male gender is 0.49 based on Australian and New Zealand census data.[21,22] The median test was applied to nonparametric continuous variables, and post hoc pairwise analyses used the Bonferroni adjustment. A P value < 0.05 was considered statistically significant. Multiple testing adjustments were not used beyond post hoc pairwise analyses because all analyses were exploratory in nature.

Results

Clinical Diagnosis and Classification

A total of 1219 eyes of 660 individuals with childhood or early onset glaucoma were included. Exact clinical phenotypes per classification are reported in Table S1 (available at www.aaojournal.org). Bilateral disease was reported in 86.7% of individuals (566/653), and 55.8% of individuals (368/660) were male, representing a male:female ratio of 1.26:1 (95% CI, 0.519–0.596, $P < 0.001$). A positive family history of glaucoma was reported in 59.9% of probands (344/574) and 76.2% (428/562) with self-reported European ancestry.

Childhood Glaucoma

Of the whole cohort, 533 eyes of 290 individuals (43.9%) were classified as having childhood glaucoma (Table 1). Primary glaucoma was more common than secondary glaucoma (223/290, 76.9% vs. 63/290, 21.7%). Four individuals had unclassified glaucoma (1.4%). Primary congenital glaucoma was the most common subtype (167/290, 57.6%), followed by JOAG (56/290, 19.3%). Infantile PCG was the most common PCG subtype (89/167, 53.3%, Table S1). Of those with JOAG, 80.4% (45/56) had HTG (Table S1). Bilaterality was significantly different across all subtypes ($P < 0.001$), where those with glaucoma associated with nonacquired systemic disease were least likely to have bilateral disease (1/6, 16.7%) compared with JOAG (53/56, 94.6%, $P < 0.001$). Gender distribution did not significantly differ between subgroups ($P = 0.61$), although an overall male:female ratio of 1.28:1 was found in the childhood cohort (95% CI, 0.503–0.620, $P = 0.008$). The PCG cohort recorded a higher male:female ratio of 1.46:1 (95% CI, 0.514–0.668, $P = 0.005$). A positive family history of glaucoma was significantly different across subgroups ($P = 0.004$). It was most commonly reported in probands with JOAG (29/45, 64.4%) and less commonly reported in probands with PCG (50/140, 35.7%, $P = 0.007$). Parental consanguinity was self-reported in 8 individuals with childhood glaucoma, of whom 5 had PCG. Median maximum IOP was highest in those with glaucoma associated with an acquired condition (48 [46–49] mmHg), but differences in IOP across subgroups did not reach statistical significance ($P = 0.07$). However, there was a statistically significant difference in the median age at disease diagnosis across subtypes ($P < 0.001$). The median age at diagnosis of those with glaucoma associated with nonacquired ocular anomalies (3 [0.2–8] years) was significantly different in both PCG (0.25 [0–0.6] years, $P < 0.001$) and JOAG cohorts (14 [12–16] years, $P < 0.001$).

Early Onset Glaucoma

A total of 686 eyes of 370 individuals (56.1%) were diagnosed with early onset glaucoma (Table 2). Juvenile open-angle glaucoma was the most prevalent subtype (271/370, 73.2%). Of these, 78.6% (213/271) had HTG, and 8.1% (22/271) had NTG (Table S1). Bilaterality was significantly different across all subtypes ($P < 0.001$), with those with JOAG more likely to have bilateral involvement (247/266, 92.9%) compared with individuals with glaucoma associated with an acquired condition (33/49, 67.3%, $P < 0.001$). An overall male:female ratio of 1.24:1 was found across all early onset glaucoma cases (95% CI, 0.502–0.605, $P = 0.008$). The distribution of gender was significantly different between groups ($P = 0.002$); glaucoma associated with acquired conditions was more common in male individuals (36/49, 73.5%), compared with JOAG (147/271, 54.2%, $P = 0.04$). Family history was significantly different between groups ($P = 0.007$); probands with glaucoma associated with an acquired condition were least likely to report a family history of glaucoma (25/45, 55.6%) compared with those with JOAG (187/246, 76.0%, $P = 0.03$). Differences in IOP between subgroups reached statistical significance ($P = 0.002$). Those with JOAG had a lower median maximum recorded IOP (29 [23-38] mmHg) compared with those with an associated acquired condition (36 [30–48] mmHg, $P = 0.03$) and nonacquired ocular anomalies (39 [28–45] mmHg, $P = 0.02$). The median maximum IOP recorded

Table 1. Childhood Glaucoma (diagnosed between age 0–<18 years)

	PCG	JOAG	Acquired Condition	Nonacquired Ocular Anomalies	Nonacquired Systemic Disease	Following Cataract Surgery	Unclassified	Total	P Value
All cases, n (%)	167 (57.6)	56 (19.3)	3 (1.0)	49 (16.9)	6 (2.1)	5 (1.7)	4 (1.4)	290 (100.0)	–
Eyes, n (%)	303 (56.8)	109 (20.5)	5 (0.9)	93 (17.4)	7 (1.3)	8 (1.5)	8 (1.5)	533 (100.0)	–
Bilateral, n (%)	138/165 (83.6)	53/56 (94.6)	2/3 (66.7)	44/49 (89.8)	1/6 (16.7)	3/5 (60.0)	4/4 (100.0)	245/288 (85.1)	**<0.001***
Male gender, n (%)	99/167 (59.3)	28/56 (50.0)	2/3 (66.7)	28/49 (57.1)	2/6 (33.3)	3/5 (60.0)	1/4 (25.0)	163/290 (56.2)	0.61*
Probands, n (%)	148 (59.2)	45 (18.0)	3 (1.2)	41 (16.4)	6 (2.4)	5 (2.0)	2 (0.8)	250 (100.0)	–
Family history, n (%)	50/140 (35.7)	29/45 (64.4)	0/3 (0.0)	20/39 (51.3)	3/6 (50.0)	2/5 (40.0)	2/2 (100.0)	106/240 (44.2)	**0.004***
European ancestry, n (%)	104/138 (75.4)	30/44 (68.2)	3/3 (100.0)	26/39 (66.7)	4/6 (66.7)	3/4 (75.0)	1/2 (50.0)	171/236 (72.5)	0.72*
Highest recorded IOP (mmHg)	30 (24–40)	40 (27–46)	48 (46–49)	35 (27–45)	31 (30–38)	37 (22–49)	40 (n/a)	32 (25–40)	0.07†
Age at diagnosis (yrs)	0.25 (0–0.6)	14 (12–16)	6 (5–6)	3 (0.2–8)	0 (0–4)	11 (0–15)	4 (3–6)	0.6 (0–7)	**<0.001†**

IOP = intraocular pressure; JOAG = juvenile open-angle glaucoma; n/a = not available; PCG = primary congenital glaucoma.
Totals for each variable may not equal the total number of cases because of missing data. Highest recorded IOP and age at diagnosis are presented as median (interquartile range). All cases include probands and nonprobands. European ancestry and family history were calculated for probands only. Bold values indicate statistical significance ($P < 0.05$).
*Fisher exact test.
†Median test.

was 15 [13–17] mmHg among individuals with NTG compared with 32 [26–40] mmHg among those with HTG (Table S1). The median age at disease diagnosis reached statistical significance between groups ($P = 0.03$). Those with nonacquired systemic disease had the youngest median age at disease diagnosis (23 [21–30] years), but post hoc analyses did not show statistical significance between specific groups.

Differences in Childhood and Early Onset Glaucoma Cohorts

Laterality ($P = 0.34$) and gender ($P = 0.90$) were similarly distributed in childhood and early onset cohorts. Probands with early onset glaucoma showed a higher prevalence of European ancestry than probands with childhood glaucoma, but this did not reach statistical significance (78.8% vs. 72.5%, respectively, $P = 0.10$). A positive family history of glaucoma was more likely to be reported in probands with early onset glaucoma compared with probands with childhood glaucoma (71.3% vs. 44.2%, respectively, $P < 0.001$). The distribution of exact clinical phenotypes per cohort is shown in Table S1. The distribution of age at diagnosis and highest recorded IOP per glaucoma subtype per cohort are shown in Figures S1 and S2 (available at www.aaojournal.org), respectively.

Genetic Results

A total of 506 (506/594, 85.2%) probands underwent genetic testing, of whom 36.8% (186/506) underwent targeted genetic testing and 63.2% (320/506) underwent whole-exome or genome sequencing. A molecular diagnosis was determined in 24.7% (125/506). The diagnostic yield was 37.6% (83/221) in probands with childhood glaucoma and 14.7% (42/285) in probands with early onset glaucoma. Genetic diagnoses were achieved through targeted genetic testing in 75.2% (94/125) of probands and whole-exome or genome sequencing in 24.8% (31/125). Genetic results are presented and discussed in the context of the whole cohort's clinical diagnosis and CGRN classification (Table S2, available at www.aaojournal.org, shows distribution of molecular diagnoses per cohort). Genetic results confirmed the clinical diagnosis in 89.6% (112/125) of probands. The remaining 10.4% (13/125) of probands underwent reexamination and were found to have other ocular or systemic features consistent with their molecular diagnosis and consequently had a change in clinical diagnosis. A molecular diagnosis for glaucoma was not achieved in any individual with glaucoma associated with acquired conditions or glaucoma following cataract surgery. The distribution of associated genes per glaucoma subtype per proband, after reclassification, are presented in Figure 1. Figure S3 (available at www.aaojournal.org) conversely shows the distribution of glaucoma subtypes per associated gene.

Primary Congenital Glaucoma

The majority of probands with PCG (135/148, 91.2%) were genetically tested, and 30.4% were given a molecular diagnosis (41/135). Biallelic variants in *CYP1B1* (n = 21, 15.6%), *CPAMD8* (n = 5, 3.7%), and *COL18A1* (n = 1, 0.7%), and heterozygous variants in *TEK* (n = 8, 5.9%), *FOXC1* (n = 5, 3.7%), and *ANGPT1* (n = 1, 0.7%) were found. One individual with a homozygous variant in *CYP1B1* reported parental consanguinity. Biallelic variants in *CYP1B1* were present in 7 of 80 male and 14 of 55 female probands with PCG who underwent genetic testing ($P = 0.02$).

After genetic diagnosis, 24.4% of PCG probands (10/41) had a reclassification of their clinical diagnosis based on reexamination. All individuals with *FOXC1* variants were consequently found to have features of ARS and were reclassified to have glaucoma associated with nonacquired ocular anomalies. One individual did

Table 2. Early Onset Glaucoma (diagnosed between age 18−<40 years)

	JOAG	Acquired Condition	Nonacquired Ocular Anomalies	Nonacquired Systemic Disease	Following Cataract Surgery	Total	P Value
All cases n (%)	271 (73.2)	49 (13.2)	44 (11.9)	5 (1.4)	1 (0.3)	370 (100.0)	–
Eyes n (%)	513 (74.8)	82 (12.0)	79 (11.5)	10 (1.5)	2 (0.3)	686 (100.0)	–
Bilateral n (%)	247/266 (92.9)	33/49 (67.3)	35/44 (79.5)	5/5 (100.0)	1/1 (100.0)	321/365 (87.9)	**<0.001***
Male gender n (%)	147/271 (54.2)	36/49 (73.5)	22/44 (50.0)	0/5 (0.0)	0/1 (0.0)	205/370 (55.4)	**0.002***
Probands n (%)	250 (72.7)	49 (14.2)	40 (11.6)	4 (1.2)	1 (0.3)	344 (100.0)	–
Family history n (%)	187/246 (76.0)	25/45 (55.6)	24/39 (61.5)	2/3 (66.7)	0/1 (0.0)	238/334 (71.3)	**0.007***
European ancestry n (%)	190/242 (78.5)	37/45 (82.2)	25/34 (73.5)	4/4 (100.0)	1/1 (100.0)	257/326 (78.8)	0.76*
Highest recorded IOP (mmHg)	29 (23−38)	36 (30−48)	39 (28−45)	35 (29−47)	23 (n/a)	30 (24−40)	**0.002†**
Age at diagnosis (yrs)	34 (29−37)	32 (30−37)	31 (25−35)	23 (21−30)	20 (n/a)	33 (28−36)	**0.03†**

IOP = intraocular pressure; JOAG = juvenile open-angle glaucoma; n/a = not available
Totals for each variable may not equal the total number of cases because of missing data. Highest recorded IOP and age at diagnosis are presented as median (interquartile range). All cases include probands and nonprobands. European ancestry and family history were calculated for probands only. Bold values indicate statistical significance ($P < 0.05$).
*Fisher exact test.
†Median test.

not have any evident ocular features of ARS after thorough reexamination, but based on systemic features associated with ARS, was reclassified into this category with other individuals with ARS.[5] Four of the 5 probands with biallelic *CPAMD8* variants were found to have features consistent with unclassified ASD,[13] and the individual with biallelic *COL18A1* variants was subsequently discovered to have Knobloch syndrome. These individuals were reclassified to have glaucoma associated with nonacquired ocular anomalies.

Juvenile Open-Angle Glaucoma

Collectively, 15.5% of tested JOAG probands across both cohorts (39/252) received a molecular diagnosis, including 30.8% (12/39) of those with childhood-onset and 12.7% (27/213) of those with early onset glaucoma.

The results consisted of biallelic variants in *CYP1B1* (n = 8, 3.2%) and *CPAMD8* (n = 1, 0.4%), heterozygous variants in *MYOC* (n = 24, 9.5%), *FOXC1* (n = 2, 0.8%), *OPTN* (n = 1, 0.4%), and *COL2A1* (n = 1, 0.4%), and copy number variants of

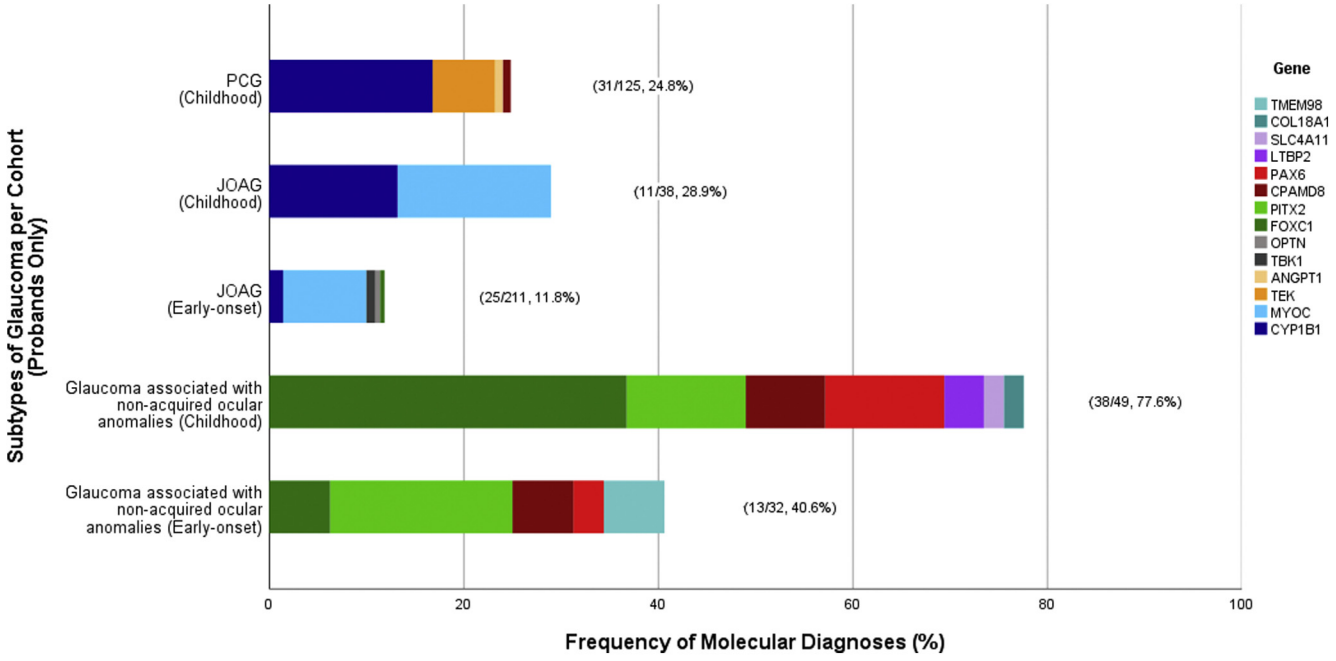

Figure 1. Frequencies of molecular diagnoses in tested probands stratified by Childhood Glaucoma Research Network (CGRN) classification (after reclassification postgenetic diagnosis). The number of genetically tested probands who had a molecular diagnosis within each cohort is included after each respective bar. Glaucoma associated with acquired conditions and glaucoma following cataract surgery were excluded because no molecular diagnoses were determined. Glaucoma associated with nonacquired systemic disease and unclassified glaucoma classifications were also excluded because of the small number of probands. JOAG = juvenile open-angle glaucoma; PCG = primary congenital glaucoma.

TBK1 (n = 2, 0.8%). Upon reexamination, the individual with biallelic *CPAMD8* variants was found to have unclassified ASD,[13] and the individual with a *COL2A1* variant had a history of retinal detachment and joint problems consistent with Stickler syndrome. One of the 2 individuals with a *FOXC1* variant,[5] who was from the childhood cohort, had a revised diagnosis of ARS upon reexamination, and the other individual did not have any ocular anomalies or systemic features consistent with ARS.

Glaucoma Associated with Nonacquired Ocular Anomalies

A molecular diagnosis was determined in 56.5% of probands (39/69) with glaucoma associated with nonacquired ocular anomalies. The most frequent variants found included heterozygous variants in *FOXC1* (n = 14, 20.3%), *PITX2* (n = 12, 17.4%), and *PAX6* (n = 7, 10.1%). Less frequent findings included biallelic variants in *LTBP2* (n = 2, 2.9%), *TMEM98* (n = 2, 2.9%), *SLC4A11* (n = 1, 1.4%), and *CPAMD8* (n = 1, 1.4%).

All individuals with an original clinical diagnosis of glaucoma associated with nonacquired ocular anomalies and *FOXC1* variants had ARS,[14] and all individuals with *PAX6* variants had phenotypes consistent with aniridia.[15] All individuals with *PITX2* variants except 1 had ARS, whereas the remaining individual had Peters' anomaly.[14] Meanwhile, biallelic *TMEM98* variants were found in individuals with nanophthalmos,[16] and biallelic *SLC4A11* variants were found in an individual with congenital hereditary endothelial dystrophy. Biallelic *LTBP2* variants were associated with microspherophakia in 1 individual who reported parental consanguinity and widespread peripheral anterior synechiae, high myopia, and phacodonesis in another. The latter individual was determined to have unclassified ASD. The individual with biallelic variants in *CPAMD8* also had unclassified ASD.[13]

Glaucoma Associated with Nonacquired Systemic Disease

A total of 71.4% of probands (5/7) with an original clinical diagnosis of glaucoma associated with a nonacquired systemic disease were given a molecular diagnosis. Two individuals with neurofibromatosis type 1 were found to have heterozygous variants in *NF1*, 1 of whom reported parental consanguinity. Genetic results also confirmed the clinical diagnoses of Weill-Marchesani syndrome (*ADAMTS17*), Nail Patella syndrome (*LMX1B*), and Stickler syndrome (*COL2A1*) in 1 individual each. No molecular diagnosis was determined for the other 2 probands who had a clinical diagnosis of Sturge-Weber syndrome.

Unclassified Glaucoma

One of 2 probands (50%) with this classification underwent genetic testing. This individual was found to have biallelic *LTBP2* variants with a history of aphakia after removal of congenital cataracts and glaucoma onset by 1 year of age. It could not be ascertained whether glaucoma preceded or followed cataract surgery.

Genotype-Phenotype Correlations

The demographic and clinical characteristics of cases associated with each gene are presented in Table 3. Biallelic variants in *CYP1B1* (n = 29, 23.2%) and heterozygous variants in *MYOC* (n = 24, 19.2%) and *FOXC1* (n = 21, 16.8%) were the most common in all probands with a molecular diagnosis (n = 125). Bilateral glaucoma was least common in individuals with *TEK* (9/12, 75.0%) and *NF1* variants (1/2, 50%). Overall, a molecular diagnosis was less prevalent in male than female individuals (73/168, 43.5% vs. 95/168, 56.5%). The number of female individuals with biallelic *CYP1B1* variants was twice the number of male individuals (24/36, 66.7% vs. 12/36, 33.3%, 95% CI, 0.490−0.814, P = 0.03). Biallelic *LTBP2* variants were exclusively found in individuals of self-reported Middle Eastern ancestry in our dataset, and 28.6% of *CYP1B1* variants were identified in probands of non-European descent.

The median age at glaucoma diagnosis was lowest in individuals with *CPAMD8* (0 [0−17] years), *TEK* (0.17 [0−0.25] years), and *CYP1B1* variants (0.14 [0−8] years), which is consistent with those who were clinically diagnosed with PCG. The median age at glaucoma diagnosis was highest in individuals with heterozygous variants in *OPTN* (33 [30−35] years) and *MYOC* (29 [15−35] years), and *TBK1* copy number variants (30 [25−38] years). These variants were found exclusively in individuals with JOAG, with the exception of 1 nonproband with a *MYOC* variant and PCG. The lowest median maximum IOP was recorded in individuals with *TBK1* copy number variants (13 [13−14] mmHg) and *OPTN* variants (18 [17−18] mmHg), consistent with their diagnoses of NTG. *TBK1* copy number variants and *OPTN* variants were found in 14.3% (2/14) and 7.1% (1/14) of probands with NTG, respectively, all of whom had European ancestry.

Discussion

The CGRN classification system for childhood glaucoma offers well-defined guidelines and enables reproducible and transparent categorization of individuals with the disease.[2] It has since been adopted by several studies,[23−28] enabling thorough and accurate comparisons of childhood glaucoma phenotypes in other populations. In this study, we did not include individuals who were glaucoma suspects because it is not the primary aim of our registry to recruit these individuals. To the best of our knowledge, this cohort represents the largest childhood glaucoma cohort of European ancestry and one of the largest international cohorts reported (290 cases). Previous published studies that used the CGRN classification include cohorts from Akron, Ohio (108 cases),[23] Miami, Florida (205 cases),[24] Egypt (207 cases),[25] South India (275 cases),[26] and Brazil (496 cases),[27] and an international study (441 cases) that included cohorts from India, United States, United Kingdom, Saudi Arabia, Ghana, Singapore, Israel, and Germany, comprising just 89 cases of European ancestry.[28]

The spectrum of childhood glaucoma diagnoses in a given study depends on the composition of the population studied and potential recruitment biases. In this study, PCG was the most prevalent subtype of childhood glaucoma (57.6%), whereas glaucoma associated with acquired conditions was the least common (1.0%). Given that a major goal of our glaucoma registry (ANZRAG) is to identify the genetic causes of glaucoma, individuals with acquired childhood glaucoma were not actively recruited (e.g., traumatic and uveitic glaucoma), explaining the lower representation of cases in this group. Individuals with glaucoma associated with nonacquired systemic disease or glaucoma after cataract surgery were similarly not actively recruited. Other studies applying the CGRN classifications reported PCG among 32% to 55% of their childhood

Table 3. Demographic and Clinical Associations of Genes Associated with Childhood and Early Onset Glaucoma Cases with a Molecular Diagnosis

Gene (Inheritance)	All Cases, n (%)	Eyes, n (%)	Bilateral, n (%)	Male Gender, n (%)	Probands, n (%)	European Ancestry, n (%)	Family History, n (%)	Highest Recorded IOP (mmHg)	Age at Diagnosis (yrs)	Cases Described Elsewhere
CYP1B1 (AR)	36 (21.4)	70 (21.7)	35/35 (100.0)	12/36 (33.3)	29 (23.2)	20/28 (71.4)	15/28 (53.6)	38 (30–40)	0.14 (0–8)	[11]
MYOC (AD)	36 (21.4)	71 (22.0)	35/36 (97.2)	16/36 (44.4)	24 (19.2)	21/24 (87.5)	24/24 (100.0)	40 (29–45)	29 (15–35)	[17]
FOXC1 (AD)	28 (16.7)	53 (16.4)	25/28 (89.3)	13/28 (46.4)	21 (16.8)	13/20 (65.0)	14/21 (66.7)	32 (24–41)	3 (0.11–14)	[5,14]
PITX2 (AD)	15 (8.9)	29 (9.0)	14/15 (93.3)	8/15 (53.3)	12 (9.6)	12/12 (100.0)	8/12 (66.7)	40 (28–52)	14 (8–21)	[14]
TEK (AD)	12 (7.1)	21 (6.5)	9/12 (75.0)	7/12 (58.3)	8 (6.4)	8/8 (100.0)	2/8 (25.0)	27 (22–37)	0.17 (0.0–0.25)	[18,19]
CPAMD8 (AR)	9 (5.4)	18 (5.6)	9/9 (100.0)	4/9 (44.4)	7 (5.6)	6/7 (85.7)	5/7 (71.4)	40 (38–44)	0 (0–17)	[13]
PAX6 (AD)	7 (4.2)	13 (4.0)	6/7 (85.7)	4/7 (57.1)	7 (5.6)	7/7 (100.0)	4/6 (66.7)	42 (39–48)	8 (4–14)	[15]
TBK1 (AD)	6 (3.6)	11 (3.4)	5/6 (83.3)	3/6 (50.0)	2 (1.6)	2/2 (100.0)	2/2 (100.0)	13 (13–14)	30 (25–38)	[12]
LTBP2 (AR)	5 (3.0)	10 (3.1)	5/5 (100.0)	2/5 (40.0)	3 (2.4)	0/3 (0.0)	3/3 (100.0)	40 (40–43)	4 (1–4)	–
OPTN (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	1/2 (50.0)	1 (0.8)	1/1 (100.0)	1/1 (100.0)	18 (17–18)	33 (30–35)	–
COL2A1 (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	1/2 (50.0)	2 (1.6)	2/2 (100.0)	2/2 (100.0)	29 (23–35)	25 (21–28)	–
TMEM98 (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	1/2 (50.0)	2 (1.6)	1/1 (100.0)	2/2 (100.0)	41 (40–42)	26 (21–31)	[16]
LMX1B (AD)	2 (1.2)	4 (1.2)	2/2 (100.0)	0/2 (0.0)	1 (0.8)	1/1 (100.0)	1/1 (100.0)	45 (29–60)	30 (30–30)	–
NF1 (AD)	2 (1.2)	3 (0.9)	1/2 (50.0)	0/2 (0.0)	2 (1.6)	1/2 (50.0)	1/2 (50.0)	35 (32–38)	0.0 (0–0)	–
ADAMTS17 (AR)	1 (0.6)	2 (0.6)	1/1 (100.0)	0/1 (0.0)	1 (0.8)	1/1 (100.0)	0/0 (0.0)	47 (n/a)	18 (n/a)	–
ANGPT1 (AD)	1 (0.6)	2 (0.6)	1/1 (100.0)	0/1 (0.0)	1 (0.8)	1/1 (100.0)	0/1 (0.0)	29 (n/a)	0.30 (n/a)	[20]
COL18A1 (AR)	1 (0.6)	2 (0.6)	1/1 (100.0)	1/1 (100.0)	1 (0.8)	0/1 (0.0)	1/1 (100.0)	22 (n/a)	11 (n/a)	–
SLC4A11 (AR)	1 (0.6)	2 (0.6)	1/1 (100.0)	0/1 (0.0)	1 (0.8)	0/1 (0.0)	0/1 (0.0)	41 (n/a)	0.20 (n/a)	–
Total	168 (100.0)	323 (100.0)	156/167 (93.4)	73/168 (43.5)	125 (100.0)	97/122 (79.5)	85/122 (69.7)	35 (27–44)	9 (0.17–25)	

AD = autosomal dominant; AR = autosomal recessive; IOP = intraocular pressure; n/a = not available.
Totals for each variable may not equal the total number of cases because of missing data. Highest recorded IOP and age at diagnosis are presented as median (interquartile range). All cases include probands and nonprobands. European ancestry and family history were calculated for probands only, and all other variables were calculated using data from all cases (where available).

glaucoma cohort,[24–28] similar to this study. The estimated incidence of PCG in Australia is 1:30 000 births,[29] but incidence figures increase up to 9-fold in populations with higher rates of parental consanguinity.[30] The high proportion of PCG cases in our cohort may be explained by a recruitment bias or may reflect the diverse ethnic background of the population studied, with 24.6% of PCG cases self-reporting non-European ancestry. The population of Australia and New Zealand is just over 30 million, thus a rate of PCG affecting 1/30 000 would suggest there would be 1000 cases of PCG (all ages) in the 2 countries, of whom we have recruited 167 (16.7% of the predicted total).

The lack of classification systems for individuals with early onset glaucoma (defined here as disease diagnosis between age 18 to <40 years) makes it difficult to understand the underlying causes in this heterogeneous group. Moreover, global prevalence rates appear to discount this age group, with reports typically including only individuals aged 40 years and above.[31] We therefore opted to apply the CGRN classifications to early onset glaucoma cases in this study. This process was simple, and individuals were assigned a diagnostic category without overlap. With this classification, JOAG was the most common diagnosis (73.2%), followed by glaucoma associated with acquired conditions (13.2%). Birla et al[32] emphasized that individuals diagnosed with glaucoma before the age of 40 years require a more formalized phenotypic classification system. Using a cluster analysis based on iris and angle morphology, they reported angle abnormalities in two-thirds of individuals with JOAG.[32] Such features may represent an otherwise distinct ocular phenotype that may be crucial for genetic analyses. We support the use of a unified classification system to group phenotypically diverse early onset glaucomas, which is offered by the CGRN classification system.[2] Further subtyping of ocular anomalies is encouraged under each CGRN classification and enables a better understanding of disease phenotypes and genetic diagnoses in this age group.

Previous studies have reported on the contribution of specific genes in childhood glaucoma (e.g., *CYP1B1*)[33] or the diagnostic yield using exome sequencing in some glaucoma subtypes (e.g., anterior segment disorders).[34] However, no studies have reported the diagnostic yield in a comprehensive cohort of heterogeneous childhood or early onset glaucoma. In total, pathogenic variants in 18 genes were reported across the entire cohort. Targeted genetic testing was successful in identifying a variant in 75.2% of probands with a molecular diagnosis, whereas whole-exome or genome sequencing was required to identify variants in the remaining probands. Similar to inherited retinal diseases and congenital cataracts, the genetic heterogeneity in our cohort supports the use of a comprehensive gene panel testing approach inclusive of all genes with evidence of association to childhood and early onset glaucoma. Additional screening for variants in the *CHRDL1* gene may be indicated where an individual has megalocornea and a diagnosis of PCG is under consideration.

Biallelic *CYP1B1* variants were the most common genetic diagnosis in PCG (15.6%). This is similar to the prevalence reported by other studies on populations of European ancestry (15%–22%),[35,36] yet lower than other populations with high consanguinity, as expected for variants associated with an autosomal recessive trait.[37] We found a significant gender difference in those with *CYP1B1* variants and PCG, with a male:female ratio of 1:2, whereas in the whole PCG cohort the male:female ratio was 1.46:1. Previous studies have reported the same trend of male preponderance in PCG,[24,25,27] whereas 2 studies reported a higher proportion of female individuals with *CYP1B1* variants and PCG.[38,39] This raises the possibility that 1 or more unidentified genes causing PCG in male individuals may be sex linked. Additionally, the higher proportion of female individuals with *CYP1B1* variants may be related to the fact that *CYP1B1* variants have been found to reduce the metabolism of 17β-estradiol, an estrogen steroid hormone that is found within the trabecular meshwork.[40] Its role in PCG pathogenesis, however, is not yet fully understood, and additional studies are needed to understand the sex bias observed in this study. Meanwhile, one-third of PCG probands had a family history of glaucoma. This reflects the current genetic landscape of PCG caused by variants in genes inherited in an autosomal recessive manner (e.g., *CYP1B1*) or an autosomal dominant manner with incomplete penetrance (e.g., *TEK*).

Heterozygous variants in *MYOC* were the major genetic cause of JOAG (9.5%). Our group previously reported *MYOC* variants in 17% of 103 individuals with JOAG with advanced visual field loss, highlighting that *MYOC* variants are associated with more severe disease in primary glaucoma.[17] *MYOC* is otherwise reported in 8% to 36% of JOAG cases and variants are typically associated with HTG,[41,42] whereas *TBK1* copy number variants and *OPTN* variants are typically associated with NTG, consistent with our study results.[12,43] Biallelic variants in *CYP1B1* were implicated in 3.2% of probands with JOAG, similar to previously reported results by our group.[11]

The highest diagnostic yield was achieved in probands with glaucoma associated with nonacquired ocular anomalies (56.5%). This is not surprising considering that the majority of this cohort comprises individuals with ARS, which has a reported diagnostic yield of 40% to 63%,[34,44,45] mainly accounted for by variants in *FOXC1* and *PITX2*. The diagnostic yield improved once probands were reclassified into this category, most of whom had an initial clinical diagnosis of PCG. We have previously reported the challenges associated with ASD diagnoses with subtle features that can be clinically diagnosed as PCG in individuals with variants in *FOXC1*.[5] The difficulty of examining the anterior segment to diagnose ASD in infants and the absence of some associated systemic features (e.g., dental anomalies) in infants can make clinical diagnoses of PCG and ASD challenging and highlight the importance of genetic testing in reaching an accurate diagnosis. This is illustrated by 1 individual in this study diagnosed with

PCG and a heterozygous variant in *FOXC1* with systemic features consistent with ARS (hearing loss, congenital heart defect) yet no ocular features of Axenfeld-Rieger anomaly found on detailed examinations under anesthesia. Despite the absence of ocular features, this individual was reclassified as having glaucoma associated with nonacquired ocular anomalies based on the presence of systemic features and genetic results consistent with ARS. A heterozygous variant in *FOXC1* was also found in an individual with JOAG who had no ocular or systemic features consistent with ARS. This phenomenon has been reported before in 2 other cases of JOAG,[46] although both individuals were reported as having posterior embryotoxon. Although posterior embryotoxon is not considered as a diagnostic feature in ARS,[8] it may represent a subtle ocular phenotype in such individuals. Individuals with PCG and biallelic *CPAMD8* variants were reclassified as having glaucoma associated with nonacquired ocular anomalies and the subtype of unclassified ASD, as described before.[13] Biallelic variants in *CPAMD8* have been reported in individuals with unclassified ASD[47] and PCG.[47,48] Currently, ASD is the more common found ocular phenotype in individuals with biallelic *CPAMD8* variants.

The number of individuals with glaucoma associated with nonacquired systemic disease in our cohort was low, most likely explained by the fact that the ANZRAG did not initially aim to recruit these individuals. However, this cohort may represent an underdiagnosed group as illustrated by the individual with a clinical diagnosis of JOAG but a genetic diagnosis indicative of Stickler syndrome (heterozygous *COL2A1* variant). This is supported by a recent study reporting systemic abnormalities in 12.9% of individuals with childhood glaucoma[49] and emphasizes the importance of referring individuals to a genetic service for a thorough medical examination to refine clinical diagnosis. Our cohort otherwise reported a molecular diagnosis in 71.4% of individuals with the remaining 2 genetically undiagnosed probands having Sturge-Weber syndrome. Sturge-Weber syndrome is caused by somatic variants in *GNAQ*, and consequently individuals require a biopsy of an affected tissue (typically skin) for molecular diagnosis.[50]

Reaching a molecular diagnosis has several benefits for affected individuals and their families. In this study, 10.4% of individuals had a change of clinical diagnosis based on genetic results. These individuals and their family members can now be accurately counseled about the mode of inheritance and the risks for relatives. At-risk family members can benefit from predictive genetic testing, and parents of affected individuals can consider reproductive options. Individuals with syndromic glaucoma can benefit from appropriate referrals for the management of associated systemic features that require specialized care. Finally, future therapeutic approaches may be gene-specific, similar to inherited retinal diseases, highlighting the importance of molecular diagnosis in precision medicine.

Study Limitations

Study limitations include missing clinical and demographic information for some participants. Furthermore, clinical diagnoses of participants were obtained by the treating specialists, which may have introduced some variation or bias. However, this reflects a genuine representation of the clinical diagnostic landscape of childhood and early onset glaucoma across Australasia. Genetic testing is an ongoing process of the ANZRAG and is therefore not complete for all individuals included in this study who may have been recruited but full genetic analyses were not yet available. Furthermore, a known limitation of exome and genome sequencing is the insufficient coverage of some exons or gene regions.[5] Therefore, it is possible that some disease-causing variants in known or novel glaucoma genes were not sufficiently covered or interrogated, including deep intronic variants, copy number variants, and structural variants. This may lead to an underestimated diagnostic rate in this cohort. Additionally, our recruitment is somewhat biased toward individuals with glaucoma suspected to be genetic in origin because this was the original design of the ANZRAG. Consequently, those with acquired glaucoma, including those with glaucoma after ocular trauma or cataract surgery, may be underrepresented, and we expect the prevalence of these conditions to be higher in the wider population. Finally, the genetic architecture of a cohort depends on its ancestry. Our cohort is predominantly of European ancestry, although 23.8% of the cohort reported a different ancestry, which reflects the diverse ancestral lineage of individuals in Australasia. The prevalence of different glaucoma subtypes and diagnostic yield in populations of non-European ancestry should be reported in future studies.

In conclusion, the present study reported the glaucoma phenotypes in the largest Australasian cohort with disease onset before the age of 40 years, according to the CGRN classification system. It is also the largest study to ascribe genetic findings according to these criteria. We have identified a diagnostic yield of 37.6% in probands with childhood glaucoma and 14.7% in probands with early onset glaucoma. These findings contribute to our understanding of childhood and early onset glaucoma phenotypes and their genetic basis. The diagnostic yield in this rare and heterogeneous disease supports the need for international collaborative efforts to identify new genetic associations. Our results emphasize the importance of accurate clinical diagnosis and the genetic heterogeneity of the disease, and support the development of a childhood and early onset genetic testing panel that will ultimately become critical in the age of gene therapy for glaucoma.

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Footnotes and Disclosures

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[1] Department of Ophthalmology, Flinders University, Flinders Medical Centre, Adelaide, Australia.

[2] Department of Ophthalmology, Royal Children's Hospital, Melbourne, Australia.

[3] Ophthalmology, Department of Surgery, University of Melbourne, Melbourne, Australia.

[4] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, Melbourne, Australia.

[5] Discipline of Ophthalmology, Save Sight Institute, Faculty of Medicine and Health, University of Sydney, Sydney, Australia.

[6] Department of Ophthalmology, The Children's Hospital at Westmead, Sydney, Australia.

[7] Department of Ophthalmology, Macquarie University Hospital, Sydney, Australia.

[8] University of Queensland Children's Health Queensland Clinical Unit, Queensland Children's Hospital, Brisbane, Australia.

[9] Department of Ophthalmology, Queensland Children's Hospital, Brisbane, Australia.

[10] Terrace Eye Centre, Brisbane, Australia.

[11] South Australian Genomics Centre, South Australian Health & Medical Research Institute, Adelaide, Australia.

[12] Robinson Research Institute, University of Adelaide, Adelaide, Australia.

[13] Adelaide Medical School, University of Adelaide, Adelaide, Australia.

[14] Department of Paediatrics, University of Melbourne, Melbourne, Australia.

[15] Department of Ophthalmology, New Zealand National Eye Centre, Faculty of Medical and Health Science, University of Auckland, Auckland, New Zealand.

[16] Eye Department, Greenlane Clinical Centre, Auckland District Health Board, Auckland, New Zealand.

[17] Lions Eye Institute, Centre for Vision Sciences, University of Western Australia, Perth, Australia.

[18] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia.

*The authors O.M.S., E.S., and J.E.C. contributed equally.

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Author Contributions:

Conception and design: Knight, Ruddle, Siggs, Souzeau, Craig

Data collection: Knight, Ruddle, Taranath, Goldberg, Smith, Gole, Chiang, Willett, D'Mellow, Breen, Elder, Vincent, Staffieri, Kearns, Mackey, Luu, Siggs, Souzeau, Craig

Analysis and interpretation: Knight, Ruddle, Breen, Qassim, Mullany, Siggs, Souzeau, Craig

Obtained funding: Mackey, Siggs, Souzeau, Craig

Overall responsibility: Knight, Ruddle, Taranath, Goldberg, Smith, Gole, Chiang, Willett, D'Mellow, Breen, Qassim, Mullany, Elder, Vincent, Staffieri, Kearns, Mackey, Luu, Siggs, Souzeau, Craig

Abbreviations and Acronyms:
ANZRAG = Australian and New Zealand Registry of Advanced Glaucoma; **ARS** = Axenfeld-Rieger spectrum; **ASD** = anterior segment dysgenesis; **CGRN** = Childhood Glaucoma Research Network; **CI** = confidence interval; **HTG** = high-tension glaucoma; **IOP** = intraocular pressure; **JOAG** = juvenile open-angle glaucoma; **NTG** = normal-tension glaucoma; **PCG** = primary congenital glaucoma.

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Correspondence:
Lachlan S.W. Knight, BHSc, MOrth, Level 2 Car Park Tenancies, 1 Flinders Drive, Bedford Park, SA, 5042, Australia. E-mail: Lachlan.WheelhouseKnight@flinders.edu.au.

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Publication F2. Quality of life in children with glaucoma: a qualitative interview study in Australia

BMJ Open

Quality of life in children with glaucoma: a qualitative interview study in Australia

Lachlan S W Knight ,[1,2] Bronwyn Ridge,[1] Sandra E Staffieri,[3,4,5] Jamie E Craig,[1] Mallika Prem Senthil,[6] Emmanuelle Souzeau[1]

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For numbered affiliations see end of article.

Correspondence to
Mr Lachlan S W Knight; lachlan.wheelhouseknight@flinders.edu.au

ABSTRACT

Objective Childhood glaucoma is a chronic vision-threatening condition that may significantly impact an individual's psychosocial well-being. There is a paucity of literature investigating the quality of life (QoL) in children with glaucoma. The aim of this study was to investigate and report on the QoL issues encountered by children with glaucoma.

Design This is a qualitative interview study. Data were collected through semistructured interviews. NVivo V.12 software (QSR International Pty Ltd, Melbourne, Australia) was used to analyse and code data to identify QoL themes. The prominence of QoL themes was determined by the number of children who raised issues connected to the corresponding theme.

Setting Interviews were conducted via telephone or videoconferencing between April 2020 and July 2021.

Participants Eighteen children with glaucoma, aged 8–17 years, who resided in Australia, were recruited from the Australian and New Zealand Registry of Advanced Glaucoma.

Results Median child age was 12.1 years (IQR: 9.7–14.5 years) and 33% were female. Seven QoL themes were identified: 'coping', 'inconveniences' and 'emotional well-being' were more prominent themes than 'symptoms', 'ocular health concerns', 'social well-being' and 'autonomy'. Adaptive coping strategies included resilience throughout clinical examinations and establishing positive relationships with ophthalmologists. These minimised inconveniences related to clinic waiting times and pupillary dilatation. External to the clinical setting, children often dissociated from their glaucoma but struggled with glare symptoms and feeling misunderstood by fellow peers. Older children aged 13–17 years commonly disengaged from their glaucoma care and expressed an unwillingness to attend ophthalmic appointments. Older children further raised issues with career options, obtaining a driver's licence and family planning under the theme of autonomy.

Conclusions The psychosocial impact of childhood glaucoma extends beyond the clinical environment and was minimised using coping strategies. Older children may require additional social and ophthalmic support as they transition into adulthood.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study used an appropriate qualitative method to develop a novel and in-depth insight into the quality of life (QoL) issues experienced in childhood glaucoma from the perspectives of children.
⇒ This study included individuals with varied disease characteristics and thus detailed the lived experience of the disease as a whole.
⇒ Participants were recruited from a national registry and thus may be more willing to participate and may be experiencing a better QoL than non-participants.
⇒ Participants were mostly of European ancestry and resided in Australia, which may limit the generalisability of the results.

INTRODUCTION

Childhood glaucoma describes a heterogeneous group of rare chronic vision-threatening disorders with onset occurring at any age from birth to less than 18 years of age.[1] It is typically characterised by elevated intraocular pressure (IOP) and irreversible optic neuropathy. Primary childhood glaucoma is caused by isolated abnormal development of the anterior chamber angle and includes primary congenital glaucoma and juvenile open-angle glaucoma.[1] Secondary childhood glaucoma includes glaucomatous disease that is associated with either other ocular anomalies (eg, aniridia, Axenfeld-Rieger syndrome), an underlying systemic condition (eg, Sturge-Weber syndrome) or an acquired ocular condition (eg, uveitis, trauma).[1] On diagnosis, surgical intervention is typical, and lifelong monitoring with or without additional surgical interventions and/or adjuvant topical therapies to manage IOP and prevent vision loss is generally required.[2] Additional symptoms can include glare and high myopia, and a child may experience cosmetic concerns associated with buphthalmos, occlusion therapy for amblyopia and spectacle wear.[3]

Children with glaucoma may experience several visual and non-visual challenges as they adapt to living with the condition. However, there is a paucity of literature exploring

the impact of these challenges on quality of life (QoL). Previous research is limited to quantitative association studies that use non-glaucoma specific patient-reported outcome measures (PROMs) that were designed to measure the impact of vision impairment on QoL (called vision-related QoL (VR-QoL))[4–7] or the impact on overall well-being (called health-related QoL (HR-QoL)).[7 8] This is because a childhood glaucoma-specific PROM does not exist. Consequently, the results from these studies may not be providing an accurate account of QoL in children with glaucoma. Nonetheless, several studies have reported that children with glaucoma who have lower best-corrected visual acuity (BCVA) experienced lower VR-QoL.[4–7] Meanwhile, a younger age has been associated with lower VR-QoL and HR-QoL.[7 8] However, there has been limited investigation as to why this trend was observed.[7 8] A qualitative inquiry is therefore required to explore disease-specific issues that are associated with QoL in children with glaucoma. Findings from this study will inform the development of a childhood glaucoma-specific PROM for future related research and clinical implementation.

METHODS

Methodology

This study used a postpositivist paradigm to identify QoL issues.[9] This approach was used because we had a theoretical interest in how glaucoma may impact a child's QoL. This was formed by prior literature and our own clinical and research experience. Postpositivism further allows the calculation of the number of children represented within each theme.[9] This was considered useful in enhancing the readability of qualitative findings for positivist researchers and clinicians (eg, ophthalmologists) who are instrumental in the care of children with glaucoma. Meanwhile, postpositivism acknowledges that the researchers' experiences may influence data collection and interpretation (ie, researcher objectivity is not entirely possible).[9]

Participants

Children were recruited from a large Australasian disease registry, the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG),[10] using a non-probability convenience sampling technique. Children were eligible to be interviewed if they currently resided in Australia, were English speaking, had a diagnosis of any subtype of glaucoma as per the Childhood Glaucoma Research Network criteria[1] and were aged between 8 and <18 years. Children aged ≥8 years are more likely to reliably and independently understand questions relating to QoL than children aged <8 years.[11] Children were excluded if they had coexisting ocular disease unrelated to childhood glaucoma or had a hearing or cognitive impairment or other disability impacting on QoL (eg, intellectual disability) as informed by their referring specialist or parent/guardian (henceforth abbreviated to parent).

Eligible children, and their parent/s, were posted an invitation to be interviewed and asked to return their interest. If both parties expressed interest, an information pack and consent form were sent. An interview was arranged once written informed consent from one parent and assent from the child were provided. If no response was received within 2 weeks, parents received a follow-up phone call. Children were deemed non-contactable after at least two unsuccessful attempts.

Children's clinical details were obtained from their most recent medical record and included: glaucoma subtype, age at diagnosis, disease laterality, BCVA (logMAR), IOP, number of surgical interventions and number of topical antiglaucoma medications currently being used. The International Classification of Diseases for Mortality and Morbidity Statistics (11th revision)[12] was used to categorise BCVA per eye. Because visual field information was not available for every child, BCVA was used as a measure of disease severity. For analysis, children's ages were grouped into 8–12 years and 13–17 years, as per the Pediatric Quality of Life Inventory V.4.0 (PedsQL).[13] Glaucoma onset at ≥4 years was considered juvenile.[1]

Interviews

A semistructured interview guide was developed from a literature review of VR-QoL and HR-QoL PROMs (see online supplemental file 1, which details the semi-structured interview guide used).[13–17] Interviews were conducted in the English language by one of two authors with qualitative research experience (LSWK and BR). LSWK is a clinical and research orthoptist, and BR is a health counsellor. No participants were under the clinical care of either interviewer. The child and parent/s were informed that the interviewers were completing a higher research degree. One-on-one semistructured interviews occurred via telephone or Cisco WebEx videoconferencing (Milpitas, California, USA), subject to the child's preference. Children aged <16 years required a parent chaperone, and parents were not to answer questions on their child's behalf. Interviews were audio-recorded and transcribed verbatim. Interview transcripts and overall findings were not returned to children for accuracy or feedback as it was considered burdensome to the child and unethical (ie, the maturity and comprehension required to understand their contents could not be assured). Instead, at the conclusion of each interview, the child was provided with a verbal summary of their responses for confirmation that they had been interpreted correctly. Interviews continued until thematic saturation was achieved (ie, the point where no new information was gained from subsequent interviews).[18] Thematic saturation occurred after the 14th interview. An additional four interviews with participants already recruited to the study were conducted to confirm data saturation. Recruitment ceased thereafter.

Data analysis

A general inductive approach was used to identify QoL themes.[19] Transcripts were systematically coded using QSR NVivo V.12 (QSR International Pty Ltd, Melbourne, Australia) by one author (LSWK) during the study recruitment period. To ensure research credibility, stakeholder coding checks were frequently and separately performed by three authors (BR, MPS and ES).[19] Major QoL themes and their subthemes were determined by grouping codes with similar or repetitive patterns of meaning[20] and were abbreviated to be consistent with our previous ophthalmic QoL research pertaining to QoL issues encountered in adults with childhood glaucoma.[21] The prominence of QoL themes was determined by the number of children who raised issues connected to the corresponding theme. Statistical calculations were performed using SPSS V.27.0 for Windows (IBM/SPSS Inc). The datasets generated for the current study are not publicly available. This is to protect the confidentiality of research participants.

Patient and public involvement

Authors (LSWK, BR and ES) presented the research aims at a national childhood glaucoma support group meeting prior to conducting the research. Engagement with attendees assisted in the development of the interview guide, and it was agreed that research findings would be disseminated back to the childhood glaucoma community.

RESULTS

Fifty-four eligible children from the ANZRAG were invited to participate and 18 (33%) were interviewed (see online supplemental figure S1, which depicts the recruitment of participants). The proportion of participants and non-participants with bilateral disease was significantly different (11/18, 61% vs 34/36, 94%, respectively, p=0.004), while all other demographic and clinical variables were similar (see online supplemental table S1). Reasons for declining to participate were not recorded due to the sensitive nature of the study.

Interviews were conducted between April 2020 and July 2021. The average interview length was 30±14 min, and the median age of children interviewed was 12.1 years (IQR: 9.7–14.5 years). Demographic and clinical characteristics of the children interviewed are detailed in table 1.

Seven QoL themes emerged from the data. The total proportion of children experiencing issues per QoL theme and coded segments per theme are shown in figure 1. Additional subthemes not presented within the results are provided in a mind map (see online supplemental figure S2).

Theme 1: coping

All children used coping strategies to manage the impacts of their glaucoma (figure 1). All children (18/18, 100%) discussed being resilient, which is an adaptive emotion-focused coping strategy (ie, a strategy that involves regulation or minimisation of negative emotions).[22]

> I've grown up with it. I've gotten used to it. I just don't pay much attention to it now. (Child aged 13–17 years)

Adaptive problem-focused strategies (ie, strategies that actively confront the problem)[22] included developing a positive relationship with their ophthalmologist (12/18, 67%), seeking and accepting support from family, friends or schoolteachers (11/18, 61%) and accepting parents' use of positive reinforcement for appointment attendance (9/18, 50%).

> I'm a lot more comfortable with [my ophthalmologist] because he's been doing it with me since basically the first time I went there… we're friends. (Child aged 8–12 years)

Several children (10/18, 56%) discussed adapting to activity limitations secondary to visual abilities or symptoms, such as photophobia. This was observed in children with bilateral (3/3, 100%) or unilateral BCVA <0.5 (3/7, 43%) and children with no BCVA impairment (4/8, 50%). Adapting to visual limitations was improved with the use of electronic devices in the classroom (eg, laptop computer) whereby text size and contrast could be manipulated. Adapting to photophobia was usually resolved with sunglasses wear. Consequently, 5/18 (28%) children explicitly stated that their glaucoma did not impact their participation in daily activities.

> A lot of [schooling] stuff is on the computers and not written on the board anymore. So yeah, like I don't really think that I have troubles. (Child aged 13–17 years)

Dissociating from one's glaucoma outside of the clinical setting and ignoring its presence was used by 8/18 (44%) children, most of whom did not have bilaterally impaired BCVA (7/8, 88%). This was considered an adaptive strategy in 4/8 (50%), 3/4 (75%) of whom were aged 8–12 years, as these children considered themselves unaffected by their glaucoma. Conversely, it was considered maladaptive in 4/8 (50%) children, irrespective of age or gender, because these children avoided asking for vision-related assistance from teachers or were disinterested in possible disease consequences.

> I'm just not interested in my eyes much. (Child aged 8–12 years)

Actively leaving medical responsibilities and decision making to their parent/s was discussed by more children aged 13–17 years compared with their younger counterparts (5/8, 63% vs 2/10, 20%, respectively). Gender, antiglaucoma medication use and BCVA did not appear influential.

Table 1 Demographic and clinical characteristics of children interviewed

Variable			n (%)*
Age at glaucoma diagnosis, years (median (range))			0.5 (0–15)
Time since diagnosis, years (median (IQR))			9.8 (7.3–13.6)
Age at interview (years)			
8–12			10 (56)
13–17			8 (44)
Gender, female			6 (33)
Laterality of glaucoma, bilateral			11 (61)
Self-reported ancestry, European			16 (89)
Subtype of childhood glaucoma			
Primary congenital glaucoma			12 (67)
Glaucoma associated with non-acquired ocular anomalies			
Aniridia			1 (6)
Axenfeld-Rieger syndrome			1 (6)
Glaucoma associated with non-acquired systemic condition			
Sturge-Weber syndrome			1 (6)
Glaucoma associated with an acquired condition			
Idiopathic uveitis†			2 (11)
Glaucoma following cataract surgery			1 (6)
Number of topical antiglaucoma medications currently using			
0			13 (72)
≥1			5 (28)
Intraocular pressure at last ophthalmic appointment, mm Hg (median (range))			18 (14–25)
Time since last ophthalmic appointment, months (median (IQR))			3.8 (2.9–7.4)
Number of surgical interventions per child (median (IQR))			2 (2–4)
Time since last ophthalmic surgical intervention, years (median (IQR))			6.7 (1.6–13.6)
Disease complications			
Corneal disease			1 (6)
Cataract			4 (22)
Molecular diagnosis identified			9 (50)
Autosomal recessive inheritance			2 (11)
Autosomal dominant inheritance			7 (39)
Vision category	**BCVA (logMAR)**	**Better eye BCVA (n, %)**	**Worse eye BCVA (n, %)**
No vision impairment	≥0.3	15 (83)	8 (44)
Mild vision impairment	<0.3–≥0.5	1 (6)	4 (22)
Moderate vision impairment	<0.5–≥1.0	1 (6)	2 (11)
Severe vision impairment or blindness	<1.0–≥1.3	0 (0)	1 (6)
Blindness	<1.3–CF	1 (6)	2 (11)
	HM or LP	0 (0)	1 (6)
	NLP	0 (0)	0 (0)

*n (%) presented unless otherwise specified.
†No underlying systemic disease was diagnosed.
BCVA, best-corrected visual acuity; CF, count fingers; HM, hand movements; LP, light perception; NLP, no light perception.

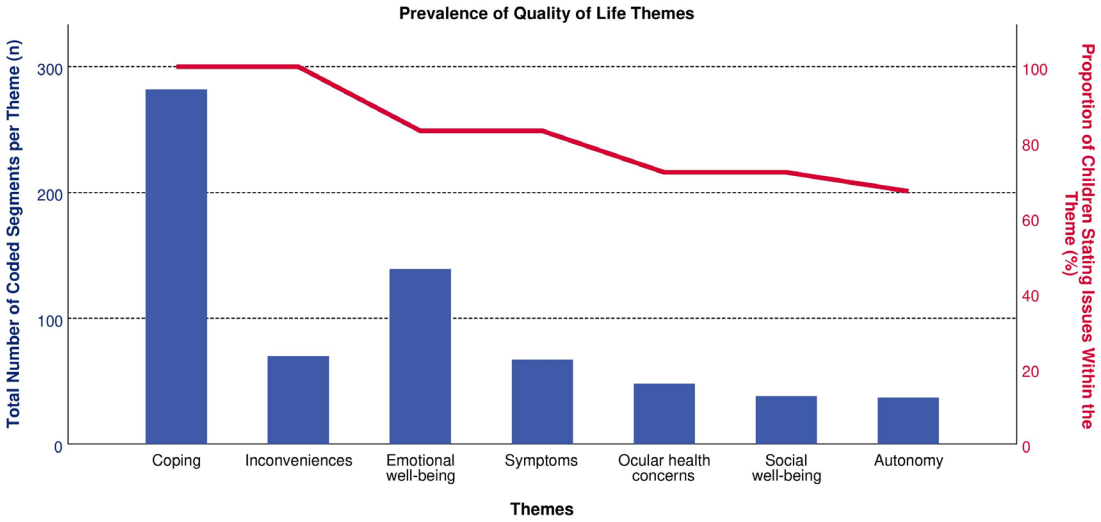

Figure 1 Quality of life themes identified in children with glaucoma. This dual y-axis chart demonstrates the total number of codes per theme (blue bar chart) and the proportion of children who discussed an issue within the theme (red line chart).

> I'd let Mum ask the questions… I'm more of a listener. Like a bystander… I'll get all the information I want out of Mum. (Child aged 13–17 years)

Furthermore, 3/4 (75%) children aged ≥16 years discussed strong feelings of wanting to avoid attending their ophthalmic appointments.

> I was just yelling and screaming… I really did not want to go [to my appointment]. (Child aged 13–17 years)

Theme 2: inconveniences

All children discussed several inconveniences related to their ophthalmic appointments or glaucoma treatment. Clinic waiting time caused boredom for 6/18 (33%) children and 5/18 (28%) discussed negative outcomes related to school absenteeism. These were exacerbated where travelling long distances for ophthalmic review was required. Conversely, 7/18 (39%) reasoned that school absenteeism was a positive experience.

> It took us like three hours to get there and to go back… I often had to skip school to go there, and it was often always the fun days. (Child aged 8–12 years)

Most children (11/18, 61%) discussed the inconvenience of having blurred vision for many hours following pupillary dilatation, while 4/18 (22%) considered a visual field test burdensome.

> I hate getting drops… everything I see is blurry for six or seven hours… They're still the worst thing that could possibly happen. (Child aged 13–17 years)

Spectacle wear was considered inconvenient and uncomfortable by 6/18 (33%) children, particularly during sporting activities. Among children who currently used topical antiglaucoma medication, 2/5 (40%) considered them bothersome.

> I don't really like wearing [glasses]… because my nose gets sweaty. (Child aged 8–12 years)

Theme 3: emotional well-being

Negative emotional experiences were discussed by 15/18 (83%) children. Feeling frustrated (13/18, 72%) or anxious (10/18, 56%) were often experienced in the contexts of requiring pupillary dilatation or performing certain clinical tests (eg, visual field test, IOP test).

> The sight field test… has like things that blink and it's just like heaps of them, and it's like in a way sort of overwhelming. (Child aged 8–12 years)

Several children (7/18, 39%) discussed feeling misunderstood at times by their friends, peers and/or schoolteachers. At times, this led to concealment of their condition.

> I like keeping [my glaucoma] a bit of a secret… Because when I try to explain - no one understands and I have to keep explaining, explaining and explaining. (Child aged 8–12 years)

Feeling self-conscious of their appearance was expressed by 6/18 (33%) children. Reasons included their eye appearance, wearing spectacles or wearing an eye patch for amblyopia therapy. These were not dependent on BCVA, gender or age with the exception that one child, with bilateral BCVA <0.5, expressed feeling self-conscious while using their white cane for mobility.

> I hate [all the photos] when I'm younger because of the big, shaded glasses and stuff… I'm not a very photogenic person. (Child aged 13–17 years)

Theme 4: symptoms

Symptoms were discussed by 15/18 (83%) children. The most common symptom raised by children was blurred

vision (13/18, 72%). Of these, 4/13 (31%) had unilateral disease, and 7/13 (54%) had no BCVA impairment. It was usually described in the context of reading the classroom board, reading small texts and playing sports that involve a small ball (eg, tennis).

> If it's small writing and I'm at the back of the class I can't always get it but if it's like medium like to big writing I can see. (Child aged 13–17 years)

Glare (8/18, 44%), sore eyes (4/18, 22%) and reduced peripheral vision (2/18, 11%) were other symptoms discussed by children, irrespective of any clinical or demographic characteristic.

> I hate the sun… It hurts my eyes… I do stay inside most of my life. (Child aged 8–12 years)

Meanwhile, reduced contrast sensitivity was discussed by 6/18 (33%) children, all of whom had bilateral disease.

> The stronger colours like blue, purple and black I can read but when it goes to like green and all of them other colours like orange I can't, it's harder for me to read what it says. (Child aged 13–17 years)

Theme 5: ocular health concerns

Several children (13/18, 72%) discussed ocular health concerns that were often experienced as worry or anxiety. Hypersensitivity of objects touching their eye was the most common concern raised (6/18, 33%), particularly by children with bilateral disease (5/6, 83%).

> One time my eye was really sore, and I got kind of worried, and kind of scared, but it turned out it was just the ingrown eyelash. (Child aged 8–12 years)

Concerns for raised IOP (5/18, 28%) and losing vision (4/18, 22%) were additionally discussed. The former was more typical among children aged between 13 and 17 years (4/5, 80%).

> When I go to the like appointment, and I get my pressures checked I get nervous of if I'm going to get like a high pressure. (Child aged 13–17 years)

Requiring future surgery (2/18, 11%), forgetting to use their antiglaucoma medication (2/18, 11%) and changing ophthalmologist (1/18, 6%) caused concerns among fewer children.

> I don't want any more surgery. I'm done… it's just really scary. (Child aged 13–17 years)

Theme 6: social well-being

Having glaucoma caused social issues for 13/18 (72%) children. Schoolyard bullying was discussed by 5/18 (28%) children irrespective of age. Bullying was attributed to their visual ability, need to wear spectacles or need for sunglasses in the schoolyard.

> There are some kids at our school that have glasses that get bullied… Those kids have tried to bully me and my friends, so we have to defend ourselves. (Child aged 8–12 years)

Several children (5/18, 28%), of whom 4/5 (80%) were aged 13–17 years, discussed feeling socially isolated by their condition due to its rarity. It was often relieved by a desire to meet another child with glaucoma.

> I'm a loner at my school… People are a bit standoffish. I don't think they really know how to approach me. (Child aged 13–17 years)

Conversely, 6/18 (33%) children, of whom 4/6 (67%) were aged 8–12 years, reasoned that they had good social well-being.

> [My friends] all know about [my glaucoma] already… They just treat me the same. (Child aged 8–12 years)

Theme 7: autonomy

Two-thirds (12/18, 67%) of children discussed issues relating to their autonomy. These were typically discussed by children aged 13–17 years compared with those aged 8–12 years (7/8, 88% vs 5/10, 50%). The main issue related to autonomy raised by younger children was that they wanted to administer their antiglaucoma medication without parental assistance. These children, however, frequently discussed being forgetful of when to use them.

> 'Most of the time I [put in the eye drops] myself and kept on forgetting. (Child aged 8–12 years)

All children aged ≥16 years (4/4, 100%) discussed issues becoming responsible for their own glaucoma care. These included actively engaging with the ophthalmologist and attending appointments without their parents, which were often met with feeling nervous or anxious.

> There's definitely questions I would like to ask but - I don't know…. I still get nervous asking. (Child aged 13–17 years)

Among children aged 13–17 years, 4/8 (50%) wanted to know what caused their glaucoma and the risk involved in passing on their glaucoma to their future children.

> I'd definitely be interested to find out where I got it from… [but] if my children [have glaucoma], I guess it should be fine. (Child aged 13–17 years)

The impact of glaucoma on their future career was discussed by 5/18 (28%) children, all of whom had bilateral or unilateral BCVA <0.5. Four (4/5, 80%) were aged 13–17 years.

> I can't actually join the Army, because of my lack of vision… It just sucks, because now I don't actually have a plan for my life. (Child aged 13–17 years)

Two children aged 13–17 years (2/18, 11%), one of whom had bilateral BCVA <0.5, discussed future issues with obtaining a driver's licence while 3/18 (17%)

children discussed issues with independently navigating environments due to their sight.

> I just think about what it'd be like if I could get a [driver's] license, when I'm driving on the road… I don't know if some person would pick on me because of the condition that I have. (Child aged 13–17 years)

DISCUSSION

To the best of our knowledge, this exploratory interview study is the first qualitative study to explore the QoL issues experienced by children with glaucoma. Six of the seven themes identified were consistent with those reported in adults with childhood glaucoma[21] and adult-onset glaucoma.[23 24] The impact of the condition on a child's autonomy was novel and provided a unique perspective of how childhood glaucoma impacts on the transition from childhood to adulthood. Each theme was relevant to all glaucoma subtypes and thus provided a thorough representation of how a child may live with glaucoma.

There are evidently several glaucoma-related non-visual and non-clinical variables that influence a child's QoL. Most notably, this includes how a child copes with their condition. This is in agreement with a recent study exploring the lived experience of adults with childhood glaucoma, which similarly identified that resilience, adaptation and establishing a positive relationship with the ophthalmologist are important coping strategies in childhood glaucoma.[21] Becoming resilient was further identified as a coping strategy in children with cystic fibrosis,[25] spina bifida[26] and type 1 diabetes.[27] This often assisted in self-management of their condition, as observed in this study whereby children, particularly those aged 8–12 years, expressed a desire to self-manage their antiglaucoma medication. Conversely, older youths with spina bifida,[26] and children with type 1 diabetes,[28] were more likely to disengage in their care over time, possibly due to having increased medical responsibilities and feeling overwhelmed. The same trend may be occurring in this study whereby children aged ≥16 years discussed issues related to disengagement in clinical care.

This possible age-related coping trend regarding disengagement may be underpinned by concurrent QoL issues. In this study, we observed a greater proportion of children aged 13–17 years who described more disruptions to QoL compared with children aged 8–12 years. These disruptions were particularly related to autonomy (becoming responsible for own care, career choices, driving, family planning), social well-being (social isolation) and ocular health concerns (increasing IOP). The latter may be particularly due to an increased understanding of glaucoma disease itself. Subsequently, these collective issues may contribute to a greater psychosocial impact of glaucoma in older children.

This hypothesis is opposite to findings in previous childhood glaucoma studies that reported lower VR-QoL and HR-QoL in younger children compared with their older counterparts.[7 8] Other characteristics including BCVA, disease laterality, gender and duration since surgery were not found to influence this age-related finding.[8] Consequently, it was hypothesised that an older child may experience better QoL as they may develop a better understanding of their condition and better coping strategies over time.[7 8] This has been referred to as the 'response shift'.[8] In contrast, our findings suggest there is an 'implications shift' whereby children appeared to be more concerned about limitations their glaucoma may place on their adult life as they enter adolescence. The apparent disparity between findings suggestive of a 'response shift' or an 'implications shift' may be explained by the studies' different approaches (ie, the use of a non-disease specific PROM to measure QoL,[7 8] compared with semistructured interviews) or the clinical and demographic differences in the cohorts studied, including children's abilities to respond to QoL-related questions. It would therefore be useful to further investigate the influence of ageing on QoL and whether the 'response shift' or 'implications shift' is more likely to dominate the lived experience. This could be explored in future qualitative studies or quantitative association studies that use a childhood glaucoma-specific PROM. Nonetheless, our age-related findings are consistent with observations reported in children aged 14–18 years with cystic fibrosis who reported a greater disease-related impact on body image, emotional state and treatment burden compared with younger children.[29] Adolescents with type 1 diabetes additionally reported issues balancing demands between medical management and non-disease related pressures of being an adolescent.[30] Disease stigmatisation, social isolation, self-image and school absenteeism concerns were otherwise experienced among children of any age with asthma and epilepsy,[31] type 1 diabetes[27 28] and juvenile idiopathic arthritis.[32] Thus, the issues identified in children with glaucoma align with the greater childhood chronic disease experience and their impact may be exacerbated when a child approaches adulthood.

Clinicians should be aware of possible issues, particularly experienced during adolescence, as they may cumulatively influence the use of maladaptive coping and lead to medical negligence. This has been reported in adults aged 18–40 years with childhood glaucoma,[21] and such coping behaviours could lead to worse visual outcomes. Consequently, adolescents may require additional support to facilitate their transition towards adulthood and medical autonomy. This could involve provision of coping skills training, which aims to increase medical competence and the use of positive coping strategies.[33] This training has been successful for children with type 1 diabetes.[33] Ancillary ophthalmic personnel (eg, orthoptists) may be best suited to facilitate this and future research could evaluate its effectiveness in children with glaucoma. Parent-to-child transfer of glaucoma self-management may otherwise begin at any age by providing children with an active voice in their care and increasing their knowledge of their glaucoma, as encouraged in

other childhood chronic conditions.[34 35] These processes, however, must be tailored to the child's maturity, visual abilities and emotional state, with consideration to potential parental anxiety over relinquishing control of care to their child, as documented in parents of children with glaucoma.[36]

It is important to recognise that the QoL issues identified in this study appeared to be raised by children irrespective of their clinical characteristics (ie, BCVA and laterality). Previous research has demonstrated that VR-QoL is negatively associated with BCVA in the better-seeing eye in children with glaucoma.[4–7] Despite this, several studies have been unable to establish whether disease laterality is associated with VR-QoL.[4 5 7] Moreover, self-reported HR-QoL has not been found to be associated with disease laterality.[7 8] This suggests that unilateral disease may still impact QoL even if the child has normal BCVA in their better-seeing eye. The results of this study may offer some insight into these contradictory findings. First, children with bilaterally impaired BCVA used adaptive technology and did not consider that their participation in daily activities was impacted. The availability and use of such technology may therefore influence how a child responds to QoL-related questions. Second, children reported subjective symptoms including glare and reduced contrast sensitivity. These are yet to be measured as variables that may affect QoL in children with glaucoma.[4–8] Glare is otherwise among the most common symptoms reported by adults with childhood glaucoma and contributed to their non-participation in outdoor activities.[21] It is therefore possible that the experience of these symptoms have a greater impact on QoL than disease laterality. Lastly, few children in this study subjectively reported that they had reduced BCVA irrespective of objective measurements and laterality. This may further contribute to unexpected or conflicting findings in quantitative association studies. Evidently, the impact of childhood glaucoma on QoL extends beyond a child's clinical characteristics and their subjective experience must be considered in clinical management of the condition.

To guide glaucoma management and enable more accurate investigation of the influence of clinical and demographic variables on QoL, a childhood glaucoma-specific PROM must be developed. Prior research have instead used VR-QoL (Impact of Vision Impairment for Children)[4–7 17] and HR-QoL measures (Kidscreen-27 questionnaire,[16] PedsQL)[7 8 13] that do not measure disease-specific QoL issues such as those identified in this study (eg, concern for IOP, feeling misunderstood due to disease rarity). A childhood glaucoma-specific PROM will substantially improve our understanding of the disease impact and inform clinicians and education providers of QoL issues encountered by children. The results of this study will assist with the identification of items for a childhood glaucoma-specific PROM.

Study limitations include that children were recruited from a national registry and interviewed after receiving parental consent and child assent. Consequently, the child and/or parent may be more willing to participate and may be experiencing a higher QoL than non-respondents and/or their parents. Furthermore, children resided in Australia and the majority were of self-reported European ancestry. Consequently, the findings of this study may only be relevant to cohorts with similar sociodemographics, healthcare and education systems and those with similar access to resources supporting visual functioning. Children with disease onset at age 16 or 17 years were unable to be recruited, likely owing to the narrow time frame between reaching adulthood and time required to conceptualise their diagnosis before agreeing to be interviewed. The experience of someone diagnosed at this age was otherwise captured in our previous study on adults diagnosed with childhood glaucoma.[21] Furthermore, more children interviewed had unilateral disease compared with non-respondents, and most children had no vision impairment in their better eye. It is unknown how these characteristics may have influenced results as thematic saturation was reached. Lastly, the interviews specifically evaluated the impact of glaucoma such that the influence of conditions unique to uveitis, aniridia, Sturge-Weber syndrome and Axenfeld-Rieger syndrome were not included in the analysis. However, it remains possible that the physical manifestations of these conditions have impacted the QoL outcomes of this study.

Despite these limitations, this study provided unique insight into the QoL issues experienced in childhood glaucoma from the perspective of the child. This rare condition may cause a considerable impact on a child's physical, emotional and social well-being, which is managed with the use of coping strategies. Overall, our findings suggest that older children may experience more QoL issues compared with their younger counterparts and hypothesise that increasing age may be associated with a lower QoL. Healthcare professionals and parents should be mindful of this trend, and social and ophthalmic interventions may be required to support a child as they transition into adulthood and achieve medical autonomy. Future research endeavours should evaluate the most appropriate method to facilitate medical autonomy and subsequently ensure that any individual with childhood glaucoma achieves the best possible long-term visual and QoL outcomes.

Author affiliations
[1]Department of Ophthalmology, Flinders University, Flinders Medical Centre, Bedford Park, South Australia, Australia
[2]Department of Ophthalmology, Women's and Children's Hospital, North Adelaide, South Australia, Australia
[3]Department of Ophthalmology, The Royal Children's Hospital Melbourne, Parkville, Victoria, Australia
[4]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia
[5]Ophthalmology, University of Melbourne, Department of Surgery, Parkville, Victoria, Australia
[6]Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Bedford Park, South Australia, Australia

Twitter Sandra E Staffieri @StaffieriSandra

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval Ethical approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee (HREC/19/WCHN/161), and the study adhered to the tenets of the Declaration of Helsinki. All child participants provided written assent and their parent or guardian provided informed written consent. Participants gave informed consent to participate in the study before taking part.

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ORCID iD

Lachlan S W Knight http://orcid.org/0000-0002-7633-5486

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Publication F3. Quality of life in adults with childhood glaucoma: an interview study

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Quality of Life in Adults with Childhood Glaucoma

An Interview Study

Lachlan S.W. Knight, BHSc MOrth,[1,2] Bronwyn Ridge, BA (Psych), GradDip (HCouns),[1] Sandra E. Staffieri, BAppSc(ortho), PhD,[3,4,5] Jamie E. Craig, FRANZCO, DPhil,[1] Mallika Prem Senthil, PhD,[6] Emmanuelle Souzeau, PhD[1]

Purpose: To explore and report on the quality-of-life (QoL) issues encountered by adults with childhood glaucoma.

Design: Exploratory qualitative study.

Participants: Forty-seven participants with childhood glaucoma (defined as disease onset <18 years) recruited from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG).

Methods: A qualitative research methodology (interpretive phenomenology) was applied, and data were collected through semistructured in-depth interviews. NVivo-12 software (QSR International Pty Ltd) was used to inductively analyze and code data to identify QoL themes pertinent to the cohort studied.

Main Outcome Measures: Quality-of-life themes and subthemes.

Results: Mean participant age was 40.0 ± 15.3 years, and 55% of participants were female. We identified 10 QoL themes pertinent to adults living with childhood glaucoma. Coping strategies and emotional well-being were the most prominent themes. Maladaptive coping strategies, including treatment nonadherence, were observed more commonly in individuals aged <40 years and those without a vision impairment or reviewed less regularly. Emotional well-being was affected by feelings of being misunderstood because of the rarity of the condition, being self-conscious of physical manifestations of the disease, and anxiety related to possible disease progression and vision loss. The effect of childhood glaucoma on family planning formed a novel QoL theme and included worry for their child to inherit the condition and an inability to fulfill parental duties. This often led to genetic counseling–seeking behaviors. Mobility issues were infrequently experienced.

Conclusions: Childhood glaucoma poses a substantial impact to the emotional well-being of adults with the condition, which is mediated by the use of coping strategies. Genetic counseling and family planning options may be important. This study supports the development of a childhood glaucoma–specific patient-reported outcome measure for assessment of the psychosocial impact of childhood glaucoma in adults. *Ophthalmology Glaucoma 2022;5:325-336 © 2021 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyglaucoma.org.

Childhood glaucoma, typically characterized by elevated intraocular pressure (IOP) and optic neuropathy, is a heterogeneous group of chronic vision-threatening disorders with onset occurring at any age from birth to less than 18 years of age.[1] The various subtypes of childhood glaucoma are classified broadly as primary and secondary. Primary glaucoma is caused by isolated abnormalities in the ocular structures that maintain normal IOP and includes primary congenital glaucoma and juvenile open-angle glaucoma. Meanwhile, secondary glaucomas have changes in other ocular structures (e.g., aniridia), have an associated systemic disease (e.g., Axenfeld-Rieger syndrome), or are caused by other ocular disease, trauma, or surgery.[1] Childhood glaucoma is largely considered to be caused by pathogenic genetic variants inherited in a Mendelian pattern of inheritance.[2] Individuals with childhood glaucoma require prompt treatment and close monitoring throughout their life span to prevent or minimize irreversible vision loss. Consequently, IOP-lowering treatments, including multiple surgeries and/or lifelong topical antiglaucoma medications, are often required.[3] The condition may be associated with other ocular signs and symptoms, particularly if the disease begins during a child's early years. These include symptoms of glare, epiphora, and high myopia, as well as cosmetic concerns related to corneal opacification, sensory strabismus, and buphthalmos.[4]

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The long-term management, disease sequelae, and uncertain visual outcome of childhood glaucoma may pose emotional, social, or physical impacts. However, there is a paucity of literature investigating the quality of life (QoL) of adults with childhood glaucoma. Recent research is limited to quantitative studies that use nonglaucoma-specific, patient-reported outcome measures (PROMs) to evaluate the lived experience of individuals with childhood glaucoma.[5–7] The PROMs used may not be evaluating QoL issues that are relevant to the condition, resulting in a possible incomplete understanding of the disease impact. Nonetheless, studies have reported considerable dissatisfaction with life[6] and lower mental health scores in adults with childhood glaucoma.[7] Moreover, no studies have investigated the impact of childhood glaucoma on family planning, which is highly relevant in the context of an inherited condition.[2] The aim of the present study is to investigate the QoL issues experienced by adults with childhood glaucoma. Findings from this study will inform the development of a childhood glaucoma–specific PROM for future research on this topic and clinical implementation.

Methods

Participants

The theoretical framework used to explore the QoL issues of adults living with childhood glaucoma was interpretive phenomenological analysis. This qualitative approach aims to provide an in-depth description of the participants' lived experience.[8] A nonprobability convenience sampling technique was used to recruit participants from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG). Briefly, the ANZRAG is a large Australasian glaucoma registry based at Flinders University, Adelaide, Australia. It is designed to identify genes associated with glaucoma, whereby all participants undergo genetic testing.[9] Participants residing in Australia were included if they had a diagnosis of glaucoma at <18 years of age in at least 1 eye (including all primary and secondary glaucoma subtypes according to the Childhood Glaucoma Research Network classifications[1]), were ≥18 years of age at the time of their interview, and were English speaking. Participants were excluded if they had coexisting ocular disease unrelated to the spectrum of childhood glaucoma, had a hearing or cognitive impairment, or had another disability affecting QoL (e.g., intellectual disability, motor disorder) as informed by their referring glaucoma specialist or individual's primary carer.

Individuals meeting the eligibility criteria were invited to participate in the study by mail and asked to return their interest. If no reply was received within 2 weeks, a follow-up phone call was initiated. Those who expressed interest in being interviewed were sent an information pack and consent form. Once written informed consent was obtained, one author (L.S.W.K.) contacted the participants to coordinate an appropriate interview time. This initial contact helped develop participant rapport before the interview. This was particularly important where an individual was visually impaired and unable to read print material easily. Participants were deemed noncontactable after a minimum of 2 unsuccessful attempts. Clinical details of participants were obtained from their medical records, including glaucoma subtype, visual acuity, disease laterality, age at diagnosis, and the number of topical antiglaucoma medications being used at the time of the interview. The glaucoma subtype was classified according to the Childhood Glaucoma Research Network criteria.[1] Disease onset at 4 years of age or later was considered juvenile.[1] Glaucoma severity was defined as advanced or nonadvanced as per the ANZRAG protocol.[10,11] Advanced glaucoma was defined as having visual field loss related to glaucoma with at least 2 of the 4 central squares having a pattern standard deviation <0.5% or a mean deviation of <−15 decibels (dB) on a Humphrey 24-2 visual field test. Where visual field testing could not be performed, advanced glaucoma was defined as the loss of best-corrected visual acuity (BCVA) due to glaucoma. To understand the structural and functional implications of an individual's glaucoma severity status, their self-reported ability to drive a personal vehicle was used because it can provide a measure of visual disability.[12] To operate a motor vehicle in Australia, an individual is required to have ≥110 degrees of the horizontal visual field, have no significant central defect within 20 degrees superior or inferior to the midline, and have binocular BCVA ≥20/40.[13] Visual acuity was categorized according to the International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision).[14] Ethics approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee, and the study adhered to the tenets of the Declaration of Helsinki.

Interviews

A semistructured interview guide was developed from a literature review of QoL issues experienced by individuals with childhood or adult-onset glaucoma (Fig S1, available at www.ophthalmologyglaucoma.org). All interviews were conducted in the English language by one author (L.S.W.K.). L.S.W.K. is a male orthoptist with clinical and research experience in childhood glaucoma and ocular genetics, and is trained in conversational interviewing. No participants were under the care of the interviewer. Participants were informed that the interviewer (L.S.W.K.) was completing a Doctor of Philosophy. One-on-one semistructured interviews occurred via telephone or Cisco WebEx videoconferencing, subject to participant preference. Participants were asked to be alone during the interview to eliminate external influences of responses. All interviews were audio-recorded and transcribed verbatim, and participants were offered to review their transcript for accuracy. Interviews continued until thematic saturation was achieved, defined as the point where no new information was gained from subsequent interviews.[15]

Data Analysis

QSR NVivo 12 (QSR International Pty Ltd) was used to systematically code the transcripts. Open coding was done by one author (L.S.W.K.) in keeping with an inductive approach.[16] This served to acknowledge and neutralize any preconceptions that may influence data analysis.[17] Coding consistency checks were performed by one coauthor (M.P.S.) to ensure the credibility of findings.[18] M.P.S. was not a treating specialist. Codes with similar or repetitive patterns of meaning were organized into major themes with subthemes.[19] Major themes were then abbreviated to be consistent with previous ophthalmic QoL research.[20–22] Any discrepancies between authors were resolved by discussion. All statistical calculations were performed using SPSS version 27.0 for Windows (IBM/SPSS Inc).

Results

A total of 130 eligible individuals from the ANZRAG were sent an invitation to be contacted about the study. Of these, 47 participants (36%) were interviewed (Fig 1). Reasons for declining to participate

were not recorded because of the sensitive nature of the study. Participant characteristics are detailed in Table 1. There were no significantly different characteristics between the participants recruited and those who could not be contacted or declined participation (Table S1, available at www.ophthalmologyglaucoma.org).

Interviews were conducted between February 2020 and March 2021. The average interview length was 66 ± 23 minutes, and mean participant age was 40.0 ± 15.3 years. The mean time elapsed between the interview and last clinical examination was 4.9 ± 4.15 months. The regularity of participants' appointments was ≤3 monthly (15/47, 32%), >3 to ≤6 monthly (25/47, 53%), and yearly (6/47, 13%). One participant reported that they no longer undergo ophthalmic examinations because they had hand movements vision and consequently did not believe ophthalmic follow-up was necessary. Glaucoma care was provided by multiple specialists at several centers across Australia. One author (J.E.C.) was identified as a treating specialist for 9 participants, but was not involved in participant recruitment, interviewing, or data analysis.

Ten QoL themes and their subthemes were developed. The total number of participants experiencing issues within the QoL theme and coded segments per theme are shown in Table 2. A mind map of the themes and subthemes is supplied in Figure S2 (available at www.ophthalmologyglaucoma.org).

Theme 1: Coping

As per Table 2, all participants used coping strategies to mediate the social, emotional, and physical consequences of childhood glaucoma. Positive adaptive coping strategies included emotion-focused strategies, which are used to regulate negative emotions.[23] These included being resilient, which was adopted by 35 participants (35/47, 74%), and accepting their eye condition, which was adopted by 24 participants (24/47, 51%). Physical exercise, meditation, using humor, and being determined to remain independent were also frequently adopted. Meanwhile, 3 participants (3/47, 6%) stated that they sought psychological support, and 40 participants (40/47, 85%) indicated they relied on family, friends, and spouses for emotional support.

> *"We were matter of fact, you did what you had to do and just... got on with life."* (P06)

> *"I think it's probably put my life in a better mindset and vision sort of thing. For myself now and [in] the future."* (P07)

Positive problem-focused adaptive strategies, which are active behaviors that directly eliminate sources of stress,[23] were used. These included adapting to disease limitations and having a positive relationship with their ophthalmologist, which were used by 37 participants (37/47, 79%) and 34 participants (34/47, 72%), respectively. The latter also eased health anxieties.

> *"Having it since I was so young ... this is what I've got and this is how I need to act to make the best use of it so I can still function."* (P38)

> *"I love my eye doctor… I've had him forever. I feel so comfortable… and trust him."* (P01)

Maladaptive coping strategies were adopted by approximately half of participants. Avoiding thoughts about their current or future glaucoma status was reported by 22 participants (22/47, 47%), of whom 15 (15/22, 68%) had no vision impairment in their better eye. Ignoring their glaucoma care, including delaying their appointments and nonadherence to antiglaucoma medication use, was reported by 21 participants (21/47, 45%), of whom 15 (15/21, 71%) had no vision impairment in their better eye and 17 (17/21, 81%) were reviewed >3 to ≤6 monthly or yearly. Meanwhile, this coping strategy was not dependent on whether an individual was currently using antiglaucoma medication or not (10/19, 53% not using medication vs. 11/28, 39% using ≥1 medication). Furthermore, there was a trend for participants aged <40 years to use maladaptive coping techniques more often than their older counterparts. In contrast, the use of positive adaptive strategies increased with age as demonstrated in Figure 2.

> *"I try not to think about it too much because I sort of can't see the situation getting better, only really worse."* (P03)

> *"I had [eye drops for glaucoma] but I never stuck to it, I kind of just gave up on it for probably like 6 months, maybe 8 months."* (P29)

Theme 2: Emotional Well-being

Having childhood glaucoma resulted in a spectrum of negative emotions in all participants. Most participants (41/47, 87%) expressed feelings of being misunderstood. This was commonly attributed to having a rare disease.

> *"It's not really a common thing for someone so young to experience… You can't really talk to anyone about it because they don't understand what it's all about."* (P03)

Feeling self-conscious (37/47, 79%) was commonly experienced due to the appearance of the eye (29/37, 78%), using vision aids (11/37, 30%), and having poor visual ability (10/37, 27%). Appearance concerns were often attributed to having buphthalmos, sensory strabismus, and corneal opacification. Eight participants further described being self-conscious of their pupil size, of whom 2 had Axenfeld-Rieger syndrome. Four participants recalled being self-conscious of their phthisical eye, which was relieved in 3 individuals who now have a prosthetic eye.

> *"It's just very cloudy and it doesn't look so nice… I probably tend to hide behind dark glasses when I can."* (P22)

Losing vision or having low vision caused many (27/47, 57%) to feel frustrated due to the associated or perceived limitations of their abilities. Of these individuals, 12 (12/27, 44%) were still able to drive a motor vehicle.

> *"I have a problem with people using blind so flippantly. And calling me blind… It's a triggering word to me."* (P10)

One-third of participants (16/47, 34%) experienced regret for several reasons. The majority of these individuals were female (11/16, 69%) or aged ≥40 years (11/16, 69%). Regrets commonly reported included not accepting or understanding their visual limitations earlier, resulting in a physical injury, and neglect of their glaucoma care, often resulting in permanent vision loss.

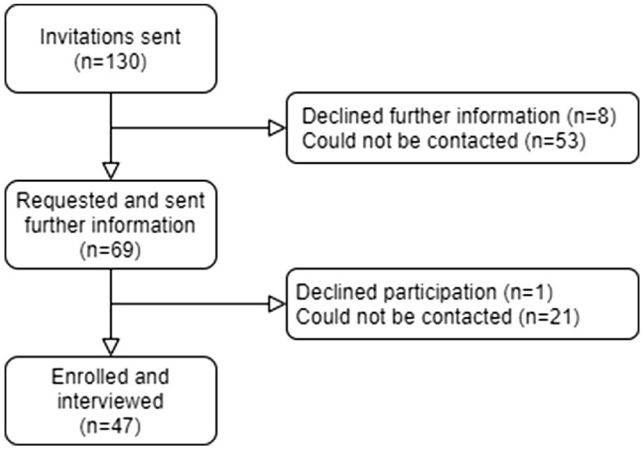

Figure 1. Flowchart depicting the recruitment of individuals who participated in the interview.

"I know it sounds crazy in retrospect, but because it didn't actually change my life, I didn't take it as seriously… [and] I have to live with that for the rest of my life." (P08)

Negative emotions were overall often mitigated by feeling hopeful for future medical advances to repair optic nerve head damage.

"I would hope that it would get better as opposed to worse with all the new medical procedures and medications available." (P01)

Theme 3: Ocular Health Concerns

Almost all participants (46/47, 98%) experienced concern for their ocular health. Disease-specific concerns such as IOP control were reported by 25 participants (25/47, 53%).

"This last time [when the pressure rose] was very stressful, like I felt sick because I was so scared, because what if the eye drops don't work?" (P44)

Requiring future glaucoma surgery caused great concern among 24 participants (24/47, 51%) irrespective of their past surgical care. Furthermore, 19 of the 30 individuals (63%) with no vision impairment in their better eye, of whom 12 (12/19, 63%) had BCVA <20/60 in their worse eye, often experienced this concern as fear and anxiety.

"I think if I would have to have my eye surgery, it would send me off the deep end… I'm really hoping I don't ever have to have that." (P26)

Many participants discussed concerns about losing their vision (25/47, 53%) or independence in the future (15/47, 32%). These concerns were expressed by 16 individuals (16/25, 64%) and 12 individuals (12/15, 80%), respectively, with no vision impairment in their better-seeing eye. Of these individuals, 9 (9/16, 56%) and 8 (8/12, 67%) had BCVA <20/60 in their fellow eye, respectively. Age and gender did not otherwise appear to be influential.

"I do worry, basically losing vision… and the impact on my family, on my career, on my life, and everything." (P27)

Other ocular health concerns included the side effects and long-term use of antiglaucoma medications and developing another eye disease later in life. Notably, 18 participants (18/47, 38%) described being hypersensitive to objects going near their eyes.

"I almost put the safety glasses on to go out and move the rubbish bin." (P31)

Changing ophthalmologists caused anxiety among 20 participants (20/47, 43%) because they were concerned about being treated by someone unfamiliar.

"He's the only ophthalmologist that I've ever seen… I'd be apprehensive about going to find another ophthalmologist." (P19)

Theme 4: Symptoms

All participants, except 2, reported unwanted visual and nonvisual symptoms (45/47, 96%). The most common visual symptoms reported by participants were glare (29/47, 62%), blurred vision (29/47, 62%), and reduced peripheral vision (25/47, 53%). These symptoms were not dependent on disease laterality, BCVA in the better eye, ability to drive a motor vehicle, or glaucoma subtype and were often described alongside having poor depth perception. Symptoms of reduced contrast sensitivity and night vision, however, were exclusive to individuals with bilateral disease but were not dependent on visual status.

"My sight is an awful lot worse outside… because of the increasing light sensitivity and glare." (P12)

Nonvisual symptoms typically included soreness and dry eyes, irrespective of antiglaucoma medication use (14/47, 30%). Ocular pain was frequently recalled to be experienced postsurgery, whereas severe headaches were described during times of IOP spikes.

Theme 5: Family Planning

Concerns regarding family planning featured highly in the cohort interviewed (43/47, 91%). Thirty-one participants (31/47, 66%) worried about their child inheriting glaucoma because they did not want them to have the same experiences or risk them being visually impaired. The majority of these individuals had vision impairment in 1 or both eyes (22/31, 71%). Furthermore, this worry was observed in 17 individuals (17/26, 65%) who had not yet had children and 14 individuals (14/21, 67%) who already had children. In addition, 23 individuals (23/30, 77%) without an affected first-degree relative expressed such worry compared with 8 (8/17, 47%) of those with a relative with glaucoma.

"I used to have nightmares about it. I actually used to wake up in the middle of the night, thinking I've — he's going to have glaucoma." (P18)

"I have been scared that I'll, you know, pass on the weaker genetics of my eyes and also for a very long time I'm really scared… that I'd go blind before I'd even be able to look my child in the face." (P47)

Consequently, 28 of the 31 participants (90%) who experienced this worry, of whom 19 (19/28, 68%) were female, indicated they sought (n = 22) or would seek (n = 6) genetic testing and

counseling for peace of mind. Of the 22 who had already sought genetic testing and counseling, 21 (21/22, 95%) were aged >30 years and 17 (17/22, 77%) had children. All individuals who indicated they would seek genetic testing were aged <30 years and did not yet have children. The inheritance pattern did not appear to influence this decision-making process. Five participants considered their reproductive options including using *in vitro* fertilization or having children through adoption, and 3 participants decided not to have children.

> *"[Genetic testing] did [give me peace of mind]… I wouldn't want someone to go through like the same things as me, so especially not one of your kids. So it did, it helped."* (P29)

> *"I will never have children because I will either require them to give me assistance or they may be born with the disorder."* (P46)

Nine participants (9/47, 19%) expressed concerns in not being able to fulfill typical parental duties. Issues raised centered on their child's safety and ability to drive their child to school or extracurricular activities. The majority of these individuals were female (8/9, 89%), already had children (7/9, 78%), or had vision impairment in both eyes and were unable to qualify for a driver's license (5/9, 56%).

> *"I want to have a wife and kids, but... I wouldn't be able to drop them off at school, or pick them up, or run errands for them… [I cannot] contribute in that way."* (P30)

These views were balanced by fewer participants (13/47, 28%) who indicated they did not feel the need to access genetic counseling. These views were not influenced by age, although 8 individuals (8/13, 62%) did not have children and the majority (11/13, 85%) had no visual impairment. This view was often attributed to having knowledge of what glaucomatous signs to look for or being confident that their child's QoL would not be affected because they were able to cope with their own condition.

> *"I feel that it never stopped me doing anything in my life... If a child has it, we'll deal with it and move from there."* (P06)

Theme 6: Inconveniences

The majority of the participants (40/47, 85%) stated that they experienced a number of inconveniences related to their condition. Participants reported being bothered by having to perform routine clinical tests (17/47, 36%), having to schedule an appointment around employment commitments (13/47, 28%), and clinic waiting time (10/47, 21%). The majority of all of the individuals who complained of clinical tests (16/17, 94%), appointment scheduling (12/13, 92%), and waiting time (10/10, 100%) were of working age (i.e., <65 years of age).

> *"I'm always rushing to get there because [of] work... You try and finish your job and − you have to run off and have your appointment."* (P41)

Inconveniences related to topical antiglaucoma medication were reported by 14 participants (14/47, 30%). Fewer participants complained of having to wear high prescription glasses (8/47, 17%) or contact lenses (5/47, 11%) due to their buphthalmos.

Table 1. Demographic and Clinical Characteristics of Participants

Variable	n (%)
Age at diagnosis	
<4 yrs	30 (64)
Years since diagnosis*	34 (23–50)
Age at interview	
18–39 yrs	23 (49)
≥40 yrs	24 (51)
Gender, female	26 (55)
Laterality of glaucoma, bilateral	43 (91)
Self-reported ancestry, European	40 (85)
Subtype of childhood glaucoma	
Primary congenital glaucoma	27 (57)
Juvenile open-angle glaucoma	11 (23)
Glaucoma associated with nonacquired ocular anomalies	8 (17)
Axenfeld-Rieger syndrome	4 (9)
Aniridia	3 (6)
Iris coloboma	1 (2)
Glaucoma after cataract surgery	1 (2)
Glaucoma severity status	
Advanced, bilateral	15 (32)
Advanced, unilateral, and nonadvanced, unilateral	15† (32)
Nonadvanced, bilateral	17‡ (36)
Self-reported ability to drive a personal vehicle	
Unable to drive	20 (43)
Advanced, bilateral	15 (32)
Advanced, unilateral, and nonadvanced, unilateral	3 (6)
Nonadvanced, bilateral	2 (4)
No. of topical antiglaucoma medications currently using	
0	19 (40)
1	16 (34)
2	11 (23)
3	1 (2)
Ocular complications	
Ocular prosthesis	5 (11)
Retinal detachment	4 (9)
Corneal transplant	3 (6)
Genetic results	
Pathogenic variant reported	27 (57)
Autosomal recessive inheritance	16 (34)
Autosomal dominant inheritance	11 (23)
Had a first-degree relative affected by glaucoma, yes	17 (36)
Parenting status, has children	21 (45)

Vision Impairment	BCVA	Better Eye BCVA (n, %)	Worse Eye BCVA (n, %)
None	20/20 − ≥20/40	30 (64)	13 (28)
Mild	<20/40 − ≥20/60	4 (9)	1 (2)
Moderate	<20/60 − ≥20/200	5 (11)	8 (17)
Severe	<20/200 − ≥20/400	3 (6)	3 (6)
Blindness	<20/400 to CF	3 (6)	5 (11)
	HM or LP	2 (4)	7 (15)
	NLP	0 (0)	10 (21)

BCVA = best-corrected visual acuity; CF = count fingers; HM = hand movements; LP = light perception; NLP = no light perception.
*Years since diagnosis is reported as median (interquartile range).
†Includes 2 unilateral cases with advanced glaucoma in 1 eye.
‡Includes 2 unilateral cases with nonadvanced glaucoma in 1 eye.

> *"If I'm out in the evening, I have to kind of plan out... Oh, I've got to be back at this time so I can put [my drops] in."* (P25)

Table 2. Major Quality-of-Life Themes Identified in Adults with Childhood Glaucoma

Theme Number	Major Quality-of-Life Theme	Participants, n (%)	No. of Coded Segments
1	Coping: Adaptive and maladaptive coping strategies are used to manage stressors related to childhood glaucoma.	47 (100)	1235
2	Emotional well-being: Disease rarity, chronicity, and sequelae mediate the emotional response.	47 (100)	1137
3	Ocular health concern: Disease incurability inflicts several ocular health concerns.	46 (98)	406
4	Symptoms: Disease permanence causes unwanted visual and nonvisual symptoms.	45 (96)	279
5	Family planning: An individual's experience of childhood glaucoma mediates decision-making in family planning.	43 (91)	227
6	Inconveniences: Disease chronicity causes several disruptions to daily life.	40 (85)	194
7	Social well-being: Peer awareness, understanding, and acceptance influence the individual's social network.	39 (83)	266
8	Activity limitation: Participation in daily life may be limited by disease sequelae.	36 (77)	185
9	Economic: Clinical costs and career options may threaten financial security.	36 (77)	123
10	Mobility: Disease sequelae may cause mobility issues.	21 (45)	72

Taking longer to perform visual tasks was expressed as an inconvenience by 9 participants (9/47, 19%) and was not exclusive to individuals with BCVA <20/60 in their better eye (5/9, 56%). Having to rely on someone else and using public transport or taxis for general travel were experienced by half of the individuals who self-reported that they did not meet visual requirements for operating a motor vehicle (10/20, 50%).

> *"How much easier is it to go and be in control of [when you leave an event] and hop into your car as opposed to, I've got to ring a taxi and I've got to wait for it?"* (P04)

Theme 7: Social Well-being

Issues pertaining to social well-being were reported by 39 participants (39/47, 83%). Having a strong desire to hide their condition from their colleagues or peers, because they did not want to appear different, was discussed by 23 participants (23/47, 49%). Such comments were more frequently made by women compared with men across the cohort (15/26, 58% vs 8/21, 38%, respectively).

> *"I don't feel like I need to…. tell everyone, 'Oh look, by the way, I can't see'.... I will never feel comfortable with it."* (P14)

Seventeen participants (17/47, 36%) recalled experiencing schoolyard bullying during their childhood, which may have had implications for their confidence in adulthood. Notably, this was experienced by almost all participants with glaucoma associated with nonacquired anomalies (7/8, 88%), 9 (9/27, 33%) with primary congenital glaucoma, and 1 (1/11, 9%) with juvenile open-angle glaucoma. Participants frequently stated they were bullied because of needing to wear glasses, wearing an eye patch for amblyopia therapy, having buphthalmos, having poor vision, or using vision aids. Two participants

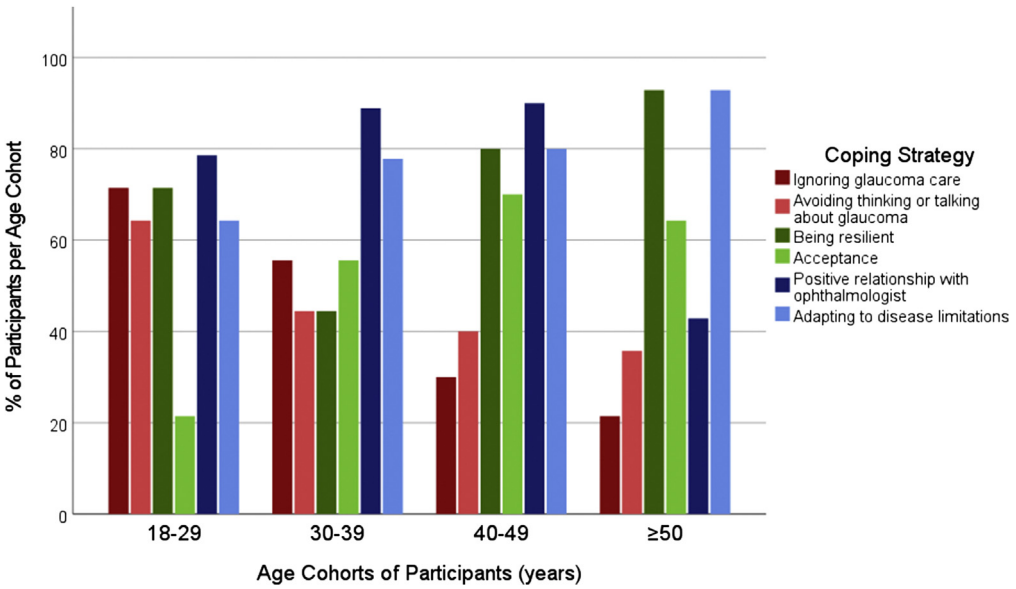

Figure 2. Comparison of coping strategies adopted in age groups of participants. Cluster bar chart comparing the percentage of participants per age group who made statements regarding the use of maladaptive coping strategies (in shades of red) and adaptive coping strategies that are emotion-focused (in shades of green) and problem-focused (in shades of blue).

attributed being bullied due to the shape of their pupil: One participant with primary congenital glaucoma had iatrogenic corectopia from surgery, and the other had pseudopolycoria secondary to Axenfeld-Rieger syndrome. However, participants often expressed that they became resilient in their adulthood due to childhood bullying.

> *"I got used to being called 'four eyes' and that sort of thing.... I think it did — has affected my — with being more shy — and less confident."* (P28)

Because of the future uncertainties of disease progression, 17 participants (17/47, 36%) expressed difficulty in establishing and maintaining close or intimate relationships. This was often attributed to fear of becoming reliant on someone and was commonly expressed by individuals aged >50 years (10/17, 59%).

> *"I wonder if someone wouldn't be interested in me because they'd be like — oh I'm going to have to take care of her because she's not going to have any eyesight."* (P44)

Receiving inadequate support in the workplace or experiencing workplace discrimination was stated by 18 participants (18/47, 38%). Conversely, 5 participants (5/47, 11%) discussed good workplace relations, whereas overall, 41 participants (41/47, 87%) stated they had good support from a variety of other established social networks, including close friends, family members, and spouses.

> *"Some of the things they said they [did a work assessment on] weren't tested on. I think it was just a way to alleviate me [of my responsibilities] without being held at a legal responsibility."* (P16)

Theme 8: Activity Limitations

Activity limitations were reported by 36 participants (36/47, 77%). Sporting activities or exercise was the most common activity that individuals with childhood glaucoma could not participate in to the extent they desired (25/47, 53%). It was more commonly reported by men compared with women (13/21, 62% vs. 12/26, 46%, respectively) and those unable to drive a motor vehicle (15/25, 60%), despite almost half (12/25, 48%) of individuals recording normal BCVA. Ball sports and team sporting activities such as Australian rules football and netball were problematic, particularly where the game was played outdoors in bright conditions. Running and cycling were also often made challenging where peripheral vision was reduced.

> *"Anything with a fast-moving ball. Unless it was coming directly at me low enough down in my field of vision, I wouldn't be able to see it coming to catch it."* (P13)

Being unable to drive a motor vehicle was almost as restrictive as participating in sporting activities (20/47, 43%). No individual with bilateral advanced glaucoma (15/15, 100%) held a driver's license. Conversely, 8 individuals (8/27, 30%) who were able to hold a driver's license found driving at night, dusk, or dawn most problematic and consequently did not drive at these times.

> *"The biggest thing in my life is that I wasn't able to drive. If I could have an eye transplant… [it would] probably change my life all the way totally."* (P41)

The ability to read near and distance objects was limited for 10 participants (10/47, 21%) and 15 participants (15/47, 32%), respectively. This was typically experienced by individuals with BCVA <20/60 in their better eye. Fourteen participants (14/47, 30%) recalled difficulty in reading the board at school from a distance, which transferred to difficulties in learning and not being able to see a presentation in a workplace or university. In contrast, 15 participants (15/47, 32%) experienced no limitation in performing daily tasks. Of these 15, 3 (3/15, 20%) were unable to drive a motor vehicle and the remaining 12 (12/15, 80%) had no visual impairment in their better eye.

> *"It takes me longer…. [to find] the one particular critical information in an entire book… A needle in a haystack, that's what it's like."* (P02)

Theme 9: Economic

The majority of participants (36/47, 77%) stated they had financial or employment concerns caused by their glaucoma. The main financial concerns were costs associated with seeing their glaucoma specialist, including the consultation fee and ancillary tests (12/47, 26%), and the cost of glaucoma medication and surgery (9/47, 19%). The former was more commonly expressed by individuals aged >50 years (8/12, 67%). The financial impact varied depending on whether the participant stated that they were currently receiving welfare payments, had a well-paying occupation, had private health insurance, or were treated in a public hospital, which incurs no cost to Australian residents. Consequently, 12 participants (12/47, 26%), all of whom were of working age (i.e., <65 years), explicitly stated that they experienced no financial burden.

> *"It's not just clinical. It's also financially really hard as well.... it's been expensive for me and my husband."* (P23)

Several participants experienced employment concerns. Twenty participants (20/47, 43%), of whom 16 (16/20, 80%) were aged <50 years, stated that they were limited in what career they were able to pursue (e.g., pilot, police officer, nurse). Eight of these individuals (8/20, 40%) had no vision impairment in their better eye, although 5 (5/8, 63%) had a vision impairment in their worse eye.

> *"I wanted to be a doctor or vet… but any deterioration [in my vision] and you know, that's what, 8 years of study, work placement, and internship down the drain."* (P30)

Moreover, several participants (13/47, 28%) were concerned that their ability to perform work tasks would be affected, often resulting in a fear of failing work performance reviews or losing their job.

> *"I was always getting into trouble for missing bits and pieces for that sort of job… I try really hard and I can't see it… and you get picked on for it."* (P13)

Theme 10: Mobility

Mobility issues were experienced by 21 participants (21/47, 45%), all of whom had visual acuity <20/40 in their worst eye. Likewise, the majority (6/8, 75%) of individuals with visual acuity <20/200 in their better-seeing eye and the majority of those unable to drive a

motor vehicle (16/20, 80%) reported mobility issues. Bumping into objects on 1 side was stated by 12 participants (12/47, 26%), of whom 11 (11/12, 92%) had BCVA <20/60 in their worst eye.

> *"If I'm walking down the outside, or if someone's coming up on my left side, like I'll usually end up moving myself over a bit too much and running myself into something."* (P47)

Difficulties in using public transport (12/21, 57%), navigating unfamiliar environments (10/21, 48%), and navigating crowded places (7/21, 33%) were also reported among those with mobility issues. All mobility issues reported did not appear to be influenced by the participant's age.

> *"People look at me now even with the cane bobbing along the street or in the shopping centre. I've got focused on what I have to do and the brain gets so tired… sometimes I get myself in a real mess!"* (P35)

Discussion

In this exploratory qualitative research study, we examined the psychosocial impact of childhood glaucoma experienced by adults of predominantly self-reported European ancestry. This study contributes to a limited body of literature that qualitatively investigates the lived experience of childhood glaucoma in adults. We performed comprehensive interviews covering all aspects of life for affected individuals. Nine of the 10 themes identified are consistent with those reported in studies involving adults with adult-onset glaucoma.[22,24] The impact of childhood glaucoma on family planning was a novel finding. Each theme was relevant to all glaucoma subtypes described and therefore provided a detailed description of the collective childhood glaucoma experience.

The most prominent theme identified was coping. The majority of the participants adopted positive coping strategies that were problem-focused (i.e., changing behaviors to mitigate the problem) and emotion-focused (i.e., regulating emotions in response to the problem), as defined by the Stress and Coping Model.[23] These included acceptance, humor, and social support, which are consistent with reports of coping strategies in adults with other hereditary ocular diseases, including retinitis pigmentosa[25] and Stargardt's disease.[26] Alternatively, maladaptive avoidance coping strategies were reported by nearly half of the individuals in this study, particularly those aged less than 40 years and those with no vision impairment in their better eye or who undergo review less regularly. To our knowledge, no studies have investigated the use of coping strategies in adults with childhood glaucoma, why this age phenomena may occur, or the effect it may have on glaucoma progression. It may be a result of younger individuals not being able to fully grasp the longevity of their glaucoma, having alternate priorities, or having negligible activity limitations, as hypothesized by Gupta et al.[5] It could additionally be due to nonacceptance of their condition, as seen in adult survivors of retinoblastoma, a childhood ocular cancer, who have been reported to avoid coping with their emotions using internalization.[27] The association between the use of avoidance coping and age is nonetheless an important trend to investigate. Denial[28] and treatment nonadherence[29] have otherwise been found to be associated with worsening visual field mean deviation in individuals with adult-onset glaucoma and binocular vision equal to or better than 20/40. Furthermore, individuals with adult-onset glaucoma aged less than 50 years have been found to be less likely to adhere to treatment.[29] Younger adults with childhood glaucoma and no vision impairment or who undergo review less regularly therefore may be more at risk of treatment nonadherence and consequent disease progression. As recommended by Horne et al.,[30] clinicians should spend time to understand reasons for nonadherence and how patients judge their need for treatment with consideration to the presence of other circumstantial stressors. Our findings support this, particularly where the use of maladaptive coping strategies is suspected.

The majority of individuals in this study expressed a range of negative emotions. These included feeling misunderstood because of the disease rarity and feeling self-conscious of their eye appearance, use of vision aids, and visual ability. These feelings have not yet been evaluated in adults with childhood glaucoma. Feeling misunderstood has been previously reported to contribute to a lower psychosocial well-being and self-image in individuals with adult-onset glaucoma.[31,32] Lower self-image, however, was attributed to a fear of falling likely due to decreased visual ability, and feeling older due to the disease rather than the association between eye appearance and use of vision aids on self-image. Moreover, these emotions may be attributed to a lack of awareness of glaucoma and public health campaigns in the general population. A previous Australian study reported that only one-third of people were able to correctly recognize glaucoma as an asymptomatic ocular condition,[33] whereas knowledge of childhood glaucoma was not assessed. Literature assessing awareness of childhood glaucoma, however, is scarce and requires evaluation in an effort to alleviate these unique negative emotions.

Concerns for self-image and being misunderstood often negatively affected social well-being. Approximately half of participants expressed a fear of being seen as different and being mistreated, resulting in concealment of their condition in a social or workplace setting. Social embarrassment and workplace discrimination have been reported by individuals with retinitis pigmentosa,[25] and Stargardt's disease,[26] and was largely attributed to one's vision impairment. Participants additionally described childhood bullying during schooling years, often due to their eye appearance or visual ability. Children aged less than 12 years with childhood glaucoma report lower psychosocial well-being compared with older children,[34,35] which may be indicative of childhood bullying. Adult survivors of retinoblastoma similarly reported schoolyard bullying due to eye appearance, having a prosthetic eye, or their facial appearance after radiation therapy to control their disease.[36] This significantly affected survivors' emotional and physical functioning, and social well-being as an adult.[36] In contrast, a minority of participants in this study discussed a lasting impact of childhood bullying, whereas the use of an ocular prosthetic made 3 individuals less self-conscious in comparison with their phthisical eye. Meanwhile, schoolyard bullying

frequently made others consider themselves more resilient, which improved their QoL as an adult. Developing improved QoL over time is referred to as the "response shift," a phenomenon commonly observed in chronic illnesses as individuals accommodate to life with their condition.[37] This may explain why some participants did not discuss issues with their social well-being. Nonetheless, the impact of childhood glaucoma on social well-being at various ages warrants further investigation, particularly because childhood experiences may have negative implications for the individual's future.

Almost all participants reported ocular health concerns including fear and anxiety about losing their vision or their independence in the future. This was particularly observed in participants with no vision impairment in their better eye and vision impairment in their fellow eye. Individuals aged more than 60 years with adult-onset glaucoma and unilateral painless vision loss have similarly been found to experience higher levels of depression, anxiety, and hopelessness compared with normal-sighted individuals.[38] These emotions were attributed to worry of future vision loss, in agreement with our observations. Meanwhile, a large cohort study from North Carolina reports anxiety and depression in 17% and 22% in adults $\geq$18 years of age with glaucoma, respectively, although it was not reported how many individuals had childhood-onset disease.[39] Although psychiatric manifestations were not formally evaluated in our population, 3 participants reported accessing psychological support because of their experience with glaucoma. Conversely, it is possible that peer support may mitigate the risk of anxiety and depression in glaucoma because many participants in this study indicated that spouses, friends, and family were their primary support. Research evaluating the presence of anxiety and depression and need for psychological support in this cohort is consequently required.

The effect of childhood glaucoma on family planning is a novel and significant issue that was discussed by the majority of participants. Two-thirds of participants expressed concern that their child may inherit the condition, become visually impaired, or have the same childhood and adult experiences. This was particularly observed where the adult was visually impaired in 1 or both eyes. Adults with retinoblastoma[40] and Stargardt disease[26] have similarly been reported to express concern for their child to inherit the condition. Participants in this study additionally experienced anxieties and worries for their own social well-being and ocular health, and these may be transferred to their child or future child. However, these concerns were experienced less commonly by individuals with an affected first-degree relative. It is possible that these individuals and their families were more familiar with glaucoma and its potential limitations and had routinely practiced normalization of their condition. This practice minimizes disease impact on daily living and is an adaptive practice common in individuals with chronic inherited disease.[41] Nonetheless, clinicians should give attention to and understand these concerns particularly when an individual is planning to have children.

Genetic counseling was sought or desired by the majority of participants who expressed concern for family planning. This observation may be biased by the fact that our cohort was recruited from a genetic registry (ANZRAG). Nonetheless, the substantial proportion of participants exhibiting this behavior implies that genetic testing and counseling are considered valuable and necessary to achieve peace of mind. Alternatively, the majority of those who did not seek genetic counseling were not visually impaired and consequently did not see a benefit of the service. Genetic testing for family planning purposes has otherwise been reported to be sought by 65% of individuals with inherited retinal diseases.[42] In survivors of retinoblastoma, 33% sought genetic testing and 36% avoided getting pregnant so that pathogenic genetic variants would not be passed on.[40] The latter behavior was discussed by 3 adults in this study. Preimplantation genetic diagnosis could be a possible alternative for these individuals to alleviate the risk of passing on a pathogenic variant. Attitudes toward this process were not discussed in this study; however, 52% of individuals with inherited retinal diseases supported the use of preimplantation genetic diagnosis.[42] With consideration to genetic counseling—seeking behaviors in other ocular conditions, our findings warrant further investigation into the attitudes and perceived benefits of genetic testing and counseling in individuals with childhood glaucoma. The results of this study otherwise support that genetic testing and counseling services should be made available and accessible to adults with childhood glaucoma undergoing family planning.

The remaining themes (symptoms, inconveniences, activity limitation, economic, and mobility) were similar to other QoL research in individuals with adult-onset glaucoma.[22,24] In a previous study that interviewed 72 individuals with adult-onset glaucoma, issues with activity limitation, emotional well-being, and conveniences were the most common.[22,24] In contrast, activity limitation was not a major theme discussed by our participants. This is likely due to the high average number of years since individuals were diagnosed with their glaucoma in our cohort and consequently participants had many years to adapt to their condition. The advancement and increased availability of adaptive technologies at the time of this study, in addition to the visual and physical capabilities of participants, may further have influenced this finding. This may additionally explain why mobility issues were discussed least by participants. Nonetheless, the issues raised within these themes reached data saturation within the cohort studied. However, it must be emphasized that the participants reported are younger than the typical adult-onset glaucoma cohort such that these issues are experienced in a different social context. In particular, the inability to fulfill parental duties or to pursue and maintain an intimate relationship or certain career trajectory may affect one's QoL to a larger extent than someone with adult-onset glaucoma who has an established family, relationship, or career before disease onset. These themes are consistent with previous reports in Stargardt's disease,[26] retinoblastoma,[43] and retinitis pigmentosa.[25] Furthermore, nonparticipation in sporting or physical activities in otherwise young and healthy individuals with a vision impairment has been associated with lower mental, social, and physical well-being.[44] However, this may change in the future with the increasing availability of competitive sports for vision-impaired individuals at highly competitive levels.

Implications for Future Research

The effect of childhood glaucoma on QoL is not yet accurately captured by current PROMs. Prior research has used PROMs or QoL measures that are designed to measure general well-being,[5–7] rather than capturing the specific effect of glaucoma. For example, the 26-item World Health Organization Quality of Life-BREF questionnaire and the 5-item Satisfaction with Life Scale, which has been completed by young adults with childhood glaucoma in India,[6] do not measure issues specific to vision loss or glaucoma. Furthermore, the National Eye Institute Visual Function Questionnaire 25, completed by adults with childhood glaucoma in Iran,[7] may not be the most appropriate tool, because its ability to measure social functioning or mental health is not considered psychometrically sound.[45] It is paramount that a quantitative measure of QoL in individuals with childhood glaucoma is performed using a childhood glaucoma–specific PROM. This will enable accurate investigation of associations between clinical characteristics and QoL scores. Consequently, clinicians would be able to identify at-risk individuals and appropriately refer such individuals to nonophthalmic services (e.g., psychology or genetic counseling services) where indicated. The development of a childhood glaucoma-specific PROM would also enable cross-cultural investigation of QoL with the assistance of international collaboration. The results of this study will assist with the identification of items, across the 10 QoL issues presented, to develop a childhood glaucoma–specific PROM.

Study Limitations

Study limitations include that participants were recruited from a registry and thus may be more willing to participate because they are experiencing a higher QoL than those who did not participate. Nonetheless, the findings were triangulated with previous glaucoma QoL research and identified several areas that have implications for clinical practice. Furthermore, the majority of participants were of self-reported European ancestry and resided in Australia. Findings may only be extrapolated to a population with similar social, cultural, ethical, and religious beliefs, and healthcare setting. However, the experiences described are representative of the wider Australian population because recruitment was from a national registry. Last, we explored QoL issues in more individuals with primary glaucoma compared with secondary forms of glaucoma. It remains possible that individuals with secondary glaucoma have more specific issues that affect QoL that were not captured in our study (e.g., systemic and dental anomalies in Axenfeld-Rieger syndrome). Nonetheless, the inclusion of individuals with different subtypes of childhood glaucoma provides detailed descriptions of the lived experience of the disease as a whole.

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[1] Department of Ophthalmology, Flinders University, Flinders Medical Centre, Bedford Park, Australia.

[2] Department of Ophthalmology, Women's and Children's Hospital, North Adelaide, Australia.

[3] Department of Ophthalmology, Royal Children's Hospital, Parkville, Australia.

[4] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia.

[5] Ophthalmology, University of Melbourne, Department of Surgery, Parkville, Australia.

[6] Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Bedford Park, Australia.

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Author Contributions:

Conception and design: Knight, Ridge, Staffieri, Craig, Prem Senthil, Souzeau

Data collection: Knight, Ridge

Analysis and interpretation: Knight, Ridge, Staffieri, Craig, Prem Senthil, Souzeau

Obtained funding: Knight, Craig, Prem Senthil, Souzeau

Overall responsibility: Knight, Ridge, Staffieri, Craig, Prem Senthil, Souzeau

Abbreviations and Acronyms:
ANZRAG = Australian and New Zealand Registry of Advanced Glaucoma; **BCVA** = best-corrected visual acuity; **IOP** = intraocular pressure; **PROM** = patient-reported outcome measure; **QoL** = quality of life.

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Correspondence:
Lachlan S.W. Knight, BHSc MOrth, Department of Ophthalmology, Flinders University, Flinders Medical Centre, 1 Flinders Drive, Bedford Park, SA, 5042, Australia. E-mail: Lachlan.WheelhouseKnight@flinders.edu.au.

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Publication F4. The caregiver experience in childhood glaucoma: an interview study

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The Caregiver Experience in Childhood Glaucoma

An Interview Study

Lachlan S.W. Knight, BHSc, MOrth,[1,2] *Bronwyn Ridge, BA(Psych), GradDip(HCouns),*[1] *Sandra E. Staffieri, BAppSc(orth), PhD,*[3,4,5] *Jamie E. Craig, MBBS, DPhil,*[1] *Mallika Prem Senthil, PhD,*[6] *Emmanuelle Souzeau, PhD*[1]

Purpose: To investigate and report on the quality-of-life (QoL) issues experienced by caregivers of individuals with childhood glaucoma.

Design: Exploratory, qualitative study.

Participants: Thirty-five caregivers of individuals with childhood glaucoma (defined as disease onset before 18 years of age) recruited from the Australian and New Zealand Registry of Advanced Glaucoma.

Methods: A qualitative research methodology (interpretive phenomenology) was applied. Data were collected through semistructured in-depth interviews. NVivo-12 software (QSR International Pty Ltd) was used to analyze, code, and organize data into QoL themes inductively.

Main Outcome Measures: Quality-of-life themes and their subthemes.

Results: The mean caregiver age was 50.2 ± 13.6 years, and 27 of 35 caregivers (77%) were mothers of an individual with childhood glaucoma. A total of 6 QoL themes were identified. Coping strategies and emotional well-being were the most prominent themes. Caregivers frequently adopted problem-focused adaptive coping strategies including partner or peer support, and normalization. A caregiver's psychosocial well-being was often impacted by feelings of guilt and regret regarding their child's delayed diagnosis, fear and anxiety related to medical and social support, and loss of control as their child developed medical autonomy. The effect of family planning from the perspective of the caregiver formed a novel QoL theme and was associated with normalization and parental confidence in management of the condition.

Conclusions: Childhood glaucoma poses a substantial threat to a caregiver's psychosocial well-being. Strategies that promote normalization, peer support, psychotherapeutic intervention, and genetic counseling may be indicated and, indeed, critical to the caregiver as they adapt to supporting their child with glaucoma. *Ophthalmology Glaucoma 2022;5:531-543 © 2022 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.ophthalmologyglaucoma.org.

Childhood glaucoma describes a group of vision-threatening conditions with disease onset occurring between birth and 18 years of age and is typically characterized by elevated intraocular pressure (IOP) and optic neuropathy.[1] Primary congenital glaucoma (PCG) is the most common type of childhood glaucoma, with disease onset before 3 years of age.[2] Childhood glaucoma requires complex and specialized lifelong surgical and conservative management. Surgical intervention is frequently required immediately on diagnosis and may be followed by several years of topical antiglaucoma therapies (i.e., eye drops) and further surgery to control IOP and maintain vision status.[3] If the disease is not treated promptly, irreversible vision impairment or blindness are likely outcomes.[3] Similarly, treatment does not guarantee a safeguard from visual morbidity, and close monitoring throughout one's lifespan is required.[3]

Diagnosis of the condition can be a stressful or traumatic experience for caregivers. This is compounded by the disease's chronicity and uncertain visual prognosis, the requirements of surgical intervention and frequent examinations under anesthetic, the child's future level of independence, and the likely genetic cause of the disease. Few studies have investigated the impact of the condition on caregivers.[4–9] Caregivers have reported a high prevalence of depressive symptoms[4–8] and high caregiver burden while caring for a child with childhood glaucoma,[5] but the literature that explores the reasons for these findings is sparse. None have yet evaluated the use of coping strategies in the context of a high caregiver burden or to

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investigate beyond clinical parameters why low emotional and social well-being may be experienced. Furthermore, decision-making around family planning from the perspective of the caregiver, who may also be affected with glaucoma, has not yet been investigated. This is critical in the context of an inherited disease. The aim of this present study was to develop a comprehensive understanding of the impact of childhood glaucoma on caregivers and the quality-of-life (QoL) issues that they encounter.

Methods

Participants

A nonprobability convenience sampling technique was adopted to recruit caregivers from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG). The ANZRAG provides one of the largest international repositories of individuals with childhood glaucoma and their caregivers, whereby participants undergo genetic testing to identify genes associated with glaucoma.[2] Therefore, it provides a suitable cohort to evaluate the effect of childhood glaucoma on QoL and family planning. Caregivers residing in Australia were invited to participate if their child had received a diagnosis of glaucoma before 18 years of age (regardless of the glaucoma subtype), were English speaking, and had or currently were having an active role in their child's glaucoma care. Consequently, more than 1 caregiver per child was accepted into the study. Participants were excluded if they had a disability impacting on their own QoL (e.g., hearing or cognitive impairment) as informed by their partner or other carer or their child had coexisting ocular or systemic disease unrelated to the spectrum of childhood glaucoma as informed by the caregiver or child's glaucoma specialist.

Eligible caregivers were invited to participate in the study by mail and asked to register their interest. On receipt of interest to be interviewed, caregivers were sent an information pack and consent form. After informed written consent was obtained, caregivers were contacted to coordinate an appropriate time to be interviewed. If no reply was received within 2 weeks, a follow-up phone call was initiated, and caregivers were deemed noncontactable after a minimum of 2 unsuccessful attempts. Clinical details of caregivers' children were obtained from their medical records at the time of the interview. The glaucoma subtype was classified according to the Childhood Glaucoma Research Network criteria.[1] Disease onset at 4 years of age or later was classified as juvenile onset.[1] Vision impairment was considered to be present if 1 eye had worse than 20/40 best-corrected visual acuity, according to the International Classification of Diseases for Mortality and Morbidity Statistics (11th Revision).[10] This level of visual acuity is required in at least 1 eye to be able to operate a motor vehicle in Australia.[11] For the purpose of analyses, details of the eldest child with glaucoma were used where more than 1 child within a family had childhood glaucoma. Ethics approval was obtained from the Women's and Children's Health Network Human Research Ethics Committee, and the study adhered to the tenets of the Declaration of Helsinki.

Interviews

To investigate the caregivers' lived experiences comprehensively, the theoretical framework of interpretive phenomenological analysis was adopted.[12] A semistructured interview guide consisting of open-ended questions was developed from a literature review of QoL issues experienced by caregivers of a child with childhood glaucoma or vision impairment secondary to another ocular condition.[4–8,13] The interview guide consisted of questions about the caregivers' experiences during the period of diagnosis and throughout various treatments and ophthalmic examinations (e.g., *How has the course of treatment and examinations impacted you as a caregiver?*). Additional questions about the social, physical, and emotional impact of the condition, with particular reference to their family life, their child's prognosis, their access to support and ability to cope, were asked (e.g., *What worries or concerns do you have for your child right now? What helps you cope with your child's current state of health?*). The interview guide and complete set of questions are provided in Figure S1 (available at www.ophthalmologyglaucoma.org). All interviews were conducted in the English language by 1 of 2 authors (L.S.W.K. or B.R.) experienced in QoL research. L.S.W.K. is an orthoptist with clinical and research experience in childhood glaucoma and B.R. is a health counselor. Participants were informed that the study was being completed in the context of higher degrees for both interviewers. No caregivers' children were under the clinical care of either interviewer. Caregivers were offered a one-on-one semistructured interview via telephone or Cisco WebEx video conferencing. For this study, all caregivers preferentially selected a telephone interview, although reasons for this were not investigated. Caregivers were encouraged to be alone during the interview to control for any external influences on their responses. All interviews were recorded and transcribed verbatim. Interviews continued until thematic saturation was reached, defined as the point where no new information was gained from subsequent interviews.[14] Caregivers were offered the opportunity to review their transcript for accuracy and to receive information on counseling services if desired.

Data Analysis

Transcripts were coded systematically and inductively using QSR NVivo version 12 (QSR International Pty Ltd) by 1 author (L.S.W.K.). Inductive, or open, coding minimizes the influence of any prior assumptions or hypotheses when analyzing data.[15] Independent parallel coding was performed by 1 author (B.R.), which involved comparing and establishing an agreement on the codes used for a subset of transcripts.[15] Stakeholder coding checks were frequently performed by 2 other authors (M.P.S. and E.S.) to assess for agreement of data interpretation and credibility of findings.[15] Codes with similar or repetitive patterns of meaning were grouped into major themes with subthemes.[16] Any discrepancies were resolved by discussion among all authors. All statistical calculations were performed using SPSS version 27.0 for Windows (IBM/SPSS, Inc).

Results

Participant Characteristics

A total of 35 eligible caregivers of an individual with childhood glaucoma were interviewed between March and September 2020. The mean interview time was 60 ± 19 minutes. The mean caregiver age was 50.2 ± 13.6 years, and 27 of 35 participants (77%) were women (i.e., a mother). Seven mother–father dyads were included. Most caregivers (32/35 [91%]) had 1 child with childhood glaucoma, whereas 3 of 35 caregivers (9%) had 2 or more children with the condition. Of the caregivers' eldest child with childhood glaucoma, 17 of 35 children (49%) were female, 10 of 35 children (29%) had bilateral vision impairment, 17 of 35 children (49%) had reached adulthood, and 31 of 35 children (89%) had a diagnosis of PCG. Additional caregiver and child characteristics are detailed in Tables 1 and 2, respectively. The exact level

Table 1. Demographic Characteristics of Caregivers

Variable	Data
Age at interview (yrs)	
30–39	8 (23)
40–49	11 (31)
50–59	10 (29)
≥ 60	6 (17)
Time since child diagnosis (yrs), median (range)	12 (0.7–61)
Female sex	27 (77)
Self-reported ancestry, European	33 (94)
Had childhood glaucoma	4 (11)
Relative (other than child) affected by childhood glaucoma	5 (14)
Genetic results, molecular diagnosis identified	
Autosomal recessive inheritance established	9 (26)
Autosomal dominant inheritance established	5 (14)
No. of children, median (range)	2 (1–6)
Had more than 1 child	25 (71)
Order of first affected child per caregiver	
First	27 (77)
Middle	2 (6)
Last	6 (17)

Data are presented as no. (%), unless otherwise indicated.

Table 2. Demographic and Clinical Characteristics of the Caregivers' First Child with Childhood Glaucoma

Variable	Data
Female sex	17 (49)
Current age (yrs)	
0–3	8 (23)
4–17	10 (29)
18–39	14 (40)
≥ 40	3 (9)
Age at time of caregiver interview (yrs), median (IQR)	16 (4–25)
Age at glaucoma diagnosis (yrs), median (range)	0.2 (0–17)
Bilateral glaucoma	31 (89)
Subtype of childhood glaucoma	
Primary congenital	31 (89)
Juvenile open angle	3 (9)
Associated with nonacquired ocular anomalies (aniridia)	1 (3)
Visual impairment*	
None in either eye	14 (40)
Unilateral	8 (23)
Bilateral	10 (29)
Too young for formal visual acuity assessment	3 (9)

IQR = interquartile range.
Data are presented as no. (%), unless otherwise indicated.
*Defined as < 20/40 best-corrected visual acuity.[10] This level of visual acuity is required in at least 1 eye to be able to operate a motor vehicle in Australia.[11] The exact level of visual acuity per child per eye is provided in Table S1.

of visual acuity per child per eye is provided in Table S1 (www.ophthalmologyglaucoma.org).

Themes and Subthemes

Six QoL themes and their subthemes emerged from the interview data. This process is outlined in Table 3, whereby codes or subthemes that have positive or negative impacts on QoL were grouped into major QoL themes. The proportion of caregivers who expressed issues within the QoL theme and the total number of coded segments per theme are illustrated in Figure 1.

Theme 1: Coping

To manage the emotional and social challenges of raising a child with childhood glaucoma, several coping strategies were adopted. These included adaptive and maladaptive coping strategies considered to be either problem-focused (i.e., actively confronting the problem) or emotion-focused (i.e., regulating or dampening negative emotions brought on by the stressors).[17]

The most common adaptive problem-focused strategy was seeking and accepting assistance provided by social and professional support systems. This was expressed by almost all caregivers (34/35 [97%]). The most valued social support system was the caregivers' spouse or partner (30/35 [86%]; henceforth collectively referred to as "partner"), particularly in the context of their child's appointments, when the child was undergoing surgery or being anesthetized, and when administering the child's medication. All caregivers within the mother-father dyads expressed the positive value of their partner. The caregivers' parents were also considered highly valuable by 22 of 35 caregivers (63%), especially in cases when other children required care or when respite care was required because of feeling sleep deprived. Sleep deprivation was attributed to staying awake because of glaucoma-related anxieties, or the child's disrupted sleep pattern after having a general anesthetic, for 4 of 35 caregivers (11%). Health care staff (13/35 [37%]), vision support services (10/35 [29%]), and psychology or counseling services (9/35 [26%]) were further considered important support systems.

> *I think it's always better if the two of you are [at the appointments] to take it in, the information . . . we were always in it together and well, we are still together so anyhow, 30 years later.* (CG09)

Most caregivers (32/35 [91%]) reflected that they normalized their child's glaucoma. This was often adopted so that caregivers could provide their child with opportunities equal to those of their child's peers. Similarly, caregivers found this process helpful in building their child's independence. Other problem-focused coping strategies included gaining knowledge of childhood glaucoma (16/35 [46%]) and modifying their own behaviors to adapt to their child's visual limitations (9/35 [26%]).

> *We've tried to normalize it as much as possible . . . her whole life doesn't revolve around her vision.* (CG24)

The most often used emotion-focused coping strategy was appreciating the child's resilience and ability to adapt to their condition (31/35 [89%]). This was regardless of the child's current age, but was used more commonly in caregivers of a child with a unilateral or bilateral vision impairment compared with caregivers of a child without a vision impairment (17/18 [94%] vs. 10/14 [71%], respectively). Sixteen caregivers (16/35 [46%]) additionally reflected that witnessing their child's ability to achieve developmental milestones provided an important means of coping.

> *Her vision impairment was more just part of her rather than anything that ever held her back.* (CG04)

Other common emotion-focused coping strategies included trusting the ophthalmologist to provide optimum care to their child (29/35 [83%]) and being grateful that their child's condition

Table 3. The Major Quality-of-Life Themes as Determined by the Grouping of Subthemes and Codes That Have a Positive or Negative Impact on Quality of Life

Theme No.	Major Quality-of-Life Theme	Positive Quality-of-Life Impacts	Negative Quality-of-Life Impacts
1	Coping	Social support	Avoiding glaucoma-related thoughts
		Normalization	Emotional detachment
		Appreciating child's resilience	Blaming health professionals
2	Emotional well-being	Managing fleeting anxiety	Feeling anxious or scared
		Feeling hopeful or grateful	Feeling shocked, guilty, or regretful
		Feeling proud of child	Feeling low or helpless
3	Medical and social support	Medical care becomes routine	Perceived that treatment is hurting child
		Positive reinforcement with child	Overprotective of child
		Community establishment	Fear of schoolyard bullying
4	Social well-being	Relationship teamwork	Relationship conflict
		Connecting with other caregivers	Trouble caring for other children
		Sharing experience	Social isolation
5	Clinical and familial control	Acceptance of disease outcomes	Wanting a cure
		Trusting the child to be autonomous	Attending appointments with adult child
		Confidence in managing disease	Worried about others caring for child
6	Family planning	Gaining knowledge of future risk	Worried about future children or grandchildren
		Confident in detecting condition	Not wanting more children
		Planning ophthalmic follow-ups	Self-blame for genetic results

had not worsened or that it was limited to their eyes (26/35 [74%]).

> *We completely trust [the ophthalmologist] . . . he doesn't give us false hope and doesn't tell us what the future looks like, he just tells us the next step.* (CG27)

Accepting their child's condition (24/35 [69%]), communicating openly about their experience (15/35 [43%]), and relating to other families with a child with vision impairment, childhood glaucoma, or both (12/35 [34%]) were additionally expressed.

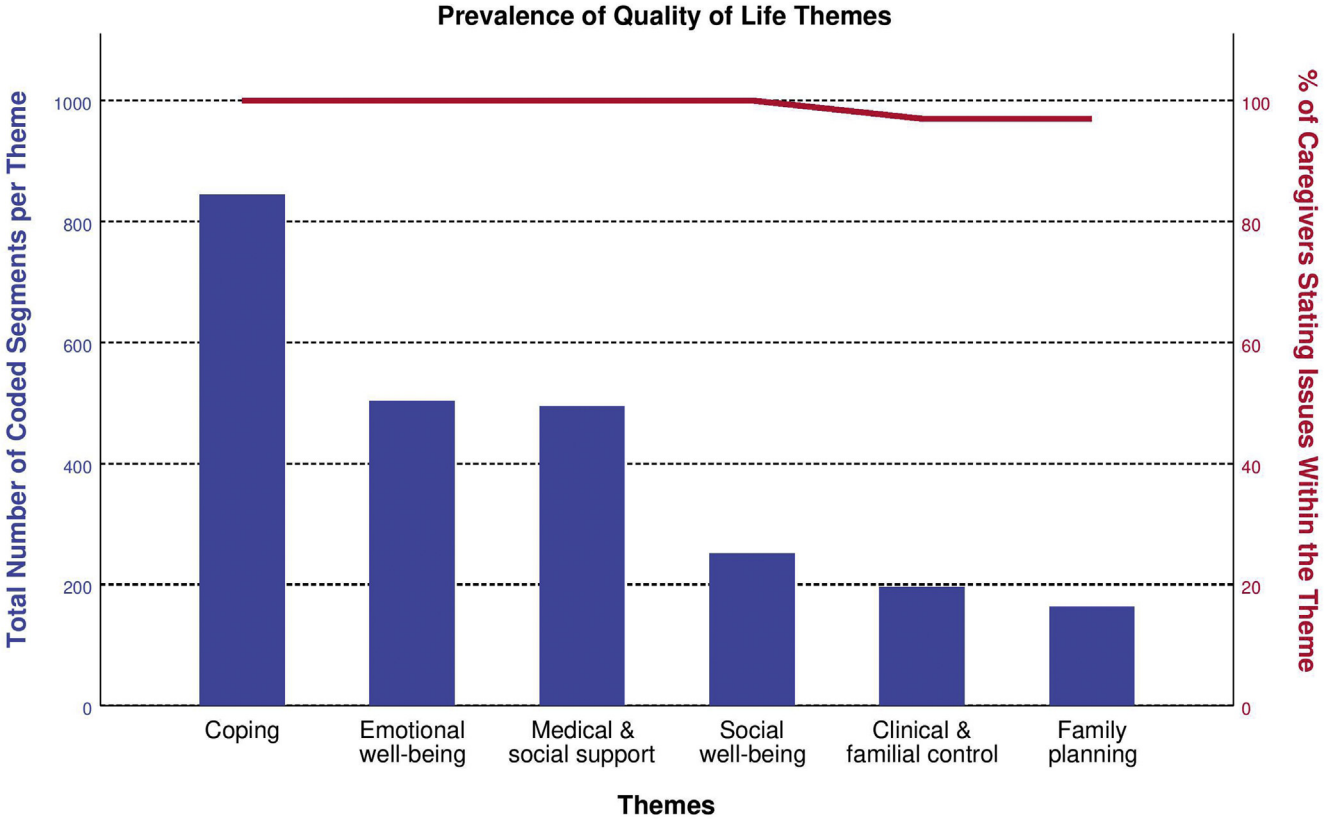

Figure 1. Dual y-axis chart demonstrating the total number of codes per theme (blue bar chart) and the proportion of caregivers who discussed an issue within the theme (red line chart) among caregivers of individuals with childhood glaucoma.

[My ophthalmologist] said to me . . . I think there's one mom [of a child who also has glaucoma] that would be really, really happy to talk to you . . . she rang me, and we had the biggest chat and it just made me feel so much better. (CG33)

Although common, caregivers used maladaptive coping strategies less frequently than adaptive coping strategies, regardless of the time since diagnosis (22/35 [63%] vs. 35/35 [100%], respectively). The most common maladaptive coping strategy was to avoid thinking or talking about their child's glaucoma (10/35 [29%]), whereas 4 of 35 caregivers (11%) explicitly stated that they became emotionally detached from their child when they were undergoing surgery as an infant. Although at times protective of feelings of anxiety, detachment often led to social isolation or an inability to bond with their child.

When she was born and got the diagnosis. . . I kind of shut off from her. It was too painful . . . I didn't really bond with her until she was 4 to 5 months . . . It became my job. I was here to medicate this child. (CG21)

Another common maladaptive strategy was blaming health professionals for not diagnosing or managing the condition earlier (7/35 [20%]). This was described exclusively by caregivers of children with unilateral or bilateral vision impairment.

If [the ophthalmologist] had picked it up the first time, would [my child] have better eyesight? . . . I've still probably got a bit of a scar about that. (CG16)

Avoiding current glaucoma-related thoughts with distraction from work, alcohol, or indulgence in comfort foods (4/35 [11%]) or suppressing thoughts of the future (5/35 [14%]) were additionally practiced by caregivers.

I don't deal with the future. That's okay, it'll happen when it happens. (CG02)

Theme 2: Emotional Well-being

The caregiver experience of childhood glaucoma presented many negative emotional experiences. Almost all caregivers (33/35 [94%]) expressed feeling anxious, particularly regarding their child's ocular surgery (19/35 [54%]) and requirement for general anesthetics (14/35 [40%]). The latter was experienced exclusively by caregivers of children with PCG because of the early age of disease onset and requirement for treatment.

I suppose it sort of tugs at your heartstrings, your baby is going to be put to sleep and taken away from you. (CG09)

Caregivers additionally experienced anxiety and fear regarding their child's current or future vision (17/35 [49%]), future ocular health (12/35 [34%]), control of IOP (12/35 [34%]), and risk of sustaining an ocular injury (11/35 [31%]), but these were often expressed as manageable anxieties with the use of coping strategies. If the child had unilateral or bilateral vision impairment, caregivers were more often anxious about their child's vision, future ocular health, and risk of injury, whereas anxiety regarding IOP was independent of vision status.

Our concern [was] if she got hit in the eye [or] if there was a sudden increase in eye pressure . . . Those sorts of things were and still are the biggest worry. (CG12)

Most caregivers (24/35 [69%]) recalled experiencing shock when their child received the diagnosis because they were unaware that glaucoma could be diagnosed in a child. Shock was followed by feelings of guilt (19/35 [54%]) and regret (18/35 [51%]), whereas shame was experienced infrequently (2/35 [6%]). These feelings were typically associated with a yearning to have a healthy child, not recognizing glaucomatous signs sooner, or not pushing the health care practitioner for a diagnosis sooner. These experiences seemed to be independent of the caregiver's gender, the glaucoma subtype, and the age at diagnosis. Among the mother-father dyads, guilt was expressed by both caregivers in 1 of 7 dyads (14%) and by only 1 of 2 caregivers in 3 of 7 dyads (43%).

She'd be squinting her eye all the time because she couldn't tolerate light. Well, I just didn't click. Nothing clicked with me because I don't really know anything about ophthalmology . . . I'd never heard of infantile glaucoma. (CG10)

Feelings of guilt in mothers were associated more specifically with possibly harming the child *in utero* with medication or alcohol intake (3/27 [11%]) or passing on a possible genetic variant (9/27 [33%]), despite 5 of 9 caregivers (56%) not having a genetic diagnosis.

It's just that you feel guilty . . . that I brought some innocent little victim into the world . . . Because when you're having a baby, it's all part of you, and you don't want anything to go wrong with it. (CG29)

Frustration was expressed by 18 of 35 caregivers (51%), with the emotion commonly associated with the lack of awareness and knowledge of childhood glaucoma from health care professionals or peers. Caregivers frequently stated that their child's glaucoma was misdiagnosed as blocked tear ducts.

I was frustrated that the midwives weren't more accepting of it, because they just couldn't see anything . . . I was kind of annoyed at myself for not pushing the matter. (CG24)

Twelve caregivers (12/35 [34%]) reflected that the first years after diagnosis brought feelings of sadness, with 4 of 35 female caregivers (11%) stating they experienced symptoms of postpartum depression and 3 of 35 caregivers (9%) describing feeling helpless. Eleven caregivers (11/35 [31%]) further described the diagnostic period as traumatic, and many recounted the day of diagnosis vividly. Of these 11 caregivers, 9 (9/11 [82%]) had their first-born child receive a diagnosis of PCG.

I remember saying, 'This has got to be the worst day of my life' . . . I felt very helpless because I couldn't get answers to questions . . . Would she have any eyesight after all this was over? It was just the whole unknown. (CG14)

Negative feelings were overcome by feeling hopeful of their child's future eye health or that a cure would be discovered, feeling proud of their child's achievements, and feeling grateful for support they have received from medical and social systems.

I'm a 'hope person' . . . My hope for her in the future is to hold her sight. (CG06)

Theme 3: Medical and Social Support

The caregiver's role in providing support was particularly centered on the medical and social needs of the child. The main medical

support tasks considered influential in the caregivers' experiences were instilling antiglaucoma medication (i.e., eye drops; 18/35 [51%]), taking the child to multiple appointments (20/35 [57%]), and managing postoperative care and postanesthetic behavior changes (12/35 [34%]). These duties seemed to be shared widely among the mother-father dyads interviewed. However, these duties were often met with stress and anxiety as caregivers reasoned that their child often resisted treatment because they were too young to understand why it was needed, or had perceived their child to be in pain. Caregivers otherwise considered these medical duties to be part of a routine.

> *No one wants to hurt their child—hold them down and pry their eyes open—a baby's not going to cooperate, are they?* (CG09)

These emotions of stress and anxiety were negated by normalizing the condition, bonding with the child, and using positive reinforcement.

> *I teach him, I'm just there, I just want to be there for him . . . there's plenty of laughing involved on those days he has procedures . . . We just try and make it a fun day.* (CG26)

Almost half of the caregivers (14/35 [40%]) additionally spoke of feeling overprotective of their child's health regardless of the age of the child or vision status.

> *The biggest challenge we have is around outdoor play because she was so light-sensitive for so long . . . When we're outside, I feel much more protective of her.* (CG25)

Caregivers often discussed the need to advocate for their child's needs to be met within the education system. Caregivers (16/35 [46%]) were particularly concerned about their child experiencing schoolyard bullying because of their visual ability or their eye appearance, including buphthalmos and strabismus, and the need to wear sunglasses because of photophobia.

> *We had really good early intervention . . . And then when she got a bit older it was sort of that fine line between, you know, making use of that support to . . . not being—wanting to be singled out as being different.* (CG05)

This led 6 of 35 caregivers (17%) to establish themselves within a community or a particular school so others would know of and support their child from a young age.

> *We're not going to stay [in this town] . . . I feel like kids that grow up with her are much less likely to bully her for her condition . . . That's something that we've taken into account in our life planning.* (CG11)

Theme 4: Social Well-being

All caregivers experienced strain on their immediate and extended familial and extrafamilial relationships in various capacities because of childhood glaucoma. Several caregivers (10/35 [29%]), 6 of 10 (60%) of whom were from 3 of 7 mother-father dyads (43%), explained that relationship conflicts were experienced commonly around the time of a child's appointment, surgery, or medication administration. Five caregivers (5/35 [14%]) reported separating from their partner, although the degree to which the child's glaucoma impacted on this decision could not be determined. Financial concerns regarding costs of glaucoma treatment were otherwise raised by 1 of 35 caregivers (3%), but this was not associated with experiencing relationship conflict.

> *I'm just snapping at [my partner] at least a day or two before the operation. We're just completely on edge and it's just daunting.* (CG27)

Alternatively, 22 of 35 caregivers (63%), 8 of 22 (36%) of whom were from 4 of 7 mother-father dyads (57%), reported that they always had good teamwork with their partner when managing aspects of their child's health, including which caregiver took the child to an appointment, who was responsible for preparing the child for surgery, or who administered medication. Among the 6 caregivers from the 3 of 7 mother-father dyads (43%) who experienced relationship conflict, each discussed that additional moments of good teamwork had occurred. The time since diagnosis between caregivers who reported undergoing a partner separation and those who reported good teamwork was similar (median, 16 years [interquartile range, 5−20 years] vs. 14 years [interquartile range, 4−25 years], respectively).

> *It was something we had to, you know, show a united front against and support each other.* (CG04)

Of the 25 caregivers who had more than 1 child, 14 of 25 caregivers (56%) expressed challenges associated with parenting, providing attention to, and bonding with their other children. The 3 caregivers who had more than 1 child with glaucoma did not express these challenges.

> *It affected our [other child] . . . [They] used to get pushed aside a lot because you know oh 'hang on mommy's just got to do these drops.' It was really, really hard . . . and it did take its toll on us.* (CG33)

More than half of the caregivers (22/35 [63%]) discussed that their extended familial and extrafamilial relationships suffered because their friends or social groups could not understand or relate to their unique experiences. At times, this led to feelings of social isolation. Consequently, more than half of caregivers (20/35 [57%]) expressed they wanted advice from other families who have had the same experience and joined several online social support groups. To reciprocate, 14 of 20 of these caregivers (70%) stated that they were interested in sharing their experiences with others, while being mindful of not reading into worst-case scenarios.

> *I think it definitely helps . . . reading someone else's story gives you a feeling of, um, I guess that you're not alone.* (CG25)

Theme 5: Clinical and Familial Control

Disease incurability and child autonomy challenged many caregivers' (34/35 [97%]) sense of control in both the clinical and familial environments. Most caregivers (24/35 [69%]) discussed feeling unable to control the disease medically and had struggled to accept that the disease had no cure. The impact of these thoughts and emotions was minimized where caregivers had accepted and normalized the clinical course of the condition or had become hopeful that a future cure would be discovered. Not feeling in control and struggling to accept the disease's chronicity were often experienced by caregivers of a female child (18/24 [75%]) and

those who expressed feelings of guilt or regret (17/24 [71%]), but did not seem to be dependent on the vision status of the child, the caregiver's age, or the number of years elapsed since the diagnosis.

> *There's no control. I can't, um, fix the problem for her or help her fix it for herself . . . we wait for potentially ultimately some sort of transplant or cure.* (CG01)

Relinquishing the role of the primary caregiver as the child developed medical autonomy presented challenges for several caregivers (28/35 [80%]). This particularly included trusting the child to develop their own autonomy for their condition (15/35 [43%]), balanced by wanting to know what happened at ophthalmic appointments (10/35 [29%]). Among these caregivers, most had children aged 18 to 39 years (11/15 [73%] and 8/10 [80%], respectively). These experiences caused 8 of 17 caregivers (47%) of adult children to continue to accompany their child to ophthalmic appointments. Meanwhile, 5 of 35 caregivers (14%) expressed worry for their child's ability to afford medical care when they reached adulthood (e.g., cost of medication, cost of specialist care in the private health care system).

> *Since he's been an adult and no longer lives at home. . . . I think he just gets into a headspace of why me, I'm not going to use [eye drops] anymore . . . I've got to let him do what he needs to do to stay well, but as a mom it—it terrifies me that he won't.* (CG32)

Meanwhile, 8 of 18 caregivers (44%) who had children younger than 18 years expressed strong concern for someone other than a family member taking care of their child such as a teacher, friend, or babysitter.

> *We're getting ready to send her off to daycare. Talking about it would make me feel like the air was being sucked out of me . . . I do worry that you know, sometimes she'll be uncomfortable, and [the teachers] won't notice.* (CG11)

Theme 6: Family Planning

Most caregivers (34/35 [97%]) discussed the effect of childhood glaucoma on family planning. Of these caregivers, 14 of 34 (41%) expressed worry that their other children would receive a diagnosis of glaucoma. Consequently, 6 of 35 caregivers (17%), of whom 4 of 6 (67%) had their firstborn receive a diagnosis of PCG, decided not to have any more children. These caregivers additionally did not have a molecular diagnosis.

> *I wanted a big family . . . [but] I never had any more children . . . That would have been devastating, to me, to bring any more into the world, like, to have [eye] problems.* (CG29)

Alternatively, 19 of 35 caregivers (54%), of whom 6 of 19 (32%) had a molecular diagnosis for their child, expressed that they were determined to have more children while of childbearing age. This was often attributed to normalizing the condition, becoming confident in how to manage childhood glaucoma, knowing what to expect, and knowing what disease signs to detect in subsequent children. Of the 4 caregivers who had childhood glaucoma, 3 did not express concern for the possibility of their child having glaucoma because they had normalized the condition. Meanwhile, 1 of 35 caregivers (3%) who had childhood glaucoma opted to use *in vitro* fertilization and preimplantation genetic diagnosis to ensure that their child would not be affected with childhood glaucoma. Among the mother-father dyads, there were 3 of 7 (43%) whereby 1 caregiver discussed having more children, whereas their counterpart did not.

> *Now we know what glaucoma is and how it is working and the results. Obviously, you get onto it early and it's nothing to be afraid of . . . [Having another child] doesn't have any sort of concern to us.* (CG28)

The time since diagnosis seemed to be associated with the decision to have further children for 12 of 35 caregivers (34%) who were of childbearing age (i.e., younger than 45 years) at the time of the interview. The 4 of 12 caregivers (33%) who did not want additional children had a child more recently diagnosed with childhood glaucoma, compared with 8 of 12 caregivers (67%) who did want further children (median, 19 months [interquartile range, 9 months−3 years] vs. 3.5 years [interquartile range, 3 years−4 years], respectively).

> *It wasn't until generally in that 15-month mark where I was like . . . 'We could have another one.' But then that was like 'Oh no but that was too scary.' . . . And then probably at two and a half . . . you know like we can do this. And if we have another one that's got glaucoma, we know what's going to happen now.* (CG21)

To control anxieties related to having another child with glaucoma, 6 of 35 caregivers (17%) discussed that they had planned for an ophthalmologist or pediatrician to examine their child's eyes immediately or shortly after giving birth.

> *When he was born, the pediatrician . . . showed me and got [his] eyes and wedged them open, and I went, yeah, right okay . . . I knew straight away that he was fine.* (CG06)

While planning for further children, 20 of 35 caregivers (57%), 8 of 20 (40%) of whom were from 4 of 7 mother-father dyads (57%), discussed accessing genetic counseling to understand their risk of having another child with glaucoma before conception. As shown in Figure 2, caregivers decided to not have further children only when no molecular diagnosis could be established (4/14 [29%]).

Reasons for not accessing genetic counseling at the time of family planning, discussed by 10 of 35 caregivers (29%), included not having a family history of the condition, not having access to testing when they were of childbearing age, believing that the genetic result would not impact their family-planning decision, or the child having a juvenile diagnosis (i.e., the child was older than 4 years of age at the time of diagnosis). Of these caregivers, 3 of 10 (30%) decided to have more children regardless. Meanwhile, 6 of 10 caregivers (60%) wanted to know the origin of their child's glaucoma and sought genetic testing sometime after they had decided not to have any more children. Guilt associated with genetic findings was reported by 2 of 35 caregivers (6%).

> *I'd prefer to know [the genetic risk] because that would make it mean that we can make informed decisions about how we have another child.* (CG25)

The implications of childhood glaucoma had a generational effect, with 16 of 35 caregivers (46%) worried that glaucoma would develop in their grandchildren. Of these caregivers, 10 of 16

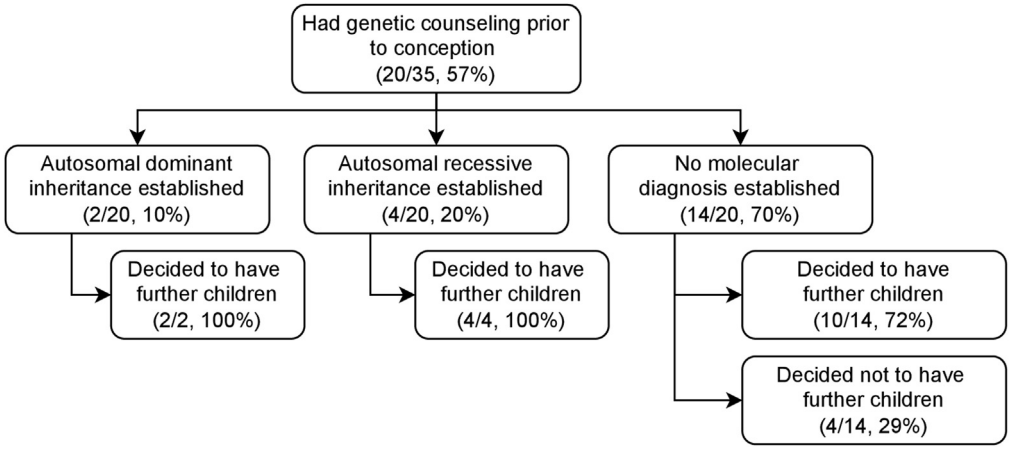

Figure 2. Flowchart depicting the decision-making process among caregivers who sought genetic counseling before conception based on the method of inheritance established for their child's glaucoma.

(63%) discussed that they wanted their child to have genetic counseling before conception.

> *Information is power . . . if it means we can somehow prevent any future children in the family [from] having it, well great, you know?* (CG31)

Discussion

The results of this exploratory qualitative interview study offer a unique, valuable, and complex insight into the psychosocial impact of childhood glaucoma from the perspective of caregivers of predominantly self-reported European ancestry and contribute to an otherwise very limited body of literature. Previous studies have been undertaken in Saudi Arabian,[6] Indian,[4,5,7,8] and Brazilian[9] caregiver populations, which may limit their extrapolation to an Australian cohort because of social and cultural differences. Of the 6 themes identified, 3 themes (emotional well-being, medical and social support, and social well-being) have broadened our understanding as to why caregivers may experience depressive symptoms, a high caregiver burden, and substantial impact on social well-being, as identified in prior literature.[4–9] Meanwhile, the impact of childhood glaucoma on coping, sense of control, and family planning were novel themes. The inclusion of both caregivers within the same mother-father dyad offered valuable and contrasting experiences from the partner (e.g., guilt, family planning), whereas the inclusion of several childhood glaucoma subtypes and the varied ages of caregivers and their children at the time of the interview provided a detailed description of the caregiver experience beyond the diagnostic period.

Coping and Social Support

Like the lived experience of adults with childhood glaucoma,[18] the major theme identified was coping. Seeking and accepting social support was identified as one of the most useful resources to manage the disease's emotional and social impacts while assuming the caregiver role. Under the stress-buffering hypothesis, social supports are considered to be protective against the effects of a chronic stressor, especially where the support directly provides a solution to the main stressor (e.g., management of childhood glaucoma).[19] Stress buffering was observed in the cohort studied, illustrated by the cohesion of the partner relationship and a shared and practical approach to the child's treatment. This same cohesive relationship and shared responsibility has been observed in parents of children with retinoblastoma, a rare childhood eye cancer.[20] Alternatively, it has been demonstrated in nonocular pediatric cancer, specifically, when the supportive caregiver's well-being is low, the partner relationship can become strained and primary caregivers can withdraw from coparenting roles.[21] This may contribute to the relationship conflicts observed in this study, particularly when caregivers reported separation from their partners. The rate of separation reported herein may further be influenced by the number of mother-father dyads interviewed, all of whom reported positive partner teamwork and relatively equally shared caregiver roles. Separation in childhood disease otherwise may be the result of an accumulation of additional stressors, as considered in the Family Stress Process.[22] This could include financial stressors,[22] but these were not identified in this study. Relationship conflict has been observed in caregivers of children with pediatric cancer[23] and juvenile idiopathic arthritis,[24] two conditions similar to childhood glaucoma in that they are characterized by remitting and relapsing patterns. In previous childhood glaucoma caregiver QoL research, studies have included caregiver cohorts with at least a 90% married status,[4,6–8] which may have prevented any analysis of the impact of partner separation or tension on the caregiver's QoL. Health care providers nonetheless should be mindful of caregivers' support systems, and future research should acknowledge partner conflict as a variable that may affect caregiver QoL.

Support groups may additionally provide stress buffering and may offset the threat of disease to emotional well-being and social isolation. As identified in this study, support

groups, whether face-to-face or online, can offer a sense of connectedness and empowerment.[25] Despite a paucity of literature, similar findings have been observed in other childhood ocular diseases, including retinopathy of prematurity[26] and retinoblastoma.[20,27] Online support groups have additionally been found to be beneficial for adults with adult-onset glaucoma and can provide a source of knowledge.[28] Alternatively, online support groups may trigger negative emotions when reading content pertaining to negative outcomes or information overload regarding treatments or procedures.[25] Caregivers in this study acknowledged this as a pitfall of online support groups. Engagement in peer support otherwise has yet to be evaluated as a variable that may offset feelings of social isolation in caregivers of children with childhood glaucoma.[4–9] Nonetheless, well-moderated peer support groups could be recommended by health care providers to supplement professional health care.[25,28]

Coping and Normalization

Normalization was the second most common coping strategy adopted. It played a role in the provision of medical and social support and the caregiver's emotional well-being and sense of control. Normalization is a dynamic process whereby caregivers aim to achieve a positive balance between providing support to the child, accommodating their needs, and maintaining typical family dynamics and role functioning.[29] It is based on how a caregiver conceptualizes the impact of a disease on daily functioning and deliberately attempts to shift the focus away from the condition and toward aspects of their lives that are less disrupted.[30] In parents of children with chronic inherited disease, normalization has been shown to increase parenting competence and confidence in their ability to provide medical and social support to the child.[31] Furthermore, normalization resulted in fleeting and manageable feelings of parental guilt or inadequacy related to the child's condition.[31] Similarly, in parents of children with visual impairment or blindness, anxiety was reduced when self-esteem was high because of psychological adjustment to the condition.[32] This phenomenon was observed in this study, whereby caregivers discussed that anxieties related to the condition were manageable. Normalization additionally promotes child resilience and autonomy, particularly through adjustment to medical procedures and adherence to treatment.[33] Caregiver observation of child resilience in this study cyclically caused caregivers to cope better. This process has been observed in parents of children with congenital heart defects whereby caregivers positively reframed their child's illness and celebrated their child's ability to cope, instead of viewing their child as vulnerable.[34] In this study, this process negated the emotional impact of the disease as evidenced by feelings of hope, gratitude, and pride in the child's abilities. Caregivers evidently should be supported to achieve normalization because it has benefits for the child and the caregiver. Mindfulness-based stress reduction programs,[35] problem-solving therapy,[36] and support groups[37] have been successful for parents of children with chronic disease to achieve normalization, and further studies could evaluate their efficacy in caregivers of children with childhood glaucoma.

Emotional Well-being

The path to achieving normalization is complicated by persistent threats to emotional well-being and the use of maladaptive coping strategies. Caregivers recalled experiencing shock, guilt, regret, and frustration and feeling traumatized, particularly at the time of diagnosis and during the child's younger years. Such feelings, collectively referred to as existential unease, are experienced as caregivers make sense of or conceptualize their child's diagnosis, learn how to cope, and come to understand their child's needs.[38] This emotional experience is mirrored in caregivers of children with congenital cataract[39] and retinoblastoma,[27] with the diagnostic period often described as a feeling of losing control and riding an "emotional rollercoaster" among a series of stressful events including surgery and medical management.[27] These feelings can cause caregivers to detach from the experience and consequently have difficulty bonding with their child,[20,40] as observed in this study. This additionally led some caregivers to experience postpartum depression. This has been observed similarly in caregivers of children with retinoblastoma[20] and retinopathy of prematurity.[40] Caregivers of children with PCG have reported a high rate of depressive symptoms,[4,5,7,8] with a recent study suggesting that this may be caused by mourning the loss of the idealization of their child's birth and parenthood.[9] Low caregiver QoL in childhood glaucoma has been otherwise associated with unemployment, having additional children with glaucoma, and caring for a child who is legally blind, which may make the caregiver vulnerable to depressive symptoms.[6] Evidently, psychological evaluation and support for caregivers of children with glaucoma may be indicated, particularly during the diagnostic period.

Changes in a child's health can disrupt the normalization process and reignite feelings of parental uncertainty, self-doubt, and guilt.[31,33] Because of the disease's unpredictability,[3] caregivers in this study often expressed concerns for their child's ocular health, social well-being, and future abilities, regardless of the child's age. These concerns are shared among caregivers of children with congenital cataracts,[41] vision impairment,[42] and retinoblastoma,[20,27] evidencing a collective caregiver experience in childhood eye disease. In this study, self-doubt, anxiety, and stress were particularly amplified when the child resisted the instillation of eye drops. This is similar to a caregiver's anguish in the setting of retinoblastoma and congenital cataract when the child resisted the insertion and removal of their prosthetic eye[20] or contact lens,[43] respectively. Further, it is possible that these parental feelings of concern, self-doubt, and anxiety throughout the child's upbringing are influencing caregivers' perception of their child's QoL. In childhood glaucoma research, caregivers have consistently underestimated or overestimated their child's QoL compared with the

child's perception of their own QoL.[44,45] This phenomenon was previously hypothesized to be caused by a child's inability to articulate their experience to the parent,[45] but exploration of the caregiver's QoL and its relationship with their perception of their child's QoL may provide insight into understanding this parent−child disparity.

Child Transitioning to Adulthood

Disease incurability and a caregiver's devotion to gaining control over the disease can cause caregivers to become overprotective and consequently inhibit their child's ability to develop autonomy.[33] Caregivers in this study often reported feeling overprotective of their child and at times were distrusting of others' care. Most importantly, caregivers seemed distrusting of their own child's autonomy of their medical condition, including when the child had become an adult. Meanwhile, the caregiver's sense of control over the disease was rarely influenced by financial stressors (e.g., surgical costs). This is likely because children with glaucoma are typically treated in a public hospital because of disease instability and complexity (e.g., requiring multiple consultations, surgeries, and anesthetics).[3] Public health care incurs no cost to Australian residents. Conversely, an adult with childhood glaucoma may opt to be treated in a public hospital or to receive private health care, which can be costly.[18] As a result, some caregivers were concerned for their child's ability to afford ophthalmic care, including medications and private health care, when they reached adulthood and became financially independent. This consequently seems to be a critical transition period from dependence on parents to child autonomy as younger adults with childhood glaucoma may exhibit poor compliance with medication and appointment attendance and may require financial assistance.[18]

Difficulties for caregivers in relinquishing control of their child's medical condition have been detailed further among caregivers of adolescents with chronic illness.[46] One of the main difficulties was the child's medication management and parental hesitation in encouraging autonomy so as not to upset the child.[46] This process of letting go may be complicated further by a caregiver's experience of chronic sorrow. Chronic sorrow is a periodic mourning or feelings of guilt or grief related to loss.[47] In childhood glaucoma, this sorrow could be reactivated when an adult child receives a poor prognosis regarding vision loss, requires another surgery, or is unable to achieve a certain career objective or other milestone, as seen in caregivers of adults with intellectual disability.[48] Chronic sorrow, in addition to distrust and overprotection, may explain why caregivers still attend appointments with their adult children. Health care professionals should be aware of these possibilities and should encourage shared parent−child management of the condition when the child and parent first are receptive to the idea.

Decision-making in Family Planning

The normalization of childhood glaucoma was seen to impact decision-making in family planning among caregivers. In this study, more caregivers were determined to have additional children when they achieved parenting confidence over time compared with those who did not, and this varied within caregiver dyads. Caregivers of children with inherited systemic genetic conditions have previously expressed self-doubt and self-blame and consequently regretted having a child or did not conceive additional children.[31] Although guilt and self-blame were observed in this study, no caregivers expressed regret for having a child, whereas 17% decided not to have additional children. Although comparative studies of inherited ocular conditions are scarce, 70% of caregivers of children with an inherited retinal disease in China[49] and 36% of unaffected parents of children with retinoblastoma in The Netherlands[50] decided not to have more children. Similarly, 43% of adults who had retinoblastoma[50] and 6% of adults with childhood glaucoma decided not to have children.[18] From the caregiver and affected adult perspectives, this low impact of having additional children in the context of childhood glaucoma is possibly the result of the disease's non−life-threatening nature, its treatability, and it generally being nonprogressive, although disease severity and outcomes can be variable.[3] This is in contrast to retinoblastoma (life-threatening, increased lifetime risk of second primary cancers)[51] and inherited retinal diseases such as retinitis pigmentosa, which results in nontreatable progressive vision loss.[52] Caregivers in this study instead were in favor of having their child's eyes checked immediately or shortly after birth, and 1 caregiver opted for preimplantation genetic diagnosis. Attitudes toward this type of reproductive option and barriers to its access (e.g., cost, availability) were not discussed in this study, but its use otherwise is supported in 52% of individuals with inherited retinal diseases.[53] Nonetheless, normalization and the often nonthreatening nature of childhood glaucoma seem to be important factors in caregivers' family planning decisions.

Genetic counseling was sought by 57% of caregivers to understand their risk of passing on any genetic variants that would cause glaucoma in their child. This may be biased by the fact that caregivers were recruited from a genetic registry (ANZRAG) and the number of mother-father dyads who sought counseling and participated in shared decision-making. Nonetheless, this rate is similar to that of studies of caregivers of individuals with inherited retinal disease and the individual themselves,[49,53] retinoblastoma survivors,[54] and adults with childhood glaucoma,[18] which report a combined rate of 33% to 60%. Although the results did not inherently impact a caregiver's decision to have more children, except where genetic diagnosis was unknown, the information was valued in planning further children and understanding the risk for future generations. For inherited retinal diseases, the main reasons for accessing genetic testing were to plan for future children who may demonstrate the condition and to prepare for novel genetic therapeutic interventions.[49] Genetic results were rarely associated with guilt and self-blame in this cohort, but this is a commonly reported theme in caregivers of children with retinoblastoma.[55] Further exploration of the perceived benefit or barriers to genetic testing in childhood

glaucoma is warranted. The results of this study otherwise support that caregivers are in favor of seeking genetic counseling, and these services should be readily available and accessible when undergoing decision-making for family planning.

Study Limitations

Study limitations include that caregivers were recruited from a national disease registry that requires consent to genetic testing for research. Consequently, caregivers may have been more willing to participate in this type of research and therefore may represent a subgroup of caregivers who may have a better experience with childhood glaucoma, who may be coping better than caregivers who did not participate, or both. Furthermore, caregivers were asked to recall the diagnostic period and as such their recounts may lack accuracy. Nonetheless, the depth of responses and developed themes have been triangulated with several ocular and nonocular childhood diseases. In addition, thematic saturation was reached. Moreover, the cohort studied includes caregivers with infant, adolescent, and adult children and a varied range of time elapsed since diagnosis, such that the lived experience is herein captured across a comprehensive disease timeline. Furthermore, caregivers were predominantly of European ancestry and resided in Australia, such that the findings may only be extrapolated to populations with similar sociodemographic features and health care settings. Public health care in Australia is provided at no cost, and this may explain why most caregivers did not experience a financial burden. The inclusion of mother-father dyads may have influenced research findings further, although differences were frequently observed between caregivers of the same dyad. Further research will be required to ascertain if these findings can be applied to other cohorts of European and non-European ancestry and to elucidate the differences between experiences of caregivers within the same dyad. Finally, we included caregivers of children with any type of childhood glaucoma, but were unable to recruit caregivers of children with acquired glaucoma (e.g., uveitic, trauma), glaucoma associated with a nonacquired systemic disease, or glaucoma following cataract surgery. These specific subtypes of childhood glaucoma may result in a different caregiver experience, particularly given that these subtypes are preceded by an underlying medical condition or ocular disease, or both, that may impose further impacts on a caregiver's lived experience. Nonetheless, our findings broadened our insights into the lived experience of caregivers of individuals with childhood glaucoma.

In conclusion, our findings provide a detailed description of the lived experience of caregivers of individuals with childhood glaucoma. Childhood glaucoma poses a substantial threat to caregivers' social and emotional well-being, sense of control, and decision-making in family planning. The impact of this threat is minimized by the use of coping strategies. Caregivers of individuals with childhood glaucoma may require support to achieve normalization, assistance in accessing peer support, and guidance in participating in shared parent-child management. Concurrently, psychotherapeutic interventions and genetic counseling could be offered in a timely manner where appropriate. Further research should evaluate the acceptability and effectiveness of such services, which ultimately aim to promote optimal disease outcomes and QoL for the child and the caregiver(s).

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Footnotes and Disclosures

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[1] Department of Ophthalmology, Flinders University, Flinders Medical Centre, Bedford Park, Australia.

[2] Department of Ophthalmology, Women's and Children's Hospital, North Adelaide, Australia.

[3] Department of Ophthalmology, Royal Children's Hospital, Parkville, Australia.

[4] Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia.

[5] Ophthalmology, University of Melbourne, Department of Surgery, Parkville, Australia.

[6] Caring Futures Institute, College of Nursing and Health Sciences, Flinders University, Bedford Park, Australia.

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Author Contributions:

Conception and design: Knight, Ridge, Staffieri, Craig, Prem Senthil, Souzeau

Analysis and interpretation: Knight, Ridge, Staffieri, Craig, Prem Senthil, Souzeau

Data collection: Knight, Ridge

Obtained funding: Knight, Craig, Prem Senthil, Souzeau

Overall responsibility: Knight, Ridge, Staffieri, Craig, Prem Senthil, Souzeau

Abbreviations and Acronyms:
ANZRAG = Australian and New Zealand Registry of Advanced Glaucoma; **IOP** = intraocular pressure; **PCG** = primary congenital glaucoma; **QoL** = quality-of-life.

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Correspondence:
Lachlan S. W. Knight, BHSc, MOrth, Department of Ophthalmology, Flinders University, 1 Flinders Drive, Bedford Park, SA, Australia, 5042. E-mail: Lachlan.WheelhouseKnight@flinders.edu.au.

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Publication F5. The phenotypic spectrum of *ADAMTSL4*-associated ectopia lentis: additional cases, complications, and review of literature

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The phenotypic spectrum of *ADAMTSL4*-associated ectopia lentis: Additional cases, complications, and review of literature

Lachlan S.W. Knight,[1] Sean Mullany,[1] Deepa A. Taranath,[1] Jonathan B. Ruddle,[2,3,4] Christopher P. Barnett,[5] Suzanne C.E.H. Sallevelt,[5] Ella C. Berry,[1] Henry N. Marshall,[1] Georgina L. Hollitt,[1] Emmanuelle Souzeau,[1] Jamie E. Craig,[1] Owen M. Siggs[1,6]

[1]Department of Ophthalmology, Flinders University, Flinders Medical Centre, Bedford Park, Australia; [2]Department of Ophthalmology, Royal Children's Hospital, Parkville, Australia; [3]Ophthalmology, University of Melbourne, Department of Surgery, Parkville, Australia; [4]Centre for Eye Research Australia, Royal Victorian Eye and Ear Hospital, East Melbourne, Australia; [5]Paediatric and Reproductive Genetics Unit, Women's and Children's Hospital, North Adelaide, Australia; [6]Garvan Institute of Medical Research, Darlinghurst, Australia

Purpose: *ADAMTSL4*-associated ectopia lentis is a rare autosomal recessive condition that is primarily associated with crystalline lens displacement. However, the prevalence of other ocular and systemic manifestations of this condition is poorly understood. In this study, we summarize the ocular and systemic phenotypic spectrum of this condition.
Methods: A cross-sectional case study series of four individuals with biallelic pathogenic or likely pathogenic *ADAMTSL4* variants was performed alongside a literature review of individuals with *ADAMTSL4*-associated ectopia lentis on September 29, 2021. Ocular and systemic findings, complications, and genetic findings of all four individuals were collected and summarized.
Results: The phenotypic spectrum across 91 individuals sourced from literature and four individuals from this case study series was highly variable. The main ocular phenotypes included ectopia lentis (95/95, 100%), ectopia lentis et pupillae (18/95, 19%), iris transillumination (13/95, 14%), iridodonesis (12/95, 13%), persistent pupillary membrane (12/95, 13%), and early-onset cataract or lens opacities (12/95, 13%). Anterior segment features other than ectopia lentis appeared to be exclusively associated with biallelic loss of function variants ($p<0.001$). Pupillary block glaucoma had a prevalence of 1%. Post-lensectomy complications included retinal detachment (6/41, 15%), elevated intraocular pressure (4/41, 10%), and aphakic glaucoma (1/41, 2%). Most individuals were not reported to have had systemic features (69/95, 73%).
Conclusions: The clinical phenotype of *ADAMTSL4*-associated ectopia lentis was summarized and expanded. Clinicians should be aware of the varied ocular phenotype and the risks of retinal detachment, ocular hypertension, and glaucoma in the diagnosis and management of this condition.

Autosomal recessive ectopia lentis associated with variants in the *ADAMTSL4* gene (Gene ID: 54507; OMIM 610113) is a rare condition [1]. The phenotypic spectrum of *ADAMTSL4*-associated ectopia lentis was initially limited to isolated ectopia lentis or ectopia lentis et pupillae, a condition in which the direction of the corectopia is opposite that of the ectopia lentis [2]. More recent reports have expanded this spectrum to include congenital iris abnormalities, high myopia, raised intraocular pressure (IOP), and retinal detachment [3,4]. Systemic features are rarely documented, and major systemic involvement has not been suggested as a feature of the condition [1,3]. Differential diagnoses for ectopia lentis include conditions with systemic involvement such as Marfan syndrome (associated with variants of *FBN1*) and Weill-Marchesani syndrome (WMS; associated with variants of *ADAMTS10*, *ADAMTS17*, *FBN1*, and *LTBP2*) [5]. In this study, we describe a series of four previously unreported individuals from three pedigrees and summarize the phenotypic spectrum of *ADAMTSL4*-associated ectopia lentis.

Correspondence to: Lachlan SW Knight, Department of Ophthalmology, Flinders University, Flinders Medical Centre, 1 Flinders Drive, Bedford Park, South Australia, Australia, 5042; Phone: +61 8 8204 6986; email: Lachlan.WheelhouseKnight@flinders.edu.au

METHODS

Participants: The participants in the cross-sectional case series were part of the Australian and New Zealand Registry of Advanced Glaucoma [6]. This registry recruits individuals with anterior segment anomalies, including ectopia lentis, regardless of their glaucoma status [6]. Ophthalmic clinical details were obtained from the participants' referring ophthalmologists. Genetic results and systemic features were obtained from the participants' geneticists. Additional investigations, including electroretinography, Pentacam

Scheimpflug imaging (Oculus, Wetzlar, Germany; for the measurement of the central corneal thickness [CCT], corneal curvature, and anterior chamber depth [ACD]), axial length measurement (Zeiss IOLMaster 500, Carl Zeiss Meditec, Jena, Germany), optical coherence tomography (OCT; CIRRUS SD-OCT, Carl Zeiss Meditec, Dublin, CA; for the measurement of the peripapillary retinal nerve fiber layer thickness), and the Humphrey visual field (HVF; Humphrey Field Analyzer; Carl Zeiss Meditec, Dublin, CA) were performed at the discretion of their referring ophthalmologist. The IOP was measured using rebound tonometry (iCare tonometer, Icare Finland Oy, Vantaa, Finland) or Goldmann applanation tonometry (GAT; Haag-Streit USA, Mason, OH). A high axial length was defined as ≥27 mm [7], and ocular hypertension was defined as IOP>21 mmHg. Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee, and this study adhered to the Tenets of the revised Declaration of Helsinki. All the participants provided their written informed consent.

Genetic testing: The genetic results were validated in a laboratory accredited by the National Association of Testing Authorities (SA Pathology, Adelaide, Australia or the Victorian Clinical Genetics Services, Melbourne, Australia). All the variants were reported using the GRCh37 reference genome, and all the *ADAMTSL4* transcripts were annotated against the canonical DNA (NM_019032) and protein (NP_061905) transcripts. For the purposes of this study, loss of function (LoF) variants were defined as those that introduce a premature stop codon (nonsense), shift the transcriptional reading frame (frameshift), or alter the two essential splice-site nucleotides immediately upstream or downstream of a coding exon (splice donor or acceptor); and all missense variants were defined as non-LoF [8].

Literature review: PubMed, MEDLINE, Scopus, CINAHL, and PsycINFO were searched using the terms "ADAMTSL4," "ADAMTS-Like protein 4" or "autosomal recessive ectopia lentis," and "ectopia lentis" or "ectopia lentis et pupillae" or "lens subluxation." No date restrictions were used. The search was last conducted on September 29, 2021 (Appendix 1).

Statistical analysis: All the calculations were performed using SPSS version 27.0 for Windows (IBM/SPSS Inc., Chicago, IL). The chi-square test with continuity correction or Fisher's exact test was used for categorical variables as appropriate. A p value of <0.05 was considered statistically significant. Multiple testing adjustments were not used, as all the analyses were exploratory in nature.

RESULTS

Clinical features: Four affected individuals from three unrelated pedigrees were included in this case study series (Figure 1). Their clinical characteristics are summarized in Table 1.

Individual A-II-2: Individual A-II-2 experienced difficulty reading the notes on the classroom board from a distance at age 6 years. She had reported learning difficulties, mild eczema, and fructose and lactose intolerance. She had no significant family history of ocular disease or collagenopathies. In the clinical examination, her best-corrected visual acuity (BCVA) was 20/32 in the right eye (OD) and 20/50 in the left eye (OS) in an outdated mild myopic correction. The anterior segment examination revealed bilateral multiple iris transillumination defects (Figure 2A) and bilateral phacodonesis, a preceding sign of ectopia lentis. Extensive persistent pupillary membranes were found bilaterally adherent to the anterior lens surface (Figure 2B). The rebound tonometry IOP, corneal curvature, and CCT were within the normal range, and the ACDs were deep (Table 1). In the dilated

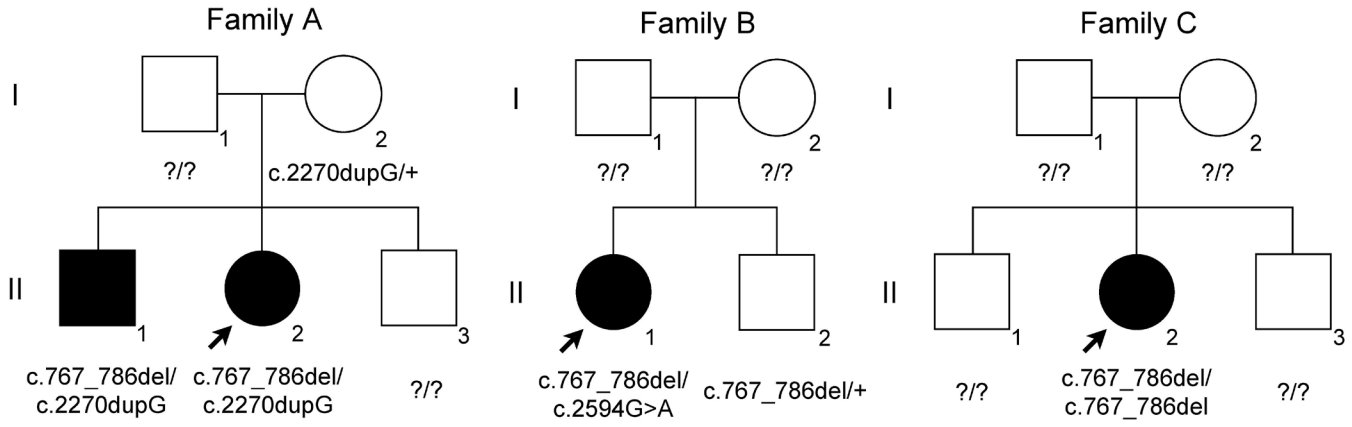

Figure 1. Pedigrees of families A, B, and C. The filled symbols denote the affected individuals. The arrow denotes the proband.

Table 1. Most recent clinical characteristics of the four individuals described in this case series.

Individual	A-II-1	A-II-2	B-II-1	C-II-2
Sex	M	F	F	F
Age at follow-up (years)	14	12	18	11
BCVA (OD, OS)	20/20, 20/20	20/20, 20/32	20/40, LP	CF, 20/63
SE (D) (OD, OS)	+0.50, −0.50	−2.0, −3.75,	+1.25 (aphakic), na	−22.5, −3.25
CCT (µm) (OD, OS)	594, 581	524, 527	632, 681	na
IOP (mmHg; OD, OS)	28, 21	16, 13	17, 9	6, 11
CC (D) (OD, OS)	42.6/44.1, 43.0/43.8	44.8/45.9, 44.1/46.2	na	na
AL (mm; OD, OS)	na	na	31.48, 31.61	27.30, 23.01
ACD (mm) (OD, OS)	4.55, 4.90[a]	4.26, 4.19[a]	na	na
Ectopia lentis	OD	OU[b]	OU	OD
PPM	OU	OU	-	-
Iris TID	OU	OU	-	-
Spherophakia	OU	OU	-	-
Iris processes	OS	-	-	-
RD	-	-	OS	-
Lensectomy	-	-	OU	-
Glaucoma	-	-	OD[c]	-
Systemic features	-	Learning difficulties, mild eczema, fructose and lactose intolerance	Motor delay, hypermobility, depression, anxiety, ASD	Learning difficulties, low vitamin D, ASD

M: male; F: female; BCVA: best-corrected visual acuity; OD: right eye; OS; left eye; LP: light perception; CF: count fingers; SE: spherical equivalent; D: diopters; na: not available; CCT: central corneal thickness; IOP: intraocular pressure; CC: corneal curvature; AL: axial length; ACD: anterior chamber depth; OU: both eyes; PPM: persistent pupillary membrane; TID: transillumination defect; RD: retinal detachment; ASD: autism spectrum disorder. [a]Ocular surgery was not performed on these individuals [b]Individual A-II-2 had phacodonesis; a preceding sign of ectopia lentis [c]Individual B-II-1 had aphakic glaucoma (i.e., glaucoma onset followed lensectomy)

examination, both lenses were clear but with posterior lentiglobus or spherophakia (Figure 2C). The mild myopic astigmatism was corrected with full-time spectacle wear, and the BCVA improved to 20/20 OD and 20/32 OS. The individual's latest clinical review was performed at 12 years of age, and the findings were unchanged.

Individual A-II-1: The brother of the proband was identified at age 13 years through family screening and was systemically well. The ophthalmic examination revealed bilateral mild myopic astigmatism with a BCVA of 20/20 in both eyes (OU). The anterior segment examination revealed iris thinning, mild iris stromal atrophy, and persistent pupillary membranes OU. Iris transillumination defects were later observed in high resolution slit-lamp imaging. The corneal curvature was normal, the ACDs were deep, and the CCTs were thick at 594 microns OD and 581 microns OS (Table 1). The gonioscopy revealed open angles and a deeply pigmented trabecular meshwork OD, and iris processes OS. Deposition of the pigment in other ocular structures (e.g., the corneal endothelium and the lens capsule) and backward bowing of the iris were not observed. The dilated examination clearly showed lens subluxation OD (Figure 2D) and posterior lentiglobus or spherophakia OU. Both fundi were unremarkable, and the optic nerve vertical cup-to-disc ratio (VCDR) was 0.3 OU. In the most recent review (at age 14 years), the individual was being monitored for ocular hypertension. Antiglaucoma medication has not yet been initiated.

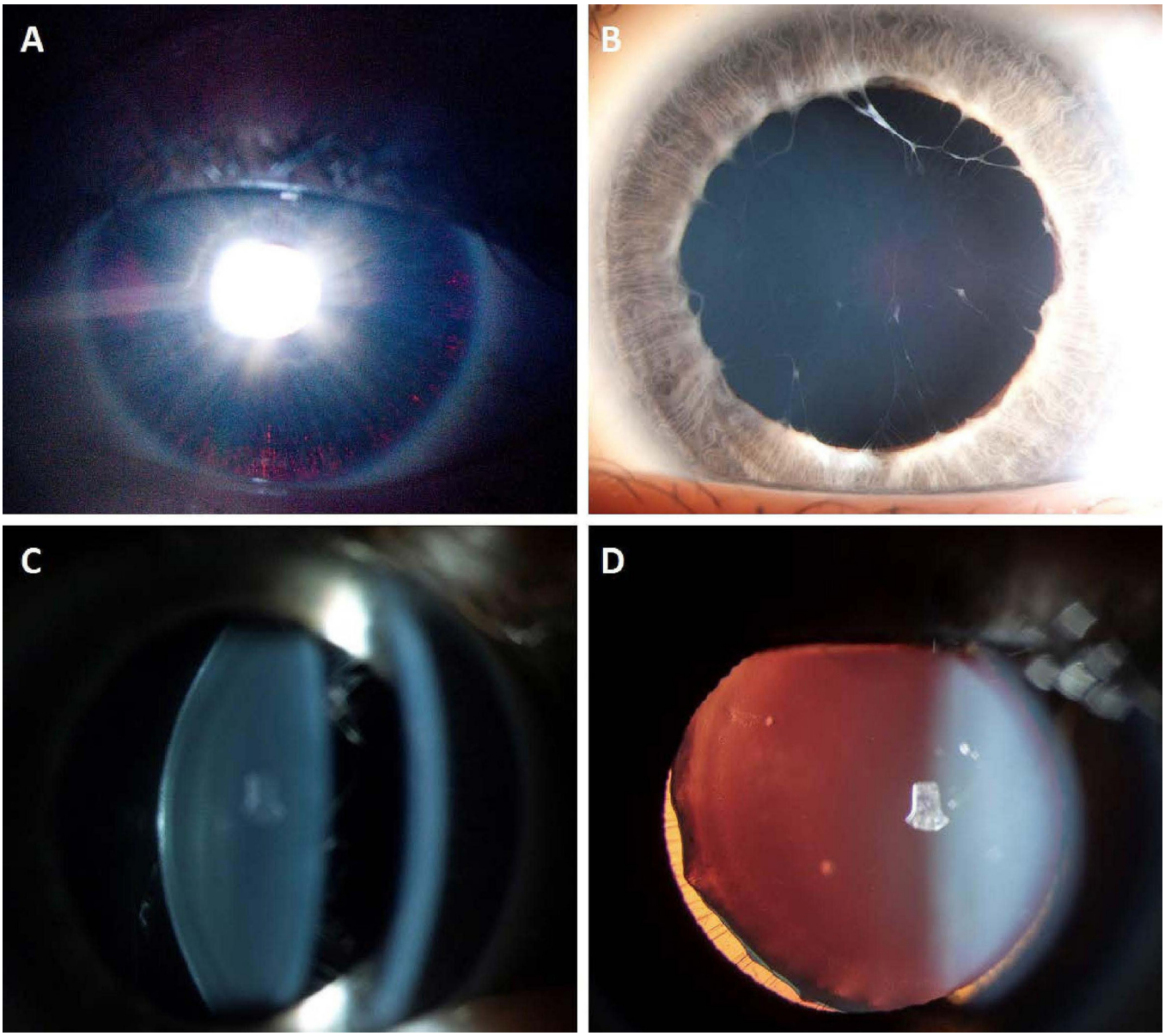

Figure 2. Clinical photography. The slit lamp imaging shows **A:** iris transillumination defects, **B:** a persistent pupillary membrane, and **C:** posterior lentiglobus or spherophakia on the slit illumination observed in Individual A-II-2. **D:** Ectopia lentis seen in Individual A-II-1 OD.

Individual B-II-1: Individual B-II-1 initially presented to an ophthalmologist at age 4 years with an uncorrected visual acuity of 20/400 OU. She was reported to have a motor delay, hypermobility, autism spectrum disorder, depression, and anxiety. There was no significant family history of ophthalmic or systemic disease. She had high myopia and lens subluxation OU, accompanied by small amplitude nystagmus and esotropia OS. Her electroretinography result was normal. With myopic correction, her BCVA improved to 20/60 OD and 20/120 OS. At age 10 years, her BCVA dropped to 20/400 OS due to worsening lens subluxation and consequent vitreous prolapse into the anterior chamber. She underwent lensectomy, pars plana vitrectomy (PPV), and prophylactic 360° retinopexy OU. As her axial lengths were high (Table 1), she was left aphakic OU. Her BCVA improved to 20/40 OD and 20/50 OS nine months post-operatively. Myopic degeneration was noted OU.

Five years post-surgery, she presented with a 2-week history of worsening vision OS. Her BCVA was 'light-perception' OS due to chronic total retinal detachment OS that was not deemed suitable for surgery. Her IOPs (in GAT) were 32 mmHg OD and 9 mmHg OS. Her CCTs were thick at

632 microns OD and 681 microns OS (Table 1), and the optic nerve head was tilted OD with peripapillary atrophy and a VCDR of 0.5. The average peripapillary retinal nerve fiber layer thickness in the OCT imaging was 79 µm. A corresponding nasal-step visual field defect was revealed in HVF 24–2 SITA Fast perimetry. Aphakic glaucoma was diagnosed, and topical glaucoma therapy was commenced. After 2 years of using latanoprost once daily, her treatment was escalated to latanoprost–timolol combination drops due to increasing IOP. In her last review (at age 18 years), her condition was stable and her IOP was controlled with latanoprost–timolol combination drops.

Individual C-II-2: Individual C-II-2 presented at the age of 11 years with chronic lens subluxation, high myopia, anisometropia, exotropia, and dense amblyopia OD. She had no family history of ophthalmic or systemic disease. She had been diagnosed with autism spectrum disorder, learning difficulties, and low vitamin D. Her BCVA was 'count fingers' OD and 20/63 OS. Her axial length OD was high but her IOP was normal (Table 1). The slit-lamp examination revealed superotemporal lens subluxation and a tilted optic disc OD. The contralateral lens and posterior segment were unremarkable.

Genetic results: Pathogenic variants in *ADAMTSL4* were identified in all four individuals (Table 2). All variants have been previously described. The frameshift variant c.767_786del has been reported as a European founder variant [9].

Literature review: A literature review identified 14 articles that described individuals with *ADAMTSL4*-associated lentis (Appendix 1) [3-5,9-19]. Across these studies, 91 individuals with homozygous or compound heterozygous variants in *ADAMTSL4* were described and included. With the inclusion of the current series, there were 95 reported individuals with *ADAMTSL4*-associated ectopia lentis. Of these, 45% (39/87) were female. The age at diagnosis was recorded in 59% (56/95) of the individuals as a median of 3 years (interquartile range: 1.1–6 years). The age at last follow-up was recorded in 61% (58/95) of the individuals as a median of 11 years (interquartile range: 6–31 years).

To investigate potential genotype-phenotype correlations, all the variants reported were considered either LoF or non-LoF (Appendix 2). Consequently, 75% (71/95) of the individuals had biallelic LoF variants, and 25% (24/95) had at least one non-LoF allele (Appendix 3). The most common genetic variant was the European founder frameshift variant c.767_786del, which was identified in 58% (55/95) of the individuals [3,5,9-11,14-17]. This variant was reported in 73% (52/71) of the individuals with biallelic LoF variants [3,5,9-11,14-17] and in 13% (3/24) of the individuals with at least one non-LoF allele (Appendix 3) [11]. Among the individuals with the European founder frameshift variant, 60% (33/55) were reported to have European ancestry [5,9,11,15,17] and 2% (1/55), New Zealand Māori ancestry [11]. The ancestry of the remaining 38% (21/55) of the individuals [3,10,14,16,17] was not reported. The ancestries reported for the other variants are listed in Appendix 4. One additional individual reported in the literature was excluded from this study, as the variant (c.1delA/p.?Met1) could not be verified as pathogenic due to the existence of alternative start codon transcripts [5].

The ocular anterior segment findings of the 95 individuals with *ADAMTSL4*-associated ectopia lentis are summarized in Table 3. All the individuals reported ectopia lentis, with 19% (18/95) reporting ectopia lentis et pupillae. Iris transillumination defects were reported in 14% (13/95), iridodonesis in 13% (12/95), and persistent pupillary membrane in 13% (12/95) of the individuals. Early-onset cataract or lens opacity was noted in 13% (12/95) of the individuals. Of these 12 individuals, 75% (9/12) had cataract or lens opacity diagnosed at <40 years of age [3-5,13], and the remaining 25% (3/12) had an unknown age at onset but had undergone cataract surgery at ≤50 years of age [16]. Anterior segment features, excluding cataract and ectopia lentis, were exclusively reported in individuals with biallelic LoF variants, as shown in Figure 3 ($p<0.001$, chi-square test with continuity correction).

Table 2. Genetic findings of the four individuals described in this case series.

Individual	A-II-1	A-II-2	B-II-1	C-II-2
cDNA	c.767_786del/ c.2270dupG	c.767_786del/ c.2270dupG	c.767_786del/ c.2594G>A	c.767_786del/ c.767_786del
Protein	p.Gln256Profs*38/ p.Gly758Trpfs*59	p.Gln256Profs*38/ p.Gly758Trpfs*59	p.Gln256Profs*38/ p.Arg865His	p.Gln256Profs*38/ p.Gln256Profs*38
Pathogenicity[a]	pathogenic/ likely pathogenic	pathogenic/ likely pathogenic	pathogenic/ likely pathogenic	pathogenic/ pathogenic

[a]Pathogenicity determined as per the 2015 American College of Medical Genetics and Genomics guidelines [41]

Few reports described the presence of deep anterior chambers in unoperated eyes (median: 3.75 mm [range: 3.00–4.10 mm]) [16], increased mean CCTs of 566.1 µm (95% CI: 515.3–616.8 µm) [15], and median CCTs of 589 µm (range: 528–630 µm) [16]. The average corneal curvature might have been normal (i.e., >42.0 D) [11] or flattened (i.e., <42.0 D) [15]. The overall average values of either of these characteristics could not be calculated, as cohort medians or means were often reported rather than individual results.

The numbers of individuals who had disease complications either from surgical intervention (i.e., lensectomy) or without surgical intervention are summarized in Table 4. Lensectomies were performed in 43% (41/95) of the individuals [3,5,9,11,12,14-16,18,19]. Of these, 32% (13/41) of the individuals were left aphakic [11,14,18], 7% (3/41) individuals were pseudophakic [3,11,12], and 61% (25/41) had an unknown phakic status [3,5,9,12,15,16,19]. Lensectomy was complicated post-operatively by elevated IOP in 10% (4/41) of the individuals [5,9,16] and by retinal detachment in 15% (6/41) of the individuals [3,5,15,16,19]. Of those with retinal detachment, 33% (2/6) underwent a combined procedure that included PPV [15]. Aphakic glaucoma developed in one individual (B-II-1) 5 years post-lensectomy (1/41, 2%). High IOP was otherwise recorded in 7% (4/54) of the individuals without lensectomy [5,10,16], and pupillary block glaucoma was diagnosed in one individual at 21 years of age [13], representing a total prevalence of 1% (1/95).

In 73% (69/95) of the individuals, systemic features were not reported (the specific systemic features are summarized in Appendix 5). There was no statistically significant difference between the prevalence of systemic features reported in individuals with biallelic LoF variants compared to individuals with at least one non-LoF variant (23/71, 32% versus 3/24, 13%, respectively, p = 0.10, chi-square test with continuity correction; Figure 3). Individual analysis of separate features (musculoskeletal and connective tissue, cardiovascular, facial dysmorphism, and development delay) did not show statistical significance between the two groups (Figure 3). Musculoskeletal and connective tissue features were otherwise the most reported features (15/95, 16%) [3,5,9,11,14,17]. Overall, there were no consistent phenotypes suggestive of an association with systemic disease. The presence of any feature was not dependent on whether an individual carried a European founder variant (Appendix 6).

DISCUSSION

This case study series reports four previously unreported individuals with *ADAMTSL4*-associated ectopia lentis and provides a detailed review of the ocular and systemic phenotype in 95 individuals reported to date [3-5,9-19]. *ADAMTSL4* is one of seven *ADAMTSL* genes that maintain the function of the extracellular matrix. ADAMTSL4 proteins are expressed in the anterior and posterior segment structures of the eye, including in the cornea (epithelium, stroma, and endothelium),

Table 3. Prevalence of ocular anterior segment features in 95 individuals with *ADAMTSL4*-associated ectopia lentis.

Ocular anterior segment features	Number of individuals in literature (n)	Individuals in this report (n)	Combined total (n)	Proportion of individuals (%)	References
Ectopia lentis	91	4[a]	95	100	[3–5,9–19]
Ectopia lentis et pupillae	18	0	18	19	[3-5,10,15-17]
Iris TID	11	2	13	14	[4,5,16]
Iridodonesis	12	0	12	13	[4,5,9,19]
PPM	10	2	12	13	[3-5,9,16]
Early onset cataract or lens opacity	12	0	12	13	[3-5,13,16]
Poor pupillary dilatation	11	0	11	12	[4,16]
Spherophakia	9	2	11	12	[3,4,9,16]
Corectopia	4	0	4	4	[16]
Iris coloboma	2	0	2	2	[5]
Lens coloboma	2	0	2	2	[16]
Posterior synechiae	1	0	1	1	[18]
Iris processes	0	1	1	1	-

TID: transillumination defect; PPM: persistent pupillary membrane; [a]Individual A-II-2 had phacodonesis; a sign which commonly precedes ectopia lentis.

Table 4. Prevalence of disease complications in 95 individuals with *ADAMTSL4*-associated ectopia lentis stratified by lensectomy status.

Complication	No lensectomy (n=54) (n, %)	Lensectomy (n=41) (n, %)	Overall prevalence (n=95) (n, %)	References
Retinal detachment	1 (2)	6 (15)[a]	7 (7)	[3–5,15,16,19][b]
High axial length[c]	3 (6)	3 (7)	6 (6)	[4,15][b]
Posterior staphyloma	1 (2)	1 (2)	2 (2)	[15]
Ocular hypertension	4 (7)	4 (10)	8 (8)	[5,9,10,16][b]
Glaucoma	2 (4)	1 (2)	3 (3)	[4,13][b]
Pupillary block glaucoma	1 (2)	0 (0)	1 (1)	[13]
Aphakic glaucoma	0 (0)	1 (2)	1 (1)	[b]
Unreported etiology	1 (2)	0 (0)	1 (1)	[4]

[a]33% (2/6) individuals had a concurrent pars plana vitrectomy (PPV)[b]Includes individuals presented in this case series [c]High axial length defined as ≥27.0 mm

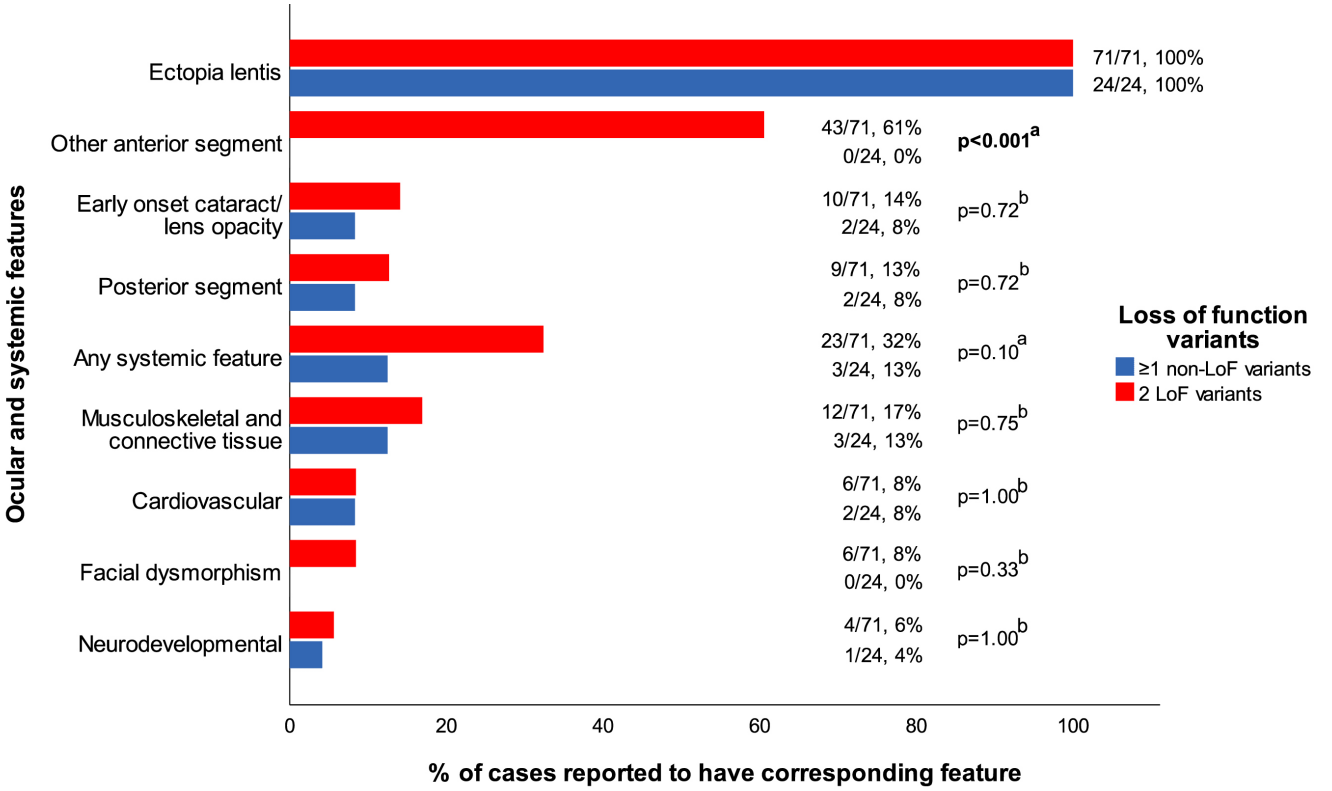

Figure 3. Prevalence of ocular and systemic features stratified by the predicted loss of the function allele count. Other anterior segment features included: ectopia lentis et pupillae, iris transillumination defect, iridodonesis, persistent pupillary membrane, poor pupillary dilatation, spherophakia, corectopia, iris coloboma, lens coloboma, posterior synechiae, and iris processes. The posterior segment features included retinal detachment, axial length ≥ 27.0 mm, and posterior staphyloma. The anterior segment features other than ectopia lentis appeared to have been exclusively associated with biallelic loss of function variants ($p < 0.001$). LoF: loss of function variant; non-LoF: non-loss of function variant. The bold values indicate statistical significance. [a]Chi-square test with continuity correction, [b]Fisher exact test.

iris stroma, trabecular meshwork, ciliary body stroma, ciliary processes, lens epithelium, choroid, sclera, and optic nerve [20,21]. Whether *ADAMTSL4* is expressed in the neuroretina remains unclear due to conflicting results of immunohistochemical and immunofluorescence studies [20,21]. It has been hypothesized that ADAMTSL4 is a fibrillin 1-binding protein that facilitates the assembly of microfibrils. Although ADAMTSL4 has not yet been isolated in the zonules, impairment of this function may result in impaired zonular formation and maintenance [20,21]. ADAMTSL4 has been isolated in the ciliary processes [21], which form the attachment site of the zonules [22]. Similarly, pathogenic *ADAMTSL4* variants have been demonstrated in a murine model to result in unstable anchorage of zonule fibers to the lens capsule [23]. This may explain the prominent phenotype of ectopia lentis.

The ocular phenotype of *ADAMTSL4*-associated ectopia lentis is highly variable. Although all the reported individuals manifested ectopia lentis, other anterior-segment anomalies have been reported with inconsistent frequency. It is unclear whether this inconsistency is a consequence of different variants, reporting bias, or age at the surgical intervention (such that early-onset cataract or lens opacity may be more prevalent). Through an investigation of genotype-phenotype correlations, our data suggested a possible association between biallelic LoF variants and additional anterior-segment features. Although the physiologic function of ADAMTSL4 is not yet fully understood, the absence of other anterior-segment features seen in individuals with at least one non-LoF variant (i.e., the missense variant) may be due to a compensatory interactive role between *FBN1* [20], *ADAMTS10* [24], and *ADAMTS17* [25] in microfibril biogenesis. Variants in these genes have also been implicated in ectopia lentis and, more particularly, in WMS (*FBN1, ADAMTS10, ADAMTS17,* and *LTBP2*) and in Marfan syndrome (*FBN1*) [26]. These findings, however, may be confounded by insufficient reporting or examination of previously described individuals and the low number of individuals with at least one non-LoF allele (25%). This observation may be further confounded by an overrepresentation of individuals with the European founder variant and their ancestry.

Iris transillumination, iridodonesis, and poor pupillary dilatation [27,28] are common features of Marfan syndrome, which further suggests a possible interaction between shared gene products (FBN1 and ADAMTSL4). In contrast, deep ACD [16] and increased CCT [15,16] are not features of Marfan syndrome, and thus, may represent important differentiating features between the two conditions [28]. However, these findings have been observed in only a few individuals, including two individuals each in this study, and should be interpreted with caution. The measurement of CCT and ACD in consecutive studies is consequently encouraged. Systemic features typically seen in Marfan syndrome (e.g., aortic root dilatation) may be differentiating features of the two conditions, but there is insufficient evidence of this [29]. Persistent pupillary membrane, which has been described in association with *ADAMTSL4*-associated ectopia lentis, is accepted to be a common congenital anomaly, observed in approximately 20% of the normal adult population [30]. Given its low reported prevalence in *ADAMTSL4*-associated ectopia lentis (13%), it is unclear whether this is a disease feature or a population or surgical artifact.

The low frequency of ocular hypertension (OHT; 7%) in individuals who did not undergo lensectomy, and low frequency of pupillary block glaucoma (1%) overall, represent additional differentiating features of other connective tissue disorders. Individuals with WMS report a glaucoma frequency of 80% [31]. Similarly, individuals with *LTBP2*-associated ectopia lentis and microspherophakia frequently report the onset of pupillary block glaucoma before approximately 10 years of age [32,33]. These differences may be due to the larger interactive role between *LTBP2* and *FBN1* in zonular stability and the consequent greater severity of lens displacement [34,35]. We hypothesize that the low rate of pupillary block glaucoma may be explained by the direction of the lens subluxation. Lens subluxation in *ADAMTSL4* is most often within the pupillary plane rather than anterior [9,11]. Similarly, in Marfan syndrome, glaucoma prevalence may be low, as lens subluxation is frequently reported to be in the pupillary plane [28]. Nonetheless, tonometry (IOP measurement) and fundoscopy are recommended in routine clinical examinations to exclude OHT or glaucoma.

Posterior-segment abnormalities seen in *ADAMTSL4*-associated ectopia lentis are relatively low, in keeping with unclear protein expression in the neuroretina [20,21]. This may be confounded, however, by the relatively young median age at the last follow-up (11 years). Most retinal detachments occurred post-lensectomy (with or without PPV) and were equated with a prevalence of retinal detachment post-lensectomy of 15%. This is comparable to a study of individuals with Marfan syndrome, which reported retinal detachment post-lensectomy in seven of 39 individuals (i.e., an 18% prevalence) [28]. Retinal detachment is a well-documented risk of surgery for ectopia lentis [36] but may occur when the axial lengths increase in response to the retinal blur caused by ectopia lentis [4]. Subsequently, the prevalence of retinal detachment in *ADAMTSL4*-associated ectopia lentis may be explained by various factors, including surgical techniques and the presence of axial myopia, rather than as a result of its

protein expression. ADAMTSL4 protein has further not been located within the vitreous humor [20,21].

Aphakic glaucoma is another well-known risk of lensectomy in children, and its risk increases with every year post-surgery [37]. This case study series reports a novel case of aphakic glaucoma in *ADAMTSL4*-associated ectopia lentis, equating to a prevalence of 2% at 5 years. This is comparable to Marfan syndrome, wherein aphakic glaucoma has been reported at least 1-year post-lensectomy in one of 43 individuals (i.e., 2% prevalence) [38]. A lensectomy for pediatric cataract after age 9 months carries a 1.8% risk of developing glaucoma 5 years post-surgery and increases to 4.1% at 10 years [37]. A lensectomy for congenital cataract between ages 0 and 2 years has an estimated risk of OHT of 9% [39], which is consistent with the rate of OHT following lensectomy that was observed in this study (10%). Subsequently, individuals who undergo lensectomy for *ADAMTSL4*-associated ectopia lentis appear unlikely to be at an additional risk of aphakic glaucoma, particularly as ADAMTSL4 proteins have not been isolated within the aqueous humor drainage structures [20,21]. Nonetheless, these individuals require long-term monitoring and management of their condition, as the risk of aphakic glaucoma may increase with age.

At present, our findings support the hypothesis that *ADAMTSL4*-associated ectopia lentis is an isolated ocular condition [1], as its systemic features do not appear to fit a compelling phenotype. This could be due to the small number of individuals reported, or potentially, the lack of investigation or reporting of systemic features, or the presence of genetic variants in other genes that were not investigated. Learning difficulties and autism spectrum disorder are novel features reported in two individuals each in this series. However, these findings are unlikely to be related to *ADAMTSL4*-ectopia lentis, as they are among the top five most diagnosed conditions in general pediatric consultations across Australia [40]. The relative risks of musculoskeletal, connective tissue, and cardiovascular disorders appeared much lower than those of other syndromes associated with ectopia lentis, such as Marfan syndrome [29]. However, surveillance of systemic features is strongly recommended, as it remains unclear whether they are a consistent finding in *ADAMTSL4*-associated ectopia lentis. Further research is required in this area.

In conclusion, *ADAMTSL4*-associated ectopia lentis is most often an isolated ocular condition. Clinicians should be aware of its unique features and the complications of performing lensectomy. The ocular phenotype overlaps with that of other disorders, including Marfan syndrome, WMS, and *LTBP2*-associated ocular disease. However, the relatively normal systemic findings appear unique to the *ADAMTSL4* spectrum, and may provide important differential diagnostic findings. Consistent and detailed reporting of *ADAMTSL4*-associated ectopia lentis is required to determine more accurate frequencies of its features and complications and to further elucidate the role of ADAMTSL4 proteins. These will guide the clinical and surgical management of the condition as well as genetic testing practices.

APPENDIX 1. FLOW DIAGRAM OF THE LITERATURE REVIEW OF *ADAMTSL4*-ASSOCIATED ECTOPIA LENTIS.

To access the data, click or select the words “Appendix 1.”

APPENDIX 2. THE CHARACTERISTICS AND FREQUENCY OF THE VARIANTS REPORTED IN 95 INDIVIDUALS WITH *ADAMTSL4*-ASSOCIATED ECTOPIA LENTIS.

To access the data, click or select the words “Appendix 2.”

APPENDIX 3. THE FREQUENCY OF COMBINATIONS OF VARIANTS IN 95 INDIVIDUALS WITH *ADAMTSL4*-ASSOCIATED ECTOPIA LENTIS.

To access the data, click or select the words “Appendix 3.”

APPENDIX 4. SELF-REPORTED ANCESTRY IN 95 INDIVIDUALS WITH *ADAMTSL4*-ASSOCIATED ECTOPIA LENTIS.

To access the data, click or select the words “Appendix 4.”

APPENDIX 5. SYSTEMIC FEATURES REPORTED AMONGST 95 INDIVIDUALS WITH *ADAMTSL4*-ASSOCIATED ECTOPIA LENTIS.

To access the data, click or select the words “Appendix 5.”

APPENDIX 6. A COMPARISON OF THE PRESENCE OF OCULAR OR SYSTEMIC FEATURES BETWEEN INDIVIDUALS WITH AT LEAST ONE EUROPEAN FOUNDER VARIANT (C.767_786DEL) AND INDIVIDUALS WHO DID NOT HAVE THE EUROPEAN FOUNDER VARIANT.

To access the data, click or select the words “Appendix 6.”

ACKNOWLEDGMENTS

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