Glaucoma

Attitudes Toward Glaucoma Genetic Risk Assessment in Unaffected Individuals

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Purpose: Integrating polygenic risk scores (PRS) into healthcare has the potential to stratify an individual’s risk of glaucoma across a broad population. Glaucoma is the most common cause of irreversible blindness worldwide, therefore effective screening for glaucoma endorsed by the population is highly important. This study assessed the attitude of unaffected individuals toward PRS testing for glaucoma, and sought to identify factors associated with interest in testing.

Methods: We surveyed 418 unaffected individuals including 193 with a first-degree relative with glaucoma, 117 who had a recent eye examination, and 108 general members of the community.

Results: Overall, 71.3% of the individuals indicated an interest in taking a polygenic risk test for glaucoma. Interest was more likely in those who believed glaucoma to be a severe medical condition (odds ratio [OR] = 14.58, 95% confidence interval [CI] = 1.15–185.50, P = 0.039), those concerned about developing glaucoma (OR = 4.37, 95% CI = 2.32–8.25, P < 0.001), those with an intention to take appropriate measures regarding eye health (OR = 2.39, 95% CI = 1.16–4.95, P = 0.019), and those preferring to know if considered to be at-risk or not (OR = 4.52, 95% CI = 2.32–8.83, P < 0.001).

Conclusions: Our results show strong interest in genetic risk assessment for glaucoma among unaffected individuals in Australia.

Translational Relevance: These findings represent a valuable assessment of interest in glaucoma polygenic risk testing among potential target populations, which will be integral to the implementation and uptake of novel PRS-based tests into clinical practice.

Introduction

Glaucoma is a degenerative condition affecting the optic nerve and can result in irreversible vision loss and blindness if left untreated. Primary open-angle glaucoma (POAG) is the most common subtype, affecting over 60 million people worldwide,1 including 3% of the population over the age of 50 years in Australia.2 It is associated with, but not dependent on, raised intraocular pressure (IOP).3 IOP is the major modifiable risk factor for POAG and is therefore the target of treatment approaches, including topical eye drops, laser treatment, or incisional surgical intervention. Other risk factors relate to individual genetic risk, including ethnicity and family history, with a 9.2-fold increased risk for first-degree relatives of individuals with glaucoma compared with controls.4 Due to the asymptomatic nature of early-stage disease, limitations of screening techniques, and challenges in diagnosis, over half of all individuals with glaucoma in developed countries and over 90% in developing countries...
are estimated to be undiagnosed. Early diagnosis is paramount given that vision cannot be restored once it is lost, and existing treatments are highly effective in preventing or slowing disease progression. Because glaucoma is the most common cause of irreversible vision loss in the world, improving screening methods and identifying at-risk individuals has the potential to significantly reduce the social and economic burden of disease.

Glaucoma is one of the most heritable common complex diseases. Both monogenic and polygenic factors contribute to glaucoma. Disease-causing variants in genes, such as MYOC and OPTN, or copy number variants in TBK1 account for less than 5% of POAG with Mendelian inheritance patterns. With recent advances in the scale of genomewide association studies (GWAS), there is increasing interest in the application of polygenic risk scores (PRS) across a variety of common diseases, including glaucoma. A PRS collates the combined risk of multiple common genetic risk variants into a single score, typically by weighting the relative effect size of each variant. Such scores may be combined with conventional risk factors to estimate overall disease risk.

Recent studies have demonstrated the utility of glaucoma PRS in risk stratification. A recent glaucoma PRS was associated with higher glaucoma risk (top 10% PRS compared to remaining 90% glaucoma OR = 4.2) as well as more rapid disease progression, and higher treatment intensity. Individuals in the top PRS decile were at 15-fold increased risk of developing advanced glaucoma compared to the bottom decile. Furthermore, high polygenic risk confers a comparable risk to monogenic variants, whereas being over 15 times more prevalent in the general population, and can also influence the penetrance and age at diagnosis. By stratifying individuals across the risk spectrum for developing glaucoma and likelihood of progression, high-risk individuals would benefit from treatment before vision loss is diagnosed, whereas low-risk individuals could benefit from community-based monitoring.

With more data supporting the clinical validity of PRS in risk stratification, such tests may soon become part of routine clinical care. Before this can occur, it is necessary to understand how such testing may be received by the general population and what key social and behavioral elements may impact implementation. The attitudes of affected individuals have been previously assessed, including for glaucoma, however, they have not been assessed in unaffected individuals who will be the ones benefiting from the test. In this study, we addressed this gap and reported the attitudes of individuals without diagnosed glaucoma toward glaucoma PRS testing, and the demographic and psychosocial factors that influence this.

### Methods

#### Study Sample

This was a cross-sectional, questionnaire-based study approved by the Southern Adelaide Clinical Human Research Ethics Committee (SAC HREC) that adhered to the Revised Declaration of Helsinki. The study sample included three different groups of individuals who may be target populations for polygenic risk testing for glaucoma and who were recruited between March 2020 and March 2021. We aimed to recruit 100 participants in each group. Using a one-sided test with multiple test correction (alpha = 0.01), 100 participants in each group will yield 100% power to detect a difference in levels of interest of 20% or more. The first group included unaffected first-degree relatives of individuals with a known glaucoma diagnosis, with participants drawn from the Australian and New Zealand Registry of Advanced Glaucoma (ANZRAG) and the Targeting At Risk Relatives of Glaucoma patients for Early diagnosis and Treatment (TARRGET) study. ANZRAG is one of the largest databases of clinical and genetic data for glaucoma in the world (regardless of glaucoma severity), whereas TARRGET is designed to provide educational material to first-degree relatives of individuals with glaucoma, with their personalized risk of developing the disease according to their family member’s clinical phenotype. The second group included people attending an optometrist for an eye assessment for conditions other than glaucoma, or those with no ocular health history who had undergone an eye assessment within the last 6 months. This group is referred to as the “optometry group.” These participants were recruited from private (Specsavers) and public (Flinders University) optometry clinics. The third group comprised members of the general community without an ocular health history, who had not undergone a recent eye examination. Recruitment occurred at Flinders Medical Centre (including the Flinders Volunteer service) and Noarlunga Hospital in Adelaide, Australia, and included Flinders volunteer members, patients, and their relatives in outpatient hospital clinics. Individuals for the first two groups were also recruited from these clinics if they had a first-degree relative with glaucoma or had a recent eye examination. Recruitment from
public hospital settings as well as public and private clinics was opportunistic. Participants were included if they had the capacity to complete the questionnaire without assistance (except if needing an interpreter). Participants were excluded if they were <18 years old or did not have the cognitive capacity to complete the questionnaire.

**Data Collection**

The questionnaire was adapted from previously published surveys23 and used Likert-like scale items. The questionnaire was first tested with 10 individuals from Flinders Medical Centre. Sociodemographic, health, cognitive, emotional, and influencing factors were used to assess association with interest in genetic testing.

**Sociodemographic**

Age, gender, ethnicity, highest level of education, and urban/rural residency were collected. Ethnicity was self-reported and classified into 10 ethnic groupings, then into categories of “European” and “non-European” ancestry. Those recorded as “unknown” were excluded from analyses involving ethnicity. Residency was based on the Australian Bureau of Statistics census data using the participants’ postcodes. Urban residency was classified as postcodes with populations greater than 50,000 persons. Rural residency included regional, rural, and remote areas of populations less than 50,000 persons.

**Health Factors**

Family history, including the number of family members affected by any form of glaucoma and their degree of relation, was self-reported by participants. Eye health factors assessed included a history of myopia, most recent eye check, and the frequency of eye checks.

**Cognitive Factors**

Cognitive factors were assessed through single-item measures with Likert-like scale response options. We assessed participants’ understanding of the heritability of glaucoma, perception of the severity of glaucoma, and perceived likelihood of developing glaucoma.

**Emotional Factors**

To assess the influence of emotion on interest in genetic testing for glaucoma, we asked participants to indicate their level of worry related to the possibility of developing glaucoma in the future using Likert-like scale response options.

**Factors Affecting Decision to be Tested and Concerns**

We assessed several factors which could affect the participants’ decision to be tested related to their own risk, their family’s risk, and advice from others. We assessed factors which would concern participants about testing, including personal anxiety, cost, future requirements, and issues relating to confidentiality and implications of results. Participants could also include additional factors or comments.

**Outcome Variable**

Interest in genetic testing for glaucoma was evaluated by assessing the likelihood to undergo genetic testing to predict personal glaucoma risk with Likert-like scale response options.

**Additional Factors**

Participants were asked about aspects of the test that would be considered important to know prior to undergoing genetic testing, the cost participants would be willing to pay, and their preferred method of receiving their results. Participants were asked to indicate how their behavior toward their eye health might change based on theoretical results of higher and lower risk of developing glaucoma, and the frequency of eye checks which they would be willing to undergo.

**Statistical Analysis**

Data were analyzed using Statistics Package for the Social Sciences (version 27.0, SPSS Inc., Chicago, IL). Descriptive statistics were used to characterize the study sample. Responses from the three groups were combined for the statistical analysis. Responses were combined into bivariate outcomes; for example, “highly unlikely” and “unlikely” were merged into an “uninterested” group, and “likely” and “highly likely” were merged as an “interested” group. Unsure or missing responses for all questions were excluded. Associations of different variables among the three groups were analyzed using 1-way ANOVA and chi-square test for association for continuous and categorical variables, respectively. The association between level of interest and covariates (sociodemographic, emotional, and cognitive variables) was performed using a univariate logistic regression model. Variables that had significance levels of $P < 0.1$ in the univariate analysis were initially included in the multivariate regression model. Multivariate logistic regression models were performed to identify factors independently associated with interest in testing ($P < 0.05$) using a backward stepwise approach.
Results

Demographic and Personal Characteristics

In total, 418 participants completed the questionnaire; 193 had at least one affected first-degree relative, 117 had had a recent eye review, and 108 were from the community. In total, 243 unaffected family members in ANZRAG and TARRGET were invited to participate in the study, and 143 completed the questionnaire, yielding a response rate of 58.8%. The other 50 participants with a first-degree relative were recruited from outpatient clinics and hospital settings. The demographic and personal characteristics of each group and the whole study sample are shown in Table 1. In summary, 66.5% were women, 95.0% were of European ancestry, 75.4% were from an urban area, and 63.8% had an education level above secondary school. The mean age of the total cohort was 62.1 years ± 13.3 years, with 28 individuals being under the age of 40 years. There was a significant difference in residency, family history, timing of last eye check, and frequency of eye checks among groups (Table 1—significant results in bold). Participants with affected first-degree relatives, those who had a recent eye check, and members of the general community did not differ by age, gender, and level of education (see Table 1). The majority (74.9%) of participants had undergone an eye check within at least the last year and over half (55.0%) reported undergoing eye checks at least annually.

Understanding of Glaucoma and Perception of Severity and Risk

In the overall cohort, 57.7% believed glaucoma was at least somewhat hereditary, with 57.7% of those having an affected first-degree relative. A large proportion (39.5%) of the total cohort were unsure about the hereditary nature of glaucoma. The majority (91.9%) of respondents considered glaucoma to be a severe medical condition, with an approximately equivalent proportion with (47.9%) and without (52.1%) an affected first-degree relative. Perception of glaucoma as a severe condition was associated with being likely to increase the frequency of eye checks if found to be at high risk (odds ratio [OR] = 7.36, 95% confidence interval [CI] = 1.32–40.89, \( P = 0.023 \)). Almost a third (31.8%) of the participants believed they were likely or highly likely to develop glaucoma in their lifetime, and 89.1% of these expressed worry about this belief. Those with at least one first-degree relative with glaucoma were more likely to believe they were at risk of developing glaucoma (OR = 5.06, 95% CI = 2.99–8.58, \( P < 0.001 \)), and were worried about this (OR = 3.75, 95% CI = 2.33–6.06, \( P < 0.001 \)). Being worried about the possibility of developing glaucoma was associated with a preference to know the glaucoma risk (OR = 2.19, 95% CI = 1.40–3.43, \( P < 0.001 \)).

Interest in Genetic Risk Prediction Testing for Glaucoma

Overall, the majority of individuals expressed an interest in genetic risk prediction testing for glaucoma, with 71.3% of respondents indicating they would be either likely or highly likely to take a test if it were available. The attitudes of each group are shown in Figure 1. Over half of those who were interested in testing (62.2%) also reported they would probably or definitely like to know more about glaucoma before being tested. Individuals with at least one affected first-degree relative were more likely to be interested in genetic testing for glaucoma than those without (OR = 2.90, 95% CI = 1.65–5.09, \( P < 0.001 \); Table 2). There was no significant difference between the level of interest between those aged below and above the age of 40 years (75.0% vs. 81.2%, respectively, \( P = 0.459 \)).

Factors Affecting Interest in Genetic Risk Prediction Testing for Glaucoma

We assessed the factors that may affect the participants’ decision to be tested (Fig. 2) and factors that may concern participants about genetic risk prediction testing (Fig. 3). After adjusting for all variables that were significant in univariate regression, interest in glaucoma genetic risk prediction testing was more common in those who believed glaucoma to be a severe medical condition (OR = 14.58, 95% CI = 1.15–185.50, \( P = 0.039 \)), were concerned about developing glaucoma (OR = 4.37, 95% CI = 2.32–8.25, \( P < 0.001 \)), had an intention to take appropriate measures regarding eye health (OR = 2.39, 95% CI = 1.16–4.95, \( P = 0.019 \)), or who preferred to know if they were at risk of glaucoma or not (OR = 4.52, 95% CI = 2.32–8.83, \( P < 0.001 \); see Table 2). The average number of factors which may affect the participants’ decision to be tested was 3.7.

The majority (75.8%) of individuals had at least one concern about genetic risk prediction testing for glaucoma, with cost being the most frequent (42.3%), followed by personal anxiety about the possibility of the test showing increased glaucoma risk (29.7%; see Fig. 3). The average number of concerns per
| Variable                          | First-Degree Relative n = 193 | Optometry n = 117 | Community n = 108 | TOTAL n = 418 | P Value |
|----------------------------------|--------------------------------|-------------------|-------------------|---------------|---------|
| **Age, y**                       |                                |                   |                   |               |         |
| Range                            | 33.0–89.8                      | 21.0–89.3         | 19.4–94.6         | 19.4–94.6     | P = 0.573* |
| Mean (standard deviation)        | 61.7 (11.2)                    | 63.2 (15.4)       | 61.5 (14.3)       | 62.1 (13.3)   |         |
| Median                           | 62.1                           | 65.4              | 66.3              | 63.3          |         |
| Missing                          | n = 1                          | n = 1             | n = 1             | n = 2         |         |
| **Gender, n (%)**                |                                |                   |                   |               |         |
| Female                           | 134 (69.4)                     | 73 (62.4)         | 71 (65.7)         | 278 (66.5)    | P = 0.437† |
| Male                             | 59 (30.6)                      | 44 (37.6)         | 37 (34.3)         | 140 (33.5)    |         |
| **Ethnicity, n (%)**             |                                |                   |                   |               |         |
| European ancestry                | 185 (95.9)                     | 114 (97.4)        | 98 (90.7)         | 397 (95.0)    | P = 0.028† |
| Non-European ancestry            | 6 (3.1)                        | 2 (1.7)           | 9 (8.3)           | 17 (4.1)      |         |
| - African                        | 2 (1.0)                        | 0                 | 1 (0.8)           | 2 (0.5)       |         |
| - Asian                          | 3 (1.6)                        | 1 (0.8)           | 3 (2.8)           | 7 (1.7)       |         |
| - Hispanic                       | 0                              | 1 (0.8)           | 1 (0.9)           | 2 (0.5)       |         |
| - Middle Eastern                 | 0                              | 0                 | 2 (1.9)           | 2 (0.5)       |         |
| - Mixed                          | 1 (0.5)                        | 0                 | 3 (2.8)           | 4 (1.0)       |         |
| Unknown                          | 2 (1.0)                        | 1 (0.9)           | 1 (0.9)           | 4 (1.0)       |         |
| **Residency, n (%)**             |                                |                   |                   |               |         |
| Urban                            | 137 (71.0)                     | 90 (76.9)         | 88 (81.5)         | 315 (75.4)    | P = 0.019† |
| Rural                            | 55 (28.5)                      | 21 (17.9)         | 16 (14.8)         | 92 (22.0)     |         |
| Unknown                          | 1 (0.5)                        | 6 (5.1)           | 4 (3.7)           | 11 (2.6)      |         |
| **Highest level of education, n (%)** |                                |                   |                   |               |         |
| Primary school                   | 2 (1.0)                        | 4 (3.2)           | 1 (1.0)           | 7 (1.7)       | P = 0.056† |
| Secondary school                 | 60 (31.1)                      | 43 (36.8)         | 39 (36.1)         | 142 (34.1)    |         |
| Vocational training              | 52 (26.9)                      | 39 (33.3)         | 40 (37.0)         | 131 (31.3)    |         |
| University                       | 77 (39.9)                      | 31 (26.5)         | 28 (5.9)          | 136 (32.5)    |         |
| Unknown                          | 2 (1.0)                        | 0                 | 0                 | 2 (0.5)       |         |
| **Family history, n (%)**        |                                |                   |                   |               |         |
| Positive                         | 193 (100.0)                    | 9 (7.7)           | 7 (7.4)           | 209 (50.0)    | P < 0.001† |
| Negative                         | 0                              | 107 (95.1)        | 87 (80.6)         | 209 (50.0)    |         |
| Unknown                          | 0                              | 1 (0.9)           | 14 (13.0)         | 0             |         |
| Positive (closest affected relative): |                                |                   |                   |               |         |
| - First-degree                   | 193 (100.0)                    | 0                 | 0                 | 193 (92.3)    |         |
| - Second-degree                  | 0                              | 7 (6.0)           | 5 (4.6)           | 12 (5.7)      |         |
| - Third-degree                   | 0                              | 1 (0.9)           | 1 (0.9)           | 2 (1.0)       |         |
| - Unknown                        | 0                              | 1 (0.9)           | 1 (0.9)           | 2 (1.0)       |         |
| **Last eye check, n (%)**        |                                |                   |                   |               |         |
| Within 6 mo                      | 63 (32.6)                      | 117 (100.0)       | 0                 | 180 (43.1)    | P < 0.001† |
| 6–12 mo                          | 82 (42.5)                      | 0                 | 51 (47.2)         | 133 (31.8)    |         |
| 1–2 y                            | 41 (21.2)                      | 0                 | 30 (27.8)         | 71 (17.0)     |         |
| More than 2 y                    | 4 (2.1)                        | 0                 | 25 (23.1)         | 29 (6.9)      |         |
| Never                            | 1 (0.5)                        | 0                 | 0                 | 1 (0.2)       |         |
| Missing                          | 2 (1.0)                        | 1 (0.9)           | 0                 | 3 (0.7)       |         |
| **Frequency of eye checks, n (%)** |                                |                   |                   |               |         |
| 3 mo                             | 2 (1.0)                        | 1 (0.9)           | 0                 | 3 (0.7)       | P = 0.003† |
| 6 mo                             | 9 (4.7)                        | 5 (4.3)           | 2 (1.9)           | 16 (3.8)      |         |
| Annually                         | 107 (55.4)                     | 61 (52.1)         | 43 (39.8)         | 211 (50.5)    |         |
| Every 2 y                        | 61 (31.6)                      | 32 (27.4)         | 34 (31.5)         | 127 (30.4)    |         |
| More than every 2 y              | 10 (5.2)                       | 13 (11.1)         | 22 (20.4)         | 45 (10.8)     |         |
| Never                            | 2 (1.0)                        | 3 (2.6)           | 6 (5.6)           | 11 (2.6)      |         |
| Missing                          | 2 (1.0)                        | 2 (1.7)           | 1 (0.9)           | 5 (1.2)       |         |

*Denotes P value calculated using one-way ANOVA.
†Denotes P value calculated using chi-square test for association. Differences in ethnicity were assessed between European and non-European ancestry.
individual was 1.4. We assessed the factors concerning individuals about undergoing genetic risk assessment for glaucoma and why participants may be less likely to take the test. These are summarized in Supplementary Figure S2. Of those who indicated being uninterested in testing, 24.6% had no concerns about the test. Having to attend follow-up appointments was the most concerning factor (37.7%), followed by the cost of the test (23.6%), potential anxiety caused by the results (20.8%), concern about how the results would affect employment (11.1%) and insurance (8.3%), confidentiality concerns (6.9%), and rather not knowing their risk (4.2%).

Behavior

In addition to assessing which factors may influence the decision to undergo genetic risk prediction testing, we assessed whether the potential result would influence attitudes toward the frequency of future eye checks. If testing were to indicate a low risk of developing glaucoma, 91.6% of individuals indicated they would not change the frequency of their eye checks. However, if testing were to indicate a high risk of developing glaucoma, 76.6% of individuals indicated they would have more frequent eye examinations. Those with an affected first-degree relative were not likely to change the current frequency of their eye examinations, regardless of whether a test indicated they were at either low risk ($P = 0.344$) or high risk ($P = 0.092$). Individuals indicated that their decision to undergo testing would be influenced more by medical advice compared to advice from family or friends (74.6% vs. 35.1%, $P < 0.001$).

Factors About Testing and Follow-Up

Finally, we surveyed aspects of genetic risk prediction testing that participants wanted to know prior to undergoing testing. These are summarized in Supplementary Figure S1. Over 77% of participants deemed cost, the test process, possible implications of results, and follow-up to be important factors to understand prior to undergoing testing. Email was the most preferred method to receive results (56.5%), followed by face to face (38.3%), and receiving a letter (35.2%), with a telephone call being the least preferred (21.5%). Several individuals commented that their preference would depend on the result, with face to face being preferred if results showed high glaucoma risk, and other methods, particularly email, being preferred if results showed low risk. A majority of participants (64.6%) indicated they would be willing to pay at least $50 for a glaucoma genetic test if required, with AUD $50 to $100 (approximately USD $40–$70 at the time of writing) being the most acceptable range (Fig. 4). Those who were willing to pay were more likely to be interested in testing (OR = 1.81, 95% CI = 1.07–3.07, $P = 0.028$) and to have completed tertiary education (OR = 1.95, 95% CI = 1.28–2.98, $P = 0.002$). Regarding the possible frequency of eye checks, 88.8% of all participants indicated they would be willing to have either biannual or annual eye examinations if required (Fig. 5).

Discussion

Genetic risk stratification for diseases with complex inheritance will become increasingly accessible with the development of PRS. Studies have previously assessed interest and attitudes toward such testing in affected and high-risk individuals for breast and colorectal cancer. To the best of our knowledge, the attitudes of those outside of an already identified at-risk population have not been investigated for any condition. Given one of the greatest potential advantages of PRS testing is population-scale risk stratification, it is crucial to understand the attitudes of the broader population toward this form of testing. Our findings provide useful insights into the attitude of unaffected individuals toward glaucoma genetic risk testing, and demonstrated a similar level of interest toward PRS testing for glaucoma among unaffected individuals (71.3%)
Table 2. Univariate and Multivariate Logistic Regression Assessing Predictors for Interest in Polygenic Risk Testing

| Variable (Demographic)                            | Univariate Logistic Regression | P Value | Multivariate Logistic Regression | P Value |
|--------------------------------------------------|-------------------------------|---------|---------------------------------|---------|
|                                                  | OR (95% CI)                   |         | OR (95% CI)                      |         |
| Age, y                                           | 0.99 (0.96–1.01)              | 0.165   | 1.67 (0.85–3.30)                 | 0.138   |
| Gender                                           |                               |         |                                 |         |
| - Male                                           | 1.00                          |         |                                 |         |
| - Female                                         | 1.71 (1.01–2.89)              | 0.045   | 1.67 (0.85–3.30)                 | 0.138   |
| Ethnicity                                        |                               |         |                                 |         |
| - Non-European                                   | 1.00                          |         |                                 |         |
| - European                                       | 1.86 (0.56–6.23)              | 0.312   |                                 |         |
| Residency                                        |                               |         |                                 |         |
| - Urban                                          | 1.00                          |         |                                 |         |
| - Rural                                          | 1.05 (0.56–1.98)              | 0.877   |                                 |         |
| Education                                        |                               |         |                                 |         |
| - School (primary or secondary)                   | 1.00                          |         | 1.28 (0.51–3.24)                 | 0.593   |
| - Tertiary (vocational training or university)    | 1.67 (0.99–2.84)              | 0.056   |                                 |         |
| Family history                                   |                               |         |                                 |         |
| - Negative                                       | 1.00                          | <0.001  |                                 | 0.111   |
| - First-degree relative                          | 2.89 (1.64–5.11)              | <0.001  | 2.05 (0.76–2.17)                 | 0.156   |
| - Other relative                                 | 0.98 (0.25–3.85)              | 0.980   | 0.24 (0.03–2.17)                 | 0.205   |
| Last eye check                                   |                               |         |                                 |         |
| - < 1 y (0)                                      | 1.00                          |         |                                 |         |
| - > 1 y (1)                                      | 1.15 (0.62–2.12)              | 0.665   |                                 |         |
| Frequency of eye checks                          |                               |         |                                 |         |
| - At least annually (0)                          | 1.00                          |         |                                 |         |
| - Every 2 y or more (1)                          | 1.02 (0.60–1.71)              | 0.954   |                                 |         |
| Perceived glaucoma heredity                      |                               |         |                                 |         |
| - Non hereditary                                 | 1.00                          | 0.018   | 1.9 (0.02–193.52)                | 0.779   |
| - Hereditary                                     | 9.14 (1.47–56.86)             |         |                                 |         |
| Perceived severity                               |                               |         |                                 |         |
| - Not severe                                     | 1.00                          | 0.009   | 14.58 (1.15–185.50)              | 0.039   |
| - Severe                                         | 18.69 (2.05–170.14)           |         |                                 |         |
| Perceived risk                                   |                               |         |                                 |         |
| - Not at risk                                    | 1.00                          | 0.005   | 1.88 (0.81–4.35)                 | 0.139   |
| - At risk                                        | 2.47 (1.32–4.63)              |         |                                 |         |
| Concern of developing glaucoma                   |                               |         |                                 |         |
| - Not worried                                    | 1.00                          |         | 4.37 (2.32–8.25)                 | <0.001  |
| - Worried                                       | 5.00 (2.87–8.72)              | <0.001  |                                 |         |
| Interest in obtaining more information about the test |                 |         |                                 |         |
| - Not interested                                 | 1.00                          |         | 1.71 (0.71–4.11)                 | 0.233   |
| - Interested                                    | 2.04 (1.16–3.59)              | 0.013   |                                 |         |
| Intention to take appropriate measures           |                               |         |                                 |         |
| - Would not change behavior                      | 1.00                          |         | 2.39 (1.16–4.95)                 | 0.019   |
| - Would change behavior                          | 5.00 (2.83–8.83)              | <0.001  |                                 |         |
| Advice to children                               |                               |         |                                 |         |
| - No                                            | 1.00                          |         | 1.15 (0.25–5.39)                 | 0.860   |
| - Yes                                           | 3.00 (1.77–5.08)              | <0.001  |                                 |         |
| Advice to family members                         |                               |         |                                 |         |
| - No                                            | 1.00                          |         | 0.49 (0.18–1.32)                 | 0.160   |
| - Yes                                           | 2.92 (1.71–4.99)              | <0.001  |                                 |         |
| Personal advice                                  |                               |         |                                 |         |
| - No                                            | 1.00                          |         |                                 |         |
| - Yes                                           | 1.34 (0.77–2.33)              | 0.304   |                                 |         |
| Medical advice                                   |                               |         |                                 |         |
| - No                                            | 1.00                          |         |                                 |         |
| - Yes                                           | 1.17 (0.64–2.13)              | 0.614   |                                 |         |
| Would rather know                                |                               |         |                                 |         |
| - No                                            | 1.00                          |         | 4.52 (2.32–8.83)                 | <0.001  |
| - Yes                                           | 6.78 (3.86–11.90)             | <0.001  |                                 |         |
Table 2. Continued

| Variable (Demographic) | Univariate Logistic Regression | Multivariate Logistic Regression |
|------------------------|-------------------------------|---------------------------------|
|                        | OR (95% CI)                   | P Value                         | OR (95% CI)                   | P Value |
| Would rather not know  |                               |                                 |                               |         |
| - No                   | 1.00                          |                                 |                               |         |
| - Yes                  | 0.378 (0.09–1.62)             | 0.190                           |                               |         |
| Anxiety                |                               |                                 |                               |         |
| - No                   | 1.00                          |                                 |                               |         |
| - Yes                  | 1.55 (0.83–2.89)              | 0.170                           |                               |         |
| Cost                   |                               |                                 |                               |         |
| - No                   | 1.00                          |                                 |                               |         |
| - Yes                  | 1.37 (0.80–2.34)              | 0.254                           |                               |         |
| Follow-up              |                               |                                 |                               |         |
| - Yes                  | 1.00                          |                                 |                               |         |
| - No                   | 1.29 (0.69–2.38)              | 0.424                           |                               |         |
| Insurance              |                               |                                 |                               |         |
| - No                   | 1.31 (0.99–9.79)              | 0.052                           |                               |         |
| - Yes                  | **3.44 (1.43–8.27)**          | **0.006**                       |                               |         |
| Employment             |                               |                                 |                               |         |
| - No                   | 1.00                          |                                 |                               |         |
| - Yes                  | 1.26 (0.56–2.82)              | 0.573                           |                               |         |
| Confidentiality        |                               |                                 |                               |         |
| - No                   | 1.00                          |                                 |                               |         |
| - Yes                  | 1.89 (0.71–4.98)              | 0.201                           |                               |         |
| Concerns               |                               |                                 |                               |         |
| - No concerns          | 1.00                          |                                 |                               |         |
| - At least 1 concern   | 1.23 (0.69–2.20)              | 0.485                           |                               |         |

Bold text in the multivariate logistic regression indicates variables which were retained in the final model. Where a variable was excluded, the listed values given related to the point at which the variable was removed from the model. Results reflect questionnaire answers provided by participants, although the authors acknowledge that some responses are not logical.

Figure 2. Factors affecting participants’ decision to be tested. Responses to the question “Which of the following factors would affect your decision to be tested? (Choose as many as appropriate).”

Compared with individuals with diagnosed glaucoma (69.4%).

Although glaucoma is the most common cause of irreversible vision loss, current screening methods are insufficient and not cost-effective at the population level. Evidence of the benefit of PRS testing was demonstrated by a previous study showing that individuals in the top decile of a glaucoma PRS distribution reach the same absolute risk of developing the disease 10 years earlier than those in the bottom decile. Glaucoma PRS testing could improve current screening strategies given the disease’s high and complex heritability, lack of environmental risk factors, asymptomatic nature of early disease, and effectiveness of early treatment options to slow
Figure 4. Cost participants would be willing to pay for a glaucoma genetic risk test. Responses to the question “If a cost were involved, how much would you be willing to pay for the test?”

Figure 5. Frequency of eye checks participants would be willing to undergo. Responses to the question “How frequently would you be willing to have an eye check?”

disease progression. Risk stratification may help to guide monitoring and treatment of high-risk individuals, as well as potentially avoiding unnecessarily regular follow-up or over-treatment of low-risk individuals. PRS may assist in deciding on monitoring frequency or context, such as by an ophthalmologist or optometrist, particularly given the difficulty in diagnosing glaucoma in the early stage of disease and the large number of individuals who are diagnosed as glaucoma suspects.

Interest in the test was not significantly associated with having a family history in the multivariate analysis, even though individuals with a family history were more likely to be interested in polygenic risk testing than those without. Previous studies have reported increased interest in PRS testing among first-degree relatives of individuals with breast cancer or colorectal cancer. These discrepancies may be due to an assumed predisposition to glaucoma and frequent monitoring already in place in this cohort.

The majority of those with an affected first-degree relative (74.1%) were drawn from existing glaucoma research databases. As part of their participation in these registries, individuals will have received information about the purpose of the research being to investigate the genetic nature of glaucoma as well as targeted glaucoma educational material, and may be more aware of the risk associated with having a family history. This is supported by our results which showed that those with an affected first-degree relative were more likely to believe they were at risk of developing glaucoma. Previous studies have shown that risk perception is often influenced by lived experience and that PRS may not alter perceived risk in these cases. Interestingly, in this study, individuals with an affected first-degree relative were not more likely to change the current frequency of eye examinations, regardless of whether a test indicated they were at either low or high risk. However, this cohort was also the one reporting the highest frequency of eye examination and may therefore feel that additional testing is not necessary.

These issues may represent a potential barrier to the uptake of PRS testing for glaucoma in this high-risk group and will need to be further investigated for successful implementation of the test and combination with existing screening methods. This is highly relevant in the context of a prediction model which showed that approximately one quarter of people will have a PRS counteracting their risk due to their family history. These individuals may be unaware of any underlying risk and will not be identified early through current screening guidelines given earlier age at screening is only recommended for those with a family history.

Individuals who believed glaucoma to be a severe condition were more likely to be interested in PRS testing for glaucoma, and were more likely to increase the frequency of their eye examinations if shown to be at high risk. Furthermore, being worried about the possibility of developing glaucoma in the future appears to be a strong motivating factor to undergo testing. However, despite 76.7% of participants indicating they would have more frequent eye checks if results showed increased glaucoma risk, this was not associated with interest in PRS testing for glaucoma. This is in keeping with other studies which have shown that knowledge of risk does not correspond to a change in risk-reducing behaviours. Previous studies have shown that motivation for undergoing genetic testing commonly stems from a conviction to altruism and desire to understand more about personal health, rather than to make preventative lifestyle behavior changes or change screening behaviours. The option to choose to know of a genetic susceptibility...
to disease may seem to be valued more than the results and their possible implications. Future research should examine whether knowledge of risk from the actual uptake of the test leads to change in glaucoma screening behaviors.

We asked participants which components of the test they would like to know more about prior to undergoing the test. The cost of the test, process involved in taking the test, implications of the results, and likely follow-up were each equally important to respondents with over 75% indicating they would want to know. Respondents indicated email as the preferred method of receiving results, with face to face, letter, and telephone call being approximately equally preferred. The majority of those who expressed willingness to pay for the test indicated AUD $50 to $100 to be an appropriate cost for the test. Whereas early indications of the likely cost of PRS testing are above $100, public preference is relevant in order to consider future cost subsidization and possible impact on uptake of the test. Moreover, concerns about insurance were significantly associated with testing in the univariate regression analysis and close to significance in the multivariate analysis. This may be particularly important in an older population who are more likely to be at risk. Our results may reflect the study population, with many being recruited from public hospitals where the provision of health services, including investigations and treatments for glaucoma, are not associated with any out-of-pocket costs for patients in Australia. Furthermore, Medicare (Australia’s universal health insurance system) subsidizes the cost of most pathology tests, thus the Australian population are generally not accustomed to paying for such tests. However, genetic tests are currently not widely subsidized. It will be important to address concerns associated with costs in the future, especially given some respondents commented that they would expect that the test would be subsidized by Medicare and cost was one of the main reasons for not being interested in testing.

Given the potential for broad population screening, ordering PRS testing, interpreting results, and communication of their significance to patients will extend beyond the clinicians directly involved in glaucoma diagnosis and management. Clinical implementation of PRS will rely on sound clinician understanding of the test and its results. It will be important to emphasize that PRS results represent a probability of individual disease risk and are therefore not diagnostic, and results will need to be interpreted in conjunction with other established clinical risk factors, in particular age. Integrated risk models that incorporate established clinical and demographic risk factors will need to be developed. Genetic counsellors have the skill set to assist individuals in making informed decisions about their results and the implications for their family members. However, their role may be most necessary for those who receive high-risk results, as the current workforce will not be able to carry the entire burden of a population-based screening test. Further research will need to evaluate the views and the needs of clinicians and healthcare professionals who may be involved in ordering PRS testing, interpreting results, and communicating their significance to the patients. Adequate resources will need to be available to upskill all clinicians and healthcare professionals who may be involved in glaucoma PRS testing.

Results should be interpreted in light of the study’s strengths and limitations. Of the total participants, 34.4% were drawn from existing glaucoma research registries (ANZRAG and TARRGET). These participants have previously demonstrated interest in glaucoma research, particularly regarding genetic studies and family history, and may therefore be more likely to report interest in glaucoma genetic testing. However, the interest toward PRS testing was still strong among individuals who were not part of existing research projects (65.6%). The majority of our study sample (95.0%) was of self-reported European ancestry, highlighting the need for further validation across other ancestral backgrounds prior to implementation. It will also be pertinent to ensure the utility of predominantly European-derived PRS instruments themselves in non-European ancestries. Furthermore, the attitudes of individuals of European ancestry may vary depending on cultural and geographic differences, such as among individuals in Australia, Northern America, and Europe. Although we have included unaffected individuals from three different groups, the study cohort may not be representative of a broader population of unaffected individuals. Additional studies would be needed to extrapolate these results to the general population. Finally, the methodology of this study relates to anticipated behaviors and future intentions and is not a representation of actual behavior. Further research should compare the uptake of PRS testing for glaucoma in those with reported interest.

PRS has the potential to stratify individual risk across a broad population for many common conditions with complex inheritance, including glaucoma. We found positive interest toward glaucoma PRS testing among three different groups of unaffected individuals and have identified possible target populations for initial clinical implementation. We have also identified factors affecting interest toward the test and potential barriers to address. Acceptability of genetic risk testing by the general population is crucial for clinical implementation to be successful.
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