Perspectives of people with inherited retinal diseases on ocular gene therapy in Australia: protocol for a national survey


ABSTRACT

Introduction: Voretigene neaprovoc-ryl (Luxturna) was approved by the Australian Therapeutic Goods Administration on 4 August 2020 for the treatment of biallelic mutations in the RPE65 gene, a rare cause of congenital and adult-onset retinal dystrophy (predominantly Leber congenital amaurosis). Previous studies have shown that individuals who might participate in gene therapy trials overestimate clinical effect and underestimate risks. However, little is known about the perspectives of patients who may be offered approved gene therapy treatment for ocular conditions (as distinct from participating in clinical trials of gene therapy). The main objective of this study is to develop a tool to assess knowledge, attitudes and perceptions of approved and future genetic therapies among potential recipients of ocular gene therapy. In addition, we aim to assess the quality of life, attitudes towards clinical trials and vision-related quality of life among this cohort.

Methods and analysis: A new ‘Attitudes to Gene Therapy for the Eye’ tool will be developed following consultation with people with inherited retinal disease (IRD) and content matter experts. Australians with IRD or their guardians will be asked to complete an internet-based survey comprising existing quality of life and visual function instruments and items for the newly proposed tool. We expect to recruit 500 survey participants from patient support groups, the practices of Australian ophthalmologists who are specialists in IRD and Australian ophthalmic research institutions. Launch is anticipated early 2021. Responses will be analysed using item response theory methodology.

Ethics and dissemination: This study has received ethics approval from the University of Melbourne (#2057534). The results of the study will be published in a peer-reviewed journal and will be presented at relevant conferences. Organisations involved in recruitment, and the Patient Engagement Advisory committee will assist the research team with dissemination of the study outcomes.

INTRODUCTION

Inherited retinal diseases (IRDs) are a group of heterogenous degenerative retinal conditions estimated to occur in up to 1 in 1000 individuals, with the major subtype retinitis pigmentosa (RP) occurring in about 1 in 4000 individuals. IRDs are now the most common cause of legal blindness of adults of working age in Australia and the UK. Thus, there is an urgent need for interventions that are aimed at preventing or reversing the ocular manifestations of these genetic conditions.

IRDs predominantly affect the retinal photoreceptors and retinal pigment epithelium (RPE), with variable phenotypes. Most cases are limited to the eye, but 20%–30% have systemic associations. In RP rod photoreceptors degenerate first, followed by cones and affected people experience nyctalopia (night blindness), constriction of the visual field and then reduction in visual acuity. Symptoms of RP may appear at birth (Leber congenital
amaurosis (LCA) phenotype), during childhood (severe early childhood onset retinal dystrophy phenotype) or in adulthood (typical RP phenotype). In cone and cone–rod dystrophy, the cones are affected first, and later the rods may be involved. Affected people may also experience haemeralopia (extreme glare) and loss of central and colour vision. The phenotype may vary between different family members with the same mutation, as exemplified in ABCA4 mutations where a single mutation in family members can result in macular dystrophy, and cone–rod dystrophy phenotypes. The RPE65 gene (OMIM 180069) is expressed in RPE cells (supporting cells for the photoreceptors), and encodes RPE65 protein, a critical component of the visual cycle and necessary for vitamin A metabolism in cells. Biallelic mutations in RPE65 lead to degeneration of photoreceptors in humans. Natural history studies show variability in age of onset, degree of severity and disease progression. Biallelic RPE65 mutations are responsible for about 10% of RP cases with LCA phenotype (LCA type 2), and about 2% of adults with typical RP phenotype (RP 20).

IRDs are genetically diverse, with over 300 responsible genes and loci identified to date in genomic and mitochondrial DNA. Gene therapy refers to a set of strategies that modify the expression of an individual’s genes or repair abnormal genes. Over 20 gene therapy products have been approved globally for systemic indications, with the two principal approaches including direct in vivo administration of a viral vehicle for gene delivery, and ex vivo therapies generating genetically engineered cells for reintroduction to the patient. Voretigene neparvovec-rxyl (Luxturna) has recently been approved in several jurisdictions for the treatment of biallelic mutations in RPE65 causing retinal dystrophy. Trials of ocular gene therapy for at least 10 IRD are underway. Gene therapy in IRD is thought to have a ‘therapeutic window’ in that it must be performed while there are residual viable photoreceptors, retinal interneurons and optic nerve.

There is limited data on the potential gains and risks of ocular gene therapy, with results limited to published clinical trials, and no long-term studies available. In general treatments of direct in vivo administration via subretinal injection of a viral vehicle for gene augmentation appear to have an acceptable safety profile. Immunogenicity is low, but inflammation can be triggered, and immunosuppression may be necessary in some cases. Future RNA-based therapies may have less risk of immune reaction.

Currently, there is limited understanding of the potential participant perspective for approved ocular gene therapy. Ganne et al demonstrated that members of the public have a low level of knowledge of genetic eye disease. Studies to date have focused on participants in early-stage clinical trials of experimental therapies, rather than those receiving approved treatments. The only study of patient-reported outcomes among potential RPE65 gene therapy trial recipients found a high information need and wish to take part in medical decisions. A 2012 study of potential participants in a choroideremia gene therapy Phase I trial revealed participant misconceptions of the value of trial participation in safety studies. Participants tended to overestimate treatment effect, underestimate possible risks and show misconceptions about the timing of treatment. A later study of potential choroideremia trial participants (NCT02077361) confirmed these findings and noted the value of early-stage published data in influencing treatment decisions and the need to improve postoperative experiences of trial participants. Similarly, Turriff et al found potential participants in a Phase I/IIa gene therapy trial for X-linked retinoschisis were motivated by therapeutic hope, although the authors considered the individuals to be realistic in their assessments.

There is an evidence-gap for understanding participant views on receiving an approved ocular gene therapy treatment, compared with participating in a clinical trial. Even in standard trials of treatments of retinal conditions, participants may have an incomplete understanding of their rights and the process. Ocular gene therapy for IRD has the potential to provide significant improvements in quality of life to patients and their families. However, like most medical and surgical procedures, there are associated risks. Hence, it is imperative that researchers and clinicians are aware of patient perspectives on the imminent arrival of approved ocular gene therapies, and use this information to facilitate patient informed consent processes, and to better inform regulatory bodies and reimbursement strategies. Thus, we aim to develop a tool to investigate the knowledge, attitudes and perceptions of the risks and benefits associated with approved and future gene augmentation therapies among people with IRDs. In addition, we aim to assess the quality of life, attitudes towards clinical trials, and vision-related quality of life among this cohort.

METHODS AND ANALYSES

Objectives

The primary objective of this study is to survey Australian patients with an IRD and/or their guardians (for minors) to identify their perceptions and understanding regarding receiving gene therapy treatment for IRD, and to evaluate the effect of key variables, such as quality of life, on perceptions and understanding.

The secondary objective is to develop a novel survey instrument to assess understanding of approved ocular gene therapy (Attitudes to Gene Therapy for the Eye (AGT-Eye) Tool), with instrument calibration and item reduction after survey responses have been received.

Study design

This will be a structured survey with non-random sampling, primarily administered via internet with a paper-based alternative available as needed. To fulfil the above objectives, we have developed a battery of survey tools, including previously validated questionnaires and...
a newly developed tool, AGT-Eye, survey. The following previously validated survey tools were selected for inclusion in the protocol:

- EQ-5D-5L Questionnaire (a generic health status score) to assess quality of life, and for use in future cost efficacy and utility calculations using published cost data.
- National Eye Institute Visual Functioning Questionnaire (VFQ-25), a patient-reported outcome instrument widely used in clinical trials to assess vision-related quality of life. Evidence of the burden of disease will be instrumental for regulatory and funding bodies.
- PACT 22 Clinical Trial Attitudes Scale to assess attitudes towards clinical trial participation, including therapeutic misconceptions. This will assist in differentiating perceptions of experimental and approved therapies.

Copyright owners of the three validated survey tools have each given permission for their use.

**Design of the AGT-Eye Tool**

A three-stage strategy was used in order to develop the items which will be included in the surveys. Communication within focus groups at each stage was implemented by internet video-conferencing and email; as in-person meetings and focus groups were discouraged during the COVID-19 pandemic.

**Stage 1: theme generation**

In the first stage an expert working committee consisting of 12 ophthalmologists with expertise in IRD (HM, FKC, JG, TLE, AWH, AK, MH, DM, JR, MS, DAT, JW) followed a Delphi process to identify domains based on their extensive knowledge of IRD gained through involvement with patients in clinical practice and their experience of running a natural history study of IRD. Statements thought to capture the latent traits within these domains were generated in a format to be evaluated against a 5-point Likert scale with responses ranging from *Strongly disagree* to *Strongly agree*. These statements were then reviewed independently by an independent multidisciplinary team expert in genetic disease and treatment (RVJ, AGC, GH, AM, BN, IS). Consensus was sought but, where needed, the senior leaders (HM, FKC and JG) arbitrated and made final decisions.

**Stage 2: involvement of target population**

A patient engagement advisory committee was recruited from patient support groups, and comprised seven people with IRD, and two parents of minors with IRD. They were provided with a link to the online REDCap database containing provisional AGT-Eye statements, along with the survey questions, and asked their opinion on the following topics:

- The appropriateness of AGT-Eye statements, including any concerns for respondents’ psychological health when answering sensitive questions.
- Additional concepts that they consider relevant which have not been covered in the provisional AGT-Eye statements.
- The accessibility and clarity of the full battery of questionnaires.
- The time required to complete the survey.
- The appropriateness of our proposed recruitment strategies (public and private ophthalmology clinics and patient support organisations).

**Stage 3: readability and clarity**

Throughout the process, draft questions were reviewed for readability, clarity and avoidance of duplication by a multidisciplinary committee consisting of researchers with backgrounds in optometry, orthoptics, biostatistics and data management (FO’H, MM, ACZ, NT, LA), all with expertise in retinal disease and online data collection, in addition to the primary investigator (HM). The final 6 domains and 22 questions are shown in table 1.

Responses will be rated on a 5-point Likert scale from 1 *Strongly disagree* to 5 *Strongly agree*. Items 4, 6, 7, 8, 12, 16 and 22 will be reversed for consistency of score interpretation. Item 2 will be scored as a mean between 1 and 5 of responses to the nine subitems. Total scores for the 22 AGT-Eye items will range between 22 and 110. The six domains will be scored as weighted means of the component individual items in a range between 1 and 5, and totalled to a range from 6 to 30. Interpretation of scores is shown in table 2.

**Future Stage 4: instrument calibration and item reduction**

Item response theory methods will be employed to refine the AGT-Eye tool using responses from the full survey. This step will involve item reduction and reassessment of domains if appropriate, as detailed below. After item reduction and reassessment of domains the final AGT-Eye score will be calculated for each respondent to be used in statistical analysis.

**Patient and public involvement**

As detailed above, input from people with IRD was sought during stage 2 of AGT-Eye development through a second working group, and their feedback was taken into consideration in the final drafting of the protocol. It is possible that the themes discussed during tool development may prompt these nine people to undertake additional independent research into gene therapy. Therefore, the nine people involved in the working group will be excluded from participating in the final survey, in order to remove a potential source of bias. There was no public involvement in protocol design.

**Survey eligibility**

Eligibility criteria includes males and females aged 18 years and above with an IRD, including syndromic forms, or the adult guardian of a person with an IRD who is aged below 18 years. IRDs are defined as retinal disorders caused by an inherited gene mutation resulting in loss of photoreceptor function accompanied by visual...
loss,\(^4\) and should have been previously diagnosed by an ophthalmologist. No prior confirmation of genotype is required. People who are carriers of IRD mutations but do not display an ocular phenotype will be excluded. People with other retinal conditions with known genetic risk factors (such as age-related macular degeneration) will be excluded in the absence of an ophthalmologist-diagnosed IRD as defined above.

Survey recruitment

Australian paediatric and adult patients with IRD will be recruited from the Australian Inherited Retinal Disease Registry and DNA Bank (a registry of 4164 IRD-affected participants from 2911 families),\(^4\) Australia’s specialist ophthalmic hospitals (Royal Victorian Eye and Ear Hospital and Sydney Eye Hospital), the ophthalmology and clinical genetics departments of the major metropolitan teaching hospitals and the private practices of the authors who are specialists in IRD. All Australian ophthalmologists will be notified through the Royal Australian and New Zealand College of Ophthalmologists and asked to forward an invitation to their eligible patients. Participants will also be recruited through four patient support groups which have given in-principal support: Retina Australia, Vision Australia, Cure Blindness Australia and UsherKids Australia.

Potential participants will be invited to participate by the partners listed above via email or letter, and a social media campaign is planned. Interested people will be

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### Table 1

<table>
<thead>
<tr>
<th>AGT-Eye domains and items</th>
<th>Awareness of treatment</th>
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<tbody>
<tr>
<td>1</td>
<td>I have good knowledge about gene therapy for inherited retinal diseases.</td>
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<tr>
<td>2</td>
<td>I have obtained information about gene therapy treatment from My ophthalmologist Other medical or health professional Registry for example, Australian Inherited Retinal Disease Register Research group Newspapers Internet Social media Patient support group Family/friends</td>
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<tr>
<td>3</td>
<td>I understand the difference between an experimental treatment provided by a clinical trial and a treatment that has already been approved by the Australian government.</td>
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<td>4</td>
<td>Gene therapy for the eye is suitable at any stage of a person’s life.</td>
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<td>5</td>
<td>Generally, gene therapy for inherited retinal disease is delivered to both eyes.</td>
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<tr>
<td>6</td>
<td>Gene therapy for the eye is injected into the blood stream through the arm.</td>
</tr>
<tr>
<td>7</td>
<td>Gene therapy and stem cell therapy are the same treatment.</td>
</tr>
<tr>
<td>8</td>
<td>Gene therapy for the eye can restore vision back to normal.</td>
</tr>
<tr>
<td>9</td>
<td>Gene therapy for the eye is a treatment that may slow down the disease.</td>
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<tr>
<td>10</td>
<td>Treatment complications to my eyes, such as permanent blindness, are possible with an approved gene therapy.</td>
</tr>
<tr>
<td>11</td>
<td>Gene therapy in my eye may have side effects elsewhere in my body.</td>
</tr>
<tr>
<td>12</td>
<td>Having gene therapy for their eye condition means a person will not pass on an eye condition to any children they may have in the future.</td>
</tr>
<tr>
<td>13</td>
<td>I may not be eligible for financial or other government benefits if my gene therapy for my eye condition is successful.</td>
</tr>
<tr>
<td>14</td>
<td>Gene therapy for inherited retinal diseases will require many years of follow-up with my eyecare practitioner.</td>
</tr>
<tr>
<td>15</td>
<td>Receiving gene therapy for my inherited retinal disease means I won’t be eligible for future genetic treatments.</td>
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#### Table 1 Continued

<table>
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<th>Awareness of treatment</th>
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</table>

Domains (bold) and items designed to measure the attitudes of people with inherited retinal disease towards gene therapy. These domains and items will be revised using item response theory after responses to the survey have been received. Italics items will be reversed in score calculations for consistency of interpretation. AGT-Eye, Attitudes to Gene Therapy for the Eye.

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Table 2 Interpretation of scores on the domains of the questionnaire

<table>
<thead>
<tr>
<th>Dimension</th>
<th>Low score</th>
<th>High score</th>
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</thead>
<tbody>
<tr>
<td>Awareness of treatment</td>
<td>Respondents have low awareness of gene therapy treatment</td>
<td>Respondents perceive they have high awareness of gene therapy treatment</td>
</tr>
<tr>
<td>Sources of information</td>
<td>Respondents require information</td>
<td>Respondents do not require information</td>
</tr>
<tr>
<td>Knowledge of clinical trials and approved treatments</td>
<td>Respondents do not understand the difference between a clinical trial and approved treatments</td>
<td>Respondents believe they understand the difference between a clinical trial and approved treatments</td>
</tr>
<tr>
<td>Timing and method of treatment</td>
<td>Respondents have low understanding of gene therapy process</td>
<td>Respondents have good understanding of gene therapy process</td>
</tr>
<tr>
<td>Understanding of outcomes</td>
<td>Respondents have low understanding of gene therapy outcomes</td>
<td>Respondents have good understanding of gene therapy outcomes</td>
</tr>
<tr>
<td>Understanding the cost and opportunity cost of treatment</td>
<td>Respondents expect to contribute personally to the cost of treatment</td>
<td>Respondents expect governments and insurers to pay for treatment and disability support services</td>
</tr>
<tr>
<td>Overall score</td>
<td>Respondents have high information need regarding gene therapy for IRD</td>
<td>Respondents have sufficient knowledge and awareness to sign informed consent if they are offered gene therapy for IRD</td>
</tr>
</tbody>
</table>

IRD, inherited retinal disease.

directed to the survey webpage to register. Participants will not be compensated for their participation.

Survey sample size

The number of participants recruited will be limited by the recruitment period (4 months) rather than the number required to statistically evaluate a hypothesis. Based on a population frequency of 1 in 2000 individuals, Australia’s population of patients with IRD is estimated at 16 000. However, many of these people will still be undiagnosed, or may have withdrawn themselves from medical care or patient support organisations (our recruitment streams). Given that responses to internet surveys are typically low, although unknown in our target population, we estimate gathering responses from 500 participants. It is anticipated that these participants will represent a range of Australians with IRD in terms of age, type and severity of condition, visual function, location of residence and socioeconomic status and comprise approximately 3% of Australians with IRD. Given this is the first instrument of its kind, the overall and subgroup scores that are required to estimate the statistical power achievable with this sample size are difficult to predict. The primary purpose of this study is to describe the distribution of responses within the population.

Consent

The consent process will be self-administered via mixed-mode approach suitable for visually impaired participants. Participants completing the online version of the study will read the online plain language statement and an online consent form. Participants will be asked to indicate consent by selecting a YES button. They will then proceed to the survey. Participants who self-complete the paper-based survey will read a plain language statement, sign one consent form and return it by mail, and keep one consent form for their records.

Survey procedure

We envisage that the majority of participants will enter data directly into the REDCap platform, which has accessibility functionality (font enlargement and text-to-speech facilities). Participants will have the option of providing identifiers (name and email address or telephone number) or remaining anonymous. A small number of older participants who do not have internet availability and/or skills (estimated to be less than 10%) will complete a paper-based survey and return it with the signed consent form to the researchers by pre-paid mail for entry into the database by study staff.

Email reminders to participate will be sent at 4 weeks by the organisations facilitating recruitment. Participants who have registered and partially completed the survey will receive automated REDCap email reminders at 2 and 4 weeks. Participants who have been mailed a paper-based survey will have a reminder letter mailed at 4 weeks.

Survey

The paper version of our survey (online supplemental files 1 and 2) shows explanatory wording and the context provided. However, most participants will complete the survey online via REDCap database software. Basic demographic data including age, gender and information relating to socioeconomic status will be collected. Participants will record if they are an affected individual or the parent of an affected child. Self-reported clinical data, such as information about symptoms, history of treatment and perceived barriers to receiving gene therapy will be recorded. Participants will complete the 22 AGT-Eye items, followed by the three previously validated questionnaires.
The time taken to complete the full survey is estimated up to 1 hour for individuals with low vision.

**Participant timeline**

Enrollment will begin early in 2021. The recruitment period will be 4 months. The project is time critical given that Voretigene neparvovec-ryzl was approved in Australia 4 August 2020, and we intend to assess knowledge prior to treatment of the first Australian patient.

**Follow-Up**

No specific follow-up is organised for the participants of the study. However, respondents will be asked if they wish to be contacted with further information on IRDs and upcoming gene therapy options in Australia and if they consent to their deidentified survey data being retained for possible future longitudinal studies (subject to future ethical approval). Respondents will also be provided with contact details for organisations that offer resources for mental health, in case the questions used in the study raise psychological concerns.

**Analyses**

The psychometric properties (such as targeting, reliability, consistency, discrimination, dimensionality and differential item functioning) of AGT-Eye will be investigated using item response theory methodology. Item reduction will be performed if appropriate. Participant scores for this instrument will be generated as both a single index value, and according to any identified subscales. Following analysis of the survey responses, items may be reworded or removed before a final version will be recommended for future use. Each of the existing instruments will be scored according to published methods.36–38

Descriptive and inferential statistics will be used to investigate the associations between demographics and self-reported clinical data and the scores in the various instruments and the correlation between instruments. Because the AGT-Eye will provide novel data, the distribution of responses will need to be assessed prior to deciding which statistical tests will provide valid inference. Subgroup comparison may be conducted via analysis of variance (>2 groups), Welch’s t test or linear regression (2 groups) in the presence of approximately normally distributed AGT-Eye scores. Otherwise, the Kruskal-Wallis test (>2 groups) or the Wilcoxon rank-sum test (2 groups) will be used. Correlation between instruments will be quantified using Spearman’s correlation coefficient. Subanalyses will be made of data submitted by persons with IRD compared with parents and guardians of people under the age of 18 years.

A narrative comparison between responses in this cohort and published findings from gene therapy clinical trial participants with eye conditions and other systemic and neurological conditions, such as Huntington’s disease, will be made. Huntington’s disease has been chosen as a comparator with IRD as both are untreatable neurodegenerative conditions. However, it should be noted that the former is a fatal condition, whereas IRDs lead to an isolated sensory loss, with no risk to life. As such, we will consider the different risk/benefit ratios that patients will need to consider, and the underlying psychological aspects to the two diagnoses. To our knowledge, there is no better comparator—we have not seen studies investigating recently approved non-gene therapies for IRD, for example.

**Data collection, management and privacy**

Deidentified data for this study will be collected using REDCap, a secure web application for building and managing online surveys and databases.36 REDCap includes a full audit trail and specified user-based privileges. Access to study data in REDCap will be restricted to the members of the study team by username and password and two-factor authentication. User access rights will enforce restricted viewing of Protected Health Information. Data will be accessible to administrators only as deidentified read-only data. Only deidentified data will be permitted to be exported for the purposes of analysis and reporting.

The REDCap platform consists of a MariaDB relational database and a web server. These servers are in a physically secure location on premise at the Centre for Eye Research Australia and managed by the CERA Information Technology team. Both REDCap and MariaDB are widely used, reliable and well-supported systems.

Participants will have the option to choose to provide their name and contact details, and allow their survey results to be identifiable (for future follow-up). This identifiable data will only be available to a limited number of researchers (as specified in our ethics approval).

Storage and destruction of data are compliant with the Australian Privacy Principles and the Australian National Statement on Ethical Conduct in Human Research. Intermittent random audit of data quality will be performed by the principal investigator, and governance procedures will be carried out by the Centre for Eye Research Australia.

**ETHICS AND DISSEMINATION**

**Ethical review**

Formal ethical approval has been granted by the Human Research Ethics Committee of the University of Melbourne (#2057534). All procedures are in accordance with the ethical standards of the Helsinki Declaration of 1975 as revised in 2014 and with Australian National Statement on Ethical Conduct in Human Research. All participants will provide consent after being informed of the nature of the study, regardless of survey administration method.

**Dissemination**

The study results will be disseminated through scientific publications in peer-reviewed journals and presentations in relevant national and international conferences.
In addition, deidentified reports of aggregate data and findings will be provided to participants, and presentations at meetings will be provided to Retina Australia, Vision Australia, Cure Blindness Australia and UsherKids Australia. The patient engagement advisory committee will also assist in result dissemination. The standardised checklists such as those from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines and relevant items from the Consolidated criteria for Reporting Qualitative studies (COREQ) checklist will be used to ensure that all relevant aspects of study design and data collection are addressed.

Data sharing, access and release
The deidentified dataset that supports the findings of this study will be made available on reasonable request, to appropriate researchers, subject to approval of an ethics amendment by the relevant Human Ethics Research committee. Requests for data access should be directed to the corresponding author, HGM. Data will be available beginning at 6 months after and ending 7 years following article publication.

DISCUSSION
IRD is now the most common cause of blindness in working age adults in Australia and the UK, and likely in other developed countries. Aside from the limited evidence that some nutritional supplements can delay progression, for example, Vitamin A supplementation for RP, there have been no treatments until 2017 when voretigene neparvovec-rzyl (Luxturna) became the first USA Food and Drug Administration-approved treatment for the very rare RPE65 mutations causing congenital and adult-onset IRD. Previous studies have demonstrated that potential gene therapy recipients lack information and have misconceptions regarding the value of trial participation and the risks of treatment. There is no information on the perspectives of persons with RPE65 gene mutations who may be eligible for this approved treatment (as distinct from participating in a clinical trial), or from other persons with IRD who may be eligible for future treatments. This study aims to fill this evidence-gap.

The project is significant in that it will:
1. Validate the first questionnaire regarding participant understanding of approved gene therapy (as distinct from clinical trials) for any indication.
2. By recruiting participants from multiple sources across Australia, including patient support groups, this project will allow a comprehensive analysis of participants’ understanding of and interest in both currently approved gene therapy and future clinical trials of new gene therapies for IRDs and a comparison between approved gene therapy and future ethics approval, and
3. Allow further collaboration with patient support groups and the patient community, necessary in planning research in rare conditions.

Potential limitations include lack of pilot data, uncertainty around sample size planning, selection bias, self-reporting of data with regard to IRD diagnosis and symptoms and misdiagnoses by ophthalmologists. Discrepancy in quality of life reporting between children and their parents/guardians is well recognised. To address this, we will perform subanalyses separately on people with an IRD, and the parents/guardians of children. Although genetic testing in IRD is now regarded as the standard of care in Australia, the majority of patients may not have a genetic diagnosis of their condition. Data capture via an internet-survey, as compared with focus groups for example, may limit the study by low response rate and reliance on information technology to survey a group of participants who may have low vision. We have sought to overcome low vision limitation by the option of hard copies of the survey to those who request it. The conventional utility measurements (EQ-5D-5L and VFQ-25) used may have limitations in this patient group.

In summary, the results of this study will delineate the perspectives of potential ocular gene therapy patients in Australia, critically timed to coincide with approval of the first gene therapy for IRD in Australia, provide a foundation methodology for future studies and generate data for future cost utility measures for this new and exciting treatment option.

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Collaborators
Contributors HM is the Principal Investigator and conceived the project, drafted the first draft of the AGT-Eye survey and was primary author of this manuscript. She is a guarantor. FKC and JG assisted in protocol development and editing of the manuscript. JR assisted in protocol development and editing of the manuscript, and also helped with the recruitment strategy (as Lead of the AIRDR). RJ assisted in coordinating multidisciplinary team input and in protocol development. NT, FO’H and ACZ assisted in protocol development, REDCap database construction and editing of the manuscript. MM assisted in protocol development, REDCap database construction and statistical expertise. LA assisted in protocol development, ethics applications, project management and editing of the manuscript. The members of the Australian Ocular Gene Therapy Group all assisted in AGT-Eye protocol development.

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Competing interests HM, FKC and RJ are members of the Australian Voretigene Expert Advisory Panel for Novartis.

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Survey of potential participant perspective on ocular gene therapy in Australia

SECTION 1 YOUR COPY
Survey of potential participant perspective on ocular gene therapy in Australia

Introduction

The Centre for Eye Research Australia invites people living with inherited retinal diseases and their parents/guardians to share their views and opinions about new potential gene therapy treatments.

For thousands of Australians living with inherited retinal diseases so far there has been little that could be done to slow down progressive vision loss.

But there are exciting new possibilities on the horizon. In fact, the first gene therapy treatment for inherited retinal diseases are expected to be available within Australia in the next few months.

To help researchers understand how we can support people in navigating information about potential gene therapy treatments, we’d like to invite anyone who is living with an inherited retinal disease to take this questionnaire.

We are also seeking input of parents and guardians of children with inherited retinal disease.

By answering these questions, you will share with us your lived experience and your views and opinions about upcoming gene therapy treatments.

This information will not only help us understand your unique perspective, but will also help us ensure people are well informed about emerging gene therapy treatments.

To take this survey, please first read the Plain English Statement for Participants that follows:

You can keep this first booklet for your own records.
Survey of potential participant perspective on ocular gene therapy in Australia

Plain English Statement for Participants

Plain Language Statement for Participants

Project title: Survey of potential participant perspective on ocular gene therapy in Australia

Researchers:
A/Prof Heather Mack (principal investigator), Dr Lauren Ayton (responsible investigator), A/Prof Fred Chen, A/Prof John Grigg, Dr Thomas Edwards, Ms Fleur O'Hare, Ms Ceecee Zhang, Prof Keith Martin

Contact: IRD@groups.unimelb.edu.au

Why is the study being conducted?
We are conducting research into the knowledge of Australian people with inherited retinal disease (IRD) regarding gene therapy for their condition. There has been a lot of progress in the field, and an Australian government approved treatment will be released shortly (Luxturna™ treatment for RPE65 retinal dystrophy), and we are interested to understand your knowledge of these treatments.

What do I need to do?
As part of this study, you are invited to complete a survey. The questions ask about how your condition has impacted your lifestyle, what you know about clinical trials in general, and what you know about government approved gene therapy to be released shortly. The survey will take about one hour to complete.

At the end of the survey you will be asked if you want to be contacted for more information on IRD genetic testing, if you want to receive a lay person summary of the report findings and if you are happy for your de-identified responses to be stored for possible future closely related studies.

Your participation is entirely voluntary.

How will be participants be selected?
Participants will be people with inherited retinal disease (IRD) who are Australian residents and English speaking, and/or their parents/guardians.

We will include people from a range of backgrounds and experiences, and therefore you will be asked to provide details of your condition and any previous experience with treatments.

Your personal details will remain confidential at all times.
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Plain English Statement for Participants

At the end of the survey, you have the option to list your contact details so that we can contact you with further information, or for future studies. This contact information will not be shared with others and will only be accessible to the named investigators in the study.

How will this research be used to benefit the community?
The survey results will assist us understanding how people with inherited retinal disease view gene treatment of their condition, and may inform future clinical trials of treatment for inherited retinal disease.

What are the risks?
There are no anticipated risks in taking part. The questions asked will not contain sensitive information. However, if you experience any distress from participation, please contact your GP for professional guidance and advice. Our research team are also available to discuss any concerns that you may have, or feelings of distress from the questions – you can contact us via email IRD@groups.unimelb.edu.au.

Additional resources are available if you do experience distress, including:

Lifeline 24 hour counselling 131114
Lifeline Victoria Suicide 24 Hour helpline 1300 651 251
Beyond Blue 1300 224 636
Veterans Counselling Service 1800 011 046
Royal Victorian Eye and Ear Hospital consumer liaison officer 03 9929 8666
Sydney Eye Hospital patient liaison officer 02 9382 7111
Retina Australia 1800 999 870
Vision Australia 1300 847 466
Survey of potential participant perspective on ocular gene therapy in Australia

Plain English Statement for Participants

Am I free to withdraw?

Participation in this study is completely voluntary and you may withdraw at any time with no risk of negative consequences.

If you choose to not participate this will not affect your relationship with your ophthalmologist or patient support group, or access to any future treatment that may become available for you. If you choose to withdraw your participation in this study, we will not be able to remove your data (as it is de-identified).

However, if you have provided us with your personal details for further contact, we can remove that from our database.

You may be in a doctor-patient relationship with one or more of the researchers listed in this study. It is important that you are aware that this potential conflict of interest will be managed in the following ways:

1. Your doctor will not know the answers you provide to the survey.
2. Your doctor will not know whether or not you participate in the study.
3. Your participation, or decision not to participate, will not affect your relationship with your doctor, or your medical care.

How do I express consent?

You will sign the consent form that appears at the end of this booklet, which you will keep for your records.

At the start of the survey questions you will sign another consent form that is returned to the researchers with your responses to the survey.
Survey of potential participant perspective on ocular gene therapy in Australia

Plain English Statement for Participants

How will my confidentiality be protected?
Your contribution to the survey will be collected and data will be stored in a secured location at the Centre for Eye Research Australia for a period of fifteen years. All participants’ personal details will be confidential. All data will be anonymized (including names, locations and conditions) and you will not be identifiable within any publications made as a result of this study.

If you provide us with your contact details at the end of the survey, we will contact you for the reasons you have selected (receiving a summary of the study findings and/or finding out more information about genetic testing in IRD).

Will participating cost me anything?
No, participating in the study is completely free of charge.

Will I be reimbursed for my time?
No, you are participating voluntarily to improve researchers’ understanding of your knowledge regarding treatments for your condition. You will not receive any payments, incentives or reimbursements for your participation.

Dissemination of results
We intend to publish the results of this study. If you indicate at the end of the survey, and leave your email address, you will receive a de-identified copy of the aggregated results at the completion of the study (anticipated in 2022).

These reports of de-identified aggregated results will also be provided to patient support groups which have assisted in participant recruitment. Study results will be disseminated to the scientific community through scientific publications in peer-reviewed journals and presentations in relevant national and international conferences.
Survey of potential participant perspective on ocular gene therapy in Australia

Plain English Statement for Participants

Ethics approval
This research project has been approved by the Human Research Ethics Committee of The University of Melbourne (project ID 2057534.2). If you have any concerns or complaints about the conduct of this research project, which you do not wish to discuss with the research team, you should contact the Manager, Human Research Ethics, Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Email: humanethics-complaints@unimelb.edu.au. All complaints will be treated confidentially. In any correspondence please provide the name of the research team or the name or ethics ID number of the research project.

Research funding
This project is being funded by the investigators, with no financial involvement from pharmaceutical companies. The project is supported in part by a 2021 research grant from Retina Australia to Drs Mack, Grigg, Chen and Ayton.

What happens now?
If you would like to participate, you can complete the attached hard copy paper form.
Or you can chose to complete the survey online at www.cera.org.au/ird-survey
If you would prefer a hard copy form, and have not already received one, please contact:

Ms CeeCee Zhang
Study Co-ordinator
Email: IRD@groups.unimelb.edu.au
Ph: (03) 9929 8621
Please also contact the researchers on the above details if you have low vision and want to dictate your answers to a researcher who will enter the data on your behalf.

What if I want more information about the study?
For additional information about the project, please email: IRD@groups.unimelb.edu.au.
Survey of potential participant perspective on ocular gene therapy in Australia

Consent form – Version 2 - 5 January 2021

I consent to participate in the research study “Survey of potential participant perspective on ocular gene therapy in Australia” and confirm that I have read the plain language statement and understood the following information.

In particular, I have noted that:

☐ Participation in this research is entirely voluntary;

☐ I am free to withdraw from this research at any time, without comment or penalty. If I withdraw I may request withdrawal of any unprocessed data previously supplied;

☐ Providing my contact details to the researchers is entirely voluntary;

☐ Any questions have been answered to my satisfaction and I understand that if I have any additional questions I can contact the research team;

☐ I have been informed that the confidentiality of the information I will provide will be safeguarded, my opinions will be treated as personal information, and my privacy respected;

☐ My de-identified data will be stored and may be utilized for future related research studies on the understanding that consent for further projects will be sought from me at that future time;

☐ I understand that I can contact the Manager, Human Research Ethics, Research Ethics and Integrity, University of Melbourne, VIC 3010. Tel: +61 3 8344 2073 or Email: humanethicscomplaints@unimelb.edu.au.

Name: ____________________________________________

Sign: ____________________________________________

Date: ____________________________________________

Thank you for reading this information. This section is for you to keep for your own records.
Centre for Eye Research Australia
Royal Victorian Eye and Ear Hospital
Peter Howson Wing
Level 7, 32 Gisborne Street
East Melbourne 3002
VIC Australia
Survey of potential participant perspective on ocular gene therapy in Australia
Survey of potential participant perspective on ocular gene therapy in Australia

Consent form – Version 2 - 5 January 2021

Please sign this second consent form, and return this booklet to the research team using the pre-paid envelope.

I consent to participate in the research study “Survey of potential participant perspective on ocular gene therapy in Australia” and confirm that I have read the plain language statement and understood the following information.

In particular, I have noted that:

☐ Participation in this research is entirely voluntary;

☐ I am free to withdraw from this research at any time, without comment or penalty. If I withdraw I may request withdrawal of any unprocessed data previously supplied;

☐ Providing my contact details to the researchers is entirely voluntary;

☐ Any questions have been answered to my satisfaction and I understand that if I have any additional questions I can contact the research team;

☐ I have been informed that the confidentiality of the information I will provide will be safeguarded, my opinions will be treated as personal information, and my privacy respected;

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Name (optional):

Sign: 

Date: ____________________________
Survey of potential participant perspective on ocular gene therapy in Australia

About you

1. Are you completing this questionnaire as a:
   - Adult patient, or
   - Parent or guardian of patient less than 18 years of age?

1a. What is the age of your child/dependent diagnosed with an IRD?

1b. What is the gender of your child/dependent diagnosed with an IRD?
   - Male
   - Female
   - Non-binary
   - I prefer not to say

2. Highest level of education you have completed
   - Primary school
   - Secondary school (Year 10 or above)
   - Trade certificate
   - Bachelor degree
   - Post-graduate degree
   - I prefer not to say
Survey of potential participant perspective on ocular gene therapy in Australia

About you

3. What is your annual household gross (before tax) income?
   - Less than $18 200
   - $18 201 - $37 000
   - $37 001 - $87 000
   - $87 001 - $180 000
   - More than $180 001
   - I’d prefer not to say

4. How many members are in your household?

5. What is your age?

6. What is your gender?
   - Male
   - Female
   - Non-binary
   - I prefer not to say
Survey of potential participant perspective on ocular gene therapy in Australia

Diagnosis, symptoms, treatment

7. What is your primary diagnosis as confirmed by your ophthalmologist?
   - □ Achromatopsia
   - □ Bietti Crystalline Dystrophy
   - □ Choroideremia
   - □ Cone Dystrophy
   - □ Cone-rod Dystrophy
   - □ Leber Congenital Amaurosis
   - □ Macular Dystrophy
   - □ Retinitis Pigmentosa
   - □ Stargardt Disease
   - □ X-Linked Retinoschisis
   - □ Other inherited retinal disease (Please specify)
   - □ Not diagnosed with Inherited Retinal Disease (You are not eligible for this study and should not continue)
   - □ I don’t know

8. Have you supplied DNA to any Australian IRD database?
   - □ Yes
   - □ No

9. Have you participated in any medical research in the past?
   - □ Yes
   - □ No
Survey of potential participant perspective on ocular gene therapy in Australia

Diagnosis, symptoms, treatment

10. Have you previously used any of the following treatments for your inherited retinal disease? Select all that apply.

☐ Acupuncture
☐ Electrical stimulation
☐ Human stem cells
☐ Vitamin A
☐ Herbal remedies
☐ None of the above

11. Describe your first symptoms, related to the inherited retinal disease. Select all that apply.

☐ Difficulty seeing at night or dusk
☐ Bumping into low lying objects
☐ Difficulty driving
☐ Difficulty adjusting from light to dark and vice versa
☐ Missing parts in vision
☐ Noticed peripheral or side vision reducing
☐ Other
☐ No noticeable symptoms
☐ Can’t recall

12. What age where you when symptoms first appeared? ____________________________
Survey of potential participant perspective on ocular gene therapy in Australia

Diagnosis, symptoms, treatment

13. Within which time period, have you experienced your most recent decline in vision?
   - Less than 6 months
   - 1 Year
   - 5 Years
   - 10 Years
   - No decline, stable vision

14. How likely are you to take up gene therapy if it was available now to you or your family members for their eye condition?
   - Very likely
   - Likely
   - Neutral
   - Unlikely
   - Very unlikely

15. What are the barriers to you receiving gene therapy for your eye condition? Select all that apply.
   - Treatment is still in early phase roll-out and I would prefer to wait
   - Treatment may not work
   - Fear of side effects
   - Out of pocket cost
   - Against my religion or personal belief
   - Loss of entitlement to government supports
   - Other

Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

This questionnaire is about your views on gene therapy. Please indicate how much you agree or disagree with the following statements:

1. I have good knowledge about gene therapy for inherited retinal diseases.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
### Survey of potential participant perspective on ocular gene therapy in Australia

#### Your views on gene therapy

2. I have obtained information about gene therapy from:

<table>
<thead>
<tr>
<th></th>
<th>Strongly agree</th>
<th>Agree</th>
<th>Neither agree or disagree</th>
<th>Disagree</th>
<th>Strongly disagree</th>
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<tbody>
<tr>
<td>My ophthalmologist</td>
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<td>Other medical or health professional</td>
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<td>Registry e.g. Australian Inherited Retinal Disease Register</td>
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<tr>
<td>Research group</td>
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<td>Family/friends</td>
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</table>
Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

3. I understand the difference between an experimental treatment provided in a clinical trial and a treatment that has already been approved by the Australian Government.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

4. Gene therapy for the eye is suitable at any stage of a person’s life.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

5. Generally, gene therapy for inherited retinal disease is delivered to both eyes.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

6. Gene therapy for the eye is injected into the blood stream through the arm.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

7. Gene therapy and stem cell therapy are the same treatment.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

8. Gene therapy for the eye can restore vision back to normal.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

9. Gene therapy for the eye is a treatment that may slow down the disease.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

10. Treatment complications to my eyes, such as permanent blindness, are possible with an approved gene therapy.
    - [ ] Strongly agree
    - [ ] Agree
    - [ ] Neither agree or disagree
    - [ ] Disagree
    - [ ] Strongly disagree

11. Gene therapy in my eye may have side effects elsewhere in my body.
    - [ ] Strongly agree
    - [ ] Agree
    - [ ] Neither agree or disagree
    - [ ] Disagree
    - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

12. Having gene therapy for their eye condition means a person will not pass on an eye condition to any children they may have in the future.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

13. I may not be eligible for financial or other government benefits if my gene therapy for my eye condition is successful.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

14. Gene therapy for inherited retinal diseases will require many years of follow-up with my eyecare practitioner.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

15. Receiving gene therapy for my inherited retinal disease means I won’t be eligible for future genetic treatments.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

16. I will lose my privacy if I undergo gene therapy, and my data will be in the public domain.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

17. If I undergo gene therapy, it will affect my eligibility or terms of conditions in life, disability or health insurance in the future.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

18. The government should pay all costs of my gene therapy.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

19. Government subsidy of my treatment would be an effective use of taxpayer money.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

20. If gene therapy for my condition was not available in my state I would consider travelling interstate to access it.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Your views on gene therapy

21. My private health insurance should pay all out of pocket costs for my gene therapy.
   - □ Strongly agree
   - □ Agree
   - □ Neither agree or disagree
   - □ Disagree
   - □ Strongly disagree

22. I would consider a payment plan for my gene therapy.
   - □ Strongly agree
   - □ Agree
   - □ Neither agree or disagree
   - □ Disagree
   - □ Strongly disagree
Health Questionnaire

English version for Australia

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Under each heading, please tick the ONE box that best describes your health TODAY.

### MOBILITY
- I have no problems with walking around
- I have slight problems with walking around
- I have moderate problems with walking around
- I have severe problems with walking around
- I am unable to walk around

### PERSONAL CARE
- I have no problems with washing or dressing myself
- I have slight problems with washing or dressing myself
- I have moderate problems with washing or dressing myself
- I have severe problems with washing or dressing myself
- I am unable to wash or dress myself

### USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)
- I have no problems doing my usual activities
- I have slight problems doing my usual activities
- I have moderate problems doing my usual activities
- I have severe problems doing my usual activities
- I am unable to do my usual activities

### PAIN / DISCOMFORT
- I have no pain or discomfort
- I have slight pain or discomfort
- I have moderate pain or discomfort
- I have severe pain or discomfort
- I have extreme pain or discomfort

### ANXIETY / DEPRESSION
- I am not anxious or depressed
- I am slightly anxious or depressed
- I am moderately anxious or depressed
- I am severely anxious or depressed
- I am extremely anxious or depressed
- We would like to know how good or bad your health is TODAY.

- This scale is numbered from 0 to 100.

- 100 means the best health you can imagine.
  0 means the worst health you can imagine.

- Mark an X on the scale to indicate how your health is TODAY.

- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =  

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National Eye Institute
Visual Functioning Questionnaire - 25
(VFQ-25)
version 2000

(SELF-ADMINISTERED FORMAT)

January 2000

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7/29/96

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version 2000

The following is a survey with statements about problems which involve your vision or feelings that you have about your vision condition. After each question please choose the response that best describes your situation.

Please answer all the questions as if you were wearing your glasses or contact lenses (if any).

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible. Remember, if you wear glasses or contact lenses, please answer all of the following questions as though you were wearing them.

INSTRUCTIONS:

1. In general we would like to have people try to complete these forms on their own. If you find that you need assistance, please feel free to ask the project staff and they will assist you.

2. Please answer every question (unless you are asked to skip questions because they don’t apply to you).

3. Answer the questions by circling the appropriate number.

4. If you are unsure of how to answer a question, please give the best answer you can and make a comment in the left margin.

5. Please complete the questionnaire before leaving the center and give it to a member of the project staff. Do not take it home.

6. If you have any questions, please feel free to ask a member of the project staff, and they will be glad to help you.

STATEMENT OF CONFIDENTIALITY:

All information that would permit identification of any person who completed this questionnaire will be regarded as strictly confidential. Such information will be used only for the purposes of this study and will not be disclosed or released for any other purposes without prior consent, except as required by law.

© R 1996
Visual Functioning Questionnaire - 25

PART 1 - GENERAL HEALTH AND VISION

1. In general, would you say your overall health is:

   (Circle One)
   - Excellent ......................... 1
   - Very Good .......................... 2
   - Good ............................... 3
   - Fair ................................. 4
   - Poor ............................... 5

2. At the present time, would you say your eyesight using both eyes (with glasses or contact lenses, if you wear them) is excellent, good, fair, poor, or very poor or are you completely blind?

   (Circle One)
   - Excellent ......................... 1
   - Good ............................... 2
   - Fair ................................. 3
   - Poor ............................... 4
   - Very Poor .......................... 5
   - Completely Blind.............. 6
version 2000

3. How much of the time do you worry about your eyesight?

(Circle One)

None of the time ....................................... 1
A little of the time ................................. 2
Some of the time ......................... 3
Most of the time ......................... 4
All of the time? .............................. 5

4. How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)? Would you say it is:

(Circle One)

None ............................................. 1
Mild ............................................. 2
Moderate ................................. 3
Severe, or ................................. 4
Very severe? .............................. 5

PART 2 - DIFFICULTY WITH ACTIVITIES

The next questions are about how much difficulty, if any, you have doing certain activities wearing your glasses or contact lenses if you use them for that activity.

5. How much difficulty do you have reading ordinary print in newspapers? Would you say you have:

(Circle One)

No difficulty at all ............................................ 1
A little difficulty ......................................... 2
Moderate difficulty ..................................... 3
Extreme difficulty ...................................... 4
Stopped doing this because of your eyesight .... 5
Stopped doing this for other reasons or not interested in doing this ................................. 6

© R 1996
version 2000

6. How much difficulty do you have doing work or hobbies that require you to see well up close, such as cooking, sewing, fixing things around the house, or using hand tools? Would you say:

(Circle One)
- No difficulty at all.............................................. 1
- A little difficulty.............................................. 2
- Moderate difficulty.......................................... 3
- Extreme difficulty........................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ................................. 6

7. Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?

(Circle One)
- No difficulty at all.............................................. 1
- A little difficulty.............................................. 2
- Moderate difficulty.......................................... 3
- Extreme difficulty........................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ................................. 6

8. How much difficulty do you have reading street signs or the names of stores?

(Circle One)
- No difficulty at all.............................................. 1
- A little difficulty.............................................. 2
- Moderate difficulty.......................................... 3
- Extreme difficulty........................................... 4
- Stopped doing this because of your eyesight .... 5
- Stopped doing this for other reasons or not interested in doing this ................................. 6

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9. Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?

(Circle One)

No difficulty at all......................................................... 1
A little difficulty............................................................ 2
Moderate difficulty......................................................... 3
Extreme difficulty.......................................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ........................................... 6

10. Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?

(Circle One)

No difficulty at all......................................................... 1
A little difficulty............................................................ 2
Moderate difficulty......................................................... 3
Extreme difficulty.......................................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ........................................... 6

11. Because of your eyesight, how much difficulty do you have seeing how people react to things you say?

(Circle One)

No difficulty at all......................................................... 1
A little difficulty............................................................ 2
Moderate difficulty......................................................... 3
Extreme difficulty.......................................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ........................................... 6

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12. Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?

(Circle One)

No difficulty at all...................................................... 1
A little difficulty......................................................... 2
Moderate difficulty..................................................... 3
Extreme difficulty...................................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ................................. 6

13. Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?

(Circle One)

No difficulty at all...................................................... 1
A little difficulty......................................................... 2
Moderate difficulty..................................................... 3
Extreme difficulty...................................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ................................. 6

14. Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?

(Circle One)

No difficulty at all...................................................... 1
A little difficulty......................................................... 2
Moderate difficulty..................................................... 3
Extreme difficulty...................................................... 4
Stopped doing this because of your eyesight.... 5
Stopped doing this for other reasons or not interested in doing this ................................. 6

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15. Are you currently driving, at least once in a while?
   (Circle One)
   Yes .................... 1  Skip To Q 15c
   No ..................... 2

15a. IF NO: Have you never driven a car or have you given up driving?
   (Circle One)
   Never drove ...... 1  Skip To Part 3, Q 17
   Gave up .......... 2

15b. IF YOU GAVE UP DRIVING: Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?
   (Circle One)
   Mainly eyesight ............... 1  Skip To Part 3, Q 17
   Mainly other reasons .......... 2  Skip To Part 3, Q 17
   Both eyesight and other reasons ... 3  Skip To Part 3, Q 17

15c. IF CURRENTLY DRIVING: How much difficulty do you have driving during the daytime in familiar places? Would you say you have:
   (Circle One)
   No difficulty at all .................. 1
   A little difficulty .................... 2
   Moderate difficulty .................. 3
   Extreme difficulty .................. 4

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16. How much difficulty do you have driving at night? Would you say you have:

(Circle One)

- No difficulty at all.......................... 1
- A little difficulty............................. 2
- Moderate difficulty......................... 3
- Extreme difficulty........................... 4
- Have you stopped doing this because of your eyesight......................... 5
- Have you stopped doing this for other reasons or are you not interested in doing this .......................................... 6

16A. How much difficulty do you have driving in difficult conditions, such as in bad weather, during rush hour, on the freeway, or in city traffic? Would you say you have:

(Circle One)

- No difficulty at all.......................... 1
- A little difficulty............................. 2
- Moderate difficulty......................... 3
- Extreme difficulty........................... 4
- Have you stopped doing this because of your eyesight......................... 5
- Have you stopped doing this for other reasons or are you not interested in doing this .......................................... 6
PART 3: RESPONSES TO VISION PROBLEMS

The next questions are about how things you do may be affected by your vision. For each one, please circle the number to indicate whether for you the statement is true for you all, most, some, a little, or none of the time.

<table>
<thead>
<tr>
<th>READ CATEGORIES:</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td>17. Do you accomplish less than you would like because of your vision?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. Are you limited in how long you can work or do other activities because of your vision? .................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. How much does pain or discomfort in or around your eyes, for example, burning, itching, or aching, keep you from doing what you’d like to be doing? Would you say:</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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For each of the following statements, please circle the number to indicate whether for you the statement is **definitely true**, **mostly true**, **mostly false**, or **definitely false** for you or you are **not sure**.

(Circle One On Each Line)

<table>
<thead>
<tr>
<th></th>
<th>Definitely True</th>
<th>Mostly True</th>
<th>Not Sure</th>
<th>Mostly False</th>
<th>Definitely False</th>
</tr>
</thead>
<tbody>
<tr>
<td>20. I <em>stay home most of the time</em> because of my eyesight.....</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>21. I feel <em>frustrated</em> a lot of the time because of my eyesight.................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>22. I have <em>much less control</em> over what I do, because of my eyesight. .................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>23. Because of my eyesight, I have to <em>rely too much on what other people tell me</em>.</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>24. I <em>need a lot of help from others</em> because of my eyesight.......................</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>25. I worry about doing things that will embarrass myself or others, because of my eyesight...............</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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Patient attitudes to clinical trials

We are seeking your opinion on future clinical trials for gene therapy. Please indicate how much you agree or disagree with the following statements.

1. New and better treatments can only be produced if patients agree to take part in clinical trials.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

2. Without the results from clinical trials, doctors would be less able to select the best treatment.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

3. Pharmaceutical companies should ensure that valid clinical trials are conducted on every drug treatment before it is generally available.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
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Patient attitudes to clinical trials

4. If most patients refused to take part in clinical trials, important developments in medicine would be seriously delayed.
   - Strongly agree
   - Agree
   - Neither agree or disagree
   - Disagree
   - Strongly disagree

5. Clinical trials are carried out according to strict rules to safeguard the interests of patients.
   - Strongly agree
   - Agree
   - Neither agree or disagree
   - Disagree
   - Strongly disagree

6. I assume that drug treatments that have been prescribed for me have already been thoroughly tested in clinical trials.
   - Strongly agree
   - Agree
   - Neither agree or disagree
   - Disagree
   - Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Patient attitudes to clinical trials

7. **Clinical trials are only conducted on drugs/treatments for which there is already evidence to show that they are likely to be effective.**
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

8. **The conduct of all clinical trials is carefully regulated to ensure that the results are valid.**
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

9. **I would want as much written information as possible about a clinical trial before I agreed to take part.**
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Patient attitudes to clinical trials

10. I would want to know before agreeing to take part that I would be free to withdraw from the clinical trial at any time.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

11. I would want to know if I would be likely to get side effects by taking part in a clinical trial before I agreed to take part.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree

12. I would only take part in a clinical trial if I thought I understood everything about it.
   - [ ] Strongly agree
   - [ ] Agree
   - [ ] Neither agree or disagree
   - [ ] Disagree
   - [ ] Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Patient attitudes to clinical trials

13. I think I would find being in a clinical trial frightening.
   - □ Strongly agree
   - □ Agree
   - □ Neither agree or disagree
   - □ Disagree
   - □ Strongly disagree

14. I would only take part in the clinical trial if I thought that my own health would benefit.
   - □ Strongly agree
   - □ Agree
   - □ Neither agree or disagree
   - □ Disagree
   - □ Strongly disagree

15. I would only take part in a clinical trial if I thought that I would not be inconvenienced by doing so.
   - □ Strongly agree
   - □ Agree
   - □ Neither agree or disagree
   - □ Disagree
   - □ Strongly disagree
Survey of potential participant perspective on ocular gene therapy in Australia

Patient attitudes to clinical trials

16. I would only take part in a clinical trial if I know which treatment I was going to receive.
   - Strongly agree
   - Agree
   - Neither agree or disagree
   - Disagree
   - Strongly disagree

17. I would only take part in a clinical trial if I was sure that the doctor treating me knew which treatment I was getting.
   - Strongly agree
   - Agree
   - Neither agree or disagree
   - Disagree
   - Strongly disagree

18. If I was satisfied with my current treatment, I would probably refuse to take a different treatment in a clinical trial.
   - Strongly agree
   - Agree
   - Neither agree or disagree
   - Disagree
   - Strongly disagree
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Patient attitudes to clinical trials

19. It is important for people like me to take part in clinical trials to confirm the value of new treatments and or medical techniques.
   □ Strongly agree
   □ Agree
   □ Neither agree or disagree
   □ Disagree
   □ Strongly disagree

20. I would take part in a clinical trial because the results should benefit patients like me in the future.
   □ Strongly agree
   □ Agree
   □ Neither agree or disagree
   □ Disagree
   □ Strongly disagree

21. I think all patients who are eligible should be asked to take part in clinical trials.
   □ Strongly agree
   □ Agree
   □ Neither agree or disagree
   □ Disagree
   □ Strongly disagree

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Patient attitudes to clinical trials

22. Unless advised by their doctor to withdraw from a trial, all patients should cooperate fully until the trial is finished.

☐ Strongly agree
☐ Agree
☐ Neither agree or disagree
☐ Disagree
☐ Strongly disagree
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Future contact

We intend to publish the results of this study. These reports of de-identified aggregated results will be provided to patient support groups which have assisted in participant recruitment. Study results will be disseminated to the scientific community through scientific publications in peer-reviewed journals and presentations in relevant national and international conferences.

Would like to receive a de-identified copy of the aggregated results at the completion of the study (anticipated early 2022) via email?

☐ Yes
☐ No

Do you consent to your data being retained for possible future longitudinal research, subject to further ethics approval?

☐ Yes
☐ No

Would you like to be contacted for possible testing to see if you have the mutation in RPE65 or any other identified mutations associated with inherited retinal dystrophy?

☐ Yes
☐ No
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Future contact

If you answer yes to any of these questions, please provide your contact details. This is entirely optional and any information will be kept confidential.

Title

First name

Last name

Email address

Phone

Thank you for your time. You are helping researchers understand patient perspectives in treating inherited retinal disease.

Yours sincerely,

Heather Mack (principal researcher), Lauren Ayton (responsible researcher), Fred Chen, John Grigg, Thomas Edwards, Fleur O'Hare, Ceeceee Zhang, Keith Martin

Please return this document in the enclosed reply paid envelope.

If the envelope is missing mail to

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East Melbourne
VIC 3002

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