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Attitudes and Informational Needs Towards Somatic Gene Therapy; A Survey of Stakeholders Affected by Inherited Retinal Disorders

THESIS

submitted in partial satisfaction of the requirements
for the degree of

MASTER OF SCIENCE

in Genetic Counseling

by

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DEDICATION

To

my family, friends, and mentors

in recognition of their unwavering support

a thought

Confusion is a gift from God. Those times when you feel most desperate for a solution, sit. Wait. The information will become clear. The confusion is there to guide you. Seek detachment and become the producer of your life.

The RZA
The Tao of Wu

and wisdom

You are the sky. Everything else – it's just the weather.

Pema Chödrön

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ABSTRACT OF THE THESIS

Attitudes and Informational Needs Towards Somatic Gene Therapy; A Survey of Stakeholders Affected by Inherited Retinal Disorders

by

Amanda Marie Shrewsbury

Master of Science in Genetic Counseling

University of California, Irvine, 2023

Professor Emerita Moyra Smith, Chair

The recent exponential development of gene-based therapies for the treatment of genetic conditions underpins the importance of understanding the attitudes and information needs of individuals who may soon be eligible for treatment, but existing research is limited. This mixed-methods study explored the attitudes and information needs of affected individuals and caregivers in the inherited retinal disorder (IRD) community specifically. Affected individuals and caregivers (N=689) completed an accessible, anonymous, online survey comprised of validated and a non-validated survey instruments that assessed attitudes and information needs related to gene therapy, vision-related quality of life, and health literacy. The results demonstrate significant optimism and interest regarding gene therapy in the IRD community and show that this interest varies by certain participant demographic characteristics. Participants also reported low self-perceived knowledge about gene therapy and a significant need for information, highlighting an opportunity for education of healthcare providers and patients.

INTRODUCTION

Inherited retinal disorders (IRDs) are a group of heterogeneous lifelong conditions

Inherited retinal disorders (IRDs) are a diverse group of degenerative retinal conditions estimated to have an incidence of 1 in 2000 to 1 in 3500 individuals in Europe and North America (Berger et al., 2010; Moore, 2017; Sen et al., 2008). IRDs are clinically and genetically heterogeneous. The clinical manifestations of IRDs are variable in their presentation and severity and can range from early-onset vision loss and legal blindness to milder dysfunction, such as isolated night blindness and mild color vision deficiency (Berger et al., 2010). Such impairments can impact an individual's quality of life, educational and employment opportunities, health status, and life expectancy (Heath Jeffery et al., 2021). Notably, IRDs are the leading cause of blindness amongst individuals aged 15 to 45 years old and are a significant cause of blindness worldwide (Cremers et al., 2018; Heath Jeffery et al., 2021; Moore, 2017). Societally, the impact of these conditions from a cost-of-illness perspective is substantial, concerning both economic costs and reduced well-being (Gong et al., 2021). For example, a recent study by Gong and colleagues (2021) found that US$13.4 to US$31.8 billion annually can be attributed to IRDs across the domains and settings of healthcare costs, individual and family productivity costs, reduced well-being, and additional socioeconomic costs (Gong et al., 2021). Together, this information underscores the importance of continued research on IRDs and efforts in policy and advocacy to mitigate the impact of IRDs.

The existing literature describes over 25 IRD subtypes with more than 280 causative genes; the reader is referred to RetNet (www.sph.uth.edu/retnet) for a comprehensive and up-to-date list of IRDs and their associated genes. Retinitis pigmentosa (RP), Leber congenital amaurosis (LCA), Stargardt disease, Usher syndrome, and achromatopsia are among the most prevalent of these conditions (Schneider et al., 2022). Isolated non-syndromic IRDs account for 70-80% of all IRDs, while 20-30% are syndromic, with extra-ocular manifestations of disease in addition to the retinal phenotype. Diagnostic yield through genetic testing is higher for some diagnoses (e.g., LCA, Usher syndrome, Bardet-Biedl syndrome) than others (e.g., macular dystrophy, cone dystrophy) (Audo et al., 2012; Glöckle et al., 2014; Weisschuh et al., 2016). A pathogenic variant is identifiable in 60-80% of individuals with an IRD (Audo et al., 2012; Glöckle et al., 2014; Schneider et al., 2022; Weisschuh et al., 2016). Identifying a molecular basis for disease is essential for predicting genotype-phenotype correlations in the clinical setting and determining eligibility for novel gene-based treatments (Tsang & Sharma, 2018).

Pathogenic IRD variants demonstrate allelic heterogeneity with different variants in a single gene, causing a mix of IRD phenotypes. IRDs also show locus heterogeneity, with a particular phenotype resulting from pathogenic variants in several genes (Sangermano et al., 2019; Schneider et al., 2022). Figure 1 below from Sangermano and colleagues (2019) illustrates the allelic and locus heterogeneity of IRDs. As an example of the complexity of IRDs, the most prevalent IRD, RP, can result from pathogenic variants in more than 60 genes and can be inherited in autosomal dominant (AD), autosomal recessive (AR), X-

linked, and digenic patterns (Hamel, 2006; Schneider et al., 2022; Tsang & Sharma, 2018). The majority of IRDs (approximately 70%) are inherited in an AR fashion, followed by AD inheritance patterns (approximately 25%), with the remainder being X-linked or mitochondrial conditions, although digenic forms of disease have also been characterized (RetNet www.sph.uth.edu/retnet; Tsang & Sharma, 2018). *De novo* mutations can also cause IRDs. For example, an estimated 1-2% of AD IRDs are from new mutations amongst individuals with no family history of the condition, and *de novo* mutations are documented among individuals with X-linked IRDs (Branham et al., 2012; Breuer et al., 2002; Neveling et al., 2012).

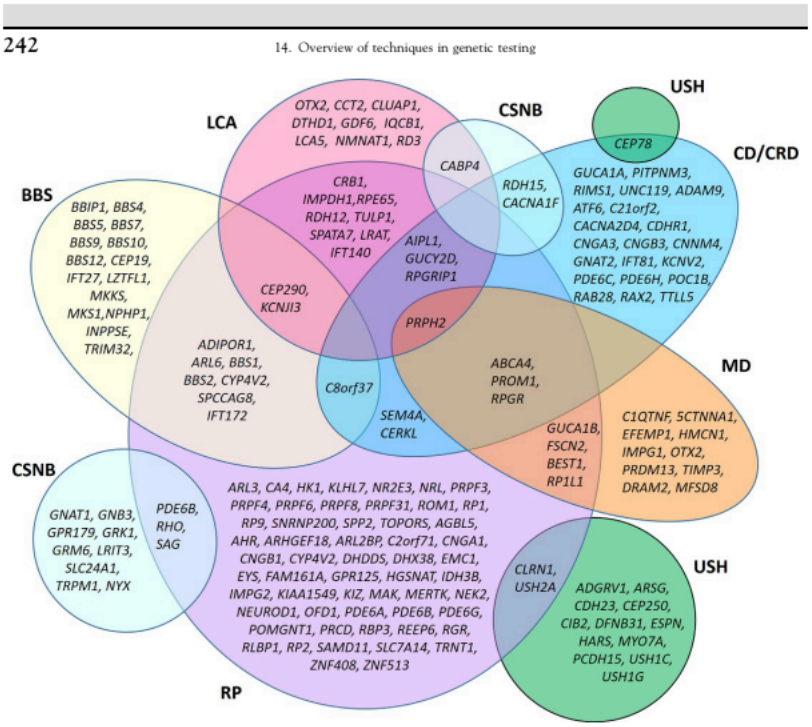


FIG. 1 Genetic heterogeneity of IRDs. A Venn diagram of the most common forms of inherited retinal disorders with overlapping regions in which the same genes are responsible for different disorders. Usher and Bardet-Biedl syndromes were selected to represent syndromic forms of retinal disease. *BBS*, Bardet-Biedl syndrome; *CD/CRD*, cone or cone-rod dystrophy; *CSNB*, congenital stationary night blindness; *LCA*, Leber congenital amaurosis; *MD*, macular degeneration; *RP*, retinitis pigmentosa; *USH*, Usher syndrome (RetNet, the Retinal Information Network, accessed December 2018).

Figure 1. Illustration from Sangermano et al. (2020) showing the genetic heterogeneity of IRDs.

One in every three individuals worldwide is estimated to be a carrier of at least one recessive IRD-causing variant, though not all combinations of variants will necessarily cause disease (Hanany et al., 2020). At a molecular level, IRDs are complicated by specific hypomorphic variants and low penetrance alleles. For example, approximately 7% of *ABCA4* mutations identified were reported as hypomorphic in a study of the worldwide carrier frequency and genetic prevalence of AR IRDs (Hanany et al., 2020). Not all combinations of genetic variants are expected to cause an IRD phenotype, which further

underscores the importance of characterizing genetic mutations related to IRDs in order to deepen our understanding of genotype-phenotype relationships and ultimately provide more individualized treatment options (Hanany et al., 2020; Jaakson et al., 2003; Yatsenko et al., 2001).

The eye is a complex and fascinating structure; aging, trauma, infection, and genetic risks can all cause a wide range of ocular diseases and disorders. However, retinal disorders are highly genetic conditions. The photoreceptor cells, which act as support cells for the retina, are essential for vision, and genetic changes in the genes responsible for retinal function can result in impaired vision. The eye is made up of the iris and the pupil, which function to let light into the eye; the cornea and the lens, which are the two major refractive structures of the eye; the sclera, which is the thick white outercoat of the eye; the choroid which contains blood vessels and connective tissue that ultimately provide nutrients for the eye; and the retina which is the innermost layer of tissue implicated in the process of phototransduction through the optic nerve (Kaplan, 2007). The retina can be categorized histologically into ten layers (Tsang & Sharma, 2018). IRDs primarily affect the photoreceptor layer, comprised of photoreceptor cells called rods and cones, and the retinal pigment epithelium (Kaplan, 2007; Tsang & Sharma, 2018). The tightly stacked photoreceptor layer of the eye contains approximately 126 million rod and cone cells combined, while the retinal pigment epithelium contains another four to six million cells (Tsang & Sharma, 2018).

The eye is considered an immune-privileged organ, given its unique anatomical and physiological properties (Kaplan, 2007). Immune-privilege is operationally defined as "an evolutionary adaptation aimed at protecting especially vulnerable organs from overwhelming inflammation that could abolish their functions and jeopardize the well-being of the individual…[and the ability to] enable selective immune responses most suitable and effective for its proper function in health and pathology" (Benhar et al., 2012). The blood-ocular barrier, the term coined for separating the fluid compartments of the eye by endothelial and epithelial cells, is an effective barrier to soluble molecules and an essential component of the eye's immunological privilege (Kaplan, 2007). The immunologic privilege of the eye, along with its accessibility and compartmentalization as an organ, is part of why ocular disorders are considered ideal candidates for gene-based therapies.

Most IRDs are classified into four broad categories, including rod-cone degenerations, cone-rod degenerations, chorioretinal degenerations, and macular degenerations, but altogether there are more than 25 different IRD subtypes with some overlap between subtypes (Fenner et al., 2022; Schneider et al., 2022). RP, the most common IRD, occurs in approximately 1 in 4000 individuals and is characterized by the primary degeneration of rod photoreceptors and secondary degeneration of cones, classifying it as a rod-cone dystrophy (Hamel, 2006). Most individuals with RP experience night blindness (nyctalopia) as one of the condition's initial symptoms. RP can progress to blindness over several decades through progressive peripheral visual field loss, which deteriorates daytime vision and decreases visual acuity (Hamel, 2006). Individuals with RP

may also experience tunnel vision, progressive loss of central vision, a progressive decline in visual acuity, and other symptoms. However, the phenotype varies between individuals and, sometimes, depends on the molecular cause (Verbakel et al., 2018). The condition's severity correlates with the Mendelian inheritance pattern, wherein X-linked RP typically presents the most severely, followed by AR RP and AD RP, respectively (Verbakel et al., 2018).

Although RP is more commonly non-syndromic, the condition is also an example of the 20-30% of IRDs that can take a syndromic form and present with extra-ocular manifestations, with Usher syndrome being the most common form of syndromic RP (Diñeiro et al., 2020; Hamel, 2006; Pierrottet et al., 2014). Individuals with Usher syndrome present with neurosensory hearing loss at birth or within the first few years to a decade of life, in addition to developing an RP phenotype (Pierrottet et al., 2014). The majority of the remaining 20-30% of syndromic IRDs can be broadly classified as inborn errors of metabolism or ciliopathies and can affect several physiological systems and organs other than the retina, including the central nervous system, the ear, skeletal, kidney, and cardiovascular systems (Tatour & Ben-Yosef, 2020; Werdich et al., 2014).

RP overlaps with other IRDs, both clinically and genetically, such as Leber congenital amaurosis (LCA) and cone-rod dystrophy (Verbakel et al., 2018). RP and LCA are often diagnostically distinguished by the age of symptom onset, rate of progression, and severity of the retinal degeneration, with patients who present with severe retinal degeneration in the first months of life diagnosed with an LCA phenotype and patients who

present later in childhood or even well into adulthood with slowly progressive symptoms diagnosed with RP (Kumaran et al., 2017; Verbakel et al., 2018). LCA is commonly associated with other ocular features, including nystagmus, diminished pupillary response to light (amaurotic pupils), hypermetropia, cataracts, keratoconus, poking, pressing, or rubbing of the eyes (oculodigitial sign), and markedly decreased or absent response to light stimulus on electroretinogram (Kumaran et al., 2017). Multiple genes, such as *CRB1* and *RPE65*, are associated with both RP and LCA. This overlap exemplifies the spectrum of retinal dystrophies and highlights the importance of continued research to understand genotype-phenotype relationships and clinical subtypes of IRDs.

The many other subtypes of IRDs are categorized based on the natural history of the disease and the types of retinal cells predominantly involved in the pathogenicity of the condition (Cremers et al., 2018). With regards to natural history, IRDs can be classified as stationary (e.g., congenital stationary night blindness (CSNB) or achromatopsia (ACHM)) or progressive (e.g., RP, cone-rod dystrophy (CRD), or Stargardt disease (STGD1)) (Cremers et al., 2018). Regarding the retinal cell types implicated in disease pathogenesis, IRDs can be classified based on primary deficits or deterioration of rod versus cone photoreceptors. However, depending on the stage of disease progression, an individual with a specific condition may experience severe dysfunction and degeneration of both rods and cones, making clinical diagnosis difficult (Cremers et al., 2018). This underscores the importance of continued research surrounding the genetic bases of IRDs.

Therapeutic options remain limited for the treatment of IRDs. Still, various management strategies that are multi-disciplinary, including counseling and visual rehabilitation, can provide benefits, and novel therapeutic options are continually emerging from research (Verbakel et al., 2018). Visual rehabilitation prioritizes the patient's functional abilities and needs, including support and training with low-vision aids, orientation and mobility training, and accessibility software (Verbakel et al., 2018). Genetic testing and counseling are essential components of the multi-disciplinary treatment approach for patients with IRDs (Hamel, 2006; Stone et al., 2012). The genetic heterogeneity of IRDs can make this process complicated. Still, when clinicians properly carry out the testing and counseling process, the characterization of the inheritance and prognosis of the condition is more precise, and clinicians can more accurately provide disease occurrence and recurrence risks to individuals and families. Additionally, exploring precision medicine approaches and treatments specific to the disease's molecular basis becomes possible (Stone et al., 2012; Strait et al., 2020).

Gene-based therapies are promising treatments for IRDs

History and overview of gene-based therapies

The investigation of novel treatments for IRDs, including gene-based therapies, is a critical avenue of research and is a significant focus of the study herein. According to the United States Food and Drug Administration (U.S. FDA, 2018), "Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use." In 2017, the U.S. FDA approved Voretigene neparvovec-rzyl

(Luxturna ™), the first *in vivo* gene therapy approved in the U.S. to treat a Mendelian condition and the first pharmacologic treatment for an IRD. The therapy treats a form of LCA caused by biallelic mutations in the *RPE65* gene (Tsang & Sharma, 2018). Immense research efforts focused on developing gene-based therapies for the treatment of IRDs have ensued worldwide after the approval of Luxturna™.

Gene-based therapy can be broadly defined as a genetic modification to prevent, halt, or reverse human disease (Kay, 2011). Gene-based therapies can be germline or somatic. Germline gene-based therapies refer to a genetic modification that will be passed on to progeny (Wirth et al., 2013). Contrarily, somatic gene-based therapies, which are the present study's focus, refer to a genetic modification that is added to host cells but does not integrate into the host genome and is not passed onto future generations (Wirth et al., 2013). The first clinical gene therapy trials began in the late 1980s, and since then, the technology has faced significant progress and setbacks (Kay, 2011).

In 1990, Michael Blaese and colleagues treated two children affected with adenosine deaminase severe combined immunodeficiency with autologous white blood cells genetically modified *ex vivo* to properly express the *ADA* gene, which is responsible for the production of adenosine deaminase (Blaese et al., 1995). This trial and subsequent trials in the early to mid-1990s demonstrated that gene therapy could be a safe and effective addition to the therapeutic regimens for specific genetic conditions. Unfortunately, tragedy struck amidst gene therapy trials in the late 1990s and early 2000s. In 1999, Jesse Gelsinger, an 18-year-old with ornithine transcarbamylase deficiency, died of multiorgan

failure four days after participation in a gene therapy clinical trial that triggered a massive immunological response in response to the viral vector used in the trial (Wirth et al., 2013). Further, several children treated for severe combined immunodeficiency (SCID) with gene therapy developed cancer following their clinical trials (Kohn et al., 2003). Unsurprisingly, these events fostered skepticism amongst the scientific community and the public and highlighted the potential dangers of gene therapy. This skepticism and various technical barriers lessened the enthusiasm toward gene-based therapies for the next decade.

However, gene-based therapies emerged again from the late 2000s and onwards as a promising treatment strategy. Technological advancements, which have removed barriers to using the technology, and the success of gene-based therapies for the treatment of several medical conditions in clinical trials catalyzed this growth (Kay, 2011). Technologically, the last decade of work in this area has resulted in an improved understanding of adeno-associated virus (AAV) vector biology, *in vivo* gene transfer methods, new strategies to evade human immune response with gene delivery vectors, products of foreign transgenes, the development of non-viral nanoparticle gene delivery mechanisms, and the discovery and rapid growth of the clustered regularly interspaced short palindromic repeats and CRISPR-associated protein-9 (CRIPSR-Cas9) gene editing method (Bulaklak & Gersbach, 2020). More than 2500 gene therapy clinical trials have been conducted or are ongoing, spanning over 35 countries (Ginn et al., 2018). Cancer is the most frequent disease treated by gene therapy, with monogenic and cardiovascular diseases following, respectively (Wirth et al., 2013).

Various factors make IRDs ideal targets for gene-based therapy. These factors include the expanding phenotypic and genotypic characterization of IRDs, improvements in our understanding of the molecular mechanisms that lead to pathogenesis through cell and animal models, the unique anatomical structure of the eye and its immune privilege, and the various functional and structural methods that are available to measure outcomes of treatment among this population (Fenner et al., 2022). To date, over 50 registered clinical trials in the United States involve gene-based therapies as an intervention for retinal disease (U.S. National Library of Medicine, 2022). For a comprehensive and up-to-date list of the ongoing IRD clinical trials, the reader is referred to the "Clinical Trial Pipeline" resource maintained by the Foundation Fighting Blindness (https://www.fightingblindness.org/clinical-trial-pipeline).

Gene-based therapy techniques for IRDs

Broadly, gene-based therapies fall into the categories of gene augmentation, gene editing, and RNA-based therapies (Kay, 2011). Gene augmentation for IRDs can be carried out using AAV and non-viral delivery vectors, while genome editing for IRDs has seen progress with the CRISPR-Cas9 system (Fenner et al., 2022). RNA-based therapies for IRDs have demonstrated potential to treat IRDs through editing via endogenous and exogenous adenosine deaminases acting on RNA (ADAR) and antisense oligonucleotides which target mRNA for gene knockdown and splicing alterations (Fenner et al., 2022). Additionally, optogenetic approaches to treat IRDs are in development, and they focus on genetically engineering retinal cells to phototransduce, thereby replacing deteriorated photoreceptors

(Fenner et al., 2022). The following paragraphs provide more detail regarding each technique, their uses with IRDs, and their challenges.

Gene augmentation, often considered "classical gene therapy," is a technique in which a wild-type copy of the disease-causing gene is inserted into target retinal cells, typically outer retinal photoreceptor and retinal pigment epithelial cells, by sub-retinal or intravitreal injection using either viral or non-viral vectors (Nuzbrokh et al., 2021). AAV vectors are the most utilized method of treatment delivery in gene therapy for IRDs. For example, Luxturna®, the first FDA-approved IRD gene therapy, utilized AAV2 to replace nonfunctioning *RPE65* in patients with LCA (Russell et al., 2017). Gene augmentation primarily focuses on restoring loss-of-function and is best suited for AR IRDs (Fenner et al., 2022). Thus, a limitation of classical gene therapy is that it is not a suitable therapeutic approach for IRD resulting from gain-of-function mutations. Addressing gain-of-function at the gene level requires other approaches, several of which are described in the following sections (Nuzbrokh et al., 2021).

Another limitation of using AAV vectors as delivery vehicles is that they have a small carrying capacity (up to 4.7kB) and can produce variable immune responses depending on the specific AAV used (e.g., use of AAV8 produces fewer neutralizing antibodies compared to AAV2) (Nuzbrokh et al., 2021). Several replacement genes associated with common IRDs, such as Stargardt disease, Usher syndrome, and LCA type 10, exceed this small carrying capacity (Ong et al., 2020). Thus, other viral vectors, including lentiviruses and non-viral delivery vectors, such as nanoparticle-based vectors, are being developed and

used more, given their lower immunogenicity and larger carrying capacity (Nuzbrokh et al., 2021). Classical gene therapy treatments comprise the majority of IRD clinical trials (Prado et al., 2020). Unfortunately, this renders the technique ill-suited for treating many IRD genotypes due to challenges regarding the cargo-carrying capacity of vector delivery vehicles and confinement to treating loss-of-function mutations or haploinsufficiency (Fenner et al., 2022).

Gene editing is one alternative method of addressing these challenges with its ability to correct pathogenic variants at the level of the host genome through the introduction of site-specific modifications (Doudna & Charpentier, 2014; Fenner et al., 2022). In 2012, scientific efforts pioneered by Jennifer Doudna, Ph.D., and Emmanuelle Charpentier, Ph.D. revealed that the native and adaptive immune system belonging to certain bacterial microbes could be manipulated and utilized in the cells of mammals and other organisms as a precise and reliable genome-editing technology (Jinek et al., 2012; E. S. Lander, 2016). This technique has seen tremendous progress in the past decade with the advancement of CRISPR-Cas9 technology, although there are other gene editing technologies such as zinc finger nucleases (ZFNs) and TAL effector nucleases (TALENs) (Doudna & Charpentier, 2014). CRISPR-Cas9 technology is a specific, accurate, efficient, and affordable genome-editing technique that has revolutionized biotechnology in the 21st century.

The CRISPR-Cas9 system works as follows: 1) the endonuclease Cas9 protein creates a complex with a sequence-specific guide RNA (gRNA) in the cell; 2) the complex

anneals to a complementary guide DNA (gDNA) sequence matching the gRNA; 3) the complex acts as a pair of "molecular scissors" and creates a double-stranded break in the gDNA; and 4) a site-specific edit is made to the host genome through DNA repair processes like homology-directed repair (HDR) or non-homologous end-joining (NHEJ) (Doudna & Charpentier, 2014; Fenner et al., 2022). Although CRISPR-Cas9 technology is rapidly advancing, the technology is not infallible. Challenges on the road ahead include the need to refine and innovate methods to improve the accuracy and precision of editing to reduce off-target effects and unintended sequence changes, the need to improve immunogenic responses to CRISPR-Cas9 components, and the need to characterize the long-term safety and efficacy of genome editing over time (Doudna, 2020). Several technological advancements that help to circumvent these problems have already seen success, such as prime editing (Anzalone et al., 2019, 2020).

Given the limitations of classical gene therapy and gene editing approaches, investigating the clinical utility of RNA-based modifications is ongoing and promising. RNA-based therapies use native biological editing processes of eukaryotic cells, including human retinal cells (Fenner et al., 2022). Endogenously, RNA editing occurs from adenosine deaminases acting on RNA (ADAR) and cytidine deaminases acting on RNA (CDAR), which catalyze single nucleotide base pair changes at specific messenger RNA (mRNA) sequences that are equivalent to A-to-G and C-to-T base pair changes functionally (Fenner et al., 2022). However, exogenously introduced antisense oligonucleotides (ASOs) can anneal to mRNA-specific sequences and impact gene expression, splicing, and protein translation,

thereby performing RNA editing (Fenner et al., 2022). Additionally, the achievement of gene knockdown driven by microRNAs (miRNAs) through the utilization of the native eukaryotic RNA interference (RNAi) mechanisms resulting in gene suppression is possible (Fenner et al., 2022). Through this method, mitrons, which are miRNA precursors, are engineered to align to specific target mRNA sequences and mechanistically initiate a gene knockdown cascade (Fenner et al., 2022). RNA-based approaches are advantageous and promising because they are mutation-agnostic mechanistically and can target various IRDs, including AD IRDs (Fenner et al., 2022). However, a primary limitation is the editing efficiency of RNA-based technologies, and further research is required to understand the efficiency level necessary to achieve clinical utility with RNA-based approaches (Fenner et al., 2022).

Optogenetics is another approach that shows promise as a gene-based therapy for IRDs. The gene-based therapies discussed until this point are particularly well suited for individuals with specific genetic variants or those with some functional ability left amongst their photoreceptor cells. However, given the vast genetic heterogeneity of IRDs and the variability between patients regarding symptom presentation and progression, there is a need for more general therapies to treat IRDs regardless of the patient's genotypic status or phenotypic progression. Optogenetics seeks to restore vision for individuals with late-stage IRDs by genetically engineering specific genes that already encode photosensitive proteins to target specific retinal cell types, thereby rendering them into replacement photoreceptor cells (Fenner et al., 2022). This approach has seen recent success, such as in a treatment

trial for advanced RP, but it is still limited in the amount of visual improvement it can provide to the patient, given the highly complex circuity of retinal neurons (Fenner et al., 2022; Sahel et al., 2021).

Gene-based therapies have experienced enormous growth in their research and use in the last decade alone. In a comprehensive review of clinical trials from the ClinicalTrials.gov database from 2010 to 2020, over 1900 registered clinical trials involving gene therapy (Arabi et al., 2022). Over 20 gene therapy products have received U.S. FDA approval since 1998, although some of these products have since been withdrawn from the market, and many others are awaiting approval (Arabi et al., 2022). As mentioned previously, Luxturna ™ is the first, and currently only, U.S. FDA and European Medical Association (EMA) approved retinal gene therapy, however many others are in clinical development for the treatment of other IRDs, including achromatopsia, choroideremia, LCA, Leber's hereditary optic neuropathy (LHON), RP, X-linked retinoschisis, Stargardt disease, and Usher syndrome (Amato et al., 2021; Michalakis et al., 2021). As an example of the ongoing research ingenuity in this area, researchers at the National Eye Institute, a part of the National Institutes of Health, have recently developed an AAV-mediated *IQCB1/NPHP5* specific gene therapy that rescues cilia function in a type of LCA caused by *IQCB1/NPHP5* mutations, after discovering that this specific type of LCA resulted in a severe ciliopathy through the use of patient-derived retinal organoids (Kruczek et al., 2022). For systematic reviews of the current gene therapy treatments in clinical trials for IRDs, the reader is referred to Amato et al. (2021) and Michalakis et al. (2021).

The ethics of gene-based therapies

Using gene-based therapies raises ethical, legal, and social implication (ELSI) questions. Scientists, clinicians, and transnational organizations have highlighted the need to engage diverse stakeholders in developing and using gene-based therapies (Allyse et al., 2019; National Academies of Sciences, 2017; Olson, 2015). Historically, patients and caregivers have been underrepresented and under-engaged in these discussions (Burall, 2018). Overall, more is understood about the attitudes and acceptability of gene-based therapies and genomic editing technologies amongst the public versus amongst patient-specific populations. It is critical to have both patient and public support and a deep understanding of their attitudes, concerns, and information needs if gene-based technologies are to be adopted and implemented broadly in our society.

A systematic review of the literature (N=41 articles) regarding public opinions and attitudes toward gene therapy and gene editing found that perceptions of these technologies were largely positive, especially for medical treatment and the amelioration of disease (Delhove et al., 2020). Not surprisingly, the public perceives somatic gene-based therapy as less controversial and more acceptable than germline gene-based therapy (Delhove et al., 2020). This topic has received considerable attention after the 2018 groundbreaking news of a biophysicist in China who genetically edited the embryos of two twin girls at the *CCR5* gene to confer human immunodeficiency virus (HIV) resistance (Allyse et al., 2019; Delhove et al., 2020). After this event, many renowned scientists and

organizations called for a global moratorium on heritable genome editing (E. Lander et al., 2019).

Across the literature, common themes have emerged regarding public opinions and attitudes toward gene-based therapies, including perceived risks, the success rate of the technology/treatment, length of benefit, treatment specifics (e.g., the reason for using the technology, the condition treated and its severity, method of delivery, and more), and various moral and ethical issues (e.g., interfering with nature or "playing God") (Delhove et al., 2020). All in all, it is vital to continue to understand both the attitudes and ethical concerns raised by gene-based technologies in order to, as a scientific community, address the most salient questions and information needs raised by public and patient populations, as their support and understanding of such treatments are foundational to the uptake of technology in society.

Attitudes and information needs regarding gene-based therapies

There is a paucity of information regarding the attitudes and informational needs of individuals affected by IRDs and their caregivers toward gene therapy and gene editing (Hoffman-Andrews et al., 2019; Mack et al., 2021; Pagliarulo et al., 2021). An attitude is operationally defined as the general evaluation that an individual holds regarding a particular topic or issue, while an information need is operationally defined as an understanding that one's knowledge is inadequate to satisfy the goals they have in understanding or applying information (Eaton & Visser, 2008; Ormandy, 2011). The literature that does exist regarding this topic has been primarily qualitative and focused on

individuals with trisomy 21 (T21), trisomy 13 (T13), trisomy 18 (T18), or sickle cell disease (SCD) (Michie & Allyse, 2019; Persaud et al., 2019; Riggan et al., 2020; Sharma et al., 2021; Snure Beckman et al., 2019). However, a handful of studies have focused on the IRD community (Hoffman-Andrews et al., 2019; Mack et al., 2022; Napier et al., 2021).

A study by Snure Beckman and colleagues reported findings from 27 qualitative interviews of parents recruited through advocacy organizations of people with T21, T13, and T18 about their attitudes toward gene editing (Snure Beckman et al., 2019). They found that participants were concerned with the morality of potential gene editing and the possibility that the treatment may change the child's identity. However, they expressed mixed feelings about the technology because they indicated optimism about the possible alleviation of life-threatening health issues and cognitive improvements.

A similar study by Michie and Allyse (2019) took a quantitative survey-based approach, in which they asked 532 family members of individuals with Down Syndrome (DS) about their views toward five different hypothetical scenarios that currently exist or are being researched for the treatment of DS symptoms. Three of the five hypothetical scenarios depicted future interventions, one of which was a genome-based intervention that could prenatally silence the extra chromosome 21. In contrast, the other two hypothetical interventions significantly altered the cognitive symptoms of DS in pediatric and adult patients, respectively. The authors found that most participants supported approving the hypothetical interventions, but that interestingly, the participant's lived experience with T21 and their perceived quality of life significantly influenced their

assessment of the prenatal genetic and pediatric cognitive interventions specifically, compared to their appraisals of adult intervention scenarios (Michie & Allyse, 2019).

One additional study focused on individuals affected by a trisomy was a qualitative analysis of responses to the open-ended questions of 2 of the hypothetical scenarios from the Michie and Allyse (2019) study (Riggan et al., 2020). The two scenarios included were the hypothetical future interventions focused on prenatal silencing of the extra 21st chromosome and the intervention focused on improving cognitive symptoms in a pediatric population. Like the previous studies, participants expressed mixed views, with a desire to improve their quality of life and simultaneous concerns over safety, personality changes, and long-term benefits (Riggan et al., 2020). A significant limitation of these three studies focused on individuals with various trisomies is that these conditions are not frontline candidates for gene-based therapies, making interpretation of the results challenging and limiting their generalizability to other populations.

Aside from studies focused on individuals with trisomies, some research has surveyed individuals within the sickle cell disease (SCD) community. A unique study by Persaud and colleagues (2019) surveyed 110 patient, caregiver, and physician stakeholders about their attitudes toward somatic genome editing in a mixed-methods study that utilized an educational video tool, an online survey, and follow-up focus groups. Overall, participants were excited and hopeful about the impact of gene editing on disease courses but also expressed concerns about safety, the need for long-term research on outcomes, and access and equity. Of importance, physician stakeholders in this study reported that

members of the SCD community often come to them for information on new and experimental treatments. This was underscored by participants reporting how little they felt they knew about gene editing prior to the study and their desire to be meaningfully engaged in discussions, ultimately highlighting information needs in this community.

Findings from a survey-based study of patients with SCD and their caregivers published by Sharma and colleagues (2021) demonstrated similar themes in terms of results. They highlighted that participants reported minimal knowledge about gene therapy treatments and sub-optimal communication from the medical community about potential treatments. This study also assessed health literacy in participants but interestingly found no association between health literacy levels and gene therapy knowledge (Sharma et al., 2021). This finding stands in contrast to previous research that has highlighted the importance of health literacy in communicating and understanding genomic information, thus warranting further investigation of this relationship (Hurle et al., 2013; Kaphingst et al., 2016). Overall, the results of studies in the SCD community underscore the importance of investigating attitudes and informational needs of patient communities regarding gene-based therapies, but of note, may be limited in their generalizability to other patient populations due to potentially remaining mistrust towards the medical community amongst the SCD community based on their historical mistreatment and marginalization.

Fewer studies within the existing literature have focused on attitudes and informational needs amongst individuals or caregivers in the IRD community specifically.

In 2019, Hoffman-Andrews and colleagues published a study detailing the findings of their qualitative interview-based study in which they interviewed 17 individuals recruited from advocacy organizations with either RP or LCA about their experience with and attitudes towards blindness and somatic and germline gene editing (Hoffman-Andrews et al., 2019). Overall, participants in this study acknowledged the potential benefits of gene editing in general, but their views on its application for treating IRDs were mixed and influenced by their own lived experiences with blindness. For example, those with later-onset blindness were more positive about gene editing for IRDs than those with earlier-onset blindness. Of note, several participants mentioned quality of life (QoL) as an essential factor in determining the availability of gene editing for a particular condition.

Additional concerns about the technology included adequate informed consent and social implications of having such a treatment, such as a fear of eliminating blindness in society or limiting the resources of blind individuals because a "cure" exists. The latter concern parallels other disability communities, including the Deaf community, which has expressed concern over using cochlear implants in children for similar reasons (Crouch, 1997; Most et al., 2007). The primary future direction recommended by Hoffman-Andrews and colleagues (2019) was to continue similar research with larger and more diverse samples.

A recent study published by Mack and colleagues (2022) reported findings from a quantitative survey-based study that assessed knowledge, attitudes, and perceptions of genetic therapies and their associations with demographic factors and vision-related QoL

in 681 individuals with IRDs and caregivers. Their study is the first to use a survey instrument called the Attitudes to Gene Therapy for the Eye (AGT-EYE) Tool specifically designed and validated in an IRD population to assess knowledge and attitudes regarding gene therapy. The AGT-EYE was developed through a multi-stage process in collaboration with expert ophthalmologists subspecializing in IRDs and clinical geneticists. Additionally, individuals in the community living with IRDs helped to develop the measure, pilot it, and increase content validity as a part of focus groups. After the initial development of the measure and utilization in an Australian population of individuals with an IRD, item response theory was used to assess the measure's psychometric properties.

Another study strength is the large sample recruited through various methods, including email and traditional mail campaigns to a national IRD registry, patient support groups, ophthalmology clinics, and hospitals via social media. Aligned with their hypotheses, they found that the vast majority (91.6%) of participants felt optimistic about potential gene therapy treatments and indicated they would undergo treatment if eligible, but that very few participants (28.3%) felt knowledgeable about gene therapy (Mack et al., 2022). Knowledge gaps among participants were primarily related to the methods and outcomes of treatment and how to find credible sources of information, which indicate a high need for information (Mack et al., 2022). This study did not find a significant relationship between vision-related QoL and attitudes toward gene therapy. Thus, further exploration of this relationship is warranted, given that participants in the study by Hoffman-Andrews and colleagues (2019) reported QoL to be an important factor when

considering gene editing and given that patients with IRDs have significantly lower QoL scores on validated measures (Schofield et al., 2022).

Lastly, Napier and colleagues (2021) reported on a qualitative-based study of 10 young adults with LCA who participated in semi-structured interviews about their attitudes toward gene therapy. Most agreed that they would enroll in treatment if given the opportunity. Several complex and important factors emerged in their hypothetical decision-making process, including trust, perception of risk and safety, self-acceptance, and identity**.**

Taken together, the literature regarding attitudes and information needs towards gene therapy amongst individuals in the trisomy, SCD, and IRD communities have highlighted the importance of including the voices of individuals living with a disability or genetic condition in discussions about potential gene-based therapies as their attitudes may differ from the general population or the prevention-oriented mindset of the medical community. However, the existing literature is limited methodologically because most studies have been qualitative, limiting sample size and the type of data that is collected; have rarely used validated interview or survey instruments; and have relied primarily on convenience sampling with patient advocacy organizations, which limits the generalizability of findings and may bias results due to the typically higher education, socioeconomic status, and involvement in research that are more common in individuals who are active in patient organizations.

Furthermore, additional research is needed to expand our understanding of patient information needs related to genetics and gene therapy. Within the existing literature, it is well established that web-based resources have become a primary, if not the dominant, source of patient information (Mack et al., 2022; McKibbin et al., 2014; Van De Belt et al., 2013). Despite the dominance of web-based resources, one study that evaluated ten online resources specific to ocular gene therapy found that the information was typically of low quality, above the reading level of the general population, and varied significantly between sources (Davuluri et al., 2021). Similarly, an interview-based study of 50 participants with IRDs found that participants had a variable and typically poor understanding of concepts surrounding genetics, genetic testing, and genetic counseling (McKibbin et al., 2014). Despite this, participants were keen to have more information accessible to those with visual impairment and from preferred sources such as trusted advocacy organizations and healthcare professionals (McKibbin et al., 2014). Together, these findings highlight the unmet informational needs of the IRD community and the importance of work in this area to best provide optimal patient care.

Present study

Accordingly, the present mixed-methods survey-based study was designed to explore the attitudes and information needs regarding gene therapy of individuals with IRDs and their caregivers. This study aimed to address several of the significant limitations of the extant literature, including methodological and sample limitations, and to expand the research in this area to understand attitudes towards gene therapy and specific patient

information needs in this domain. Mixed-methods research designs involve the use of both quantitative and qualitative data in a study, providing researchers the ability to, "enrich their results in ways that one form of data does not allow" (Hanson et al., 2005). For example, a mixed-methods study allows a research team to still generalize findings from a sample to a population given the advantages that quantitative data provides regarding sample size, whilst simultaneously gaining a fuller understanding of topics of particular interest (e.g., with open-ended questions embedded in a survey or via focus groups). Indeed, Hanson and colleagues (2005) were precise in saying that, "results of precise, instrument-based measurements, may, likewise, be augmented by contextual, field-based information" through mixed-methods studies, as this type of research-design has seen significant growth in its use in the past decade (Johnson & Onwuegbuzie, 2004).

METHODS

Ethical Compliance

The Institutional Review Board (IRB) at the University of California, Irvine (UCI) approved this research and classified it as IRB Exempt, Category 2i (Protocol #1592).

Theoretical Perspective and Objective

This was a mixed-methods study that utilized an online survey of quantitative questions (n = 76) and open-ended qualitative questions (n = 2). Affected individuals and caregivers of affected individuals within the inherited retinal disorders (IRD) community were recruited to examine their attitudes and information needs about gene therapy. Given that a primary limitation in the extant literature is the predominant use of qualitative study designs, thus significantly limiting sample size, we sought to build upon this body of literature with our study design.

Recruitment and Data Collection

To be eligible to participate, participants had to reside in the United States, be 18 years of age or older, and be able to complete the survey in English. No prior genetic diagnosis was required nor confirmed. Individuals with and parents/caregivers of an individual with syndromic and non-syndromic IRDs were eligible to participate.

The survey was distributed through the UCI Qualtrics platform, a secure cloud-based platform for creating and distributing web-based surveys. Recruitment avenues included email, social media, and word-of-mouth through IRD patient support groups,

advocacy organizations serving visually impaired individuals, relevant social media groups and channels, and through local ophthalmology clinicians. Regarding patient advocacy organization and support groups, the survey was distributed by the Foundation Fighting Blindness, the American Council of the Blind, the Choroideremia Research Foundation, Guide Dogs for the Blind, Hope in Focus, and the Usher Syndrome Coalition. Participants were not compensated for their participation.

For participants who could not complete the survey online and could not obtain assistance from a caregiver, family member, or friend, the option to complete the survey over the phone verbally with a research assistant was provided. Only 3 such responses were collected this way, and these responses were marked accordingly in the data set.

Over a 12-week period (November 4, 2022, and January 31, 2023), individuals aged 18 years or older with an IRD and parents/caregivers (over the age of 18) who are the caregiver of an individual with an IRD of any age participated in this anonymous online survey.

Survey Design

The aim when designing the survey was to ensure that the survey was accessible, perceivable, operable, understandable, and robust for individuals with a range of visual abilities, as suggested by WCAG 2.0 Guidelines (Web Content Accessibility Guidelines 2.0, 2023). For example, font size, navigation buttons, and a consistent ordering of responses to questions were considered, among other considerations. The survey instrument adhered to all accessibility guidelines set forth by the Qualtrics platform (Qualtrics, 2023).

The survey was tested with desktop and mobile screen reader technology (e.g., Apple VoiceOver). Further, the survey was pilot tested by ten lay individuals, the research team, and individuals in leadership positions at the Choroideremia Research Foundation.

Survey Instruments and Scoring

A battery of survey instruments, including previously validated questionnaires and non-validated questionnaires developed by the research team, were included in the survey to fulfill the study objective. A complete copy of the survey instrument as it appears from the affected individual's perspective, including branch/skip logic, is located in Appendix A. The caregiver version of the survey is identical, with minor adaptations to fit the caregiver's perspective. For all validated measures, permission was obtained to use the instrument and to adapt the instrument language and verbiage to fit the caregiver's perspective. Caregivers were asked to provide their own responses to survey questions rather than the response they felt their dependent would give, unless otherwise noted.

Demographics

Demographic questions included information about participant's age, gender, highest level of education, marital status, annual household income, racial and ethnic identity, primary language, religion, primary IRD diagnosis, whether a genetic test was used to confirm the diagnosis, details of first symptoms, whether an accessibility aid was used to complete the survey, and how the individual learned of the survey. Participants were also asked whether they had already received gene therapy as part of a clinical trial or an FDA-approved treatment. Caregivers were asked to respond to demographic

questions with their own demographic information, except for specific demographic questions that asked the caregiver for direct information about their dependent's condition and treatment.

Gene Therapy Education

Following the demographics portion of the survey, participants were provided brief, written information about gene therapy. Educational information included an overview of the technology and how it works, as well as its current clinical use. (Appendix B).

Attitudes to Gene Therapy for the Eye (AGT-EYE) tool

The previously validated 22-item Attitudes to Gene Therapy for the Eye (AGT-EYE) tool was utilized, with permission, to assess attitudes toward gene therapy (Mack et al., 2021, 2022; McGuinness et al., 2022). The AGT-EYE was developed through a multi-stage process in collaboration with expert ophthalmologists subspecializing in IRDs and clinical geneticists. Additionally, individuals in the community living with IRDs helped to develop the measure, pilot it, and increase content validity as a part of focus groups. After the initial development of the measure and utilization in an Australian population of individuals with an IRD, item response theory was used to assess the measure's psychometric properties. This assessment demonstrated strong item reliability. Responses to the AGT-EYE are rated on a five-point Likert scale ranging from 1 (Strongly disagree) to 5 (Strongly agree). Detailed scoring and interpretation guidelines can be found in Mack et al. (2021) and Mack et al. (2022).

The 22-item measure comprises six thematic subscales, including a) sources of information, b) knowledge of gene therapy methods, c) awareness of potential gene therapy outcomes, and d) perceived value of treatment. AGT-EYE items 4, 6, 7, 8, 12, and 16 were reverse coded prior to subscale quantitation in accordance with the scoring guidelines. Mean subscale scores range from 1-5. In this study question 2, which comprises subscale A (sources of information), was asked in a yes or no format instead of as a Likert type question on a scale of 1 to 5 and thus the subscale A score was not computed. For subscales B (knowledge of methods) and C (awareness of outcomes), higher scores represent greater knowledge and awareness. For subscale D (perceived value), higher scores represented a higher perceived value of having gene therapy.

Closed and open-ended question(s) regarding attitudes to gene therapy

After completing the portion of the survey with the AGT-EYE tool, participants were asked to respond yes or no to a question asking whether they would receive a gene therapy treatment now if it were offered for their condition, and they were also provided with an open-ended text box and prompted to share additional thoughts or concerns that remained.

Information Needs and Preferences Scale

The research team developed a series of 7 questions assessing participant information needs and preferred sources of information for inclusion in the survey. Several of these questions were adapted from a study by Pagliarulo and colleagues (2021). The content of the questions included participants' preferred sources of information, sources

from which they had previously received information, and the types of information that participants most desired. For each question, participants were provided with either a list of information sources or a list of types of information and asked to select all options that applied to them. The final question provided participants with an open-ended text box and prompted them to share any additional thoughts and concerns related to their information and education needs.

Brief Health Literacy Screen (BHLS)

The BHLS is a validated 3-item measure widely utilized to assess health literacy accurately and quickly (Chew et al., 2004). Psychometrically, the BHLS has acceptable reliability (α 0.74-0.80) and validity. The instrument consists of the following questions: 1) How often do you have someone help you read hospital materials?; 2) How confident are you filling out medical forms by yourself?; 3) How often do you have difficulty learning about your medical condition because of difficulty understanding written information?. Responses to questions 1 and 3 are on a 5-point response scale of always, to sometimes, to often, to occasionally, to never. Responses to question two are on a 5-point response scale of extremely, to quite a bit, to somewhat, to a little bit, to not at all. To score the measure, item 2 is reverse-scored, and the responses to all three items are summed subsequently. Scores range between 3 and 15, with higher scores indicating higher subjective health literacy.

Given the nature of visual impairment in the IRD population and the focus of the questions on reading and writing, the following words were adapted in each question, with

permission of the scale's authors, in order to make the questions more appropriate for a visually impaired population: 1) the word "read" was changed to "understand"; 2) the phrase "filling out" was changed to "completing"; 3) the phrase "written information" was changed to "informational resources". Additionally, the following preface was provided before participants responded to the questions, with permission of the scale's authors: "Think about your ability to understand these materials after the use of any supportive devices or technologies, such as a screen reader, and after working with any caregivers that assist you."

National Eye Institute (NEI) Visual Functioning Questionnaire 25 (VFQ-25)

The NEI-VFQ 25 is a validated 25-item self-report outcome measure widely used in clinical trials and among ophthalmologic specialists to measure QoL related to visual impairment and functioning specifically (Mangione et al., 2001). Psychometrically, the NEI-VFQ 25 has demonstrated acceptable reliability (α 0.71-0.85) and validity. Complete scoring details and guidelines, including creating a composite score and 12 sub-scale specific scores, are detailed online. Caregivers were asked to report on the quality of life of the person they care for, and not their own quality of life.

Data Approach & Aims

Data management and statistical analyses were completed using SPSS version 27. Surveys responses that did not include completed eligibility criteria, surveys missing all data, surveys that only included the demographics measure, and respondents that indicated their condition was a "macular degeneration" or "age-related macular

degeneration (AMD)" were removed prior to data analysis. Additionally, cases with a completion of the survey in less than or equal to 180 seconds were deemed unreliable and removed.

The primary aim of this study is to describe attitudes towards gene therapy, informational needs and preferences related to gene therapy, health literacy, QoL, and respondent demographic characteristics. The secondary aim of this study is to explore how attitudes towards gene therapy, informational needs and preferences related to gene therapy, health literacy, and QoL vary based on demographic factors. These aims were further broken down into a series of specific objectives, which were completed using descriptive statistics and inferential tests.

For the primary aim, continuous variables were described using means, standard deviations, and in some cases interquartile ranges; categorical variables were described using frequencies and percentages. For the secondary aim, inferential analyses were used to compare participant characteristics and scores on the different measures. Independent-Samples t-tests were used to compare the means of binary groups for continuous normally distributed variables. One-way Analysis of Variance (ANOVA) was used to compare the means of continuous variables when there were more than two groups. Chi-Square tests were used to examine the difference between categorical variables. Pearson's correlation coefficient was used to measure the statistical association between continuous variables. Binary logistic regression was used to assess how well a continuous independent variable predicted a categorical dependent variable, as well as to determine the goodness-of-fit of

the model. While analysis of the qualitative data was not a part of the primary or secondary aim of the study, the responses to the 2 open-ended qualitative questions in the survey which asked participants about additional concerns related to gene therapy or informational needs were coded by the lead research and a research assistant. A brief presentation of several observed qualitative themes is presented in the results section, accompanied by illustrative quotes.

RESULTS

Participants

A total of 739 respondents began the survey. After removing ineligible responses, 689 participants were available for analysis, most of whom were adults with an IRD (*n* = 652 adults with an IRD, *n* = 37 caregivers). Participants were not required to respond to each question in the survey. Thus, the total number or percentage of participants reported for each analysis varies based on how many participants answered that question.

Participant characteristics are shown in Table 1. For the respondents who were adults with an IRD, the majority were age 50 or older (*n* = 422, 65%), half were female (*n* = 326, 50%), and retinitis pigmentosa was the most common diagnosis (*n* = 338, 52%), followed by macular dystrophy (*n* = 89, 14%). The 37 caregivers responding (5%) were younger (*n* = 20, 54%, below age 50), predominantly female (*n* = 31, 84%), and retinitis pigmentosa was the most common diagnosis among their dependents (*n* = 11, 30%), followed by juvenile macular dystrophy (*n* = 6, 16%), choroideremia (*n* = 6, 16%), and Leber congenital amaurosis (LCA) (*n* = 5, 14%). Due to the small number of caregivers responding, between-group comparisons of affected individuals and caregivers using inferential statistics were not performed due to the large discrepancy between the sample sizes and related concerns of power. However, the responses of both groups across all variables are described simultaneously to show the similar trend in responses.

The majority of adults with an IRD reported that symptom onset occurred at 18 years of age or older (*n* = 364, 56%). Most said that their condition was non-syndromic (*n* =

522, 80%) and that their diagnosis had been confirmed by a genetic test (*n* = 516, 79%). The vast majority had not received gene therapy, either as a part of a clinical trial (*n* = 616, 95%) or an FDA-approved treatment (*n* = 640, 98%). Twenty-six adults with an IRD (4%) had received a gene therapy treatment as a part of a clinical trial, and only three adults with an IRD (1%) had received an FDA-approved gene therapy treatment. As expected, caregivers reported earlier symptom onset, with 84% of caregivers (*n* = 31) indicating that their dependent was symptomatic before 18 years of age and nearly 30% of the sample indicating that their dependent was symptomatic within the first year of life (*n* = 11, 30%). This was expected because while the survey was open to caregivers with dependents of any age, most of the caregivers were responding related to their child (*n* = 30, 81%). 81% of caregivers (n = 30) reported that their dependent's condition was non-syndromic. Only two dependents had received gene therapy as a part of a clinical trial (5%), and no dependents had received gene therapy as a part of an FDA-approved treatment. Given that individuals with RP made up more than half of the sample, a separate graph showing the age of symptom onset for these individuals is shown in Figure 2.

The majority of respondents had a bachelor's degree or higher (*n* = 366 adults with an IRD, 56%; *n* = 27 caregivers, 73%), were married (*n* = 405 adults with an IRD, 62%; *n* = 30 caregivers, 81%), earned $50,000 or more in annual household income (*n* = 368 adults with an IRD, 56%; *n* = 29 caregivers, 78%), and were Christian (*n* =364 adults with an IRD, 56%; *n* = 24 caregivers, 65%). Most respondents were white (*n* = 525 adults with an IRD, 81%; *n* = 33 caregivers, 89%) and spoke English as the primary household language (*n* =

588 adults with an IRD, 90%; *n* = 35 caregivers, 95%). Spanish was the next most common household language for individuals for whom English was not the primary household language (*n* = 9, 1%). Comparatively, in the general U.S. population 34% of individuals surveyed had a bachelor's degree or higher, about 50% were married, 71% identified as Christian, 76% were White, and 22% spoke a language other than English at home with Spanish being the next most common household language (U.S. Census Bureau, 2022). Thus, the sample in the current study reported higher levels of factors related to socioeconomic status.

Participants mainly found out about the survey through patient advocacy organizations and research groups (*n* = 505 adults with an IRD, 78%; *n* = 27 caregivers, 73%) despite targeted recruitment efforts on behalf of the research team to recruit more individuals from ophthalmology clinics and providers directly. Overall, 4% of individuals with an IRD (*n* = 28) and 5% of caregivers (*n* =2) heard about the survey through a healthcare provider. Twenty-two of these individuals and caregivers indicated that they were not actively part of a patient advocacy organization or research group, thus limiting the likelihood that they would have otherwise learned of the survey. With regards to accessibility aids, 32% of individuals with an IRD (*n* = 207) stated that they used an accessibility aid to complete the survey, with screen readers (*n* = 96, 46%) and screen magnifiers (*n* = 49, 24%) most used by these individuals.

Table 1. *Participant Demographic Information*

	Respondent status	
	Adult patient (*n* = 652)	**Caregiver (*n* = 37)**
Age, years, *n* (%)		
18 to 25	14 (2%)	0 (0%)
25 to 34	41 (6%)	4 (11%)
35 to 44	57 (9%)	11 (30%)
44 to 49	68 (10%)	5 (14%)
50 to 59	136 (21%)	9 (24%)
60 to 69	177 (27%)	2 (5%)
70 and above	109 (17%)	4 (11%)
Prefer not to say	8 (1%)	0 (0%)
Missing	42 (6%)	2 (5%)
Gender, *n* (%)		
Man	279 (43%)	4 (11%)
Woman	**326 (50%)**	**31 (84%)**
Transgender	1 (0.2%)	0 (0%)
Prefer not to say	1 (0.2%)	0 (0%)
Missing	44 (7%)	2 (5%)
Highest level of education completed, *n* (%)		
High school	47 (7%)	0 (0%)
Some college	100 (15%)	5 (14%)
Associate's degree	69 (11%)	2 (5%)
Bachelor's degree	184 (28%)	15 (41%)
Master's degree or above	182 (28%)	12 (32%)
Another level of education	20 (3%)	1 (3%)
Prefer not to say	5 (1%)	0 (0%)
Missing	45 (7%)	2 (5%)
	Adult patient	**Caregiver**
Marital Status, *n* (%)		
Married	**405 (62%)**	**30 (81%)**
Single	103 (16%)	2 (5%)
Divorced/Separated	70 (11%)	2 (5%)
Widowed	23 (4%)	1 (3%)
Prefer not to say	4 (1%)	0 (0%)
Missing	47 (7%)	2 (5%)

Table 1 continued. *Participant Demographic Information*

	Respondent Status	
	Adult patient (*n* = 652)	**Caregiver (*n* = 37)**
Annual household income, *n* (%)		
Less than $25,000	46 (7%)	0 (0%)
$25,000 to $50,000	96 (15%)	1 (3%)
$50,000 to $100,000	157 (24%)	4 (11%)
$100,000 to 200,000	137 (21%)	16 (43%)
More than $200,000	74 (11%)	9 (24%)
Prefer not to say	91 (14%)	5 (14%)
Missing	51 (8%)	2 (5%)
Racial and ethnic identity[a], *n* (%)		
White or Caucasian	**525 (81%)**	**33 (89%)**
Native American	6 (1%)	0 (0%)
Asian or Asian American	18 (3%)	0 (0%)
Latinx or Hispanic	44 (7%)	1 (3%)
Black or African American	15 (2%)	0 (0%)
Middle Eastern/North African	3 (1%)	0 (0%)
Another identity	6 (1%)	0 (0%)
Prefer not to say	12 (2%)	1 (3%)
Missing	48 (7%)	2 (5%)
	Adult patient	**Caregiver**
Religion, *n* (%)		
Christian	**364 (56%)**	**24 (65%)**
Jewish	21 (3%)	2 (5%)
Muslim	3 (1%)	0 (0%)
Buddhist	2 (0.3%)	0 (0%)
Atheist	20 (3%)	1 (3%)
Agnostic	33 (5%)	1 (3%)
Not religious	102 (16%)	6 (16%)
Hinduism	1 (0.2%)	0 (0%)
Another religion	14 (2%)	0 (0%)
Prefer not to say	35 (5%)	1 (3%)
Missing	57 (9%)	2 (5%)

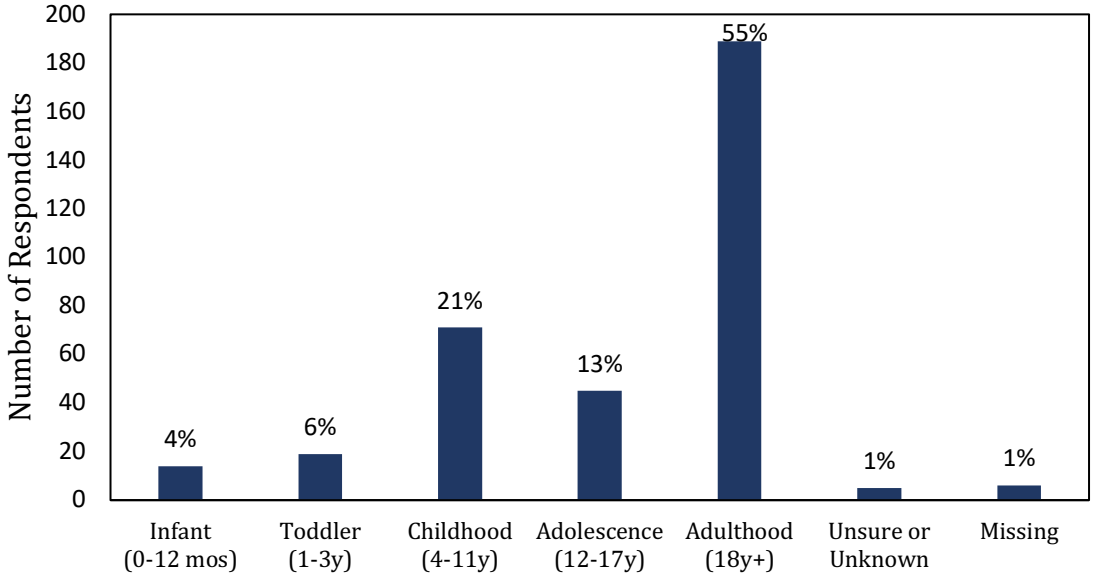
[a]Percentages for this variable will not add to 100% because participants were allowed to select more than one racial/ethnic identity

Table 1 continued. *Participant Demographic Information*

	Respondent status	
	Adult patient (*n* = 652)	**Caregiver (*n* = 37)**
Type of IRD, *n* (%)		
Retinitis pigmentosa	**338 (52%)**	11 (30%)
Usher syndrome	56 (9%)	4 (11%)
Macular dystrophy	89 (14%)	6 (16%)
Cone rod dystrophy	36 (6%)	0 (0%)
Choroideremia	35 (5%)	6 (16%)
Leber congenital amaurosis	12 (2%)	5 (14%)
X-linked retinoschisis	10 (2%)	1 (3%)
Achromatopsia	5 (1%)	1 (3%)
Bardet-Biedl syndrome	3 (1%)	0 (0%)
Best disease	7 (1%)	0 (0%)
Doyne's honeycomb retinal dystrophy	3 (1%)	0 (0%)
Unsure or unknown	16 (3%)	0 (0%)
Another condition	38 (6%)	3 (8%)
Missing	3 (1%)	0 (0%)
Age of onset, *n* (%)		
Infant (0-12 mos)	43 (7%)	11 (30%)
Toddler (1-3 yrs)	37 (6%)	5 (14%)
Child (4-11 yrs)	107 (16%)	10 (27%)
Adolescent (12-17 yrs)	75 (12%)	5 (14%)
Adult (18 and older)	**364 (56%)**	3 (8%)
Unsure or unknown	16 (3%)	3 (8%)
Missing	10 (2%)	0 (0%)

Items in bold indicate ≥50% of responses.

Figure 2. Age of Symptom Onset for Individuals with RP



Attitudes Towards Gene Therapy

The vast majority of participants indicated that they would receive a gene therapy treatment now if it were offered as a treatment for their IRD (n = 590, 91%; Figure 3A) or for their dependent's IRD (n = 36, 97% of caregivers; Figure 3B). Participant interest in receiving gene therapy was analyzed for differences between categorical groups of select respondent characteristics with Chi-Square analyses (Table 2). There was a significant relationship between interest in receiving gene therapy if it were offered now and age of symptom onset when comparing individuals who experienced symptom onset in infancy to all other individuals, with those who experienced onset during infancy less likely to indicate they would take gene therapy, $X^2(1, 618) = 5.21$, $p = 0.02$. However , there was not a significant relationship when comparing interest among all six symptom onset categories

(infant, toddler, child, adolescent, adult, unsure/unknown), $X^2(5, 618) = 5.31$, $p = 0.38$, or when comparing individuals who were 18 an older to those who were younger than 18, $X^2(1, 603) = 0.41$, $p = 0.52$. There was not a significant difference in the interest of receiving gene therapy between individuals who had a syndromic condition versus individuals who had a non-syndromic condition $X^2(2, 621) = .35$, $p = 0.84$. When comparing individuals with RP, a group that made up over half of the sample of affected individuals, to all other diagnoses, there was a significant relationship, and individuals with RP were more likely to indicate they would receive gene therapy now if it were available compared to individuals with other diagnoses, $X^2(1, 625) = 4.92$, $p = 0.026$. There was not a significant difference in health literacy scores (BHLS scale) for individuals who were interested in receiving gene therapy now compared to those who were not, $t(608) = -0.82$, $p = 0.75$, and there was also not a significant difference between quality of life scores for the two groups, $t(607) = 3.60$, $p = 0.21$. *Responses* to the AGT-EYE scale are further detailed below.

Figure 3A. Percentage of Adults with an IRD that would and would not receive gene therapy if it were offered now

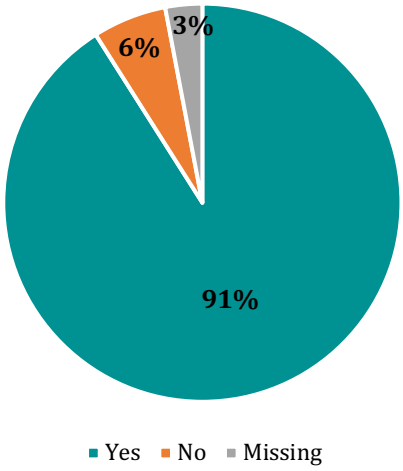


Figure 3B. Percentage of Caregivers who would want their dependent to receive gene therapy if it were offered now

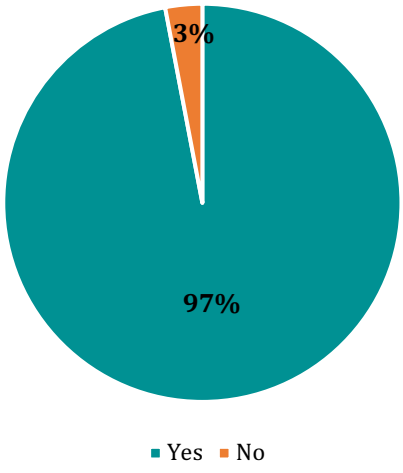


Table 2. *Chi-Square Analyses of Gene Therapy Interest among Select Categorical Variables*

	Participant Interest in Receiving Gene Therapy			
	Yes (*n*)	**No (*n*)**	***p*[a]**	***X*² (*df*)**
Age of Onset (All groups)			0.38	5.31 (5)
Infant	37	6		
Toddler	34	2		
Child	98	5		
Adolescent	68	4		
Adult	330	19		
Unsure or unknown	14	1		
Total	581	37		
Age of Onset (Two Groups)			**0.02**	**5.21 (1)**
Infancy	37	6		
Non-Infancy	544	31		
Total	581	37		
Age of Onset (Two Groups)			0.52	0.41 (1)
18 and older	330	19		
Younger than 18	237	17		
Total	567	36		
Syndromic Condition			0.84	0.35 (2)
Syndromic	75	6		
Non-Syndromic	477	29		
Unsure or unknown	32	2		
Total	584	37		
IRD Type			**0.03**	**4.92 (1)**
Retinitis Pigmentosa (RP)	317	13		
All other conditions	271	24		
Total	588	37		

[a]*p* values from Chi-Square analysis. Analyses that achieved statistical significance ($p \leq 0.05$) are in bold.

Attitudes Towards Gene Therapy for the Eye (AGT-EYE) tool

Collapsed responses to the AGT-EYE scale, including the percentage of responses corresponding to each five-point Likert category and the specific subscale that each AGT-EYE question corresponds to, for both individuals with an IRD and for caregivers, are shown in Table 3. Subscale A of the AGT-EYE, which evaluates sources of information about gene therapy among participants, is excluded from this table because in our study, due to an error in data collection, participants were only asked to mark whether they had or had not received information from each source, instead of being asked to rank each source of information on a five-point Likert scale. The results of question 2, which comprises subscale A, are described directly below and no additional information about the subscale was computed.

Individual items. The vast majority of respondents (*n* = 584, 90% of individuals with an IRD; *n* = 35, 94% of caregivers) agreed or strongly agreed that they understood the difference between a clinical trial and an FDA-approved treatment. However, only 51% of individuals with an IRD (*n* = 331) and 49% of caregivers (*n* = 18) agreed or strongly agreed that they had good knowledge about gene therapy for IRDs. The top three sources of information about gene therapy that participants had received information from were (Subscale A) the internet (n = 335, 51% individuals with an IRD; *n* = 20 54% caregivers), a disease registry (*n* = 337, 58% individuals with an IRD; *n* = 19, 51% caregivers), or their ophthalmologist (*n* = 213, 33% individuals with an IRD; *n* = 15, 41% caregivers).

Subscale B of the AGT-EYE (Table 3) evaluated participants' self-reported knowledge of gene therapy methods. Responses to this subscale showed inconsistent knowledge across questions indicating that participants were not sure of the details of treatment. Over half of the respondents with an IRD (*n* = 373, 57%) and 41% of caregivers (*n* = 15) agreed or strongly agreed that gene therapy was suitable at any stage of life, which is considered incorrect based on the scoring guidelines of this measure (McGuinness et al., 2022) . The next most common response was "neither agree nor disagree" (*n* = 204, 31% of individuals with an IRD; *n* = 12, 32% of caregivers). Nearly half of the respondents with an IRD answered "neither agree nor disagree" when asked if gene therapy is delivered to both eyes (*n* = 290, 45%), which is considered true, while 22% of respondents (*n* = 140) disagreed/strongly disagreed and 33% (*n* = 215) agreed/strongly agreed. The pattern of responses among caregivers was similar but more evenly split amongst each category (see Table 3). However, when asked whether the therapy is injected into the bloodstream through the arm, which is considered false, nearly half of the respondents with an IRD answered, "neither agree nor disagree" (*n* = 309, 47%), while 44% of respondents (*n* = 285) correctly disagreed/strongly disagreed. The majority of caregivers (*n* = 25, 68%) correctly disagreed/strongly disagreed with this question. The majority of participants with an IRD (*n* = 437, 67%) and caregivers (*n* = 26, 70%) correctly disagreed/strongly disagreed that gene therapy and stem cell therapy were not the same treatment.

Subscale C of the AGT-EYE evaluated participants' awareness of potential gene therapy outcomes (Table 3). The correct answers to the questions in this subscale cannot

be fully predicted, as stated in the scoring guidelines from the scale's authors (McGuinness et al., 2022). The responses to the following two questions are considered more likely to be true than false. For these questions, the majority of respondents correctly agreed/strongly agreed that gene therapy for the eye is a treatment that can slow down disease progression (*n* = 496, 76% of individuals with an IRD; *n* = 30, 81% of caregivers) and that the treatment will require many years of follow up with an eyecare provider (*n* = 472, 72% of individuals with an IRD; *n* = 30, 81% of caregivers).

The responses to the following three questions are considered more likely to be false than true. For these questions, less than half of individuals with an IRD (*n* = 291, 44%) correctly disagreed/strongly disagreed with the statement that gene therapy for the eye can restore vision back to normal. In contrast, the majority of caregivers correctly disagreed/strongly disagreed (*n* = 22, 59% of caregivers). The majority of respondents correctly disagreed/strongly disagreed that their privacy would be breached if they underwent gene therapy treatment (*n* = 453, 70% of individuals with an IRD; *n* = 28, 76% of caregivers). The majority also knew that undergoing gene therapy treatment would mean they could still pass their genetic condition to future offspring (*n* = 463, 71% of individuals with an IRD; *n* = 29, 78% of caregivers).

Participants that agreed/strongly agreed with the statement that gene therapy can slow down disease progression (*n* = 496, 76% of individuals with an IRD; *n* = 30, 81% of caregivers) and with the statement that gene therapy for the eye can restore vision back to normal (*n* = 68, 10% of individuals with an IRD; *n* = 5, 14% of caregivers) are considered to

have positive expectations of outcomes to gene therapy treatment. There is a large disparity in the percentage of respondents that agreed with the latter statements. It is possible that, as the authors of the measure suggested, agreement with these items reflects positive expectations of outcomes. Still, it is also possible that this sample of participants is well-educated about the current progress and results of ongoing gene therapy trials, most of which do not suggest a complete restoration of vision, and are expressing realistic optimism for symptom improvement but not a cure.

Subscale D of the AGT-EYE (Table 3) focused on the perceived value of gene therapy treatment, specifically with regard for economic factors. The majority of respondents agreed or strongly agreed that government subsidy of gene therapy treatment would be an effective use of taxpayer money (*n* = 412, 63% of individuals with an IRD; *n* = 30, 81% of caregivers) and that their private health insurance should pay all the costs of their gene therapy treatment (*n* = 364, 56% of individuals with an IRD; *n* = 23, 62% of caregivers). However, participants were in less agreement that the government should pay all costs associated with their gene therapy treatment (*n* = 191, 29% of individuals with an IRD agreed/strongly agreed; *n* = 18, 49% of caregivers agreed/strongly agreed). Most participants agreed or strongly agreed that they would consider traveling to another state to access a gene therapy treatment if it was not available in their state (*n* = 566, 87% of individuals with an IRD; *n* = 35, 94% of caregivers) and the majority would consider a payment plan for their gene therapy treatment (*n* = 423, 65% of individuals with an IRD; *n* = 30, 81% of caregivers).

Table 3. *Collapsed response frequencies to the items of the AGT-EYE*

Subscale	Item		Response, *n* (%)		
			Agree/ strongly agree	**Neither agree/ disagree**	**Disagree/ strongly disagree**
B. Knowledge of methods	1	I have good knowledge about gene therapy for inherited retinal diseases	**AFD: 331 (51)** CGV: 18 (49)	AFD: 159 (24) CGV: 8 (22)	AFD: 159 (24) CGV: 11 (30)
	3	I understand the difference between an experimental treatment provided in a clinical trial and a treatment that has already been approved by the FDA or American government.	**AFD: 584 (90)** **CGV: 35 (95)**	AFD: 31 (5) CGV: 1 (3)	AFD: 32 (5) CGV: 1 (3)
	4 (F)	*Gene therapy for the eye is suitable at any stage of a person's life.*	**AFD: 373 (57)** CGV: 15 (41)	AFD: 204 (31) CGV: 12 (32)	AFD: 71 (11) CGV: 19 (27)
	5 (T)	Generally, gene therapy for inherited retinal disease is delivered to both eyes.	AFD: 215 (33) **CGV: 22 (59)**	AFD: 290 (45) CGV: 10 (27)	AFD: 140 (22) CGV: 12 (32)
	6 (F)	*Gene therapy for the eye is injected into the blood stream through the arm.*	AFD: 47 (7) CGV: 1 (3)	AFD: 309 (47) CGV: 11 (30)	AFD: 285 (44) **CGV: 25 (68)**
	7 (F)	*Gene therapy and stem cell therapy are the same treatment.*	AFD: 33 (5) CGV: 4 (11)	AFD: 174 (27) CGV: 7 (19)	**AFD: 437 (67)** CGV: 26 (70)
C. Awareness of potential outcomes	8 (F)	*Gene therapy for the eye can restore vision back to normal.*	AFD: 68 (10) CGV: 5 (14)	AFD: 283 (43) CGV: 10 (27)	AFD: 291 (45) **CGV: 22 (60)**
	9	Gene therapy for the eye is a treatment that may slow down the disease.	**AFD: 496 (76)** **CGV: 30 (81)**	AFD: 127 (20) CGV: 6 (16)	AFD: 17 (3) CGV: 1 (3)
	10	Treatment complications to my eyes, such as permanent blindness, are possible with an approved gene therapy.	**AFD: 364 (56)** **CGV: 25 (68)**	AFD: 225 (35) CGV: 9 (24)	AFD: 49 (8) CGV: 3 (8)
	11	Gene therapy in my eye may have side effects elsewhere in my body.	AFD: 230 (35) CGV: 18 (49)	AFD: 288 (44) CGV: 12 (32)	AFD: 117 (18) CGV: 7 (19)
	12 (F)	*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.*	AFD: 76 (12) CGV: 5 (14)	AFD: 100 (15) CGV: 3 (8)	AFD: 463 (71) **CGV: 19 (78)**

Table 3 continued. *Collapsed response frequencies to the items of the AGT-EYE*

Subscale	Item		Response, *n* (%)		
			Agree/ strongly agree	Neither agree/ disagree	Disagree/strongly disagree
C cont.	13	I may not be eligible for financial or other government benefits if my gene therapy for my eye condition is successful.	AFD: 183 (28) CGV: 7 (19)	AFD: 317 (49) CGV: 17 (46)	AFD: 139 (21) CGV: 13 (35)
	14	Gene therapy for inherited retinal diseases will require many years of follow-up with my eyecare practitioner.	**AFD: 472 (72)** **CGV: 30 (81)**	AFD: 142 (22) CGV: 6 (16)	AFD: 24 (4) CGV: 1 (3)
	15	Receiving gene therapy for my inherited retinal disease means I won't be eligible for future genetic treatments.	AFD: 93 (14) CGV: 4 (11)	AFD: 321 (49) CGV: 16 (43)	AFD: 219 (34) CGV: 17 (46)
	16 (F)	*I will lose my privacy if I undergo gene therapy, and my data will be in the public domain.*	AFD: 40 (6) CGV: 2 (5)	AFD: 145 (22) CGV: 7 (19)	**AFD: 453 (70)** **CGV: 18 (76)**
	17	If I undergo gene therapy, it will affect my eligibility or terms of conditions in life, disability or health insurance in the future	AFD: 44 (7) CGV: 2 (5)	AFD: 281 (43) CGV: 14 (38)	AFD: 317 (49) **CGV: 21 (57)**
D. Value of treatment	18	The government should pay all costs of my gene therapy.	AFD: 191 (29) CGV: 18 (49)	AFD: 258 (40) CGV: 9 (24)	AFD: 188 (29) CGV: 10 (27)
	19	Government subsidy of my treatment would be an effective use of taxpayer money.	**AFD: 412 (63)** **CGV: 30 (81)**	AFD: 162 (25) CGV: 5 (14)	AFD: 63 (10) CGV: 2 (5)
	20	If gene therapy for my condition was not available in my state I would consider traveling interstate to access it.	**AFD: 566 (87)** **CGV: 35 (95)**	AFD: 43 (7) CGV: 1 (3)	AFD: 27 (4) CGV: 1 (3)
	21	My private health insurance should pay all out of pocket costs for my gene therapy.	**AFD: 364 (56)** **CGV: 13 (62)**	AFD: 192 (29) CGV: 12 (32)	AFD: 79 (12) CGV: 2 (5)
	22	I would consider a payment plan for my gene therapy.	**AFD: 423 (65)** **CGV: 30 (81)**	AFD: 157 (24) CGV: 4 (11)	AFD: 55 (9) CGV: 3 (8)

AGT-Eye Items were asked in sequence from 1 to 22. Italicized items are reversed in score calculations for the subscales for consistency of interpretation. Items in bold indicates >50% of responses. Percentages across the columns may not add up to 100 percent because respondents were not required to answer each question. AFD = Affected Patients. CGV = Caregivers. T = Questions considered to be true. F = Questions considered to be false or more likely to be false than true.

AGT-EYE Subscale quantitation and relationship with demographic parameters.

Table 4 shows the mean scores and standard deviations across the AGT-EYE subscales for the individuals with an IRD. Subscale responses ranged from one to five. There were no differences between the AGT-EYE subscale scores between males and females, respondents who had a college degree compared to those who did not, individuals who experienced symptom onset as an adult compared to those who experienced onset before adulthood, and respondents who indicated that they would receive a gene therapy treatment now if it were available for their condition versus those who would not (Table 3). However, when comparing the AGT-EYE Subscale B (Knowledge of Methods) scores for individuals with RP (M = 3.42, SD = 0.43) compared to individuals with any other diagnosis (M = 3.46, SD = 0.48) there was a significant difference $t(647) = -1.06$, $p = 0.03$. There was not a significant difference in the other subscales scores when comparing individuals with RP to individuals with any other diagnosis (Table 4). The inferential analysis did not include the caregiver sample, as described previously, but their subscale scores are described in Table 4. The perceived value of gene therapy subscale (subscale c) was the only subscale with a noticeable difference between the means of the two groups (M = 3.68, SD = 0.58 for individuals with an IRD; M = 4.03, SD = 0.52 for caregivers).

Table 4. *AGT-EYE subscale scores and variations between select respondent characteristics*

	AGT-EYE subscale					
	Methods (Subscale B)		**Outcomes (Subscale C)**		**Value (Subscale D)**	
	Mean (SD)	***p*[a]**	**Mean (SD)**	***p*[a]**	**Mean (SD)**	***p*[a]**
Subscale Score						
Affected	3.43 (0.45)		3.40 (0.32)		3.68 (0.58)	
Caregiver	3.51 (0.44)		3.42 (0.23)		4.03 (0.52)	
Gender						
Male	3.50 (0.46)		3.40 (0.31)		3.75 (0.58)	
Female	3.42 (0.44)	0.78	3.42 (0.33)	0.76	3.65 (0.58)	0.98
Age of Symptom Onset						
18 and older	3.39 (0.46)		3.39 (0.32)		3.66 (0.55)	
Younger than 18	3.50 (0.42)	0.09	3.43 (0.30)	0.46	3.73 (0.59)	0.37
Highest Education						
Associate's degree or less	3.51 (0.45)		3.45 (0.29)		3.73 (0.56)	
Bachelor's degree or above	3.37 (0.42)	0.38	3.36 (0.31)	0.84	3.64 (0.61)	0.34
Diagnosis						
Retinitis Pigmentosa (RP)	3.42 (0.43)		3.41 (0.31)		3.69 (0.61)	
All other conditions	3.46 (0.48)	**0.03**	3.41 (0.34)	0.27	3.68 (0.55)	0.34
Ready to take GT						
Yes	3.44 (0.45)		3.40 (0.33)		3.72 (0.57)	
No	3.40 (0.49)	0.57	3.50 (0.28)	0.28	3.23 (0.60)	0.57

[a]*p* values from Independent Samples T-Test. Analyses that achieved statistical significance ($p \leq 0.05$) are in bold.

Information Needs and Preferences Scale

Participants in this study reported a wide variety of information needs and preferences. When asked to select who they would most like to receive information about gene therapy from a list of sources (Figure 4a), participants most commonly indicated that they would prefer to receive information from a healthcare provider (*n* = 389, 60% of individuals with an IRD; *n* = 26, 70% of caregivers), a patient advocacy or support group (*n* = 99, 15% of individuals with an IRD; *n* = 7, 19% of caregivers), healthcare websites (*n* = 50, 8% of individuals with an IRD; *n* = 1, 3% of caregivers), or pharmaceutical and biotechnology companies (*n* = 38, 6% of individuals with an IRD; *n* = 1, 3% of caregivers). Some participants, albeit fewer, were interested in receiving information from the Foundation Fighting Blindness (FFB) specifically (*n* = 17, 3% of individuals with an IRD), a friend, family member, caregiver or colleague (*n* = 9, 1% of individuals with an IRD; *n* = 17, 46% of caregivers), social media (*n* = 8, 1% of individuals with an IRD), an academic or private research-based institution (*n* = 7, 1% of individuals with an IRD; *n* = 1, 3% of caregivers), non-healthcare websites (*n* = 3, 1% of individuals with an IRD), other media such as TV, radio, or newspaper (*n* = 1, 1% of individuals with an IRD), a government based healthcare institution (*n* = 1, 0=1% of individuals with an IRD), or another source (*n* = 11, 2% of individuals with an IRD). Five individuals with an IRD (1%) expressed that they were not interested in learning about gene therapy.

For participants that indicated they had already received information about gene therapy (Figure 4b), a wide variety of sources were reported including healthcare providers (*n* = 288, 44% of individuals with an IRD; *n* = 19, 51% of caregivers), patient

advocacy or support groups (*n* = 241, 37% of individuals with an IRD; *n* = 18, 49% of caregivers), healthcare websites (*n* = 197, 30% of individuals with an IRD; *n* = 18, 49% of caregivers), pharmaceutical and biotechnology companies (*n* = 129, 20% of individuals with an IRD; *n* = 9, 24% of caregivers), social media (*n* = 96, 15% of individuals with an IRD; *n* = 19, 51% of caregivers), a family member, friend, or colleague (*n* = 105, 16% of individuals with an IRD; *n* = 11, 30% of caregivers), other media such as TV, radio, or newspaper (*n* = 80, 12% of individuals with an IRD; *n* = 5, 14% of caregivers), non-healthcare websites (*n* = 57, 9% of individuals with an IRD; *n* = 5, 14% of caregivers), the FFB (*n* = 29, 4% of individuals with an IRD; *n* = 1, 3% of caregivers), an academic or private research-based institution (*n* = 13, 2% of individuals with an IRD), and government-based healthcare institutions (*n* = 5, 1% of individuals with an IRD. Individuals who indicated they had received information from the FFB reported this through a free-response text box that all participants were shown. Thus, other individuals who have received information from FFB may have selected the 'patient advocacy or support group' response option. A group of participants expressly indicated that they had never received information about gene therapy (*n* = 93, 14% of individuals with an IRD; *n* = 5, 14% of caregivers).

Participants who indicated they had received information about gene therapy from a healthcare provider (*n* = 288, 44% of individuals with an IRD; *n* = 19, 51% of caregivers; HCP) were asked follow-up questions regarding which types of healthcare providers they had received information from and what kinds of information they wished their HCP had discussed that they did not. Of those participants who had already received information from an HCP (Figure 4c), information was mainly received from an ophthalmologist (*n* = 256, 89% of individuals with an IRD; *n* = 17, 89% of caregivers) or a genetic counselor (*n* =

124, 43% of individuals with an IRD; *n* = 6, 32% of caregivers). Fewer participants had received information from other HCPs, including a geneticist (*n* = 27, 9% of individuals with an IRD; *n* = 4, 21% of caregivers), a primary care provider (*n* = 14, 5% of individuals with an IRD; *n* = 2, 11% of caregivers), a nurse practitioner or physician assistant (*n* = 7, 2% of individuals with an IRD), an optometrist (*n* = 4, 1% of individuals with an IRD), or another HCP (*n* = 8, 3% of individuals with an IRD; *n* = 1, 5% of caregivers).

Participants who had already received information wished that their HCP had discussed a variety of topics with them that they did not (Figure 4d), including potential side effects (*n* = 134, 47% of individuals with an IRD; *n* = 9, 47% of caregivers), cost or insurance coverage (*n* = 129, 45% of individuals with an IRD; *n* = 7, 37% of caregivers), general information about the treatment and how it works (*n* = 119, 41% of individuals with an IRD; *n* = 7, 37% of caregivers), the length of benefit (*n* = 113, 39% of individuals with an IRD; *n* = 7, 37% of caregivers), safety (*n* = 111, 39% of individuals with an IRD; *n* = 7, 37% of caregivers), follow-up care (*n* = 106, 37% of individuals with an IRD; *n* = 6, 32% of caregivers), or another topic such as eligibility, information about clinical trials, and potential effects on offspring (*n* = 6, 2% of individuals with an IRD).

All participants were asked to select the top three types of information regarding gene therapy they had the strongest desire or need to receive (Figure 4e). The majority of participants wanted general information about the treatment and how it works (*n* = 429, 66% of individuals with an IRD; *n* = 24, 65% of caregivers), followed by safety (*n* = 364, 56% of individuals with an IRD; *n* = 18, 49% of caregivers), potential side effects (*n* = 357, 55% of individuals with an IRD; *n* = 22, 56% of caregivers), cost or insurance coverage (*n* =

340, 52% of individuals with an IRD; *n* = 16, 43% of caregivers), length of benefit (*n* = 247, 38% of individuals with an IRD; *n* = 17, 46% of caregivers), follow-up care (*n* = 106, 16% of individuals with an IRD; *n* = 4, 11% of caregivers), or another topic including eligibility, effectiveness, effects on offspring, how to access treatment, or information about where the biological components of the treatment were derived from (*n* = 25, 4% of individuals with an IRD; *n* = 3, 8% of caregivers).

Figure 4a. Top three preferred information sources

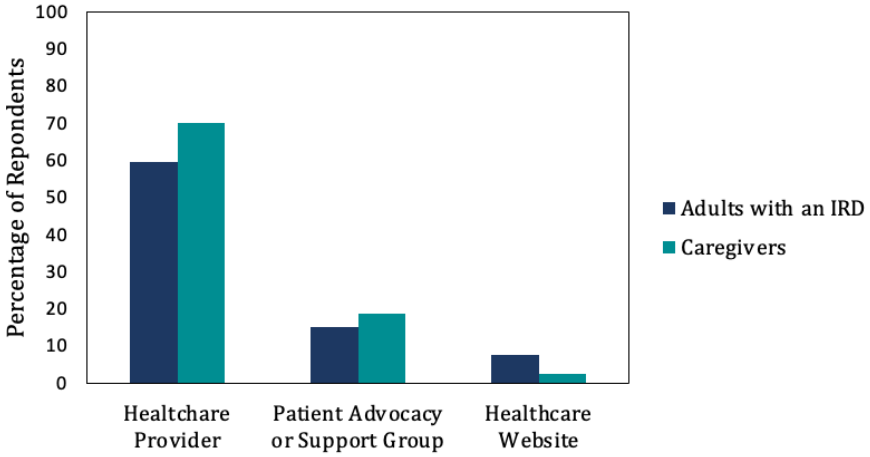


Figure 4b. Top three sources of information for participants who had already learned about gene therapy

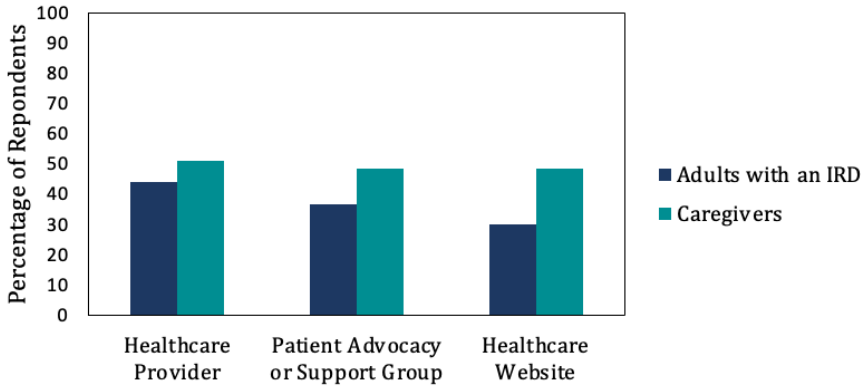


Figure 4c. Healthcare Providers Most Commonly Discussing Gene Therapy

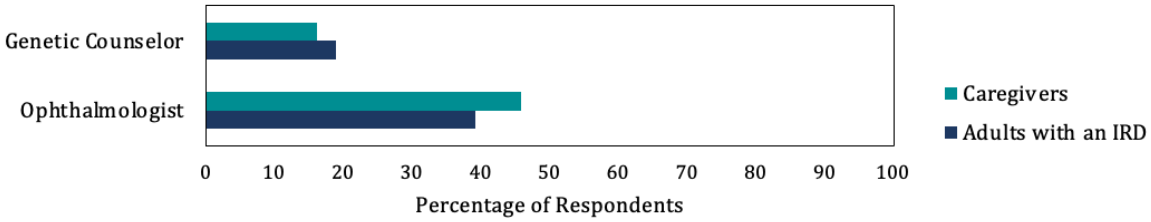


Figure 4d. Top three types of information those who had received information wished their HCP discussed

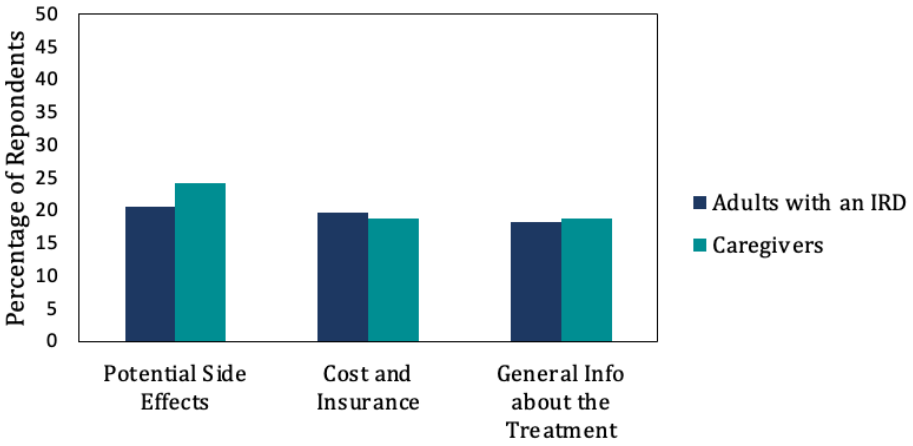


Figure 4e. Top Three Most Desired Types of Information

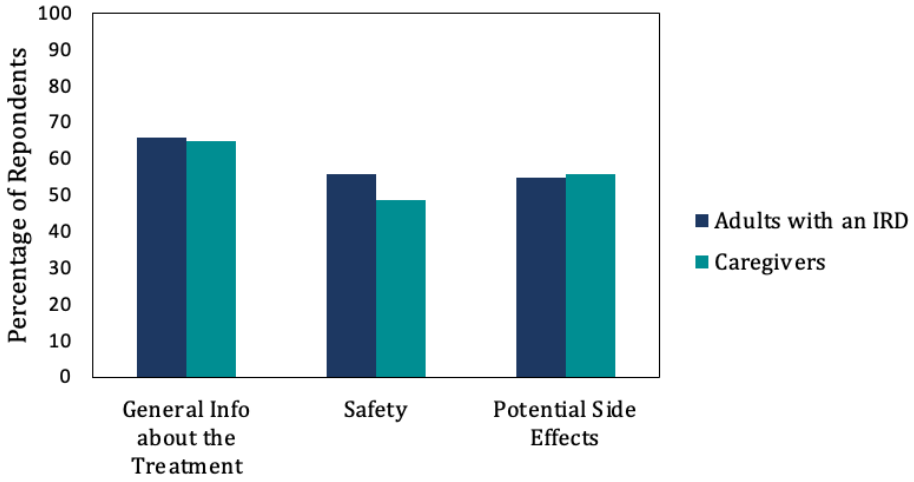


Figure 4. *Most common responses to information needs and preferences questions amongst participants.* **4a** Most preferred information sources, **4b** top three received information sources reported by participants who had already learned about gene therapy, **4c** healthcare providers that were most reported to have discussed gene therapy, **4d** top three types of information that participants wished their healthcare provider had discussed with them if they had already learned about gene therapy, **4e** top three most desired types of information amongst all participants.

Quality of Life and Health Literacy

National Eye Institute (NEI) Visual Function Questionnaire 25 (VFQ-25) and Brief Health Literacy Screen (BHLS)

Detailed subscale score information, including the median and interquartile range (IQR) for the NEI-VFQ-25, are shown in Table 5. The median composite NEI-VFQ-25 score reported by individuals with an IRD was 49 (IQR: 36-63), the mean was 50, and participant scores could range from 0 to 100. The median composite NEI-VFQ-25 score reported by caregivers was 67 (IQR: 35-77), and the mean was 60. Caregivers were asked to report on the quality of life of the person they care for, not their quality of life.

The median total BHLS score reported by individuals with an IRD was 4 (IQR: 3.3-4.7), the mean was 3.87, and participant scores could range from 1 to 5. The median total BHLS score reported by caregivers was 4.7 (IQR: 3.7-5), and the mean was 4.3. Caregivers were asked to respond with how they perceive their health literacy, not the health literacy of the person they care for.

Comparison of the AGT- EYE subscales, the NEI-VFQ-25 subscales and composite score, and the BHLS composite score.

Evaluating the relationship between the AGT-EYE subscale scores, the subscale and composite scores of the NEI-VFQ-25, and the composite score of the BHLS revealed weak or no correlations (Table 6). Evaluating the relationship between the NEI-VFQ-25 and BHLS composite scores showed a significant moderate Pearson correlation, $r(618) = 0.41$, $p < 0.001$. Logistic regression was used to analyze the relationship between the different AGT-EYE subscales and participant interest in receiving or not receiving a gene therapy

treatment now. In the first model, the AGT-EYE Subscale B (Knowledge of Methods) did not significantly predict interest in receiving a gene therapy treatment ($\chi 2$ (1) = 0.47, p=0.50). In the second model, the AGT-EYE Subscale C (Awareness of Outcomes) did not significantly predict interest in receiving a gene therapy treatment ($\chi 2$ (1) = 3.42, p=0.06), although the model was trending towards significance. However, in the third model the AGT-EYE Subscale D (Perceived Value of Therapy) was found to significantly predict interest in receiving a gene therapy treatment, ($\chi 2$ (1) = 24.75, p<0.001), accounting for 11% of the variance (Nagelkerke R^2). Participants who had higher perceived value of gene therapy were 4.04 times more likely to be interested in receiving a gene therapy treatment.

Table 5. *Distribution of National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) composite and subscale scores among individuals with an IRD and caregivers*

	Median (Interquartile Range)	
	Adult patient (n=652)	**Caregiver (n=37)**
NEI-VFQ-25 total and subscales		
Composite score	49 (36-63)	67 (35-77)
General health	75 (50-75)	75 (50-100)
General vision	40 (20-60)	60 (20-80)
Ocular pain	88 (75-100)	100 (75-100)
Near activities	50 (25-67)	58 (25-79)
Distance activities	42 (33-58)	50 (33-75)
Vision-specific social functioning	50 (38-75)	75 (47-100)
Vision-specific mental health	38 (19-56)	50 (31-81)
Vision-specific role difficulties	50 (25-75)	63 (25-88)
Vision-specific dependency	50 (25-75)	75 (33-83)
Driving	0 (0-50)	0 (0-56)
Color vision	75 (50-100)	100 (50-100)
Peripheral vision	25 (25-75)	50 (25-75)

Table 6. *Pearson's correlation between AGT-Eye subscale scores, NEI-VFQ-25, and BHLS among individuals with an IRD*

	AGT-EYE subscale					
	Methods		**Outcomes**		**Value**	
	ρ	**(r)**	**ρ**	**(r)**	**ρ**	**(r)**
NEI-VFQ-25						
Composite score	0.21	(-0.05)	0.33	(0.04)	0.24	(-0.05)
General health	**0.01**	**(0.10)**	0.74	(0.01)	0.12	(0.07)
General vision	**0.01**	**(-0.12)**	0.17	(0.06)	0.91	(0.01)
Ocular pain	0.13	(0.06)	0.80	(-0.01)	0.78	(0.01)
Near activities	0.26	(-0.05)	0.12	(0.06)	0.86	(0.01)
Distance activities	0.06	(-0.08)	0.84	(0.01)	0.43	(-0.03)
Vision-specific social functioning	**0.02**	**(-0.09)**	0.78	(-0.11)	0.11	(-0.06)
Vision-specific mental health	0.41	(0.03)	0.25	(0.05)	**0.01**	**(-0.16)**
Vision-specific role difficulties	0.78	(0.01)	0.29	(0.04)	0.09	(-0.07)
Vision-specific dependency	0.38	(-0.04)	0.27	(0.05)	**0.02**	**(-0.10)**
Driving	**0.01**	**(-0.14)**	0.78	(-0.01)	0.94	(-0.01)
Color vision	0.15	(-0.06)	0.20	(0.05)	0.34	(0.04)
Peripheral vision	0.24	(-0.05)	0.52	(-0.03)	0.61	(-0.02)
BHLS	**0.01**	**(0.14)**	0.07	(0.07)	0.60	(0.02)

Pearson correlation's (r) showing the relationship between the NEI-VFQ-25 composite and subscale scores and the AGT-EYE subscales, and the relationship between the BHLS scale and the AGT-EYE subscales. *p* = the significance level of the Pearson correlation. Correlations of 0.0 to 0.4 or 0.0 to -0.4 are considered weak, 0.4 to 0.6 or -0.4 to -0.6 are considered moderate, and 0.6 to 0.8 or -0.6 to -0.8 are considered strong. Correlations achieving statistical significance ($p \leq 0.05$) are bolded.

Qualitative Questions about Gene Therapy and Information Needs

Participants who completed the survey could share additional thoughts and concerns about gene therapy and their information needs and preferences surrounding gene therapy treatments through an open-ended text box. A complete and thorough analysis of this qualitative data is beyond the scope and aims of this thesis, but below are some recurrent themes and interesting quotes observed when looking at the qualitative data.

Theme: General Knowledge and Information Need

Participants had many questions and concerns about how gene therapy treatments work, what is involved in receiving treatment, the associated follow-up, the potential risks, possible outcomes, and much more. As one participant stated,

> "I really need to know a nice, well-rounded information set – what are the benefits, risks, potential side effects, and costs associated with a treatment. How often is the treatment to be administered (a daily pill, a shot every few weeks…)."

Some participants were also concerned from an ethical stance about where the biological components of the gene therapy treatment have been derived from. One individual stated,

> "If there are any connections, directly or indirectly, with abortion, you must disclose this information to all so that decisions to participate are based on each individual moral conscience."

Several individuals were frustrated about the limited information they had received from healthcare professionals. One respondent said,

"I wish my specialists were more informative and transparent about this future option."

Another individual expressed similar feelings,

"I don't feel that I receive enough information about gene therapy progress from anyone.

Another participant received information from their specialists, but they were not hopeful,

"None of my current physicians offer optimistic responses to any of my questions concerning gene therapy."

Other individuals felt that they did not even know how to access information about gene therapy outside of their specialists. For example, one participant said,

"I wish I knew how/where to access up to the minute info."

These responses highlight the high gene therapy information needs for individuals with IRDs and their caregivers.

Theme: Cost

Unsurprisingly, participants were concerned over the potential cost of gene therapy treatments. Their concerns were wide-ranging, including the worry that the treatment would only be available to the wealthy and that there would be no government or insurance help. For example, one participant said,

"The cost for gene therapy is astronomical and patients will need help."

While another participant stated,

"I feel with all the taxes I have paid working all these years with a disability, the least the government could do is either pay for my [treatment] or give me more money to live on."

Another participant was concerned about what would happen to the cost balance of their treatment if they were to pass away and said,

"I would not want the unpaid balance of that service to be passed on to my heirs if I had passed away."

These responses highlight the wide-ranging concerns over the cost of gene therapy treatment.

Theme: Eagerness for treatment

Participants repeatedly referenced a strong desire for treatment to be available quickly. At times, this interest in treatment was without regard to potentially traveling far for treatment or the possible outcomes. One individual stated,

"I want more information. I want to make this study just as urgent for the world as it is for my son and I."

Along similar lines, another individual said,

"I am anxiously waiting for any treatment that would help me see better."

Another participant described the emotional gravity they have felt and their desire for help,

"It's a depressing mind fuck to know you are [slowly] losing your sight…help us now."

One participant expressed sadness over the limited progress in treatment that had been made for their particular condition,

"This is disappointing. Not so much for him but we thought the research would be farther along for our grandchildren who may have inherited the eye disease."

Lastly, one participant alluded to the infinite distance they would travel for treatment,

"I would give my left arm and travel anywhere in the world to have the opportunity to be a part of a gene therapy trial."

These responses reflect the overwhelmingly positive perception of gene therapy amongst individuals in this sample.

Theme: Efficacy and Safety

Participants expressed varying sentiments over safety and efficacy. These concerns ranged from knowing information about the effectiveness of the treatment and the outcomes of previous recipients to understanding all the possible risks. To illustrate this, one participant said,

"I would want to know the success rate and be able to read stories of individual's personal experiences and what changed following the treatment - both the pros and cons."

Along similar lines, another participant stated,

"The availability of therapy alone would not be enough to determine a decision. Efficacy of treatment and other factors in addition to availability would be required to decide."

Several participants expressed apprehension about any of the risks a gene therapy treatment could pose. For example, one individual said,

"I would accept gene therapy treatment only if it meant… risks were minimal."

Another participant similarly expressed the following,

"Unless I know no further damage would occur, I would not risk."

Importantly, these responses show that while the participants are excited and hopeful about gene therapy, they still have many remaining concerns, which underpins the importance of addressing the high information need for these individuals.

DISCUSSION

This study was the first in the United States, to the best of our knowledge, to assess the attitudes and informational needs towards gene therapy of people with inherited retinal disorders (IRDs) (n = 652) and their caregivers (n = 37) using validated measures. This study aimed to describe the attitudes and information needs toward gene therapy among people with IRDs and their caregivers. The distribution of self-reported diagnoses among participants in this study was consistent with the phenotypic breakdown of IRDs among other large cohorts in the literature (Carss et al., 2017; Chen et al., 2021; Mansfield et al., 2020; Perea-Romero et al., 2021).

The results of this study demonstrate the significant interest in gene therapy as a potential treatment option among individuals with IRDs and their caregivers, as most participants reported positive attitudes towards gene therapy and its potential benefits. However, participants in this study reported various concerns related to possible gene therapy treatment and a high information need, underscoring the importance of enhancing and ensuring the accuracy of potential sources of information about gene therapy for patients with an IRD or their caregivers.

A primary finding from this study was the overwhelming and significant interest in receiving gene therapy, with 91% of patients and 97% of caregivers responding that they would receive treatment if it were offered now to them or their dependent. This high rate of interest aligns with findings from a recent study published by Mack and colleagues (2022), which surveyed individuals with IRDs and their caregivers in Australia about their perspectives on ocular gene therapy, where they found that 91% percent of participants

indicated they would take up gene therapy if it was available to them or their family member for their IRD, and mirrors findings from other research among people with different systemic genetic conditions (Aiyegbusi et al., 2020). In the present study, participants also expressed a high perceived value of gene therapy in general, with over 60% agreeing that government subsidy of treatment would be an effective use of taxpayer money, over 85% agreeing that they would travel to other states for gene therapy treatment, and over 65% agreeing they would consider a payment plan for gene therapy. The results also demonstrated that an individual's perceived value of gene therapy predicted their interest in receiving a gene therapy treatment. However, their knowledge of how gene therapy works and their understanding of treatment outcomes did not predict their interest in receiving treatment.

The very high interest in receiving gene therapy and high perceived value of therapy among study participants contrast with the reality that there currently is only one FDA-approved ocular gene therapy available in the U.S. Although there are over 15 gene-based therapies for IRDs planned or in progress in a clinical trial as of Spring 2023, the complexity of clinical trial implementation and the genetic heterogeneity of IRDs leaves the majority of IRD patients unsure of whether they currently qualify for a clinical trial of if they will qualify in the future. Given that the likelihood of widespread introduction of additional gene therapies for this population is still many years away, this intense interest and high perceived value suggest very optimistic attitudes towards gene therapy for IRDs. It also highlights the critical need for clinicians to manage patient expectations and points to a window of opportunity for information sources to provide accurate and realistic updates about gene therapy progress to patients and providers (Benjaminy et al., 2015).

Interestingly, this study found that individuals who experienced symptom onset of their condition during infancy were less likely to indicate that they would receive a gene therapy treatment now if it were available than individuals who experienced symptom onset after infancy. This finding aligns with results from other qualitative studies in the literature that has found participants who became blind in adolescence or adulthood feel more negatively about their blindness and to be more interested in gene-based therapies than individuals who became blind earlier in life (e.g., Hoffman-Andrews et al., 2019). Some individuals who experience severe vision impairment or blindness from early on in life may consider their vision condition an integral part of their identity, compared to those who experience vision loss later in life.

Although participants raised questions and concerns throughout the survey, their strong interest and optimism toward gene therapy as a treatment was evident. Interestingly, only about 50% of both groups of participants felt they had a good knowledge base about gene therapy for IRDs. Notably, only 28% of participants in the study conducted by Mack and colleagues thought they had a good knowledge of gene therapy, indicating a possible difference in self-perceived knowledge levels among individuals in the Australian IRD community and those in the U.S. IRD community. Given that Luxturna was first approved in the U.S., the accompanying news of gene therapy and excitement may have contributed to the more widespread awareness of gene therapy among the IRD community in the U.S. However, additional demographic or location-specific factors may contribute to the difference in self-perceived knowledge between the groups. Knowledge gaps are unsurprising because gene-based therapies are still considered a new technology. However, they demonstrate the importance of a team-based healthcare

approach in which participants can receive information appropriate to their comprehension level and tailored to their personal information needs.

Similar to previous research, this study found that knowledge of genetics concepts, including gene therapy methods and outcomes of gene therapy, varied among the participants and is an area that information sources should focus on in the future (Chapman et al., 2019; Mack et al., 2022). For example, nearly half of the participants responded "neither agree nor disagree" when asked if gene therapy is injected through the arm into the bloodstream, which is considered false for ocular gene therapies. However, of note, hematologic blood therapies may be delivered this way. A few specific items from the validated AGT-EYE measure could have been misleading or subject to interpretation, personal knowledge, and individual experience, such as asking individuals whether gene therapy is delivered to both eyes, which was considered true. Nearly half of the respondents were neutral in their response to this specific question, while about one-fourth of respondents disagreed, and one-third agreed. The only currently FDA-approved ocular gene therapy available on the market is administered separately at spaced intervals to both eyes. Therefore, participants who knew about gene therapy delivery to both eyes, albeit at different times, may have disagreed with the question based on this knowledge or their personal experience. Nonetheless, these results reiterate variable knowledge among participants, even in a highly educated cohort, underscoring the importance of targeted education for patients and caregivers in the IRD community. As more gene therapy treatments enter clinical trials or become approved, ensuring effective education and clearing up knowledge gaps will be paramount so that patients and providers can provide informed consent.

Overall, participants expressed a high need for multiple types of information, with general information about the treatment and how it works, safety information, and potential side effects being the most desired. Many participants also wanted information regarding the length of benefit and follow-up care, and especially information about cost and insurance coverage. Luxturna, the first gene therapy for patients with a hereditary condition and the only FDA-approved gene therapy is priced at $850,000 for the treatment of both eyes (Salzman et al., 2018). While insurance coverage is possible for gene therapy treatments such as Luxturna, payers are still early in the process of considering authorization and how to develop sustainable reimbursement models for gene therapy (Barlow et al., 2019). Barlow and colleagues (2019) found that in a qualitative study of United States payers, nearly 30% were just beginning to learn about gene therapies, while 40% described a watch-and-wait approach, and about 30% were actively engaged in incorporating gene therapy-related costs into their plan premiums.

Since the FDA approval of Luxturna in 2017, the foray into non-conventional payment models has begun. For example, Spark Therapeutics has offered agreements to payers that include rebates at various time points if the treatment does not reach efficacy and clinical success metrics (Salzman et al., 2018). Even to individuals working in the healthcare sector, cost and insurance coverage are complex topics to understand. Patient advocacy organizations and clinicians working with patients and caregivers in the IRD community must be ready to discuss the nuances of this topic and be willing to learn about the evolving state of cost and reimbursement for gene therapy to enhance patient access to treatment.

Healthcare providers (HCPs), patient advocacy and support groups, and healthcare websites were the primary sources of information among participants in this study. Given that healthcare websites are commonly utilized as a source of information, clinicians and patient advocacy organizations must direct patients to reliable sources of online information since many online sources discussing ocular gene therapy can be of low quality, written above the education level of the general population, and vary significantly between sources (Davuluri et al., 2021). There are several quality resources available to patient populations and the general public regarding genetics and gene-based therapies, such as those from specific patient advocacy organizations or the genomics educational resources from the National Human Genome Research Institute (NHGRI; https://www.genome.gov/About-Genomics/Educational-Resources).

While ophthalmology providers were the most reported HCPs providing information and may facilitate most access to treatment options for patients with an IRD, genetic counselors are HCPs uniquely trained in understanding and communicating complex genetic concepts. They can complement the care team for IRD patients and help assure that individuals with IRDs receive comprehensive information (Sutherland & Day, 2009). Interestingly, participants in this study who had already received information about gene therapy from an HCP still reported wishing their HCP had discussed similar topics to those of interest among individuals who had not yet received information about gene therapy. This result highlights a window of opportunity for clinician education regarding specific gene therapy concepts for IRDs and how to communicate these concepts effectively to patients and caregivers.

The vision-related quality of life scores among participants in this study were low, with the median score among individuals with an IRD being 49 out of a scale of 100 (Mack et al., 2022). This finding is similar to other studies of IRD cohorts. Still, it contrasts with the vision-related quality scores in typical working populations (nearly 90 out of 100), even among populations where 17% have mild eye conditions such as dry eye or strabismus (Hirneiß et al., 2010). As illustrated by several of the quotes in the qualitative results section of the study, several participants emphasized their condition's impact on their quality of life, suggesting merit in further exploration of the relationship between quality of life and participant attitudes regarding gene therapy and participant information needs.

Strengths

This study had several key strengths, including the large sample size, participant feedback indicating excellent survey accessibility, use of validated survey instrument tools, and assessment of key health-related variables like quality of life. This study's large sample size was the result of a diverse recruitment strategy that targeted patient advocacy groups, including groups specific to individuals with IRDs and those who were open to individuals with vision impairment more generally. The recruitment strategy included a social media campaign and attempts to collaborate with local ophthalmology providers for patient outreach.

While feedback about the accessibility of the survey was not explicitly solicited, multiple participants reached out via email. They provided positive feedback about the suitability of the survey for individuals with vision impairment. Additionally, the bulk of

literature in this area has been limited to qualitative designs and small sample sizes and has not used validated survey instrument tools. This study successfully addressed these limitations, using a mixed-methods design that included several validated survey instrument tools and two specific to individuals with vision impairment (i.e., AGT-EYE tool and NEI-VFQ-25). The NEI-VFQ-25, which measures health-related quality of life in individuals with vision impairment, helps provide descriptive information about the quality of life in this population and also helps make a case for the substantial disease burden in this group. Appreciation of this burden may impact treatment coverage by payers.

Limitations

Limitations of this study include that most participants were recruited through patient advocacy organizations, were of higher socioeconomic status than the general population in the U.S., and relied on visually impaired participants completing a text-based online survey. Most participants reported learning of the study through a patient advocacy organization or research group (e.g., Foundation Fighting Blindness, a treatment-focused organization). Thus, participants in this study may have been more likely to be motivated and active in the IRD community and more interested in participating in research studies than the rest of the IRD population. This is a limitation that many studies in the rare disease space face. While the research team made a concerted effort to recruit individuals outside of patient advocacy organizations by attempting to collaborate with ophthalmology clinicians in the local area of the research team, implementing a social media campaign on Facebook, Instagram, and LinkedIn, and administration of the survey information to patient organizations that are focused more broadly on blind and visually impaired

individuals instead of just individuals with IRDs (e.g., American Council of the Blind), recruitment from non-advocacy sources was limited.

Further, the participants in this study tended to be of higher socioeconomic status than individuals in the general U.S. population. They differed from U.S. averages regarding education level, household income, and marital status. Additionally, more participants in this study identified as White/Caucasian and reported English as their primary household language compared to the general U.S. population. Given this, it is not clear if the results of this study can be extrapolated to more diverse samples of individuals with an IRD or their caregivers.

Lastly, the vast majority of participants in this study were visually impaired, and thus the study's delivery method via an online survey may not be optimal for this population. Over one-third of individuals with an IRD reported using an accessibility aid, such as a screen reader or screen magnifier, to complete the survey. Although our survey was designed with accessibility in mind and was pilot-tested among lay and visually impaired individuals, the survey-based nature may have contributed to difficulty responding completely, and some potential participants may have chosen not to take the survey due to a perceived barrier in access. This highlights the importance that all survey-based studies in the IRD community be held to high standards of accessibility and compatibility with accessibility aids such as screen readers and magnifiers. However, additional survey methods (such as in-person or paper surveys) may aid in further recruitment.

Future Directions

Continued research investigating the attitudes towards gene therapy and information needs of patients and caregivers with IRDs and other patient and caregiver populations is necessary to facilitate the mainstream adoption of gene-based therapies as these technologies continue to become available. Future studies should build upon the knowledge of the current literature while addressing primary limitations. For example, studies should aim to recruit participants outside patient advocacy organizations, participants with different socioeconomic status levels, or participants who speak other languages which would necessitate translation and validation of survey materials in different languages. These studies could also incorporate validated survey instrument tools, as this study did, to facilitate comparisons with previously reported findings.

A more detailed investigation of how to best address participant information needs and how to develop tailored educational resources is essential. While participants in this study reported internet resources as a primary source of information, previous literature has found that internet resources can be challenging to understand and misleading (Davuluri et al., 2021). Thus, additional research should explore developing and delivering credible educational materials in multiple formats that are easy for patients to understand and accessible to individuals with vision impairment.

CONCLUSION

Gene therapy can change the lives of individuals living with an IRD. Still, it is imperative to understand and address the attitudes and information needs of individuals with IRDs and their caregivers. The results of this study illustrate the significant interest, optimism, and hope in emerging gene therapies among the IRD community. However, this interest and optimism were paralleled by relatively low self-perceived knowledge of gene therapy and a significant desire for more information. Access to accurate and comprehensive information about gene therapy from various sources, including healthcare providers, healthcare websites, and patient advocacy organizations, will help individuals with IRDs and their caregivers make empowered decisions about their healthcare. Following the diverse attitudes towards gene therapy among individuals with IRDs and their caregivers, sources of information should tailor their communication to the specific education needs of this community. In addition to ongoing research into gene therapy for IRDs, more effective and accessible sources of information for patients, caregivers, and healthcare providers must be developed for this group of conditions. Genetic counselors are healthcare professionals who are well suited to play a role in the development of these materials and in conveying this information to patients and families .

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Appendix A – Complete Survey

University of California, Irvine Study Information Sheet

Attitudes and Informational Needs towards Somatic Gene Therapy and Gene Editing; A Survey of Stakeholders Affected by Inherited Retinal Disorders

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Thank you for your interest in this research study.

Please read the information below to learn more about what your participation will involve. Please ask questions about anything that you do not understand or have concerns about. Amanda Shrewsbury is available to answer your questions; please use the phone number or email listed above to contact her.

You are being asked to participate in a research study. Participation in this study is voluntary. You may choose to skip questions you do not wish to answer. You may refuse to participate or discontinue your involvement at any time without penalty or loss of benefits. You are free to withdraw from this study at any time before you complete the survey by exiting the survey. Once you have completed the survey, you will not be able to withdraw. Your responses will not be linked to you and the researchers will not be able to identify your responses.

The survey is designed to learn more about the attitudes of people with Inherited Retinal Disorders and their caretakers towards gene therapy treatments. We are also interested in learning your preferences regarding receiving more information about these treatments in the future.

<u>The survey should take 10 minutes to 40 minutes to complete.</u>

You are eligible to participate in this study if you have been diagnosed with an Inherited

Retinal Disorder (IRD) **OR** are the caregiver or someone diagnosed with an IRD. You must be at least 18 years old, live in the United States, and be able to complete the survey in English.

There are no direct benefits from participation in the study. However, this study may help healthcare professionals better understand the viewpoints of individuals and families living with Inherited Retinal Disorders towards gene therapy treatments and the best ways to provide information about such treatments. This could inform future healthcare practices and availability of patient-centered educational information.

Possible risks/discomforts associated with the study are boredom when completing the survey. There is also the possibility that answering questions regarding options for treating vision impairments could be upsetting to some study participants.

All research data collected will be stored securely and confidentially on a secured and password protected computer owned by the lead researcher, and within a password protected folder on the device.

Researchers will use your survey responses to conduct this study. Once the study is done using your responses, we may share them with other researchers so they can use them for other studies in the future. We will not share your name or any other private identifiable information that would let the researchers know who you are. We will not ask you for additional permission to share this de-identified information.

Questions?

If you have any comments, concerns, or questions regarding this study please contact the researchers listed at the top of this form. If you have questions or concerns about your rights as a research participant, you can contact the UCI Institutional Review Board by phone, (949) 824-6662, by e-mail at IRB@research.uci.edu or at 160 Aldrich Hall, Irvine, CA 92697-7600.

What is an IRB?

An Institutional Review Board (IRB) is a committee made up of scientists and non-scientists. The IRB's role is to protect the rights and welfare of human subjects involved in research. The IRB also assures that the research complies with applicable regulations, laws, and institutional policies.

If you want to participate in this study, click the "next" button in the bottom right hand corner of this page to start the survey.

End of Block: Intro and Informed Consent

Start of Block: Eligibility Criteria

The next several questions are about your eligibility to complete this survey and require a response. If you do not respond to the eligibility questions, the "next" button in the bottom right hand corner of the screen will not take you to the start of the actual survey. We thank you in advance for your contributions to this project!

To move through the questions in this survey, please continue to click the "next" button in the bottom right hand corner of the screen.

Page Break

Have you been diagnosed with an Inherited Retinal Disorder (IRD)?

Examples include Retinitis pigmentosa, Usher syndrome, Stargardt disease, juvenile macular dystrophy, cone-rod dystrophy, achromatopsia, and other conditions.

- ○ Yes (1)
- ○ No (2)

Skip To: If Have you been diagnosed with an Inherited Retinal Disorder (IRD)? Examples include Retinitis pigm... = No

Display This Question:

If Have you been diagnosed with an Inherited Retinal Disorder (IRD)? Examples include Retinitis pigm... = No

Are you a caregiver for someone who has been diagnosed with an Inherited Retinal Disorder (IRD)?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Are you a caregiver for someone who has been diagnosed with an Inherited Retinal Disorder (IRD)? = No

Display This Question:

If Are you a caregiver for someone who has been diagnosed with an Inherited Retinal Disorder (IRD)? = Yes

What is your relationship to the individual that you are a caregiver for?

- ○ Parent (1)
- ○ Other; please specify your relationship through the text entry box below (2)

_____

Display This Question:

If Are you a caregiver for someone who has been diagnosed with an Inherited Retinal Disorder (IRD)? = Yes

How old is the individual that you are a caregiver for?

Please use the text entry box below to type their age

_____

Are you 18 years of age or older?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Are you 18 years of age or older? = No

Do you live in the United States?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Do you live in the United States? = No

Can you complete this survey in English?

- ○ Yes (1)
- ○ No (2)

Skip To: End of Survey If Can you complete this survey in English? = No

End of Block: Eligibility Criteria

Start of Block: Measure: Nature of the condition (AFFECTED)

This is the start of the survey. We thank you in advance for your time completing this survey.

You may stop the survey at any time, although we strongly encourage you to complete the entire survey to help healthcare professionals understand your experiences and opinions.

The survey will automatically save your progress, and you may return to complete the survey for up to 1 week if you need to take a break and return at a later time. You will need to return to the survey on the same device and same internet browser.

Page Break

Question 1 of 78 **What specific Inherited Retinal Disorder do you have?**

- ○ Retinitis Pigmentosa (RP) (1)
- ○ Usher Syndrome (2)
- ○ Stargardt Disease (3)
- ○ Juvenile macular dystrophy (4)
- ○ Cone rod dystrophy (5)
- ○ Achromatopsia (6)
- ○ Unsure or unknown (7)
- ○ A different condition; please specify in the text entry box below (8)

_____

Question 2 of 78 **Has your diagnosis been confirmed by a genetic test?**

- ○ Yes (1)
- ○ No (2)
- ○ Unsure or unknown (3)

Question 3 of 78 **When did you first begin to experience symptoms of your condition?**

- ○ As an infant; 0-12 months old (1)
- ○ As a toddler; 1 to 3 years old (2)
- ○ As a child; 4 to 11 years old (3)
- ○ As an adolescent; 12 to 17 years old (4)
- ○ As an adult; 18 years and older (5)
- ○ Unsure or unknown (6)

Question 4 of 78 **Is your retinal condition a part of a broader condition that affects multiple parts of your body?**

For example, the condition affects your hearing ability in addition to your vision. Examples of these types of syndromes may include Usher Syndrome or Bardet-Biedl Syndrome.

- ○ Yes (1)
- ○ No (2)
- ○ Unsure or unknown (3)

Question 5 of 78 **Have you received gene therapy as a part of a clinical trial?**

- ○ Yes (1)
- ○ No (2)

Question 6 of 78 **Have you received gene therapy as a part of an FDA approved treatment?**

- ○ Yes (1)
- ○ No (2)

Page Break

End of Block: Measure: Nature of the condition (AFFECTED)

Start of Block: Measure: Attitudes towards gene therapy (AFFECTED)

The following questions relate to your thoughts about a technology called gene therapy. Gene therapy is not widely available yet to treat inherited retinal disorders (IRDs), but there are many ongoing clinical trials, as well as one FDA approved treatment in the U.S. for the treatment of some forms of RPE65-associated retinal disorders, such as one form of Leber's congenital amaurosis.

Our body is made up of millions of cells. Each of those cells contains our genetic information in the form of genes. Genes hold the instructions for how our body grows and functions. Changes to the typical genetic information, also known as mutations or pathogenic variants, cause IRDs.

Gene therapy is a technology that may treat or prevent disease or disease progression by adding a working copy of a gene to stand in for the changed gene causing a disease.

This type of treatment is typically targeted to a certain body part, and the changes made by this treatment <u>cannot</u> be passed down to children or future children.

Page Break

Question 7 of 78 **I have good knowledge about gene therapy for inherited retinal diseases.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 8 of 78 **For the following question you are allowed to select more than one response option.**

I have obtained information about gene therapy treatment from...

- [ ] My ophthalmologist (1)
- [ ] Other medical or healthcare professional (2)
- [ ] Disease Registry. For example, the My Retina Tracker Registry through the Foundation Fighting Blindness (3)
- [ ] Research group (4)
- [ ] Newspapers (5)
- [ ] Internet (6)
- [ ] Social media (7)
- [ ] Patient support group (8)
- [ ] Family or friends (9)

Question 9 of 78 **I understand the difference between an experimental treatment provided by a clinical trial and a treatment that has already been approved by the FDA or American government.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 10 of 78 **Gene therapy for the eye is suitable at any stage of a person's life.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 11 of 78 **Generally, gene therapy for inherited retinal disease is delivered to both eyes.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 12 of 78 **Gene therapy for the eye is injected into the blood stream through the arm.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 13 of 78 **Gene therapy and stem cell therapy are the same treatment.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Page Break

Question 14 of 78 **Gene therapy for the eye can restore vision back to normal.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 15 of 78 **Gene therapy for the eye is a treatment that may slow down the disease.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 16 of 78 **Treatment complications to my eyes, such as permanent blindness, are possible with an approved gene therapy.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 17 of 78 **Gene therapy in my eye may have side effects elsewhere in my body.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 18 of 78 **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 Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 19 of 78 **I may not be eligible for financial or other government benefits if my gene therapy for my eye condition is successful.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 20 of 78 **Gene therapy for inherited retinal diseases will require many years of follow-up with my eyecare practitioner.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 21 of 78 **Receiving gene therapy for my inherited retinal disease means I won't be eligible for future genetic treatments.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 22 of 78 **I will lose my privacy if I undergo gene therapy, and my data will be in the public domain.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 23 of 78 **If I undergo gene therapy, it will affect my eligibility or terms of conditions in life, disability or health insurance in the future.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Page Break

Question 24 of 78 **The government should pay all costs of my gene therapy.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 25 of 78 **Government subsidy of my treatment would be an effective use of taxpayer money.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 26 of 78 **If gene therapy for my condition was not available in my state I would consider traveling interstate to access it.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 27 of 78 **My private health insurance should pay all out of pocket costs for my gene therapy.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Question 28 of 78 **I would consider a payment plan for my gene therapy.**

- ○ Strongly Disagree (1)
- ○ Disagree (2)
- ○ Neither agree nor disagree (3)
- ○ Agree (4)
- ○ Strongly agree (5)

Page Break

Question 29 of 78 **Would you receive a gene therapy treatment now, if it were offered as a treatment for your condition?**

- ○ Yes (1)
- ○ No (2)

Question 30 of 78 **Please feel free to share any additional thoughts or concerns about gene therapy as a treatment for IRDs that you feel were not addressed in the previous questions. You may use the text entry box below to do so.**

_____

End of Block: Measure: Attitudes towards gene therapy (AFFECTED)

Start of Block: Measure: Information needs (AFFECTED)

You are 25% complete with the survey! We appreciate your continued time.

Page Break

Question 31 of 78 **From which of these sources would you <u>most</u> want to learn about gene therapy for IRDs from? You may only select one response.**

- ○ Healthcare provider (1)
- ○ Healthcare websites (2)
- ○ Pharmaceutical or biotechnology companies (3)
- ○ Patient advocacy or support groups (4)
- ○ Non healthcare websites (5)
- ○ Social media; For example, Facebook, Twitter, Youtube, or Instagram (6)
- ○ Other media; For example, TV, radio, or newspaper (7)
- ○ Friend, family member, caregiver, or colleague (8)
- ○ I do not want to learn information about gene therapy for IRDs (9)
- ○ Another source; please specify in the text entry box below (10)

_____

Question 32 of 78 **For the following question you may select all responses that apply**

From which of these sources have you already received information about gene therapy for IRDs?

- [ ] Healthcare provider (1)
- [ ] Healthcare websites (2)
- [ ] Pharmaceutical or biotechnology companies (3)
- [ ] Patient advocacy or support groups (4)
- [ ] Non healthcare websites (5)
- [ ] Social media; For example, Facebook, Twitter, Youtube, or Instagram (6)
- [ ] Other media; For example, TV, radio, or newspaper (7)
- [ ] Friend, family member, caregiver, or colleague (8)
- [ ] I have never received information about gene therapy for IRDs (10)
- [ ] Another source; please specify in the text entry box below (9)

_____

Display This Question:

If For the following question you may select all responses that applyFrom which of these sources hav... = Healthcare provider

Question 33 of 78 **For the following question you may select all responses that apply**

Which of your healthcare providers have discussed gene therapy with you?

- ☐ Ophthalmologist (1)
- ☐ Primary care provider or general practitioner (2)
- ☐ Genetic counselor (3)
- ☐ Geneticist (4)
- ☐ Nurse practitioner or physician assistant (5)
- ☐ Another healthcare provider; please specify in the text entry box below (6)

_____

Display This Question:

If For the following question you may select all responses that applyFrom which of these sources hav... = Healthcare provider

Question 34 of 78 **For the following question you may select all responses that apply**

What are some things you wish your healthcare provider had discussed with you about gene therapy that they <u>did not</u> discuss?

- ☐ General information about the treatment and how it works (1)
- ☐ Cost or insurance coverage (2)
- ☐ Length of benefit (3)
- ☐ Safety (4)
- ☐ Potential side effects (5)
- ☐ Follow up care (6)
- ☐ Another topic not listed here; please specify in the text entry box below (7)

_____

Question 35 of 78 **For the following question you may <u>select up to 3 responses</u>. Please <u>select up to 3 responses</u> that are most important to you**

What information about gene therapy do you have the strongest desire or need for?

- ☐ General information about the treatment and how it works (1)
- ☐ Cost or insurance coverage (2)
- ☐ Length of benefit (3)
- ☐ Safety (4)
- ☐ Potential side effects (5)
- ☐ Follow up care (6)
- ☐ Another topic not listed here; please specify in the text entry box below (7)

_____

Question 36 of 78 **Please share any other thoughts about your information needs that you would want your healthcare team to know if you were eligible for a gene therapy treatment.**

You may use the text entry box below to do so

_____

End of Block: Measure: Information needs (AFFECTED)

Start of Block: Measure: Health literacy (AFFECTED)

Page Break

Question 37 of 78 **How often do you have someone help you understand hospital materials?**

Think about your ability to understand these materials <u>after</u> the use of any supportive devices or technologies, such as a screen reader, and after working with any caregivers that assist you.

- ○ Always (1)
- ○ Often (2)
- ○ Sometimes (3)
- ○ Occasionally (4)
- ○ Never (5)

Question 38 of 78 **How confident are you completing medical forms by yourself?**

Think about your ability to complete these materials <u>after</u> the use of any supportive devices or technologies, such as a screen reader, and after working with any caregivers that assist you.

- ○ Extremely (1)
- ○ Quite a bit (2)
- ○ Somewhat (3)
- ○ A little bit (4)
- ○ Not at all (5)

Question 39 of 78 **How often do you have problems learning about your medical condition because of difficulty understanding informational resources?**

Think about your ability to understand information about your condition <u>after</u> the use of any supportive devices or technologies, such as a screen reader, and after working with any caregivers that assist you.

- ○ Always (1)
- ○ Often (2)
- ○ Sometimes (3)
- ○ Occasionally (4)
- ○ Never (5)

End of Block: Measure: Health literacy (AFFECTED)

Start of Block: Measure: Quality of life (AFFECTED)

You are halfway through the survey! We appreciate your continued time.

Page Break

Question 40 of 78 **In general, would you say your overall health is...**

- ○ Excellent (1)
- ○ Very Good (2)
- ○ Good (3)
- ○ Fair (4)
- ○ Poor (5)

Question 41 of 78 **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?**

- ○ Excellent (1)
- ○ Good (2)
- ○ Fair (3)
- ○ Poor (4)
- ○ Very Poor (5)
- ○ Completely Blind (6)

Question 42 of 78 **How much of the time do you worry about your eyesight?**

- ○ 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)

Question 43 of 78 **How much pain or discomfort have you had in and around your eyes (for example, burning, itching, or aching)?**

- ○ None (1)
- ○ Mild (2)
- ○ Moderate (3)
- ○ Severe (4)
- ○ Very Severe (5)

Page Break

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).

Question 44 of 78 **How much difficulty do you have reading ordinary print in newspapers?**

- ○ 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)

Question 45 of 78 **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?**

- ○ 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)

Question 46 of 78 **Because of your eyesight, how much difficulty do you have finding something on a crowded shelf?**

- ○ 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)

Question 47 of 78 **How much difficulty do you have reading street signs or the names of stores?**

- ○ 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)

Question 48 of 78 **Because of your eyesight, how much difficulty do you have going down steps, stairs, or curbs in dim light or at night?**

- ○ 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)

Page Break

Question 49 of 78 **Because of your eyesight, how much difficulty do you have noticing objects off to the side while you are walking along?**

- ○ 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)

Question 50 of 78 **Because of your eyesight, how much difficulty do you have seeing how people react to things you say?**

- ○ 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)

Question 51 of 78 **Because of your eyesight, how much difficulty do you have picking out and matching your own clothes?**

- ○ 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)

Question 52 of 78 **Because of your eyesight, how much difficulty do you have visiting with people in their homes, at parties, or in restaurants?**

- ○ 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)

Question 53 of 78 **Because of your eyesight, how much difficulty do you have going out to see movies, plays, or sports events?**

- ○ 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)

Page Break

Question 54 of 78 **Are you currently driving, at least once in a while?**

- ○ Yes (1)
- ○ No (2)

Display This Question:

If Are you currently driving, at least once in a while? = No

Follow up question (55) **Have you never driven a car or have you given up driving?**

- ○ Never drove (1)
- ○ Gave up (2)

Display This Question:

If Have you never driven a car or have you given up driving? = Gave up

Follow up question (56) **Was that mainly because of your eyesight, mainly for some other reason, or because of both your eyesight and other reasons?**

- ○ Mainly eyesight (1)
- ○ Mainly other reasons (2)
- ○ Both eyesight and other reasons (3)

Display This Question:

If Are you currently driving, at least once in a while? = Yes

Follow up question (57) **How much difficulty do you have driving during the daytime in familiar places?**

- ○ No difficulty at all (1)
- ○ A little difficulty (2)
- ○ Moderate difficulty (3)
- ○ Extreme difficulty (4)

Display This Question:

If Are you currently driving, at least once in a while? = Yes

Question 58 of 78 **How much difficulty do you have driving at night?**

- ○ 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)

Display This Question:

If Are you currently driving, at least once in a while? = Yes

Follow up question (59) **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?**

- ○ 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)

Page Break

The next questions are about how things you do may be affected by your vision.

Question 60 of 78 **Do you accomplish less than you would like because of your vision?**

- ○ All of the time (1)
- ○ Most of the time (2)
- ○ Some of the time (3)
- ○ A little of the time (4)
- ○ None of the time (5)

Question 61 of 78 **Are you limited in how long you can work or do other activities because of your vision?**

- ○ All of the time (1)
- ○ Most of the time (2)
- ○ Some of the time (3)
- ○ A little of the time (4)
- ○ None of the time (5)

Question 62 of 78 **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?**

- ○ All of the time (1)
- ○ Most of the time (2)
- ○ Some of the time (3)
- ○ A little of the time (4)
- ○ None of the time (5)

Page Break

Question 63 of 78 **I stay home most of the time because of my eyesight....**

- ○ Definitely true (1)
- ○ Mostly true (2)
- ○ Not sure (3)
- ○ Mostly false (4)
- ○ Definitely false (5)

Question 64 of 78 **I feel frustrated a lot of the time because of my eyesight...**

- ○ Definitely true (1)
- ○ Mostly true (2)
- ○ Not sure (3)
- ○ Mostly false (4)
- ○ Definitely false (5)

Question 65 of 78 **I have much less control over what I do, because of my eyesight. ...**

- ○ Definitely true (1)
- ○ Mostly true (2)
- ○ Not sure (3)
- ○ Mostly false (4)
- ○ Definitely false (5)

Question 66 of 78 **Because of my eyesight, I have to rely too much on what other people tell me...**

- ○ Definitely true (1)
- ○ Mostly true (2)
- ○ Not sure (3)
- ○ Mostly false (4)
- ○ Definitely false (5)

Question 67 of 78 **I need a lot of help from others because of my eyesight...**

- ○ Definitely true (1)
- ○ Mostly true (2)
- ○ Not sure (3)
- ○ Mostly false (4)
- ○ Definitely false (5)

Question 68 of 78 **I worry about doing things that will embarrass myself or others, because of my eyesight...**

- ○ Definitely true (1)
- ○ Mostly true (2)
- ○ Not sure (3)
- ○ Mostly false (4)
- ○ Definitely false (5)

End of Block: Measure: Quality of life (AFFECTED)

Start of Block: Measure: Demographics (AFFECTED)

You are almost to the end of the survey! We appreciate your time.

Page Break

Question 69 of 78 **How old are you?**

- ○ 18 to 25 years old (1)
- ○ 25 to 34 years old (2)
- ○ 35 to 44 years old (3)
- ○ 44 to 49 years old (4)
- ○ 50 to 59 years old (5)
- ○ 60 to 69 years old (6)
- ○ 70 years old and above (7)
- ○ Prefer not to answer (8)

Question 70 of 78 **How would you describe your gender?**

- ○ Man (1)
- ○ Woman (2)
- ○ Transgender man (3)
- ○ Transgender woman (4)
- ○ A gender identity not listed above; please use the text entry box below to describe your gender identity if you'd like (5) _____
- ○ Prefer not to answer (6)

Question 71 of 78 **What is the highest level of education you have completed?**

- ○ Master's degree or above (1)
- ○ Bachelor's degree (2)
- ○ Associate's degree (3)
- ○ Some college (4)
- ○ High school (5)
- ○ Another level of education; please use the text entry box below to describe your education if you'd like (6) _____
- ○ Prefer not to answer (7)

Question 72 of 78 **What is your marital status?**

- ○ Married, legal civil union, or registered domestic partnership (1)
- ○ Single (2)
- ○ Divorced (3)
- ○ Separated (4)
- ○ Widowed (5)
- ○ Prefer not to answer (6)

Question 73 of 78 **What is the level of your annual household income?**

- ○ Less than $25,000 (1)
- ○ $25,000 to $50,000 (2)
- ○ $50,000 to $100,000 (3)

○ $100,000 to $200,000 (4)

○ More than $200,000 (5)

○ Prefer not to answer (6)

Question 74 of 78 **The choices below may not encompass your entire identity, but for the purposes of this survey please select the choice that most accurately describes your racial and ethnic identity.**

You may select more than one option

☐ White or Caucasian (1)

☐ Native American (2)

☐ Asian or Asian American (3)

☐ Latinx or Hispanic (4)

☐ Black or African American (5)

☐ Middle Eastern or North African (6)

☐ Native Hawaiian or Pacific Islander (7)

☐ A racial and ethnic identity not listed above; please use the text entry box below to describe your racial and ethnic identity (8)

_____

☐ Prefer not to answer (9)

Question 75 of 78 **Is English the primary language that you speak at home?**

- ○ Yes (1)
- ○ No (2)

Display This Question:

If Is English the primary language that you speak at home? = No

Follow up question **What is the primary language that you speak at home?**

Please use the text entry box below

_____

Question 76 of 78 **What is your religion?**

- ○ Christian (1)
- ○ Jewish (4)
- ○ Muslim (6)
- ○ Buddhist (7)
- ○ Hinduism (14)
- ○ Atheist (8)
- ○ Agnostic (9)
- ○ Not religious (10)
- ○ A religion not listed here; please use the text entry box below to specify your religion (11) _____
- ○ Prefer not to answer (12)

Question 77 of 78 **Where did you find out about this survey?**

- ○ Patient advocacy organization or research group (1)
- ○ Ophthalmology clinic or healthcare provider (2)
- ○ Another way; please specify in the text entry box below (3)

_____

Display This Question:

If Where did you find out about this survey? = Ophthalmology clinic or healthcare provider

Are you actively involved in a patient advocacy organization or research group?

- ○ Yes (1)
- ○ No (2)

Question 78 of 78 **Did you use any accessibility aids to complete this survey?**

An example would be a screen reader.

- ○ Yes (1)
- ○ No (2)

Display This Question:

If Did you use any accessibility aids to complete this survey? An example would be a screen reader. = Yes

What accessibility aid are you using to complete this survey?

- ○ Screen reader (1)
- ○ Unsure or unknown (2)
- ○ Another accessibility device; please specify in the text entry box below (3)

_____

End of Block: Measure: Demographics (AFFECTED)

Appendix B – Gene Therapy Education Information

The following questions relate to your thoughts about a technology called gene therapy. Gene therapy is not widely available yet to treat Inherited Retinal Disorders, but there are many ongoing clinical trials, as well as one FDA approved treatment called Luxturna for the treatment of Leber's Congenital Amaurosis.

The information below provides you with some background information about this technology and how it works:

Our body is made up of millions of cells. Each of those cells contains our genetic code in the form of genes. Genes hold the instructions for how our body grows, develops and functions. Changes, also known as mutations, to normal genes are what cause Inherited Retinal Disorders.

Gene therapy is a technology that treats or prevents disease by adding a new gene into cells to help fight a disease, or by adding a working copy of a gene to stand in for the changed gene causing a disease.

This type of treatment does not change a person's genetic code forever, and the changes made by this treatment cannot end up being passed down to any children.