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ARTICLE

Gene therapy: perspectives from young adults with Leber's congenital amaurosis

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AIMS/PURPOSE: To investigate Leber congenital amaurosis (LCA) patients' expectations, decision-making processes and gene therapy-related concerns.
METHODS: Using a qualitative approach, we explored perceptions of gene therapy and clinical trials among individuals with LCA. Young adults with a clinical diagnosis of LCA were recruited through the Ocular Genetics Programme at the Hospital for Sick Children. Semi-structured interviews were conducted with ten patients and analysed following the principles of qualitative description.
RESULTS: Study participants were aware of ongoing gene therapy research trials and actively sought information regarding advances in ophthalmology and vision restoration. The majority of participants would enrol or were enrolled in a gene-replacement therapy trial, while a minority was ambivalent or would not enrol if provided an opportunity. Participants attributed different values to clinical trials, which influenced their willingness to participate. Intrinsic factors related to coping, adaptation to vision loss and resilience also influenced decision-making.
DISCUSSION: This study highlights the complex factors involved in gene-therapy-related decision-making and acts as a proponent for adopting patient-centred care strategies when counselling individuals considering gene therapy or clinical trial participation.

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INTRODUCTION

Leber congenital amaurosis (LCA) describes a group of autosomal recessive retinal dystrophies with early onset in childhood. It is a severe retinal degeneration where blindness or severe visual impairment can develop in early childhood. Genetic analysis of individuals with LCA identified over 17 genes, of which bi-allelic *RPE65* variants account for 8–10% of LCA cases [1]. Genetic diagnosis of LCA has helped to better counsel families, understand the underlying disease processes and develop therapies mostly tailored to the gene defect [2, 3].

In Canada, Ophthalmology entered the realm of clinical gene therapy for inherited retinal degenerations (IRDs) only in October 2020 when Luxturna, the first gene therapy to successfully treat patients with bi-allelic *RPE65* variants and a related retinal degeneration, was approved by Health Canada. Early successes in clinical trials for Luxterna served as a stepping stone for numerous ongoing or planned gene-replacement therapy trials for IRDs [4].

Studies have shown that there are parent and public support for clinical research for new therapies, including gene therapy, involving children across diverse medical specialities [5, 6]. How adults, particularly those who have experienced low vision their entire life, will perceive these therapies is less well understood. To optimise patient-centred care, it is important to consider the perception of LCA patients of this type of genetic intervention and determine their expectations regarding therapy, outcomes, and impacts on their life.

Using a qualitative approach, we explored the perspectives of patients with LCA regarding their vision loss, how it affects their lives, the potential importance and meaning of vision restoration, and their awareness of gene therapy clinical trials. We also explored expectations for visual improvement, motivations, and barriers related to participation in gene therapy and personal factors that contribute to their decision-making processes.

SUBJECTS AND METHODS

Study design

A qualitative study was designed to explore patients' perspectives of their disease and the upcoming gene therapies and related clinical trials. The study was approved by the Research Ethics Boards at the Hospital for Sick Children and respected the Declaration of Helsinki.

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Table 1. Participant demographics ($n = 10$).

Demographic	*n* (%)
Sex	
Male	5 (50%)
Female	5 (50%)
Proband	6 (60%)
Affected sibling of a proband	4 (40%)
Age	
Mean (years)	24.4
Range (years)	19–30
Mean Age of Onset	≤6 months

Table 2. Summary of participant's descriptions of meaningful improvements in vision.

Meaningful improvement in vision	Number of participants ($n = 10$)
To read print	4
To differentiate objects	3
To recognise people	3
To drive	2
To see colour	2
To see street lights	2
Prevent deterioration of vision	1
Have vision close to 20/20	1

Participants

Potential participants were identified by convenience sampling through the Ocular Genetics Programme at The Hospital for Sick Children from a pre-existing database of 109 patients with a clinical diagnosis of LCA. Inclusion criteria were English-speaking male and female patients with the clinical diagnosis of LCA, and between the ages of 18 and 30, as many participants in published gene therapy clinical trials fall into this age category. Individuals with cognitive impairments were excluded. Of the 109 patients, 29 met inclusion criteria and were invited to participate in the study via telephone contact by their genetic counsellor. The primary author (MPN) then contacted those interested in order to review study details and obtain informed consent.

Data collection

A single investigator (MPN) conducted 30–70 min semi-structured telephone interviews that included questions on patient identity, meaningful visual improvements, participation in gene therapy trials and motivation to do so, and perceived benefits, risks and limitations. The interview guide was developed through a literature review and input from genetic counselors, ophthalmologist, medical geneticist and a researcher in health policy and services. The interview guide ensured that a consistent set of topics were explored across participants while allowing the interviewer flexibility to probe new topics that arose within each interview. Following the interview, participants were given time to share additional information about living with vision loss and/or gene therapy. Data collection continued until the point of thematic saturation [7].

Data analysis

Interviews were audiotaped and transcribed; transcripts for each participant were then manually coded and analysed for emerging themes by the primary author following the principles of qualitative description detailed by Thorne et al. [7]. To ensure data reliability and validity, three members of the study team, also genetic counsellors, independently reviewed original transcripts and themes, and discussed coding discrepancies until consensus was achieved.

RESULTS

Study participants

Eleven individuals expressed interest in participating in the study, and ten met inclusion criteria (Table 1). Five males and five females participated at a mean age of 24.4 years.

Themes identified

The qualitative analysis identified three major themes and subsequent subthemes expanded upon below: (1) Meaningful Vision; (2) Participating in Gene Therapy Clinical Trials, (2.1) Expectations, (2.2) Motivations and Barriers; and (3) Personal Factors, (3.1) Upbringing/Environment, (3.2) Self-Esteem, (3.3) Self-Acceptance, (3.4) Coping.

Meaningful vision. Participants were asked what they would consider being a meaningful improvement in their vision (Table 2). For many, meaningful vision was not limited to one specific parameter. While some (4) indicated that 'being able to read or see print, even if it required the use of assistive devices' would be meaningful, another individual wanted the independence and ability to read without using assistive devices as this takes a longer time.

Other common responses included recognising faces (3), identifying stoplights at intersections (2), and being able to drive (2), and one wanted to decreased reliance on their partner (Table 3). Three participants expressed that identifying and differentiating between objects would ease functioning in daily life, allow for more independence and lift the burden of asking others for help. Two participants wished to see colour; for one participant, this was the only improvement they shared as being meaningful. In contrast to this response, another participant described the only meaningful improvement in vision: gaining 20/20 vision or as close as possible. One individual would be satisfied to maintain their current level of vision to not have to continue to adapt to the gradual vision loss they were experiencing (Table 3).

Participating in gene therapy clinical trials: expectations, motivations, barriers. Most participants actively sought information regarding advances in ophthalmology and vision restoration, they were all aware of ongoing gene therapy research trials, and many were able to describe the basis of this technology. Of the ten participants, two were enrolled in a gene-replacement trial, five indicated the desire to participate if given the opportunity, two were ambivalent about participating in the trials, and one would not participate if given the opportunity.

Expectations: *General expectations* The two participants enrolled in a clinical trial at the time shared their expectations for visual improvements before receiving gene therapy. One individual did not describe a desired level of improvement pre-trial and tried not to think about possible outcomes to prevent feeling disappointed with the trial. The other participant expected some vision improvement based on personal research and perceived this potential benefit to outweigh any risks perceived with gene therapy, including losing their current vision.

Of the five individuals who would participate but were not currently enrolled, all but one expressed that they would take whatever improvements they could get. One participant required a guarantee of their described level of meaningful vision to enrol in such a study (Table 3).

Two individuals were ambivalent; they grew comfortable living with low vision but also wanted proven efficacy from the therapies. The individual who did not want to participate in gene therapy trials would avoid experimental techniques that did not have proven efficacy and known side effects or risks. In addition,

Table 3. Illustrative participant quotes for each theme.

Themes	Quotes
(1) Meaningful Vision	*a. "I would say anything, but a meaningful improvement would be one that, say, enables me to see, like, see at night or maybe even drive so that, you know, my wife doesn't have to do everything." [GT09]*
	b. "My sight to stabilise and not get weaker,… it's deteriorated over the years, but it's, you know, the past year or two where it's deteriorating even more, like, at a pace that I can notice. And, you know, if there was something out there to stop it from changing, then that would suffice for me/…/It would make me feel that, you know, I wouldn't have to keep adapting to change" [GT11]
(2.1.1) General Expectations	*c. "If it's not going to make a meaningful difference in my life, then I don't really see the point" [GT07]*
	d. "I'm always a little bit afraid of trying something that's sort of in an experimental phase/…/I'm also a little concerned about how those improvements would actually change my life and make it difficult in other ways/…/I would never be the guinea pig for it." [GT06]
(2.1.2) Adaptation to Sight	*e. "I would have to learn how to read print. I would have to learn a new world… How would I learn everything because I learned the world in a different way" [GT01]*
	f. "…So, you know… You know, and I'm used to coping with things on my own. So, I don't think I would be needing any support" [GT07]
	g. "If someone was to say to me… give you full vision, like, sight you've never had"… it would be scary because all of the sudden you're able to see all this detail you've never seen before. And, do you really want to see all that detail, right?" [GT11]
	h. "It would be very hard for me to deal with feelings of relief from others. Kind of how do I deal with sort of my past life? And, you know, if I woke up tomorrow and could see 20/20, would that… would I then see people's… You know, if there were certain people in my life that had not been very kind of discriminatory or, you know, whatever the word, you know, just not very open minded and all of a sudden, they see that I can see and they, quote, "want to be your friend" it would create a lot of issues for me. I'm not really sure how easy that would be to handle actually. So, yeah, I think it would change a lot of things. I don't think it would change… Hopefully I'd still come out of it being myself, which is the most important thing; but I think it would definitely be major. There'd be a lot of life changes out of that." [GT06]
(2.1.3) Identity and Self-Perception:	*i. "I would have more hopes of doing things I think and I would feel more comfortable. And I think I would be less nervous." [GT01]*
(2.2) Motivations and Barriers	*j. "I trust my doctor more than I would probably trust a researcher whom I've never met before/…/If it's gone through, like, this huge process, then yeah, you know, then it's obviously legit; otherwise it wouldn't have happened." [GT07]*
(3.1) Upbringing/Environment	*k. "…people like to eat steamed fish. ….. when there's a steamed fish in front of me it's hard for me to, you know, pick apart the bones and just, you know, pick out the flesh without ruining the whole fish. So, my parents' solution to that is to, you know, just kind of convince me that I don't like fish, so they don't have to teach me to do it or they don't have to… and they don't have to do it for me…/…/I would say it has made me more timid." [GT09]*
	l. "I did all the chores and everything. And then, I worked in bakery. And now, I'm going to college. So, I don't seem to be missing out on anything" [GT05]
(3.2) Self-Esteem	*m. I think sometimes blindness or maybe other disorders cause self-esteem to grow low. And, you know, I think this will, you know, kind of grow it and make it better and because the people will have hope" [GT01]*
(3.3) Self-Acceptance	*n. "If you'd asked me ten years ago, does this have to do with your identity, I would have said no way because my idea is, the way I look at it I have a condition; I don't have an illness/…/it was something that I did not like to kind of factor into my identity. And, I think now I'm starting to realise that there are certain things to kind of, you know, embrace" [GT06].*
	o. "It's part of who I am/…/you've got to be proud of who you are and you've got to accept yourself and that's all aspects of yourself, right, just like someone would need to accept if they have red hair versus black hair." [GT11]
	p. "Some people look at you differently when they see you have a visual impairment and a lot of people think you can't do a lot of things and people have to do it for you and stuff like that; but, at the same time, it all comes with education. You have to kind of educate people" [GT08]

Legend: [GT#] - participant identifier.

there was a fear that improvement in their vision might create unforeseen challenges.

Adaptation to sight Participants identified expectations related to coping and adaptation to visual improvements. Some patients anticipated challenges learning to use vision to function in a sighted world (Table 3). Although many participants identified that there would be a lot to learn if their vision was improved, not all participants thought they would need help in this transition and adaptation process (Table 3). Some individuals felt it would not be difficult to adjust to visual improvements if they were simply restoring vision to a level prior to deterioration; however, they felt it might be anxiety-provoking to suddenly experience dramatically improved vision (Table 3). One individual anticipated psychological and emotional difficulties that could also accompany improvements in vision (Table 3).

Identity and self-perception How a meaningful improvement in vision was perceived to affect one's identity and self-perception varied between participants. One participant believed that changes in their vision would positively alter their outlook on life, while others could not define how their identity would change (Table 3). For some, this was because they had never experienced improvements to their vision and felt unable to predict internal reactions to having better sight. In contrast, others predicted

personal transformations but could not determine the extent and impact it might have on self-perception.

Motivations and barriers: Participants shared motivations and perceived benefits and risks of enrolling in trials. A primary motivation was the belief or hope of experiencing an improvement in their vision. Some individuals would be more inclined to participate if they knew someone who enrolled and reported a positive experience with gene therapy; this individual should be of comparable age and gender and share a similar life experience with the participant. For other participants, a motivating factor and benefit would contribute to medical advancements and knowledge that would ultimately benefit others.

When asked how willing they were to receive gene therapy, if it was found to be successful in research trials and became available clinically, all participants said they would likely receive therapy if offered as routine by their ophthalmologist. They expressed greater trust in a hospital procedure than a research test because of the successes and lack of risks perceived to be associated with those circumstances (Table 3). The two individuals enrolled in clinical trials would enrol in future clinical trials if they were eligible. Both shared similar views and would prefer to continue research trials with their current research team rather than a new team. Reasons included trust, good working relationships, and the fact that the current team would have intricate knowledge of their ocular history.

Demonstrated improvements from early trial results motivated some, while a lack of long-term success and proven efficacy were barriers for others. Several participants considered the loss of their current vision to be a risk of gene therapy. Others feared it would not lead to gains in vision or that gains would be followed by regression. Some individuals spoke about the probability of adverse outcomes; they would not participate if risks associated with gene therapy were equally likely to occur as an improvement in vision. Many individuals were unsure what risks would be associated. However, one wondered about cancer in the eye and another about developing an illness due to the gene and/or viral vector. Still, some participants did not associate any particular risks with gene therapy itself.

Personal factors. During the interviews, participants shared a number of their experiences with low vision and revealed a range of personal factors that influence how they orient to low vision. This included upbringing and current environment, self-esteem, self-acceptance, and coping with and adapting to low vision.

Upbringing/environment: One major influence for participants to pursue gene therapy was their childhood experience with low vision, as well as their current environment, particularly regarding the level of support and acceptance of family members, peers and strangers. Some spoke about the limitations they experienced in childhood and how this has shaped their character (Table 3). Others did not feel that they were treated any differently or that their vision held them back in any aspect of their lives; they felt accepted for who they were (Table 3).

Self-esteem: Throughout the interviews, many participants spoke about how their self-esteem has been affected by their LCA diagnosis. Their self-esteem fluctuated throughout their lives, with lower self-esteem occurring most often in adolescence, usually due to feeling different from their peers (Table 3). Other participants thought their vision had little or no effect on their self-esteem and self-confidence as young adults despite having lower self-esteem during childhood and adolescence.

Self-acceptance: Self-acceptance was identified in individuals who have overcome low self-esteem. It was evident when speaking about identity, experiences with peers, and education and career paths. Similar to self-esteem, self-acceptance has been an ongoing process that may have taken more time for some than for others (Table 3). Many of these young adults shared that their LCA diagnosis shaped their being and that they would likely be very different had they not had the same experiences. Individuals who fully accepted their low vision spoke with a sense of confidence about their self-identity (Table 3).

Self-acceptance was also demonstrated through their comfort in discussing their vision with others. All participants shared that they are open to discussing their low vision with family, friends and new acquaintances; however, it can be a repetitive process of which they tire. A number of the participants spoke about ignorance and lack of knowledge in the general public about blind and low vision populations. Some individuals took on the role of educators when speaking about LCA and stressed the importance of informing others about their abilities and capabilities (Table 3).

Coping: Participants shared how they coped with low vision. Though some were mentally prepared for a life with low vision, coping was challenging when participants felt isolated from friends and family who did not want to talk about it. Many explained that coping is an ongoing process, regardless of self-acceptance. One participant shared that coping has gone hand in hand with their adaptation to vision loss and that perspective was an important part of the coping process. The prospect of meaningful visual improvements was often associated with independence, and for one participant, coping with their low vision was more difficult as an adult than it was as a child.

DISCUSSION

The purpose of this study was to explore how young adults with LCA perceive gene therapy using a qualitative approach. This work identified numerous factors that influence decision-making to receive gene therapy or participate in a gene therapy trial. Various complex personal factors that shape identity, self-esteem, and expectations highlight the need to attend to these factors/experiences through patient-centred care. This medical framework looks to incorporate the patient's perspective in patient care [8].

For adolescents and adults, vision loss can be a difficult adjustment. Many individuals affected with progressive retinal dystrophies find themselves in a phase of constant adjustment. Outcomes to adjustment and coping are closely linked to the perception that personal identity includes vision impairment [9, 10]. In the context of clinical care, it is, therefore important to explore how the role of personal identity influences one's decision to partake in or consider receiving gene-replacement therapy to improve vision.

In this study, the definition of meaningful improvement in vision varied between participants. Most participants wanted to improve their independence through new abilities, including reading text and driving. Greater independence was perceived to increase the opportunity for new experiences. Independence was also linked to many aspects of behavioural autonomy, which can be established by mastering skills, including self-regulation, implementation of personal decisions and pursuit of goals [11, 12]. Individuals with LCA may perceive themselves to have limited behavioural autonomy due to their low vision, which can explain why a meaningful improvement in vision is often correlated to increased independence. Determining the patient's sense of behavioural autonomy would help in clarifying their expectations about independence.

Patients with retinitis pigmentosa may struggle to maintain independence and be highly motivated to participate in research trials [13]. In this study, most participants were willing to enrol in gene therapy clinical trials. Motivations and barriers to participation in gene therapy trials discovered in this work are similar to

other disease-specific populations and perceptions from the general public [14–17]. However, this study identified vision-specific motivations that included the hope for visual improvement, sense of contribution to medical research, low perceived risk of complications, and trust in researchers/clinicians associated with the trial [18]. Barriers included lack of proven efficacy and long-term results, fear of temporary improvement only, loss of current vision, no visual improvements or potential adverse health effects.

An advantage of the qualitative approach is the opportunity to explore underlying personal characteristics that influence an individual's responses, such as factors that contribute to the willingness to participate in gene therapy trials by assessing participants' expectations, motivations, and hesitancies. Individuals alluded to the theme of self-protection in various ways when referring to motivations and expectations for gene therapy. For some, this was demonstrated by minimising expectations for vision improvement, while others exhibited self-protection by abstaining from enrolment until gene therapy can guarantee a defined level of improvement.

For some individuals, trust came with knowledge. Some participants wanted to conduct their own research about a therapy, while others were more inclined to participate if their ophthalmologist administered the gene therapy or after speaking to someone who had been in a trial and reported a positive experience, trusting the account of others. The trust towards the patient's ophthalmologist highlights the importance of keeping the community of eye care providers educated and informed about treatment opportunities [18].

Perceived risks of gene therapy influenced willingness to participate in these clinical trials. Several factors prompted hesitation to participate in a clinical trial, including losing current sight, not gaining sight, adverse health effects and lack of data supporting efficacy. While risk averse individuals were less willing to enrol in gene trials, most participants were willing to enrol in gene therapy trials suggesting they are highly motivated to restore vision.

An individual's degree of self-acceptance of being visually impaired influenced the decision-making process. Participants who reported less acceptance of low vision were motivated to undergo therapy to gain more vision and independence but predicted disappointment if gene therapy could not increase vision. Individuals who had accepted their vision loss were less concerned if gene therapy could not provide a meaningful visual improvement. These individuals also described higher self-esteem. This aligns with studies in the deaf population, where individuals who identify as deaf have higher self-esteem due to self-acceptance [19].

Factors that influence identity contribute to the development of resilience, which is formed by achieving positive adaptation in the face of adversity [20]. Meyer [21] described blindness as a continual struggle with adversity and demonstrated that adults with visual impairments report challenges in their social interactions [22]. Participants in this study shared adverse experiences and challenges, which included interacting with others ignorant to their abilities, including difficulties in education and academics. Resilient participants had a positive adaptation to low vision. In this study, some participants anticipated functional and emotional issues to accompany potential changes in vision. Clinicians have a role in considering the patient's qualms and suggesting tools to build resilience to best adapt to vision change.

As such, with the insight patient's perspectives provide in considering gene therapy, this paper highlights the value of patient-centred care. One way to incorporate this framework into practice could include incorporating recently developed IRD-tailored patient-reported outcome measure (PROM) questionnaires into our practices [23, 24].

Study limitations

This work captured detailed descriptions that provide insight into adult LCA patient perceptions of gene therapy and related clinical trials. We acknowledge that patients' perceived motivations and barriers may differ depending on the nature of their condition, the stage of their condition, their experience with the condition and the technology utilised in the trial. Including a larger participant sample could enable us to explore these nuances.

This is the only study exploring the perception of adult LCA patients on gene therapy. As several clinical trials now include children [3], including the perspectives of children and their caregivers about gene therapy would be worth exploring to best guide the decision-making processes and optimise patient and family-centred care.

In summary, most LCA participants were willing to enrol in gene therapy trials if provided the opportunity. Other factors contributing to the decision-making process included trust, risk perception and self-protection. Individual perspectives on gene therapy also varied based on an individual's self-acceptance, identity, and personal resilience, which are, in part, developed through adaptation to low vision, experiences and interactions within each individual's social environment. This study highlights the complex factors involved in gene-therapy-related decision-making and provides insight for eye care providers, both in patient's perceptions on gene therapy and the inherently the advantages of patient-centred care. New information should be disseminated broadly to allow a realistic description of the expectations from gene therapy trials. It may be useful to implement a preparatory questionnaire or systematically assess PROM in this patient population to better understand the patient, guide decision-making and set clear expectations.

SUMMARY

What was known before

- We explored the perspective of adult patients with LCA on gene therapy. Though most patients were interested, not all were. Patients have confidence in their primary eye provider to provide guidance.

What this study adds

- There were no such studies at time of submission. This work highlights the value of including the patient perspective in order to optimise decision making and that their expectations must be explored.

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AUTHOR CONTRIBUTIONS

MN: Study design, data collection and analysis, paper writing. KS: Paper finalisation, edits. RZH: Supervision, study design, data analysis, edits. CS: Supervision, study design, edits. DC: Supervision, study design, edits. JS: Data analysis. MD: Data analysis. EH: Supervision, study design, paper finalisation, edits.

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COMPETING INTERESTS

EH is consultant for Novartis and on a DSMB (for Sanofi Atsena). The authors declare no competing financial interests related to this publication.

ADDITIONAL INFORMATION

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