CADTH

CADTH COMMON DRUG REVIEW

Ethics Review Report

VORETIGENE NEPARVOVEC (LUXTURNA)

(Novartis Pharmaceuticals Canada Inc.)

Indication: Vision loss, inherited retinal dystrophy

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	January 2021
Report Length:	2 Pages

CADTH

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

Tables

Figure

Objective

The purpose of this report is to describe and summarize the ethical considerations raised explicitly in the literature associated with the use of voretigene neparvovec for the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy.

Research Question

This report addresses the following research question:

- What are the ethical considerations raised in the published literature relevant to the use of voretigene neparvovec for the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic retinal pigment epithelium 65 kDa protein (RPE65) gene mutations and who have sufficient viable retinal cells?

Methods

Data Collection: Review of Empirical and Normative Ethics Literature

A review of the empirical (i.e., focused on explaining *what is* through observation) and normative (i.e., focused on explaining *what ought to be* through argumentation) ethics literature was conducted to identify literature relevant to the identification of the potential ethical considerations related to the use of voretigene neparvovec.

Literature Search Methods

The search for literature identifying explicit ethical considerations was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist (www.cadth.ca/resources/finding-evidence/press).[1] The search strategy is available on request.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) through Ovid, the Cumulative Index to Nursing and Allied Health Literature (CINAHL) through EBSCO, and Scopus. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The main search concepts were *voretigene neparvovec* (Luxturna) and *retinal dystrophy*. This enabled the broad capture of the experiences and views of people with retinal dystrophy that might be applicable to individuals who could be candidates for voretigene neparvovec.

Search filters were applied to limit retrieval to citations related to empirical and normative ethical considerations. Retrieval was not limited by publication date but was limited to the English or French language. The search was completed on June 3, 2020.

Literature Screening and Selection

The selection criteria can be found in Table 1.

Eligible reports were those published in English or French that explicitly identified normative or empirical ethical considerations relating to the use of voretigene neparvovec.

Descriptions of the experiences of adult and pediatric patients with vision loss due to inherited retinal dystrophy were sought because they related to the potential use of voretigene neparvovec. Descriptions of the experiences of family members of patients with vision loss due to inherited retinal dystrophy were also included. The following types of articles and publications were included: primary or secondary research, normative analysis, opinion, commentary, and book or book chapter.

Table 1: Selection Criteria

Population	Adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells
Interventions	Voretigene neparvovec or standard of care
Context	Any health system
Outcomes	Ethical considerations arising in the use of voretigene neparvovec or the experience of living with retinal dystrophy
Article and publication types	Primary or secondary empirical research, normative analysis, opinion, commentary, and book or book chapter

RPE65 = retinal pigment epithelium 65 kDa protein.

The selection of relevant literature proceeded in 2 stages. In the first stage, the title and abstracts of citations were screened for relevance by a single reviewer. Articles were categorized as *retrieve* or *do not retrieve* according to the selection criteria outlined in Table 1 and whether it:

- explicitly provided a normative analysis (i.e., focused on explaining *what ought to be* through argumentation) of an ethical consideration arising in the use of voretigene neparvovec or from experiences of living with retinal dystrophy relevant to the indicated population
- presented empirical research (i.e., focused on explaining *what is* through observation) directly addressing an ethical consideration arising in the use of voretigene neparvovec or from experiences of living with retinal dystrophy relevant to the indicated population
- explicitly identified, but did not investigate empirically, an ethical consideration arising from the use of voretigene neparvovec or from experiences of living with retinal dystrophy relevant to the indicated population.

In the second stage, the full-text reports were reviewed by the same reviewer. Reports meeting the aforementioned criteria were included in the review; reports that did not meet these criteria were excluded. Members of the CADTH review team were consulted to resolve uncertainties related to the eligibility of full-text reports.

Data Extraction

One reviewer extracted basic details on publication characteristics using a data extraction form. The following publication details were recorded: first author, article title, publication objectives, characteristics of study design and methodology, date of publication, country with which the first author is affiliated, and key findings identified that related to ethical considerations.

Data Summary

One reviewer conducted 2 cycles of coding. In the initial coding phase, the publications were reviewed for ethical content. The Core Model 3.0 (Ethical Analysis Domain)[2] questions

deemed by EUnetHTA (European Network for Health Technology Assessment) as "critically important" were used as a guide to identify and categorize ethical considerations related to the use of voretigene neparvovec. The Core Model was chosen because it is a wide-ranging framework; the assessment questions in the domain are intended especially for identifying ethically relevant issues and conflicts.[2] This guiding framework highlights the context of the technology and focuses on the following topics: benefit-harm balance, autonomy, respect for persons, justice and equity, legislation, and ethical consequences of the health technology assessment.

Once identified, passages related to ethical content were coded using qualitative description methods.[3] The initial descriptive coding of the reports focused broadly on categories concerning the ethical considerations described. Major themes and sub-codes were identified through repeated readings of the data.[3] Once sub-codes emerged, they were deductively applied to all reports in the set, and the ethical content was summarized and sorted into the thematic categories. This review focused on ethical considerations relating specifically to the use of voretigene neparvovec. Other ethical considerations raised in the literature but not related to the use of voretigene neparvovec (e.g., family planning of individuals with genetic mutations or gene editing to prevent the occurrence of inherited retinal diseases[4]) were outside of the scope of the current review and are not included in the summary.

NVivo 11[5] was used to extract and manage these data.

Results

Description of Included Publications

A total of 399 citations were identified in the literature search. Following the screening of the titles and abstracts, 370 citations were excluded and 29 potentially relevant reports from the electronic search were retrieved for full-text review. Of these potentially relevant reports, 20 publications were excluded for various reasons, such as they did not explicitly describe ethical considerations related to the use of voretigene neparvovec (n = 16),[6-21] they noted that ethical considerations related to the use of therapy exist without identifying what those considerations entailed (n = 2),[22,23] or they described the experiences of a population that were not transferable to the indicated population (n = 2).[24,25] Nine publications met the inclusion criteria and were included in this report. Figure 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart of the study selection process.

Details regarding the characteristics of the included publications are reported in Table 2. One of the included reports[4] was specifically on the topic of voretigene neparvovec for the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy. One report examined the development and delivery of gene therapy and cell therapy to individuals with retinal dystrophy,[26] and 1 study reported individuals' perspectives on gene editing and gene therapy specifically for the treatment of retinitis pigmentosa and Leber congenital amaurosis.[27] The remaining 6 studies[28-33] reported the experiences of individuals living with inherited retinal dystrophies that were transferable to the indicated population.

Key Ethical Considerations From the Literature

Patient Diagnosis and Selection

A molecular diagnosis of *RPE65* mutations must be obtained to determine candidacy for treatment with voretigene neparvovec. The authors of a position paper[26] noted that a molecular diagnosis is an essential factor in equitable access to gene therapy.

Authors of a study[4] noted the importance of having genetic testing conducted by those with ophthalmic genetics expertise who are able to interpret the results for the patient, in collaboration with a genetic counsellor. The authors noted that inaccurate genetic test results can provide patients with incorrect information about their diagnosis and may result in inappropriate and/or ineffective treatment or potentially no treatment for patients who would be eligible.[4]

Treatment Decision-Making and Management of Expectations

Overall, people with inherited retinal conditions held diverse attitudes with respect to gene therapy for visual conditions, and these attitudes were shaped by their experiences with blindness.[27] The authors of 1 publication suggested that diverse attitudes point to a need for shared decision-making and careful consideration of individuals' perceived quality of life when discussing treatment possibilities.[4] Decision-making discussions should be clear about the risks and benefits of the treatment and should clarify patients' expectations.[4] Furthermore, the authors noted it was important for patients and their parents to understand that voretigene neparvovec is a treatment and not a "cure" (p. 675)[4] and that the long-term effectiveness is currently unknown.

The Medicalization of Blindness and Its Effect on Stigma

Some participants with inherited retinal conditions noted that treatment for blindness could remove social barriers, such as discrimination (particularly related to employment), negative social attitudes, and lack of accessibility.[27] Participants also noted, however, that therapies could potentially exacerbate those social barriers for people living with blindness who might not be eligible for treatment.[27] Additionally, participants expressed concern about the way that messaging surrounding gene therapies communicated by researchers, family members, and the media frames blindness as something that needs to be "fixed" (p. 7),[27] which might contribute to discriminatory attitudes toward blindness and increase stigma.

Some participants with inherited retinal conditions expressed concern that the implementation of gene therapies might have a negative impact on how sighted people raise their blind children, leading them to "go through life waiting for a cure rather than living life" (p. 8).[27]

Challenges Related to Adjusting to and Living With Visual Impairment

Participants with inherited retinal conditions observed that attitudes toward blindness might differ between individuals who were blind from an early age and those who became blind later in life.[27] In 1 study sample, participants who became blind in adolescence or adulthood expressed more negative feelings about being blind, and the impact it had on their lives, than those who had been blind since birth or childhood.[27]

Living with visual impairments has been identified as a potential cause of feelings of inferiority and low self-esteem, affecting individuals' social relationships and leading to reduced academic achievement, poor social adjustment, and struggles with employment.[28,29,33] Participants lamented the increasing loss of autonomy and independence that underscored their condition.[28,30] Not being able to engage in their usual activities had implications for individuals' sense of identity and led to feelings of isolation or feeling like a burden or nuisance to others.[28,32]

Young Children as a Vulnerable Population

In 1 study, participants with inherited retinal conditions raised concerns about autonomy and the process for obtaining consent for treatment when parents make decisions for children.[27] Although parents are often asked to make decisions on behalf of their minor children, some participants expressed concerns about sighted parents making decisions on behalf of their children based on a limited understanding of life as a blind person.[27] Moreover, the authors of 1 review[4] on gene therapy for *RPE65*-related retinal disease noted additional considerations of risks for children under the age of 5, for whom the post-operative examination for complications may be difficult and who could require additional exposure to anesthesia to ensure potential complications are treated quickly.

Costs to Caregivers and Society

Some authors noted that indirect costs related to visual impairment can include the costs of non–health care resources such as accommodations for school and informal caregiving support.[4,29]

Inherited retinal diseases affect the quality of life and emotional well-being of not only the individuals with the condition, but also their family members.[29,32] Anxiety levels among family members of individuals with retinitis pigmentosa, for example, are very close to those of adults with retinitis pigmentosa themselves.[29]

Limitations

This review is limited by the lack of published literature examining ethical considerations relevant to the use of voretigene neparvovec for the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy. No published ethical analyses were retrieved on the topics of voretigene neparvovec or retinal dystrophies. One study examined broad challenges, including ethical considerations, related to *RPE65* gene-replacement trials.[4]

The absence of published ethical analyses does not indicate that ethical considerations are not present. Indeed, some retrieved studies[14,23] noted that ethical issues related to gene therapy had yet to be solved. (Note: these studies, which pointed to ethical considerations but provided no further details or analysis, were omitted from the final set of reports in accordance with the selection criteria.)

Finally, this review is limited to the ethical considerations explicitly discussed in the published literature. Some of the results and insights raised relating to clinical benefits and costs are discussed more comprehensively in the clinical and pharmacoeconomic review sections.

Figure 1: Flow Diagram for Inclusion and Exclusion of Publications

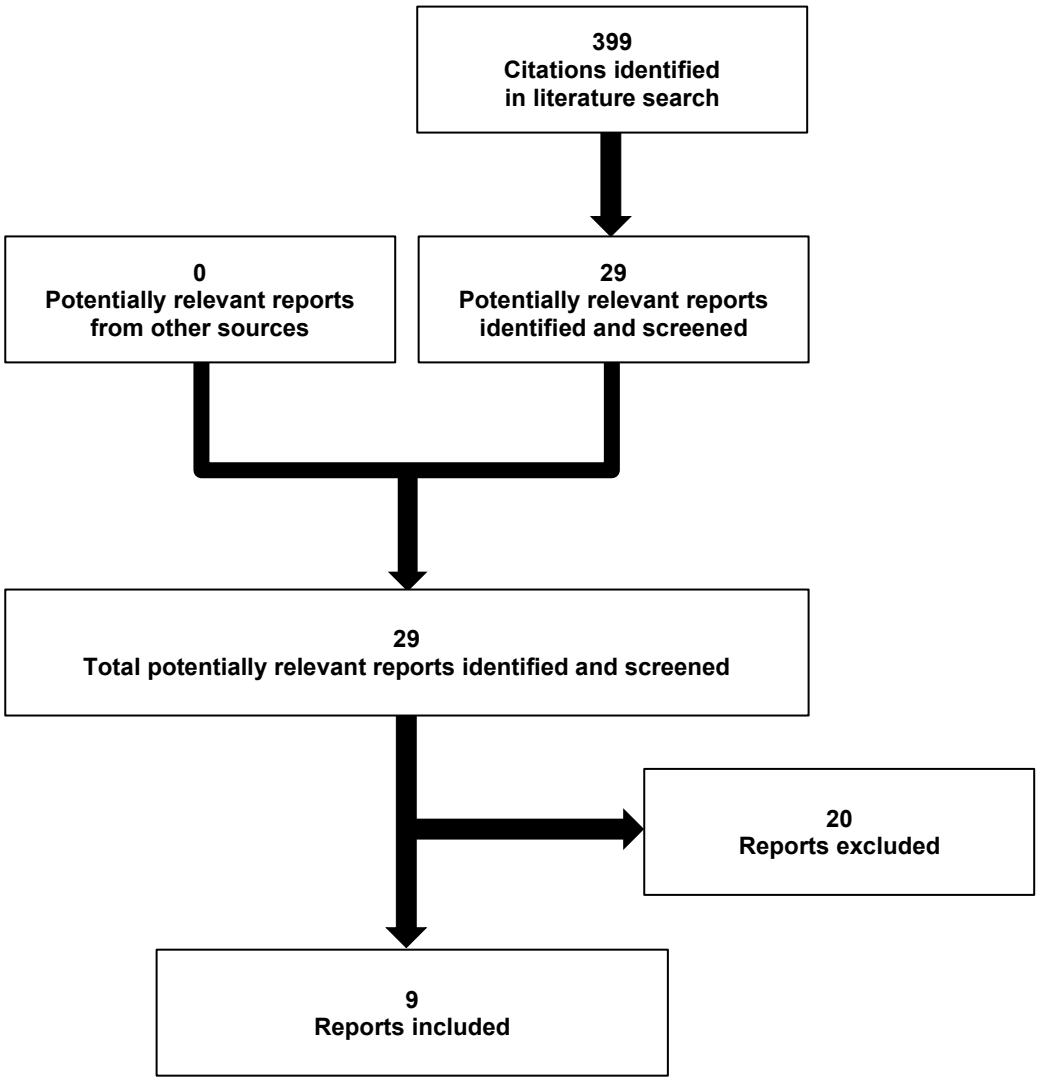

Table 2: Details of Included Publications

First author (year)	Country	Publication type	Objective	Key ethical considerations	Funding source
Garip (2019)[28]	Studies included were from Australia, Brazil, Ireland, Netherlands, Republic of Korea, UK, and US	Systematic review	The aims of this systematic review and the meta-synthesis were to combine qualitative findings on coping strategies and quality of life in people with RP. The objectives were: • to identify coping strategies used by adults living with RP • to present how these findings may inform interventions to improve quality of life in this population.	Policies are needed to ensure the workplace and public settings are conducive for people with RP to engage in daily activities. For people living with RP, behavioural and psycho-educational interventions focusing on acceptance of the condition, communication skills to explain abilities and help needed from others, and planning ahead for dealing with progressive vision impairment can be offered to develop skills to self-manage RP. For health care professionals, interventions for raising awareness of the impact of communication style on people's emotional states and variations in people's need for factual, emotional, and practical information related to an RP diagnosis could be developed to help facilitate better adaptation and coping with the condition.	This article was written during a research sabbatical supported by the University of Derby.
Hoffman-Andrews (2019)[27]	US	Qualitative study	To explore the views of people with RP and LCA toward gene editing for somatic, germline, and enhancement applications, both related to these conditions and more generally, and how these attitudes are informed by their experiences with and attitudes toward blindness.	Participants in this study, even when they expressed concerns about gene editing, still believed it had potential benefits and thought research, at least for some medical applications, should continue. Many also raised concerns about how the	Not reported.

First author (year)	Country	Publication type	Objective	Key ethical considerations	Funding source
				clinical use of gene editing could impact blind people and society. Many individuals may consider their blindness to be an important and valuable part of who they are. Freedom of choice and informed consent — including accurate, unbiased information about the lives of blind people for sighted parents considering gene editing for their children — are vital. And societal investment in accessibility and inclusion must not be impacted by the prospect of a "cure" or treatment for certain forms of blindness, nor should access to resources be impacted by an individual's choice to access gene editing.	
Miraldi Utz (2018)[4]	US	Review	To discuss *RPE65* gene-replacement trials and highlight the results of a trial for the treatment of *RPE65*-associated retinal dystrophy. To highlight the challenges with patient selection, counselling, access to care, and implications for future gene therapy trials.	Challenges arise in diagnosis, informed consent, cost, and access to treatment. The development of innovative disease-specific outcome measures to determine the efficacy of voretigene neparvovec help to pave the way for other gene therapy trials.	Not reported.
Thompson (2015)[26]	An international group of clinicians and scientists convened in Italy	Position paper	To define the next steps needed to accelerate the development and delivery of gene therapy and cell therapy to a broad cross-section of retinal dystrophy patients in the next decade and beyond.	A critical goal for moving the field forward is to obtain a genetic diagnosis for every patient in the retinal dystrophy population.	Not reported.

First author (year)	Country	Publication type	Objective	Key ethical considerations	Funding source
Chacón-López (2014)[29]	Spain	Review	To review the history of functional repercussions of RP in terms of education, affect and emotional state, and family relationships of adolescents and young people with RP. To suggest psychological and educational actions aimed at making work with young people and adolescents with RP easier.	Adolescence is a complex period for any individual, particularly someone with a degenerative disease. Understanding how they feel and how they face their condition should translate into a higher quality of life.	Not reported.
Bittner (2010)[30]	US	Qualitative study	To explore the successful ways in which legally blind RP patients manage their vision loss, and the stressful challenges that ensue, by means of effective coping strategies.	RP patients recognize that stress will arise from their visual impairment and, while some stress-management techniques are specific to their vision loss, most others reflect general ways to relieve stress. Some patients will plan activities around their daily fluctuations in vision or will slow down to wait for their vision to recover. The coping strategies used most widely were humour and laughter, social support from others with RP, increased awareness, and prioritizing. Patients expressed preferences for different coping approaches for stress, and although various types of activities were mentioned, many were forms of escape or distraction.	Not reported.
Fourie (2007)[31]	Ireland	Qualitative self-study	To understand the author's personal identity and attitudes toward	Individuals may feel threatened by the perceived loss of normalcy in a society	Not reported.

First author (year)	Country	Publication type	Objective	Key ethical considerations	Funding source
			blindness following a diagnosis of RP. To transform private experience into public insight and solutions.	that seems to highly value “normal.”	
Jangra (2007)[32]	Canada	Cross-sectional study	To measure specific domains of psychosocial adjustment to visual loss in a sample of patients who are legally blind as a result of RP using the Psychosocial Adjustment to Illness Scale.	Individuals with RP have difficulty adjusting to their vision loss, particularly with respect to health care orientation, vocational environment, social environment, and extended family relationships.	Not reported.
Hayeems (2005)[33]	US	Qualitative study	To explore the process of adjusting to the loss of visual function associated with RP through a qualitative approach. To develop a model for ophthalmologists to consider in their efforts to understand and lessen their patients’ suffering.	The proposed adjustment model is a way of understanding the process of adjusting to RP and could assist ophthalmologists in meeting their moral obligation to lessen patients’ suffering.	This project was made possible by an anonymous gift.

LCA = Leber congenital amaurosis; RP = retinitis pigmentosa; RPE65 = retinal pigment epithelium 65 kDa protein.

References

1. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. *J Clin Epidemiol.* 2016;75:40-46.
2. EUnetHTA Joint Action 2 Work Package 8, HTA Core Model ® version 3.0 2016; www.htacoremodel.info/BrowseModel.aspx. Accessed 2020 Aug 20.
3. Sandelowski M. Whatever happened to qualitative description? *Res Nurs Health.* 2000;23(4):334-340.
4. Miraldi Utz V, Coussa RG, Antaki F, Traboulsi EI. Gene therapy for RPE65-related retinal disease. *Ophthalmic Genet.* 2018;39(6):671-677.
5. QSR International Pty Ltd. *NVivo Version 11 [computer program].* 2015.
6. Combs R, McAllister M, Payne K, et al. Understanding the impact of genetic testing for inherited retinal dystrophy. *Eur J Hum Genet.* 2013;21(11):1209-1213.
7. Korf BR, Rehm HL. New approaches to molecular diagnosis. *JAMA.* 2013;309(14):1511-1521.
8. McVeigh E, Jones H, Black G, Hall G. The psychosocial and service delivery impact of genomic testing for inherited retinal dystrophies. *J Community Genet.* 2019;10(3):425-434.
9. Ogawa J, Bodurtha J. Gene therapies show promise for pediatric treatment. *Contemp Pediatr.* 2020;37(3):26-28.
10. Justus S, Zheng A, Tsai YT, et al. Genome editing in the retina: a case study in crispr for a patient-specific autosomal dominant retinitis pigmentosa model. *Genome Editing*: Springer International Publishing; 2016:149-162.
11. Bainbridge JW, Tan MH, Ali RR. Gene therapy progress and prospects: the eye. *Gene Ther.* 2006;13(16):1191-1197.
12. Hows J. Adult stem cell therapy beyond haemopoietic stem cell transplantation? An update. *Transpl Immunol.* 2005;14(3-4):221-223.
13. Trenaman L, Pearson SD, Hoch JS. How are incremental cost-effectiveness, contextual considerations, and other benefits viewed in health technology assessment recommendations in the United States? *Value Health.* 2020;23(5):576-584.
14. Canto-Soler V, Flores-Bellver M, Vergara MN. Stem cell sources and their potential for the treatment of retinal degenerations. *Invest Ophthalmol Vis Sci.* 2016;57(5):ORSFd1-9.
15. Chacón-López H, López-Justicia MD, Vervloed MPJ. Psychological and educational recommendations for working with young people with retinitis pigmentosa. *Sch Psychol Int.* 2011;35(4):357-369.
16. Charters L. Blazing a new trail in gene therapy for retinal disease: achievements, trends highlighting promise for new treatment options. *Ophthalmology Times.* 2020;45(2):16-16.
17. Gilbert C, Foster A. Childhood blindness in the context of VISION 2020--the right to sight. *Bull World Health Organ.* 2001;79(3):227-232.
18. Hamel CP. Cone rod dystrophies. *Orphanet J Rare Dis.* 2007;2:7.
19. Hamel C. Retinitis pigmentosa. *Orphanet J Rare Dis.* 2006;1:40.
20. Jay M, Evans K. Retinal dystrophies and genetic counselling. *Acta Ophthalmol Scand Suppl.* 1996(219):5-7.
21. Potrata B, McKibbin M, Lim JN, Hewison J. "To perpetuate blindness!": attitudes of UK patients with inherited retinal disease towards genetic testing. *J Community Genet.* 2014;5(3):215-222.
22. Apatoff MBL, Sengillo JD, White EC, et al. Autologous stem cell therapy for inherited and acquired retinal disease. *Regen Med.* 2018;13(1):89-96.
23. Enzmann V, Yolcu E, Kaplan HJ, Ildstad ST. Stem cells as tools in regenerative therapy for retinal degeneration. *Arch Ophthalmol.* 2009;127(4):563-571.
24. Bertelsen M, Linneberg A, Rosenberg T. Socio-economic characteristics of patients with generalized retinal dystrophy in Denmark. *Acta Ophthalmol (Oxf).* 2015;93(2):134-140.
25. Chaumet-Riffaud AE, Chaumet-Riffaud P, Cariou A, et al. Impact of retinitis pigmentosa on quality of life, mental health, and employment among young adults. *Am J Ophthalmol.* 2017;177:169-174.
26. Thompson DA, Ali RR, Banin E, et al. Advancing therapeutic strategies for inherited retinal degeneration: recommendations from the Monaciano Symposium. *Invest Ophthalmol Vis Sci.* 2015;56(2):918-931.
27. Hoffman-Andrews L, Mazzoni R, Pacione M, Garland-Thomson R, Ormond KE. Attitudes of people with inherited retinal conditions toward gene editing technology. *Mol Genet Genomic Med.* 2019;7(7):e00803.
28. Garip G, Kamal A. Systematic review and meta-synthesis of coping with retinitis pigmentosa: implications for improving quality of life. *BMC Ophthalmol.* 2019;19(1):181.
29. Chacón-López H, López-Justicia MD, Vervloed MPJ. Psychological and educational recommendations for working with young people with retinitis pigmentosa. *Sch Psychol Int.* 2014;35(4):357-369.
30. Bittner AK, Edwards L, George M. Coping strategies to manage stress related to vision loss and fluctuations in retinitis pigmentosa. *Optometry.* 2010;81(9):461-468.

31. Fourie RJ. A qualitative self-study of retinitis pigmentosa. *Br J Vis Impair.* 2007;25(3):217-232.

32. Jangra D, Ganesh A, Thackray R, et al. Psychosocial adjustment to visual loss in patients with retinitis pigmentosa. *Ophthalmic Genet.* 2007;28(1):25-30.

33. Hayeems RZ, Geller G, Finkelstein D, Faden RR. How patients experience progressive loss of visual function: a model of adjustment using qualitative methods. *Br J Ophthalmol.* 2005;89(5):615-620.