ABOUT THE AUTHORS

Melissa Lu, MD

Dr. Melissa Lu is currently a first-year ophthalmology resident at the University of Montreal, where she also obtained her medical degree.

Author Affiliations: Department of Ophthalmology, University of Montreal, Montreal, Quebec
Department of Ophthalmology, Hôpital Maisonneuve-Rosemont, Montreal, Quebec

Daniel Milad, MD

Dr. Daniel Milad is a third-year ophthalmology resident at the University of Montreal in Montreal, Canada. Dr. Milad completed his medical degree at Laval University. His research interests are centered around the integration of new technologies in ophthalmology, with a particular focus on the application of artificial intelligence and extended reality in vitreoretinal surgical and medical conditions. His work was recognized at the University of Montreal's 34th Ophthalmology Research Day with the Roch Gagnon Podium Presentation award and at the 2023 Retina Case Conference Canada with the Best Medical Retina Presentation award. Dr. Milad's academic contributions, including several publications and reviews in peer-reviewed journals, reflect his dedication to the evolving landscape of ophthalmological practice and research.

Author Affiliations: Department of Ophthalmology, University of Montreal, Montreal, Quebec
Department of Ophthalmology, Hôpital Maisonneuve-Rosemont, Montreal, Quebec

ABOUT THE AUTHORS

Cynthia X. Qian, MD, FRCSC

Dr. Cynthia X. Qian is an Associate Professor in the Department of Ophthalmology at the University of Montreal, where she is also Chief of the Retina Service. She is the Vice President of the Canadian Retina Society, the chair of Royal College Retina AFC Committee, and the CPD Council Chair for the Canadian Ophthalmological Society. As an FRQS clinical research scholar, her research focuses on pediatric retinal diseases, therapies in inherited retinal diseases, and clinical trials in age-related macular degeneration and diabetic retinopathy. Cynthia has garnered notable accolades beyond her contributions to academia,. In 2018, she was honoured as "The Young Professional of the Year" by the Young Chamber of Commerce of Montreal. In 2019, she was recognized as one of Canada's Top 40 under 40, and in 2021, she earned distinction as one of the top 5 early-career physicians of the year by the Collège des Médecins.

Author Affiliations: Department of Ophthalmology, University of Montreal, Montreal, Quebec
Department of Ophthalmology, Hôpital Maisonneuve-Rosemont, Montreal, Quebec
Department of Ophthalmology, Hôpital Sainte-Justine, Montreal, Quebec

Gene Therapy Updates for Inherited Retinal Dystrophies

Introduction

Inherited retinal dystrophies (IRDs) encompass a group of genetically diverse disorders, each uniquely influencing distinct retinal cell pathways and retinal areas. IRDs currently affect an estimated 5.5 million individuals worldwide, exerting a profound impact on the quality of life of those affected.[1] Depending on the mutated gene, typical presentations often manifest as colour or night blindness, or peripheral vision blindness progressing to complete blindness.[2] Consequently, patients grappling with IRDs face not only the physical challenges of their condition, but also endure significant psychosocial and economic repercussions.[3]

Historically, IRDs were diagnosed and classified based solely on clinical characterization, with no available treatment options. However, advances in genetic characterization have led to the identification of over 270 causative genes, enabling the development of more targeted therapies aiming to restore the function of these mutated genes.[2] It is therefore not surprising that this remains an active field of research, aiming to find treatments that can potentially slow down, halt, or even reverse vision loss.

This review aims to provide an updated summary of the current state of IRD treatments, and to discuss recent advancements and emerging therapeutic strategies. The main classifications that will be explored are macular dystrophies; stationary cone dystrophies; rod-cone dystrophies; Leber congenital amaurosis (LCA); and chorioretinal dystrophies. In this review,

Disease	Gene/vector delivery	Phase	Status	Sponsor	Trial number
X-linked Retinoschisis	RS1/rAAV Intravitreal	I	Recruiting	Zhongmou Therapeutics	NCT06066008
	RS1/AAV.SPR Subretinal	I/II	Recruiting	Atsena Therapeutics Inc.	NCT05878860
	RS1/rAAV2 Intravitreal	I/II	Completed	Applied Genetic Technologies Corp	NCT02416622
	RS1/AAV8 Intravitreal	I/II	Active, not recruiting	National Eye Institute (NEI)	NCT02317887
Achromatopsia	CNGA3/rAAV Subretinal	I/II	Recruiting	STZ eye trial	NCT02610582
	CNGA3/rAAV Subretinal	I/II	Active, not recruiting	Applied Genetic Technologies Corp	NCT02935517
	CNGA3/AAV2 Subretinal	I/II	Completed with results	MeiraGTx UK II Ltd	NCT03758404
	CNGB3/rAAV Subretinal	I/II	Active, not recruiting	Applied Genetic Technologies Corp	NCT02599922
	CNGB3/AAV2 Subretinal	I/II	Completed with results	MeiraGTx UK II Ltd	NCT03001310
Retinitis Pigmentosa	RLBP1/AAV8 Subretinal	I/II	Active, not recruiting	Novartis Pharmaceuticals	NCT03374657
	PDE6A/rAAV Subretinal	I/II	Active, not recruiting	STZ eye trial	NCT04611503
	PDE6B/AAV2 Subretinal	I/II	Recruiting	Coave Therapeutics	NCT03328130
	RPGR/AAV Intravitreal	I	Recruiting	Frontera Therapeutics	NCT05874310
	RPGR/AAV capsid variant Intravitreal	I/II	Active, not recruiting	4D Molecular Therapeutics	NCT04517149
	RPGR/rAAV2 Subretinal	I/II	Recruiting	Applied Genetic Technologies Corp	NCT03316560
	RPGR/rAAV2 Subretinal	II/III	Not yet recruiting	Applied Genetic Technologies Corp	NCT04850118
	RPGR/AAV2/5 Subretinal	I/II	Completed	MeiraGTx UK II Ltd	NCT03252847
	RPGR/AAV5 Subretinal	III	Recruiting	Janssen Research & Development, LLC	NCT04671433
	RPGR/AAV5 Subretinal	III	Recruiting	Janssen Research & Development, LLC	NCT04794101
	RPGR/AAV8 Subretinal	I/II	Completed	NightstaRx Ltd, a Biogen Company	NCT03116113
	MERTK/rAAV2 Subretinal	I	Completed	King Khaled Eye Specialist Hospital	NCT01482195
	USH2A/AON Intravitreal	I/II	Completed	ProQR Therapeutics	NCT03780257
	USH2A/AON Intravitreal	II	Terminated	ProQR Therapeutics	NCT05085964
	USH2A/AON Intravitreal	II/III	Active, not recruiting	ProQR Therapeutics	NCT05158296
	USH2A/AON Intravitreal	II/III	Terminated	ProQR Therapeutics	NCT05176717
	RHO/AON Intravitreal	I/II	Active, not recruiting	ProQR Therapeutics	NCT04123626

Disease	Gene/vector delivery	Phase	Status	Sponsor	Trial number
Leber Congenital Amaurosis	RPE65/rAAV2 Subretinal	I	Active, not recruiting	University of Pennsylvania	NCT00481546
	RPE65/rAAV2 Subretinal	I	Completed	Spark Therapeutics	NCT00516477
	RPE65/rAAV2 Subretinal	I	Completed	Hadassah Medical Organization	NCT00821340
	RPE65/rAAV2 Subretinal	I/II	Completed	Applied Genetic Technologies Corp	NCT00749957
	RPE65/rAAV2 Subretinal	I/II	Completed	Nantes University Hospital	NCT01496040
	RPE65/rAAV2 Subretinal	I/II	Completed	University College, London	NCT00643747
	RPE65/rAAV2 Subretinal	III	Active, not recruiting	Spark Therapeutics	NCT00999609
	RPE65/AAV2/5 Subretinal	I/II	Completed	MeiraGTx UK II Ltd	NCT02781480
	RPE65/AAV9 Subretinal	I	Recruiting	Xinhua Hospital, Shanghai Jiao Tong University School of Medicine	NCT06088992
	REP65/AAV9 Subretinal	I/II	Recruiting	HuidaGene Therapeutics Co., Ltd.	NCT05906953
	CEP290/CRISPR/Cas9 Subretinal	I/II	Active, not recruiting	Editas Medicine, Inc.	NCT03872479
	CEP290/AON Intravitreal	I/II	Terminated	ProQR Therapeutics	NCT03913130
	CEP290/AON Intravitreal	I/II	Completed with results	ProQR Therapeutics	NCT03140969
	CEP290/AON Intravitreal	II/III	Active, not recruiting	ProQR Therapeutics	NCT03913143
	CEP290/AON Intravitreal	II/III	Recruiting	ProQR Therapeutics	NCT04855045
Choroideremia	REP1/AAV Intravitreal	I	Active, not recruiting	4D Molecular Therapeutics	NCT04483440
	REP1/rAAV2 Subretinal	I/II	Completed	University of Oxford	NCT01461213
	REP1/AAV2 Subretinal	I/II	Completed with results	Spark Therapeutics	NCT02341807
	REP1/rAAV2 Subretinal	I/II	Completed	University of Alberta	NCT02077361
	REP1/AAV2 Subretinal	II	Completed	University of Oxford	NCT02407678
	REP1/AAV2 Subretinal	II	Completed with results	Byron Lam	NCT02553135
	REP1/AAV2 Subretinal	II	Completed	STZ eye trial	NCT02671539
	REP1/AAV2 Subretinal	II	Completed with results	Biogen	NCT03507686
	REP1/AAV2 Subretinal	III	Completed	Biogen	NCT03496012

Table 1. Comprehensive overview of clinical trials for targeted therapies in common inherited retinal diseases (as of January 1, 2024).

Phase III clinical trials (registered on clinicaltrials.gov) were selected for literature analysis. In cases where no Phase III trials were available, Phase I or II clinical trials with results were analyzed. Stationary rod dystrophies as well as progressive cone and cone-rod dystrophies will not be discussed, as available studies for these disorders are limited to the preclinical phase (**Table 1**).

Gene Therapy

Gene therapy involves the introduction or modification of genetic material within cells to replace the function of mutated genes. The eye is an ideal target for gene therapy because of its tight blood-ocular barrier, making it relatively immune privileged. In addition, the retina is readily accessible, and a patient's response to therapy can easily be monitored through clinical examinations and imaging. Managing monogenic autosomal-recessive and X-linked mutations is facilitated by the loss of function of these abnormal proteins.[4] Conversely, dominant mutations are less amenable to genetic therapies, as the abnormal gain-of-function proteins impede the action of the correctly synthesized ones post-treatment.[4]

In gene therapy, three main approaches are used to address mutations. The first, and most prevalently used, is gene augmentation.[4] This technique is uniquely employed for monogenic recessive or X-linked inherited diseases, and introduces a wild type copy of the pathogenic gene into target retinal cells, thereby augmenting the production of a functional protein.[4] Second, gene editing may be used for dominant mutations.[4] This involves the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR-Cas9) technology, where a gene-specific guide RNA is linked to a Cas9 endonuclease and identifies, cuts and removes specific portions of DNA to be replaced.[4] The downside to this technique, however, is the potential of creating novel mutations.[4] Last, gene inactivation can also be used for dominant mutations.[4] Here, small interfering RNAs (siRNAs) or antisense oligonucleotides (AONs) can correct or block the production of the mRNA transcribed from the mutated DNA gene.[4]

Subretinal and intravitreal injections are the most common modes of delivery. Subretinal injections are used for outer retinal targets and require smaller amounts to achieve a therapeutic effect.[5] They are locally administered between photoreceptors and the RPE layer, and complications resemble those of pars plana vitrectomy.[5] Intravitreal injections are used for inner retinal targets, but are more immunogenic and it is harder to transduce photoreceptors and RPE cells because of the barrier effect from the inner limiting membrane.[5]

Apart from AONs, genetic therapy is delivered to target retinal cells via viral or non-viral vectors. Within viral vectors, adeno-associated vectors (AAV) have a smaller gene size carrying capacity (4.5 kb to 4.9 kb) and do not integrate into the host's genome.[6] Lentiviruses (LV) carry genes up to 8 kb but integrate the host's genome, causing a small risk of insertional mutagenesis.[6] On the other hand, non-viral vectors have a lower risk of genotoxicity and immunogenicity, but have a lower specificity and are less stable than viral vectors.[6]

Macular Dystrophies

Macular dystrophies include Stargardt disease, Best vitelliform macular dystrophy (BVMD), X-linked retinoschisis (XLRS) and pattern dystrophies. In this review, Stargardt disease, BVMD and XLRS will be discussed.

Stargardt disease

Inherited in an autosomal recessive manner, **Stargardt** affects 1:8000 to 1:10,000 individuals, making it a leading cause of juvenile macular degeneration.[7] Patients affected by this dystrophy often have a mutated ATP-binding cassette sub-family A gene (ABCA4).[7] Lack of this protein causes toxic accumulation of bisretinoid compounds in the RPE, leading to RPE dysfunction and causing visual impairment.[7] The main obstacle in developing therapies for this gene is its large size (6.8 kb).[7] Preclinical studies are currently exploring the use of non-viral delivery systems such as covalently closed and circular DNA (C3DNA).[7] Studies on porcine and non-human primate retinas have provided evidence of sustained ABCA4 protein expression up to six months post-treatment, showing promising results for possible human applications in the future.[7]

Best Vitelliform Macular Dystrophy

Best disease is usually inherited in an autosomal dominant pattern and affects 1:10,000 individuals.[8] It is caused by a mutation in the BEST1 gene, responsible for the expression of the transmembrane protein Bestrophin 1, which is

greatly implicated in the calcium homeostasis of the RPE.[9] Best disease evolves through six stages, from the subclinical/previtelliform phase where the fundus appears normal, to the vitelliform stage with classic egg yolk lesions on the macula, gradually evolving toward the atrophic stage.[9] The most commonly reported symptoms are vision dimness, metamorphopsia and scotoma, but these symptoms vary largely between individuals.[9] Although genetic testing is needed for definitive diagnosis, there are no available pre-clinical or clinical gene therapy studies.

X-linked retinoschisis

X-linked retinoschisis causes predominant central vision loss in 1:5,000 to 1:25,000 males and is associated with a mutation in the retinoschisin 1 gene (RS1).[10] This retinoschisin membrane protein is involved in retinal cell layer organization and cell adhesion, explaining why patients develop macular schisis that may even extend to the peripheral retina.[10] As opposed to subretinal injections, intravitreal gene therapy delivery is the preferred approach, as patients have a higher predisposition to retinal detachments.[10] Although preclinical studies have shown effective gene augmentation therapies in non-human models, the results of two Phase I/II trials introducing AAVs intravitreally (AAV8-RS1) showed inflammation in almost all patients with no improvement in visual function.[10]

Stationary Cone Dystrophies

Stationary cone dystrophies such as achromatopsia and blue cone monochromatism represent a group of IRDs characterized by a stable and non-progressive impairment of cone photoreceptors. As achromatopsia is the more classic example, it will be discussed in this review.

Achromatopsia

Achromatopsia (ACHM) is an autosomal recessive, inherited disorder affecting approximately 1:30,000 people.[11] It is characterized by the early, insidious loss of photoreceptor cones, leading to vision loss; colour blindness; hemeralopia; photophobia; and nystagmus.[11] Approximately 90% of patients with ACHM carry mutations in the cyclic nucleotide-gated channel alpha 3 (CNGA3) or beta 3 (CNGB3) gene, which encodes essential components of the phototransduction cascade.[11] Although there are currently no approved therapies, ongoing Phase I and II AAV gene augmentation clinical studies, including two that have shown gains in visual acuity and contrast sensitivity in all nine treated patients with CNGA3 mutations, are underway.[12]

Rod-cone Dystrophies

Rod-cone dystrophies include retinitis pigmentosa (RP), Usher syndrome, enhanced S-cone syndrome, and Bietti crystalline dystrophy. In this review, RP and Usher syndrome will be discussed.

Retinitis pigmentosa

Retinitis pigmentosa is the most common IRD, affecting 1:4,000 people.[13] It can be inherited through autosomal dominant, autosomal recessive, or X-linked genetic patterns, reflecting its complex genetic etiology. It is characterized by primary rod and secondary cone Degeneration.[13] Symptoms include nyctalopia, followed by progressive peripheral visual field loss.[13]

Accounting for up to 15% of all RP cases, X-linked RP is the most severe form of the condition.[13] Seventy to seventy-five percent of these patients have mutations in the GTPase regulator gene (RPGR), a protein involved in ciliary transport and critical in maintaining photoreceptor integrity.[13] In a Phase I/II dose escalation gene augmentation trial (AAV2/5-RPGR), six out of seven patients treated with low or intermediate doses showed stability or improvement in retinal sensitivity at 12 months.[14] In the higher dose cohort however, two out of three treated patients showed signs of inflammation and no signs of visual improvement.[14]

The USH2A gene codes for usherin, a protein necessary for basement membrane and photoreceptor integrity.[15] In patients with Usher syndrome Type 2a and some non-syndromic forms of RP, mutations have been found in the USH2A exon 13, leading to clinical studies using an AON designed to skip this exon (QR-421a).[15] In the STELLAR study, all 20 treated patients had visual acuity improvement, objectified by an average gain of six letters or improvement in total retinal sensitivity at 48 weeks post-treatment.[15] There were no reported serious adverse events.[15]

Leber Congenital Amaurosis

Commonly inherited in an autosomal recessive manner and affecting 1:50,000 to 1:100,000 people, **LCA** is one of the most severe

forms of retinal dystrophy.[16] In addition to severe vision loss, patients often have accompanying sensory nystagmus, near-absent pupillary response, and a non-detectable electroretinogram response.[17] Voretigene neparvovec-rzyl (AAV2-hRPE65v2) is currently the only FDA approved gene therapy for IRDs. Recent surgical technique enhancements avoid bleeding and inadvertent macular hole formation.[18] This subretinal gene augmentation therapy targets biallelic RPE65 mutations frequently found in LCA type 2 patients, accounting for up to 16% of all LCA cases.[16] The RPE65 gene is responsible for converting trans-retinyl esters to 11-cis-retinols, and its dysfunction leads to an inability to regenerate pigments in photoreceptors.[16] Recent clinical studies have demonstrated sustained partial rescue of photoreceptor function for up to four years post-treatment.[16] This was objectified via multi-luminance mobility tests, visual field testing, and full-field stimulus tests.[16] The most commonly reported adverse event post-treatment was central retinal thinning.[19]

In type 10 LCA, the gene encoding the centrosomal protein 290 (CEP290) is frequently mutated, leading to faulty photoreceptor cilia function.[20] In Phase 1b and II clinical trials, AONs (QR-110) have been used to correct the faulty mRNA before protein translation.[20] Five out of 11 treated patients showed a -0.3 logMAR improvement in visual acuity one year post-treatment; the most common adverse event was the development of cataracts.[20] A Phase III trial has been completed, although its results are yet to be released.[21] In addition, there are ongoing Phase I/II clinical trials using the CRISPR-Cas9 system to eliminate the IVS26 mutation in this same CEP290 gene.[21]

Chorioretinal Dystrophies

Chorioretinal dystrophies are a distinct subgroup of IRD characterized by progressive degeneration in both the choroid and retina. The most prevalent example, choroideremia (CHM), will be discussed in this review.

Choroideremia

CHM is an X-linked recessive dystrophy affecting 1:100,000 to 1:200,000 males.[22] It is characterized by the centripetal loss of photoreceptors, RPE cells and the choriocapillaris, even reaching the fovea in severe cases.[23] Patients begin to report nyctalopia and peripheral vision loss in late childhood, progressing to near-complete vision loss by the age of 40.[23] Choroideremia is caused by a mutation in the CHM gene, which encodes the Rab escort protein 1 (REP1), an enzyme essential for intracellular trafficking of vesicles.[23] A recent Phase III STAR study treating one eye per patient with an either low or high dose of timrepigene emparvovec (BIIB111/AAV2-REP1) allowed patients to gain in visual acuity when compared to the control eye.[22] However, the number of treated patients meeting this three-line improvement did not reach statistical significance, which is why there has been no regulatory approval.[22] In Phase I and II clinical trials, there were rare cases of adverse events, with two cases of retinal holes over a non-functional retina and one case of intraretinal immune response.[22]

Conclusion

In summary, ongoing research endeavours are focused on the development of sustainable gene therapies for IRDs, previously considered untreatable. The primary challenges include the development of delivery methods with reduced immunogenicity, ensuring enduring treatment effects, and establishing therapies that minimize host mutagenesis. Optimal treatment candidates appear to be patients with early-stage diagnoses and gradual disease progression, as these factors provide a broader window for treatment before the degeneration of target cells. This article provides an overview of a select number of ongoing clinical studies, indicating a cautious yet hopeful outlook for the future of IRD treatments.

Correspondence:

Dr. Cynthia Xin-Ya Qian
Email: cynthia.xin-ya.qian@umontreal.ca

Financial Disclosures:

M.L.: None declared.
D.M.: None declared.
C.Q.: None declared.

References:

1. Ben-Yosef T. Inherited retinal diseases. Int J Mol Sci. 2022 Nov 3;23(21):13467.
2. Chawla H, Vohra V. Retinal Dystrophies. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK564379/
3. Gong J, Cheung S, Fasso-Opie A et al. The impact of inherited retinal diseases in the United States of America (US) and Canada from a cost-of-illness perspective. Clin Ophthalmol Auckl NZ. 2021 Jul 1;15:2855–66.
4. Drag S, Dotiwala F, Upadhyay AK. Gene therapy for retinal degenerative diseases: progress, challenges, and future directions. Invest Ophthalmol Vis Sci. 2023 Jun 1;64(7):39.
5. Kansara V, Muya L, Wan CR, et al. Suprachoroidal delivery of viral and nonviral gene therapy for retinal diseases. J Ocul Pharmacol Ther. 2020;36(6):384–92.
6. Lipinski DM, Thake M, MacLaren RE. Clinical applications of retinal gene therapy. Prog Retin Eye Res. 2013 Jan;32:22-47.
7. Wang L, Shah SM, Mangwani-Mordani S et al. Updates on emerging interventions for autosomal recessive ABCA4-associated Stargardt disease. J Clin Med. 2023 Sep 27;12(19):6229.
8. Tsang SH, Sharma T. Best vitelliform macular dystrophy. Adv Exp Med Biol. 2018;1085:79–90.
9. Tripathy K, Salini B. Best Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2024 Jan 8]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK537290/
10. Ku CA, Wei LW, Sieving PA. X-linked retinoschisis. Cold Spring Harb Perspect Med. 2023 Sep 1;13(9):a041288.
11. Michalakis S, Gerhardt M, Rudolph G et al. Achromatopsia: genetics and gene therapy. Mol Diagn Ther. 2022;26(1):51–9.
12. Fischer MD, Michalakis S, Wilhelm B et al. Safety and vision outcomes of subretinal gene therapy targeting cone photoreceptors in achromatopsia: a nonrandomized controlled trial. JAMA Ophthalmol. 2020 Jun 1;138(6):643-51.
13. Verbakel SK, van Huet RAC, Boon CJF et al. Non-syndromic retinitis pigmentosa. Prog Retin Eye Res. 2018 Sep;66:157-86.
14. Newswire MP. Late-Breaking 12-Month Data of RPGR Gene Therapy Shows Statistically Significant and Continued Vision Improvement in Patients with X-Linked Retinitis Pigmentosa [Internet]. MultiVu. [cited 2024 Jan 8]. Available from: https://www.multivu.com/players/English/8798151-janssen-rpgr-gene-therapy-data-in-patients-with-x-linked-retinitis-pigmentosa/
15. ProQR Announces Positive Results from Clinical Trial of QR-421a in Usher Syndrome and Plans to Start Pivotal Trials | ProQR Therapeutics [Internet]. [cited 2024 Jan 8]. Available from: https://www.proqr.com/press-releases/proqr-announces-positive-results-from-clinical-trial-of-qr-421a-in-usher-syndrome-and-plans-to-start-pivotal-trials
16. Nuzbrokh Y, Ragi SD, Tsang SH. Gene therapy for inherited retinal diseases. Ann Transl Med. 2021 Aug;9(15):1278.
17. Chacon-Camacho OF, Zenteno JC. Review and update on the molecular basis of Leber congenital amaurosis. World J Clin Cases WJCC. 2015 Feb 16;3(2):112–24.
18. Qian CX, Rezende FA. Surgical technique enhancements for successful subretinal gene therapy delivery. Can J Ophthalmol [Internet]. 2023 Oct 23 [cited 2024 Jan 8];0(0). Available from: https://www.canadianjournalofophthalmology.ca/article/S0008-4182(23)00309-5/fulltext
19. Deng C, Zhao PY, Branham K et al. Real-world outcomes of voretigene neparvoyec treatment in pediatric patients with RPE65-associated Leber congenital amaurosis. Graefes Arch Clin Exp Ophthalmol. 2022 May;260(5):1543–50.
20. Russell SR, Drack AV, Cideciyan AV et al. Intravitreal antisense oligonucleotide sepofarsen in Leber congenital amaurosis type 10: a phase 1b/2 trial. Nat Med. 2022;28(5):1014–21.
21. Home | ClinicalTrials.gov [Internet]. [cited 2024 Jan 8]. Available from: https://www.clinicaltrials.gov/
22. Lam BL, Davis JL, Gregori NZ. Choroideremia gene therapy. Int Ophthalmol Clin. 2021;61(4):185–93.
23. Abdalla Elsayed MEA, Taylor LJ, Josan AS et al. Choroideremia: the endpoint endgame. Int J Mol Sci. 2023 Sep 20;24(18):14354.