The last 25 years brought a spectacular amount of knowledge on the genetic basis of inherited retinal disorders and a paradigm shift on how they can be managed. We entered the era of gene therapy for inherited retinal degenerations (IRDs).

October 15, 2020, was a historic day for all Canadians, as the first gene therapy treatment (Luxturna) was approved by Health Canada for an autosomal recessive IRD due to RPE65 variants. Further announcements about payment scheduling and delivery platforms will follow, once defined. This announcement is of great importance and is a significant step forward. It is expected that this treatment will become available in the near future.

The first IRDs described were retinitis pigmentosa (RP) by Donders in 1857, followed by the discovery of Leber congenital amaurosis (LCA) by Leber in 1869. For almost 150 years, ophthalmology residents were taught and patients and families were told that there is nothing to do for these devastating diseases. For ~4 million IRD patients around the world, that was a grave message. We now know that this is incorrect. There are over 270 genes underlying retinal disorders. If you want to make a difference, the first step is to identify the genetic cause of the condition and its inheritance and provide related counseling (https://www.fightingblindness.ca/resources/genetic-testing-for-inherited-retinal-diseases/).

Most of the newer therapies for IRDs require gene identification, and these are gene specific. RPE65-related IRD is a model for this.

RPE65 was discovered and cloned in 1993 by the late Dr. Christian Hamel, a Montpellier native, while he was working with Michael Redmond at NIH. Though Dr. Hamel passed away last year, he did witness the incredible revolution stemming from their discovery going from the bench to the bedside, a wonderful example of translational research but also personalized medicine.

RPE65 mutations cause severe early onset IRDs like RP and LCA. Canine and mouse studies in the late 1990s and early 2000s showed that replacing RPE65 was safe and effective in improving the retinal function and mobility of the animals that received gene therapy. The treatment consists of a subretinal injection of the normal-sequence RPE65 transgene packaged into inactivated viral particles (adeno-associated virus, AAV-2). The virus then delivers the RPE65 gene construct to the retinal pigment epithelium (RPE) cells, and the RPE65 protein is made, leading to...
restitution of the vitamin A cycle and production of the photon-capturing 11 cis retinal, which was previously absent.

The pioneering work of the groups of Jean Bennett, Sam Jacobson, Robin Ali, and many others is responsible for the first landmark results in humans in 2008, published in the *The New England Journal of Medicine* and *Proceedings of the National Academy of Sciences of the United States of America*.\(^1\)–\(^4\) Interestingly, our standard-of-care visual testing and go-to endpoints like early treatment diabetic retinopathy study (ETDRS) (developed for diabetic retinopathy), electro-retinogram (ERG), and Goldmann and Humphrey visual fields (developed for glaucoma) did not show much improvements. However, the patients said that they were seeing better. The realization that the outcome measures we were using were not reflecting the patient experience and were not designed for IRDs with the loss and death of photoreceptors led to the development of several new important tests or endpoints: full-field sensitivity testing (FST), pupillometry, and the multiluminance mobility test (MLMT), the latter being approved by the FDA as a primary endpoint.

The FST documents the rod and cone sensitivity of the entire retina even when the ERG is not recordable, and pupillometry tests the neuronal pathway between rod, cones, ganglion cells, and the midbrain, back to the Edinger-Westfall nucleus, the oculomotor nerve to the pupillary sphincter muscles. Other new testing also include the optical coherence tomography, which measures the “live” photoreceptors by the ellipsoid zone (EZ line); MLMT, which aims to measure the entire spectrum of functional vision; and microperimetry (MP), which measures the sensitivity of the central 30° in exactly known and repeatable retinal locations.

In December 2017, the phase 3 results showed safety and improvement of mobility at low luminance and improved visual fields in kids and adults.\(^4\) Lasting effects were seen for up to 10 years. Later that year Luxturna was approved by the FDA in the United States and later in Europe by EMA. On October 15, 2020, Luxturna was approved by Health Canada for individual > 3 years old carrying 2 disease-causing RPE65 mutations with viable retina. To get to this historic moment, it took at least 30 years of work. Although this took far too long, major hurdles encountered were solved and bypassed, and it is hoped that new knowledge will be implemented faster in the near future. This therapeutic pipeline from RPE65 to Health Canada approval is now in place and is the pathway for other gene therapies and other IRD treatments such as drugs, stem cells, a bariatric gene editing system CRISPR, and other types of gene editing.

We can be proud of Canada, its academic institutions, and the group of vision scientists for bringing this field forward. We must thank the Canadian granting agencies, the Fighting Blindness Canada foundation, and the Sick Kids and Montreal Children’s Hospitals foundations for their unending support, which has brought us to this day. There is no turning back now; times have changed.

In conclusion, we are at the dawn of a new era in vision science and ophthalmology. IRD patients can now be assessed with renewed vigor and enthusiasm, with new information to deliver, new visual testing and retinal imaging methods, and importantly, encouraging for genetic testing to be done. Genetic testing is now covered by all provincial health care systems, but because the interpretation of genetic results is not trivial, genetic counsellors and medical genetic specialist must be involved. Fighting Blindness Canada developed a national registry to keep these patients identifiable and informed (please see [https://www.fightingblindness.ca/resources/patient-registry-for-inherited-retinal-diseases/](https://www.fightingblindness.ca/resources/patient-registry-for-inherited-retinal-diseases/)).

We must also be optimistically cautious. While giving hope to over 20 000 Canadian IRD patients, we must remember that this is only one gene (RPE65 disease is ~8% of LCA and RP) and it is not a cure. The effect varies between patients depending on their genetic variants and the stage of the disease, as gene therapy works only in living cells. So not all RPE65-deficient patients are eligible for the surgeries. Patients with mutations in other genes are not eligible yet. But here again lies more hope, because at least 5 other therapies are in phase 1, 2, or 3 of development and hopefully will follow the successful path of RPE65.

For more information, see [https://www.fightingblindness.ca/](https://www.fightingblindness.ca/) and [https://www.clinicaltrials.gov/](https://www.clinicaltrials.gov/).

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**References**


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**Footnotes and Disclosure**

Dr. Elise Heon and Dr. Robert Koenkoop do not have any conflicts of interest.