Canadian Vision 2020 White Paper

VISION RESEARCH

This paper was developed by Fighting Blindness Canada, the Canadian Council of the Blind, and the CNIB Foundation with feedback from members of the Canadian vision loss community. It outlines themes in the area of vision research, as well as recommended actions for government, industry, and other stakeholders. The recommendations—bolded throughout the paper—provide a general framework for policy and advocacy activities in 2020 and beyond. What final form a recommendation takes, who it is directed towards, and in what context it is articulated will be determined by each stakeholder.

Introduction

At the outset of 2020, a symbolic year for those connected to vision loss, it is clear that Canadian ophthalmology and vision care are part of a global and transformative boom. After decades of foundational research, innovative approaches in gene therapy, stem cells, pharmaceuticals, and other fields are leading to major discoveries, and in some cases producing viable treatments for eye diseases.

The impact of the gene therapy Luxturna cannot be understated: approved by the FDA in 2017, the first ocular gene therapy to reach market is a treatment for those with a subtype of Leber congenital amaurosis (LCA). At the same time, new variations of existing medicines are redefining the standard of care, ground-breaking technologies such as Argus and the MIGS category, discussed below, are offering life-changing solutions, and patient-oriented research is driving a new paradigm that prioritizes the needs and perspectives of patients.

Developed out of survey responses from Canadian patients, caregivers, researchers, scientists, health practitioners, policymakers, and more, this paper uses the emblematic year of 2020 as an opportunity to reflect on key advancements and hurdles in vision research, and to consider what they mean for Canadians living with vision loss. It also imagines what the next years and decades may have in store as this exciting field continues to advance.

The Landscape in 2020: Key Developments in Vision Research

Luxturna may be the most obvious sign of the value and success of gene therapy in ophthalmology, but the treatment is part of a broader trajectory of significant advances in ocular genetics over the last several years, as evidenced by the numerous gene therapy clinical trials currently up-and-running across the globe. Several approaches, including Luxturna, adhere to the “classical” model of gene therapy. These use a vector of some kind, typically a virus, to insert a functioning copy of a gene to restore certain functions affected by a mutated copy. Other approaches are focused on editing genes instead of inserting new ones.

An enormously important technology has become central to these efforts. Called “CRISPR-Cas9,” the technique was developed out of an existing mechanism in nature that allows

bacteria to identify and edit the DNA of invading viruses. In Canada and elsewhere, scientists are now using CRISPR to edit genes with incredible accuracy, and it is likely only a matter of time before we see clinical applications in ophthalmology materialize. More recently, an approach called “prime editing” has allowed researchers to edit smaller lines of DNA to achieve even more precise results. The human eye has emerged as a key site for cutting-edge approaches using these and other technologies.[1]

The emerging field of optogenetics has attracted attention as well, and for good reason. Researchers in this area are combining genetic methods with optical technology to provide light sensitivity in cells. They have shown in the lab that this approach has the potential to turn retinal cells that are spared in diseases into cells resembling photoreceptors, which are responsible for converting light into information for the brain. If translated into clinical applications, this could have an enormous impact on those with degenerative genetic conditions such as retinitis pigmentosa (RP), which is characterized by a gradual loss of photoreceptors.[2]

In another field, epigenetics, researchers have been making progress by studying the factors outside of genetic mutation that contribute to eye diseases. These include environmental and age-related factors that play a role in far-reaching diseases such as age-related macular degeneration (AMD), diabetic retinopathy (DR), glaucoma, and cataracts.[3] This work has shown that it may be possible to treat vision loss by modifying aspects of our phenotype—the interaction of our genes with the environment—instead of the underlying genetic code.

Despite the explosion of activity in ocular genetics, the promise of stems cells has not diminished—far from it. Researchers in this field have made enormous progress turning stem cells into the kinds of cells that are central to vision and that are often lost or compromised in ocular diseases—in particular, photoreceptors and the retinal pigmented epithelial (RPE) cells that nourish and sustain them. Though incredible work has taken place with RPE cell replacement in recent clinical trials, a hurdle for photoreceptor replacement continues to involve pinpointing the best methods for delivering cells developed *in vitro* into the human eye and supporting their connection within the host retinal circuitry. Thankfully, progress is underway to create biomaterials, vectors, and other support mechanisms that would do just that, as well as biological systems that could remotely “shut down” unwanted effects once the cells are introduced to a live, biological environment.[4]

Ethical concerns over the use of stem cells have complicated the field’s advancement in the past. While those debates continue to unfold in certain contexts, the proven viability of induced pluripotent stem cells (iPSCs) has assuaged many concerns and accelerated research

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[1] Ali, R. Ocular gene therapy: introduction to the special issue. *Gene Therapy* 19, 119–120 (2012) doi:10.1038/gt.2011.189

[2] Henriksen, B.S., Marc, R.E., Bernstein, P.S. Optogenetics for retinal disorders. *J Ophthalmic Vis Res* 9(3), 374-382 (2014) doi:10.4103/2008-322X.143379

[3] Desmettre, T.J. Epigenetics in age-related macular degeneration (AMD). *J Fr Ophtalmol* 41(9), 407-415 (2018) doi:10.1016/j.jfo.2018.09.001

[4] Liang, Q., Monetti, C., Shutova, M.V. *et al*. Linking a cell-division gene and a suicide gene to define and improve cell therapy safety. *Nature* 563, 701–704 (2018) doi:10.1038/s41586-018-0733-7

enormously. Derived from living adult cells, usually from the skin, iPSCs hold immense promise for regenerative medicine, providing what could be a near-limitless supply of cellular material for any number of therapies, and giving adult patients the opportunity to use their own cells for procedures. Researchers are already exploring methods for collecting and storing iPSCs for scientific investigation and therapeutic use, what would amount to vast “libraries” of ethically-derived cellular material.[5] If late-stage clinical trials are successful in testing these cells in the treatment of eye diseases, inherited or otherwise, there is little doubt that patients could benefit from such a resource.

Major players in pharma and biotech are involved in pushing both ocular genetics and stem cells forward, but technological devices are also attracting investment. So-called bionic eyes—retinal implants such as the Argus device—are becoming more sophisticated each year, and wearable devices such as the Canadian-based eSight are already helping those with certain forms of vision loss to see better. In the glaucoma space, a new set of procedures and devices called minimally invasive glaucoma surgery (MIGS) have been adopted in some contexts, and though their use in Canada continues to be limited and somewhat ad hoc, MIGS shows that there is a promising space for novel devices and surgeries in the treatment of eye diseases.

Alongside implants and devices, new methods and technologies in diagnostics have a very bright future, having made incredible headway over the last several years. Finding new ways to treat vision loss and blindness is central to the future of ophthalmology, but so too are new ways of detecting eye diseases in the first place. If a disease is diagnosed early enough, preventative measures could be put in place that may make treatment unnecessary. This is the case in a disease such as AMD, for instance, which if caught during its “dry” form can be monitored closely and controlled through vitamins and lifestyle changes.

At the same time, the value of routine eye exams continues to be shown in Canada and elsewhere.[6] These may not constitute an exciting advancement in the field, but they remain a staple of good vision health management and should be supported as extensively as possible within public plans, particularly for those populations at risk. Those populations include older Canadians, of course, but there is evidence showing that young children should also be screened thoroughly as a means of catching early and congenital diseases so that they can be managed as early as possible.[7] At the same time, the collaborative delivery of health care services, streamlined and centralized wait queues for specialists, the use of online learning tools, and other innovations all have the potential to improve how and when eye diseases are diagnosed.

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[5] Holmqvist, S., Lehtonen, Š., Chumarina, M. *et al*. Creation of a library of induced pluripotent stem cells from Parkinsonian patients. *npj Parkinson's Disease* 2, 16009 (2016) doi:10.1038/npjparkd.2016.9

[6] Jen, Y., Buys, Y., Xiong, J. et al. Government-insured routine eye examinations and prevalence of nonrefractive vision problems among elderly. *Can J Ophthalmol* 48(3), 167-172 (2013) doi:10.1016/j.jcjo.2013.01.002

[7] Marshall, E.C., Meetz, R.E., Harmon, L.L. Through our children’s eyes—the public health impact of the vision screening requirements for Indiana school children. *J of American Optometric Association* 81(2), 71-82 (2010) doi.org/10.1016/j.optm.2009.04.099

Computation is playing a role in these endeavours. Advanced algorithms and machine learning have shown promise as effective tools for earlier diagnosis. For example, researchers in Canada and abroad are developing complex computer programs that can rapidly examine fundus images—photographs of the back of the eye—to differentiate healthy eyes from diseased ones. This would normally be done painstakingly by a trained specialist, but it is possible for the algorithms to do the work significantly faster, lightening the load on clinicians and leading to faster and in some cases more accurate diagnoses for patients.[8] These and similar innovations in software development—often referred to as forms of artificial intelligence—have the potential to fundamentally transform the diagnostic landscape.

Translational science has also become a central focus in the health sciences , encompassing efforts to take learnings from the lab and translate them into treatments and cures. For example, there is a strong emphasis on translation in both gene and stem cell therapy, with both showing promise to lead to new medicines and interventions. But there is also consensus in the scientific community, and in ophthalmology in particular, that basic or foundational science should not be ignored. These are investigations that tell us something about how our biology functions—for example, how cells interact with one another, or how specific genes inform proteins that perform essential tasks. These and similar investigations laid the foundations for translational science and many advanced technologies, including CRISPR. If we ignore or abandon them now, we will limit the kind of translational work that can be done in the future. Our best approach is to find a balance between basic and translational science, one that takes advantage of today's opportunities while also laying groundwork for the science and treatments of tomorrow.

Institutions and Infrastructure: Supporting Vision Research in Canada

There is widespread agreement among patients and researchers that Canada needs to finance and develop more clinical trials for eye diseases. According to a pivotal study in 2009, our country lags significantly behind the U.S. in clinical trials,[9] and since that time many European countries have surpassed us. Though many trials now recruit globally, there is little doubt that Canadian patients would benefit from a more robust and active clinical trial infrastructure at home. **At the same time, Canadian clinical trials are integral to Canadian research: expanding our ability to do trials will help advance national research agendas in ophthalmology and other disciplines. Organizations such as Clinical Trials Ontario are essential partners in the effort to attract clinical trials to Canada. Those efforts should be supported by public and private stakeholders to ensure they are effective and nationally unified.**

The subject of funding is of course central to clinical trials, but it extends beyond them. Government funding for scientific research has diminished over the last several years, and the country's four main research agencies received no new money in the 2019 federal budget. According to the Advisory Panel for the Review of Federal Support for Fundamental Science in

[8] Wei Ting, D.S., Pasquale, L.R., Peng, L. *et al*. Artificial intelligence and deep learning in ophthalmology. *Br J Ophthalmol*. 103(2), 167-175 (2019) doi: 10.1136/bjophthalmol-2018-313173
[9] Silversides, A. Clinical trials: the muddled Canadian landscape. *CMAJ* 180(1), 20-22 (2009) doi.org/10.1503/cmaj.081897

2017, Canada is unique in that federal funding for scientific research is less than 25 percent of overall research funding, placing the country well below the OECD average.[10] Canadian vision scientists have managed to excel in the face of these austerity measures, advancing work that has led to incredible discoveries, but they do so in the face of enormous financial constraints. Many researchers express concerns over the fact that that new talent is being blocked from entering the field as a result of a widespread underfunding of key academic and research institutions.

There is little doubt, then, that underinvestment has affected the overall workforce of vision health researchers and practitioners in Canada, and it is clear that gaps in care are emerging as a result. This has a profound impact on how those with vision loss access treatment and vision care, particularly in rural areas, where ophthalmologists and optometrists are in shorter supply. **It is important that we develop measures to ensure the current vision health workforce is effectively meeting the demands of Canadian patients, and that it is expanding in accordance with the growing number of Canadians affected by vision loss.**

If Canada is going to prepare its vision health workforce in this way, it is important that we have a clear picture of the scale of the problem. Unfortunately, while there are some examples of Canadian research pulling from population health studies conducted abroad, little to no published work has been done to identify and examine Canadian populations with vision loss. This includes those living with lesser-known, typically inherited forms of vision loss such as RP, LCA, Stargardt disease, Usher syndrome, X-linked retinoschisis, Bardet-Biedl syndrome, choroideremia, and many more. If Canada is successful in integrating new gene therapies under development into its public health care system, patients with inherited diseases will be the first to benefit. Knowing more about the relevant populations will help this process significantly; not knowing stands as a potential barrier to preparing policies and frameworks that support the future of ocular medicine.

As such, new and more wide-ranging population health studies are needed to identify and better understand Canada's vision loss community, and to better inform research and funding decisions. Similarly, socioeconomic and "burden of illness" research is required to understand the impact of vision loss on Canada's labour force and economy, calculating factors such as treatment costs and lost working hours for patients and caregivers. Insights into how vision loss impacts the lives of Canadians affected by it are similarly crucial. This kind of work spotlights the experiences of those most directly affected by new treatments and health innovations, and it reflects the uniqueness of our country's particular demographics and geography—for instance, the distinct challenges faced by patients living in rural and remote communities. Without the requisite forms research, we are lacking a clear picture of the overall impact of eye diseases and sight loss, extending from the personal, more intimate burdens experienced by patients to the broader social, economic, cultural, and institutional ramifications they are closely associated with.

[10] http://www.sciencereview.ca/eic/site/059.nsf/vwapj/ExecSummary_April2017-EN.pdf/$file/ExecSummary_April2017-EN.pdf

The Canadian Survey on Disability gives us a superficial understanding of some of the issues facing people with seeing disabilities, most notably in relation to employment and education. However, there is a great need to dig deeper and better understand the barriers that people with vision loss face in terms of discrimination in the workplace, educational institutions, and society in general. Technology has also had an enormous impact on people with vision loss, but there is very little research that helps us understand the nature and extent of the impact of technology, nor best practices for their use and implementation. The role of transportation in the lives of those with vision loss is similarly unexplored: people with seeing disabilities face significant barriers to travel within the cities in which they live, as well as further afield, by rail and air, and within Canada and internationally. In order to facilitate full participation in society, and especially accessibility to employment, it is essential that transportation planning be based on extensive research on accessible transportation needs and the lived travel experience of people with seeing disabilities.

There are other research gaps that need to be addressed: braille literacy is recognized as a major contributor to the literacy of blind children, for example, yet research into braille usage in Canada is almost non-existent. At the same time, despite the importance of rehabilitation services for those living with vision loss, there is a paucity of research in this area as well. Treatments either exist or are in development for many conditions, but the fact remains that many with visual impairments rely on rehabilitation services to improve their functional vision, their ability to navigate, their familiarity and comfort with assistive devices, and more. **For the complete integration of people with vision loss into society it is essential that research funders and academic institutions pay more attention to these and other forms of patient-centered research.**

In the face of diminishing funds and an unclear picture of national populations with vision loss, Canadian universities, research hospitals, and other centres of excellence have nonetheless managed to advance ground-breaking work, forming valuable collaborations and driving productive efforts in research, clinical practice, and more. **There is still a need, however, for a unified research agenda and corresponding set of goals to ensure we are working collaboratively and collectively towards a better landscape for those with vision loss.** In the U.S., the National Institutes of Health (NIH) sets an annual research agenda that includes a vision component informed by the National Eye Institute, its vision arm. This creates opportunities to respond to needs in the vision loss community and capitalize on opportunities presented by research and funding.

In Canada, our corresponding agency is the Canadian Institutes of Health Research (CIHR), which invests federal funds into national research projects. The CIHR is composed of thirteen institutes, each with its own agenda, and though these represent a range of important categories and diseases, vision does not have its own institute, unlike the National Eye Institute. Instead, the priorities of vision research are typically divided among the existing institutes, sometimes finding support and representation in the Institute of Ageing (IA) or Genetics. Similarly, the peer review committees that work under CIHR to review and recommend proposals are wide-ranging, but there is no review table dedicated exclusively to ophthalmology or vision research. This may lead to insufficient funds being directed towards the vision research projects we know are required to equip Canada for the future of

ophthalmology and vision care. Indeed, this may already be the case: a well-cited study showed that $37.5 million was spent in 2009 on all organizations across the country focused on vision research. This is a meager amount for such an important and expansive field, especially in comparison to the $4.4 billion impact of vision loss on the economy due to lost productivity, a number reported in the same study.[11]

Despite the lack of a national vision funding initiative, provincial initiatives dedicated to vision research exist around the country, and do important work to support and advance research in vital areas. In Quebec, for example, the Vision Health Research Network (VHRN), funded by a Quebec government agency called *Fonds de la Recherche en Santé du Québec* (FRQS), provides funding to foster national and international collaborations and access to specialized infrastructure and tissue banks. The VHRN is also committed to supporting efforts to train the next generation of vision researchers by funding scholarships and awards. **Such research building initiatives are essential to achieve the ultimate goal of improving care and developing treatments for patients living with various vision impairments.**

There are currently sixteen ophthalmology departments and two optometry schools embedded within universities across Canada. Added to these are various centres of excellence in hospitals and the private sector that have a partial or full focus on vision. While these institutes are essential drivers of vision research and clinical service, there are still opportunities for collaborative work and resource-sharing that are being left on the table. For example, the development of new, dedicated centres of excellence that fund vision research and serve the patient community could lead to enormous progress. This is particularly the case for patients with inherited and rare conditions, who are often underserved as a result of resources being directed towards more widespread diseases. This is perhaps most explicit in the state of genetic testing in Canada: patients with inherited retinal diseases are often blocked from publicly-funded testing services as a result of the scarcity of genetic councillors and the availability of testing facilities.

New centres of excellence and research buildings dedicated to vision could attract additional funding, facilitate networking among existing researchers and clinicians, and function as important cites of vision health care that connect patients to relevant specialists, including genetic counsellors, patient navigators, low vision experts, and others. In many cases the vision health resources we require are already in place, but gaps emerge due to a lack of integration, networking, and government support.

Visionary Extrapolations: The Future of Vision Research

Despite challenges in funding, coordination, and infrastructure, many in the vision loss community are optimistic regarding the future of vision research in Canada and abroad. In commentaries provided for the development of this paper, researchers and patients highlighted advancements in “clinical trials,” “new research and equipment,” and “integrated and open access” as being possible within the next five years. Over a twenty-five-year period, on the other hand, they identified developments such as “personalized medicine,” “use of stem cells,”

[11] Cruess, A.F., Gordon, K.D., Bellan, L. *et al*. The Cost of Vision Loss in Canada 2. Results. *Can. J Ophthalmol* 46(4), 315-318 doi: 10.1016/j.jcjo.2011.06.006

“tissue transplants,” and increased “genetic mapping” as likely to occur, with several echoing one respondent’s forecast that “blindness will no longer exist.” Reviewing the list of achievements in vision science and the delivery of care over the last several decades, it is no wonder that many Canadians are hopeful regarding this future. In many cases, these and other comments can be seen as extrapolations that project outward from the existing landscape of innovative and cutting-edge research, which in key areas is poised to be translated into tangible treatments and cures.

At the same time, these more hopeful extrapolations are balanced against a kind of weary skepticism that can be traced through other comments. Referring to the promise of a treatment for RP, one respondent wrote that “I’ve been hearing ‘five years’ for way too long.” Other community members expressed similar hesitations, a reminder that the road towards treatments has been a long and arduous one for many patients, especially those with genetic conditions. In a way, these are extrapolations as well, taking as their basis the hurdles and dead-ends that are experienced by any large-scale scientific undertaking.

A hesitant approach to the future of vision science is also a reminder that scientific progress does not happen of its own accord. It is a collective endeavour that must be nurtured and driven forward—it must be socially and economically supported to achieve its ends. As we move into a new decade and envision the future of our collective efforts to end blindness and vision loss, it is important to recognize the work that lies ahead of us, and to understand that it involves building new policies, tools, and frameworks to support the incredible progress in vision research that is already underway.