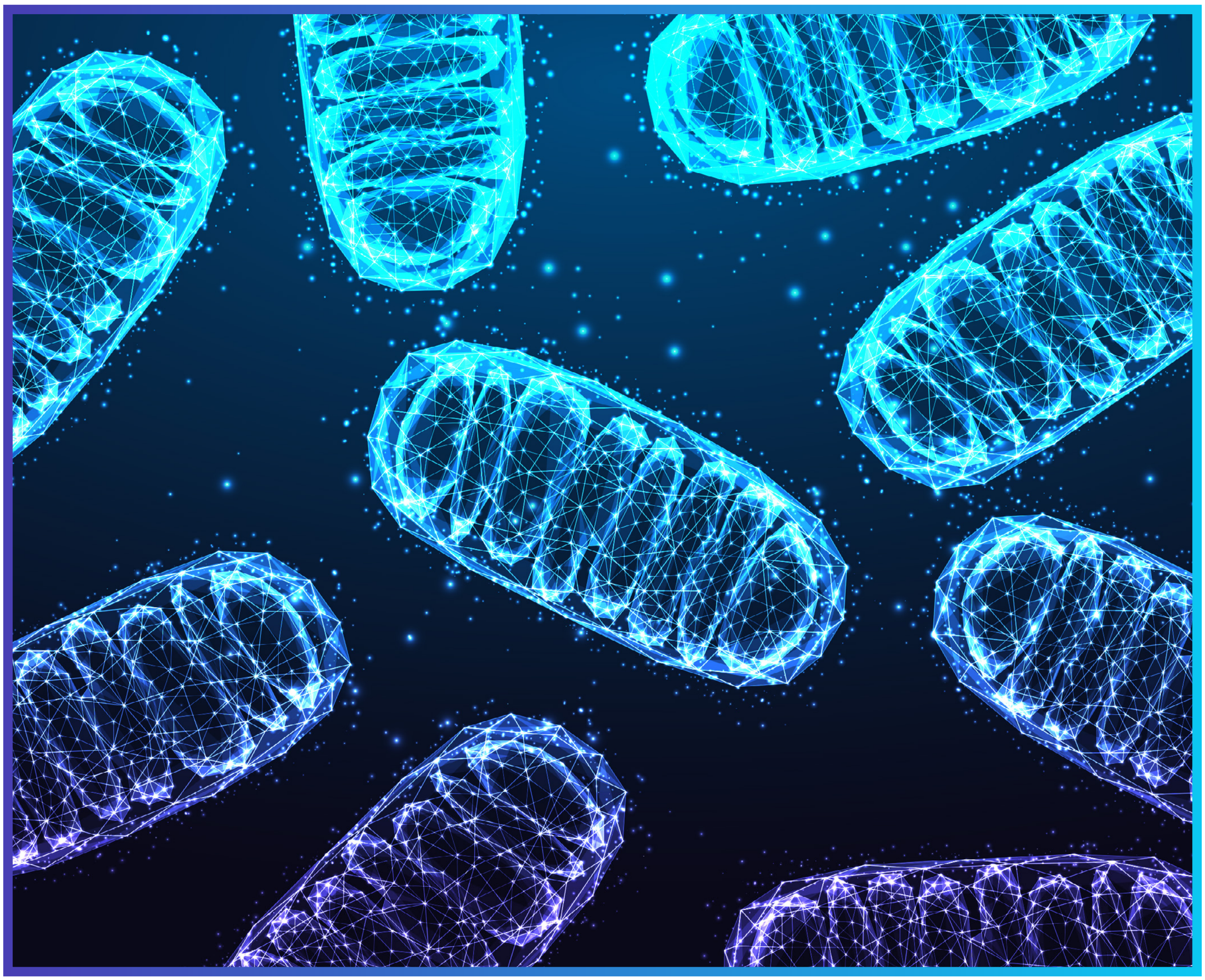
OCTOBER 2024

Leber Hereditary Optic Neuropathy

A GIVING SMARTER GUIDE



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About Us

About the Milken Institute

The Milken Institute is a nonprofit, nonpartisan think tank focused on accelerating measurable progress on the path to a meaningful life. With a focus on financial, physical, mental, and environmental health, we bring together the best ideas and innovative resourcing to develop blueprints for tackling some of our most critical global issues through the lens of what's pressing now and what's coming next.

About the Science Philanthropy Accelerator for Research and Collaboration

MI Philanthropy's Science Philanthropy Accelerator for Research and Collaboration (SPARC) works to develop, launch, and lead initiatives that fund medical research and invest to accelerate the development of tools and treatments that will bring better health to millions of people. Our expertise lies within a number of medical research fields, including neuroscience, mental health, oncology, rare disease, and immunology. We partner with philanthropists, leading them through complex medical research and clinical systems and guiding pathways for philanthropy to create a healthy, equitable world.

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Foreword

"LHON robs you of your independence."

"I have so much to give. This disease took away my livelihood, my ability to support my family."

"All I wanted was a healthy child. I struggle to overcome the guilt that I did this to my child."

"I want to be able to see my new baby's face, see her graduate, see her walk down the aisle."

"It's devastating not to be able to see."

"It's impacted my decision to have kids."

"It impacts the whole family."

"It's a rare disease, but when it runs in your family, it's not rare."

Leber Hereditary Optic Neuropathy (LHON) is a mitochondrial disease that can result in sudden loss of central vision.

These are the voices of the LHON Community. We hear their sentiments and life journeys every day; they are what drove LHON Collective to work with the Milken Institute's Science Philanthropy Accelerator for Research and Collaboration (SPARC) to advance the science and work toward a cure for LHON.

Anyone carrying an LHON mutation is at risk of suddenly becoming legally blind at any point in their life. A woman carrying an LHON mutation, with or without vision loss, will pass the mutation to all of her children.

It is past time to listen to these voices and accelerate the path to a cure, all while improving the lives of people living with LHON. This guide is the result of the Milken Institute's SPARC team and dozens of researchers, clinicians, and industry experts from around the world who have so openly shared their insight to aggregate the present cumulative understanding and frame priorities going forward. It is our hope that this is a first step toward changing the outcome of this diagnosis and turning the dream of a cure into a reality.

Malinda Marsh, Chris Marsh, and Lissa Poincenot
Founders, LHON Collective

Executive Summary

As individuals, we rely on visual perception—sight—more than any other sense to navigate the world. Leber hereditary optic neuropathy (LHON) is a rare disease that leads to sudden and irreversible loss of vision, typically in the pivotal years of adolescence and early adulthood. Most LHON patients rapidly reach and surpass the legal blindness threshold and must quickly relearn how to navigate a world in which they can no longer recognize faces, drive, or read—a process that incurs significant social, emotional, and financial burdens. There is no cure for LHON, and there are no therapeutics available to reliably prevent, halt, or reverse the onset or progression of LHON vision loss.

LHON is among the most common inherited mitochondrial diseases. Tens of thousands of individuals worldwide are living with LHON vision loss, and more become legally blind each day. The cause of LHON is generally known, but the mechanisms underlying its pathogenesis have only partially been discovered.

LHON can be classified as an optic neuropathy, mitochondrial disease, and neurodegenerative disease, presenting opportunities for shared insights into cross-cutting disease mechanisms. Alignment across disease areas has the potential to expand the number of patients who could benefit from LHON research and create a market for multi-indication therapeutics. The complexities of LHON create an expansive research field that offers investigators numerous opportunities to deepen their understanding of the disease mechanisms and explore therapeutic strategies aimed at shifting the trajectory from vision loss to vision preservation and restoration.

LHON research and clinical communities face significant constraints because of the field's small size and limited financial resources. Government funding for LHON research, as highlighted by an analysis in this report, has been insufficient to catalyze the progress needed in the field. Although private funding has provided some support to individual investigators, it predominantly consists of sporadic, one-time, small-dollar grants and has not reached the scale needed to compensate for limited government funding. The chronic lack of reliable and sufficient funding poses major challenges for researchers striving to establish and maintain long-term LHON research programs, breaking momentum and the ability to efficiently move from discovery to clinical application. To transform the LHON therapeutic landscape for patients, a more expansive and coordinated effort to address these funding gaps is essential.

Philanthropic Opportunities to Drive LHON Research and Development

LHON Collective partnered with the Milken Institute Science Philanthropy Accelerator for Research and Collaboration (SPARC) to identify areas where strategic investment could advance the LHON field. This report reviews the current scientific landscape and funding trends, and outlines an LHON Research Roadmap that incorporates insights from key stakeholders within and beyond the LHON field. Highlighted are the most impactful opportunities for philanthropic investment to foster a collaborative, strategic, and focused effort to advance LHON research and therapeutics.

Philanthropic investment in the following areas can catalyze significant advancements in the LHON field.

1. Collect comprehensive patient data.

Comprehensive patient data and paired biological samples, collected longitudinally during regular clinic visits scheduled at defined intervals, as well as from post-mortem tissues, are invaluable resources for investigators to understand the natural course of disease and guide hypothesis-driven research and clinical trial design. High-quality data and biorepositories support every step along the research and development pipeline, from early discovery through clinical trials.

2. Foster a robust research and development ecosystem.

A robust research ecosystem is the foundation of an efficient and productive therapeutics pipeline. In the LHON field, there is a pressing need to bolster tools, resources, and foundational research to support the entire research process from initial discovery to clinical application. Prioritizing investments in disease models, retinal ganglion cell biology, biomarker discovery, neuroprotection, and drug repurposing can accelerate the discovery and development of targeted therapeutics.

3. Invest in platform technologies and partnerships.

Platform technologies, such as optimized gene therapy, mitochondrial gene editing, cell reprogramming, cell replacement therapy, and artificial intelligence–driven drug discovery, offer broad applications across a variety of diseases, including LHON and others sharing similar disease mechanisms or cell types. Partnering with developers of these technologies through data sharing, grants, contracts, and equity investments, and with researchers in aligned diseases, to overcome the small market potential of therapeutics developed for a rare disease will raise awareness of LHON and ensure the availability of these technologies as research tools and therapeutics for the field.

4. Support patient-centered clinical trials.

Patient-centered clinical trials focus on aligning the metrics used to evaluate the safety and efficacy of therapeutics with the patients' needs, reflecting their lived experiences and expectations for treatment. Clinical trials for vision-related therapeutics traditionally use visual acuity as an endpoint, but measurable improvements in this metric do not always correspond to functional improvements for LHON patients. Supporting efforts to incorporate patient-reported data into research and clinical trial design, in alignment with regulators and other stakeholders, will increase the likelihood that the therapeutics that make it to market actually improve quality of life.

5. Raise LHON awareness in clinical settings and build a talent pipeline.

The rarity of LHON, coupled with its limited research funding, means that few medical or graduate students are exposed to the disease as a potential career focus. This scarcity of specialized expertise contributes to prolonged diagnosis times and diminished quality of care for patients. It also impedes growth and innovation in LHON research. Raising awareness of LHON in clinical settings through targeted clinician education and fostering a sustainable talent pipeline via funding for medical students, graduate students, and early career investigators can simultaneously improve the standard of care and stimulate innovation in diagnostics and therapeutics.

Overview of LHON

Clinical Features

Leber hereditary optic neuropathy (LHON) is a rare mitochondrial disease that typically leads to sudden and irreversible loss of a person's central vision. Central vision is the part of the visual field that comes into focus when the eyes are fixed in one direction; it provides the high-resolution images and sharpness of detail necessary for recognizing faces and for activities such as reading and driving. In LHON, a small blur in the central vision, called a scotoma or blind spot, develops and, over the course of weeks or months, rapidly increases in size (Figure 1). Though the rate of progression and severity of vision loss varies significantly among individuals, most LHON patients become legally blind or worse (see **Appendix** for additional context on blindness). A patient's light perception and ultimate levels of peripheral vision and color vision will influence their ability to navigate the world independently and the types of accommodation needed to support daily life.

Figure 1. Example of LHON Vision

Although the size, density, and location of the scotoma (blind spot) in the visual field will vary between individuals and determine the severity of LHON vision loss, most LHON patients will become legally blind, impacting their ability to recognize faces, drive, and read.

Healthy Vision

LHON Vision

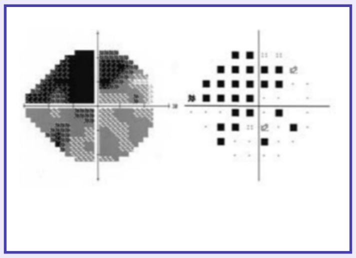
Source: Milken Institute (2024)

Though vision loss is the predominant manifestation and hallmark of the disease, LHON patients can have symptoms in other systems of the body as well. Reported nonvisual symptoms include cardiac arrhythmias, nonspecific muscle pain or weakness, and neurological abnormalities, such as postural tremor; peripheral neuropathy, numbness, or pain; movement disorders; and, in a small subset of patients, a co-occurrence of LHON with multiple sclerosis (LHON-MS). LHON involving nonvisual symptoms, with or without vision loss, is referred to as LHON plus.

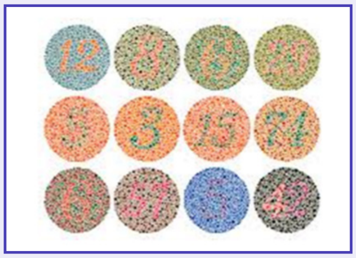
Figure 2. Clinical Evaluation of Vision

A variety of tests are used to measure and track changes in LHON vision, including sharpness of vision (visual acuity), size and location of the blind spot (visual field), and variability in perception of color (color vision).

Visual acuity measures the sharpness of vision at a standard distance. It is evaluated by testing a patient's ability to distinguish letters or symbols in an eye chart. A visual acuity of 20/200 marks the threshold for legal blindness and signifies the need to be 20 feet away to discern what someone with normal vision can see from 200 feet.



Visual field tests map peripheral vision, the total area a patient sees when eyes are set on a central focal point. Mapping peripheral vision is a way to identify the size and location of the blind spot, or scotoma, and is done by evaluating responses to white light moving around the field of vision.



Color vision tests measure ability to perceive and distinguish colors including sensitivity to color and hue, discernment between color classes, or deficiencies in color vision. Color vision is evaluated using a variety of tools including color plates (shown here), matching tests for color and brightness, and arrangement tests for sequencing colors.

Sources: Milken Institute (2024), based on visual acuity modified from **doi:10.1016/j.xcrm.2024.101437** *(2024), visual fields modified from* **doi:10.1016/j.ajo.2005.12.045** *(2024), and color vision modified from the* **American Optometric Association** *(2024)*

Clinical diagnosis of LHON usually involves collecting family history and assessing visual function. Tests of visual function typically include measuring visual acuity to evaluate sharpness of vision, mapping visual fields to locate the blind spot and determine its size, and assessing color vision for sensitivity, confusion, and deficiency (Figure 2).

A physical examination of the eye involves visually inspecting the surface at the back of the eye, called the fundus, to identify abnormalities in blood vessels and the optic disc. The optic disc, also called the optic nerve head, is the passageway for a specific type of neuron that carries signals from the retina to the brain for visual processing. This neuron is the retinal ganglion cell, and the axons or fibers of these cells are packaged into bundles to form the optic nerve (Figure 3). The optic nerve can also be observed and measured for degeneration as a marker of its integrity and LHON progression or stage because it is the loss of retinal ganglion cells and degeneration of the optic nerve that causes loss of vision in LHON patients.

LHON: Off the Chart

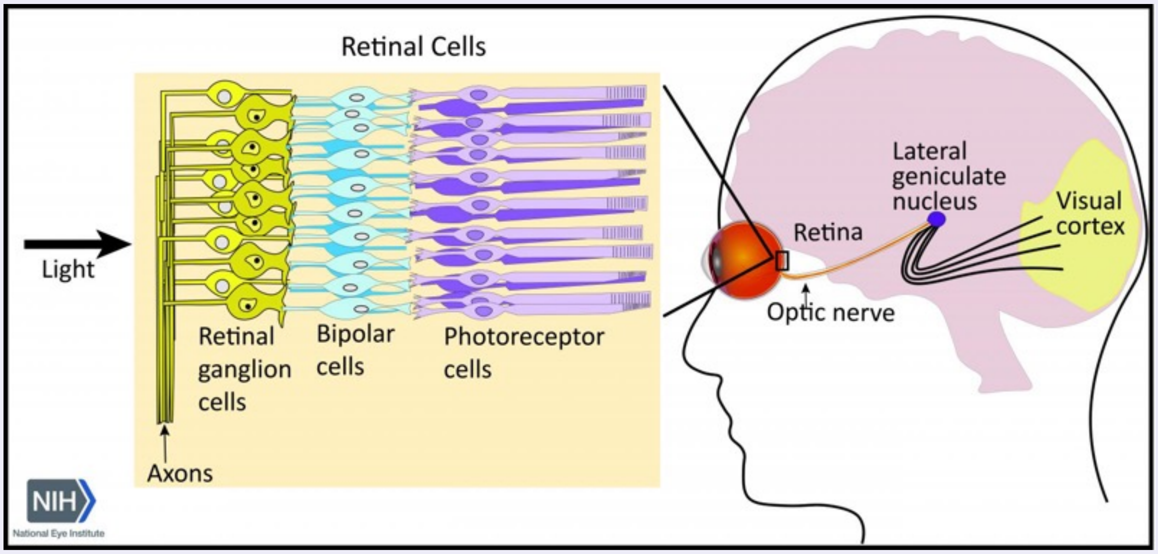
The visual acuity of LHON patients typically stabilizes at levels far worse than 20/200, though standardized eye charts only measure to 20/200, the threshold for legal blindness. This discrepancy complicates both the measurement and detection of changes in visual acuity, which impacts patient care and management. Historically, visual acuity has been the gold standard for evaluating therapeutic efficacy in clinical trials, but LHON's extreme visual impairment challenges this metric. Specialized low-vision eye charts with larger, high-contrast letters or symbols can assess a wider range of visual acuities. However, once visual acuity falls below 20/800, it is considered "off chart," and further evaluation involves less precise methods, such as detecting hand gestures (for example, counting fingers or waving).

A 15-letter improvement in visual acuity, equivalent to three lines on a logMAR eye chart (as shown in Figure 2), is considered clinically meaningful by the US Food and Drug Administration (FDA), and a 10-letter improvement, or two lines, by the European Medicines Agency (EMA). LHON patients can achieve such improvements and still have visual acuities that are off chart. Given the profound vision loss of LHON patients, there is a critical need for researchers, regulators, and sponsors to agree on clinical trial endpoints, such as changes in scotoma size, that effectively reflect real-world improvements in vision for LHON patients.

LHON is often initially misdiagnosed as optic neuritis, a symptom of multiple sclerosis, or one of several other vision-affecting diseases. Key differentiating features indicative of LHON include sudden vision loss that affects both eyes, typically starting in one eye six to eight weeks before the second eye (though simultaneous vision loss in both eyes occurs in about 25 percent of cases); absence of pain with vision loss or eye movement; pupils that continue to respond to light regardless of disease stage or severity of vision loss; and identifiable changes in retinal ganglion cell structure and function. Genetic testing can usually provide a definitive LHON diagnosis.

Figure 3. The Visual Pathway

Retinal ganglion cell axons bundle together to form the optic nerve, which transmits signals from the eye to the visual cortex in the brain. LHON vision loss happens suddenly when this connection is broken as retinal ganglion cells die, causing degeneration of the optic nerve.



Source: Courtesy of National Eye Institute, National Institutes of Health (2021)

Causes, Risk Factors, and Epidemiology

LHON is primarily an inherited mitochondrial disease. Mitochondria, specialized structures in cells responsible for energy production and other important cellular signaling functions, have their own genes and genome collectively referred to as mitochondrial DNA (mtDNA). Unlike nuclear DNA, which is inherited from both parents, mtDNA—and consequently hereditary mitochondrial diseases—are strictly inherited through maternal lines due to mitochondria being contributed exclusively by the egg during conception. Mutations in mtDNA are the most common cause of LHON, with greater than 90 percent of cases being linked to three known point mutations in the NADH dehydrogenase (ND) subunit genes: ND4, ND6, or ND1. The remaining cases stem from ultrarare mtDNA mutations, specific combinations of mtDNA mutations, or nuclear DNA mutations that affect mitochondrial genes or function.

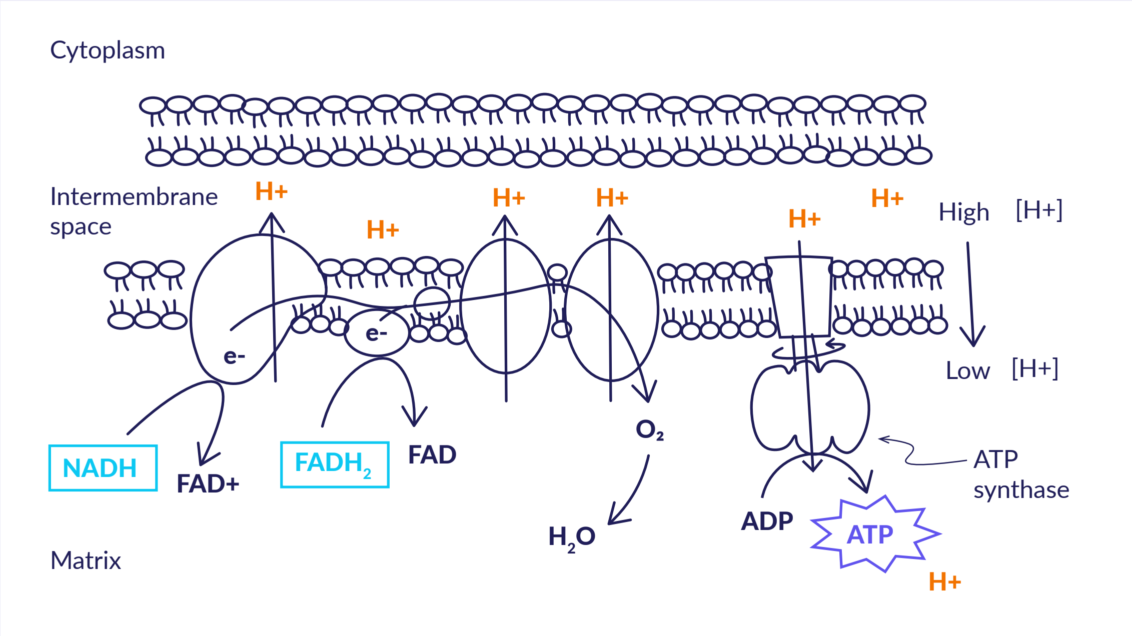
For individuals who have a genetic predisposition for LHON, tobacco smoking and other exposures to smoke, heavy alcohol consumption, and certain pharmaceuticals toxic to mitochondria, including some antibiotics, may influence the onset and severity of vision loss. Sex also plays a significant role, with about 75 percent of LHON patients being male. Vision loss peaks sharply in males aged 14 to 26 (median age 20 years) but shows a more even distribution in females, typically between 19 and 45 (median age 30 years), although vision loss can occur at any age in both sexes.

Globally, LHON prevalence—the proportion of people in a population who have the disease at a given time—is estimated to be between 1 in 25,000 and 1 in 50,000 people. It is difficult to nail down a more precise number due to underdiagnosis, variability in prevalence across regions, and limited population-wide studies. In the United States, several thousand people are living with LHON vision loss, and an estimated 100 new cases arise per year. Not all individuals with an LHON mutation will lose vision, in fact, most will not; understanding these dynamics is a critical knowledge gap in the LHON field.

Disease Mechanisms

LHON is most often caused by disease-specific mutations in mtDNA, although other genetic variants have also been associated with LHON pathology. LHON mutations are primarily found in the first component, Complex I, of the electron transport chain, an essential energy-generating process in cells. The electron transport chain is a series of multiprotein complexes embedded in the inner mitochondrial membrane (Figure 4). Electrons are shuttled through these complexes using electrochemical gradients, releasing energy at each step to power a molecular motor at the end of the chain that produces adenosine triphosphate (ATP), the principal energy currency of living cells.

Figure 4. LHON Mutations Disrupt the Activity of Complex I in the Electron Transport Chain



Source: Modified from **Khanacademy.org** *(2024)*

LHON mutations disrupting Complex I compromise electron transport through the chain, leading to a bioenergetic crisis that starves cells of energy, impairing vital functions. This disruption also causes an imbalance in electron flow, resulting in the premature release of electrons that react with oxygen to form reactive oxygen species (ROS), a primary cause of oxidative stress. Accumulated ROS damage cellular structures and alter signaling pathways, including the activation of programmed cell death pathways.

In conditions of energy deprivation and oxidative stress, retinal ganglion cells become highly susceptible to cell death signals, making them particularly vulnerable to Complex I mutations. The death of retinal ganglion cells causes progressive degeneration of the optic nerve, ultimately resulting in sudden loss of central vision for the patient.

Therapeutic Landscape

Currently, there is no cure for LHON, and the United States has no FDA-approved therapies. In Europe, the drug idebenone (Raxone) has gained approval from the EMA for patients aged 12 and older but only under the exceptional circumstances for rare diseases provision. This decision was driven by the lack of available treatments for LHON, evidence indicating some improvement in vision, and its acceptable safety profile.

Idebenone, a synthetic analog of coenzyme Q10 (CoQ10), assists in carrying electrons along the electron transport chain from Complexes I and II to Complex III. A real-world study assessing idebenone's effectiveness beyond clinical trials has shown clinically relevant benefit, including improvements in visual acuity and stabilization of residual vision in certain patients. Factors such as disease stage, specific mtDNA mutation, age at symptom onset, and sex influence these outcomes. Notably, there remain no treatments to prevent, halt, or functionally restore vision loss in LHON patients.

Gene Therapy Clinical Trials

Gene therapy is being investigated as a potential treatment for LHON. In LHON, where the genetic mutation affects Complex I and mitochondrial function, this approach aims to deliver a non-mutated gene to partially restore Complex I activity directly within the mitochondria of affected cells. This process involves packaging a non-mutated gene along with a mitochondrial targeting sequence, which acts like an address, into an engineered viral vector. Once injected into the eye, the vector releases the contents of the package into cells, and the mitochondrial targeting sequence guides the non-mutated gene to the mitochondria. As of July 2024, three gene therapies using this approach were being evaluated in clinical trials:

- **LUMEVOQ®** (lenadogene nolparvovec, GenSight Biologics) is a gene therapy for patients with an ND4 mutation that is set for a Phase III trial to validate earlier results demonstrating safety and improvements in visual acuity.

- **NR082** (Neurophth Therapeutics, Inc.) is a gene therapy for patients with an ND4 mutation in a Phase I/II trial enrolling patients in the United States to establish safety and efficacy following a series of trials conducted in China that demonstrated safety and improvements in vision for some patients.

- **NSF-02** (Neurophth Therapeutics, Inc.) is a gene therapy for patients with an ND1 mutation in a Phase I/II trial enrolling patients in the United States and China to establish safety, tolerability, and efficacy.

Delivering functional copies of a mutated gene directly to the mitochondria may be an attractive therapeutic option. However, practical challenges remain in optimizing the delivery method, targeting the mitochondria, and ensuring safety and affordability.

Alignment with Other Diseases

LHON arises from mitochondrial dysfunction and culminates in degeneration of the optic nerve due to the sudden progressive loss of retinal ganglion cells, a specialized type of neuron. This disease mechanism places LHON within multiple disease classes, including mitochondrial diseases, optic neuropathies, and neurodegeneration. Mitochondrial diseases include all genetic disorders that negatively impact mitochondrial function. Mitochondrial diseases are complex and can have highly variable signs, symptoms, and severities affecting one or more organ systems. Optic neuropathies include all diseases that involve damage to the optic nerve, impacting vision. Neurodegenerative disorders occur when cells in the central nervous system deteriorate, resulting in a broad spectrum of symptoms, including cognitive decline and impaired motor function. Although individual diseases have their own unique characteristics, underlying pathologies, and clinical presentations, several diseases within each of these classes share common features with LHON, namely disruption of Complex I activity or other causes of mitochondrial dysfunction and/or damage to retinal ganglion cells.

Examples of these diseases include:

- **Leigh syndrome and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome**, two mitochondrial diseases caused by genetic mutations that disrupt Complex I activity. Leigh syndrome leads to regression in physical and cognitive abilities and can result in respiratory failure, while MELAS is characterized by seizures, muscle weakness, and neurological deficits;

- **dominant optic atrophy**, which is primarily caused by genetic mutations in the OPA1 gene that disrupt mitochondrial dynamics leading to progressive degeneration of the optic nerve;

- **optic neuritis**, or inflammation of the optic nerve, commonly associated with multiple sclerosis or other diseases caused by damage to the outer casing of nerves, that can lead to retinal ganglion cell death;

- **glaucoma**, a group of diseases characterized by loss of retinal ganglion cells and the gradual, progressive, irreversible loss of vision;

- **Alzheimer's disease**, in which changes in the retina, including retinal ganglion cell loss, may be an early harbinger of disease associated with cognitive decline and a potential marker of disease progression; and

- **Parkinson's disease**, in which vision impairment, an established nonmotor symptom, may be linked to retinal ganglion cell loss contributing to reductions in contrast sensitivity, color vision, and visual acuity.

Every investment in LHON research has implications for other mitochondrial diseases, optic neuropathies, and neurodegenerative disorders; the reverse may also be true. The LHON research landscape presents fertile ground for breakthrough discoveries. Strategic investment in key research areas that intersect diseases, for example, understanding the molecular pathways determining the fate of retinal ganglion cells, is an efficient and cost-effective way to accelerate research and development by encouraging cross-pollination of ideas and knowledge, and may also broaden the scope of therapeutic possibilities.

Funding for LHON Research

To understand the flow of research dollars toward LHON and identify funding gaps where philanthropic capital can be transformative, Milken Institute SPARC conducted an analysis of public and private LHON research funding over the past decade. The purpose of this analysis was to identify trends and funding priorities in the field over time. Note that this analysis cannot offer a comprehensive list of funders because of incomplete reporting and limited public availability of data essential for evaluating relevance to the LHON field, such as project titles, dollar amounts, or duration of support.

Most LHON research in the United States (US) is funded by the federal government through the National Institutes of Health (NIH) and, more specifically, by the National Eye Institute (NEI) at the NIH. Recognizing that LHON research networks are global, this analysis also touches on funding by other governments where data are available. In addition to public funding, SPARC explored sources of private funding. Although nonprofit organizations are contributing research dollars to vision-related and mitochondrial diseases, none has public disclosures to suggest it is contributing significant financial resources specifically to LHON. Limited identification of LHON-specific private funding may stem from low philanthropic support or incomplete reporting per project, leading to an incomplete picture of LHON research funding.

Increased sharing of funding details, similar to those shared at the federal level, could help expand research funding efforts and confirm gaps and opportunities in the field. Overall, SPARC's analysis underscores a lack of reliable and sufficient funding for LHON; a coordinated effort is needed to establish and sustain funding for a robust LHON research ecosystem.

Public Funding

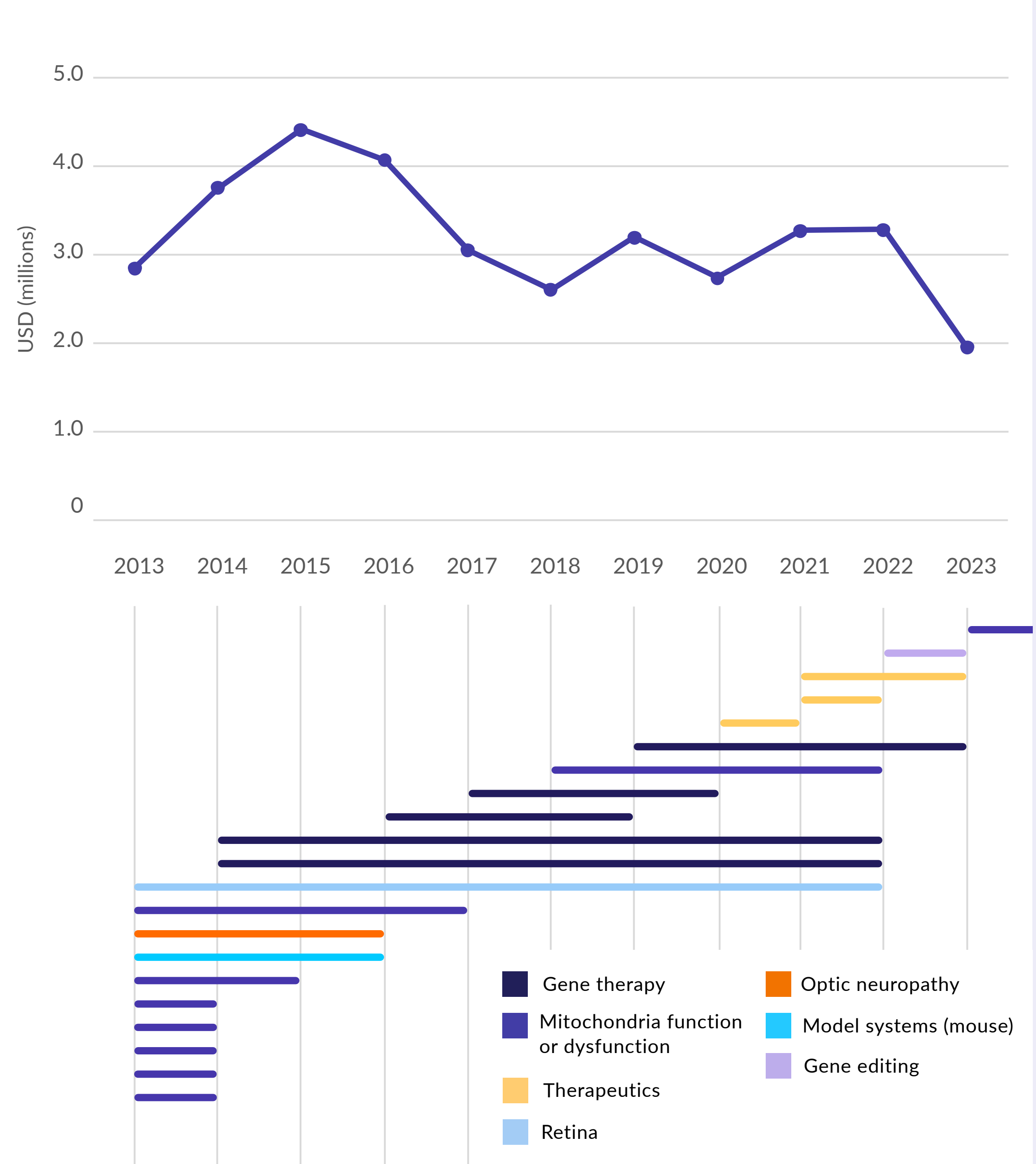
US Government

The primary source of funding for LHON research in the US comes from the federal government, through the NIH, in the form of extramural research grants awarded to universities and other research institutes outside the NIH. In roughly a 10-year span (fiscal years [FY] 2013–2023), the NIH allocated a total of $35.2 million to 21 distinct LHON-related research projects. This funding reached its highest point at $4.41 million in 2015 and fell to its lowest point at $1.95 million in 2023 (Figure 5). These dollar amounts are nominal relative to the estimated $25 billion deployed by the NIH for extramural research within the past year alone.

To gain insights into the LHON funding landscape, Milken Institute SPARC analyzed funding trends and priorities across various topic areas and grant types. From FY2013 to FY2023, over half of the NIH research funding allocated to LHON (51.8 percent) was dedicated to gene therapy research and clinical trials. A significant portion, approximately 21.8 percent, supported studies related to mitochondrial function or dysfunction relevant to LHON. In contrast, less than 10 percent of the funding has been directed toward non-gene therapy therapeutics, and no funding has been allocated to basic discovery in critical domains such as retinal ganglion cell biology, biomarker identification, or mechanisms of neuroprotection aimed at preventing vision loss in LHON (Table 1).

These findings highlight the dominant focus on gene therapy within LHON research, which has fallen short of efficacy expectations while neglecting investment in the fundamental understanding of the disease's mechanisms. Such foundational knowledge is crucial for informing therapeutic strategies, including gene therapy. Additionally, this analysis identified potential areas where diversification of research investment could enhance scientific understanding and treatment options for LHON.

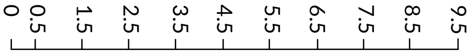
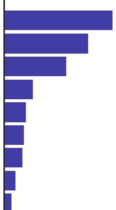
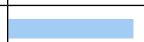
Figure 5. NIH Funding for LHON Research By Year



Note: Colored horizontal bars below the graph represent topic areas and duration of grant awards.

Source: Milken Institute analysis of NIH RePORTER, FY2013–2023 (2024)

Table 1. A Decade of NIH Funding for LHON Research by Topic Area

LHON relevant keywords in project title	Funding by project, USD (millions)	Project counts (%) (FY2013–2023)	Total funding, USD (%) (FY2013–2023)
			
Gene therapy		5 (23.8)	$18,212,988 (51.8)
Mitochondria function or dysfunction		9 (42.9)	$7,686,120 (21.8)
Therapeutics		3 (14.3)	$3,021,997 (8.6)
Retina		1 (4.8)	$2,820,224 (8.0)
Optic neuropathy		1 (4.8)	$1,693,605 (4.8)
Model systems (mouse)		1 (4.8)	$1,519,338 (4.3)
Gene editing		1 (4.8)	$225,000 (< 1)
Biomarkers		0 (0)	$0 (0)
Retinal ganglion cell biology		0 (0)	$0 (0)
Neuroprotection (prevention)		0 (0)	$0 (0)
Total		21 (100)	$35,179,272 (100)

Source: Milken Institute analysis of NIH RePORTER, FY2013–2023 (2024)

The distribution of grant types awarded also offers valuable insights into the LHON research landscape. The largest portion, approximately 44 percent, has been allocated through R01 and similar grants, typically supporting long-term projects led by established investigators (Table 2). Around 17 percent of funding has been dedicated to grants that support the next generation of LHON scientists and to development of research resources for the field. An additional 3 percent supports grants for exploratory research, including pilot and feasibility studies. Notably, about 34 percent of LHON grant funding has been channeled into cooperative agreements with the NIH for clinical trial development and execution.

Innovation in the field, represented by small business innovation grants, has received 2 percent of the funding (Table 2). This breakdown underscores the potential impact of directing resources toward early career investigators, development of research resources for the field, exploratory research projects, and innovative, high-risk, high-reward projects to further enrich the LHON research ecosystem.

Table 2. Distribution of LHON Funding by Grant Type

Use	Grant Types	Grant counts (%) (FY2013–2023)	Total funding, USD (%) (FY2013–2023)
Research	R01, P01	9 (43)	$15,489,803 (44)
Cooperative agreements (clinical studies with NIH support)	UH3/UG3, U10/UG1	3 (14)	$11,993,757 (34)
People and research resources	R15, R24, R35, F30	4 (19)	$6,033,618 (17)
Pilot and feasibility studies	R21, SC2	3 (14)	$1,087,094 (3)
Small business innovation	R43	2 (10)	$575,000 (2)
Total	11	21 (100)	$35,179,272 (100)

Source: Milken Institute analysis of NIH RePORTER, FY2013–2023 (2024)

Within the NIH, the NEI has sponsored 47.6 percent of LHON grants, amounting to 73.8 percent of the total research funding allocated to LHON over the past decade. Although the NEI has become the primary funder, LHON research has also received support from several other NIH institutes and centers. As of the latest fiscal year, 2023, LHON research is being funded by three NIH institutes: the NEI, the National Center for Advancing Translational Sciences (NCATS), and the National Institute of General Medical Sciences (NIGMS) (Table 3).

Table 3. A Decade of Funding for LHON Research by NIH Institute

NIH Institute/ Center	Grant counts (%) (FY2013–2023)	Number of years of LHON grant support (FY2013–2023)	Average funding per year of support, USD (%) (FY2013–2023)	Total funding, USD (%) (FY2013–2023)
NEI	10 (47.6)	11	$2,360,597 (52.2)	$25,966,569 (73.8)
NINDS	3 (14.3)	6	$544,856 (12.0)	$3,269,134 (9.3)
NCATS	1 (4.8)	3	$729,332 (16.1)	$2,187,997 (6.2)
NIA	2 (9.5)	6	$342,965 (7.6)	$2,057,792 (5.8)
NIGMS	3 (14.3)	5	$202,868 (4.5)	$1,014,340 (2.9)
NICHD	1 (4.8)	2	$294,266 (6.5)	$588,532 (1.7)
NIEHS	1 (4.8)	2	$47,454 (1.0)	$94,908 (< 1)
Total	**21 (100)**	**NA**	**$4,522,338 (100)**	**$35,179,272 (100)**

NEI (National Eye Institute); NINDS (National Institute of Neurological Disorders and Stroke); NCATS (National Center for Advancing Translational Sciences; NIA (National Institute on Aging); NIGMS (National Institute of General Medical Sciences); NICHD (Eunice Kennedy Shriver National Institute of Child Health and Human Development); NIEHS (National Institute of Environmental Health Sciences)

Source: Milken Institute analysis of NIH RePORTER, FY2013–2023 (2024)

In addition to the NIH, the US federal government funds biomedical research through Congressionally Directed Medical Research Programs within the Department of Defense (DoD). Between FY2013 and FY2023, the DoD awarded grants totaling approximately $19 million and $141 million to research projects investigating optic neuropathies and mitochondrial diseases, respectively, including a single $319,000 grant for an LHON project in FY2019. The DoD makes funding decisions in coordination with the NIH to help ensure diversity across the government-funded research portfolio. Within this broader context, LHON research accounts for 11.2 percent of the total funding allocated to optic neuropathies and 5.5 percent of the total funding allocated to mitochondrial diseases.

International Governments

In many countries outside of the US, funding is awarded to Centers of Excellence or as meritbased awards to independent investigators to fund institutes, research programs, or laboratories instead of individual projects that can be linked to a dollar amount. Additionally, few countries maintain comprehensive, searchable databases available to the public that would enable an unbiased survey of their research funding landscapes. We know from the acknowledgments and funding sections of published LHON research papers that scientists and clinicians abroad are receiving funding from government sources including the UK National Institute for Health Research (NIHR) and Medical Research Council, the Australian Research Council and National Health and Medical Research Council, the Canadian Institutes of Health Research, the German Federal Ministry of Education and Research and the German Research Foundation, the Italian Ministries of Health and Research, the supranational European Research Council, the Ministry of Science and Technology of the People's Republic of China and the Natural Science Foundation of China, and the Ministry of Science and Technology of the Government of India, among others.

Data on LHON-specific projects are notably limited. A small number of data points sourced from the NIH World RePORT and the NIHR, from across the UK, Australia, and Canada, suggests that a typical LHON grant award amounts to $300,000 per year for a duration of three to five years, with a range extending from US$12,900 to US$1.7 million (currencies converted at December 2023 rates). It is crucial to acknowledge, however, that these data are far from complete.

Regardless of country, there is consensus among researchers in the field that a major barrier to progress in LHON research is access to sufficient and sustained government funding. LHON research is being sidelined worldwide as investigators shift their research priorities to adjacent fields that provide more reliable and abundant funding opportunities (for example, glaucoma). This problem is pervasive—even the leading researchers in the field are unable to secure consistent funding from government sources to support and sustain their LHON research programs because of the general lack of funding earmarked for LHON research.

Private Funding

Based on the available data, private funding for LHON research over the past decade has been intermittent and relatively modest, typically taking the form of one-time grants meant to support the generation of preliminary data. LHON Project Fund and the International Foundation for Optic Nerve Disease are two examples. Although this funding has been beneficial to individual investigators, it has not been sufficient to drive the transformative change needed in the LHON field.

Beyond LHON-specific funding, several other nonprofit organizations contribute significant funding to general biomedical research, research in eye diseases that cause vision loss, including optic neuropathies, and mitochondrial diseases that have funded individual LHON projects (for example, Wellcome Trust [UK], Fight for Sight [UK], Mito Foundation [Australia], and Mitocon [Italy]). However, even among foundations focused on disease areas relevant to LHON, most have disease-specific priorities that do not include LHON and do not publicly release the grants and amounts awarded, or the data are sporadic and not up to date, posing challenges to assessing their relevance to LHON.

Philanthropic Opportunities: An LHON Research Roadmap

Our analysis of the current state of LHON research and funding has identified key knowledge, research, and resource gaps, highlighting pivotal opportunities for growth and innovation in the LHON field. This report comes on the heels of the 35th anniversary of the discovery of the first mitochondrial mutation associated with LHON vision loss. Since then, breakthroughs in genetics and pioneering advances in research tools and technologies have transformed the scientific landscape. Each of the opportunities presented in this roadmap is a strategic entry point for funders to leverage these advances and accelerate the research and discovery process with the goal of delivering diverse therapeutic options to prevent, halt, and reverse LHON vision loss (Figure 6). Moreover, each opportunity builds a foundation for answering the critical remaining questions regarding LHON biology (**Appendix**).

Figure 6. LHON Research Roadmap Timeline

<table>
<tr><th>Goal</th><th>Today</th><th>2 years</th><th>5 years</th><th>10 years</th></tr>
<tr><td rowspan="3">Collect comprehensive patient data</td><td colspan="2">Identify and gather existing patient data worldwide</td><td colspan="2"></td></tr>
<tr><td colspan="3">Establish unified protocols for post-mortem tissue collection within existing biobanks</td><td></td></tr>
<tr><td></td><td colspan="3">Establish and grow centralized data and biorepositories across global regions</td></tr>
<tr><td rowspan="3">Foster a robust research and development ecosystem</td><td colspan="2">Catalog and characterize existing in vitro and in vivo LHON models</td><td colspan="2"></td></tr>
<tr><td rowspan="2"></td><td colspan="2">Fund the development, characterization, and validation of new models</td><td></td></tr>
<tr><td colspan="3">Fund retinal ganglion cell biology, biomarker discovery, and neuroprotection research</td></tr>
<tr><td rowspan="2">Invest in platform technologies and partnerships</td><td colspan="3">Expand LHON’s presence in the optic neuropathy and neurodegeneration communities</td><td></td></tr>
<tr><td colspan="2"></td><td colspan="2">Build partnerships based on data and resource sharing, grants, contracts, and equity investments</td></tr>
<tr><td rowspan="2">Support patient-centered clinical trials</td><td colspan="2">Develop survey instruments and apps to support patient-reported data collection</td><td colspan="2"></td></tr>
<tr><td></td><td colspan="2">Convene relevant stakeholder groups to establish functional outcome measures and clinical trial endpoints</td><td></td></tr>
<tr><td rowspan="2">Raise LHON awareness in clinical settings and build a talent pipeline</td><td colspan="4">Provide funding to develop and deliver a high-quality CME course</td></tr>
<tr><td colspan="4">Invest in scholarships, fellowships, a mentorship network, and research grants to support students and early investigation</td></tr>
</table>

Source: Milken Institute (2024)

1. Collect Comprehensive Patient Data

Gap

Patient data and biological samples are the foundation for understanding a disease, its underlying cause(s), and natural progression, and informing hypothesis-driven research and clinical trial design. **In LHON, biological samples are rare, and the patient data that exist are fragmented across clinics and patient registries around the world.** Among the existing patient data and biological samples, many have been collected without consensus standards or protocols, making it difficult to pool them for research. The need for a coordinated, large, prospective, standardized data set that includes clinician-reported data, patient-reported data, and biological samples—from affected and unaffected mutation carriers—is one of the greatest needs and will likely remain an evergreen need to propel the science and therapeutic development forward.

Goal

To establish comprehensive patient data repositories and biorepositories globally, we recommend the following activities:

1. Identify and gather existing patient data worldwide to build a unified retrospective data set. Use this data set as a baseline to set standards and consensus protocols, and identify gaps in the data that need to be addressed in future data collection.

2. Establish unified protocols and standards for harvesting, processing, and storing LHON-relevant post-mortem tissues, including the brain, optic nerve, and eyes, within existing biobanks.

3. Establish centralized data and biorepositories across global regions to gather longitudinal clinician- and patient-reported data alongside biological samples from both affected and unaffected carriers (i.e., individuals who have an LHON mutation with or without vision loss). Use standardized data practices and consensus protocols for collection.

Value

Investing in these activities will reduce duplication of efforts and data fragmentation, increase patient involvement and research enrollment, and improve the consistency and completeness of the data, which are prerequisites for high-quality research. The resulting repositories will serve as an invaluable resource for natural history studies and to advance therapeutics research by providing a baseline against which to validate disease models, compare therapeutic interventions, and develop data-driven treatment strategies. Because high-quality patient data are rare, repositories also foster collaboration among clinicians, scientists, and industry stakeholders within and between disease networks.

Impact

Achieving this goal will improve the field's understanding of the natural course of disease. It will also offer the potential to identify secondary factors that predict the likelihood and severity of vision loss, reveal disease subtypes, identify biomarkers with clinical and research applications, and shape the design and evaluation metrics of clinical trials.

2. Foster a Robust Research and Development Ecosystem

Gap 1

Model systems are the backbone of an efficient and productive research and development therapeutics pipeline. Cell and animal models, organoids, and human tissues each contribute something unique along the path from basic discovery through preclinical drug development. Perturbation experiments in models can demonstrate how mutations and other genetic variations or secondary factors impact biochemistry and drive pathogenicity. Such experiments lead to a better understanding of the disease and make it possible to determine how to counteract disease mechanisms to prevent, treat, or reverse a disease process and—further down the path—to assess safety and efficacy of experimental therapeutics.

The LHON field has developed a number of research tools specific to LHON, including fibroblasts, cybrids, patient-derived induced pluripotent stem cell (iPSC) models, and a handful of mouse models, each recapitulating some aspect of the disease, to study Complex I biochemistry and the effects of select therapeutics. However, there is consensus among investigators and drug developers that **more and better-suited models are needed to support an efficient and productive end-to-end research and development therapeutics pipeline** for LHON.

Goal

We recommend supporting the field in establishing a core set of well-characterized LHON disease models through the following:

1. Catalog and characterize existing in vitro and in vivo LHON models. Creating a database of well-characterized models will reduce duplication of efforts in model generation, help investigators select the optimal models to address their specific research questions, and improve reproducibility and validation of studies by providing a reliable reference for comparing experimental outcomes across research groups.

2. Fund the development, characterization, and validation of new LHON models. New models would cover more mutations and types of genetic variation and expand the diversity of model systems to include, for example, zebrafish, organoids, ex vivo, and in silico models.

Value

Establishing a core set of well-characterized disease models will enable researchers to comprehensively capture the diverse ways LHON manifests in patients and enable better comparisons of experimental results across studies and among laboratories, ensuring the validity of research findings and safety and efficacy of therapeutic candidates. Disease models are indispensable tools for uncovering disease mechanisms, identifying therapeutic targets and biomarkers, and rapidly testing and validating hypotheses, early discoveries, and experimental therapeutics.

Impact

Achieving this goal will catalyze the research discovery and therapeutic pipeline, providing a deeper understanding of the disease, accelerating therapeutic development, and enhancing translatability from the laboratory to the clinic. The robustness and reliability of research findings across a variety of models elevate confidence in the safety and efficacy of candidate therapeutics, laying a solid foundation for their progression through the therapeutic development pipeline.

Gap 2

Basic discovery (e.g., mechanisms of pathogenesis) and drug repurposing research have complementary roles to play in the therapeutic discovery process. Mechanistic research provides the foundational knowledge for identifying key molecular pathways that drive disease and/or promote resilience and may point to biomarkers and therapeutic targets, inform therapeutic strategies, and contribute to our understanding of other mitochondrial diseases or forms of neurodegeneration. Mechanistic knowledge can also be used in drug repurposing, using high-throughput screens of existing compounds to identify drug candidates, to select compound libraries and the most appropriate screening assays. These screens use disease models, e.g., fibroblasts or zebrafish, biochemical assays, and computational methods to systematically identify existing small molecule compounds for activity against the mechanisms that drive disease. **While investigators know what is happening to cause vision loss in LHON, the underlying mechanisms of how and why it is happening have not been discovered yet.**

Goal

To close gaps in mechanistic understanding and streamline therapeutic discovery, we recommend funding research in the following areas:

1. **Retinal ganglion cell biology.** Retinal ganglion cells are the key players in LHON vision loss; patterns of their degeneration are well-characterized but the mechanisms that underlie this degeneration remain largely unknown. Basic research focused on understanding how retinal ganglion cell survival or death is determined by circulating chemical messengers, physical and mechanical forces, and interactions with neighboring cells will provide a deep understanding of the mechanisms that drive vision loss, potentially revealing therapeutic targets and treatment strategies that can be tailored to individual patients.

2. **Biomarker discovery.** Biomarker research is an investment in patient care, therapeutic development, and improved outcomes. In LHON, where vision loss is sudden and variable between individuals, biomarkers may provide early indicators of disease onset and progression, enabling timely interventions to prevent or halt vision loss and monitor vision recovery. Furthermore, biomarkers may offer insights into the underlying mechanisms of LHON and aligned diseases, accelerating discovery and development of targeted therapeutics, and acting as an outcome measure for evaluating the effectiveness of these therapies in both preclinical studies and clinical trials.

3. **Neuroprotection.** Neuroprotection is a term used to describe strategies aimed at protecting and preserving neurons, including retinal ganglion cells, from damage and degeneration. Understanding mechanisms of neuroprotection may lead to the prevention of LHON vision loss. This might include targeting mechanisms of oxidative stress, mitochondrial dysfunction, or inflammation, all of which have been implicated in LHON pathogenesis. Because LHON shares features with other mitochondrial diseases, optic neuropathies, and forms of neurodegeneration, advancements in neuroprotection have broad implications for multiple patient populations.

Value

Supporting basic research and drug repurposing sets the stage for unraveling the complex biological mechanisms underlying disease and identifying drug targets and potential drug candidates more efficiently. This will create a data-driven therapeutic discovery process and expedite translation of discoveries from the laboratory to the clinic. In addition to predicting what will work, the knowledge gained from this research will contribute to understanding translational failures, putting a cycle of continuous improvement in motion.

Impact

Achieving this goal will catalyze a productive and diversified therapeutic pipeline that offers more and better therapeutic options to prevent, halt, and reverse LHON vision loss, with the potential to transfer discoveries and therapeutics to related diseases.

3. Invest in Platform Technologies and Partnerships

Gap

Academic scientists and biotechnology companies are working on platform tools and technologies that could reinvent the research and discovery pipeline and therapeutic landscape for a variety of diseases. For LHON, this includes optimizing the delivery of gene therapies, gene editing in mtDNA, cellular reprogramming, cell replacement therapy, and artificial intelligence for drug discovery and development. **LHON is on the radar of a few gene therapy and gene editing endeavors, but as a rare disease, it may not have the market potential on its own to attract scientists and companies looking for use cases for their technologies.** LHON does, however, sit within multiple disease classes, and together, these rare mitochondrial diseases and more common optic neuropathies and neurodegenerative diseases comprise a significantly larger patient population to become a compelling use case for multi-indication therapeutics. Building partnerships through knowledge and resource sharing and investment will meet the critical need for bringing novel tools and technologies to a field that, historically, has been constrained in its capacity to innovate because of its small size and limited access to funding.

Goal

To forge mutually beneficial multi-stakeholder relationships and build LHON awareness, we recommend the following:

1. Expand LHON's presence in optic neuropathy and neurodegeneration disease networks by supporting the research and clinical communities by joining or initiating data-sharing collaboratives, attending or convening scientific conferences for diseases with common mechanisms or cell types, and highlighting platform technologies that are of mutual benefit.

2. Bringing platform technologies to the LHON research and patient communities by building partnerships based on data and resource sharing, and the use of grants, contracts, or equity investments to support their development and commercialization. The work to rigorously aggregate biological samples from patients, if made openly available, will attract more commercial R&D to the space.

Value

Investing in platform tools and technologies and aligning with various disease areas can increase efficiency and cost-effectiveness, broaden therapeutic options, and position LHON as the gateway to addressing unmet medical needs across diseases, thereby benefiting multiple patient populations simultaneously.

Impact

Achieving this objective will advance scientific knowledge and potentially bring new therapies to market and/or overcome current limitations of therapeutics in development, not only for LHON but also for related diseases. This approach establishes credibility and a positive reputation, attracting more investors and other stakeholders for future endeavors.

4. Support Patient-Centered Clinical Trials

Gap

Clinical trials evaluating therapeutics for vision-related diseases usually rely on improvements in visual acuity, measured by reading lines on an eye chart, as the primary endpoint. Yet, for most **LHON patients, these measurements do not necessarily reflect meaningful functional benefits. Bridging this gap between clinical metrics and patient realities poses a significant challenge, particularly in aligning regulatory requirements with patients' needs and preferences.** Recognizing that vision is both objective and subjective, incorporating the lived experience and perspective of patients is a particularly important, but largely missing, piece in research and clinical trial design. Prioritizing patient-reported outcomes in LHON research and development will foster a more nuanced understanding of therapeutic efficacy and alignment with the actual needs of patients.

Goal

We recommend **bridging the gap between regulatory requirements and patient realities in the following ways:**

1. Support efforts to develop patient-reported outcomes and well-being, including the development of survey instruments and apps to gather and analyze patient-reported data, and inform clinical research.

2. Convene relevant stakeholder groups, including patients, drug developers, clinical trialists, regulatory agencies, and payors to establish functional outcome measures and endpoints for clinical trials.

Value

Aligning trial endpoints with patients' lived experiences strengthens transparency and accountability in the drug development process, instilling confidence in both patient communities and regulatory agencies. Building this trust lowers barriers to patient recruitment to clinical trials, a challenge for rare diseases, and incentivizes industry partners to commit to the development of promising drug candidates.

Impact

Achieving this goal will ensure that future therapeutics for LHON are evaluated against measures that are relevant and meaningful to those directly affected by the disease. Empowering patients to participate in shaping research protocols builds partnerships that ultimately drive more effective and patient-centered care.

5. Raise LHON Awareness in Clinical Settings and Build a Talent Pipeline

Gap

A notable gap in LHON patient care is early and accurate diagnosis. Because LHON is so rare, patients and their families often find themselves on a diagnostic odyssey with minimal support or resources, navigating the health-care system and identifying specialists as they are dealing with sudden and unexplained vision loss. Most start by seeking care from an optometrist or ophthalmologist, though a neuro-ophthalmologist is most likely to make the diagnosis.

In the US, there were only 635 neuro-ophthalmologists as of April 2023, in contrast to nearly 19,000 ophthalmologists. Neuro-ophthalmology is the smallest subspecialty of ophthalmology (approximately 75 percent of neuro-ophthalmologists complete residencies in ophthalmology; the other 25 percent come from neurology); not all patients will have access to a neuro-ophthalmologist, and not all neuro-ophthalmologists will have experience with LHON.

The rarity of the disease is exacerbated by limited government funding, which contributes to a lack of exposure to the disease among medical and graduate students in research programs, shrinking the pool of professionals who even consider building a career around LHON patient care and research.

Goal

To build LHON awareness and a talent pipeline, we recommend the following targeted efforts to increase awareness, educational tools, and support for specialized training:

1. Provide funding to build and deliver a high-quality continuing medical education (CME) course to educate clinicians adjacent to neuro-ophthalmology (e.g., optometrists, ophthalmologists, neurologists) about LHON to raise awareness and shorten the diagnostic timeline.

2. Invest in scholarships, fellowships, a mentorship network, and research grants for medical students, graduate students, and early career investigators to build a talent pipeline.

Value

Building a talent pipeline is an organic way to foster collaboration, creating a vibrant ecosystem where partnerships are formed, knowledge and ideas are exchanged, and resources are shared. It also elevates the standard of care by creating a network through which to disseminate best practices and evidence-based standards of care. Further, it provides long-term sustainability, ensuring continuity of expertise and leadership in LHON patient care and research.

Impact

Achieving this goal will (1) bring specialized expertise and a dedicated focus to LHON, ensuring that all patients receive tailored, high-quality care from professionals with in-depth knowledge of the disease's nuances and complexities and (2) enhance research capacity and drive innovation leading to the development of new diagnostics, therapeutics, and treatment strategies.

Conclusion

LHON is a rare disease that causes sudden and irreversible loss of central vision, often striking individuals in late adolescence and early adulthood—the most critical periods for building education, careers, and families. While coping with the emotional and social costs of sudden blindness, patients must also bear the financial burden associated with adaptive technologies, specialized training, accessibility modifications, rehabilitation, psychological support, reduced workforce participation, and changes in employment outlook. In the United States alone, the broader economic impact of blindness surpasses $16,000 per patient per year. Today, no treatments are available to reliably prevent, halt, or reverse LHON vision loss. However, the field is poised for discovery, with potential breakthroughs hinging on overcoming its small size and limited financial resources.

The challenges faced by the LHON field are common across rare diseases. Patient samples are scarce, government funding for research is limited, and awareness and incentives for industry investment are low. Nevertheless, there are opportunities through collaborative partnership and strategic philanthropy to transform this landscape into a sustainable, interdisciplinary, patient-centric research ecosystem centered on LHON. This ecosystem would provide adequate and reliable financial support to build an efficient and productive research and development pipeline to move discoveries from the laboratory through commercialization.

Advancing any of the priority areas identified in this report will help create favorable conditions to accelerate research and discovery of therapeutics, benefiting not only LHON but also diseases with shared mechanisms or cell types. Some opportunities have overlapping objectives; all are important factors for de-risking translational research and attracting industry partners to bring more and better therapeutics to market and ensuring high-quality, evidence-based care for all LHON patients.

Appendix

Defining Blindness

The definition of blindness varies depending on context (e.g., medical, legal, or educational) and global region. Blindness is generally defined as severe visual impairment that affects a person's ability to do everyday activities. It is important to recognize that blindness is a spectrum; varying types and degrees of visual impairment fall under this term. Blindness may be defined based on visual acuity (sharpness of vision), visual fields (peripheral vision), or a combination of these factors.

The chart below maps visual acuity to functional vision ranges recommended by the International Council of Ophthalmology (ICO), a global network of ophthalmologists and ophthalmology societies, to various definitions of visual impairment and blindness. These definitions have been established by governments, the World Health Organization (WHO), and the US Centers for Medicare and Medicaid Services (which uses ICD-9-CM). WHO's definition is aligned with the tenth revision of the International Classification of Disease (ICD-10) and is the most commonly used definition for research studies globally.

Visual Acuity		
USA (20 ft)	UK, AUS (6 m)	Decimal
20/12.5	6/3.8	1.6
20/16	6/4.8	1.25
20/20	**6/6**	**1.0**
20/25	6/7.5	0.8
20/32	6/9.5	0.63
20/40	6/12	0.5
20/50	6/15	0.4
20/63	6/19	0.32
20/80	6/24	0.25
20/100	6/30	0.2
20/125	6/38	0.16
20/160	6/48	0.125
20/200	**6/60**	**0.10**
20/250	6/75	0.08
20/320	6/95	0.063
20/400	6/120	0.05
20/500	6/150	0.04
20/630	6/190	0.03
20/800	6/240	0.025
20/1000	6/300	0.02
20/1250	6/380	0.016
20/1600	6/480	0.0125
20/2000	**6/600**	**0.01**
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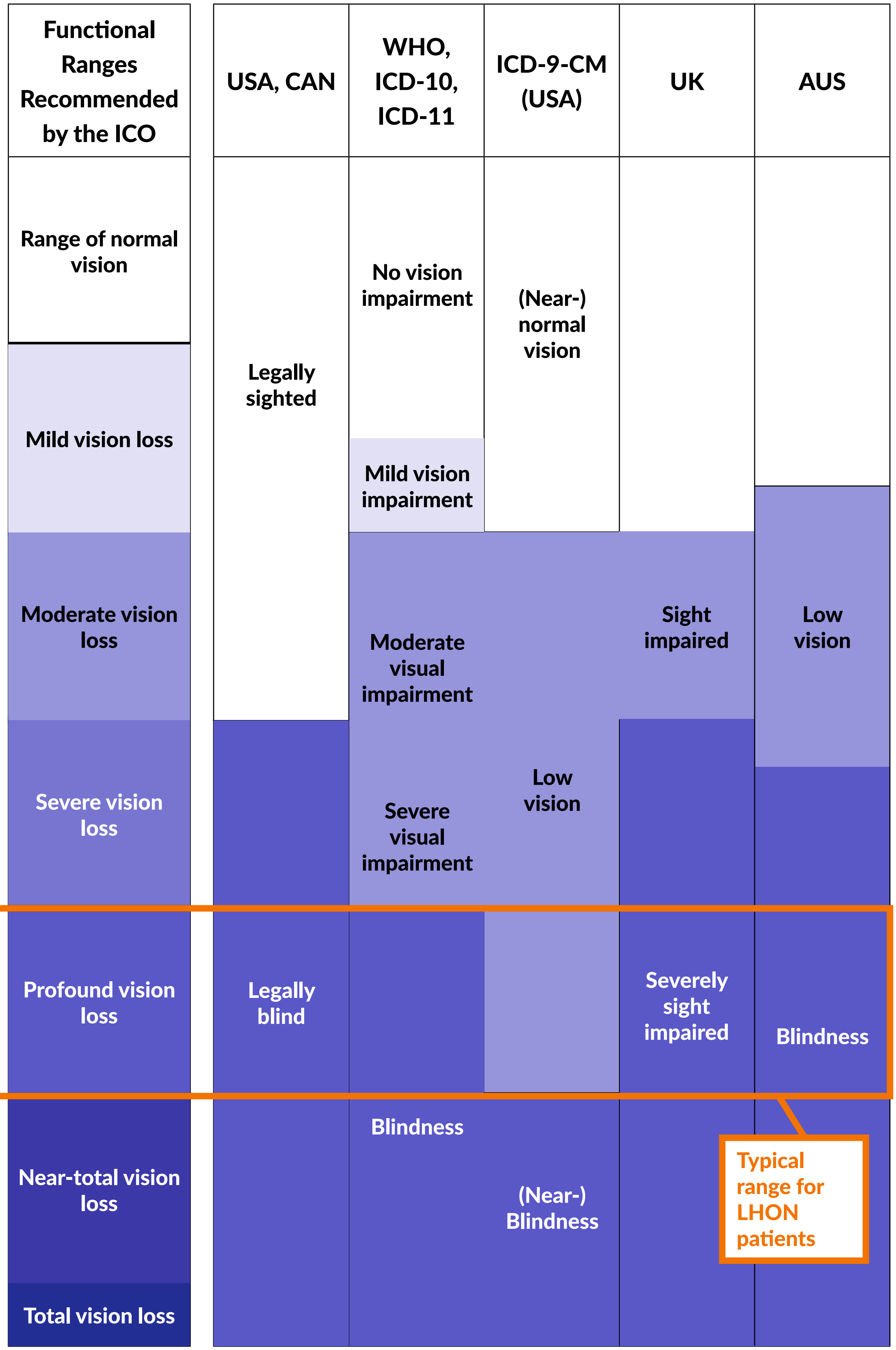
No light perception		



Source: Milken Institute (2024), modified from Ento Key https://entokey.com/causes-and-prevention-of-vision-loss/

Visual acuity is assessed by how well a person can discern letters or symbols on a standardized chart from a fixed distance, typically 20 feet (or six meters). Reported as a fraction or decimal, this measurement indicates the clarity of vision compared to someone with normal eyesight at that distance. While chart designs and testing distances may vary across countries, the fundamental concept remains consistent.

Visual acuity serves various purposes, including the determination of legal blindness. This designation is governmental rather than medical and is used to establish eligibility for support services and benefits. In most countries, individuals with a visual acuity of 20/200 or worse are considered legally blind. LHON patients usually far exceed this threshold, typically stabilizing in the range of 20/600 to 20/800. According to ICO guidelines, this level of vision loss is classified as profound.

Research Priorities in LHON

In February 2024, Milken Institute SPARC, in partnership with LHON Collective, convened a select group of scientists and clinicians to chart a path forward for LHON. The gathering included experts in LHON and aligned diseases or biological mechanisms, model systems, and artificial intelligence and big data. The goal was to identify key priorities for philanthropic investment in LHON research. Together, this group identified strategic areas where investment can catalyze a productive and diversified therapeutic pipeline that offers more and better treatment options to prevent, halt, and reverse vision loss in LHON patients.

Investigators know *what* is happening to cause vision loss in LHON, but the underlying mechanisms of how and why it is happening are still open research questions. This type of foundational knowledge is crucial for informing therapeutic strategies. Through discussion with experts within and beyond LHON, Milken Institute SPARC has identified five key questions with the greatest potential to advance the field.

What are the drivers of catastrophic vision loss in LHON ?	Most cases of LHON are associated with a few known point mutations in mitochondrial DNA (mtDNA) that disrupt normal Complex I activity. However, these mitochondrial mutations are not the only disease-causing mechanisms, and a mutation alone is not sufficient to cause vision loss. Penetrance of the disease is low outside of known LHON pedigrees, and the course and severity of vision loss are variable and can be influenced by genetic background, age, sex, and environmental exposures. Understanding the interplay of these factors is vital for designing strategies to prevent, halt, and reverse LHON vision loss.

What are the regulatory mechanisms that govern the survival or death of retinal ganglion cells (RGCs)?	RGC death is what leads to LHON vision loss. RGCs are selectively vulnerable to LHON mutations, and their pattern of progressive death is a hallmark of the disease. Various factors, including metabolic changes, the microenvironment, and specific mechanisms of cell death, contribute to RGC vulnerability. However, it is unclear why, when, and how RGC cell death is triggered. Unraveling these mechanisms may lead to novel therapeutic targets.
How do heteroplasmy and mitochondrial dynamics contribute to LHON onset and progression?	Heteroplasmy levels in affected and unaffected LHON mutation carriers are not regularly measured, but heteroplasmy thresholds may be a key factor in determining onset and severity of vision loss. Heteroplasmy can impact mitochondrial dynamics, including mitobiogenesis and mitophagy, and vice versa. Mitochondrial dynamics are tightly regulated to maintain cellular function. Both heteroplasmy and mitochondrial dynamics can be modulated, for example, by gene editing and small molecule compounds, respectively. Understanding these processes in LHON has the potential to change the therapeutic landscape.
What therapeutic strategies can be developed to promote neuroprotection and preserve vision in LHON patients?	Past neuroprotection efforts in LHON have included trials with antioxidants such as coenzyme Q10 and idebenone to reduce oxidative stress and support mitochondrial function. Nicotinamide (vitamin B3) has shown promise by mitigating mitochondrial and metabolic dysfunction in retinal diseases such as glaucoma. Focusing on safeguarding retinal ganglion cells from mitochondrial damage, rather than treating existing damage, may lead to more effective prevention strategies. Moreover, advancements in neuroprotection strategies for LHON could have broader implications for other neurodegenerative and retinal diseases where similar mitochondrial dysfunction plays a role.
What novel biomarkers can be identified to support patient care and research?	Currently, the most common biomarker for LHON is an imaging technique used to capture structural changes in RGCs, although functional measures such as electrophysiology and small molecule metabolites have also been explored. The identification of more robust and sensitive biomarkers could be a game-changer to help unravel the heterogeneity of the disease and improve diagnostic tools, identify drug targets, track progression and therapeutic response, stratify patients into risk groups, and provide better outcome measures for clinical trials.

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Acknowledgments

We sincerely thank the experts, scientists, clinicians, physician-scientists, policymakers, and government leaders working in LHON and related fields for generously sharing their time and insights with us. Their openness in discussing their work and sharing broader knowledge of their respective fields was invaluable in shaping this report. These discussions deepened our understanding of the challenges and opportunities in LHON and highlighted how philanthropy can drive meaningful progress in the field.

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