Table of Contents

DRAFT

DRAFT

Introduction

NEI Mission and Statutory Authority

The National Eye Institute (NEI) was established by Congress in 1968 as part of the Public Health Service (Public Law 90-489). For over 50 years, NEI has been the world leader in funding and directing eye and vision research. As part of this strategic planning effort, NEI recruited key stakeholders to modernize the Institute's mission statement with respect to public health needs and the biomedical landscape.

The mission of the National Eye Institute is to eliminate vision loss and improve quality of life through vision research. To achieve this mission, NEI provides leadership to:

- Drive innovative research to understand the eye and visual system, prevent and treat vision diseases, and expand opportunities for people who are blind or have low vision
- Foster collaboration in vision research and clinical care to develop new ideas and share knowledge across other fields
- Recruit, inspire, and train a talented and diverse new generation of individuals to expand and strengthen the vision workforce
- Educate health care providers, scientists, policymakers, and the public about advances in vision research and their impact on health and quality of life

Organization of NEI

NEI supports eye and vision science through: 1) extramural research, soliciting, supporting, and managing approximately 1,700 research grants, cooperative agreements, and training awards made to scientists at more than 270 medical centers, hospitals, and universities in the U.S. and around the world; and 2) intramural research, conducting laboratory and clinical research based in facilities at the National Institutes of Health (NIH) campus in Bethesda, Maryland.

In 2020, Michael F. Chiang, M.D., became the third appointed Director in the 52-year history of NEI. Dr. Chiang leads 500 employees organized in four scientific divisions, and nine administrative offices (Figure 1). NEI is served by two external oversight committees. The National Advisory Eye Council (Council), mandated by the Public Health Services Act, serves to 1) advise the NEI Director on matters carried out by the Institute; 2) provide a second level of review of grant applications; 3) approve specific NEI activities such as workshops and special funding announcements; and 4) provide input into program planning. The Board of Scientific Counselors evaluates the quality of the intramural research programs.

DRAFT

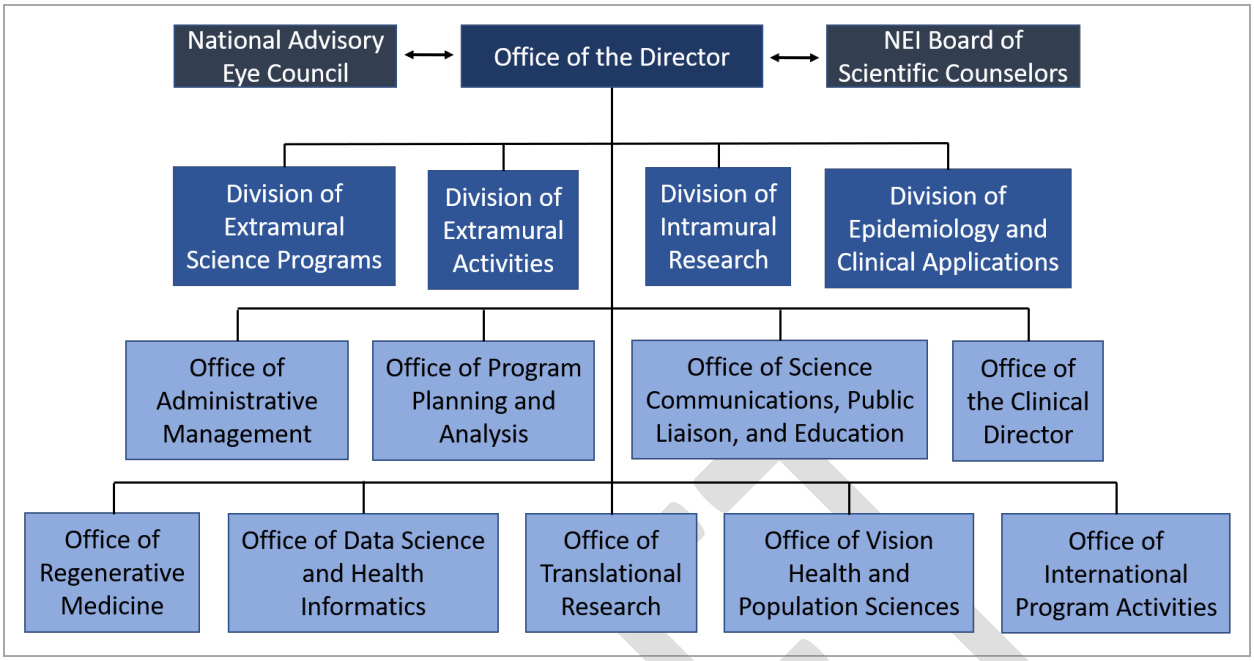


Figure 1. NEI Organizational Chart

The Division of Extramural Science Programs (DESP) serves the NEI extramural community through management of grants and cooperative agreements, including research training grants and small business awards. The Division of Extramural Activities (DEA) works closely with DESP through its Grants Management and Scientific Review Branches and oversees Council. The Division of Intramural Research (DIR) comprises over 300 staff mostly distributed among 24 Principal Investigator-led research groups and seven core facilities. The Division of Epidemiology and Clinical Applications (DECA) develops and conducts human population studies focusing on causation, prevention, and treatment of eye and vision disorders. The NEI Clinical Director manages the overall NEI clinical program, which provides clinical access, resources, and oversight of clinical operations to support the translational research activities of the NEI Intramural Research program.

NEI Strategic Planning

NEI recognizes that new ideas and concepts are constantly emerging, and that the main engine for scientific discovery and innovation is investigator-initiated research. The most important priority is to support the highest quality research that will help achieve the mission of NEI. At the same time, NEI recognizes the value of strategic planning to identify and target key areas of interest. NEI was one of the first Institutes at NIH, in 1973, to develop a strategic plan for research. This document, finalized in 2021, is the ninth comprehensive plan for NEI.

Recent NEI Planning Efforts. Since NEI was established by Congress over 50 years ago, strategic planning activities have culminated in a series of national plans and workshop reports. These planning efforts have relied primarily on the expertise of NEI-funded investigators and the vision community to review the state of the science and describe research required to advance progress in treating visual disorders and blindness. The last plan was published in August 2012: Vision Research: Needs, Gaps, and Opportunities (PDF 2.8 MB) and was organized around

DRAFT

NEI's six core extramural research programs: 1) Retinal Diseases; 2) Corneal Diseases; 3) Lens and Cataract; 4) Glaucoma and Optic Neuropathies; 5) Strabismus, Amblyopia, and Visual Processing; and 6) Low Vision and Blindness Rehabilitation.

The 2012 NEI planning process also highlighted the need to unify the vision community behind a large cross-cutting, impactful goal, which subsequently became known as the Audacious Goals Initiative (AGI). AGI started with an ideation prize challenge, broadly seeking audacious yet feasible ideas to transform vision care. Following a large planning summit in 2013, NEI announced the audacious goal to restore vision through regeneration of retinal neurons and neural connections. Since then AGI has been an interactive endeavor, with public workshops, townhall meetings, and scientific steering committees providing extensive stakeholder input into design and execution of individual initiatives, ultimately resulting in several research consortia working together to solve specific challenges.

21st Century Cures Act and the NIH-Wide Strategic Plan. In 2016 Congress passed the 21st Century Cures Act (Public Law 114-255), which mandated that NIH and its Institutes develop strategic plans at least every six years. Furthermore, all Institutes were instructed to follow a common template. NIH developed the *NIH-Wide Strategic Plan, Fiscal Years 2016–2020: Turning Discovery Into Health*, with four broad objectives: 1) Advance Opportunities in Biomedical Research; 2) Set Priorities; 3) Enhance Stewardship; and 4) Excel as a Federal Agency by Managing for Results. Subsequent NIH and each Institute's strategic plans map to the NIH strategic plan template. The Cures Act also stipulated a more proactive focus on health disparities and women's health research.

Planning Process. NEI Strategic Planning is conducted under the auspices of Council, with direction from the NEI Director. The NEI Office of Program Planning and Analysis (OPPA) led a trans-NEI team to coordinate planning. Council provided concept clearance to conduct a cross cutting NEI Strategic Plan consistent with requirements in the 21st Century Cures Act. The strategic planning process relied heavily on community input and consisted of two phases: 1) an information gathering phase; and 2) an implementation phase. Beyond reviewing and establishing scientific priorities, NEI also proposed goals for improving research resources, scientific support (e.g., training and workforce development), communication and outreach efforts, administrative efficiency, and stewardship of federal resources.

Areas of Emphasis. In October 2019, Council endorsed a cross-cutting approach to planning, organized around seven Areas of Emphasis (AoEs) within three research domains (Figure 2). These AoEs represent key interdisciplinary areas of opportunity in vision research. This is different from previous plans, which were organized around NEI core scientific programs.

DRAFT

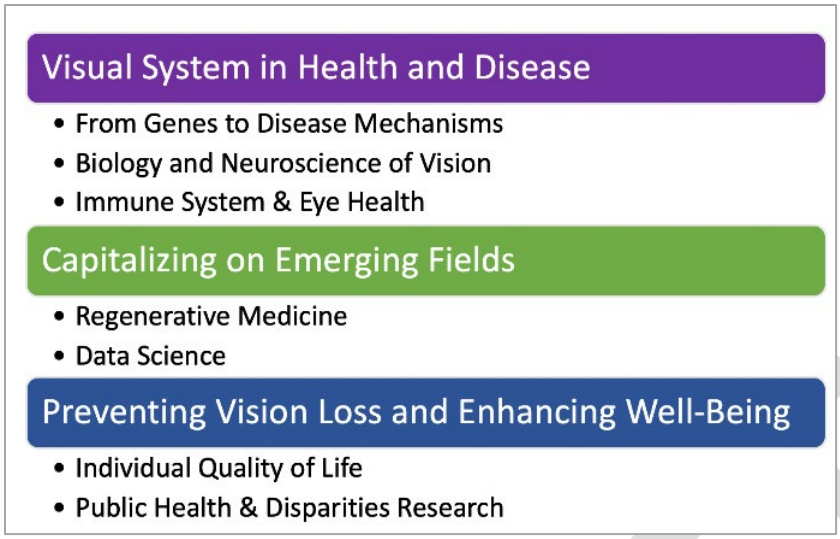


Figure 2. 2020 Vision for the Future Strategic Plan cross-cutting areas of emphasis

Request for Information. On November 15, 2019, NEI issued an RFI to the research community, health professionals, patient advocates, professional societies, and the general public soliciting input on vision research needs, gaps, and opportunities. NEI received a robust response and incorporated input by including specific expertise and topics of discussion in subsequent scientific panel meetings. NEI provided all panelists with full RFI feedback for review and analysis. For more information, please refer to a summary of the RFI results in Appendix 1.

Expert Panels. For each AoE, NEI created panels of 12-13 experts, with the aim of fostering dialogue across traditional vision research disciplines and capitalizing on scientific opportunities. Each panel was led by two external scientific co-chairs, along with NEI program and policy staff. NEI aimed to achieve panel diversity with respect to gender, race and ethnicity, age, geography, terminal degree (e.g., PhD, MPH, MD, OD), areas of expertise, background (e.g., within vs. outside current NEI portfolio), and occupation (e.g., researcher, clinician, advocate). Each panel provided written input and then met three times via videoconference in the spring and summer of 2020 to discuss NEI's scientific needs, gaps, and opportunities. High-level outputs of the panel discussions are described in the Areas of Emphasis sections.

Stakeholder Feedback. During plan development, highlights of progress were presented publicly in the open session of Council, which meets three times per year. Before finalizing the plan, NEI sought broad input on the draft narrative by soliciting public comments using the same distribution plan as the initial RFI, and by requesting feedback from sister NIH Institutes.

Implementation of Key Recommendations. In collaboration with Council, NEI will generate an implementation plan to advance strategic opportunities and fund research in response to this plan. In preparation for implementation, NEI has already established two new offices: the Office of Vision Health and Population Sciences and the Office of Data Science and Health Informatics.

DRAFT

The COVID-19 Pandemic: Impact on the Vision Community

The pandemic transformed almost every aspect of our lives, and exposed health disparities. Shortly after lockdowns began in March 2020, NEI engaged in dialogs with expert panelists regarding the impact on research, vision care, and quality of life of individuals with vision loss.

Effects on the overall research enterprise. The concerted effort by the NIH and the global biomedical community to focus on combating the virus resulted in an unprecedented pace for development of diagnostics, treatments, and vaccines. Yet the work of the larger research community has been heavily impacted by restricted access to facilities, budget shortfalls, and loss of time-sensitive data and resources, as well as scientific workforce attrition. NEI and NIH recognize that reduced productivity means that many funded projects will have failed to meet projected milestones. NIH guidance instructs reviewers "to disregard situations due to the COVID-19 pandemic, e.g., temporary declines in productivity, availability of key personnel, proposed patient populations, animal facility shutdowns, etc."[1]

SARS-CoV-2 and vision research. Research on SARS-CoV-2 and the eye may have long-term disease-causing and treatment implications for COVID-19 and related conditions with manifestation of ocular signs. Studies indicate that up to 30 percent of COVID positive patients have ocular surface diseases associated with SARS-CoV-2,[2] which has implications for understanding systemic disease and transmission. As with other viruses such as Zika and Ebola, viral persistence in ocular fluids may lead to complications during convalescence. Researchers examined the eye as a potential entry portal for SARS-CoV-2 infections, though the risk of transmission appears low according to existing data. Research on long-term consequences of SARS-CoV-2 is important to determine its effects on ocular conditions, such as optic neuropathy and retinal diseases. NEI researchers adapted adenovirus research to SARS-COV-2, applying machine learning algorithms to predict clinical outcomes based on viral sequence variants.

Impact on individuals with eye disease and people with vision impairments. NEI is seeking to understand and mitigate short and long-term COVID-19 risks with respect to vision care and for individuals with impaired vision. The pandemic exposed underlying challenges in eye care delivery and health disparities, particularly for vulnerable groups such as the economically disadvantaged and those with low vision, limited access to internet, and reliance on public transit. Additional work in these areas will have public health impact on eye care that generalizes beyond this pandemic. Eye care professionals and their patients need evidence-based practice guidelines to avoid unnecessary clinic visits and out-of-pocket expenses. Although telehealth has reduced in-person ocular examinations, it cannot replace all vision care, may not be a viable option for individuals with chronic conditions and/or special needs, and may require new imaging devices. The public health burden of this pandemic, such as forestalling regular medical checkups, may not be fully evident for years.

---

[1] NOT-OD-21-026, Extended Guidance for Applicants Preparing Applications During the COVID-19 Pandemic, November 4, 2020, https://grants.nih.gov/grants/guide/notice-files/NOT-OD-21-026.html

[2] Ulhaq, Z. S., & Soraya, G. V. (2020). The prevalence of ophthalmic manifestations in COVID-19 and the diagnostic value of ocular tissue/fluid. Graefe's Archive for Clinical and Experimental Ophthalmology, 258(6), 1351-1352. https://link.springer.com/article/10.1007/s00417-020-04695-8

DRAFT

NEI Extramural Research

The NEI Extramural Program is divided into six core programs, corresponding to anatomical and clinical subspecialties. Although this planning effort is organized around cross-cutting AoEs to provide a new perspective on vision research, the plan will be largely implemented through initiatives and workshops layered on top of the NEI core program structure (Figure 3).

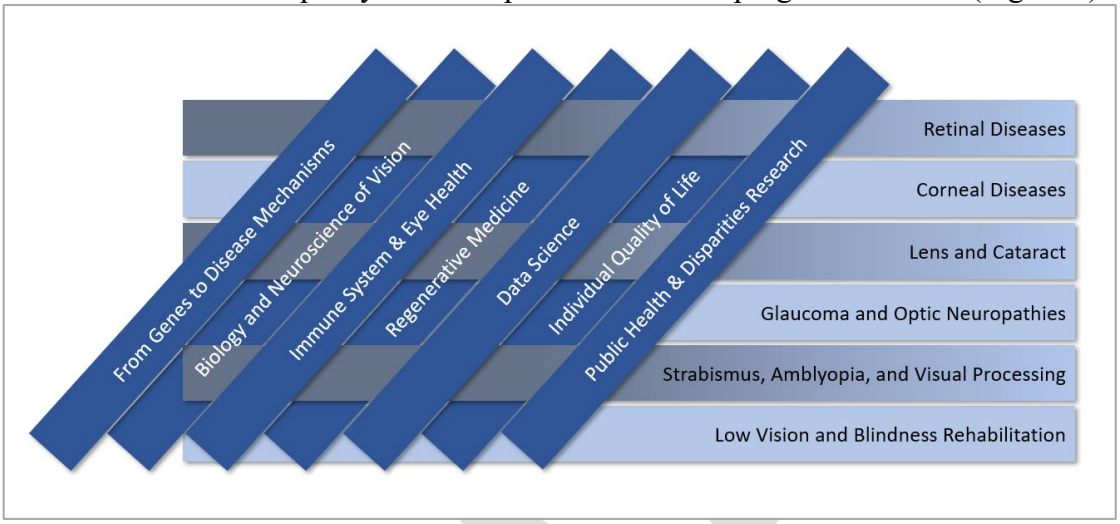


Figure 3: Seven cross cutting areas of emphasis in this plan intersect with each of the six core extramural programs.

Managing for Results—Portfolio Analysis

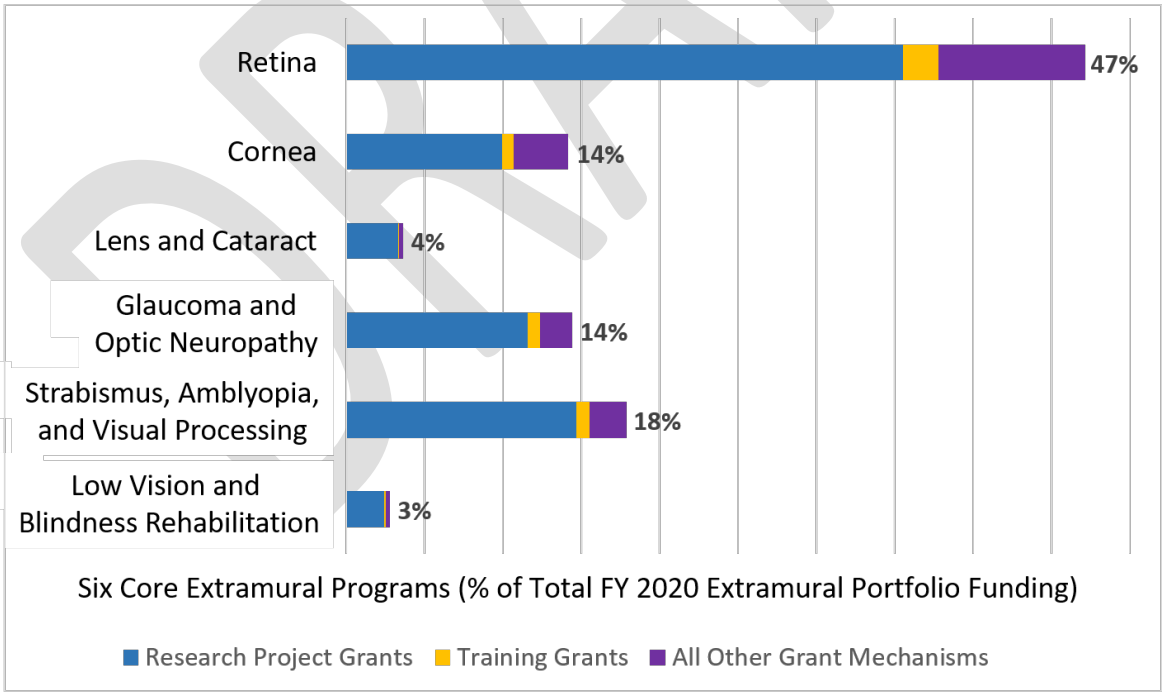


Figure 4: Six core programs represented as percentage of total DESP portfolio.

Of the $824 million appropriated by Congress to NEI in Fiscal Year (FY) 2020, 85 percent was distributed to universities and research centers across the country. Within each of the six core program areas, there are mechanisms for basic and translational research, training, small business

DRAFT

grants, research resources, and collaborative clinical trials and networks (Figure 4). Funding decisions are based on scientific priorities, potential impact, and opportunities. For each core program, NEI program analysts review funding metrics and conduct portfolio analyses to track progress, which are regularly reported to Council.

NEI places special emphasis on recruiting and retaining talent, with special consideration for new applicants to NIH and early-stage investigators (ESI). ESIs are research applicants who have completed their terminal research degree or end of post-graduate clinical training, whichever is later, within the past 10 years and who have not previously competed successfully for a substantial NIH independent research award.

DRAFT

Extramural Core Programs—Retinal Diseases

The retina is the remarkably thin layer of tissue at the back of the eye where photoreceptor cells (rods and cones) absorb light and convert it to an electrical signal, which is then processed by a web of interconnected retinal neurons before being transmitted to the brain. The energetically active photoreceptors are nourished by a layer of support cells called the retinal pigment epithelium (RPE); the entire complex is fed by an intricate network of blood vessels, both within and underneath the retina (the retinal and the choroidal vasculature). There are also light-sensing functions that are independent of rods and cones, such as control of pupil size, sleep–wake cycles, and possibly seasonal moods.

The Retinal Diseases program represents the largest fraction (47 percent) of the NEI Extramural portfolio (Figure 4). The diseases studied include age-related macular degeneration (AMD), diabetic retinopathy (DR), retinopathy of prematurity (ROP), retinal detachment, ocular inflammation, and inherited retinal conditions such as retinitis pigmentosa (RP) and color blindness. This program includes a significant basic science portfolio aimed at understanding the normal biology and disease mechanisms of the retina, RPE, and choroidal blood supply, which function together and must be considered as a unit for understanding disease progression. The retina is the only part of the brain that can be directly imaged through optical instruments. The retina also offers an avenue to study neuroscience, including cell-cell communications, synapses, and cell circuitry. Learning how the five major classes of retinal neurons (photoreceptor cells, bipolar cells, horizontal cells, amacrine cells, and ganglion cells) develop and form connections is the first step in understanding how the brain works and has been critical in developing the next generation of artificial retinal prostheses.

Recent Accomplishments After decades of NEI supported genetic, animal model, and clinical studies, and research optimizing gene therapy in the eye, the long promise of precision medicine arrived in December 2017 with the U.S. Food and Drug Administration (FDA) approval of the first gene therapy for a genetic disease, *RPE65*-associated-Leber Congenital Amaurosis (LCA). Not only does treating this severe form of childhood blindness improve a person's night vision and ability to see objects, but it also enables them to perform critical functional tasks such as navigating the environment. With this proof of concept, NEI is funding a whole pipeline of clinical and preclinical studies to develop gene therapies for other inherited forms of vision loss.

NEI-supported research has successfully employed single cell technology to obtain a cell atlas of the human retina and retina organoids. The atlas is based on individual cellular gene expression profiles and is critical in understanding retinal diseases with genetic associations, many of which are cell-type specific.

Optical coherence tomography (OCT) is a noninvasive, high resolution imaging technology used to visualize deep layers of the retina in cross-section for diagnosis of retinal and optic nerve diseases. NEI researchers developed hand-held OCT devices designed for use in children or bed-bound individuals. Wider availability of such devices could aid low cost diagnosis and monitoring of retinal diseases in the population.

DRAFT

Extramural Core Programs—Corneal Diseases

The cornea is the transparent layer at the front of the eye. While this clear structure may appear simple, it is really an elegant, complex living tissue, critical for preventing infectious agents or debris from entering the eye. The cornea forms the primary refractive (light bending) element in the optical path that focuses light on the retina. All of this is possible due to unique functional properties of the three primary corneal tissue layers (endothelium, central stroma, epithelium), the resident immune cells, and the sensory nerves. The corneal epithelium has one of the highest densities of sensory nerve endings in the body, which explains its susceptibility to pain. Although the cornea has no blood vessels, ocular surface tissues remain nourished and healthy by tears and aqueous humor, the clear fluid that fills the space between the cornea and lens.

A significant proportion of visits to eye care professionals in the United States are to correct refractive errors, treat ocular surface disorders such as dry eye, or provide emergency care for ocular trauma. Understanding the normal and diseased cornea and tear-secreting glands is essential to reduce the burden of visual disorders worldwide, and cornea-related research represents 14 percent of the NEI extramural portfolio (Figure 4) including research on tears, the ocular surface and stroma, correction of refractive error by contact lens or laser therapy, inflammation, infection, immunity, and corneal transplantation.

Recent Accomplishments Minor damage to the cornea can often be repaired and reconstructed by stem cells that reside in the limbus, the margin that borders the cornea and the sclera (white part of the eye). NEI limbal stem cell research has explored regeneration in the anterior surface to preserve its role as a barrier to microbes and environmental damage, leading to one of the first therapeutic uses of transplanted stem cells to resurface the outer layer of the cornea. Similarly, as part of an ongoing NEI clinical trial to increase the proliferative abilities of cell regeneration in patients, surgeons were able to replace corneal epithelial tissue from patients who experienced damage from chemical burns, using stem cells derived from their other (healthy) eye. This procedure, a first of its kind to occur in the U.S., was a major step for regenerative medicine.

Preventing the rejection of donor tissue is important for corneal transplantation, which is a procedure often required for disorders such as keratoconus. Recent research targeted chemokines (molecular signals released by tissues to invoke the immune system) and their receptors to prevent rejection of corneal grafts. Furthermore, artificial corneas, developed with NEI support, are now commercially available. Advantages of an artificial cornea include greater accessibility, given limited supply of donor cornea tissue, and reduced risk of post-surgical complications.

Corneal pain can result from a variety of causes including inflammatory diseases such as dry eye, neurological diseases, and common surgical procedures like LASIK. Currently, there are two approved drugs to treat dry eye disease (DED), but their effectiveness can vary based on individual conditions. A small phase I clinical trial found that a new DNase enzyme-based eye drop is safe, well-tolerated, and has potential to reduce the severity of a tear-deficient autoimmune form of DED. Another therapeutic, an ocular surface immune globulin eye drop, which directly builds on mechanistic studies funded by NEI, was demonstrated to be safe and efficacious in a pilot clinical trial.

DRAFT

Extramural Core Programs—Lens and Cataract

The healthy lens is optically clear and flexible. Loss of lens transparency (cataract) and/or reduced ability to focus on near objects with age (presbyopia) are correctable visual impairments that afflict a large portion of the global population. Although cataract surgery is an effective procedure, some areas of the world do not have the logistics resources or trained personnel to meet the needs of the population. Even in the U.S., cataract remains a significant cause of blindness and low vision, especially for individuals with unoperated cataract due to limited access to care or lack of ability to pay, as well as for a small percentage of individuals who experience rare but potentially blinding surgical complications.

Areas of research supported by the NEI Lens and Cataract Program include the basic science areas of genetics, biochemistry, biophysics, and cell biology; the developmental and aging processes; as well as the development and management of cataract and presbyopia. Understanding the mechanics of eye proteins can also help uncover other systemic conditions that affect the aging population, such as Alzheimer's, Parkinson's, and Huntington diseases. Examining the stability and reactions of specific eye proteins when faced with environmental exposures (e.g., ultraviolet light, cigarette smoke, air pollution) has provided insight on how the process of aging can damage the lens. Presbyopia results from the loss of elasticity, the ability for the lens to change shapes based on structural proteins. NEI research has identified key roles for two important components, connexins and aquaporins, that influence lens cell architecture and are likely to relate to its transparency and flexibility.

Recent Accomplishments Researchers have been exploring ways to inhibit or delay the progression of cataracts by targeting specific lens fibers. A recent study using a rodent model system found that immune cells can move along lens fibers in response to injuries in the eye. This mechanism may facilitate the ocular immune system-mediated recovery from complications of cataract surgery or eye trauma.

Congenital cataract has an incidence of two to six cases per 10,000 children.[3] A recent NEI study followed infants who underwent cataract surgery and showed that the risk of developing glaucoma was substantial between ages one through 10, regardless of prior lens implantation. This study challenges the belief that replacing a child's lens with an implanted one protects them from developing glaucoma and underscores the need for long-term glaucoma surveillance.

Although cataract surgery is safe and effective, unoperated cataract surgery remains one of the leading causes of visual impairment in the U.S. Research on a chemical, lanosterol, suggested it could reverse incorrect folding of lens proteins, which precipitate the formation of cataracts. Lanosterol treatment of transgenic mice with a cataract-causing protein mutation resulted in a significant reduction of lens opacity. These results open the door to a pharmaceutical solution for cataract and may have broader implications in other protein-misfolding diseases.

[3] Solebo, A. L., & Rahi, J. S. (2017). Epidemiology of congenital cataract. In Congenital Cataract (pp. 15-25). Springer, Cham.

DRAFT

Extramural Core Programs—Glaucoma and Optic Neuropathies

Glaucoma, the second leading cause of blindness, is a family of diseases involving both the front (anterior chamber) and back of the eye (retina and optic nerve). Glaucoma causes damage and death to retinal ganglion cells (RGCs), the neurons whose axons comprise the optic nerve, leading to vision loss and blindness. In some cases, the disease begins with fluid build-up in the anterior chamber of the eye resulting in elevated intraocular pressure (IOP), a modifiable risk factor. Primary open-angle glaucoma (POAG) is the most common form of the disease; other forms include closed-angle, congenital, and glaucoma secondary to other ocular conditions such as eye injury, infection or inflammation, and complications of steroid administration. Other significant risk factors include age, family history, and ethnicity. POAG is a leading cause of visual disability and a major public health challenge that disproportionately impacts specific populations, such as African American and Latino/Hispanic groups.

The NEI Glaucoma and Optic Neuropathies Program includes studies involving basic science, clinical management, epidemiology, and neuroprotection strategies aimed at regenerating the optic nerve. Anatomy and cell biology studies model the front of the eye and fluid outflow through key tissues that regulate IOP. Restoring function to regenerated RGC axons requires formation of functional synapses at the appropriate targets. The portfolio covers other diseases of the optic nerve (neuropathies), including immune-mediated optic neuritis, and gene therapy. For example, a clinical trial for a mitochondrial gene mutation in Leber Hereditary Optic Neuropathy (LHON) is currently underway.

Recent Accomplishments An NEI international study examining the health disparity of POAG in populations of African descent identified a risk variant in *APBB2*, a gene known to be involved in the amyloid protein processing pathway, suggesting that the neurotoxicity seen in POAG may result from incomplete clearance of amyloid and other neurotoxins from the optic nerve. The power of genome-wide association studies (GWAS) to identify genes associated with common diseases like glaucoma depends on comparing tens of thousands of cases and controls. Multi-ethnic meta-analyses using the NEI Glaucoma Human Genetics CollaBORation Heritable Overall Operational Database (NEIGHBORHOOD) and international studies of 34,179 cases and 349,321 controls have identified 127 gene loci associated with POAG. Most of these genes have effects across European, Asian, and African ancestries, and highlight mechanisms related to abnormal development, neurodegeneration, and mitochondrial dysfunction.

The relationship between elevated IOP and RGC death in glaucoma may involve neural support cells called astrocytes, which release a toxin that kills RGCs in response to elevated IOP. Astrocytes are ubiquitous in the brain, so therapies targeting this pathway might not only address neurodegeneration in glaucoma but also other common neurological disorders such as Alzheimer's, Parkinson's, and Amyotrophic Lateral Sclerosis (ALS).

NEI supported researchers have developed a diagnostic device for the early detection of glaucoma. The device integrates virtual reality with wireless recording of brain activity to assess eye communication with the brain. This technology can allow eye care providers to noninvasively measure glaucoma progression and manage care.

DRAFT

Extramural Core Programs—Strabismus, Amblyopia, and Visual Processing (SAVP)

Vision researchers are at the forefront of understanding fundamental processes in the brain and have played major roles in the trans-NIH BRAIN Initiative. The visual cortex, which processes and interprets visual information relayed by the eyes, is a complex network of many specialized brain regions that process different aspects of an image. The largest and best understood area is the primary visual cortex, which recognizes forms and shapes and is connected with regions of the brain that control eye movements, store long-term memory, and plan movements. Other areas in the visual cortex detect motion and depth, place objects within the visual field, and analyze images to interpret meaning. Strabismus is a condition in which the eyes are not aligned properly, and can result from refractive error, disorders of ocular muscles and their innervation, or central neural mechanisms that control eye muscle movements. Short-term ocular misalignment can cause double vision, whereas chronic misalignment in children can cause amblyopia, a potentially blinding condition in which the brain ignores signals from one eye.

Studies in SAVP comprise the second-largest program at NEI, accounting for 18 percent of the portfolio (Figure 4). Research includes the causes and treatments for strabismus and amblyopia, as well as basic science projects investigating the anatomy, physiology, development, and plasticity of visual pathways. The program also includes computational neuroscience and psychophysics, the science of perception.

Recent Accomplishments An essential aspect of research in this area involves studying connections within the brain. NEI-supported research is taking advantage of modern cell and molecular tools to answer questions about how RGCs develop the appropriate synaptic connections to neurons in the lateral geniculate nucleus (LGN), a relay center for the visual pathway. These studies have shown that during development, retinal neurons instruct the appropriate patterns of synaptic connection to the LGN by using two classes of supportive cells: astrocytes and interneurons. Understanding these developmental processes is the key to designing medical interventions aimed at improving rehabilitative plasticity.

NEI- and BRAIN- research showed promising results in a study using two approaches to provide electrical stimulation to visual cortex. In sighted research participants, the stimuli were delivered with standard grids used prior to epilepsy surgery. In a blind participant, the stimuli were from the Orion prosthetic device (Second Sight Medical Products), which sits on the cortical surface between the two brain hemispheres. By using moving stimulation patterns, the research team successfully calibrated the systems so that stimulation conveyed the image of a letter being drawn. The blind participant was able to reproduce letters on a touchscreen. This was an important first step toward developing useful visual cortical protheses.

Neuroscientists are challenging theories about visual processing of optic flow, the translation and expansion of motion information, by tracking subjects' natural movements and measuring the flow of visual stimuli on the retina. Innovative methods such as these serve as a gateway to spur cutting-edge research.

DRAFT

Extramural Core Programs—Low Vision and Blindness Rehabilitation

Low vision is a term used for vision impairment that interferes with daily activities and is not correctable with medical or surgical therapies, spectacles, or contact lenses. Although low vision most often includes loss of sharpness or acuity, there may also be reduced field of vision, abnormal light sensitivity, distorted vision, or loss of contrast. Visual impairment can range from mild to severe, and over two-thirds of people affected are older than 65 years of age, where the leading causes are AMD, glaucoma, DR, cataract, and optic nerve atrophy. In the elderly, this increases the risk of falls and fractures, and often leads to isolation and depression. Visual impairments also affect infants and children, due to conditions such as ROP, deficits in the visual centers of the brain, juvenile cataract, and retinal abnormalities. In children, beyond impacting quality of life, this can have major consequences on educational advancement and future opportunities for employment.

The NEI Low Vision and Blindness Rehabilitation Program supports research aimed at development of accessibility devices, as well as training strategies to enhance quality of life for visually impaired individuals. The portfolio includes engineering approaches and human perception studies aimed at optimizing residual vision or providing sensory substitution for blind individuals or those with low vision. It also supports basic research into the changes that occur in the visual and other sensory systems resulting from partial or total loss of vision.

Recent Accomplishments Stroke damage to visual cortex causes visual field loss (such as hemianopia) or cortical blindness. For many patients, recovery of that vision is elusive. Recent NEI supported work suggests that plasticity may be possible with visual training regimens and that the timing of these rehabilitation efforts could be key to post-stroke or post-concussion visual field recovery. Combining advanced training procedures and noninvasive brain stimulation has shortened the amount of training time required and early training has helped in reducing visual field loss.

Navigating safely and independently is challenging for people with visual impairments who cannot rely on visual cues in the environment. NEI research has developed smartphone apps that enable visually impaired users to navigate through myriad settings. These navigation assistance apps use computer vision algorithms to identify crosswalks, read informational signs, and interpret 2D maps of indoor and outdoor environments.

One important area of research is aimed at the development of lens and prism approaches for remapping areas of visual space on parts of the retina that are still functional. One such project has developed prototypes for eyewear fitted with a system of prisms to aid patients with peripheral field loss in dynamic walking situations. The prisms are designed to provide simultaneously a direct view of the intact visual field and a prismatic-shifted viewing of the blind field to give a more complete perspective of extra-personal space.

DRAFT

Cross-Cutting Extramural Research Resource Programs

The NEI Extramural Program provides resources to promote translation of vision research from the bench to the clinic: Core Resources, Conference Grants, Training and Career Development, Translational Research Program, Collaborative Clinical Research, and Small Business Programs.

Core Resources. The NEI Center Core Grant Program (P30) provides funds for infrastructure support to NEI grantees. The purpose of this program is to afford resource and/or service cores to groups of NEI R01 investigators to enhance research activity, foster collaborations, and increase efficiencies by centralizing resources and technical expertise within an institution. NEI also supports common NIH resource efforts such as the Human Tissue and Organ Research Resource, the Knockout Mouse Production and Phenotyping Project, and protein and genomic sequencing centers.

Conference Grants. The NEI Conference Grant Program (R13 and U13) provides funds for scientific workshops and other meetings to explore and clarify a defined problem and to coordinate efforts to address it. The program places highest priority on supporting graduate students, postdoctoral fellows, and newly appointed faculty members to participate in meetings, and on enhancing diversity of women, minorities, and persons with disabilities in the planning, implementation, and participation in meetings.

Training and Career Development. To strengthen the vision workforce, NEI trains students, fellows, and clinicians in basic and clinical research through institutional and individual pre- and post-doctoral training awards, career development awards, and loan repayment programs. Career training grants aim to expand the workforce of clinician-scientists (K08) and patient-oriented researchers (K23). Some of the individual awards are targeted to expand diversity (diversity F31 pre-doctoral fellowship to graduate students, and the recently added diversity F32 post-doctoral fellowship).

Translational Research Program on Therapy for Visual Disorders. The Translational Research Program (R24) provides funds for developing novel therapies and medical devices to treat and assist people with visual disorders. The program offers opportunities for multidisciplinary research collaborations to develop rapid and efficient translation of innovative laboratory research findings into clinical therapies.

Collaborative Clinical Research. NEI has substantial involvement in supporting complex, multi-center clinical studies using the cooperative agreement mechanism. There are grant funding mechanisms to support preparation for launching a complicated trial. NEI supports two large clinical research networks (for pediatric eye diseases and retinal diseases). In addition, NEI supports clinical trials in diseases such as AMD, ROP, glaucoma, uveitis, dry eye, trachoma, cataract, retinal vein occlusion, optic neuropathy, myopia, and convergence insufficiency. NEI also funds grants conducting secondary analyses of existing clinical data.

Small Business (SBIR/STTR) Programs. Small Business Innovative Research (SBIR; R43/R44) and Small Business Technology Transfer Research (STTR; R41/R42) programs are statutorily required for federal funding agencies. At NEI, these programs are particularly robust. These programs provide early-stage capital for innovative small U.S. companies to

DRAFT

engage in federal R&D for the express purpose of commercialization. While often high risk, these technologies are expected to have strong commercial potential with the goal of improving vision health, saving sight, or assisting blind and visually impaired individuals. While both the SBIR and STTR programs are divided into three phases, only the first two receive federal funds. In the past 15 years, the NEI Small Business program has funded hundreds of small businesses, of which approximately 40 have reached various levels of commercial success such as patient uptake, product sales, patent applications, strategic partnerships, and public health outcomes. Through community outreach and engagement, NEI SBIR/STTR programs have enjoyed relatively strong representation by socioeconomically disadvantaged and/or women-owned businesses.

Recent Accomplishments In the ophthalmic imaging field, innovative OCT systems (Bioptigen) and a compact multi-modal, adaptive optics and line-scanning ophthalmoscope--based retinal imager (Physical Sciences Inc.) have been successfully developed and marketed after obtaining FDA 510(k) clearance. A handheld pediatric vision scanner capable of detecting all forms of amblyopia (Rebiscan) and a portable, low-cost autorefractor for determining refractor error to provide an eyeglass prescription (QuickSee, PlenOptika) have been developed to assist in clinical screening, to deploy for surveys and research studies, and to provide eyeglasses, particularly for underserved areas around the world. Significant advances have been made in AI-based automatic DR screening tools, and several products with sensitivity and specificity comparable to professional human graders have successfully secured FDA 510(k) clearance (Eyenuk and VisionQuest; *see sidebar in Data Science chapter*). A minimally invasive therapeutic strategy for dry AMD employing photobiomodulation (LumiThera, Inc.) is currently under study in large-scale clinical trials. Other SBIR successes include commercial release of innovative eyeglasses and contact lenses for color blindness (EnChroma) and an artificial cornea (KeraMed).

DRAFT

Scientific Planning in the NEI Intramural Research Program

While the vast majority of NEI funds are distributed as extramural research grants, the NEI also supports a vibrant program of basic, clinical, and translational research through the Intramural Research Program (IRP) located on the NIH campus. The largest component of the NEI IRP is the DIR, led by the NEI Scientific Director and comprising approximately 300 staff distributed among 24 principal investigator-led research groups and seven core facilities. The smaller DECA is closely associated with activities of the NEI Clinic, providing education and consultation on clinical studies and conducting larger-scale epidemiological and population-based research.

Organizing Principles

High-risk, high-impact, and more nimble research. Research programs in the NEI IRP are supported almost entirely with federally allocated funds. Unlike scientists in the extramural community (e.g., at universities), intramural scientists do not access funding through the competitive NIH grant process and are, in fact, ineligible for most federal grants. This unique funding model means that budgets are relatively stable, and that IRP scientists can be nimbler in their research choices. They can change direction quickly and pursue higher impact projects that, because of their higher risk, might not receive support through the peer-review process.

Emphasis on translational work. IRP prioritizes research with potential to be translated into the clinic. Key NEI examples include pioneering work in adaptive optics technology for imaging the back of the eye, and the development of an induced pluripotent stem cell-based "patch" that is now in a first-in-human clinical trial for treatment of AMD.

Unparalleled Clinical Center. The NIH Clinical Center – "America's Research Hospital"– is different from typical academic medical centers in that every patient is part of a research protocol. Patients come from all over the world, often with rare, debilitating conditions for which there are no satisfactory treatments. Absent revenue-generating pressures, IRP clinician/scientists enjoy unparalleled freedom to study questions of their choice and to spend as much time as necessary with their patients. Moreover, the seamless integration of the Clinical Center into the research environment provides superb opportunities to conduct translational research leading to clinical trials. The NEI Clinic pioneers many first-in-human therapy trials, often looking at safety and efficacy. A number of databases and biospecimen repositories maintained by the NEI Clinic are important resources for the ocular disease research community.

Rare disease research. Studying rare diseases often adds to the basic understanding of common disease. The NIH Clinical Center specializes in rare diseases, with access to a unique patient base. The NEI Clinic is important to the NIH Undiagnosed Disease Program, a national patient referral program, where ophthalmic findings are often critical to making the diagnosis. The NEI National Ophthalmic Disease Genotyping and Phenotyping Network (eyeGENE®) is a genomic medicine initiative that facilitates research into the mechanisms of rare inherited eye diseases and accelerates pathways to treatments.

Investment in talent. The guiding philosophy in the IRP is to hire creative and talented scientists with a diversity of backgrounds and experiences. NEI places a priority on hiring entry-level investigators and emphasizes training, promoting, and retaining a diverse workforce.

DRAFT

First-in-human trial of a patient-derived stem cell-based therapy for AMD

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss. Drug treatments for the neovascular ("wet") form have transformed eye care. Yet there is no treatment for the more common geographic atrophy ("dry") form, which involves death of retinal pigment epithelium (RPE) tissue, the single layer of cells in the back of the eye that nurtures and supports the light-detecting photoreceptor cells. As RPE cells die, the photoreceptors eventually also die, resulting in blindness.

A team of scientists in the NEI IRP wanted to treat AMD by replacing dying RPE tissue with tissue derived from the patient, which should pose a lower risk of immune rejection after transplantation. The therapy involves removing a few blood cells from the patient and converting them into induced pluripotent stem cells (iPSCs), which have potential to form almost any type of cell in the body. These stem cells are coaxed into RPE cells which are grown as a confluent monolayer on a three-dimensional biodegradable scaffold.

The clinical trial journey began by confirming functional authenticity of these *in vitro* RPE monolayers and by evaluating the transplantation protocol in animal models of AMD. The team innovated surgical techniques and tools, including an instrument they designed to insert the iPSC-derived RPE patch under the retina in the correct orientation. With clear evidence that the patch integrated in the animal retina and prevented blindness, the team began recruiting AMD patients in the first U.S. clinical trial of patient-derived stem cell therapy.

As a manufacturing quality control measure, the team developed an AI-based image analysis tool that detected markers of RPE maturity and function in tissue patches to increase likelihood of efficient patch integration. Under the phase I/IIa clinical trial protocol, 12 patients with advanced-stage geographic atrophy will receive the iPSC-derived RPE implant in one eye and be closely monitored for at least one year to confirm safety.

High research standards. NEI Principal Investigators (PI) are reviewed at least once every four years by the Board of Scientific Counselors. Unlike the peer review process for grants, the BSC reviews the PI's entire program, looking retrospectively at what has been accomplished, and prospectively at what is planned.

Collaborative environment. The NIH IRP is a highly collaborative research environment and home to leading scientists covering the full spectrum of biomedical disciplines and techniques. Trans-NIH core facilities democratize access to cutting edge services and technical resources. NEI supports several of its own cores that are available at no cost to NEI scientists.

Strategic Planning and Future Directions

A search process for a new NEI scientific director is underway and expected to be completed in 2022. Working with the new NEI Director, Michael F. Chiang, the new scientific director will help establish IRP research priorities, recruiting strategies, and priorities for allocating resources including equipment, operating expenses, personnel, and space.

NEI Strategic Plan: Areas of Emphasis

Research Domain: Visual System in Health and Disease

From Genes to Disease Mechanisms

Charge: *How can the identification of ocular disease genes be leveraged to develop new strategies, models, and tools for elucidating genetic and environmental interactions at the cellular and systems level, and thereby accelerate mechanistic understanding and therapy development?*

Background

Until recently, doctors could administer a test and tell patients they had inherited a gene that causes blindness, but there was no treatment to prevent blindness from developing. Now a new gene therapy is changing the lives of children who might have experienced a lifetime of blindness from a form of the genetic disease called Leber Congenital Amaurosis (LCA). In 2017, when the FDA approved Luxturna® for treatment of LCA for patients with mutations of the *RPE65* gene, it was the first such innovation in any field of medicine and finally achieved the protracted promise of gene therapy. Introduction of a functional copy of the *RPE65* gene to LCA patients with *RPE65* gene mutations resulted in partially restored visual function, first in animal models, then in patients with LCA. Gene therapy for LCA represents a monumental achievement not only for traditional bench-to-bedside drug development but also a demonstrated utility of personalized genetics in improving the health of patients with intractable inherited diseases.

Unlike diseases caused by a single gene mutation, complex diseases such as AMD, glaucoma, myopia (nearsightedness), and DR often involve interaction of many genes and environmental factors. Once again, vision research innovators led the way, pioneering the first successful Genome Wide Association Studies (GWAS) to discover genetic risk factors for complex diseases. Not only did the watershed discovery of complement factor genes associated with AMD risk point to new therapy targets, it also validated the genomics methodology that is now used throughout biomedical research. However, clinical trials to block the complement pathway have yet to pan out, suggesting complicated interacting disease mechanisms which may originate early in life, long before signs and symptoms appear. This experience is not unique and while genetic associations have been reported for many diseases, clear understanding of underlying biological mechanisms are frequently lacking. Nonetheless, these diseases, many of which are linked to aging, likely have pathological mechanisms that can be uncovered using established and novel research strategies. Clearly defined disease mechanisms are crucial for the movement of potential therapies from the bench to the clinic.

Highlights of Progress and Ongoing Major Initiatives

The eye serves as an ideal target for innovating and applying genetic technology advances

Just as the 1960s space race spinoffs fueled technological paradigm shifts, the human genome project kicked off the "-omics" revolution, making genomic, transcriptomic, proteomic, and other omics technologies cheaper and more accessible. Combining these new omics approaches with recent computational advances like advanced data analytics and artificial intelligence (AI)

DRAFT

have made them even more powerful. The eye is a natural target for innovative research, due to its accessibility for surgery and imaging, ocular immune privilege, and well-characterized genetics. A game-changing advance—gaining single-cell resolution in transcriptomic analyses—enables researchers to focus on individual cell types that had been difficult, if not impossible, to separate from surrounding tissue. Integrative biology approaches, including mass spectrometry platforms, reveal biology patterns and help answer research questions that evaded previous reductionist experimental methodology. By combining clinical phenotype data with genomic, transcriptomic, and proteomic datasets, researchers now have considerably more tools (e.g., imaging and genetic markers) for predicting disease development and progression, such as in DR and glaucoma. New tools help define the roles of non-coding RNA species in ocular disease. To investigate disease mechanisms and manipulate candidate gene factors, researchers can use human tissue models derived from induced pluripotent stem cells (iPSCs) and 3-D organoids.

First-in-human gene editing trial to repair mutation in rare form of blindness

The field of gene therapy is once again being transformed, this time by the gene editing technology named CRISPR. Editas Medicine, a biotechnology company built on work accomplished by NEI researchers, is conducting the world's first-in-human trial utilizing CRISPR genome editing medicine to help individuals with vision loss in Leber Congenital Amaurosis caused by a mutation in the *CEP290* gene. CRISPR has also transformed research on disease mechanisms by facilitating direct manipulations of genes more efficiently and easily than before. Additionally, CRISPR technology has been used to create catalytically inert Cas9 fusion proteins, which have a wide range of applications, including *in vivo* (inside the body) reversible gene expression modifications; epigenomic engineering; and genomic imaging. These new tools, platforms, and models will open new horizons for vision researchers attempting to uncover the genetic contributions to sight-threatening diseases.

Non-coding regulatory regions of genes control expression in different cell types

When the Human Genome Project was completed at the turn of the 21st Century, it was determined that only about one percent of the genome coded for proteins that create the structure and function of our cells. But the NIH ENCODE Project estimates about 80 percent of the genome encodes regulatory information, largely involved in tightly regulating gene expression by cell type, timing, and environmental factors. Regulation manifests as chemical modifications to DNA, epigenetics, or the cell-type specific pattern of tightly packed structure of DNA and proteins called chromatin. Vision researchers have made significant strides in deciphering the genome by establishing the relationships among gene regulatory factors (e.g., DNA-binding transcription factors, chromatin remodeling enzymes, regulatory long non-coding RNAs) and gene expression patterns in ocular tissues. These chromatin-based epigenetic pathways guide eye development and play roles in many age-related diseases (e.g., cataract, DR, AMD).

Cell miscommunication drives disease

Understanding how gene variants lead to ocular disease requires understanding gene regulation, mechanisms, and pathways. Genetics research has demonstrated a persistent theme—defective cell communication is linked to ocular diseases:

DRAFT

- *Unfolded protein response (UPR)*: Some diseases, such as certain forms of cataract, are potentiated by UPR, the biochemical signaling cascade that cells use to avoid accumulation of toxic protein fragments by engulfing and recycling them.
- *Epithelial-to-mesenchymal transition (EMT)*: A cell signaling pathway that helps control cell movement identity, EMT is involved in vision diseases in response to outside stressors and post-surgical complications. Research suggests EMT may explain why some individuals develop a complication called posterior capsular opacification after cataract surgery.
- *Growth factor signaling*: Transforming growth factor beta (TGFβ), a growth factor that controls multiple cell signaling pathways involved in gene regulation, is suspected of being related to loss of blood-retinal barrier integrity in AMD patients with a specific gene mutation (*HTRA1*). Another form, TGFβ2, may play a role in glaucoma pathogenesis, as increased levels of this protein have been found in the aqueous humor of glaucoma patients.
- *Inflammation*: Maintenance of healthy vision requires finely tuned cell-cell communication and balance of pro- and anti-inflammatory responses in the eye, with immune dysregulation now identified as a contributing factor in multiple chronic eye diseases (e.g., AMD, uveitis).
- *Oxidative stress*: Ocular tissue is sensitive to environmental insults such as ultraviolet light, smoking, and high sugar diets. These factors can increase oxidative stress, a biochemical imbalance characterized by increase in free radical molecules, which can lead to increased production of proinflammatory signals and growth factors, tissue damage, and programmed cell death. In the cell, mitochondria can regulate oxidative stress, and impaired mitochondria has been linked to a wide range of ocular diseases such as optic neuropathy, AMD, and DR.

Large collaborations identified genetic risk factors in glaucoma and other complex diseases

Genomics research has demonstrated the need for large consortia and team science. NEI has led international collaborations to identify and explore the roles of gene variants in disease mechanisms in AMD, glaucoma, DR, Fuchs' dystrophy, and myopia. Over 200 genes have been linked to myopia, although their roles remain unresolved. The most common form of myopia has been shown to be strongly influenced by environmental factors. NEI initiated the International AMD Genetics Consortium (AMDGene), bringing together independent teams to harmonize their genomics efforts and increase statistical power. The consortium has published its findings since 2013, recently identifying 163,000 rare protein variants across 34 loci in AMD patients.

Similarly, despite being strongly heritable, the genetic underpinnings of Primary Open Angle Glaucoma (POAG) had long-remained elusive. The NEI Glaucoma Human Genetics CollaBORation (NEIGHBOR) identified over 130 genetic variants associated with elevated intraocular pressure, a key POAG risk factor, from 140,000 patients in the U.S. and Europe. These variants allowed the consortium to develop an experimental tool that predicts a patient's risk of developing glaucoma with 75 percent accuracy. The NEI African Descent and Glaucoma Evaluation Studies (ADAGES) have focused on a cohort of over 3,000 African Americans to identify new genetic markers and bridge those with the biological risks underlying health disparities in glaucoma. The success in identifying genes associated with complex diseases is both a triumph of collaborative science and a scientific imperative for moving from genes to

DRAFT

disease mechanisms. Capitalizing on the momentum generated by these studies requires construction of large curated datasets.

NEI community resources catalyze clinical research

It took 24 years from the discovery of *RPE65* gene to the FDA approval of gene therapy. While the arc of research is long, NEI funds community resources to expedite translation from gene discovery to understanding cellular mechanisms and developing therapies. For example, the Diabetic Retinopathy Clinical Research (DRCR) Retina Network brings together academic centers and community practices to perform clinical trials that test drug safety and efficacy. Having achieved success in the form of new therapies for DR, DRCR expanded into the Retina Network to study other diseases like AMD. Furthermore, eyeGENE® is a centralized research platform focusing on rare diseases and gene discovery, and has been recently transferred to the Biomedical Research Informatics Computing System (BRICS), hosted by NIH to improve public access to data. This ocular rare disease infrastructure has enabled a pipeline of gene therapies poised for clinical translation. The Eye Genotype Expression database (EyeGEx), developed by NEI investigators, provides a GWAS data analysis resource for researchers in the community. This community-accessible infrastructure helps speed introduction of new therapies to the clinic.

Research Needs, Gaps, and Opportunities

Build centralized curated databases

Although the genome has been parsed to unprecedented levels, there is an underrepresentation of ocular tissues in publicly available genomic, transcriptomic, and epigenetic databases.

- Curate databases to publicly share disparate data and establish standard data representation models for the community. Multi-omic analyses can help identify new pathogenic mutations in ocular disease genes and improve understanding of their mechanisms.
- Develop and implement bioinformatics and machine learning algorithms into datasets to aid genetic discovery and analysis. This might include analysis of whole exome sequencing, epigenetics, gene transcription network identification via ChIP-seq, studies of histone modifications, metabolomics, or redox/proteomics analyses.

DRAFT

AMD Integrative Biology Initiative creates a stem cell research resource

While genomics research has strongly associated AMD with specific gene variants (e.g., *CFH* and *HTRA1*/*ARMS2*), the pathways and mechanisms have not been verified. Investigators increasingly believe integrative or systems biology approaches are necessary to uncover their role in pathogenesis. Thus, NEI launched the AMD Integrative Biology Initiative, which makes iPSCs derived from the Age-Related Eye Disease Study (AREDS2) participant cohort available to researchers along with their associated genomic and clinical datasets. In addition to making iPSCs derived from participants available, researchers have access to participants' deidentified genomic and ocular imaging data so they can tease out associations between high-risk gene variants and molecular and clinical phenotypes. Moving forward, all of these data will be augmented, shared, and accessed by researchers throughout the community.

Bridge gaps in model system development

Well-defined animal and cell-based model systems constitute the foundation of both basic and translational research. Yet, many existing models for complex disease do not reproduce all the phenotypes seen in human patients or accurately reproduce relevant human anatomy. To complement animal models, NEI has recently stimulated significant progress in generating human cell-based model systems, including iPSCs, 3-D organoids, and tissues-on-a-chip. Human tissue cultures offer greater fidelity to human gene/cell mechanisms but lack the systems level complexity of animal models.

- Establish standards and best practices for developing cell-based models (including co-cultures of different cell types).
- Address gaps in animal models, such as a model with high density of cone photoreceptors like the primate fovea. To study connections between genes and disease mechanisms, create animal models engineered to provide temporal and/or spatial control of gene expression.

Identify genomic targets underlying health disparities

GWAS have been extensively used to find gene variants associated with ocular disease. Most of this work has been done in populations of European descent, whereas POAG disproportionately impacts African Americans, Latinos/Hispanics, and American Indian populations. Studies in different racial populations suggest different genetic risk factors and disease mechanisms, implying that POAG therapies may be tailored to an individual's genetic background. NEI has recently funded GWAS focused on underrepresented communities such as ADAGES, which studies the genetics influencing glaucoma in African American populations, and the POAAGG Study, assessing the association between gender and glaucoma among African Americans, while examining demographic, systemic, and behavior risk factors. Health disparities research should go beyond describing differences; efforts need to identify biological explanations for the differences (e.g., corneal thickness correlates with glaucoma risk in African Americans). Social determinants that influence health across the age spectrum may exert epigenetic effects.

DRAFT

- Target genomic studies for common and rare diseases in understudied minority populations and investigate precision medicine for disease therapy. Results from POAG conducted with different racial populations indicated different genetic risk factors and disease mechanisms, implying that POAG therapies may need to be tailored to an individual's genetic background.
- Evaluate the clinical impacts of disparities affecting vulnerable populations, such as the economically disadvantaged, and those with disabilities or limited access to healthcare. For example, eyeGENE® is shifting its focus to rural populations, underrepresented minorities, and ultra-rare disease populations.

Balance rare and complex disease research

Although rare diseases affect small portions of the population, they often cause debilitating, irreversible blindness as the result of unique pathologies. For example, Stargardt disease and Retinitis Pigmentosa (RP) blind over 100,000 Americans despite being considered rare diseases, and present a pressing need for new therapeutic development in addition to complex blinding diseases like AMD. Unique pathologies in the eye can sometimes provide insights for treating diseases in other organs and vice versa (e.g., Usher Syndrome, Sjögren's syndrome).

- Continue to study blinding diseases with the most severe, immediate impact.
- Integrate multiple factors when studying rare diseases, such as unique research potential and total disease burden across an individual's lifespan. Rare diseases often present important research opportunities, potentially providing new insights into vision mechanisms and other ocular disease pathways. For example, Stargardt dystrophy provides insights for AMD, some rare forms of cataract and glaucoma yield knowledge about the more common forms, and Fuchs' corneal dystrophy informs disease mechanisms of more common corneal diseases.
- Build on progress in gene therapy for both rare and complex diseases.

Lead new progress in gene therapy

Unique advantages of the biology of the eye, such as well characterized genetics, robust animal models, ocular tissue accessibility, relative immune isolation, and the ability to treat one eye and have the other as a control, have led to pioneering gene therapy successes for rare ocular diseases. Building off this progress, gene-based therapy trials are underway or poised to begin for rare diseases including RP, Usher syndrome, choroideremia, Leber Hereditary Optic Neuropathy, and retinoschisis. For decades, NEI has invested in vector development (the modified virus or nanoparticle that delivers the therapeutic gene into the cell) and has conducted extensive preclinical tests to ensure safety and optimized drug delivery. Additionally, gene therapy may offer new solutions for treating complex diseases such as AMD and DR.

- Optimize gene delivery for the eye. Different viral systems may provide specific targeting for specific cell types or allow for packaging of larger genes than is possible using adeno-associated viral vectors. Non-viral gene delivery systems, such as nanoparticles, are non-immunogenic, customizable, and can deliver large genes. Optimization of gene promotors can improve targeting of cell-type, timing, and cellular conditions.
- Develop and validate outcome measures to assess impact in clinical trials. These should include structural and functional metrics and may vary based on patient age and disease state.

DRAFT

- Explore strategies to treat complex disease such as down-regulating expression of specific genes or gene editing.

Understand and combat angiogenesis in vision disease

When disease interrupts blood supply to tissues, it results in hypoxia (inadequate oxygen), which can lead to angiogenesis (abnormal growth of new blood vessels). Some leading causes of irreversible vision loss are retinal vascular diseases including AMD, DR, ROP, and retinal vein occlusion. Angiogenesis has also been implicated in inflammatory diseases like herpes stromal keratitis in the cornea. The vision research community has made great strides in using new imaging modalities to track the development of vascular abnormalities in disease. For example, OCT and OCT-angiography (OCT-A) have become ubiquitous in clinical practice to identify individuals at risk for vision loss due to abnormal blood vessel growth in the eye.

- Collaborate with angiogenesis researchers in other fields to encourage innovation across research disciplines, such as oncology, which has developed successful drugs for blocking angiogenesis. Vision researchers can leverage advantages of the eye, such as advanced imaging, genetics, and AI to test new therapies.
- Expand the study of angiogenesis in the retina, including interactions with neural retina to understand regulatory effects of different cell types on one another and effects on pathophysiology of disease and vision. Collaborate with imaging researchers to examine new image biomarkers (e.g., OCT, OCT-A) for ocular disease.

Integrate research on disease mechanisms and public health impacts of refractive error

Many Americans exhibit different types of refractive errors, blurred vision caused by changes in the shape of the eye that keeps light from focusing correctly. Over the last few decades, there has been a particularly dramatic increase in the prevalence of myopia at a rate too rapid to be explained by genes alone. Severe myopia is also linked to a variety of other potentially blinding ocular diseases, such as myopic maculopathy, glaucoma, retinal detachments, and cataracts.

- Focus on the underlying genetic, physiologic mechanisms, and environmental factors related to refractive error development to address this increasing public health concern. For example, can children spending time outdoors in broad spectrum sunlight mitigate their genetic risk for severe myopia? Elucidating these complex interacting mechanisms may point the way towards new prevention strategies.

Understand the connections between aging and eye diseases

As the population in the U.S. skews older, age-related diseases such as cataract, glaucoma, AMD, and presbyopia present critical public health challenges. The confluence of research on aging and vision will provide different perspectives and tools to approach common problems. For example, vision scientists have been collaborating with Alzheimer's Disease researchers to identify ocular biomarkers for diagnosis and to monitor disease progression. Researchers are also exploring parallel mechanisms and manifestations of Alzheimer's Disease and AMD. Furthermore, the aging eye may be at greater risk from oxidative stress. Recent work suggests critical events in eye development and disease are affected by redox status, which is the balance

DRAFT

between antioxidant defense systems and reactive oxygen species (ROS). Research on the components and their impact on this system can provide promising approaches for preventing, delaying, or treating ROS-related diseases in the aging eye, such as cataracts.

- Improve aging model systems for vision research; there are limitations in using acute models to study chronic diseases like glaucoma.
- Examine the roles of redox biology and mitochondrial function in ocular health. Redox perturbations can contribute to age-related diseases like glaucoma, cataract, and AMD.
- Dissect gene and environmental networks that connect aging and eye diseases.
- Identify ocular biomarkers (e.g., OCT) that may be used to predict, diagnose, or monitor age-related disorders such as Alzheimer's Disease. Explore parallel mechanisms and manifestations of systemic and ocular disease (e.g., Alzheimer's Disease and AMD).

DRAFT

Biology and Neuroscience of Vision

Charge: *Visual neuroscience covers disparate specialties including corneal nerves, oculomotor system, photoreceptors and phototransduction, retinal circuitry, optic nerve, and central visual processing. What are the unifying issues, common problems, or top priorities of vision neuroscience research that NEI should address?*

Background

Vision is the dominant sensory modality in humans, occupying roughly one third of the cortex and dozens of subcortical regions in the brain[4]. Visual processing starts with neural responses in the retina, the thin tissue at the back of the eye containing photoreceptor cells. The retina is part of the central nervous system (CNS) and has been a cornerstone for innovation in neuroscience research. The unique experimental accessibility and highly ordered anatomy of retinal circuitry have enabled rigorous investigations of synaptic and circuit function. Thus, the retina serves as a model system for understanding the function of brain circuits.

The retina communicates with the rest of the brain via impulses in the optic nerve, which is made of RGC axons. In the brain, most image processing information is relayed through the thalamus and midbrain, before projecting to the visual cortex. NEI supports a robust portfolio of research on visual processing in the brain, which itself serves as the model for how the brain is organized and how it functions. NEI has supported the work of seven Nobel Prize laureates, starting with foundational research by Hubel and Wiesel, who identified the functional organization of visual cortex and critical periods that use visual activity to shape brain development.

The neurobiology of the eye involves more than vision. Intrinsically photosensitive retinal ganglion cells (ipRGCs) play roles in visual perception and are also crucial for regulation of circadian rhythms, sleep, pupil constriction, melatonin levels, and development. The cornea contains the highest density nerves of any tissue in the human body and these nerves convey pain and homeostatic information. The brain sends outgoing messages (efferents) to the lacrimal glands for releasing tears, and to the oculomotor system to control blink and eye movements.

Most vision-related problems have a neural component, including retinal degenerative diseases, like AMD; retinopathies that impact survival of retinal neurons; color blindness; diseases affecting the optic nerve, such as glaucoma, optic neuritis and multiple sclerosis; dry eye and corneal pain; and visual processing disorders, such as amblyopia, a developmental condition whereby the brain suppresses information from one eye. NIH uses an inclusive definition of neuroscience that includes research on retina cellular biology, glaucoma biomechanics, cortical circuitry and maps, and perception studies: three quarters of the NEI research portfolio fits within this category. Similarly, the trans-NIH BRAIN Initiative, which does not come from NEI funds, is substantially weighted toward vision, with about 45 percent of funding awarded to teams that include NEI investigators and/or vision research.

[4] Van Essen, D. (2004) Organization of visual areas in macaque and human cerebral cortex. In *The Visual Neurosciences* (Vol 1), (Chalupa and Werner, eds) pp. 507-521, MIT Press

DRAFT

NIH Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative

The NIH BRAIN Initiative, launched in 2014, is developing the imaging and functional tools to revolutionize our understanding of the human brain. NIH leads this public-private initiative and coordinates partners from industry, academia, and other federal research agencies. The initiative has multiple foci, such as creating a complete census of the types of cells in the brain and their properties, developing new technologies for large-scale recording and manipulating neural activity, and inventing the next generation of technologies for observing and controlling the activity of neurons in the human brain. A second stage of research is now underway to apply newly developed tools to dissect specific circuits and systems in the brain. NEI support of vision neuroscience positions the field as a central topic in future BRAIN research.

BRAIN Initiative Highlights

- BRAIN Investigators generated a **complete retinal cell atlas**, first in mouse, then in human, using Drop-seq, a technique that analyzes different cell types in complex tissues.
- The online game, **EyeWire**, is a citizen science project that has amassed a 3-D interactive online "museum" of retinal cell types and their connections with other neurons. EyeWire uses crowdsourcing to help trace neurons and their synapses from 2-D grayscale serial electron microscopy images of mouse retina into colorful 3-D representations of the neurons. Since 2012, EyeWire gamers have mapped thousands of retinal neurons, including nearly 400 retinal ganglion cells. The EyeWire BRAIN project is using genetic control tools to understand the functional connectome and ultimately behavior.
- Using a dataset collected by a consortium of laboratories and led by NEI investigators, the **Machine Intelligence from Cortical Networks** (MICrONS Explorer) program is developing a visualization tool that features excitatory cortical neurons from mouse primary visual cortex.
- The **Orion** brain prosthesis holds promise for blind individuals to have some functional vision perception by electrically stimulating the visual cortex directly in response to images captured by a spectacle-mounted camera. Blind study participants have reported a range of visual experiences, such as being able to tell when approaching a doorway, differentiating sidewalk from grass, and even reproducing letters on a touchscreen with striking correspondence between projected and perceived shapes of the letters.

Highlights of Progress and Ongoing Major Initiatives

NEI leverages trans-NIH Neuroscience initiatives for connectomics and neurotherapeutics

NEI operates within a larger neuroscience community at NIH, with significant investment in the **NIH BRAIN Initiative** (see sidebar) and the **Blueprint for Neuroscience** (BPN). BPN is a collaborative framework that includes 14 NIH Institutes and Centers (IC) whose mission includes support for research on the nervous system. By pooling resources and expertise, BPN identifies cross-cutting areas of research and addresses challenges too large for any single IC.

The current NEI contribution of $4.5 million/year is the third largest among BPN institutes. One successful BPN project is the Human Connectome Project (HCP). Connectomics is the study of maps of neuron connections in a tissue, and HCP aims to collect comprehensive, high resolution maps of neuronal connections, resting state and activity-driven functional imaging, genetics, and behavioral data from a large cohort of participants, including developing children during critical developmental stages, and an aging adult population. NEI is now leveraging the HCP database for collecting and sharing data on subjects with relevant diseases. NEI supports two disease-state projects: one to examine changes in visual cortical connectivity following central visual field loss, and another to establish human connectomes in low-vision, blindness, and following sight restoration.

Another successful BPN collaboration was the establishment of a neurotherapeutics network aimed at translating bench science to new therapies for disease. The network helps academic researchers navigate the drug development arena through funding for research, expert consultants, and contracts for formulation and toxicology. Three drug development projects are approaching Phase I clinical trials, including one from an NEI investigator with a promising new therapy for dry AMD, for which there is currently no available treatment.

Neuroscience toolbox provides resolution from molecules to circuits to function

Imaging and AI. A field as broad and tantalizing as neuroscience is perpetually innovating and integrating disparate technologies, from imaging to genetic engineering to physiology to AI. Vision neuroscientists have traditionally driven many of these innovations, but also recognize opportunities to adopt technology from other disciplines, resulting in a flexible toolbox to study neurobiology structure, function, and behavior. For example, adaptive optics (AO) is a tool, originally developed in astronomy, that uses deformable mirrors to compensate for optical aberrations enabling real-time resolution of individual photoreceptors and other retinal structures noninvasively. AO researchers can track changes over time, returning to the same cells months or years later, to detect structural rearrangements and dysfunction of the retina in disease. Another imaging tool uniquely suited for the eye, OCT, noninvasively reveals cross-sections of the retinal neural layers. These imaging technologies, coupled with AI, become powerful diagnostic tools to model visual function. Multi-photon fluorescence imaging in awake rodent models allows precise temporal and spatial resolution of individual synapses (boutons) as they function; this is fundamentally advancing our understanding of visual processing.

Molecular biology. The molecular revolution has transformed neuroscience. High throughput sequencing has profiled cell types and disease states in the visual system. RNA-seq has advanced understanding of gene expression from individual cells in the retina, enabling the identification of retinal cell types, investigation of gene networks driving retina development, and insightful comparisons across retinal regions and species. Gene editing using CRISPR can help understand the role of specific proteins in neurons and can be used for vision therapies. Introducing opsin proteins renders them sensitive to light; therapeutically, these optogenetic manipulations in retina neurons restored visual perception in animal models with dysfunctional photoreceptors.

DRAFT

Physiology and computational neuroscience. Neuroscience is unique among the disciplines for its study of neuron cells, which are excitable and communicate electrically with one another, ultimately leading to perception and behavior. Computational neuroscience has driven models of brain processing and function and is often powered by simultaneous recording of the electrical activity of numerous neurons using multielectrode arrays in the visual system or by whole brain functional imaging (fMRI, PET). New optical methods enable surveillance of a whole population of cells with reasonably fast temporal resolution. Multielectrode recordings have enabled documenting spontaneous retinal waves critical for early patterning *in utero*, defining functional connectivity within the retina at the resolution of single photoreceptors, and identifying the brain areas involved in vision driven-motor tasks. The fundamental research of visual processing is important for treating brain-based visual impairment and developing visual prosthetic devices.

Atlas of retinal cells and their connections provides new foundation for neuroscience

There are five major classes of neurons in the retina (photoreceptors, bipolar cells, amacrine cells, horizontal cells, RGCs), which are traditionally subdivided either by their anatomy (location, size, shape, neurite arborization) or their electrical responses to stimulation. New methods that combine these parameters with gene expression profiles have allowed research teams to systematically catalog all the subtypes, confirming known cells and identifying subsets, illuminating cell diversity and function across retinal regions. High resolution imaging methods—including 3-D electron microscopy and labelling cells with viral vectors—are expediting connectomics, identifying novel circuits, and enhancing our understanding of neuronal diversity in the retina. This will inform computation models of the retina and provide a larger picture of neuronal circuit dynamics in states of health, disease, and injury.

Primate-specific fovea has unique properties distinct from other regions of the retina

The fovea is a pit in the retina packed with cone cells, and the spot where visual acuity is the highest. In mammals, a fovea is present only in simian primates. Genetic profiling has helped distinguish and classify subtypes of retinal neurons and highlight differences between foveal and peripheral retina. Functional analysis of primate foveal and peripheral cones demonstrates differences in their physiological responses to light. This knowledge will improve understanding of the unique properties of human foveal vision (which drives high-accuracy daytime vision) and shed light on mechanisms of diseases affecting central vision, most notably AMD.

Non-image forming ocular neuroscience complements sight pathways

Alternative light detection pathways. Non-image forming ipRGCs use a protein, melanopsin, to independently detect light and have a role in regulating the circadian clock, pupil light responses, and mood. They also modulate the information transmission rates of other RGCs.

Ocular pain. Ocular pain causes significant morbidity, and is frequently associated with dry eye disease (DED), which affects nearly one tenth of adult Americans, particularly women and the older population.[5] Recent findings have revealed neural mechanisms for pain versus itch and

[5] Farrand, K. F., Fridman, M., Stillman, I. Ö., & Schaumberg, D. A. (2017). Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. American journal of ophthalmology, 182, 90-98.

their differential expression in corneal versus conjunctival tissues. Emergence of *in vivo* imaging of corneal nerves allows direct assessment of nerve damage in the corneal epithelium, which can increasingly be correlated with functional problems. While DED can arise from tear deficiency, it involves a broad group of anterior surface issues that cause a sensation of dry eye pain.

Oculomotor control. The combination of technical advances, neurophysiology, and modeling has made the oculomotor system the best understood motor system in the primate brain. This is critical not only for clinical reasons (e.g., strabismus, misalignment of the eyes), but also for demonstrating fundamental principles of how the brain uses sensory input, including vision, to generate behavior. New technologies provide opportunities to study natural vision in freely moving experimental subjects, and approaches involving naturalistic visual input and modeling are improving the understanding of interactions between movement and vision. Building on the successes in understanding brain processing and leveraging the elegance of precise visual control and the capacity for primates to learn complex tasks, visual system researchers have pioneered the study of higher-level processes such as decision-making and attention.

Research Needs, Gaps, and Opportunities

Understand systems neurobiology of visual processing, psychophysics, and behavior

Although a systematic understanding of retinal computations and mechanisms is within view, fundamental gaps in knowledge exist regarding the role of the retina and the processing of visual signals in higher brain regions.

- Understand retinal processing and functional differences between subtypes of neurons. There are over 20 types of RGCs in primates and over 60 types of amacrine cells. Even within subtypes, regional processing differs in foveal versus peripheral retina.
- Create a neuron census and understand the computational and network connectivity roles in interconnected vison-processing brain areas. Furthermore, the role of non-neuronal cells such as glia and endothelial cells is critical for understanding degenerative and vascular diseases.
- Dissect the visual pathways that emerge within the retina and drive the rest of the brain. Early research identified magno- and parvo-cellular pathways relaying messages from retina to thalamus to cortex. Now, researchers can identify at least 40 parallel pathways, but their functional differences and interactions are not clear.
- Elucidate the mechanisms, circuits, and neural computations for non-image-forming vision, including how light regulates circadian rhythms, sleep, hormone levels, and mood.

Coordinate research on cerebral visual impairment

Cerebral (or cortical) visual impairment (CVI) is an umbrella term for subnormal visual function resulting from injury to vision processing centers, including higher order association areas in the brain. Etiologies include perinatal brain damage (*see sidebar in Individual Quality of Life section*). CVI has distinct clinical features compared to brain-based visual impairment later in life, since damage to the visual pathways in CVI occurs during the window of visual

DRAFT

Clinical Endpoints in Neuro-Ophthalmology Workshop

In June 2019, NEI and FDA hosted a workshop on Neuro-Ophthalmology, particularly to develop meaningful clinical endpoints for optic nerve damage (neuropathy). Clinicians have relied on an eye chart to assess eye health since the 19th century, yet there is no simple measure of the brain's visual function. Functional vision can be measured through behaviors and the study of perception (psychophysics). There need to be improved tests of visual function, including those that can accurately diagnose people who are unable to report what they are experiencing. There is also a need to adapt metrics to assess low vision in visually impaired individuals. Low vision research suffers the drawback of lacking reproducible visual metrics across scales of function. Similarly, there are few objective and quantitative assessments of occupational therapy interventions for ocular motor dysfunction.

FDA has a guidance document specifying qualifications of patient-reported outcomes, and does not recognize the NEI Vision Function Questionnaire, which measures the dimensions of self-reported vision-targeted health status for persons with chronic eye diseases. In general, ophthalmology lacks well-defined endpoints compared to fields such as cardiology and neurology. Optic neuropathies have different stages during disease progression and different functional outcomes during and after treatment.

The workshop recommended categorizing reported outcomes of conditions objectively and choosing which of those quantifiable measures are best suited for assessing the conditions. It also recommended the need to develop and validate a tool to measure visual function using patient-reported outcomes, like multiple sclerosis or stroke assessments. To ensure data collection and interpretation is consistent across clinical studies with evolving methods of measurement and output, consistent definitions are needed.

development. In a 2007 study, CVI diagnosis accounted for roughly one quarter of children with visual impairment in the U.S. from birth to age three.[6] Children with CVI may have subnormal vision despite an otherwise healthy eye exam, and therefore the condition has historically been under recognized. Individuals with CVI may exhibit a constellation of impairments, including cerebral palsy and cognitive delay, further complicating accurate diagnosis and treatment. Prevention and management strategies will require better understanding the causes of CVI.

- Partner vision care professionals with relevant scientific and stakeholder communities on CVI workshops or initiatives that bring together different expertise, including rehabilitation specialists, educators, and patient families.
- Conduct careful clinical phenotyping to identify quantifiable biomarkers of disease to allow for more accurate diagnosis, risk prediction, and evaluation of treatment efficacy over time.
- Create an evidence-based age-appropriate test battery and CVI classification system that measures visual parameters such eye movement kinematics, visual field function, visual

[6] Hatton, D. D., Schwietz, E., Boyer, B., & Rychwalski, P. (2007). Babies Count: the national registry for children with visual impairments, birth to 3 years. Journal of American Association for Pediatric Ophthalmology and Strabismus, 11(4), 351-355.

attention and neglect, spatial vision, visual crowding, color vision, and other perceptions. Metrics used to assess stroke or traumatic brain injury (TBI)-mediated visual dysfunction could serve as a starting point.

- Understand the neural basis of CVI. New functional imaging technologies can anatomically isolate affected regions in patients.
- Explore neuroplasticity-based therapies. Amblyopia and stroke rehabilitation can be used as models to apply to injury in the developing brain.
- Research and disseminate effective clinician awareness strategies to increase timely recognition and diagnosis of CVI when rehabilitation would be most effective.

Harness neurodevelopment and plasticity in degenerative disease and injury

Visual neural circuitry is not fully wired at birth but relies on visual stimulation. For example, children develop amblyopia (lazy eye) when their brains do not receive a clear image from the eyes during the critical early period of development. Also, the *Regenerative Medicine* section and the NEI Audacious Goals Initiative are focused on restoring vision through regeneration of the retina and optic nerve. Recapitulating development to facilitate RGC reconnecting to distal brain targets could require harnessing brain plasticity, which is the ability of the neurons to form and reorganize synaptic connections, especially in response to experience or injury. In the cortex, neuroplasticity is central for learning and memory. Plasticity could be maladaptive when the wrong connections form—leading to undesirable or harmful consequences. Harnessing adaptive plasticity by understanding the most receptive disease stages and knowing which cells to modulate will be critical for successful neuro-regenerative therapies.

- Compare developmental plasticity and adult plasticity in the normal retina, in disease (e.g., glaucoma, retinal degeneration), and in brain-based visual impairments (e.g., amblyopia, TBI). The visual system is a model for CNS plasticity because of the ability to manipulate visual experience in adulthood, as well as during development before and after birth.
- Compare neurodegeneration in retina versus other brain regions involved in vision. Determine if gene expression in different neuron types relate to connectivity and cell function under regular homeostasis and during varying levels of stress, injury, or aging.
- Investigate plasticity induced by cell death, and track how plasticity is impacted (e.g., reversed or amplified) by vision-restoration therapies like gene therapy or cataract surgery. Can neuroplasticity be harnessed to guide therapy development? Determine how plasticity and rewiring affect disease progression in the central versus the peripheral nervous systems.
- Manipulate extracellular matrix factors and immune cells in perineuronal nets (PNN) as potential therapeutic approaches to modulate plasticity. PNNs surround some types of neurons and regulate neural plasticity. In visual cortex, PNNs appear during development and are implicated in closing the critical period for visual plasticity.

Overcome neurobiological challenges to next generation prosthetics

Restoring sight to blind individuals using a microelectrode array to stimulate visual processing centers was science fiction until 2013, when FDA approved the first retina prosthesis, ARGUS

DRAFT

II. Visual cortex prostheses are now undergoing clinical trials. Next generation prostheses may take advantage of technologies such as optogenetics, chemogenetics, and nanotechnology.

- Determine minimum specifications (e.g., resolution, visual field size) needed to provide useful vision. Empirical results from existing prosthetics and from regenerative therapies suggest users can identify objects and perform tasks with only sparse visual information.
- Integrate knowledge of cell type diversity into prosthetic design. One gap in prosthetic development is stimulating the right cell types at the right time, for example, to avoid simultaneously stimulating excitatory and inhibitory neurons in a circuit.

Explore mechanisms underlying ocular pain and itch

Ocular pain is primarily mediated by sensory nerves in the cornea, while itch is primarily mediated by sensory nerves in adjacent ocular tissues, such as the conjunctiva. Pain and itch have a significant impact on daily living and quality of life, but research in this area falls outside the typical spheres of both vision research and pain research. Ocular pain has many different causes such as injury to corneal nerves (including refractive surgery), infections, and aging. Pain may also manifest as an extreme sensitivity to light, or photophobia. Clinical diagnoses and treatment are further complicated by evolving definitions of ocular pain and DED. Another poorly understood neurological eye condition is blepharospasm, involuntary tight closure of the eyelids, which is thought to involve basal ganglia control of eyelid muscles.

- Develop ocular pain and itch initiatives focused on interdisciplinary research.
- Define neural and molecular mechanisms that mediate corneal sensation, ocular itch, reflex tear production, and photophobia, including potential therapeutic targets.
- Compare mechanisms underlying peripheral and central ocular pain.
- Determine if changes in corneal innervation are associated with persistent ocular pain, including in conditions that mediate small fiber neuropathies.
- Understand why plasticity following acute injury (e.g., refractive surgery) causes dry eye and pain sensation, but regular weekly turnover of the epithelium does not lead to pain.

Recognize special requirements for animal models in neurobiology

While visual neuroscientists use a number of animal models including cat, rabbit, tree shrew, and ferret, the dominant models are rodents, which are cheaper, quicker, and easily manipulated with genetics tools, and nonhuman primates (NHP), which provide a closer reflection of the human system because they possess a retinal specialization lacking in other mammals, called the fovea.

- Promote synergy between labs that work on different animal models.
- Expand technological advances or neuroscience discoveries made in one model to other systems and research questions.
- Advance NHP research techniques and primate research centers infrastructure.
- Leverage partnerships to facilitate access to human and NHP tissue for research. While access to eye tissue is limiting for some types of research, particularly electrophysiology, which requires fresh tissue, many logistical, philosophical, and procedural challenges exist,

DRAFT

such as protocol regulations and guidelines, which delay obtaining and transporting human tissues over long-distances while preserving them for research.

DRAFT

Immune System and Eye Health

Charge: *The eye is a relatively unique, isolated "immune-privileged" compartment, yet many chronic eye diseases including dry eye disease, uveitis, age-related macular degeneration, and optic neuritis have an immune component. Furthermore, ocular therapies must be designed to function in concert with ocular immunity. How can NEI develop cross-cutting program priorities and overarching goals for ocular immunology, infection, and inflammation biology?*

Background

The eye has a unique, nuanced relationship with the immune system. Skin grafts survived prolonged periods of time in rabbit eyes instead of generating an immune response, which led to the concept of "ocular immune privilege" in which the eye is excluded from immune system surveillance. Clinically, this led to the success of corneal transplantation, which was accepted at rates unlike any other organ grafts, and in 1905 became one of the first successful transplants of human tissue. The ocular surface must protect against the external environment yet also maintain optical clarity, which is compromised by inflammation. In the retina, the pigment epithelium was believed to maintain the blood-retinal barrier that prevented infiltration of immune cells into the retina. Breaches in the blood-retinal barrier brought about by ocular trauma, for example, were known to allow the immune system greater access to ocular tissue, resulting in bilateral inflammation severe enough to threaten patients' sight. While the eye may be isolated from the main immune system in the body, it is becoming clear that the eye has its own immune system. Recent findings suggest the eye is protected by its own specialized immune cells.

Paradoxically, lags and gaps in progress within this field result from early success in treating ocular immune diseases. Corticosteroids, an older class of anti-inflammatory drugs, were found to be relatively effective at treating eye inflammation such as uveitis. For many patients, though, corticosteroids do not help to prevent vision loss. Also, these drugs have significant side effects such as increased risk of glaucoma, cataract formation, and opportunistic infection. Thus, alternative therapies are warranted.

Understanding immune signaling pathways may lead to new ocular therapies. Neurodegenerative diseases of the eye are now recognized to have immune system involvement. Landmark genomic studies of AMD identified the significant role played by complement genes from the innate immune system, but that breakthrough in 2005 has yet to yield new therapies. Recently, the role of the microbiome in modulating immune factors has shown therapeutic promise for inflammatory diseases. Vision-threatening and painful viral infections, such as herpes zoster ophthalmicus (HZO) and herpes simplex virus (HSV), have some clinical similarities in that primary infection is followed by latency, and recurrent infection is frequently associated with chronic and/or recurrent ocular disease, both of which can lead to loss of vision. Furthermore, the future success of potential vision-saving interventions like viral vector-based gene therapy and regenerative medicine will depend on controlling immune reactions to local and systemic therapies. The immune system and its relationship with the ocular surface and anterior segment, the retina, and the optic nerve is changing how we understand eye health.

DRAFT

Highlights of Progress and Ongoing Major Initiatives

Specialized cells maintain balance in the ocular immune system

The identity and function of specialized immune cells in the eye remains an emerging topic of interest for vision researchers. Regulatory T (T_{reg}) cells are especially relevant to corneal health, reducing immune reactions and inducing tolerance to ocular antigens. Animal models with dysfunctional or absent T_{reg} cells exhibit reduced tolerance. In animal models of dry eye disease (DED), T_{reg} cells help mitigate symptoms. Corneal transplant can be an effective therapy for scarring due to injury, infections, or diseases like keratoconus or Fuchs' dystrophy, but can be complicated by graft rejection. Recent work indicates T_{reg} cells play a pivotal role in promoting corneal allograft survival, providing insights into corneal transplant rejection as well as into rejection of other organs after transplantation. Beyond the cornea, T_{reg} cells promote remission in both uveitis patients and in animal models of noninfectious uveitis.

Manipulating gut microbiome may improve eye immune health

Another strategy to regulate inflammatory eye disease is through understanding the microbiome, which is the population of commensal microorganisms that reside in or on tissues in the human body, including the skin, oral cavity, nasal cavities, genitourinary system, intestinal tract, and conjunctiva. Through symbiotic evolution with the immune system, the gut microbiome may play a key role in training, activating, and regulating immune responses, often preventing overreactions that can lead to autoimmune and inflammatory dysfunctions, such as in uveitis, glaucoma, and AMD. Recent advances incorporating bioinformatics tools coupled with Next Generation genomic DNA sequencing have enabled characterization of microbiome metagenomics, opening the door to species-level understanding of microbiota.

Shifts in the populations of different microbial species have been found to activate intestinal T-cell receptors to promote uveitis and autoimmune responses in the eyes of animal models. In key advances, investigators were able to alter autoimmune uveitis through modulating the gut microbiome, such as through fecal transplants. Short-chain fatty acids and other interventions that target gut microbiota increased immunoregulatory cells, which suppressed the ocular immune reaction in animal models. Microbiome modulation through probiotics also mitigated models of uveitis and dry eye disease. Commensal microbiota-induced immune responses mediated progressive neurodegeneration in glaucoma.

Alternatives to steroids prove effective in treating uveitis

Uveitis is one of the leading causes of immune-mediated vision loss and is often treated with anti-inflammatory corticosteroid drugs, which carry potential side-effects including glaucoma and cataract. New clinical studies address the goal of reducing clinicians' reliance on corticosteroids. The NEI Multicenter Uveitis Steroid Treatment randomized clinical trial (MUST), for example, tested whether a fluocinolone acetonide implant was comparable to systemic corticosteroids supplemented with other immunosuppressive drugs (i.e., the current standard of care) in improving patients' functional vision. Other trials test the efficacy of adalimumab (HUMIRA®), an FDA-approved biologic drug targeting tumor necrosis factor alpha

DRAFT

(TNFα). The SYCAMORE trial found TNFα blockade was effective at preserving vision in patients with juvenile idiopathic arthritis (JIA), a disease that causes inflammation in multiple tissues and causes uveitis in children; the ADJUST trial will test whether visual acuity preservation in JIA will persist after adalimumab is no longer administered. The ADVISE trial will test the efficacy of adalimumab in uveitis patients in comparison to conventional immunosuppressive drug therapy.

New treatments for ocular herpes and other infectious diseases

HZO is caused by reactivation of the varicella-zoster virus (also known as shingles) in adult eyes. Characterized by inflammation, decreased vision, and severe pain, HZO infection has a significant impact on quality of life for many patients with shingles. Although clinicians currently have few tools to combat the ocular pain associated with HZO, emerging approaches may help suppress the activity of the virus itself to improve patients' quality of life: 1) Shingrix, a recombinant zoster vaccine, received FDA approval in 2017 and is now recommended by the Centers for Disease Control and Prevention to adults over 50 years of age to prevent virus reactivation; 2) The NEI Zoster Eye Disease Study is a randomized clinical trial of valacyclovir to test its effectiveness at reducing HZO complications. However, current antivirals do not reduce latent herpes infection and other approved therapies provide limited efficacy and often need to be combined with steroids, with serious potential side-effects, to reduce symptoms. Also, valacyclovir may cause renal toxicity. Thus, there is a need to develop new antiviral therapies.

NEI has dedicated support to understanding and treating other infectious diseases that are endemic internationally. In the wake of the recent Ebola virus outbreak in West Africa, NEI investigators studied the long-term ocular complications as part of the PREVAIL III study. Even when the immune system clears virus from the rest of the body, some viruses like Ebola and Zika persist in ocular tissues. NEI researchers studied the persistent effects of Ebola virus infections in multiple tissues, including the eye. Other infectious diseases, such as infectious uveitis, may interact with commensal bacteria residing on the ocular surface. Trachoma, caused by the *Chlamydia trachomatis* bacteria, irritates and scars the inner surface of the eyelid and leads to damage of the ocular surface. While largely eradicated in the U.S., it is a major public health concern in Africa, South America, and the Middle East. The ongoing FLAME trial will test the efficacy of fluorometholone in treating trachoma that arises from post-surgical complications. Other NEI trials are either preventative (e.g., public health strategies to mass treat target populations with antibiotics), surgical, or post-surgical.

Molecular tools allow immunologists to tease out roles of individual cells

Recent advances in cellular and molecular biology have proven invaluable for dissecting the components of the immune system in the eye. Single-strand and single-cell RNA sequencing (RNAseq) allows investigators to profile and identify individual immune cells in a tissue and determine how their presence influences health and disease. This powerful technique has been used in cell fate mapping studies that track cell division and development to determine how immune cells in the eye specialize. Similarly, RNAseq can be used to study retinal microglia and other resident immune cells in the eye which help maintain visual function as well as

DRAFT

neuroinflammation and ocular autoimmunity. Combined with CRISPR, a revolutionary gene editing technology, investigators are targeting precise therapies for immune disease in the eye.

SIDEBAR – NEI Anterior Segment Initiative (ASI)

The front of the eye known as the anterior segment (e.g., cornea, iris, lens) has a unique interface with the external environment, maintaining an optically clear pathway for light and images to reach the retina while protecting the eye from external dangers. NEI designed the ASI to parallel its Audacious Goals Initiative (AGI); both efforts involve close interaction with the external scientific community for all phases of planning and implementation. While NEI routinely studies the anterior segment through existing programs, one goal of the ASI is to attract new talent from adjacent disciplines to tackle pressing challenges and address gaps in the research portfolio. In FY 2020, NEI received robust responses to a public Request for Information on unmet anterior segment research needs and unique opportunities. Key topic areas that emerged were dry eye disease, ocular pain, inflammation, and ocular microbiome. These topics largely overlap with the *Immune System and Eye Health* Area of Emphasis, and many of the panel suggestions were immediately incorporated in the design and implementation of the ASI.

NEI established core criteria to help prioritize future workshops and targeted funding opportunity announcements: 1) innovative new approaches and research topics, beyond the scope of the existing portfolio; 2) multi-disciplinary research involving multiple components of the anterior segment; possibly involving diverse mechanisms and their interactions; 3) fostering cross-disciplinary research and collaboration with expertise from outside the vision community.

Research Needs, Gaps, and Opportunities

Create new models for inflammation and immune homeostasis

Immune homeostasis represents a dynamic balance of activation and regulation of innate and adaptive immune cells. An immune response can involve both positive acute and chronic leukocyte activation, mobilization, and infiltration, and negative regulatory factors. The opportunity to apply this dynamic framework to eye health and disease requires a better understanding of all these factors and their mechanisms within the ocular microenvironment.

- Elucidate regulatory mechanisms supporting ocular health and function, with the goal of designing new and improved therapies to restore tissue homeostasis. T_{reg} cells promote tissue health by releasing specific targeted factors that reduce inflammation and immune activation. Conversely, research suggests damage to the cornea or lens and subsequent immune response can lead to cataract progression. Due to technical limitations, most T_{reg} research has been limited to animal models, but it is important to expand to human tissue systems.
- Investigate neurobiology roles for immune factors that challenge orthodoxy and examine whether "immune" factors are playing nontraditional roles for vision function. Recent research suggests the brain has its own resident immune system to respond to infections, with CNS specific T cells serving as gatekeepers to control entry of immune cells from the rest of the body. Some resident immune cells are crucial for recovery from traumatic brain injury.

Additionally, immune messenger proteins, cytokines, leaking into the brain have cognitive and behavioral effects and may also have protective effects for neurons. Building on parallels between ocular and CNS immune privilege, the brain research community may provide valuable support by informing study design and new models.

Many immune-mediated ocular diseases are chronic and complex. Yet, there has been an over reliance on acute models of disease, which have been extrapolated for chronic disease models. New models and systems could discover how gene variants associated with immune regulation mediate disease. For example, classic genomic studies associated complement factors with AMD, but there is scant evidence that activation of complement initiates AMD; clinical trials with complement inhibitors have not been successful. Regenerative animal models, such as zebrafish and amphibians, could be exploited to understand how injury/inflammation is directed to heal and regenerate.

- Establish better chronic disease models to identify and study the regulatory factors that are lost when tissues progress from healthy to disease states. Current AMD immunology models focus on positive factors, rather than regulatory responses that quell immune responses. What factors in a tissue make it protective, permissive, or vulnerable to inflammatory responses?
- Explore the relationship between the eye and autoimmune diseases such as Multiple Sclerosis (MS), a chronic autoimmune disease with disproportionate burden on women. Optic neuritis and intermediate uveitis are associated with MS.
- Understand the role of resident retinal cells in promoting immune homeostasis such as the role of microglia activation and cytokine regulation in DR. Despite being critical for aging and neurodegeneration, immune cells are hard to study in the retina as they account for such a small fraction of the total cell population.

Explore the connection between the microbiome and ocular immunity

The human body is home to multiple microbiome populations unique to distinct mucosal surfaces. These microbiome populations, especially from the intestinal tract, interact with host tissues to regulate immune activity and have been linked to numerous diseases when dysregulated. NEI is planning a workshop to explore the clinical significance of a resident microbiome population specific to the ocular surface. The opportunities in this nascent field require developing methodologies and animal models (e.g., the germ-free animal model) to look at physiologically relevant microbiome interactions with the immune system.

- Characterize normal versus abnormal microbiota in the gastrointestinal tract and ocular surface. Develop a system to test the impact of individual species on ocular health and the environmental influences on microbial populations. AI might be used to predict the disease state based on microbial sequence constituency.
- Investigate the interaction between dysbiotic microbiota and immunomodulation. Identify several possible groups of commensal microbial mimics for autoreactive T cell activation (e.g., fungal, viral, bacterial, dietary, foreign body). Molecular mimicry is a structural resemblance to host molecules that allow microbes to evade host defenses.

DRAFT

- Explore methodologies and models to examine therapeutic potential of microbiota-based interventions like fecal transplants, antibiotics, diet, and probiotics.
- Customize individualized regimens of immunomodulatory treatments based on patients' microbiome profiles. Elucidate new mechanisms of action and side effects of commonly used immunosuppressive agents on intestinal flora.

Relate immunosenescence to immune privilege

Immunosenescence refers to age-related decline in the function of both the innate and adaptive immune systems. The changes in immune responses impact immune privilege in the eye and thus affect disease susceptibility. Age is a risk factor for many ocular diseases from AMD to glaucoma to cataract to dry eye disease, yet age is not accurately reflected in many disease models used in the research community.

- Incorporate age as a biological variable when developing new models for immune-mediated diseases. Older animals will be better models to study immunosenescence and immune privilege and how they impact disease pathobiology.
- Leverage multisystem and interdisciplinary collaborations focusing on cellular senescence (e.g., the NIH Common Fund Cellular Senescence Initiative).

Mitigate ocular infectious diseases

Recent outbreaks have renewed interest in infectious diseases due to observations of ocular complications in patients infected with Ebola virus, Zika virus, and SARS-CoV2. Technological advances in response to SARS-CoV2 can be applied to ocular infections (e.g., molecular diagnostics and antibody-based therapies).

- Verify observations of long-term ocular complications in COVID-19 patients and determine which treatments show efficacy.
- Test the potential association and mechanisms of ocular hypertension and glaucoma secondary to cytomegalovirus (CMV) infection.
- Understand viral latency and herpetic disease mechanisms that pertain to infections with varicella-zoster and herpes simplex viruses. Improved research infrastructure, including greater access to improved animal models, clinical trials, and methodologies, are needed to develop the next generation of antiviral therapeutics and vaccines. This could be augmented by partnering with neurovirologists and neuroimmunologists who have studied infectious diseases in tissues similar to those found in the eye.

Improve imaging, biomarkers, and data analytics

Early detection could allow for more effective treatment of immune-mediated diseases and allow for greater preservation of visual function. The lack of clear biomarkers for early disease, however, limits clinicians' ability to do this. Biomarker identification requires a greater understanding of disease pathobiology and an ability to noninvasively screen patients.

- Expand access to patient tissue samples to help address deficits in current animal models of disease, which often fail to recapitulate highly relevant human disease hallmarks.

DRAFT

- Apply AI to imaging, metabolomics, and genomic datasets to aid in identification of biomarkers for disease surveillance. Combined with deep sequencing and improved quantitative imaging methods, these tools can identify pathogens and model co-infections and their interaction on the combined immune response.
- Develop clinical phenotyping for emerging infectious diseases.
- Distinguish autoimmune, autoinflammatory, and infectious disease reactions reliably in the clinic. For autoimmune disease, what are the causative autoantigens? For autoinflammatory disease, what are the intraocular triggers? For infectious disease, what is the most expeditious way to identify all possible intraocular pathogens?

Develop targeted therapeutics for ocular immune-related diseases

Corticosteroids help patients with immune-related diseases preserve their visual function, but with serious side effects and risk to vision. Furthermore, their mechanisms of action and disease pathobiology remain largely unknown.

- Identify targeted therapeutics or non-steroidal anti-inflammatory drugs for immune-related diseases. These studies require large patient enrollment to account for the wide variations seen with phenotypes and drug responses.
- Improve drug delivery methodologies. Local drug delivery may limit systemic side effects.
- Develop infrastructure to facilitate investigations of immune diseases from clinical and basic science perspectives. This could include whole genome sequences, clinical data, and an ocular tissue repository, such as intraocular biopsies from uveitis cases.

Monitor systemic immune responses to therapy

Immune system responses to new interventions such as cell and gene therapies need to be understood to maximize their overall effectiveness.

- Determine what immune considerations should be tested when developing new therapies. How do gene therapies, cell-based therapies, drug therapies, biologics, and vaccines differ in relation to immune response?
- Identify peripheral blood immune markers corresponding to ocular inflammatory phenotypes.
- Establish protocols to modulate the inflammatory response to intravitreal gene therapies or cell-based therapies without causing harm.
- Understand how eradication or recolonization of gut microbiota impacts immune surveillance.

DRAFT

Research Domain: Capitalizing on Emerging Fields

Regenerative Medicine

Charge: *How can we build upon the leadership that vision research provides in the field of Regenerative Medicine? How can we expand on the progress of the Audacious Goals Initiative (AGI) to accelerate translation of new therapies that fix or replace damaged or diseased tissues previously thought to be irreparable?*

Background

Regenerative Medicine is a translational research field at the intersection of tissue engineering and molecular biology, and involves replacing, engineering, or regenerating cells, tissues, or organs to restore or establish normal function. Vision researchers have innovated in regenerative medicine approaches including some of the first stem cell-based clinical studies in 2011, the pioneering work of stem cell-based eye cup formation in 2012, the first gene therapy to be FDA-approved for an inherited disorder in 2017, and the first corneal transplant made from induced pluripotent stem cells (iPSCs) in 2019 (Figure 5). Shortly after developing the previous Strategic Plan in 2012, NEI launched AGI to solve clinical challenges while engaging in cross-cutting research. The goal of "restoring vision through regeneration of neurons and their connections in the eye and visual system" has anchored NEI as a leader in this field. Many major causes of blindness, including AMD, glaucoma, DR, and other forms of retinal degeneration, result from death of key cells in the neural retina or the retinal pigment epithelium (RPE). Regenerative medicine approaches have successfully recreated these cell types in the lab from stem cells and are working to integrate them back into the eye to replace dead or dying cells in human disease.

Gene therapy and genome editing were covered in the section *From Genes to Disease Mechanisms*. However, there has been confluence of genetic and cellular engineering technologies. For example, cell replacement therapies can be genetically manipulated to edit mutations, add therapeutic genes, or regulate expression of specific genes prior to transplantation into patients. In addition to tailoring treatments to specific patient needs, genetically engineered cell therapies may improve neuronal survival and integration or protect against graft rejection by the immune system.

To accelerate progress in regenerative medicine, NEI established a new office in 2020. The Office of Regenerative Medicine (ORM) facilitates collaboration among scientists across the NIH and other federal agencies, academia, and nonprofit and private research sectors. ORM helps NEI coordinate AGI, 3-D Retina Organoid Challenge, AMD Integrative Biology Initiative, NIH Regenerative Medicine Innovation Project, as well as other stem cell-related activities. Improving the dissemination of new tools and advances coming from a variety of relevant programs is an important role for the new office.

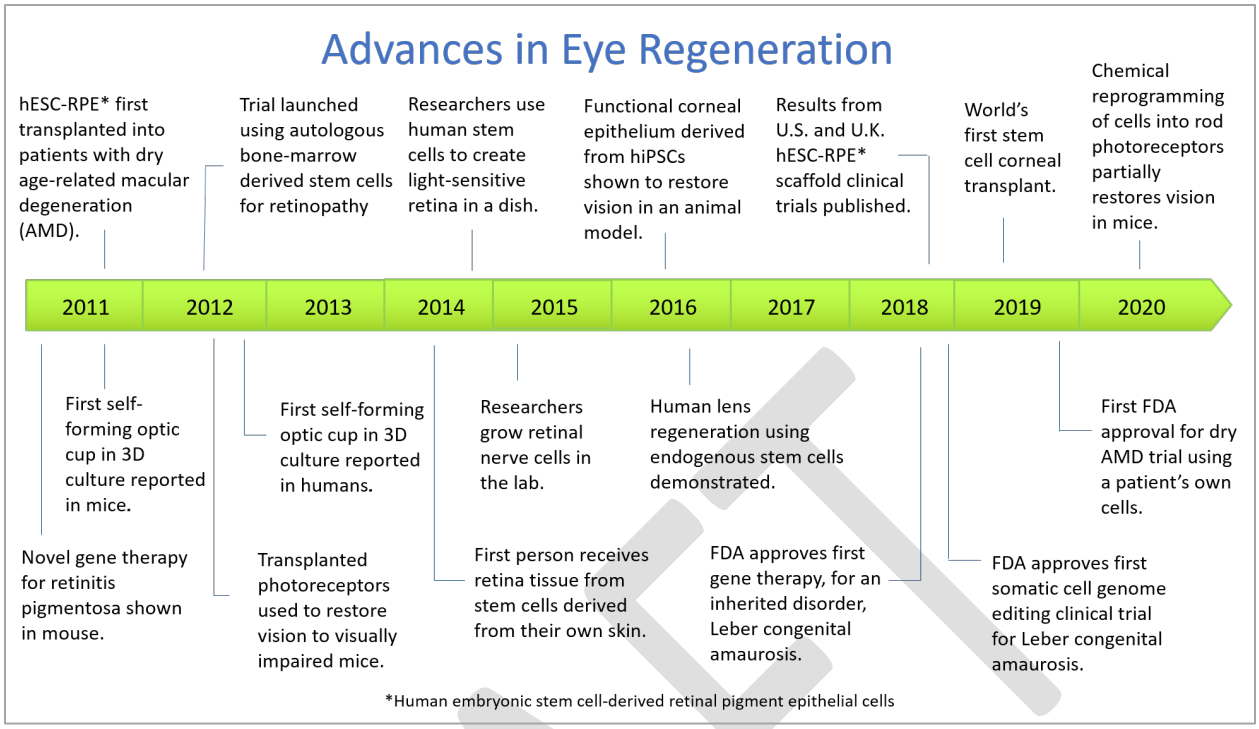


Figure 5. Timeline of major gene and cell-based advances to regenerate the eye

Highlights of Progress and Ongoing Major Initiatives

NIH launches first U.S. clinical trial of patient-derived iPSC-based therapy

In December 2019, NEI announced the launch of the first-in-human phase I clinical trial to test the safety of a novel patient-specific stem cell-based therapy to treat geographic atrophy, which is the "dry" form of advanced AMD and currently has no treatment. This protocol prevented blindness in animal models and uses replacement tissues derived from the patient's own cells, thereby minimizing the risk of tissue rejection. The therapy involves taking a patient's blood cells and, in a lab, converting them into iPSCs. These iPSCs are then programmed to become RPE cells, the type of cell that dies early in geographic atrophy and leads to blindness. The iPSC-derived RPE tissue is grown on a biodegradable scaffold designed to promote the integration of the cells within the retina. Surgeons then transplant it into the retina. (*For more information, see sidebar in the Intramural Research chapter).*

DRAFT

Audacious Goals Initiative (AGI)

AGI traces its origins to the 2012 NEI strategic plan and the Audacious Goals Challenge, a prize competition that challenged the vision community to set ambitious goals for meeting the greatest needs over the next 10 to 15 years. Prompted by a recurring theme among the winning concepts, NEI set the goal of "restoring vision through the regeneration of neurons and neural connections in the eye and visual system," and specified photoreceptors and retinal ganglion cells (RGCs) as research targets. Photoreceptors are cells in the light-sensing tissue in the retina. These cells absorb and convert light into electrical signals, which are sent to other cells in the retina including the RGCs and eventually to the brain, where they are processed into the images we see. NEI based its choice to pursue cell replacement therapies on preclinical advances in iPSC technology and studies in animal models showing that transplantation of stem cell-derived precursor cells can restore vision. Studies of fish and amphibians showed that some vertebrates utilize endogenous regenerative factors to rebuild the retina after injury, giving hope that a similar regenerative strategy could be recapitulated in humans.

AGI is catalyzing fundamental research that will enable restoration of vision through regeneration of the retina. AGI has launched three key consortia, representing 16 projects and $62 million in funding.

- The AGI Functional Imaging Consortium is addressing the technical needs and opportunities for imaging cells of the visual system to track regenerative therapies.
- The AGI Regenerative Factor Discovery Consortium is identifying factors that control cell regeneration in the visual system.
- The AGI Translation-Enabling Models Consortium is developing animal models with closer fidelity to human eye disease, a crucial step toward testing therapies in clinical trials.

Beyond direct funding, AGI has generated interest in cell transplantation and endogenous reprogramming strategies from the vision research community, helping to expand the NEI regenerative medicine portfolio with additional investigator-initiated grants.

NEI anticipates that early phase clinical trials to replace retinal neurons will begin in the next few years, as advances from the AGI-funded consortia converge. AGI workshops, town halls, and symposia are informing plans to build capacity for human studies. AGI is fostering a collaborative, cross-disciplinary approach in which diverse teams share their unique expertise and creativity. Crucial to this approach have been the AGI external scientific oversight committees, which champion collaboration and data sharing, and oversee the progress of the consortia. Furthermore, with the guidance of an external steering committee, AGI is facilitating new ways of advancing science across the NEI portfolio. Importantly, NEI-funded disease models are setting the stage for clinical studies of cell replacement therapies for several diseases and conditions affecting vision. Although AGI is aimed at restoring vision, the technologies and methods being developed are having an impact across regenerative medicine.

Coaxing retinal ganglion cells to form appropriate connections between eye and brain

While many groups have transplanted RPE and photoreceptors in rodents, transplantation and integration of RGCs remain a much bigger challenge because the axons must travel long distances down the optic nerve to find targets in the brain. However, in the last few years researchers have been able to show that transplanted primary RGCs survive, migrate, and make functional synaptic connections in healthy adult rats. Many of the transplanted cells grew projections to the proper brain targets and responded to light. The results present a promising

approach to develop cell replacement strategies in diseased retinas with degenerating RGCs. Expanding this research to better understand optimal donor cells and recipient integration is a major goal for the AGI-funded translation-enabling models consortium for ultimate application to various diseases and conditions resulting in blindness or low vision.

3-D Retina Organoid Challenge (3D ROC)

In 2016, Congress directed NEI to create a challenge program in new areas of research to accelerate cures for retinal diseases. NEI assembled retina experts as well as scientists and engineers from other disciplines with experience in creating tissue organoids. The workshop outlined design parameters for generating retina organoids.

Retina organoids are model systems 'growing in a dish' that mimic the structure, function, and complexity of the human retina. They can serve as a platform to study underlying causes of retinal diseases, test new drug therapies, and provide a source of cells for transplantation. The 3-D Retinal Organoid Challenge (3D ROC) was developed as a three-part, $1.1 million prize competition to generate a retinal organoid that responds to light. Technological breakthroughs in this area could allow researchers and physicians to better understand, diagnose, and treat retinal diseases. After the ideation and proof-of-principle phases, this prize competition has entered its third phase and hopes to recognize advances to model and develop drugs for retinal diseases in September 2022.

While regenerative medicine has made great progress growing retinal neurons and transplanting them into the retina, a key remaining challenge for the AGI is regrowing RGC projections to the brain. Natural inhibitory factors block growth of new RGC axons. Researchers have shown that drugs can interrupt these inhibitory factors to partially regenerate damaged RGC projections in mice, but they did not grow all the way to the brain targets. The researchers then improved on this technique using insights from developmental neurobiology: neurons need to respond to visual stimulation as well as chemical cues for proper patterning of neural circuitry. Because regeneration mirrors development, the researchers then tested whether visual activity would aid regeneration of existing neurons by having mice view high-contrast image patterns. The visual stimulation, combined with the drugs, promoted nerve fiber growth that enabled them to connect to their correct brain targets. Not only did this regimen accelerate growth 500 times faster than untreated neurons, but treated mice also showed some restoration of sight.

Extracellular vesicles transmit therapeutic properties of stem cells

Extracellular vesicles (EVs) are membrane enclosed packages containing RNA, proteins, and lipids secreted by parent cells, and include submicron-size microparticles and nanometer-size exosomes. EV secretions from mesenchymal stem cells have been shown to protect cells of the eye that are damaged by disease or injury. Researchers determined that these protective effects are mediated by microRNA, molecules that interfere with or silence gene expression. This has been applied toward neuroprotection in glaucoma, in which RGCs are damaged: rats treated with stem cell-derived vesicles only lost a third of their RGCs following optic nerve injury, compared with 90 percent loss in untreated rats. Extracellular vesicles and other factors secreted by mesenchymal stem cells have also been shown to enhance corneal wound healing after injury. A clinical trial funded by the U.S. Department of Defense is underway to assess these factors in treating patients with chemical or thermal injuries in the hope of preventing blindness.

DRAFT

Restoring vision through cell reprogramming

Damage to photoreceptor neurons can lead to full or partial blindness, as in AMD, Usher syndrome, and RP. Retinal neurons do not regenerate on their own in mammals. However, in some amphibian and fish species, such as zebrafish, support cells in the eye called Müller glia can divide in response to injury and turn into photoreceptors and other retinal neurons. The zebrafish can thus regain vision after severe retinal injury. NEI researchers coaxed mammalian Müller glia cells into becoming retinal neurons. After injury, zebrafish increase expression of a transcription factor, Ascl1. Induced expression of this factor in mice enabled Müller glia to regenerate inner retinal neurons (bipolar and amacrine cells), which were able to integrate successfully into the retinal circuit and respond to light flashes, much like the normal inner retinal neurons. In later studies, a two-stage genetic reprogramming process induced Müller glia to make new rod photoreceptors that integrated into visual pathway circuitry and communicated with other retinal neurons. These studies show the feasibility of reprogramming Müller glia to regenerate lost neurons and photoreceptors in the mammalian retina.

Regenerative biomaterials and limbal stem cells contribute to corneal therapies

Biomaterials, including decellularized collagen and natural and synthetic biopolymers, have been designed for use in corneal regenerative medicine. These scaffolds have dual functions in replacing needed physical structure and supporting stem and adult cells of the ocular surface, specifically the stroma and endothelium. Continued work in identifying biomaterials with ideal properties is required to optimize strength, biocompatibility, optical clarity, and immune response. Tunable biomaterials with appropriate stiffness, nanoscale features, and embedded factors, such as peptides and growth factors, have been designed, but await additional evaluation. 3-D printing of corneas has become possible and may further enhance these constructs. Several bioengineered constructs are being evaluated in clinical trials around the world.

Corneal limbal cells are responsible for renewing the front layer of the transparent cornea. In thousands of patients with limbal stem cell deficiency (LSCD), loss of these cells causes pain and visual impairment from chronic inflammation, abnormal blood vessel growth, and opaque corneas. An NEI clinical trial is testing the safety, feasibility, and efficacy of transplanting expanded autologous limbal cells in patients where the disease only affects one eye. The cell cultivation technique employed has been optimized and standardized using current good manufacturing practices by using only defined reagents without animal products. The NIH Regenerative Medicine Innovation Project has supported another project to treat LSCD. Researchers identified a limbal cell marker, ABCB5, which has allowed them to isolate, purify, and expand limbal stem cells in quantities sufficient for transplantation. New sources of stem cells for repopulating the limbal cell niche are under investigation, including iPSCs.

Cell replacement therapy provides promising results for cornea regeneration

Corneal endothelial cells (CECs) line the inside layer of the cornea and maintain its optical clarity by pumping solutes and fluid out. CECs degenerate in certain inherited diseases and acquired conditions, including after cataract surgery. These cells can be replaced by corneal transplant surgery but stimulating their endogenous recovery or replacing them with cultured

DRAFT

endothelial cells would greatly expand access for patients, given limitations in corneas available for transplantation. Researchers have identified how to culture and expand donor human CECs, with efficacy demonstrated in pre-clinical models. Previous studies have shown Rho-kinase (ROCK) inhibitors are able to accelerate cornea wound healing and initial clinical studies combining CEC transplantation with ROCK inhibitor pharmacotherapy have been promising.

Stem cell technologies can generate human lenses

Researchers can now produce large numbers of light-focusing human micro-lenses, called lentoids, from stem cells. The micro-lenses display similar morphology, cellular arrangement, mRNA, and protein expression to human lenses. These human lentoids provide a large-scale platform for defining molecular disease mechanisms caused by cataract risk factors, for anti-cataract drug screening, and for clinically relevant toxicity assays.

Research Needs, Gaps and Opportunities

Evaluate benefits of different stem cell sources

There are different sources of stem cells, but to-date, no one method has proven itself to have distinct advantages over the others in all instances. The development and use of human iPSCs are facilitating the study of human eye development and disease mechanisms, as well as the development of novel therapies, but there is a need to share patient-derived cell lines, develop isogenic controls, and reproduce and validate protocols.

- Explore the potential of different cell therapies through parallel regenerative medicine strategies: cells from unrelated donors (allogeneic), one's own cells (autologous), or harnessing innate repair mechanisms (endogenous) via *in vivo* reprogramming.
- Decode the significance of genetic and epigenetic alterations in pluripotent stem cell lines. This may help reduce variation in efficiency and safety of successful retinal differentiation for downstream applications of drug screening, disease modeling, and cell transplantation.

Increase capacity and scale of cell manufacturing

A major hurdle facing both allogeneic and autologous cell therapies involves manufacturing. Incorporation of automated processes for retinal cell transplants would minimize variability and improve efficiency of the process.

- Incorporate automation into the cell manufacturing process and AI into quality control monitoring. AI could be implemented with inline process sensors or integrated through emerging tools in synthetic biology and gene editing.
- Develop cryopreservation methods and Good Manufacturing Practice-grade cryostorage media for live cell products to increase capacity for bulk production and timed shipment of products. Increasing scalability will facilitate multisite clinical trials.

Assess cell integration and function

Once any cell types have been transplanted, tools and technologies to assess their survival, integration into tissues, and impact on visual function would be extremely helpful. For example, barriers to retinal cell integration include inflammation, scarring, and oxidative stress. Tools and

DRAFT

techniques from the NIH BRAIN Initiative may allow for a better understanding of these aspects, including whether retinal circuitry has been restored and integrated into the visual cortex.

- Explore use of autofluorescent endogenous markers to distinguish host versus transplanted cells using imaging modalities, such as hyperspectral imaging and super continuum OCT.
- Leverage single-cell sequencing and cellular barcoding to determine cell fates of transplanted precursor cells and to determine whether the engineered cells are maturing and connecting.
- Engineer advanced anatomic and functional imaging of transplanted cells to facilitate pre-clinical testing and characterization of transplant integration.
- Explore the therapeutic benefit of material transfer from transplanted cells. Material transfer is the phenomenon by which healthy transplanted donor cells transfer RNA or proteins to the host cells. In tissue transplantation studies (e.g., replacing photoreceptors in a dysfunctional retina), grafted donor cells may be integrating with host tissue and function as replacement tissue, and/or may be transferring material and thereby altering the host cells. It is important to understand the conditions and mechanisms under which material transfer can occur and the extent to which it might be broadly applicable for the field of regenerative medicine.
- Refine surgical procedures and improve scaffolds for cell delivery to enable widespread testing of cell replacement strategies in humans.

Understand extracellular vesicle biology in the visual system and their potential for therapy

EVs serve important physiological roles in eye health and development through long-distance cell-cell communication and can impact success of regenerated tissue transplantation, such as material transfer observed in the retina.

- Explore EV potential in regenerative medicine or for drug delivery. EVs may be easier to deliver than cells, but may have receptors that could trigger an aberrant immune response. Encapsulated cells producing EVs might offer another technique useful to the field.
- Integrate EVs and cell therapy research to determine if the potency or the therapeutic effect is increased when compared to either strategy alone.

Develop cell reprogramming and genome editing applications for ocular therapies

Instead of cell replacement, cell reprogramming and genome editing of diseased or degenerating cells *in situ* may afford another approach that avoids many current challenges of transplantation. There is the potential to reprogram RPE, Müller glia, and even rods into cone photoreceptors. New genome editing technologies could theoretically be used, beyond correcting inherited or spontaneous disease-causing mutations in endogenous genes, for other therapeutic applications.

- Study the safety and efficacy of small molecule, RNA, and protein delivery for inducing directed differentiation or transdifferentiation reprogramming, a process in which cells can be transformed without undergoing an intermediate step.
- Test and manipulate cell reprogramming and gene therapy strategies in *in vitro* platforms such as human retinal and corneal organoids and 3-D RPE-choroid cultures.
- Engineer cells to promote transplantation by increasing cell engraftment, enabling cell tracking, or allowing vascularization or migration of transplanted cells *in situ*.

DRAFT

Manage the immune response to optimize regenerative therapies

Although the retina has traditionally been considered immune-privileged, suppression of the host immune response to unrelated donor cells is needed to improve long-term integration. Additional cell engineering, genome editing, and biomaterials may modulate the host immune system.

- Determine the immune response to different types of cell and gene-based therapy products and optimize immune suppression regimens to assess short and long-term risk-benefit.
- Optimize methods for local drug delivery into the eye in the context of individual host profiles. Local drug delivery could inform strategies to understand immune suppression and mitigate the immune response beyond the use of steroids.

Foster diverse collaborations for cell and gene-based therapies

In basic research, understanding how some animals such as salamanders and fish regenerate their retinas may provide clues for modulating the host environment in humans. At the same time, leveraging observations of human diseases may provide insights about the principles that transplanted, reprogrammed, and edited cells follow. Lessons regarding neural regeneration in a diseased or injured environment may also come from spinal cord injury, and neurodegenerative diseases such as Parkinson's or Amyotrophic Lateral Sclerosis (ALS).

- Encourage researchers who study regeneration in different model systems to share insights.
- Promote dialogue and collaborations among regenerative medicine disciplines including auditory and olfactory, spinal cord and peripheral nerve, and the wider neuroscience and bioengineering community.
- Partner academia with industry to accelerate therapies by providing the resources and diverse expertise necessary to design and conduct preclinical and clinical studies.

DRAFT

Data Science

Charge: *Identify strategic investments in data science to position vision research to 1) optimize data management and data sharing while preserving safeguards and ethical protections; and 2) maintain leadership in informatics and artificial intelligence (AI).*

Background

Data science is the interdisciplinary field that extracts knowledge and insights from "Big Data". When Ray Kurzweil gave the 2008 keynote address for the Association of Research in Vision and Ophthalmology (ARVO) annual meeting, he discussed the "law of accelerating returns," where human history shows an exponential rate of technological change over the centuries. As a result, there have been fundamental changes in the way we approach a problem. As he predicted, supercomputers, data science, and AI have evolved from buzzwords to integral and indispensable components of vision research.

The Human Genome Project ushered in the "omics" era of biomedical research, where new tools enabling genomics, proteomics, and metabolomics provided comprehensive information about a system. The fact that a clear lens and a dilated pupil allow an eye doctor to see into the retina and examine disorders noninvasively has propelled vision research to the forefront of transformative digital imaging. Furthermore, electronic health record (EHR) data are far more readily available than they had been in the past, which creates unprecedented possibilities for integrating healthcare data with imaging and genetic information. This has accelerated the need for data science to stay one step ahead of the flood of biomedical data available to vision researchers.

Meanwhile, researchers have developed a growing number of analytic tools, including increasingly powerful artificial intelligence (AI) and machine learning (ML) methods. Pioneering computer models can accurately diagnose eye diseases such as DR and AMD from retinal photographs (showing the light-sensing, inner lining of the eye) and OCT images (showing a cross-section of the retina). The vision field has led innovation in these areas: the first FDA-approved autonomous AI system in any medical area was for DR. These models, along with applications that integrate EHR data, have demonstrated the transformative power of predictive analytics. The ability to link a vast array of data from sources such as sensors and monitors also adds challenges to protecting patient privacy and maintaining data fidelity, requiring new methods for explaining risk, earning trust, and engaging participants. In addition to the potential for information technologies to revolutionize healthcare, opportunities also span the spectrum from molecular- and cellular-focused research to population-level research studies.

Data science is evolving rapidly, so NIH and NEI must strategically position resources to stay ahead of the curve. As NEI invests in generating unprecedented volumes of data, there must be accompanying investments for storing, managing, analyzing, and sharing it. Despite many sources of data, non-overlapping research foci limit the ability to leverage disparate data types, and relevant publicly available data are sparse. Manual processes used to combine heterogeneous data sets are complex and error prone. To minimize costs and maximize scientific benefit, it is important to forge collaborations with non-ocular focused research groups to facilitate the collection and integration of vision-related data in other large-scale biomedical research efforts. Several federally funded, large-scale research efforts, such as the NIH All of Us Program and the

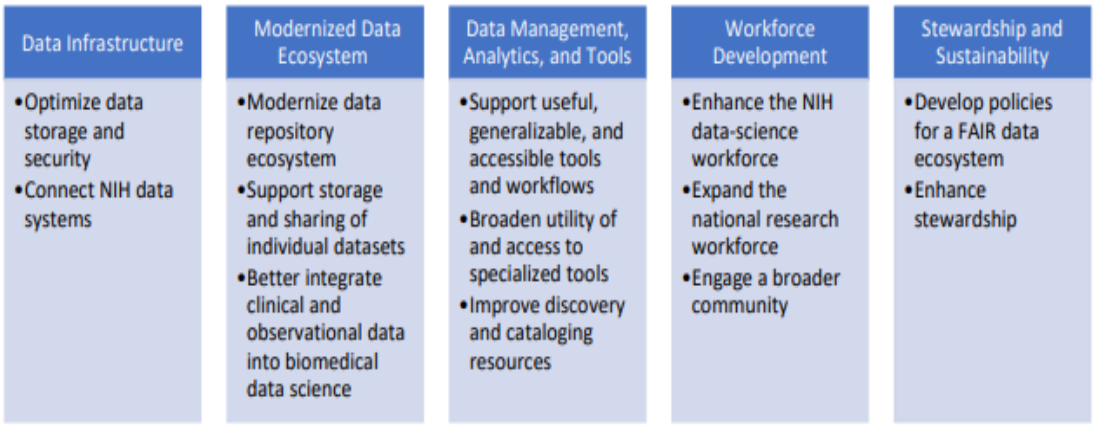
DRAFT

Genotype-Tissue Expression (GTEx) Project, include little vision-specific data. Collaborations with such efforts could facilitate opportunities to generate knowledge on which ocular signs and symptoms manifest within a broader context of human health and disease states.

NIH Strategic Plan for Data Science

NIH supports the generation and analysis of substantial quantities of biomedical research data, including numerous quantitative and qualitative datasets arising from fundamental research, clinical studies, and observational and epidemiological studies.

Storing, managing, standardizing, and publishing the vast amounts of data produced by biomedical research is a critical mission for the NIH. In support of this effort, NIH released its first Strategic Plan for Data Science in June 2018 that provides a roadmap for modernizing the NIH-funded biomedical data science ecosystem.



Generation of most biomedical data is highly distributed and is mainly produced by relatively small research groups. Data exists in a wide variety of formats, which complicates the ability of researchers to find and use data generated by others and creates the need for extensive data "cleaning." Proper handling of the vast domain of data being generated is a challenge for NIH and the biomedical research community. The NIH Strategic Plan for Data Science describes NIH's approach toward addressing these challenges.

The paucity of large-scale, standardized data coupled with the lack of researchers with experience in both vision research and computational methods provide a basis for including this topic area in this Strategic Plan. Not only does data science represent a new focus for NEI, but aspects of data science also intersect all the other areas of emphasis.

Highlights of Progress and Ongoing Major Initiatives

NIH publishes plans for data science stewardship

The NIH Strategic Plan for Data Science is the agency's approach to move toward a common architecture, infrastructure, and set of tools upon which individual ICs and scientific communities will build and tailor to their specific needs. Accessible, well-organized, secure, and

efficiently operated data resources are critical to modern scientific inquiry. The NIH Plan sets five overarching goals: Data Infrastructure; Modernized Data Ecosystem; Data Management, Analytics, and Tools; Workforce Development; and Stewardship and Sustainability. The NIH plan aims to build off four foundational tenets of data management and stewardship: Findability, Accessibility, Interoperability, and Reusability, known as the FAIR Principles. This NEI Strategic Plan is intended to build data science priorities in alignment with the NIH plan, while focusing on the strengths and needs of vision research. Another NIH initiative, the NIH Policy for Data Management and Sharing, was published in October 2020, and is intended to foster a culture of data stewardship by creating a flexible framework for establishing research-project-specific Data Management and Sharing plans. Open-source software and code sharing along with the increase in the amount of data available to researchers has resulted in novel knowledge generation and an explosion of unique data science projects. The increase in sharing practices promote reproducible science, builds on the work already completed, and enables collaboration.

Artificial Intelligence Based Devices for Disease Screening

Over the past decade, the success of new therapies has been remarkable in slowing or even reversing DR. NEI recommends people with diabetes receive annual eye exams; with early detection and treatment, vision loss is preventable in most cases. But even as the prevalence of diabetes grows, many individuals have limited access to retina specialists. Automated screening can reduce costs and expedite referrals and treatment for patients.

NEI support of the small business EYENUK has led to FDA approval for EyeArt®, an automated AI-based noninvasive tool that screens for early to mild stages of DR. It is designed for the primary care setting, streamlining the referral process to eye care providers. Using EyeArt®, clinicians can photograph a patient's retinas, upload the photos to a cloud-based analysis system, and get results in a matter of seconds. EYENUK harnessed a type of AI (deep learning) and used over 375,000 images to train the EyeArt® system to identify DR in the photos. A clinical trial showed greater than 90 percent agreement between results from the EyeArt® system and assessments by human experts.

A handful of automated AI-tools for detecting DR have become available in recent years: in 2018, iDx-DR was the first algorithm approved by the FDA, although it requires the use of a specific camera system. EyeArt® works with all fundus camera devices. Another NEI funded small-business, VisionQuest Biomedical, Inc. has developed the EyeStar DR screening system, trained on retinal images from people from diverse ethnicities; it has been tested in remote, under-resourced communities in the Southwest U.S. and Mexico.

These are a few examples of automated tools with promising application for telemedicine and mobile clinics to meet patients in their communities. DR is a leading cause of blindness, with an annual economic impact of $4.3 billion in the U.S. Rapid screening and detection of early-stage DR, with appropriate follow-up, can minimize the number of people who experience blindness.

Disclaimer: The founder of EYENUK, Kaushal Solanki, served as an expert on the NEI Data Science panel.

Vision research is at the cutting edge of ML and AI for clinical care

The prevalence of high-performance computing, hardware, and storage have enabled the training of very-large-parameter networks, a previously impossible feat. This, along with availability of quantitative digital imaging, has advanced ML and AI for eye care. At the patient level, AI tools developed through NEI grants can be used to screen rural and underserved communities for common conditions such as DR and AMD. NEI has supported research that has led to several AI based diagnostic systems, such as IDx-DR (2018) and EyeArt® (2020). In January 2020, FDA fast-tracked an algorithm developed by NEI researchers to screen premature, low birthweight infants at risk for retinopathy of prematurity (ROP), a condition in which prompt intervention can prevent lifelong blindness. NGoggle is an easy-to-wear device that can assess vision loss by analyzing the signals sent between the brain and eyes of a patient. This portable system based on AI and virtual reality can improve diagnostic testing for glaucoma, a leading cause of blindness.

The era of AI and ML in medicine has led to the creation of methods and analytical tools that can ingest heterogeneous, multifactorial data to learn hidden, complex latent relationships. An experienced doctor can look at the retina and diagnose a patient with DR or AMD based on specific retinal features, such as the configuration of the blood vessels, plaques, or spots that may indicate cell death. ML also relies on experience in the form of training computers to learn patterns in thousands of images, along with the "ground truth" clinical information such as a specific disease state. An AI algorithm iteratively trains itself to recognize which image features are important for diagnosis, while ignoring artifacts, like spurious shadows. Not only can AI reliably classify disease with higher accuracy than many doctors, but these algorithms have shown success in predicting the patient's age, sex, racial ancestry, smoking history, and likelihood of developing various ocular and non-ocular diseases. In the future, one can envision some routine medical diagnostics handled by AI, with improvements in the quality, cost, and accessibility of care.

AI integration provides innovative strategies for product design

Beyond diagnosis, AI plays an important role in product design and development. Scientists at NEI used AI to optimize manufacturing of cell therapy products by developing a way to convert patient-derived stem cells into replacement retina cells for use in an AMD clinical trial. However, the researchers needed to test the clinical-grade product to verify which cells function appropriately and are suitable for therapy. Thus, they developed a model using AI to predict cell therapy function based on the shape and texture features of single cells. (*For more information, see sidebar in the Intramural Research chapter).*

As neuroscientists decode how our brain processes information, AI, including model designs inspired by the brain called "artificial neural networks," are replicating the way humans learn and paving the way for machine-brain interfaces. Existing visual prosthetic devices turn images into electrical impulses delivered to the retina, providing users with significant vision impairment the ability to see bright lights and high contrast edges. Next-generation prosthetics will take advantage of the healthy visual processing layers deep within the retina, bypassing diseased regions. An NEI team is constructing a prosthetic using a camera mounted on eyeglasses that sends processed images to the inner retina stimulating a person's own neural code

DRAFT

representation of the 3-D world. With this device, the brain should be able to interpret pre-processed visual information.

For individuals with low vision, head-mounted displays have been around for many years but have seen major improvement with the advancement of AI. Several products are currently on the market as medical devices that use vision tracking, virtual reality, augmented reality, and optical coherence reading methods to improve visual function, acuity, and quality of life. Image processing algorithms developed by AI and ML, are being applied to address a wide variety of impairments, from central visual field defects, decreased contrast sensitivity, and visual image processing difficulties. Optimizing AI algorithms to an individual's needs shows great potential for helping people experiencing all types of vision impairment.

NEI lays the foundation for data infrastructure and data ecosystem modernization

The availability of large, complex data sets creates a need for enhanced computational understanding and tools. Vision research has been transformed by an enormous increase in the availability of data in the clinical realm (e.g., EHR, imaging, functional testing, wearable activity sensors) and in multi-omics datasets (e.g., single-cell RNASeq, whole-genome sequencing, metabolomics). Recognizing the need for a framework that allows researchers to understand the datasets available for sharing and collaboration, NEI has put in place new resources, such as the NEI Data Commons, which provides a central location for several NEI applications and data sets available to researchers. The site includes adaptive optics software packages, common data element resources, and, where informed consent documents allow, clinical trial data and images that can be used to train analytic models.

Supporting the NEI Data Commons is the BRICS platform, which houses data from several clinical trials to facilitate secondary use for analytic purposes as well as the potential for linking data across studies. Currently available studies include the National Ophthalmic Genotyping and Phenotyping Network (eyeGENE®), Patient Reported Outcomes with Lasik (PROWL), and Age-Related Eye Disease Studies (AREDS). AREDS2 and eyeGENE® both include clinical and genetic information, images, and the ability to access biospecimens.

Research Needs, Gaps, and Opportunities

In February 2021, NEI publicly announced the formation of the Office of Data Science and Health Informatics to coordinate existing activities within the NEI and across NIH and provide a nidus for new trans-agency programs in data collection, sharing, and interoperability.

Facilitate creation, storage, and sharing of big data for vision research

Big data is commonly defined as data that has large volume, velocity, and variety and is too large for traditional methods to parse. Biomedical data is just one area of big data that has the potential to be used to improve health and advance scientific discovery.

- Advance standards for data collection in vision science, including imaging, clinical, and animal data. Expand on existing NEI collaborations (e.g., PhenX, LOINC, NLM, ClinGen, OMOP, USCDI), and promote the use of standards more broadly through policy. Continue to

encourage grantees to use standards where they are already available and to create and share new standards that are created, including in model organisms and functional studies.

- Improve interoperability among imaging modalities, accessibility to commonly calibrated raw data, and expand access to genomics, epigenomics, and transcriptomics data that are underrepresented in publicly available data.
- Develop and validate imaging methods for identifying clinical disease biomarkers; for enhancing disease diagnosis, classification, and prediction; and for standardizing quantitative metrics among different devices.
- Create resources and incentives to facilitate data sharing. Data sharing is essential for expedited translation of research results into knowledge, products, and procedures to improve human health. In October 2020, NIH issued a Data Sharing Policy (effective January 2023), which requires NIH funded researchers to prospectively submit a plan outlining how scientific data from their research will be curated, managed, and shared.
- Prioritize representation of diverse populations in NEI clinical research studies. Encourage and develop clinical, genomic, imaging, biomarker datasets that represent the diversity of populations (e.g., demographic, age, ancestry, region of the country, disease prevalence).
- Develop template informed-consent language and technology to address privacy concerns for broad data and image sharing, with a specific focus on guidelines for biometric features of retinal images. Engage partners to address unique data sharing concerns of communities (e.g., American Indian/Alaska Native populations, immigrants, individuals with rare conditions, sexual and gender minorities).
- Create a centralized knowledgebase listing projects, data types, access requirements, and contact information to encourage collaboration among data generators and data scientists.
- Combine deep genetic sequencing technology and health informatics methods to develop disease surveillance networks.

Develop opportunities in artificial intelligence for vision science

Programs or applications that allows computers to perform a task that is typically completed by humans are considered AI. Machine learning and deep learning are types of AI that can enable and improve these tasks. An example of AI is the use of computer systems that can determine the diagnosis rendered solely from facets discerned from a patient's fundus image.

- Accelerate the development of ML in vision science with a focus on explainable AI models and applications that are transparent in the identification of key features and descriptive in their prediction and classification strength.
- Improve AI methods for integration of cross-modality data for analysis (e.g., EHR, imaging, genomics, metabolomics, clinical phenotyping).
- Explore ways to train models using distributed learning, without the need to share raw data or create a data repository.
- Develop a large 'golden cohort' of human subjects' data coupled to clinical vision information, genomics, and biospecimens such as the UK Biobank or NIH All of Us.
- Produce guidelines for addressing bias in data sharing, ML, and AI, and encourage broad dissemination of both positive and negative research findings.
- Encourage and enforce data standardization for large studies to ensure that new data collection initiatives can be combined and are 'machine-actionable'.

DRAFT

- Generalize AI data management and sharing tools and methodologies used for omics and clinical research to the full breadth of NEI research, including model systems, mechanistic studies and basic science.
- Explore ways that NEI can foster collaborations with technology leaders in industry.

Promote training and expand workforce in data science

Finding individuals with experience in the fields of data science, AI, and computer science, as well as expertise in vision research can be a challenge. Individuals with proficiency in technical skills are heavily recruited by private tech companies.

- Create centers or core facilities where expertise in vision science, data science and computational learning can be concentrated, and training programs can be developed. In addition to training data scientists in vision concepts, centers can train clinical and research graduate students with a vision science focus in data science through didactics and rotations.
- Enhance the diversity of the workforce through focused training programs aimed at underrepresented groups and non-research institutions.
- Bridge the gap between biomedical and data science expertise by encouraging interactions between data generators and data scientists. One way to accomplish this may be to develop scientific challenges and competitions using an open data or software resource, or inter-disciplinary initiatives.
- Collaborate with other federal agencies that support the education of computer scientists at all levels, including the National Science Foundation (NSF).
- Create opportunities for established researchers to learn data science principles and practices.

Build on computational advances in vision research

Improvements in storage systems, processing speeds, and analytical techniques have led to advances in the ability to collect, store, process, review, and share data, software, and code.

- Develop a federated/distributed network for identifying and sharing large datasets.
- Improve computational experimentation and code sharing by developing a cloud-based sandbox for vision science researchers, like NSF XSEDE or NIH AnVIL.
- Expand incentives to validate and share code, develop tools that are readily shared and/or operate in the cloud, and develop best practice guidelines for algorithm validation, documentation, code construction and commenting.
- Incentivize or fund open source software development that allows reading/writing, standardizing, and converting data as well as ML models.
- Use computational tools to address accessibility to improve quality of life for those experiencing vision impairment.
- Explore opportunities to identify, harmonize, and integrate small data sets and identify best practices for data management and sharing.

DRAFT

Research Domain: Preventing Vision Loss and Enhancing Well-Being

Individual Quality of Life

Charge: *While vision research is often focused on preventing or reversing vision loss, how can NEI address the needs and perspectives of individuals, including those living with blindness or low vision, to advance their independence and improve quality of life?*

Background

NEI maintains that research provides a gateway for those with vision loss to access interventions that foster independence and enhance quality of life. Despite decades of progress in diagnosis and treatment of ocular disease, 4.2 million Americans over age 40 live with uncorrectable visual impairment,[7] with increasing numbers anticipated as the population ages. Whether congenital or acquired and whether a result of disease or injury, individuals with impaired vision due to uncorrectable causes must learn to live with their condition by navigating a largely visual world, relying on their other senses and making use of accessibility devices and adaptive equipment. The purpose of vision rehabilitation is to help individuals with visual impairment continue to perform tasks such as transportation use, education and employment opportunities, and independent living. This is accomplished by maximizing an individual's remaining vision and substituting for diminished sight through various interventions. The experience of vision loss varies greatly across affected individuals. Rehabilitation must be tailored to an individual's needs, including whether the impairment is ocular- or brain-based and whether residual vision remains. While optical lenses and magnifiers have served as the mainstay of accessibility devices for visual impairment, the digital age has created a dramatic expansion of technologies, including devices that enlarge or dictate text, interpret pictures, and communicate to the individual about their environment. These technological advancements can also serve as a bridge to allow those who live in rural or underserved communities to access the benefits of vision rehabilitation more fully. Also, there is increasing recognition that visual impairment is often accompanied by comorbidities such as hearing loss, cognitive loss, mental illness (e.g., depression), psychosocial issues (e.g., social isolation), and other systemic diseases.

Furthermore, there is increasing interest in incorporating patient perspectives in many areas of medicine, especially in the context of clinical trials, where health-related quality of life assessments are more frequently used as outcome measures for evaluation of interventions. This has led to its importance not only in research but also in regulatory processes. In 2000, NEI, in collaboration with the RAND Corporation and several academic centers, developed the NEI Visual Functioning Questionnaire (NEI-VFQ) to measure self-reported visual health status for a number of ocular conditions. The NEI-VFQ has been translated into numerous languages and is currently available free of charge. In the 2016-2017 Strategic Priorities of the FDA, the agency committed to partner with patients to ensure that patient perspectives are incorporated as evidence in regulatory decisions, including both patient preference information and patient reported outcomes. FDA has actively partnered with various stakeholders to develop a number of vision-related questionnaires on specific diseases and treatments.

[7] Centers for Disease Control and Prevention, Fast Facts of Common Eye Disorders. Published June 9, 2020. Accessed January 30, 2021. https://www.cdc.gov/visionhealth/basics/ced/fastfacts.htm.

DRAFT

Highlights of Progress and Ongoing Major Initiatives

Low Vision and Blindness Rehabilitation program prioritizes quality of life research

The NEI extramural program in *Low Vision and Blindness Rehabilitation* supports research on vision rehabilitation, accessibility and assistive technologies, and neuroplasticity. Neuroplasticity, the process by which the brain changes and rewires itself in response to experience, is a key component of rehabilitation. The program attracts innovative engineering applications that address specific challenges faced by individuals with visual impairment. These include mobility and navigation, engaging with written and interactive screen-based content, and performing myriad other activities necessary to independently live and care for oneself, termed "activities of daily living." NEI also supports the development and refinement of visual prostheses, building on the ARGUS II retinal prosthesis approved by the FDA for RP in 2013. Notably, only a small fraction of people who can benefit from vision rehabilitation actually receive it; the National Health Interview Survey found that 12.4 percent of individuals with low vision reported using assistive or adaptive devices in 2017.[8]

Basic research unlocks complexities of brain-based visual impairment and neuroplasticity

The past decade has seen improved characterization of brain-based visual impairment, such as Cerebral (Cortical) Visual Impairment (CVI) and Traumatic Brain Injury (TBI). CVI results from damage to the brain from a variety of causes, such as oxygen deprivation or trauma suffered *in utero* or during early development. This results in a deficit in the brain's ability to process visual information (see sidebar) and is often diagnosed in early childhood. By contrast, TBI often occurs later in life, following, for example, a severe sports injury, car accident, or blast injury. Neuroimaging now allows researchers to identify and characterize the clinical profile of CVI and TBI more accurately through changes in brain processing patterns. Advances in research have also led to improved understanding of neuroplasticity, allowing those with vision loss to learn new ways to sense the world by using touch and sound as substitutes for vision.

Visual restoration trials expand options for those with ultra-low vision

Because the severity of vision loss resulting from different causes varies greatly, terminology helps distinguish broad categories: low vision is an uncorrectable vision loss that interferes with daily activities, whereas ultra-low vision is a more extreme impairment where perception is limited to crude shapes, movement, and light sources. NEI research has resulted in a range of advances from vision-restoration trials for those with ultra-low vision. Pioneering gene therapies such as Luxturna®, the first FDA-approved targeted gene therapy in any field of medicine, have provided some restoration of vision in individuals with inherited retinal degenerative diseases. Brain-based visual prostheses, supported by NEI and the NIH BRAIN Initiative, generate artificial vision signals in place of damaged brain tissue. While these technologies are game-changing, they currently are able to restore only limited vision, necessitating individualized rehabilitation plans to train individuals to live and adapt to their newly acquired visual abilities.

[8] Centers for Disease Control and Prevention, National Health Interview Survey. Published November 15, 2019. Accessed January 30, 2021. https://www.cdc.gov/visionhealth/vehss/data/national-surveys/national-health-interview-survey.html.

Technology provides an opportunity to augment vision for everyday activities

Advances in optical interventions are providing new opportunities to improve a person's ability to see in a wide range of settings. Examples include hand-held devices to magnify reading material; compact, spectacle-mounted devices called bioptics that enhance distance vision for driving; and specialized prisms to expand the field of vision in patients impacted by stroke. These devices can aid individuals who, for example, are walking along a crowded sidewalk, shopping, or cooking. Wearable digital technology enables virtual and/or augmented reality to assist the user in navigating city streets, airports, or public transit. Improved quality and usability of portable electronic magnification devices have resulted in their increased popularity. Major improvements in screen reading and screen enlargement technologies are making the digital world more accessible to those with visual impairment, including mobile apps with accessibility software to support reading, activities of daily living, and navigating within and outside the home. The utility of new devices can now be evaluated using state-of-the-art virtual simulators.

Efficacy research provides real-world insights on low vision and rehabilitation applications

The scope and quality of research in low vision rehabilitation has expanded through development and validation of new instruments to evaluate an individual's vision and ability to function in real-world settings. These include studying practical performance measures necessary for independent living, such as reading and digital communications, transport, education, work, engagement in hobbies, and community integration. This research also employs surveys which capture a broad array of person-reported outcome measures. Improved methods of analyzing survey data allow scientists to validate and better interpret questionnaire responses. Development of new tools to assess ultra-low vision supports studies of vision restoration. Randomized clinical trials have demonstrated the clinical effectiveness of visual accessibility devices and vision rehabilitation training for people with mild or moderate vision loss due to diseases of the macula. However, feedback on how to improve the usability of current rehabilitation modalities and ways to optimize training for people with different abilities are necessary to ensure the sustainable application of devices and services.

Visual Function Questionnaires provide patient perspectives

Paired with the administration of functional tests, questionnaires provide a comprehensive approach to assess quality of life for people with low vision. In addition to the NEI-VFQ, a number of questionnaires were developed to evaluate vision related quality of life. These include questionnaires similar to the NEI-VFQ, such as the Impact of Vision Impairment (IVI) questionnaire developed in Australia. Others were designed for specific diseases such as cataract (the VF-14), or for the pediatric population (Pediatric Eye Questionnaire). The NEI-Refractive Error Quality of Life Questionnaire (NEI-RQL) was created to evaluate health-related quality of life with different refractive errors. These questionnaires are additional methods of expression to evaluate individuals' opinions and may rank their preference compared to other health states.

Patient Reported Outcomes enhance vision health decision-making

The FDA focus on patient perspectives involves a number of clinical outcome assessments, including the patient reported outcome, which is defined as information on the patient's health as directly reported from the patient using questionnaires, numeric rating scales, or even diaries. Examples of recently developed patient reported outcome questionnaires include one designed

DRAFT

for persons undergoing refractive surgery, PROWL. Others were developed for the use of premium intraocular lenses to treat cataract and presbyopia, and the use of minimally invasive glaucoma surgery procedures.

Research Needs, Gaps, and Opportunities

Update vision related quality of life measurements and patient-reported outcomes

Although a number of instruments have been developed to measure vision-related quality of life and patient reported outcomes, important gaps persist. The NEI-VFQ has not been recognized by the FDA to be a valid questionnaire due to the need to incorporate other activities and to expand the subscales used for each domain.

- Revise and update the NEI-VFQ, and develop new instruments with the input of FDA and other stakeholders, including individuals with visual impairments representing different profiles of onset and severity. Questions revolving around activities on the original questionnaire (e.g., reading a newspaper) have become outdated.
- Develop patient reported outcome instruments for retinal diseases like AMD and DR. The FDA has indicated the importance of patient reported outcomes in the regulatory processes.

Individualize rehabilitation for different types of visual impairment

Although vision rehabilitation is accepted as an important part of healthcare for individuals with low vision, the field is not standardized. This hinders effective research, uniform provision of quality care, and reimbursement by insurance payers. Furthermore, while vision research has focused on diagnosis and treatment of ocular causes of vision loss, the field is in the early stages of understanding brain-based vision loss from conditions such as CVI, TBI, or stroke. Different rehabilitation strategies are needed for brain-based, compared with ocular, causes of vision loss.

- Develop and evaluate evidence-based practices for rehabilitation of ocular- and brain-based visual impairments based on standardized outcome measures, including those that incorporate preferences of individuals with low vision. This should include collaborators when appropriate (e.g., neurologic professionals, occupational and physical therapists, educators, and others for brain-based impairment).
- Design personalized approaches to rehabilitation, considering comorbidities an individual may have, such as hearing impairment, arthritis, or cognitive decline, which would necessitate integrating treatment plans with clinical areas outside eye care (e.g., audiology, rheumatology, geriatrics, neurology). This may also include evaluation of "navigator" programs to connect individuals with newly diagnosed uncorrectable vision loss to an array of services, such as vision rehabilitation, vision support groups, and counseling if indicated.
- Enhance the ability to diagnose brain-based visual impairments quickly and accurately, assess the range of abilities present, and design treatment strategies tailored to a given individual. Factor in the natural history of normal visual development to better understand the natural history of CVI, improve diagnosis of subtle cases, and distinguish CVI improvement from normal maturation.
- Study the application of advanced imaging techniques to examine the causes of brain-based visual impairment and how neural connections can be modulated to affect function. This might include real-time pharmacokinetics and visual tasking in parallel with fMRI.

DRAFT

Explore research encompassing comorbidities and integrated care management

Many individuals with visual impairment also require management of co-existing health conditions, such as arthritis, hearing loss, cognitive impairment, or other physical limitations. Children with CVI may also have autism, cerebral palsy, or developmental delays. These comorbidities may not always be readily apparent to providers and may interfere with plans to provide optimal management of health care and rehabilitation.

- Identify the comorbidities most commonly associated with eye and vision diseases and estimate their joint prevalence among individuals of various ages and the influence they confer on quality of life. Seek to include expertise outside the vision research field.
- Evaluate the impact of integrated care management among individuals of all ages with vision loss, with the goal of arriving at optimal strategies for care, for example, by reducing the risk of overmedication and optimizing the efficiency of time spent in doctors' offices.

Connect neuroscience/neuroplasticity with vision rehabilitation research

It has been difficult to model neuroplasticity in humans, particularly how the brain compensates and adjusts to vision loss.

- Investigate the brain's capacity to adapt to different degrees of visual impairment at cellular and mechanistic levels.
- Link neural changes following visual impairment (cortical reorganization) to an individual's behavior in terms of real-world function, rehabilitation, and need for retraining to maintain skills necessary to optimize quality of life.
- Identify individual predictors of successful outcomes of various visual prostheses and other restorative approaches to cope with vision loss and improve quality of life.

Promote research in telemedicine/telehealth, technology, and communications

Telemedicine refers to the remote delivery of healthcare services from provider to patient, while telehealth is a broader term that also includes disease surveillance, health promotion, and other population health activities. Modern society increasingly relies on technologies such as computers and mobile devices, and the trend toward broad adoption of telehealth that accelerated during the COVID-19 pandemic may have permanent impact. This may improve access to eye care, such as for those in rural and medically underserved areas. However, for blind and low vision individuals, telehealth platforms built around visual engagement pose unique challenges.

- Establish the efficacy, accessibility, affordability, and acceptability of telehealth for ophthalmic conditions in sighted and visually impaired individuals, including methods to use telehealth as a modality for visual rehabilitation.
- Create user-friendly innovations to support accessibility of mobile devices for those with visual impairment. For example, mobile applications utilizing cameras and other sensors could be extended for visual impaired individuals by rendering and presenting graphics in non-visual forms (e.g., tactile or auditory) or by applying computer vision and AI methods to identify objects in the environment.
- Optimize head-worn electronic accessibility devices to help those with visual impairment engage visual cues for navigation and other tasks. Effective use of these devices is currently limited by size, weight, visual resolution, and tendency to cause symptoms of cybersickness.

DRAFT

Research and develop resources for education and employment

A quality education, including reading, writing, and effective communication skills, is often not accessible to children and young adults who are blind or have severe visual impairments. Furthermore, individuals with visual impairment experience an exceedingly high rate of under- and unemployment, leading to a cascade of social, economic, and quality of life challenges.

- Identify a range of predictors of academic success for children who are visually impaired and quantify each predictor to establish the utility of various educational tools (e.g., braille, portable electronic devices, tactile graphics).
- Collaborate with educators to identify tools and techniques that foster play as learning in children with vision loss to increase communication, literacy skills, and healthy interactions.
- Develop educational resources for visually impaired children and their parents, which can be used by states and localities to support "remote learning" when Individualized Education Program guides and paraprofessionals normally present in classrooms are unavailable.
- Identify individual and contextual predictors of safe, successful, gainful employment. These predictors could then be translated into new technologies or devices.
- Understand structural and societal barriers to the integration of visually impaired individuals into the workforce, including access to adaptive devices that may be costly for employers.

Build collaborative research efforts to improve driving, navigation, and pedestrian safety

Independent navigation is a pillar of independent living, including access to education and employment opportunities and engagement with the world. Individuals with visual impairment who aspire to drive a motor vehicle or walk on busy streets may face significant challenges.

- Partner with other agencies to develop and measure the efficacy of traffic strategies employing auditory, tactile, and visual cues to improve pedestrian safety. Promote safer crosswalks for all pedestrians, especially the blind and visually impaired.
- Collaborate with relevant stakeholders to develop improved systems for teaching and evaluating the skills of drivers with low vision, using vehicles equipped with driving assist technologies. Determine efficacy of advanced driver assistance systems, including autonomous driving cars, for safe operation by visually impaired individuals.

Integrate mental health and wellness into holistic vision care

Individuals with vision impairments can experience social isolation, and feelings of frustration, sadness, or loss leading to increased stress, anxiety, and depression. The NEI Low Vision Depression Prevention Trial in 2014 demonstrated the efficacy of behavioral interventions integrated with vision rehabilitation to reduce depression in individuals with AMD.

- Establish best practices for screening individuals with eye and vision disease to identify mental health or psychosocial issues. Coordinating care between vision and mental health providers may facilitate timely mental health interventions.
- Develop interventional strategies to improve well-being in the context of vision loss.
- Measure how vision loss and mental health are related, including how factors such as age of onset, cultural differences, living conditions, and individual coping strategies can be used. Develop tactics to improve engagement with social support networks and how to optimize the use of vision rehabilitation services to improve mental wellness.

DRAFT

Cerebral (Cortical) Visual Impairment (CVI): Gaps in knowledge

Causes of Visual Impairment. Complications from premature birth are a leading cause of CVI. During the second half of pregnancy, the rapidly developing brain is particularly vulnerable to certain types of injury. In some cases, a condition called periventricular leukomalacia (PVL) can arise from damage to developing neurons and support cells in the brain, especially in areas responsible for motor function and subcortical visual pathways. As a result, infants with PVL have a higher likelihood of developing CVI and cerebral palsy. CVI can also result from complications affecting full-term childbirth, such as infection or prolonged oxygen deprivation, or brain malformations during fetal development. Seizure, metabolic, and genetic disorders have been linked with CVI, as has early trauma such as shaken baby syndrome.

Impact on Visual Function. Children with CVI exhibit a range of visual deficits and each case is unique. The extent of visual dysfunction is influenced by the underlying cause or brain areas affected. These children may have poor visual acuity, visual field deficits, strabismus, and higher-order visual processing deficits that interfere with attention and recognition. For example, in a crowd, faces of family members may be unrecognizable, or a favorite toy may be undetectable in a cluttered box. Difficulty coordinating motor movements using visual cues can be challenging.

Clinical and Public Health Impact. CVI has become a leading cause of visual impairment in children in the U.S. and around the world. In a national registry of children with visual impairment in the U.S. from birth to age 3, CVI was the most prevalent diagnosis (24%).[1] More children are at risk for CVI because advances in neonatal care have dramatically improved survival rates of extremely premature infants (those born earlier than 28 weeks' gestation). Meanwhile, treatment of childhood blindness caused by some other disorders has improved in developed countries. As a result, CVI now accounts for a greater percentage of vision impairment among children.

Diagnosis, Management, and Rehabilitation. Evidence-based guidelines for diagnosing CVI are lacking. If a child is not meeting age-appropriate visual developmental milestones (such as holding direct eye contact, or reaching for objects), CVI may be among the list of potential diagnoses, especially if there is a history of prematurity or early injury to the brain. CVI assessment should consider both visual function and functional vision. Visual function, evaluated during an examination of eye health, measures visual acuity, visual fields, and eye movements. Functional vision, which refers to an individual's ability to use vision for daily activities, is assessed by contextual-based behavioral testing. Many people with CVI have problems with functional vision despite normal visual function. Rehabilitative strategies are often visually dependent, underscoring the importance of addressing the underlying CVI.

NEI research helped establish CVI as a unique condition causing significant visual impairment. Groundbreaking imaging studies revealed differences in how the brain of an individual with CVI processes vision compared with patterns seen in ocular-based vision loss. Research has also revealed that CVI management requires different approaches than ocular causes of vision loss, and schools for the blind have successfully adopted new techniques to teach children with CVI. However, we are in the early stages of understanding CVI, and more research is needed to accurately diagnose and optimally treat those affected.[1]

Hatton, D. D., Schwietz, E., Boyer, B., & Rychwalski, P. (2007). Babies Count: the national registry for children with visual impairments, birth to 3 years. JAAPOS, 11(4), 351-355.

Public Health and Disparities Research

Charge: *Visual impairment and blindness are significant public health problems in the U.S. despite major biomedical research advances to detect and treat eye disease. What research can facilitate translation of basic and clinical advances to improve vision and preserve sight for all? This population health perspective explores the intersecting fields of epidemiology, health services, and health disparities, including women's and minority health.*

Background

Visual impairment and blindness remain leading causes of disability in the U.S. Surveys over the past decade reveal people's fear of losing their independence and quality of life due to blindness. Loss of vision results from a variety of diseases and conditions, some correctable and others not. These diseases and conditions do not manifest across the population equitably, and disparities based on age, sex, race/ethnicity, socioeconomic status, and geography are commonly reported. Functional vision impacts the ability to work, navigate one's home and neighborhood, engage with others, and maintain one's health. Loss of vision represents an economic burden to society from lost productivity and a higher incidence of falls, accidents, and depression. Given the wide-ranging impacts of visual impairment and blindness on individuals, their families, and society at-large, loss of vision represents an enormous public health problem for the U.S.

Building upon on recommendations including the 2016 National Academies of Sciences, Engineering, and Medicine (NASEM) report,[9] this chapter explores vision research through the intersecting fields of epidemiology, health services, and health disparities. Preventing vision loss involves understanding the burden of diseases and conditions and requires identifying gaps in providing appropriate vision health services to high-risk groups, such as older adults, children, and those in rural and urban underserved communities. Inability to access and afford services disproportionately affects certain communities, and efforts to increase uptake of vision health care must be sensitive to regional and cultural differences in outreach, messaging, and delivery.

Existing national public health initiatives, summarized in the next section, address topics such as eye and vision diseases and their diagnosis or management. Identifying and implementing these research priorities could yield progress towards reducing unnecessary visual impairment and may inform efforts to deliver vision care more equitably and efficiently. The infrastructure of these broadly based federal efforts is such that it requires the time, patience, and input of trans-agency government partners to convene subject matter expertise. It also requires a willingness to negotiate focus areas among an array of competing priorities, the ability to secure funding to measure milestones, and a competency to foster collaborations outside of government. These components are necessary to make inroads in education, health promotion, and adoption of health practices. Recognizing the importance of a concerted federal effort in population health, NEI aims to raise the profile of vision and eye-related issues on the national health agenda.

[9] National Academies of Sciences, Engineering, and Medicine. 2016. Making Eye Health a Population Health Imperative: Vision for Tomorrow. Washington, DC: The National Academies Press. https://doi.org/10.17226/23471. Available online at: https://www.nap.edu/catalog/23471/making-eye-health-a-population-health-imperative-vision-for-tomorrow

DRAFT

Highlights of Progress and Ongoing Major Initiatives

Healthy People Initiative sets goals to promote prevention behaviors

Led by the Department of Health and Human Services (HHS) Office of Disease Prevention and Health Promotion, the Healthy People Initiative establishes science-based, decade-long national objectives to improve the health of all Americans to live high quality, longer lives free of preventable diseases, disabilities, injuries, and premature death. Beginning in 1990, and every 10 years since, this initiative has established an agenda with objectives and benchmarks that address health disparities and health equity. This encourages collaborations across communities and sectors, such as government, non-governmental organizations, and advocacy groups, thereby empowering individuals to make informed health decisions. The Healthy People 2030 Initiative, launched in August 2020, contains a chapter with the following core vision objectives associated with valid, reliable, nationally representative data and evidence-based interventions:

- Increase the proportion of children aged 3 to 5 years who get vision screening
- Increase the proportion of adults who have had a comprehensive eye exam in the last 2 years
- Reduce vision loss in children and adolescents
- Reduce vision loss from DR, glaucoma, cataract, AMD, refractive errors
- Increase the use of vision rehabilitation services by people with vision loss
- Increase the use of assistive and adaptive devices by people with vision loss

Additional high-priority vision objectives that either currently do not have reliable baseline data or not associated with evidence-based interventions include:

- Increase the number of states and DC that track eye health and access to eye care
- Increase access to vision services in community health centers
- Understand factors impacting use of protective eyewear in occupational and recreational settings
- Understand the impacts of screen time on eye development and vision loss

USPSTF systematically reviews evidence to make health care recommendations

Comprised of an independent panel of experts in disease prevention and evidence-based medicine, the U.S. Preventive Services Task Force (USPSTF) reviews the literature to issue recommendations for clinical practice and identifies evidence gaps that warrant additional research. USPSTF documents its methods for each review in a publicly available Procedure Manual and makes its findings available in a searchable web-based tool to help clinicians identify preventive practices applicable to their patients. Processes that USPSTF uses align with NASEM standards for guidelines development. NEI, NIH, and other federal agencies are tasked annually to augment additions to the literature and to support research that gather data necessary to bridge USPSTF-identified gaps. Recent USPSTF vision-related evidence gaps focused on glaucoma screening, screening of older adults for impaired visual acuity, vision screening for adults with obstructive sleep apnea, eye issues related to primary prevention practices for adults with cardiovascular disease, and vision screening in children ages 6 months to 3 years.

DRAFT

NEHEP works with partner organizations to promote eye health

Health literacy, equity, and effective outreach are cornerstones of public health. The National Eye Health Educational Program (NEHEP), an NEI-sponsored national network of public and private partner organizations, targets outreach and education towards professionals and the public. NEHEP promotes eye health particularly among population groups at greater risk of eye disease and vision loss, encourages prevention of unnecessary vision loss through early detection and treatment of disease, and aims to improve quality of life of those with low or no vision by demonstrating the benefits of vision rehabilitation. The NEHEP strategic plan emphasizes a multi-pronged strategy of communication, partnership, and engagement to bridge vision research with best practices in health education and health literacy, outreach to at-risk communities, and targeted educational materials for effective messaging with various populations. (*See National Eye Health Education Program (NEHEP) Strategic Plan* chapter)

NEI clinical studies advance the prevention and treatment of vision problems

Through its intramural and extramural research programs, NEI elucidates knowledge on the burden and impact of vision and eye-related issues. These include observational, epidemiologic studies to quantify eye disease prevalence and incidence in defined populations and clinical trials of interventions conducted largely within the confines of the vision community. To expand its reach beyond traditional academic medicine, NEI continues to support collaborative networks of scientists, optometrists, and ophthalmologists such as the DRCR Retina Network and the Pediatric Eye Disease Investigator Group to evaluate the comparative effectiveness of therapies and preventive strategies in real-world settings at over 200 practice sites across the U.S. Additionally, NEI has partnered with other Institutes at NIH, with colleagues at other agencies within HHS, and across the government to leverage resources by adding ocular components into larger collaborative research projects. These efforts aim to uncover or better understand health conditions that coexist with vision and eye-related issues.

Research Needs, Gaps, and Opportunities

In February 2021, NEI publicly announced the formation of the Office of Vision Health and Population Sciences to coordinate existing activities within and across NIH and provide a focal point for new trans-agency programs to launch and remediate disparities in eye health.

Bolster efforts to gather current epidemiologic data on eye diseases and conditions

NEI has supported the addition of eye components to national surveys from which findings on the epidemiology of common eye and vision disorders have been published (e.g., National Health Interview Survey, National Health and Nutrition Examination Survey). This is a cost-effective strategy to keep vision as an important topic area on the national agenda, to estimate the national burden relative to other conditions, to capture aspects of vision or eye disease in the context of associated conditions and uncover factors not previously known to be important, and to incorporate facets indicative of social determinants of health. NEI has also funded a variety of population-based epidemiologic studies, clinical trials, and health services research projects.

DRAFT

It is important to recognize that population-based studies have limitations. For example, some may be restricted in content and deployed within defined settings using predetermined, often long-negotiated, data collection parameters. As a result, findings might not be generalizable (e.g., gaps in geographic representation; underrepresentation of communities such as American Indian/Alaska Natives, children or older adults, uninsured and underinsured populations, and institutionalized people including the incarcerated). Moreover, the demographics of the U.S. has changed dramatically over the past two decades. Regularly updated nationally representative data that focus on racial and ethnic minority populations are crucial to reflect current demographics, ensure sufficient power for analyses, and inform vision and eye-related programs and policies.

Future epidemiologic studies, clinical trials, and health services research require sound study design; rigorous and standardized definitions for disease, impairment, and disability; careful selection of controls and comparators; careful and thorough measurement of data including items that can be interrogated for socio-cultural and economic context; assessment of bias and potential confounders; and reproducible statistical evaluations with appropriate inferences.

- Collect data to develop population estimates, identify key risk factors for eye and vision disorders, quantify impact on quality of life, and inform resource allocation.
- Design research infrastructure that facilitates sharing of data, tools, and expertise to inform best practices.
- Increase efforts to harmonize research methods and facilitate comparison of vision and eye data across studies and settings. For example, data from clinical trials can be combined in meta-analyses for healthcare providers to incorporate findings in their practices, for patients to make informed decisions, and for professional organizations to develop guidelines.
- Expand co-funding of initiatives with trans-NIH arrangements and other federal agencies.

Strengthen community engagement and public outreach

Community engagement and health literacy are critical for working with the public, including underserved and vulnerable populations, and for gaining their trust to participate in population-based epidemiologic studies and clinical trials. Community engagement is also a powerful tool to catalyze behavioral and environmental changes that will improve public health and make access to vision and eye health care more equitable.

- Increase public awareness of the personal and societal burdens of visual impairment and blindness. Expand interactions with the public to inquire about issues that people identify as important or find to be lacking.
- Engage with leaders and members of underrepresented populations and seek their input when designing research studies and implementing findings.
- Create opportunities for public sector stakeholders to interact with organizations representing and/or providing care for visually impaired individuals, as well as with non-governmental and philanthropic organizations.

DRAFT

Identify factors that facilitate or hinder the delivery and use of vision care services

Appropriate and timely provision of vision care requires that patients, health care professionals, and policy makers have the evidence to make informed decisions. Such evidence includes the economic burden of vision-related conditions on society; assessment of patient preferences, such as motivators or barriers that drive care uptake; and the social and behavioral impacts of vision loss and vision rehabilitation. Expanding research efforts requires going beyond traditional population-based studies and incorporating broader expertise outside vision research.

- Conduct behavioral research on patients and providers regarding health promotion, disease prevention and accessing care. This includes qualitative research to understand patient needs, preferences, and willingness to comply with eye health recommendations. Health services research also focuses on access to affordable vision care, particularly for eye diseases that require expensive treatments with considerable out-of-pocket costs or eye conditions that involve recurring expenses (e.g., eyeglasses).
- Recruit health and behavioral economists to the vision research space, such as cost-effectiveness research and studies evaluating the reduction of chronic health risks and increased quality of life associated with vision-related therapies and interventions.
- Support studies that examine the utility, cost, and utilization of various modalities to deliver preventive and therapeutic vison care. For example, COVID-19 has resulted in broader use of telehealth. There is a need for studies to evaluate services such as interim virtual visits to check-in between regular appointments or to determine whether an acute episode of ocular symptoms requires an in-person visit.
- Support research at the nexus of social determinants of health and the healthcare system (e.g., integration of community resources into health care, individual decision-making regarding vision healthcare). This includes intervention research that address factors related to vision loss such as healthcare access and quality; and implications of factors such as education, health literacy, employment status, housing density, transportation availability, region of the country, and comorbidities. Incorporating social and behavioral approaches is essential to understanding decisions made within a diverse contemporary American society.

Promote health equity by expanding diversity in the research workforce and environment

Addressing vision-related conditions requires diversity of scientific disciplines, experiences, and demographics. Researchers from similar backgrounds as their research participants may elicit more trust, have a deeper understanding of challenges faced by those populations, and be better poised to formulate specific questions. Research on health disparities needs to shift from solely documenting their pervasiveness (e.g., where, when, how, and why they occur) and towards a more inclusive, multidisciplinary approach to remove barriers and promote equity.

- Recruit clinicians, clinician scientists, and researchers with appropriate cultural sensitivities working with underrepresented groups to study the eye health and vision care needs of underserved populations. For example, establish or expand programs for promising students and trainees, including those from other disciplines, and provide opportunities for well-trained researchers from diverse backgrounds to serve as co-investigators.

DRAFT

- Develop educational training programs or facilitate continuing education of individual clinicians or scientists from diverse backgrounds (e.g., sociology, nutrition science, audiology, gerontology) to collaborate on important issues in vision research.

Eye Health Disparities in Women and Racial/Ethnic Minority Populations

In December 2016, Congress passed the 21st Century Cures Act, which enjoins NIH to develop strategic plans with particular emphasis on women's health, minority health and health disparities. Development of this NEI plan included focused expert panel discussions on addressing health disparity populations, especially those at elevated risk for vision loss. For example, the "Genes" panel proposed targeted genomics studies, such as glaucoma studies in Hispanic/Latino and African American populations; the "Immunology" panel focused on autoimmunity and causes of dry eye in women; the "Data Science" panel recommended ensuring representative population studies and avoiding biasing AI algorithms that are trained on non-diverse populations.

NEI has a long history of supporting epidemiological research of eye diseases in defined cohorts.[1] NEI clinical trials have also generated data that has been leveraged through secondary analyses.[2] Recent NEI projects include a multicenter investigation on the prevalence of common eye conditions among Hispanic/Latino populations and a trial evaluating different approaches to enhancing adherence to glaucoma medication among African Americans. In consultation and coordination with the National Institute of Minority Health and Health Disparities, NEI continues to expand the scope and types of vision research that can bridge the gaps of health disparities and increase diversity of the workforce are necessary to promote health equity.

The advancement of women's health also depends on an integrative research approach across all health sectors, including vision. In consultation and coordination with the NIH Office of Women's Health Research and external researchers and stakeholders, NEI incorporates methods and analyses aimed at understanding sex as a biological variable in ocular conditions. Recently, efforts to capitalize on research opportunities at the front of the eye through the start of the NEI Anterior Segment Initiative will include further examination of conditions that disproportionately affect women, such as dry eye, Sjögren's syndrome, and ocular effects of migraines. Further exploration and incorporation of research methods and analyses aimed at addressing these and other conditions are important to improve women's health and vision and eye health for all.

[1]African American Eye Disease Study, African Descent And Glaucoma Evaluation Studies, Amblyopia in Astigmatic Children with the Tohono O'odham Nation, Baltimore Eye Survey, Baltimore Pediatric Eye Disease Study, Barbados Eye Study, Beaver Dam Eye Study, Chinese American Eye Study, Framingham Eye Study, Los Angeles Latino Eye Study, Multiethnic Pediatric Eye Disease Study, Wisconsin Epidemiologic Study of Diabetic Retinopathy

[2]Age-Related Eye Disease Study I & II, Diabetic Retinopathy Study, Comparison of Age-related Macular Degeneration Treatments Trials, Evaluating Acute-Phase Retinopathy of Prematurity Study, and The Ocular Hypertension Treatment Study

Enhancing Stewardship, Priority Setting, and Scientific Research Capacity

The NIH-Wide Strategic Plan (Fiscal Years 2016-2020) identified elements for setting priorities and enhancing stewardship. NEI stewardship efforts and priority setting policies are consistent with the NIH plan. To enhance stewardship, NEI engages in strategic partnerships and initiatives to recruit, train, and retain a talented and diverse workforce. This plan outlines additional efforts NEI is undertaking to expand workforce diversity programs at different career stages.

Cultivating Research Workforce Diversity, Recruitment, and Retention

A workforce comprised of people trained in different disciplines and from different backgrounds enables more innovative and impactful research. Recognizing this, NEI is implementing multipronged strategies to foster diversity. NEI is an active participant in the NIH UNITE Initiative that addresses structural racism and discrimination within the NIH-supported and greater scientific community. In September 2020, NEI established a Diversity, Equity & Inclusion (DEI) Council, dedicating a team of employees to focus on DEI priorities at the institute level. The Council aims to foster organizational change by creating strategies, frameworks, policies, and procedures for accelerating the achievement of DEI goals. The first charge includes providing recommendations through a strategic plan and roadmap to build a more diverse, equitable, and inclusive workplace.

The NEI Diversity in Vision Research and Ophthalmology program (DIVRO) provides hands-on vision research training and mentoring for students from underrepresented backgrounds. Created within the NEI IRP in 2011, DIVRO has hosted over 70 interns, of whom 45 percent were African American, over 40 percent were of Hispanic/Latino backgrounds, and the remainder were from Native American and multiracial populations. Women have comprised over 60 percent of DIVRO participants. In 2015, the program expanded to include students with disabilities when NEI hosted its first deaf student. DIVRO was originally limited to students from high school, college, graduate school, and medical school, but NEI is now expanding the program (DIVRO 2.0) to include more experienced trainees, applied science researchers, and collaborators, such as scientists with expertise outside vision research.

While NEI has a long track record of success supporting the diversity pre-doctoral research training fellowships (F31 funding mechanism), NEI recently added a postdoctoral diversity fellowship (F32 funding mechanism). NEI has also recently expanded commitments to NIH-wide diversity initiatives. These include the Maximizing Opportunities for Scientific and Academic Independent Careers program (MOSAIC); the BRAIN Initiative K99/R00, which facilitates transition of promising postdoctoral researchers from underrepresented groups to faculty positions throughout the country; and the NIH Blueprint F99/K00 Diversity Specialized Pre-doctoral to post-doctoral fellow Advancement in Neuroscience (D-SPAN) award. NEI is also expanding support for research grant administrative supplements that support hiring and training

DRAFT

researchers from diverse backgrounds.[10] In FY 2020, NIH added a Loan Repayment Program for Health Disparities and NEI funded the first award in this category.

NEI recognizes that groups underrepresented in research may experience social, institutional, and environmental barriers that restrict career advancement. NEI is committed to promoting greater representation across the research enterprise, with inclusion of visually impaired individuals and those from underrepresented populations in administrative, communication, clinical, and foundational research roles. The AoE panels, including the panel on Public Health and Disparities Research, emphasized the importance of training and retaining a diverse workforce in achieving vision health objectives.

Priority Setting

Priority setting and funding decisions are based on multiple factors, including peer review, disease burden, and scientific opportunity. The NIH-Wide Strategic Plan considers many public health factors beyond disease burden, such as the value of eradicating certain diseases and studying rare diseases.

Priority setting in the implementation plan. For this strategic plan, NEI Council identified seven cross-cutting AoEs to organize and prioritize research. Expert panels in each AoE identified needs, gaps, and opportunities. As with previous plans, NEI staff, in consultation with Council, will lead development of initiatives to implement these priorities and designate topics as having high program relevance (HPR). Grant applications discussed and approved by Council for HPR become top funding priorities in the NEI pay plan. As part of this planning process, NEI has also established two new offices: the Office of Vision Health and Population Sciences, and the Office of Data Science and Health Informatics.

Performance metrics. NEI is expanding its capacity to conduct robust portfolio analyses and make evidence-based program decisions by hiring and training new analysts. The NIH Office of Portfolio Analysis (OPA) has developed new bibliometric and text mining tools that enable outcome and topic cluster analyses. NEI plans to collaborate across NIH to engage and innovate in the burgeoning "Science of Science Management" efforts.

Research opportunities presented by rare diseases. Planning panels were asked to balance priorities of rare versus common diseases, and the consensus was to pursue both. Rare diseases often provide unique insights behind biological mechanisms of vision. The recent success of gene and cell therapy has demonstrated the potential to treat and maybe cure certain rare diseases. NEI funds a robust portfolio of rare disease research and is a funding agency within the International Rare Diseases Research Consortium.

NEI has maintained the eyeGENE® Network since 2006 to facilitate research into the causes and mechanisms of rare inherited eye diseases. This public-private partnership connects scientists with people who have a rare inherited eye disease and want to participate in clinical research. Having accrued over 6,400 participants, eyeGENE® continues to identify new

[10] Research Supplements to Promote Diversity in Health-Related Research, Updated May 29, 2020, https://grants.nih.gov/grants/guide/pa-files/pa-20-222.html.

disease-causing genes and empowers individuals with the knowledge of the genetics associated with their diagnosis.

Efforts toward eradicating a disease. Trachoma, a bacterial infection that causes corneal scarring, is a significant cause of preventable blindness worldwide. Treatment of trachoma became possible in the 1990s following the development of azithromycin, an antibiotic against the bacterium that causes trachoma, *Chlamydia trachomatis*. NEI has conducted several large-scale trials in trachoma-endemic regions of the world, which also suffer from overcrowding and poor sanitation. These trials have demonstrated that mass antibiotic treatments are an effective public health strategy for eliminating trachoma.

Enhancing Impact through Leveraging Partnerships

NEI leverages its resources through strategic partnerships within and beyond NIH.

Partnering with Department of Defense (DoD). NEI collaborates with the DoD Vision Research Program (VRP), which was established by Congress in FY 2009 to fund impactful military-relevant vision research such as traumatic eye injury. VRP receives more qualified applications than it can fund each year. Therefore, NEI and DoD signed a Memorandum of Understanding in 2019 to expedite application sharing where review criteria are harmonized such that NEI could fund competitive VRP applications that fit within its mission without requiring reapplication.

Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative. NEI is part of the NIH BRAIN Initiative, which was launched in 2014 as part of the 21st Century Cures Act to understand the human brain. This initiative includes partners from industry, academia, and other federal agencies. NEI program staff are represented on all trans-NIH BRAIN workgroups, and vision research is heavily represented in BRAIN awards. (*See BRAIN Initiative sidebar in the Biology and Neuroscience of Vision section)*.

NIH Blueprint for Neuroscience Research.

NEI is part of the NIH Blueprint, which is a collaborative network of NIH Institutes, Offices, and Centers that aims to accelerate transformative discoveries in brain function spanning multidisciplinary research. Within this network, the Blueprint Neurotherapeutics program provides support to develop new drugs for nervous system disorders by addressing research hurdles from early-stage studies to clinical testing. Blueprint recently funded early-stage to phase I safety studies for a new drug therapy targeting dry AMD, providing foundational steps for researchers and biopharmaceutical companies.

NSF partnership on Collaborative Research in Computational Neuroscience (CRCNS).

NEI is one of nine NIH Blueprint Institutes participating in the NSF CRCNS program. Through CRCNS, NSF and its domestic and international partners support collaborative activities to advance understanding of nervous system structure and function, mechanisms underlying neural disorders, and computational strategies used by the nervous system.

DRAFT

Smart Health and Biomedical Research in the Era of Artificial Intelligence and Advanced Data Science.

NEI participates in this collaboration between NIH and NSF, which aims to address technological and data science challenges that require fundamental research and development of new tools, workflows, and methods. NEI areas of interest include new technology, data science, informatics, telemedicine, and AI. Research aimed at improving eye and vision health in rural, inner-city, and other underserved and at-risk populations is a high priority.

Universities and National Institutes Transatlantic Eye (UNITE) Consortium. The NEI partnership with the UK National Institute for Health Research-Moorfields Eye Hospital was established in May 2012 to focus on ocular immunology and expanded to other institutions in 2020. A common protocol for operations and research is being developed for joint implementation by all partners, including exchange of researchers in the laboratories, weekly lab meetings, data exchange, joint IP, and joint publications.

Other public-private partnerships. NEI partnered with the New York Stem Cell Foundation (NYSCF) to create a widely available resource for the research community. Leveraging clinical and genomic datasets generated in the NEI Age-related Eye Disease (AREDS2) trial, NYSCF has produced patient-derived induced pluripotent stem cell (iPSC) lines corresponding to these data. (*For more information, see the* AMD Integrative Biology Initiative *sidebar in From Genes to Disease Mechanisms section*)

Ensuring Accountability and Managing Risks

The Risk Management Program at NEI was developed in coordination with NIH to proactively identify and mitigate risks to the Institute's objectives, strategy, and mission. Traditional risk management focuses on identifying and mitigating risk within program and project areas. Enterprise Risk Management looks across organizational silos and individual programs, addressing risks as an interrelated portfolio. The culmination of this process creates the NIH Enterprise Risk Management Profile, an internal information management tool leveraging diverse data to articulate top priority NIH-level risks.

Optimizing Research Management and Support Operations

The NEI Office of Administrative Management's (OAM) primary goal is to create alignment between the Institute's scientific mission and the delivery of management and administrative services that ultimately facilitate the NEI Directors' scientific vision and goals. The OAM operates as an advisor and strategic business partner. This includes management and analysis of operations, property and finance, and administrative support for research, such as services related to human resources, travel, acquisitions, information technology, and facilities maintenance. To do this, OAM must continue to be agile and effective in meeting changing scientific priorities.

OAM is developing a strategic plan to execute organizational assessments and strategies on administrative priorities. This plan, which will be released in fall 2021, is being developed in consultation with NEI research divisions and offices. The goal is to align OAM with the future

DRAFT

needs of NEI, building on the advances that have already been made to better navigate the demands of the science, to better balance the workflow and to build on OAM's strengths.

NEI must provide robust infrastructure and leverage modern technology to support the current and future clinical and scientific research needs. OAM will continue to assess and implement the scientific information technology strategy to enhance the network, high-performance scientific storage, data management, and data sharing solutions. This effort will involve active engagement and collaboration within NEI, as well as NIH to ensure effective use of central services; exploring, piloting, and investing in new information technology solutions; staff training; and incorporating privacy and security safeguards to the protect the integrity, confidentiality, and availability of NEI's cutting-edge research data and systems.

DRAFT

National Eye Health Education Program (NEHEP) Strategic Plan

In 1988, Congress established NEHEP, directing NEI to increase its commitment to prevention of blindness through public and professional education programs and the encouragement of regular eye examinations. NEHEP develops evidenced-based vision health provider education and public outreach programs, which emphasize early detection, sight preservation, and vision rehabilitation. NEHEP focuses on common eye diseases and populations at higher risk of eye health disorders, including older people, those with diabetes, and African American and Hispanic/Latino communities. NEHEP reaches out to other at-risk populations, such as people living in underserved urban and rural areas. With the total economic burden of vision loss estimated in 2011 to be $139 billion,[11] NEHEP efforts can improve functional vision and quality of life, while decreasing individual and societal costs.

NEHEP includes a cohort of over 60 national organizations. Over the next few years the Program intends to build on a framework for partnerships and activities to promote vision health in six program areas: Diabetic Eye Disease, Glaucoma, Low Vision, Vision and Aging, ¡Ojo con su visión! Eye Health for Hispanics/Latinos, and Write the Vision: Eye Health for African Americans. These goals are outlined in more detail in the *NEHEP Strategic Plan 2020-2023*, which includes a renewed emphasis on partnership development and project evaluation. This plan incorporates input from the NEHEP Planning Group—12 professionals in ophthalmology, optometry and health education—and builds upon best practices in health education, health literacy and cultural competency based on current research.

NEHEP's strategic vision is directly tied to that of NEI, as well as to the research breakthroughs that NEI scientists and grantees will make over the next several years. Additionally, future NEHEP activities are informed by the vision health objectives from the Healthy People 2030 Initiative, which emphasize evidence-based interventions to preserve sight and prevent blindness. In addition, the overall NEHEP strategy is influenced by the 2016 NASEM report. This report calls for leaders in the field to make eye health a national priority through a variety of means, including facilitating public awareness about the importance of eye health and providing evidence-based information. NEHEP aims to reach this goal through implementation of activities related to four specific objectives: Partnership, Outreach, Education, and Evaluation. In five years, NEHEP hopes to see a significant increase in vision awareness, knowledge, and action towards preventing eye disease across a broad range of stakeholder audiences, reducing vision impairment, and educating those with uncorrectable vision about accessibility devices that improve quality of life.

[11] Cost of Vision Problems: The Economic Burden of Vision Loss and Eye Disorders in the U.S.. 2013. https://www.preventblindness.org/sites/default/files/national/documents/Economic%20Burden%20of%20Vision%20Final%20Report_130611_0.pdf.

DRAFT

¡Ojo con su visión! Pilot Project

A major focus for NEHEP in 2020 was planning and executing a pilot project to measure the impact of the program **¡Ojo con su visión!**, which targets Hispanic and Latino populations, who are at higher risk of eye diseases such as glaucoma and diabetic retinopathy, in its educational outreach about eye disease and vision health.

NEHEP worked with Ventanillas de Salud (Windows to Your Health), a NEHEP partner organization with a presence at Mexican consulates in all 50 states. NEHEP trained community health workers (CHW) affiliated with Ventanillas de Salud at two sites, New York City and Phoenix, who then educated the community about symptoms and diagnosis of diabetic eye disease. If necessary, individuals were referred for dilated eye exams. NEHEP also developed local resources for individuals to overcome barriers to making an appointment, (e.g., insurance, transportation, and access issues). When the novel coronavirus shuttered New York City and limited in-person meetings, NEHEP transitioned to a digital education format. In all, 270 adults completed the program and about a quarter made appointments with an eye doctor.

DRAFT

Bold Predictions

The following "Bold Predictions" are aspirational vision research goals, potentially within reach, but by no means guaranteed. They are not an exhaustive list but were chosen to illustrate the range of NEI research. Despite the risks associated with making short-term predictions, it is important that NEI continues to place high hopes on the ability to push the boundaries of innovation faster than ever before.

1. Efficacy of the first induced pluripotent stem cell (iPSC)-derived products will be demonstrated in patients with age-related macular degeneration (AMD).
2. Artificial intelligence tools will improve detection and management of conditions such as glaucoma and diabetic retinopathy, and educational programs will be developed to help clinicians apply these tools in real-world settings to result in improved outcomes for patients.
3. A complete catalog of retinal cells types will be created in multiple mammals and will reveal their gene-expression profiles, circuit connectivity, and contribution to vision.
4. Control over the expression of genes in specific cell types will enable the restoration of vision to those suffering from retinal degeneration.
5. Strategies for treating chronic intractable inflammatory eye disease will be developed based on manipulating the gut microbiome through a combination of antibiotics, dietary interventions, fecal transplants, and probiotics.
6. Telehealth will be used for remote screening and management of common eye and visual diseases, and will improve eye care accessibility for people with limited mobility or residing in medically underserved areas.
7. Infrastructure for large-scale sharing and analysis of vision-related data, including definitions and standardization of data elements and biomarkers across multiple data types, will enable knowledge discovery and predictive disease modeling.
8. Neuroplasticity research will enable therapeutic strategies that reprogram an adult brain to behave like a developing brain with the ability to form and reorganize synaptic connections in response to injury or vision loss.
9. Newly discovered genes will be leveraged to develop candidate therapies for glaucoma.
10. New therapies to control the balance between immune tolerance and immune reaction will transform treatment of ocular inflammatory disease, greatly reducing the need for risky steroid medications.
11. Mobile applications utilizing cameras and other sensors will be developed for individuals with low vision by rendering graphical information into non-visual forms (e.g., auditory or tactile) and by applying AI methods to identify objects in the environment.
12. Improved understanding of the circuitry and mechanisms of corneal pain from conditions such as dry eye, neurological diseases, and refractive surgery will lead to new therapies.
13. Multi-omic analysis will help identify new pathogenic mutations in ocular disease genes and improve understanding of their mechanisms.

DRAFT

14. Vision-related quality of life and patient-reported outcome instruments will be developed for common visual diseases and will be incorporated into outcome measures for clinical trials and quality improvement programs.
15. Development of advanced, noninvasive functional imaging technologies at the cellular level will enable real-time assessment of regenerative interventions in the visual system.
16. Research incorporating social determinants of health will lead to new strategies for improving eye and vision disease prevention behaviors such as compliance with eye exams and medications, particularly in populations that experience health disparities.
17. Immunosuppression strategies needed for successful gene and cell-based therapies will be developed and applied to provide optimal treatments that are tailored to the disease, the individual, and the regenerative medicine approach.

DRAFT

Appendix

Appendix 1: Strategic Plan First Request for Information (RFI): Methodologies and Results Summary

RFI Instrument

To kick off the Information Gathering phase of strategic planning, NEI published an RFI to the scientific research community, health providers, patient advocates, professional societies, and the general public regarding the Research Domains and Areas of Emphasis. The scope covered the time since the 2012 NEI Plan.

- What are the most significant scientific discoveries in vision research since 2012?
- What new opportunities have been enabled by scientific discoveries or technology development?
- What needs and gaps in research, health, and quality-of-life should be addressed by NEI?

Methodology

The RFI was open from November 15, 2019, through January 9, 2020, via a web form on the NEI homepage, though comments were accepted via email beyond the deadline. The RFI was advertised through various stakeholder networks including the NIH Guide, Federal Register, emails to NEI grantees, 64 NEHEP partner organizations, and other stakeholder distribution lists (e.g., Association for Eye and Vision Research, American Public Health Association). Based on the information provided in the comments, NEI staff categorized responses by area of emphasis or the broader research domain.

Summary Results

RFI Respondent Affiliation	Number (Total: 252)
Parents/Citizen Advocates	55
Academics	54
Anonymous/Affiliation Unknown	49
Teachers/Specialists/Schools for Blind or Visually Impaired	29
Clinicians/Medical Professionals	25
General Public	15
Society/Associations	13
Government	11
Industry	1

DRAFT

Respondents: NEI received 252 responses. Many respondents were from the research community or patient/parent/citizen advocates. Other responses came from teachers/specialists, clinicians/medical professionals, professional societies/organizations, government, and industry. Almost 20 percent of respondents remained anonymous.

Topic Distribution: Most of the comments related to *Biology and Neuroscience of Vision*, followed by *Individual Quality of Life*, and *Public Health & Disparities Research*. Two-thirds of the total comments focused on Cerebral (Cortical) Visual Impairment (CVI), which is now a leading cause of childhood blindness in the U.S.

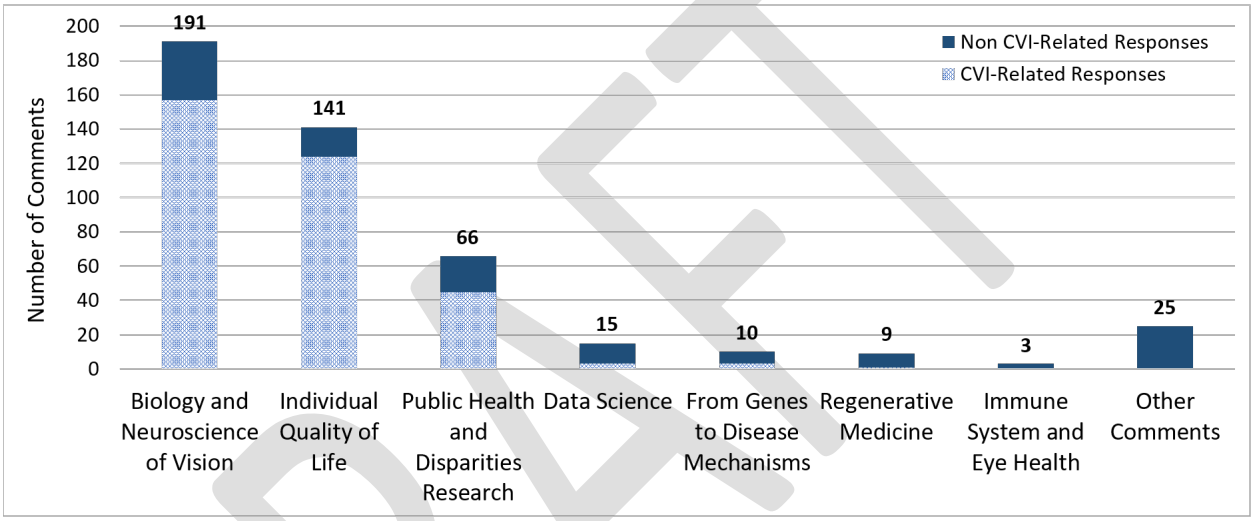


Figure 6: **RFI comments categorized by Area of Emphasis**. The numbers above the bars represent the tally of comments received for each AoE; responses that addressed multiple AoEs were counted more than once. 25 comments did not correspond to any AoE. Patterned fill represents comments addressing CVI.

The results of this RFI were used to inform expert panel selection and the topics for discussion. Panelists were provided the full responses to the RFI, and the results were discussed during panel calls.

Appendix 2: Strategic Plan Second Request for Information: [Pending]

DRAFT

Appendix 3: Strategic Plan Contributors [pending]

Area of Emphasis Panels

*Panel Co-chair
†Council member
ΦNIH Staff
Unless otherwise noted, titles and affiliations reflect positions at the time panelists reviewed the first draft (~Aug 2020)

From Genes to Disease Mechanisms

Renu Kowluru, Ph.D.* †
Professor – Ophthalmology, Visual, and Anatomical Sciences
Wayne State University School of Medicine

Vasilis Vasiliou, Ph.D.*
Professor – Epidemiology; Ophthalmology and Visual Science
Yale School of Medicine

Ales Cvekl, Ph.D.
Professor – Ophthalmology and Visual Sciences; Genetics
Albert Einstein College of Medicine

Stephen P. Daiger, Ph.D.
Professor – Environmental and Genetic Sciences; Ophthalmology and Visual Science
The University of Texas Health Science Center

Elizabeth C. Engle, M.D.
Professor – Neurology; Ophthalmology; Medicine (Genetics and Genomics)
Boston Children's Hospital, Harvard Medical School

Nataliya V Gordiyenko, Ph.D.Φ
Health Scientist Administrator
National Eye Institute, DESP

Michael Hauser, Ph.D.
Professor – Medicine; Associate Professor – Ophthalmology
Duke University School of Medicine

Scott Henke, Ph.D.Φ
Postdoctoral Research Fellow
National Eye Institute

Salil A. Lachke, Ph.D.
Associate Chair and Professor – Biological Sciences
University of Delaware

Peter Lwigale, Ph.D., M.S.
Associate Professor – Biosciences
Rice University

Patsy Nishina, Ph.D.
Professor – Genetics and Genomics
The Jackson Laboratory

Louis Pasquale, M.D. †
Scientific Advisory Board Co-Chairman
The Glaucoma Foundation, Mount Sinai Hospital

Eric A. Pierce, M.D., Ph.D.
Professor – Ophthalmology
Massachusetts Eye and Ear; Harvard University

Grace Shen, Ph.D.Φ
Health Scientist Administrator
National Eye Institute, DESP

Stephen H. Tsang, M.D., Ph.D.
Professor – Ophthalmology
Columbia University

Christine F. Wildsoet, O.D., Ph.D.
Professor – Optometry and Vision Science
U.C. Berkeley School of Optometry

Nora Wong, M.P.H.Φ
Health Science Policy Analyst
National Eye Institute, OPPA

Charles Wright, Ph.D.Φ
Health Scientist Administrator
National Eye Institute, DESP

DRAFT

William Guido, Ph.D.*
Professor and Chair – Department of Anatomical Sciences & Neurobiology
University of Louisville, School of Medicine

Monica Vetter, Ph.D.*
Chair – Department of Neurobiology and Anatomy
University of Utah, School of Medicine

Jose-Manuel Alonso, M.D., Ph.D. †
Associate Professor – Department of Biological Sciences
SUNY College of Optometry

Sue A. Aicher, Ph.D.
Professor – Chemical Physiology and Biochemistry
Oregon Health and Science University, School of Medicine

Edward Callaway, Ph.D.
Vincent J. Coates Chair in Molecular Neurobiology
Salk Institute for Biological Studies

Michael Do, Ph.D.
Associate Professor – Neurology
Harvard University, Boston Children's Hospital

Greg Field, Ph.D.
Assistant Professor – Neurobiology
Duke University School of Medicine

Martha Flanders, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Shefa Gordon, Ph.D.ϕ
Director – Office of Program Planning and Analysis
National Eye Institute, OPPA

Tom Greenwell, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Vladimir Kefalov, Ph.D.
Dr. Bernard Becker and Janet R. Becker Distinguished Professor in Ophthalmology
Washington University School of Medicine

Glen Prusky, Ph.D.
Director – Laboratory for Visual Disease and Therapy
Burke Neurological Institute

Tonia S. Rex, Ph.D.
Professor – Ophthalmology and Visual Sciences
Vanderbilt University Eye Institute

Tiffany Schmidt, Ph.D.
Associate Professor – Neurobiology
Northwestern University

Mohor Sengupta, Ph.D.ϕ
Health Science Policy Analyst
National Eye Institute, OPPA

Marc A. Sommer, Ph.D.
W. H. Gardner, Jr. Associate Professor – Biomedical Engineering
Duke University

Rachel Wong, Ph.D.
Professor, Chair – Biological Structure; Neuroscience
University of Washington, School of Medicine

DRAFT

David A. Leib, Ph.D.*
Professor – Microbiology and Immunology
Dartmouth University, Geisel School of Medicine

Jennifer E. Thorne, M.D., Ph.D.*
Chief – Division of Ocular Immunology
Johns Hopkins University School of Medicine

Sangeeta Bhargava, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Dong Feng Chen, M.D., Ph.D.
Associate Professor – Ophthalmology
Harvard Medical School

Elisabeth Cohen, M.D.
Professor – Ophthalmology
New York University Langone School of Medicine

Reza Dana, M.D., M.Sc., M.P.H.
Claes H. Dohlman Professor – Ophthalmology
Harvard Medical School

Andrew D. Dick, M.D.
Professor – Ophthalmology
University of Bristol

Maria Disotuar, Ph.D.ϕ
Postdoctoral Research Fellow
National Institute of Allergy and Infectious Diseases

Thomas Ferguson, Ph.D.
Professor – Ophthalmology and Visual Sciences
Washington University School of Medicine

Russell N. Van Gelder, M.D., Ph.D.†
Professor – Ophthalmology
University of Washington

Shefa Gordon, Ph.D.ϕ
Director – Office of Program Planning and Analysis
National Eye Institute

Phoebe Lin, M.D., Ph.D.
Associate Professor – Ophthalmology
Oregon Health and Science University

Daniel Martin, M.D.
Professor – Ophthalmology
Cleveland Clinic

George McKie, D.V.M., Ph.D., dip. A.C.V.O.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Jerry Niederkorn, Ph.D.
Professor – Ophthalmology
The University of Texas Southwestern Medical Center

H Nida Sen, M.D., M.H.Sc.ϕ
Lasker Clinical Research Scholar
National Eye Institute

Charles Wright, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Steven Yeh, M.D.
Professor – Ophthalmology
Emory University

DRAFT

Regenerative Medicine

Valeria Canto-Soler, Ph.D.*
Associate Professor – Ophthalmology
University of Colorado, School of Medicine

Jeffrey Goldberg, M.D., Ph.D.*
Blumenkranz Smead Professor and Chair – Ophthalmology
Byers Eye Institute at Stanford University

Steven M Becker, Ph.D.ϕ
Director, Office of Regenerative Medicine
National Eye Institute, ORM

Kapil Bharti, Ph.D.ϕ
Senior Investigator – Ocular and Stem Cell Translational Research Section
National Eye Institute

Katia Del Rio-Tsonis, Ph.D. †
Professor – Department of Biology
Miami University

Maria Disotuar, Ph.D.ϕ
Postdoctoral Research Fellow
National Institute of Allergy and Infectious Diseases

Shefa Gordon, Ph.D.ϕ
Director – Office of Program Planning and Analysis
National Eye Institute

Mark S. Humayun, M.D., Ph.D.
Professor – Ophthalmology
University of Southern California, Roski Eye Institute

Lisa Neuhold, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

James G. Patton, Ph.D.
Stevenson Professor – Department of Biological Sciences
Vanderbilt University

Rajesh C. Rao, M.D.
Leonard G. Miller Professor – Ophthalmology and Visual Sciences
University of Michigan, Kellogg Eye Center

Maryann Redford, D.D.S., M.P.H.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Amber Reed, B.P.H.ϕ
Program Specialist
National Eye Institute, ORM

Tom Reh, Ph.D.
Professor – Department of Biological Structure
University of Washington, School of Medicine

Mark I Rosenblatt, M.D., Ph.D., M.B.A., M.H.A.
Professor – Ophthalmology
University of Illinois, College of Medicine

Krishanu Saha, Ph.D.
Associate Professor – Biomedical Engineering
University of Wisconsin, Madison

Anna La Torre, Ph.D.
Associate Professor – Department of Cell Biology and Human Anatomy
University of California, Davis, School of Medicine

Marco A. Zarbin, M.D., Ph.D. †
Professor and Chair – Department of Ophthalmology & Visual Sciences
Rutgers University

DRAFT

Data Science

Michael F. Chiang, M.D.*ϕ
Former affiliation: Professor – Ophthalmology,
Oregon Health and Science University
Current affiliation: Director – National Eye Institute

Aaron Lee, M.D., M.Sc.*
Assistant Professor – Ophthalmology
University of Washington

Dennis M. Levi, O.D., Ph.D.ᵀ
Professor – Optometry and Vision Science
University of California, Berkeley

Farran Briggs, Ph.D., Sc.M.
Associate Professor –Neuroscience
University of Rochester Medical Center

Eric Buckland, Ph.D.
Founder and CEO
Translational Imaging Innovations

James Gao, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Kerry Goetz, M.S.ϕ
Director – Office of Data Science and Health
Informatics
National Eye Institute

Jonathan Haines, Ph.D.
Chair – Department of Population and Quantitative
Health Sciences
Case Western Reserve University

Zhihong (Jewel) Hu, Ph.D.
Senior Image Processing Research Engineer
Doheny Eye Institute

Paek-Gyu Lee, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Elizabeth Pike, J.D., L.L.M.
Associate General Counsel
Patient-Centered Outcomes Research Institute

Marylyn D. Ritchie, Ph.D.
Director – Center for Translational Bioinformatics
University of Pennsylvania, Institute for Biomedical
Informatics

Joel S. Schuman, M.D.
Director – NYU Langone Eye Center
New York University, Tandon School of Engineering

Ayellet V. Segrè, Ph.D.
Assistant Professor – Ophthalmology
Harvard University, Ocular Genomics Institute

H. Sebastian Seung, Ph.D.
Evnin Professor – Neuroscience
Princeton Neuroscience Institute

Kaushal Solanki, Ph.D.
Founder and Chief Executive Officer
Eyenuk, Inc.

Jerome R. Wujek, Ph.D.ϕ
Health Scientist Administrator, Retired
National Eye Institute, DESP

DRAFT

Individual Quality of Life

Ava K. Bittner, O.D., Ph.D.*
Associate Professor – Ophthalmology
University of California, Los Angeles

Lotfi B. Merabet, O.D., Ph.D., M.P.H.*
Associate Professor – Ophthalmology
Harvard University, Massachusetts Eye and Ear Institute

Kimberly R. Avila, Ph.D.
Assistant Professor
George Mason University

Rachel Bishop, M.D., M.P.H.ϕ
Health Science Policy Analyst
National Eye Institute

Audun Brunes, Ph.D.
Researcher
Norwegian Center for Violence and Traumatic Stress Studies

James Coughlan, Ph.D. †
Senior Scientist
Smith-Kettlewell Eye Research Institute

Donald Everett, M.A.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Mary Elizabeth Hartnett, M.D. †
Calvin S. and JeNeal N. Hatch Presidential Endowed Chair – Ophthalmology and Visual Sciences
University of Utah, Moran Eye Center

Gordon E. Legge, Ph.D.
Distinguished McKnight University Professor – Psychology
University of Minnesota

Susan A. Primo, O.D., M.P.H.
Professor – Ophthalmology
Emory University

L. Penny Rosenblum, Ph.D.
Director of Research
American Foundation for the Blind

Joan Stelmack, O.D., M.P.H.
Clinical Associate Professor – Ophthalmology
University of Illinois, College of Medicine

Bonnielin Swenor, M.P.H., Ph.D.
Associate Professor – Ophthalmology
Johns Hopkins University, Wilmer Eye Institute and Bloomberg School of Public Health

Cheri Wiggs, Ph.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

Mark E. Wilkinson, O.D.
Director –Vision Rehabilitation Service
University of Iowa, Carver Family Center for Macular Degeneration

Nora Wong, M.P.H.ϕ
Health Science Policy Analyst
National Eye Institute, OPPA

DRAFT

Public Health and Disparities Research

Susan A. Cotter, O.D, M.S.*
Professor – Optometry
Marshall B Ketchum University, Southern California College of Optometry

David C. Musch, Ph.D., M.P.H.*
Professor – Ophthalmology and Visual Science; Epidemiology
University of Michigan, Kellogg Eye Center

Eduardo C. Alfonso, M.D. †
Professor, Chair, and Director – Ophthalmology
University of Miami, Bascom Palmer Eye Institute

Megan E. Collins, M.D., M.P.H.
Assistant Professor – Ophthalmology
Johns Hopkins University, Wilmer Eye Institute & Berman Institute of Bioethics

Adam R. Glassman, M.S.
Director of Research Quality Assurance
Jaeb Center for Health Research

Kirk Greenway, M.A., M.P.H.
Principal Statistician and Director – Division of Program Statistics
Indian Health Service

Eve J. Higginbotham, S.M., M.D.
Professor and Vice Dean for Inclusion and Diversity – Ophthalmology
University of Pennsylvania, Perelman School of Medicine

Charlotte Joslin, O.D., Ph.D.
Associate Professor – Ophthalmology; Epidemiology and Biostatistics
University of Illinois College of Medicine

Janet L. Leasher, O.D., M.P.H.
Professor – Optometry
Nova Southeastern University College of Optometry

Jimmy Le, M.A., Sc.D.ϕ
Health Scientist Administrator
National Eye Institute, DESP

David J. Lee, Ph.D.
Professor – Public Health Sciences
University of Miami

Kevin Stroupe, Ph.D.
Acting Director – Center of Innovation for Complex Chronic Healthcare (CINCCH)
Department of Veterans Affairs

James C Tsai, M.D., M.B.A.
Professor, Chair, and Director – Ophthalmology
New York Eye and Ear Infirmary of Mount Sinai

Nora Wong, M.P.H.ϕ
Health Science Policy Analyst
National Eye Institute, OPPA

DRAFT

NEI Staff—Strategic Plan Coordination Team

Rachel Bishop, M.D., M.P.H.
Health Science Policy Analyst

Jennifer Burrell, B.A.
Staff Assistant – Office of the Director

Kerry Goetz, M.S.
Director – Office of Data Science and Health Informatics

Shefa Gordon, Ph.D.
Director – Office of Program Planning and Analysis

Amber Reed, B.P.H.
Program Specialist – Office of Regenerative Medicine

Mohor Sengupta, Ph.D.
Health Science Policy Analyst – OPPA

Nora Wong, M.P.H.
Health Science Policy Analyst – OPPA

Charles Wright, Ph.D.
Health Scientist Administrator –DESP

NEI Staff—Additional Content and Review

Neeraj Agarwal, Ph.D.
Health Scientist Administrator – DESP

Houmam Araj, Ph.D.
Health Scientist Administrator – DESP

Kathleen Andersen, Ph.D.
Director – Division of Extramural Activities

Brian P. Brooks, M.D., Ph.D.
Clinical Director– NEI

Emily Chew, M.D.
Director – Division of Epidemiology and Clinical Applications

Michael F. Chiang, M.D.
Director – NEI

Mary Frances Cotch, Ph.D.
Director – Office of Vision Health and Population Sciences

Ellen Liberman, Ph.D.
Health Scientist Administrator – DESP

Sheldon Miller, Ph.D.
Advisor to the NEI Director

Archana Mohale, M.S
Chief Information Officer—NEI

Jessica Ryan, B.A., M.B.A.
Chief – Management Policy and Analysis Branch

Lilly Sadler, B.S.
Senior Management Analyst – OAM

David Schneeweis, Ph.D.
Acting Director – Division of Intramural Research

Michael A. Steinmetz, Ph.D.
Director – Division of Extramural Science Programs

Brian Trent, M.P.A.
Executive Officer – NEI

Santa Tumminia, Ph.D.
Deputy Director – NEI

Maria Zacharias, B.A.
Director – Office of Science Communications, Public Liaison, and Education

DRAFT

Appendix 4: Acronyms

AGI	Audacious Goals Initiative
AI	Artificial Intelligence
AMD	Age-related Macular Degeneration
AO	Adaptive Optics
AoE	Area of Emphasis
AREDS	NEI Age Related Eye Disease Studies
BPN	Blueprint for Neuroscience
BRICS	Biomedical Research Informatics Computing System
CHW	Community Health Workers
CNS	Central Nervous System
Council	National Advisory Eye Council
CRCNS	Collaborative Research in Computational Neuroscience
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CVI	Cerebral (or Cortical) Visual Impairment
DEA	Division of Extramural Activities
DECA	Division of Epidemiology and Clinical Applications
DED	Dry Eye Disease
DEI	Diversity, Equity, and Inclusion
DESP	Division of Extramural Science Programs
DIR	Division of Intramural Research
DIVRO	NEI Diversity in Vision Research and Ophthalmology Program
DR	Diabetic Retinopathy
D-SPAN	Diversity Specialized Pre-doc to post-doc fellow Advancement in Neuroscience
eyeGENE	National Ophthalmic Disease Genotyping and Phenotyping Network
FDA	Food and Drug Administration
fMRI	Functional Magnetic Resonance Imaging
FISMA	Federal Information Security Management Act
FOA	Funding Opportunity Announcement
HCP	Human Connectome Project
HPR	High Program Relevance
IC	NIH Institutes and Centers
IOP	Intraocular Pressure
ipRGCs	Intrinsically Photosensitive Retinal Ganglion Cells
iPSC	Induced Pluripotent Stem Cell
IRP	Intramural Research Program
LASIK	Laser Assisted *In Situ* Keratomileusis
LCA	Leber Congenital Amaurosis
LGN	Lateral Geniculate Nucleus

DRAFT

ML	Machine Learning
MOSAIC	Maximizing Opportunities for Scientific and Academic Independent Careers
NASEM	National Academies of Sciences, Engineering, and Medicine
NEHEP	National Eye Health Education Program
NEI	National Eye Institute
NHP	Non-Human Primate
NSF	National Science Foundation
NYSCF	New York Stem Cell Foundation
OAM	NEI Office of Administrative Management
OCT	Optical Coherence Tomography
OCT-A	OCT-Angiography
OPPA	Office of Program Planning and Analysis
PET	Positron Emission Tomography
PHI	Protected Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
PNN	Perineuronal Nets
POAG	Primary Open-Angle Glaucoma
RFI	Request for Information
RGCs	Retinal Ganglion Cells
ROP	Retinopathy of Prematurity
RP	Retinitis Pigmentosa
RPE	Retinal Pigment Epithelium
SBIR	Small Business Innovative Research Program
STTR	Small Business Technology Transfer Research Program
TBI	Traumatic Brain Injury
VRP	Department of Defense Vision Research Program

3044
3045

DRAFT

3046

3047 # Acknowledgements; photo credits [pending]

3048

3049

DRAFT