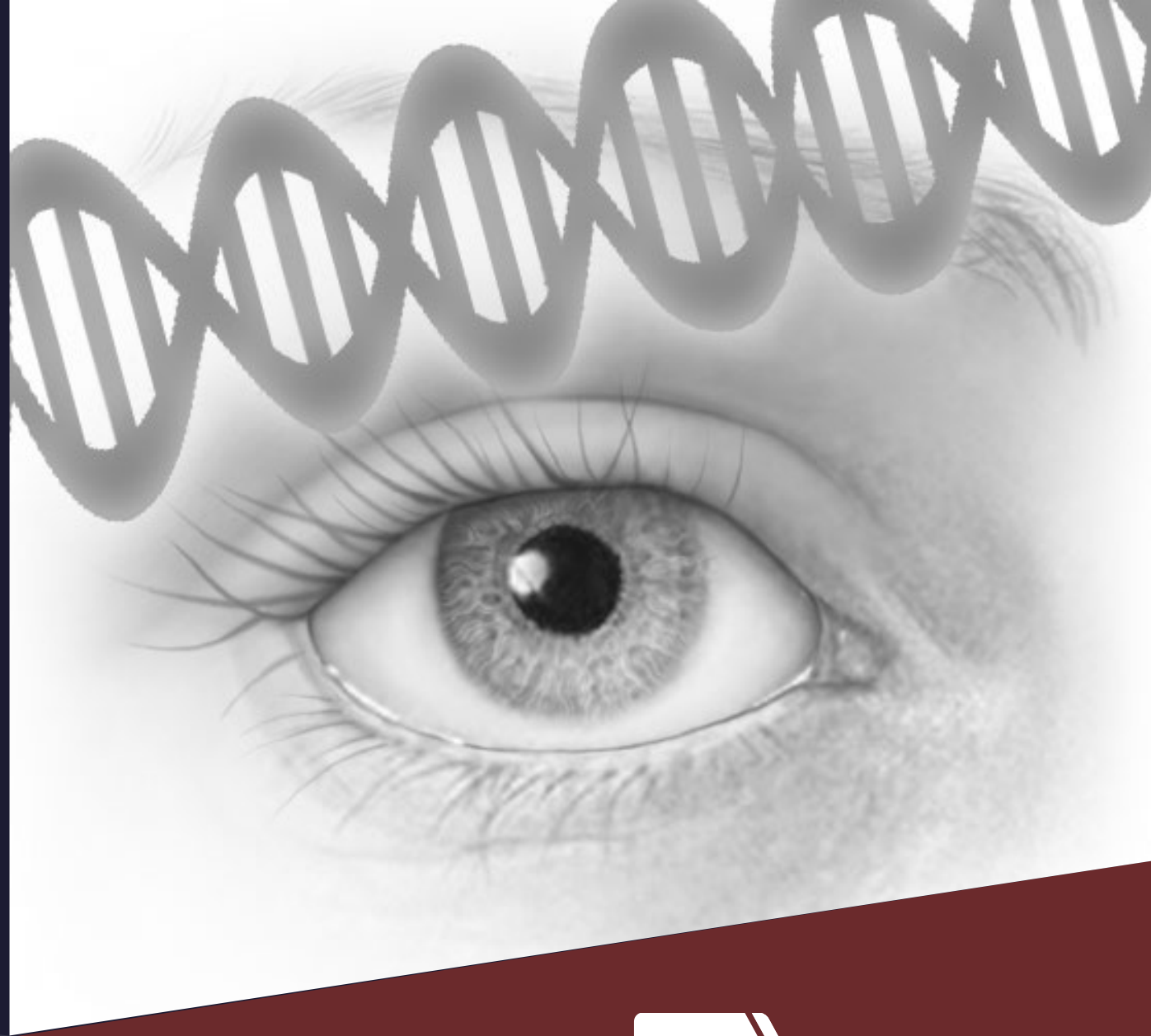
National Eye Institute
Research Today...Vision Tomorrow

Genomics, Genetics, and the Eye

Michael F. Chiang, M.D.
Director, National Eye Institute
National Institutes of Health
Twitter: @NEIDirector

National Advisory Council for Human Genome Research
September 13, 2021

About NEI



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What Was My Background?

- Applications of biomedical informatics to clinical care & research
- Telehealth (retinopathy of prematurity): validation → standard of care
- Artificial intelligence (ROP): FDA Breakthrough Status
- Genotype-phenotype correlation in ROP
- Data science & "big data":
  - Research program involving EHR implementation, design, efficiency
  - American Academy of Ophthalmology Medical Information Technology Committee: leadership role in national EHR implementation plan
  - AAO IRIS Registry: leadership role in development & implementation (now ~500M eye exams from ~80M unique patients)

Why Does Vision Work Matter?

- **Impact on quality of life**: blindness is among conditions that Americans fear most, work that matters
  - Daily living: driving, recognizing people, reading
  - How we experience the world, link to emotion
  - Risk of isolation, depression, acceleration of dementia
- **Impact on science**: enormous, broad
  - NEI: 8 Nobel Prize winners (initially Hubel & Wiesel)
  - Many seminal innovations occurred first in eye & visual system → accessible setting for generalizable research


Research

JAMA Ophthalmology | Original Investigation

Public Attitudes About Eye and Vision Health

Adrienne W. Scott, MD; Neil M. Bressler, MD; Suzanne Ffolkes, BA, MA; John S. Wittenborn, BS; James Jorkasky, MBA

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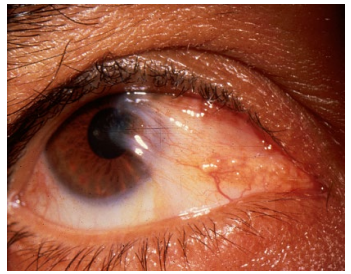
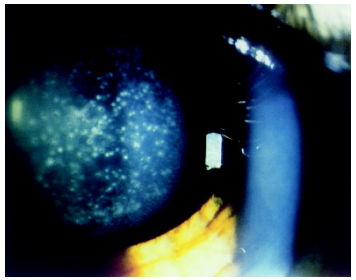
Public Health Challenges of Vision & Eye Care

- How many people are affected by vision problems?
  - **US**: 150M with vision limitation, 7.1M with low vision (≤20/40), 1.1M with blindness (≤20/200), annual economic burden $50B
  - **Global**: 250M with low vision (≤20/40) or blindness (≤20/200)
  - Increasing as population ages
- **Public health & economic impact** to society: lost productivity, falls, depression, accelerated dementia
- Eye disease: ranked 9th in **global disease** burden (after perinatal conditions, lower respiratory infections, HIV/AIDS, unipolar depressive disorders, diarrheal diseases…)

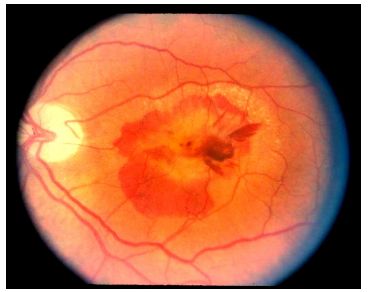
Pterygium



Cataract



Macular degeneration



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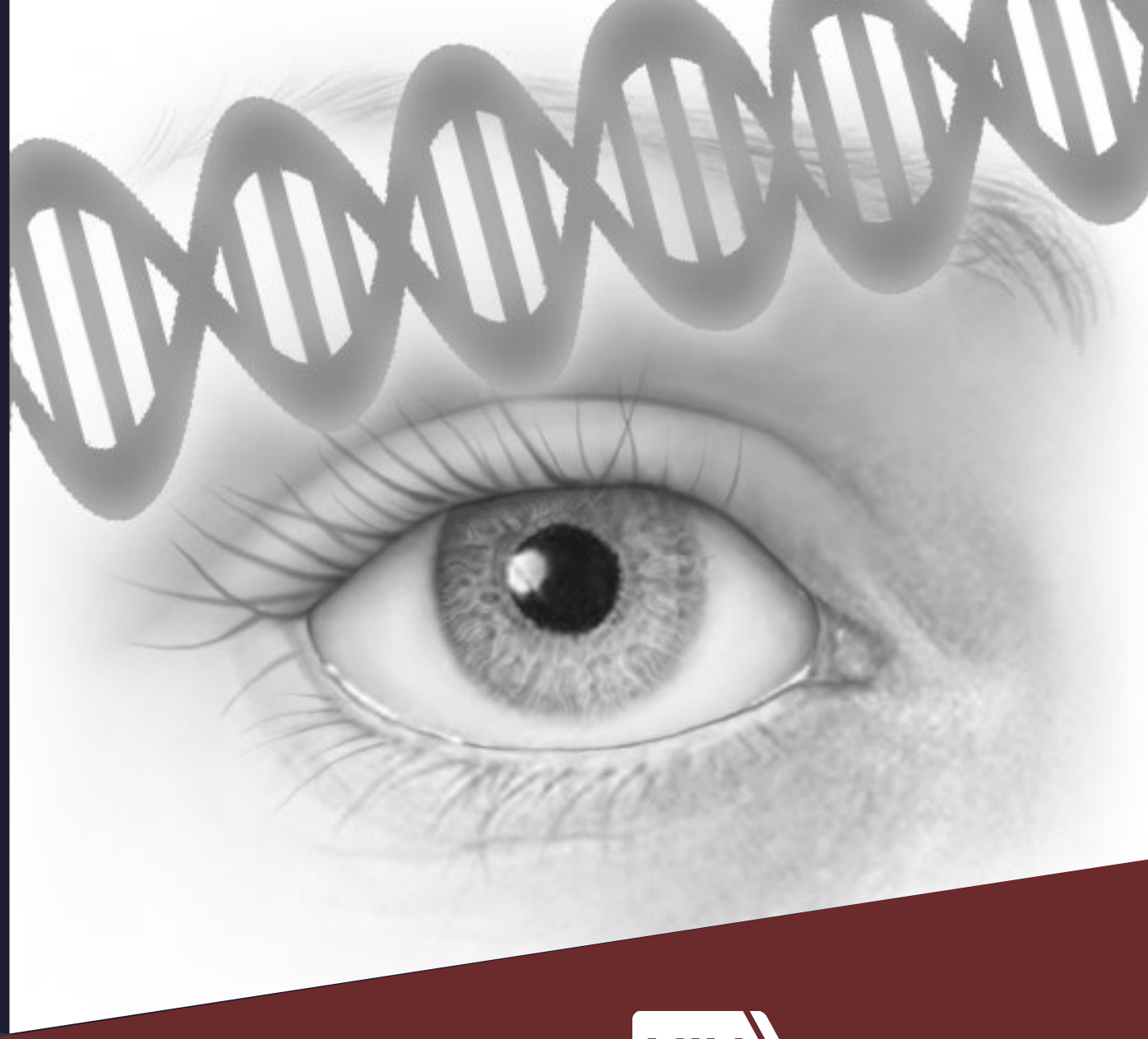
Eye Diseases Prevalence Research Group. Arch Ophthalmol 2004; 122:495-505.
Frick KD, et al. Arch Ophthalmol 2007; 125:544-50.
Flaxman AD, et al. JAMA Ophthalmol 2021 May 13:e210527.

Some of What We've Done: Genetics & Genomics



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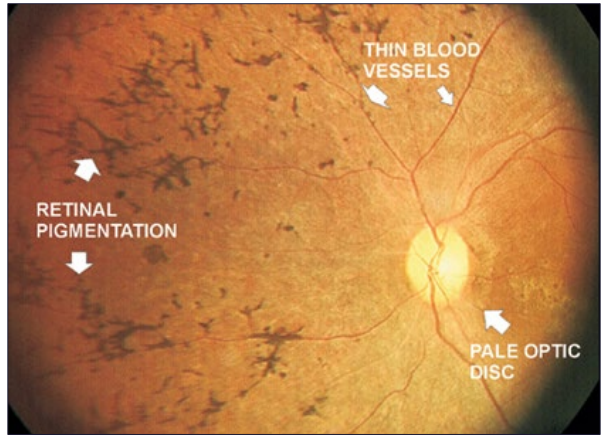
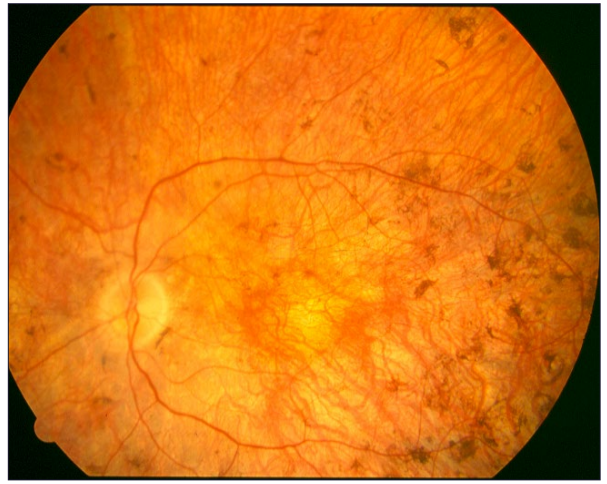
Innovation: Mendelian Disorders (Rare Retinal Dystrophies)

- Opportunities for collaboration in gene-based (in addition to morphological) nomenclature?

Pathway	Genes causing retinal dystrophy	Phenotypes
Phototransduction	CNGA1, CNGB1, GUCA1B, RHO, PDE6A, PDE6B, PDE6C, SAG, CNGB3	adRP, arRP, adMD, dCSNB, Oguchi disease, arCORD
Visual cycle	ABCA4, RGR, RLBP1, BEST1, IRBP, RPE65, CA4, RDH12, IDH3B, ELOVL4, PITPNM3, GUCY2D	adRP, arRP, arMD, adMD, arCORD, adCORD, arLCA, choroidal sclerosis
Phagocytosis of ROS	MERTK	arRP
Retinal development	CRX, NRL, NR2E3, SEMA4A, RAX2, PROM1, TSPAN12, TULP1, OTX2	adRP, arRP, adLCA, arLCA, adCORD, adMD, FEVR
Ciliary structure	CEP290, RP1, USH2A, CRB1, RP2, RPGR, RPGRIP1, LCA5, OFD1, MYO7A, USH1C, DFNB31, CDH23, PCDH15, USH1G, GPR98, BBS1-BBS10, TRIM32, BBS12, BBS13, AHI1	adRP, arRP, xlRP, arLCA, JS, BBS, USH, xlCORD, xlCSNB, MKS, LGMD2H, MKKS
Photoreceptor structure	RDS, ROM1, FSC2	adRP, digenic RP, adMD
mRNA splicing	HPRP3, PRPF8, PRPF31, PAP1, TOPORS	adRP
Others	ASCC3L1, SPATA7, EYS, KLHL7, RD3, KCNV2, RIMS1, CACNA2D4, ADAM9, CNNM4, TRPM1, CABP4, OFD1	adRP, arRP, arCOD, arLCA, adCORD, CORD, arCORD, JS





Innovation: Gene Therapy

- Infants with Leber Congenital Amaurosis (20 years ago): "we can provide supportive care"
- **First FDA-approved gene therapy for an inherited disease** → precision medicine (LCA – RPE65)
  - RPE65 gene cloning & knockout mouse (1993-1998, T. Michael Redmond, NEI)
- **First in-human CRISPR** gene editing (CEP290-driven LCA)
- **Accessibility of eye for exam, outcome measures, surgery**

Video courtesy of Jean Bennett, MD, PhD (University of Pennsylvania)
Russell S, Bennet J, Wellman JA, et al. *Lancet* 2017;390:849-60.

Gene Therapy Era

FDA NEWS RELEASE

FDA approves novel gene therapy to treat patients with a rare form of inherited vision loss

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For Immediate Release: December 18, 2017

Español

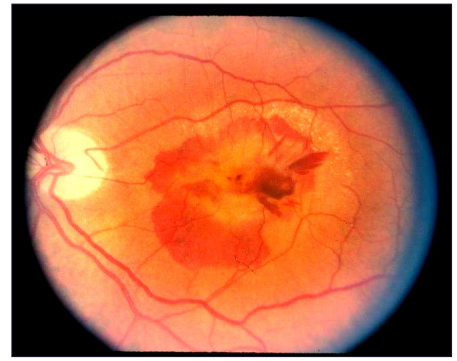
The U.S. Food and Drug Administration today approved Luxturna (voretigene neparvovec-rzyl), a new gene therapy, to treat children and adult patients with an inherited form of vision loss that may result in blindness. Luxturna is the first directly administered gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene.

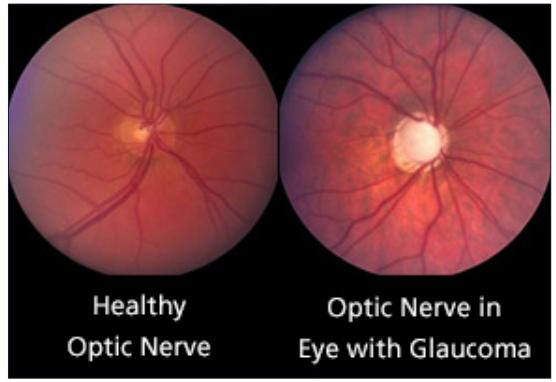
2021
***RPE65* added to the ACMG 3.0 secondary findings genes**

- ABCA4 – Stargardt disease
- CHM – X-linked choroideremia
- CNGA3 – Achromatopsia
- CNGB3 – Achromatopsia
- GUCY2D – Leber congenital amaurosis
- MERTK – Retinitis pigmentosa
- MYO7A – Usher syndrome
- PDE6B – Retinitis pigmentosa
- RLBP1 – Retinitis pigmentosa
- RPGR – X-Linked RP
- RPGRIP1 – Leber congenital amaurosis
- RS1 – X-linked retinoschisis
- USH2A – Usher syndrome (Dual vector, ASO)
- CEP290 – Leber congenital amaurosis (ASO, CRISPR)

Innovation: Complex/Common Disorders

- Age-related macular degeneration (AMD)
  - Degeneration of the retina that occurs during aging ("wet" or "dry"): loss of retinal pigment epithelium (RPE) & subsequently photoreceptors
  - 2005: **GWAS** → link between Complement Factor H (CFH) and AMD (accounts for 40-50% of disease risk)
  - AMD consortia & subsequent studies (some co-funded by NHGRI): numerous additional loci, many tied to complement
- Glaucoma: progressive degeneration of optic nerve
  - NEIGHBORHOOD Consortium: international consortium co-funded by NEI, NHGRI, and others → found >133 loci linked to high IOP risk and glaucoma (European, Asian, African ancestries)
- Fuchs' corneal dystrophy: leading cause of corneal transplant
  - GWAS: 4 loci (78% of disease risk)





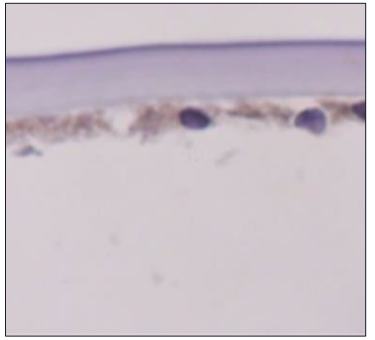


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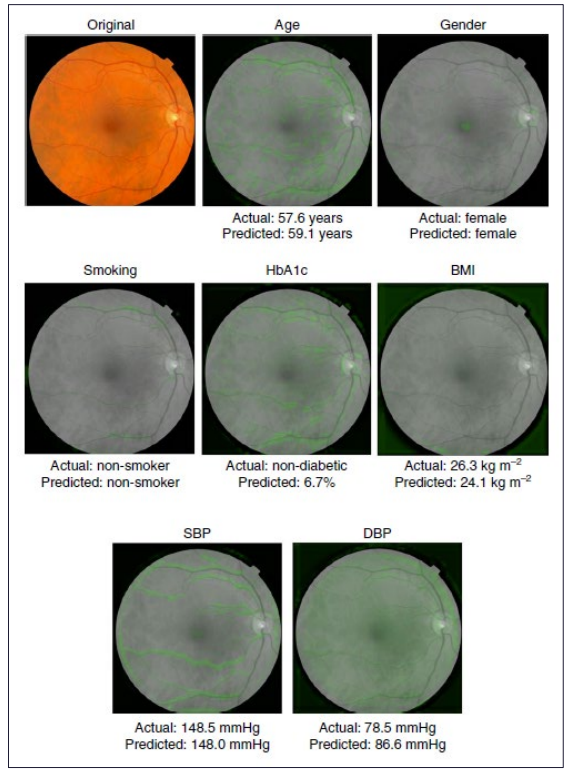
Image from Glaucoma Research Foundation
Klein at al. Science 2005; 308:385-9.

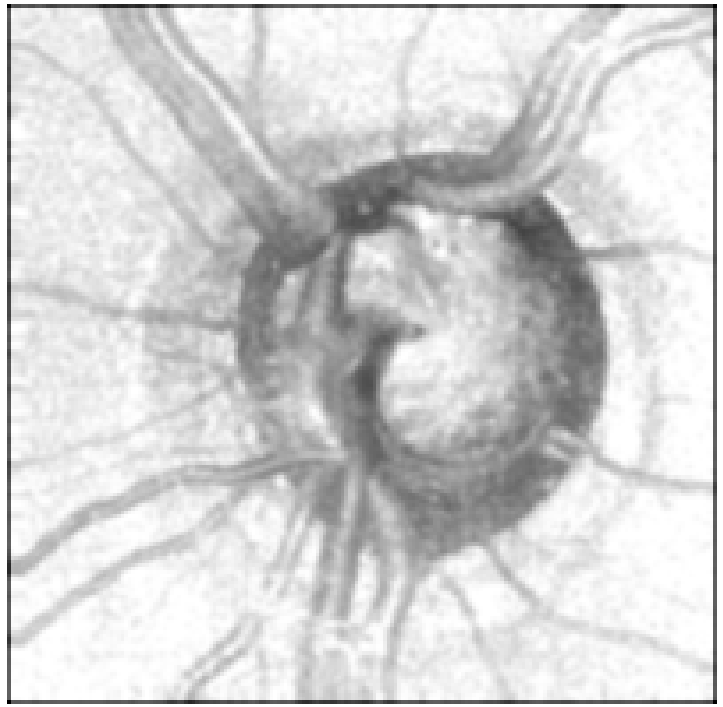
Innovation: Artificial Intelligence for Medicine

- **First FDA-cleared autonomous AI system in any medical field** (Abramoff et al, NPJ Digit Med 2018)
- Knowledge discovery regarding systemic health (Poplin et al, Nat Biomed Eng 2018)
- Prediction of AMD progression (Yim et al, Nat Med 2020)



Eye as a Model System: Imaging

- **Retinal photography** (e.g. ETDRS: standardized diabetic retinopathy reading centers, in use since 1968)
- **OCT**: revolution in research & clinical care, **qualitative to quantitative**
- High-speed Fourier-domain OCT → to 3D volumetric imaging
- **OCT Angiography**: noninvasively detect flow & motion, capillary-level resolution, potential to generalize across other fields (structure & function)



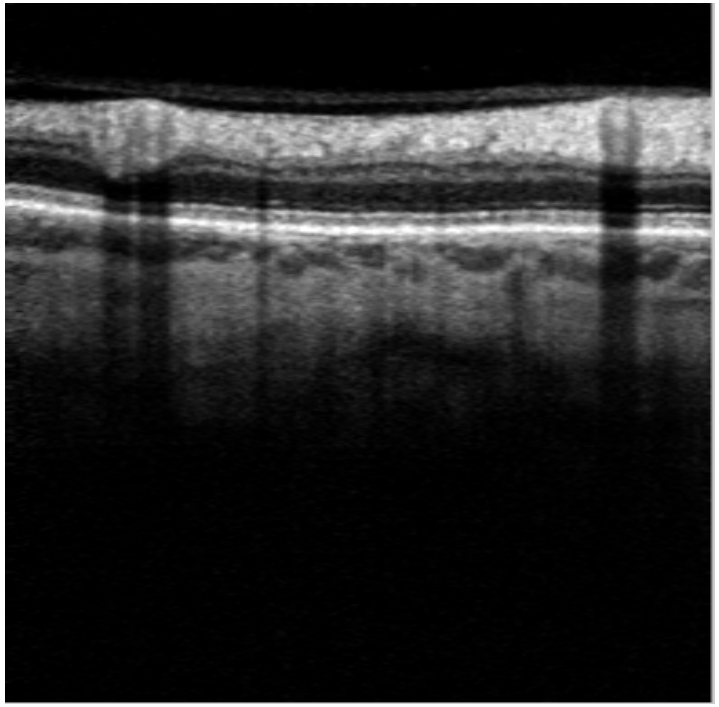
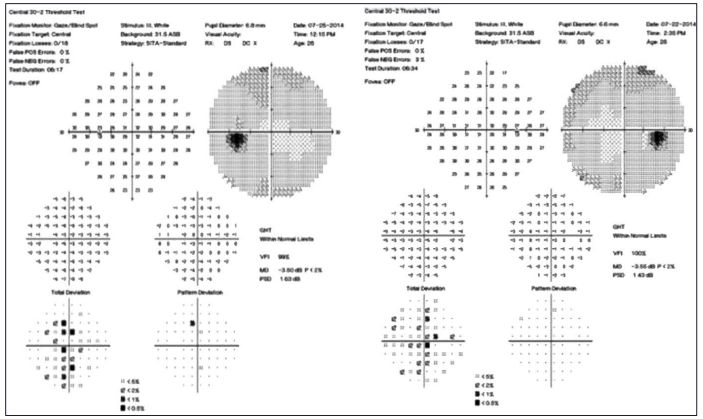


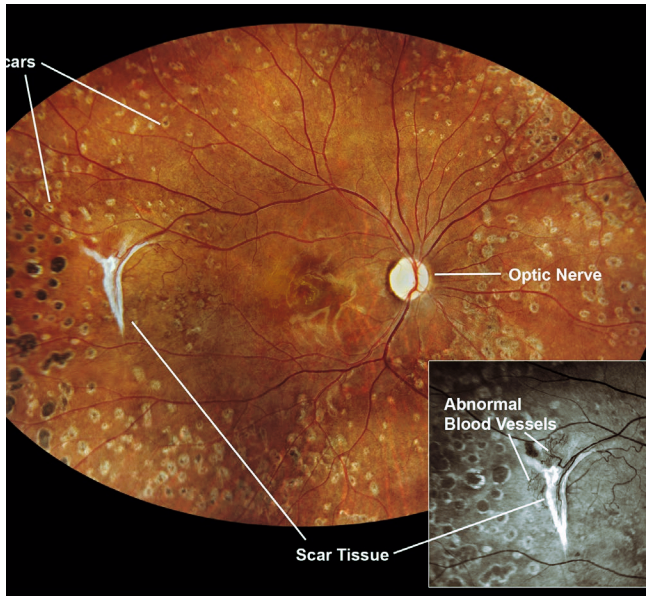
Image and video courtesy of David Huang, MD, PhD, and Yali Jia, PhD (OHSU Casey Eye Institute)

Windsor MD et al. *Am J Ophthalmol* 2018; 185:115-22
Hormel TT, et al. *Prof Retin Eye Res* 2021 Mar 22:10965

Eye as a Model System: Functional Data & Accessibility

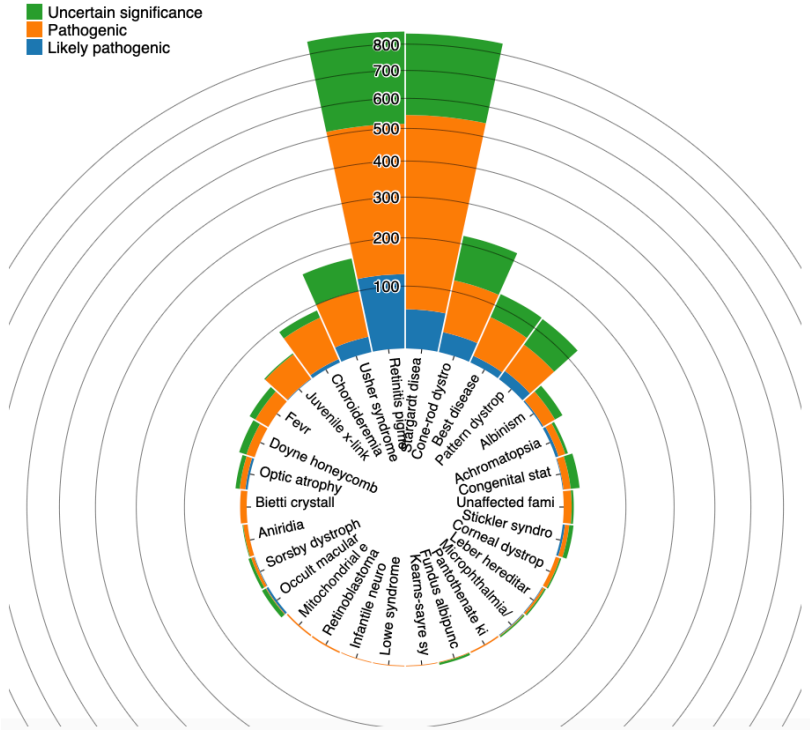
- Functional outcome measures (quantitative, validated):
  - Visual acuity
  - Perimetry & microperimetry (retinal function & vision loss in periphery), contrast & color sensitivity
  - Maze tests
- Accessibility for study
  - Retina as part of the brain: neurodegerative diseases like Alzheimer's can be detected in the eye
  - Vasculature in choroid & retina: changes in vasculature from diseases like diabetes can be measured
  - Immunology in the eye: noninfectious uveitis (form of immunity)
  - Cell-based and gene-based therapies: complex tissues are accessible & trackable





eyeGENE®: NEI Genetic repositories

- National network of ophthalmic CLIA-certified laboratories, private and academic clinical organizations and their patients, and the vision research community
  - Centralized **diagnostic genotyping** for patients & research
  - **Research repository**: DNA/tissue coupled to anonymous phenotypic information for discovery research
  - **Database resource**: phenotype information (clinical data, images, lab data) for disease research and future opportunity for trials participation
  - Increase public & professional **awareness**: value of diagnostic genetics for ophthalmic medical care



National Ophthalmic Disease Genotyping Network
eyeGENE®

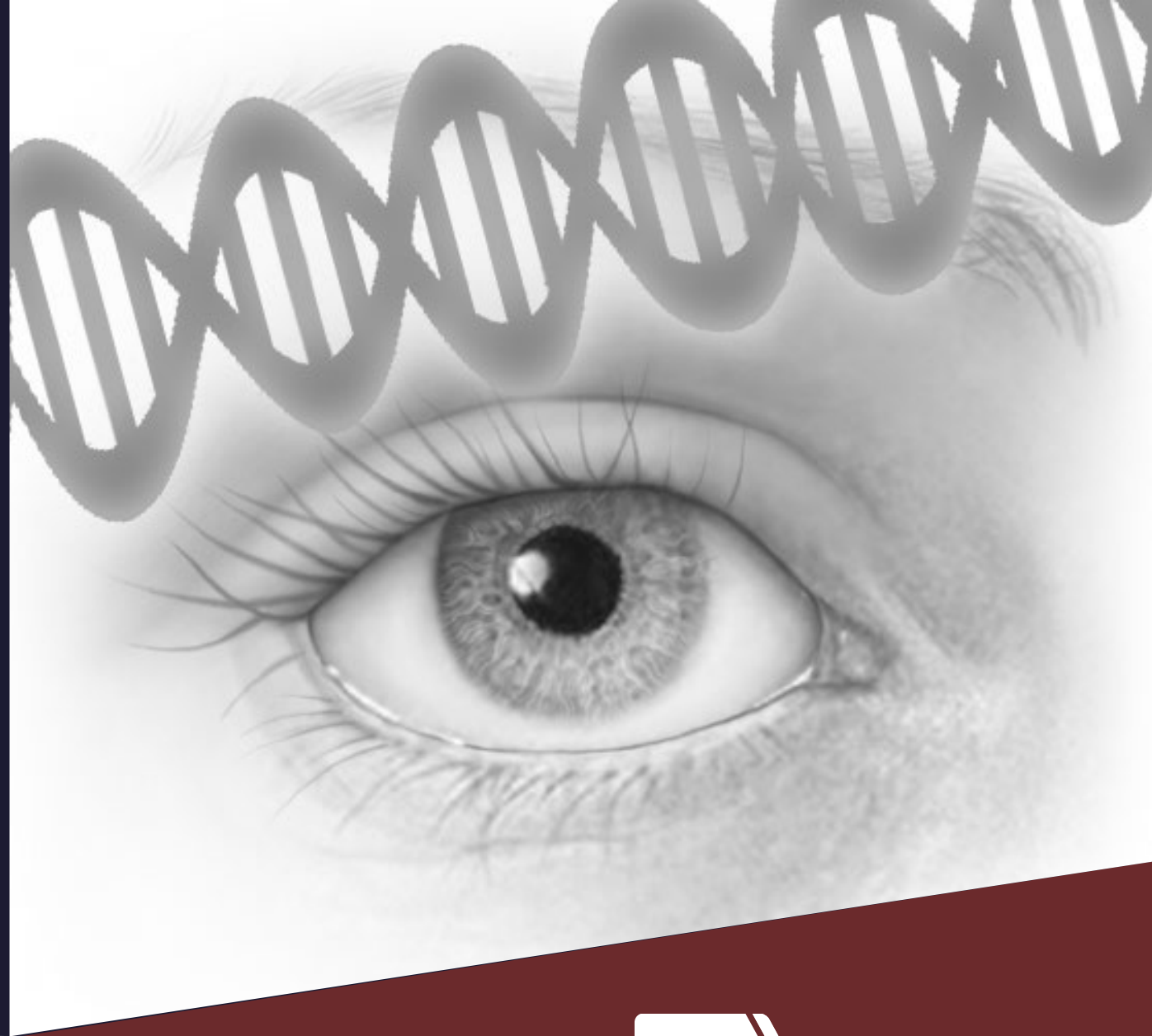
Rob Hufnagel, M.D., Ph.D.

Kerry Goetz

NIH National Eye Institute

https://eyegene.nih.gov

Where We're Heading: Strategic Plan, Potential Collaborations with NHGRI



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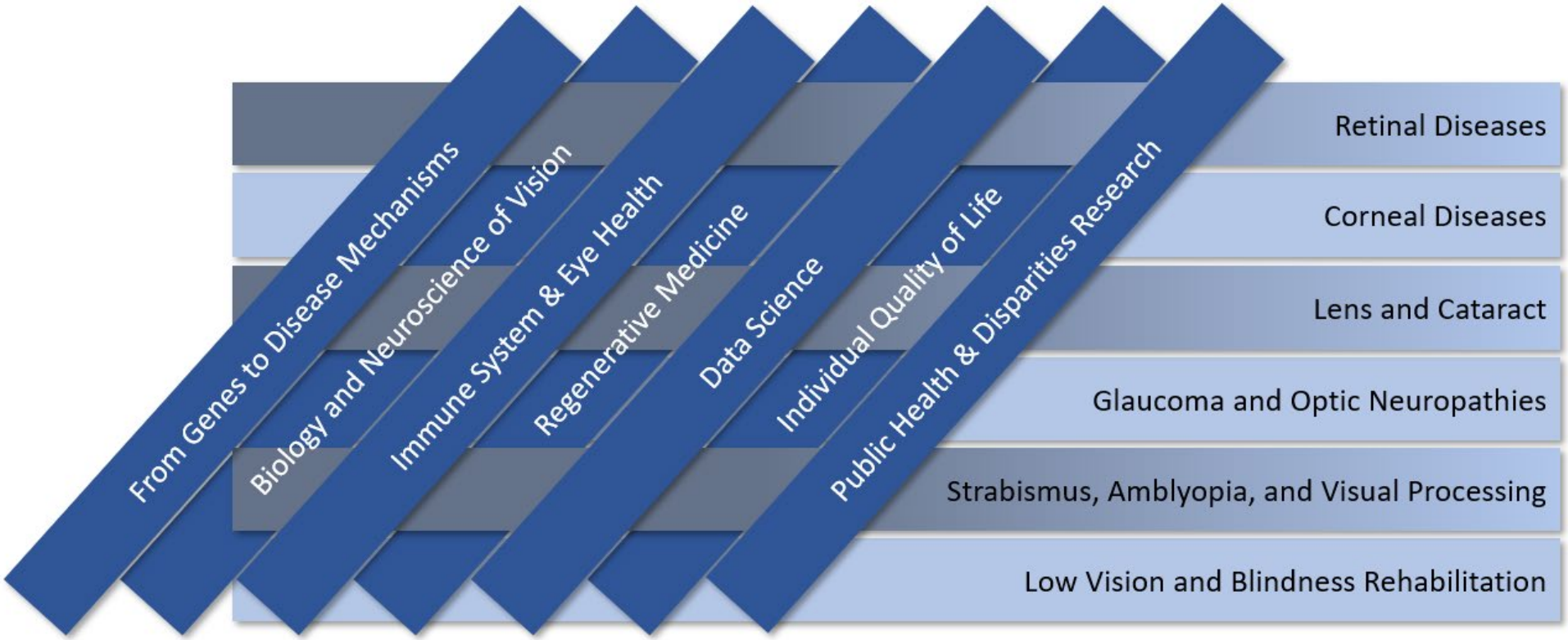
Revised NEI Mission Statement: First Since 1968

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 require vision rehabilitation
- 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.

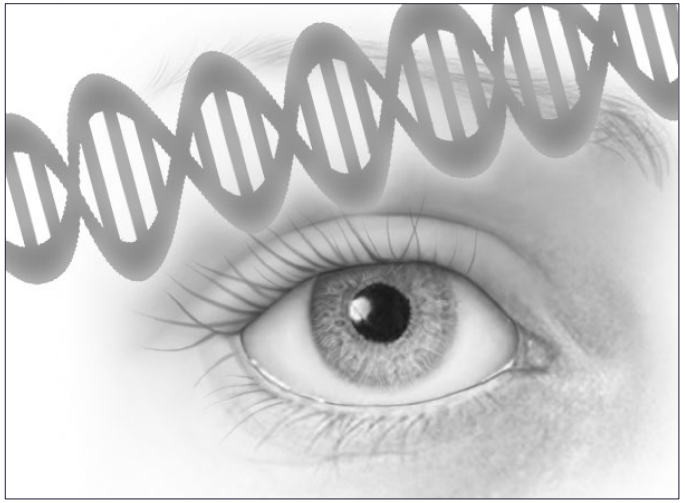
NEI Strategic Plan (Coming Nov 2021)

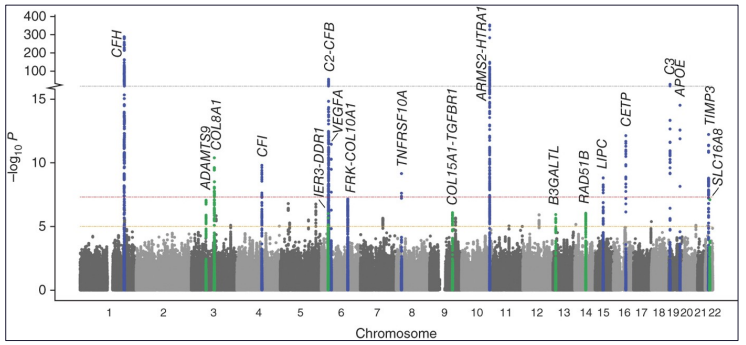
7 Cross-Cutting Areas of Emphasis



Mendelian vs. Complex Genetic Diseases

- Thousands of known genetic mutations causing eye disease
- Mendelian Eye Diseases: single mutation, typically rare
  - Underlying disease biology → therapeutics
- **Common Eye Diseases**: typically complex, often interaction of **multiple genes & environmental factors**
- Innovation: Genome-Wide Association Studies → risk factors & risk alleles for common eye diseases
  - AMD: Complement Factor H variant → increased risk 7.4x, role of immune system in AMD pathogenesis
  - AMD consortia: 34 loci with 52 independent variants
  - Yet little success from clinical trials to block complement pathway → **must understand biological mechanisms to develop therapies**





AMD Gene Consortium. Nat Genetics 2013; 45:433-9

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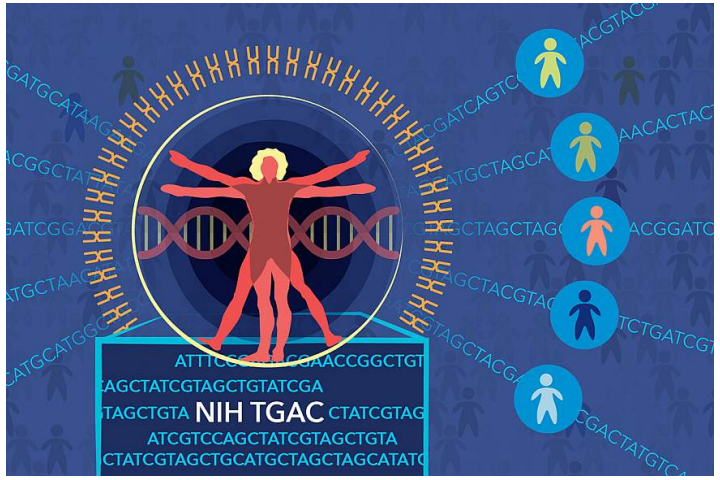
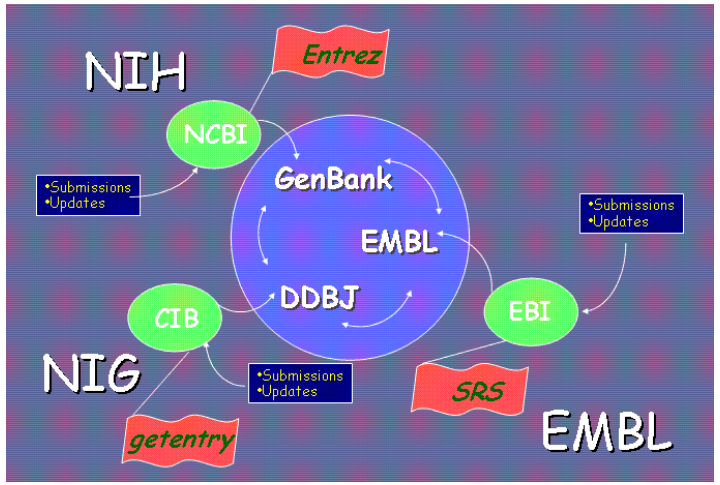
Opportunity: Large-Scale Curated Databases

- Understanding complex systems interactions: need **research networks & databases**
  - Publicly-available genomic, transcriptomic, epigenetic databases → under-representation of ocular tissue data
- Need: curate databases to **publicly share data** & establish **standard data representations**
  - Multi-omics analysis: identify new pathogenic mutations in disease genes, help understand mechanisms
  - Combine results from multiple smaller studies
- Need: **bioinformatics & machine learning algorithms** to aid genetic discovery & analysis
  - Examples: analysis of WES, epigenetics, gene transcription network identification (ChIP-seq), metabolomics, proteomics





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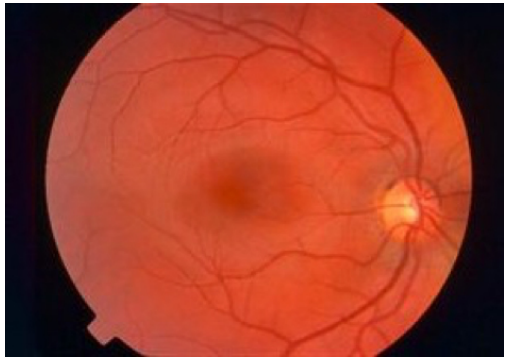
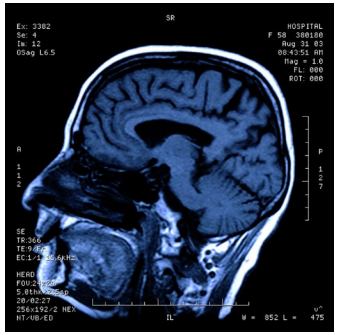
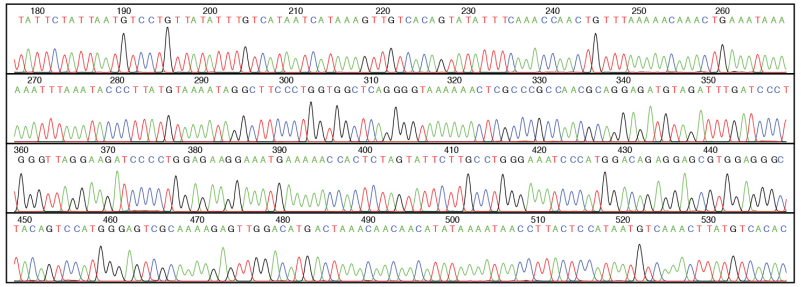
Challenge: Privacy and De-Identification

- Large research infrastructure based on data sharing
- **Are retinal images biometrics?**
  - HIPAA PHI: "biometric identifiers (e.g., retinal scans, fingerprints)…"
  - In practice: considered de-identified (e.g., journal publications), but evolving (e.g., GDPR)
  - What about radiological images? Genetic sequence data…?
  - Benefits of "objective" data (e.g. images, genetics): anchor subjective data (e.g. EHRs, racial/gender bias, social determinants of health)
- **Need: domain consensus about privacy risks vs. research/societal benefits**
  - Ocular image WG (Chairs: Emily Chew [NEI], Joel Schuman [NYU]
  - **Role of collaboration with genomics community?**







DNA sequence data from an automated sequencing machine

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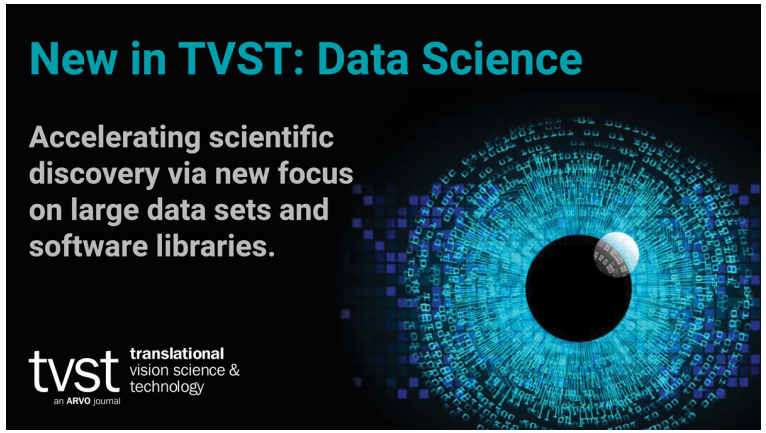
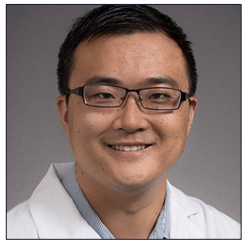
Datasets & Software Libraries: Why Share?

- **Advancement of science** through data/code re-use, re-analysis, development of new methodologies
  - Improved data quality through iterative review by others
  - Facilitate community **standards for data representation**
- **Strengthen field** → best scientists will be drawn to best datasets for analysis
- **NIH Data Sharing Policy (Jan 2023)**: need explicit plan
- Other **incentives** for data sharing ("carrot")
  - **New publication type**: academic credit, citations, findable
  - How to effect gradual culture shift in community? Promotion & tenure? Other ways to promote value to data sharing & harmonization?





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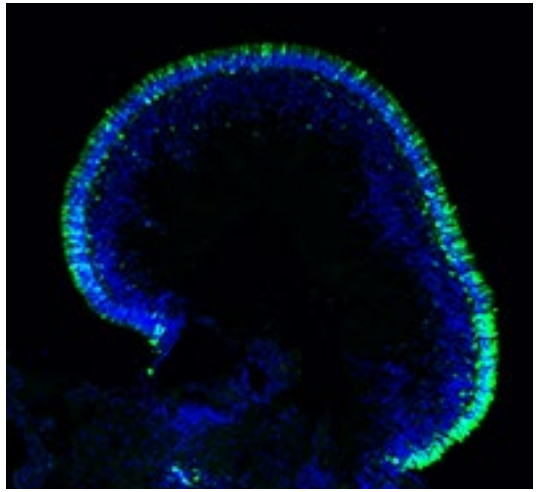
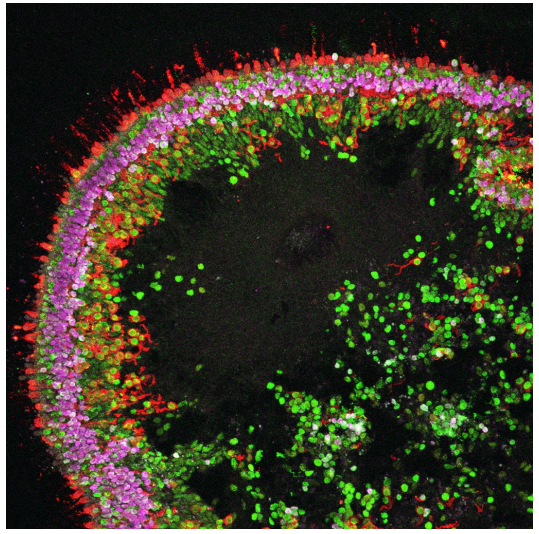
https://grants.nih.gov/grants/policy/data_sharing/

Zarbin MA et al. Trans Vis Sci Technol 2021, Vol. 10, 20.doi: https://doi.org/10.1167/tvst.10.8.20

Opportunity: Model System Development

- Well-defined animal & cell-based model systems: essential for basic and translational research
- Animal models: often do not represent unique attributes of primate retina and visual cortex
  - **Need to address gaps in animal models** (e.g. fovea: cones)
  - **Need methods for temporal & spatial control of gene expression** to study connections between genes & disease mechanisms (e.g. optogenetics)
- Human cell-based models (e.g., iPSCs, 3D organoids): often lack systems-level complexity of animal models
  - **Need standards & best practices for developing cell-based models**





Images courtesy of Anand Swaroop (NEI) and David Gamm (Wisconsin)

Topics for Discussion

- Importance of genetics, genomics, data science for NEI strategic plan
- Potential areas for collaboration…
  - Development of gene-based (as opposed to purely morphological) nomenclature for ophthalmic genetic diseases
  - Infrastructure & guidelines for public data sharing
  - Development of standard data representations for data sharing
  - Incentives for data sharing (e.g. publications, promotion & tenure, team science)
  - Data privacy: guidelines & best practices
  - Others?