

Innovative Approaches to Research to Care

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“Game Changers in Vision”

Innovative Approaches to Research to Care

2015 Focus on Eye Health National Summit

Prevent Blindness

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Presented by

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Age-related Macular Degeneration



One American becomes blind every 11 minutes, the largest proportion of these due to age-related macular degeneration (AMD), the leading cause of irreversible blindness in Americans over the age of 55



Age-related Macular Degeneration

United States & Europe

- ~20 million with AMD
(>50 million worldwide)
- ~3-4 million with advanced disease
- Prevalence will increase to ~30 million by 2020
- A large proportion of the healthcare budget for visual impairment is spent on AMD
(\$343B/year; \$255B/year is direct care)

*Taylor et al 2004; Coogan et al 2004; Garnett et al 1999;
<http://www.rightdiagnosis.com> 2015*



Age-related Macular Degeneration

Personal 'Costs'

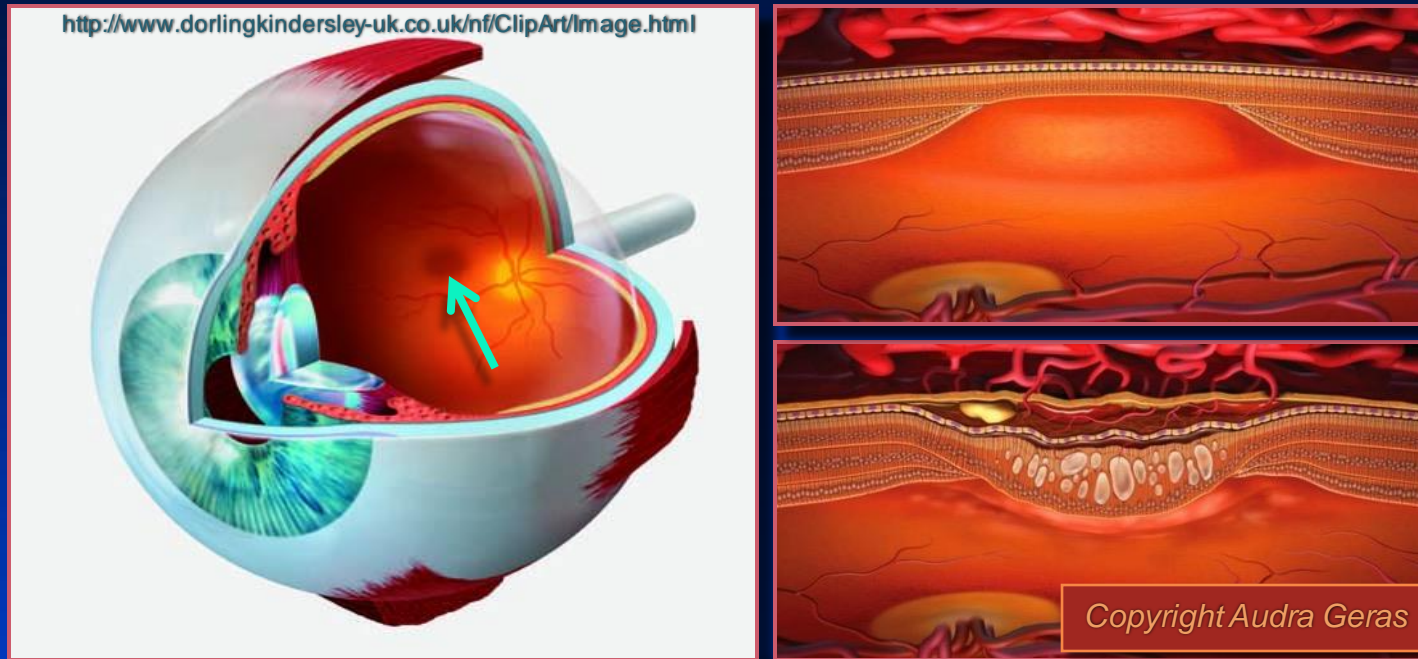
The consequences for those affected are real!!

- Loss of independence
 - Anxiety
 - Depression
 - Social isolation
- Visual hallucinations
- Premature mortality

Unacceptable!

Age-related Macular Degeneration

The Macula

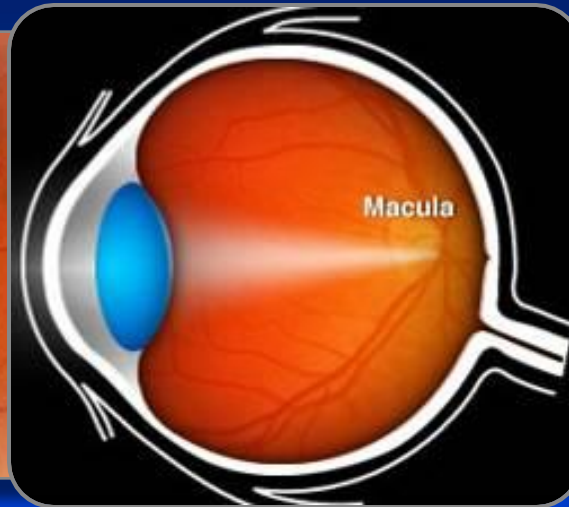


The macula -- a highly specialized region of the retina responsible for fine acuity vision -- is predilected for degeneration in AMD

Age-related Macular Degeneration

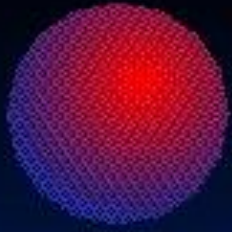
- Diagnosed at its earliest stages by the deposition/appearance of drusen, a hallmark clinical risk factor of the disease

*Early -
“Dry”*



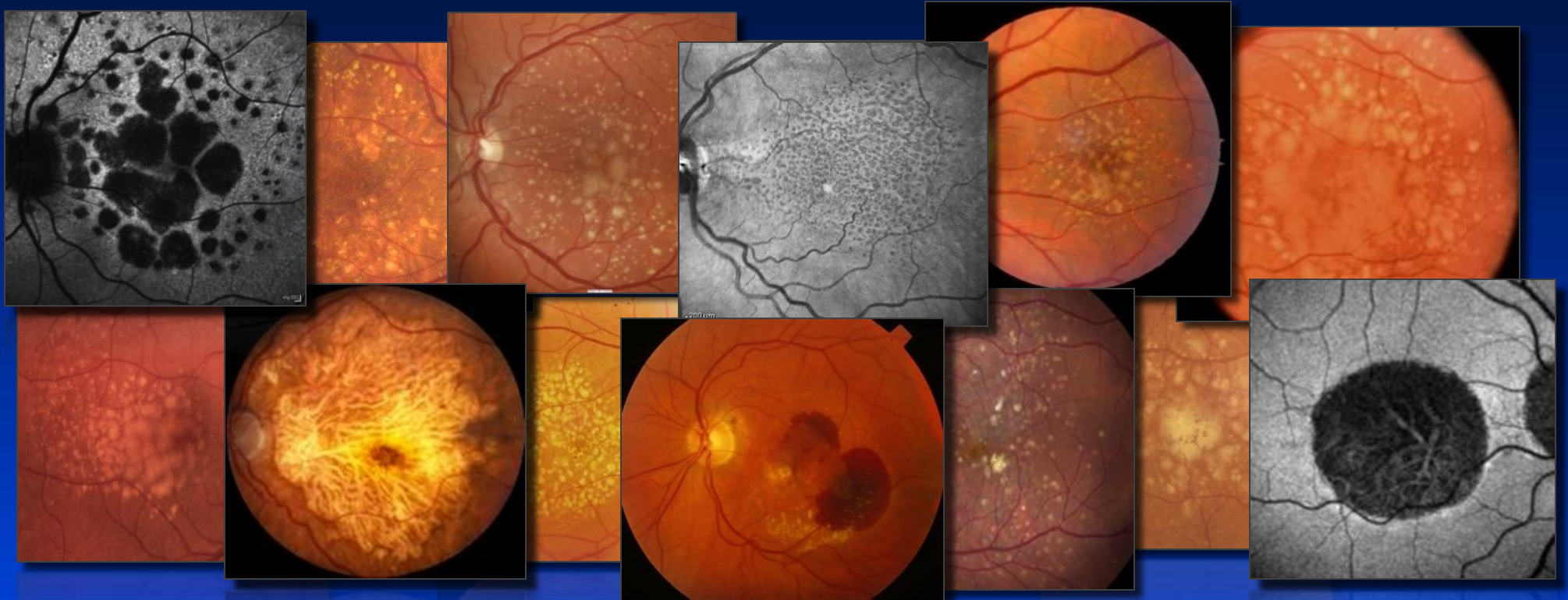
*Late -
“Wet”*

- Progresses to late stage disease in ~20-25% of individuals with early stage disease



Age-related Macular Degeneration

AMD Phenotypes



Diverse clinical phenotypes of both early-stage ('drusen') & late-stage (GA, CNV, PCV, RAP) AMD exist



Research to Treatments

Game Changers: Overview

Goal

- To gain a robust understanding of AMD disease biology in order to identify disease-associated pathways & druggable targets

Game Changers


- Resources (eyes, patients, data)
- Teams (multidisciplinary, dedicated, focused)
 - Partnerships (expertise; shorten time from bench to bedside)

John A. Moran Eye Center

Center for Translational Medicine



The major focus of the CTM is being directed toward the 'identification & validation' of therapeutic targets for early stage AMD & its co-segregating diseases



Research to Treatments

Game Changers: Resources

- Patient-based cohorts & resources

- ✓ AMD case-control, prospective, family-based & population-based cohorts
 - access to >85,000 DNA samples
- ✓ Utah Population Database (UPDB) & Electronic Data Warehouse (EDW)
 - ✓ LDS genealogical archives
 - ✓ CMS records
 - ✓ CEPH & Human Genome Project cohorts
- ✓ Other disease cohorts (e.g. Intermountain Healthcare cardiovascular)

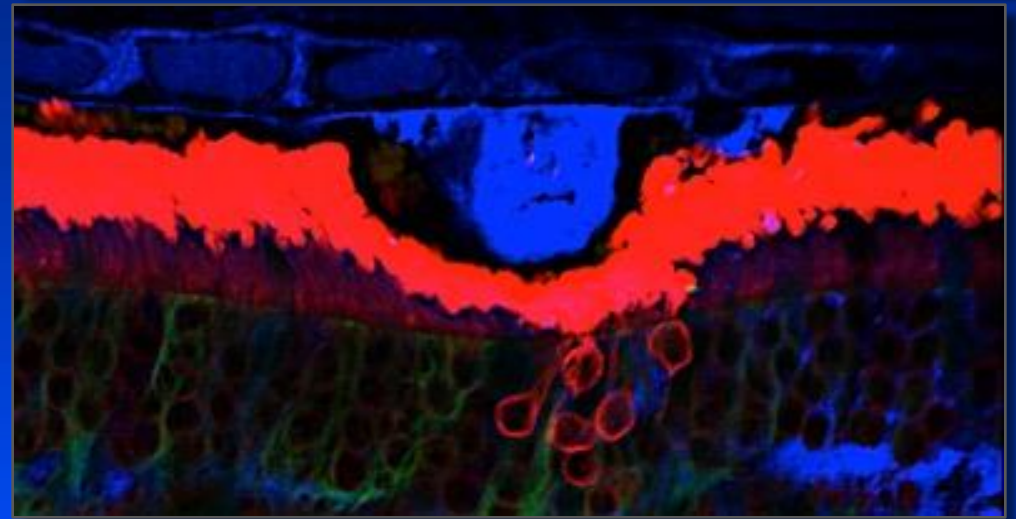
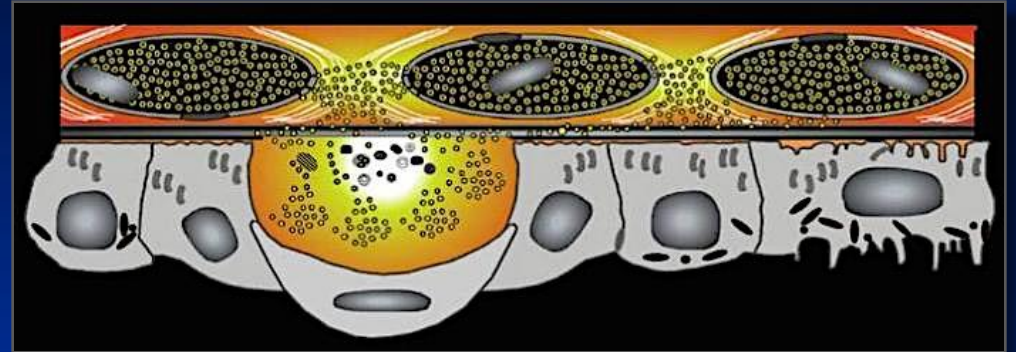
- Donor eye & tissue repository

- ✓ >6,500 pairs from well characterized donors
(ascertain ~1 donor/day; blood from all Utah organ donors)
 - ✓ Medical & ophthalmological data
 - ✓ Sera, plasma, urine & other tissues
 - ✓ Many diseases represented

AMD & Complement

A Major AMD-associated Pathway Revealed

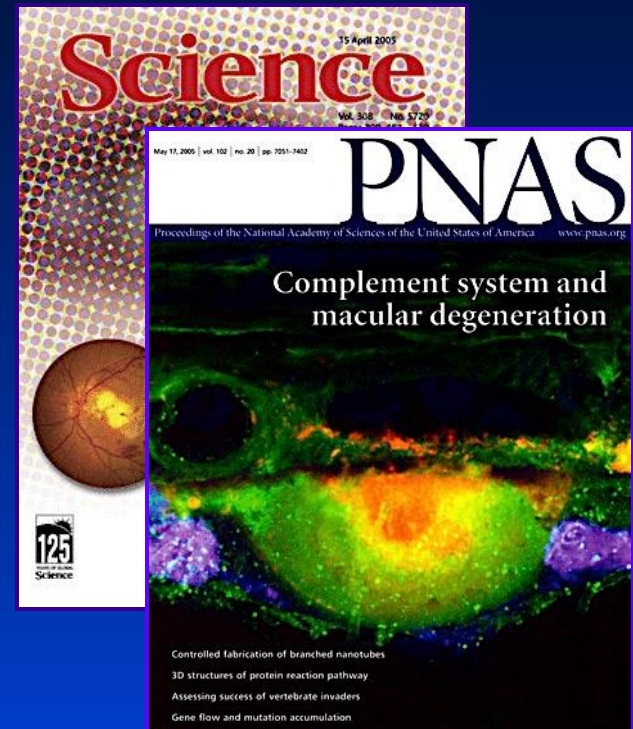
- *Guiding Concept:* Analyses of drusen in **human donor eyes** might provide insights into AMD-associated pathways
- This approach revealed that the complement system -- an important pathway in the immune system -- is abnormal in AMD



AMD-associated Genes

The First AMD-associated Gene is Identified

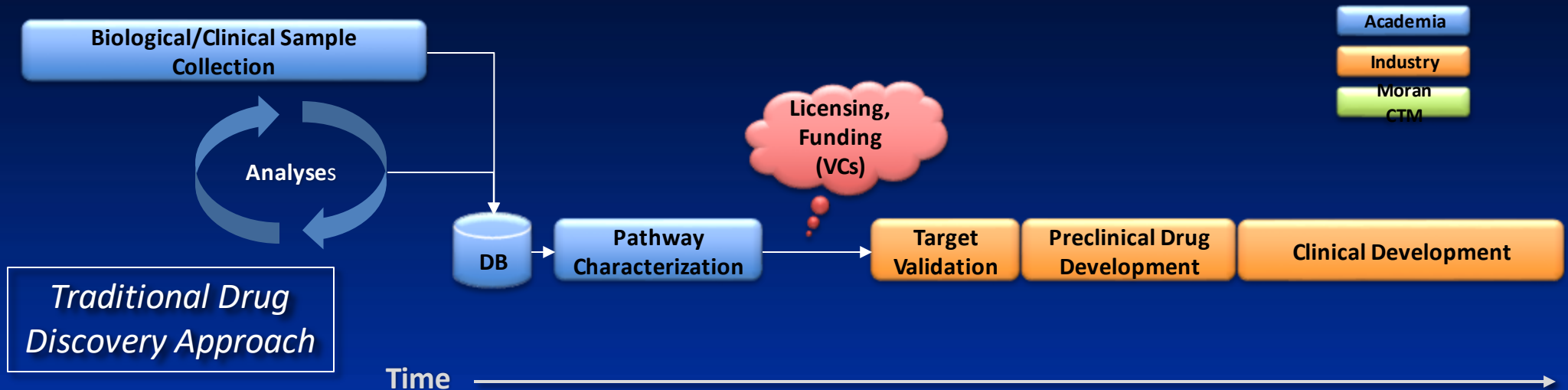
- This discovery -- & the use of human patient DNA samples -- led directly to identification of the first major AMD-associated gene
- A second major gene was discovered a year later
- These two genes account for greater than 85% of all risk for developing AMD



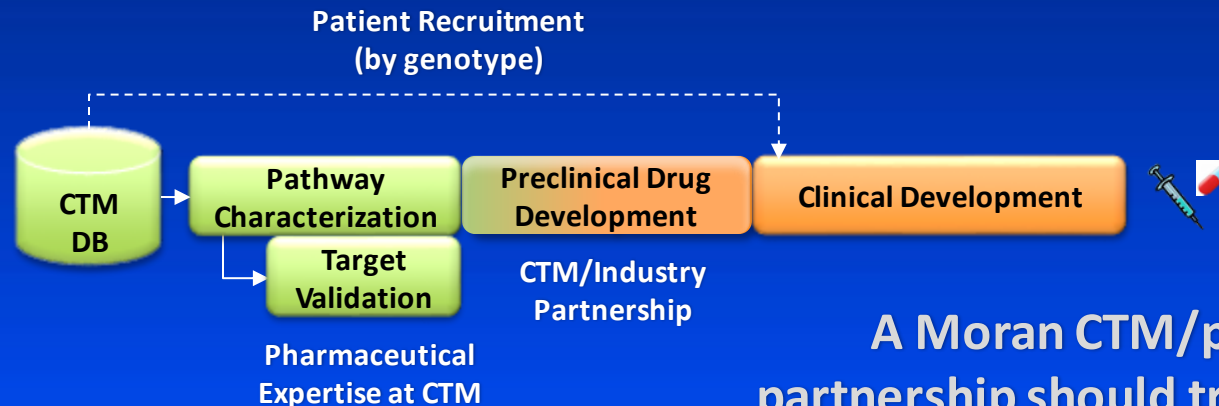
Hageman, et al., *PNAS USA* 30, 2005
Edwards, et al., *Science* 308, 2005
Haines, et al., *Science* 308, 2005
Klein, et al., *Science* 308, 2005

Research to Treatments

Game Changers: Teams & Partnerships



- Talented Team
- Unique Biological & Clinical Resources
- Novel Scientific Discoveries
- Intellectual Property
- Strong Collaborations
- Finances

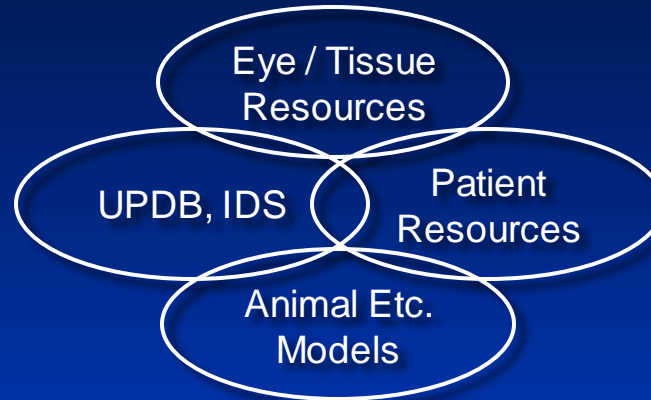


Moran CTM/Industry Approach

A Moran CTM/pharma partnership should trim years off the drug development timeline

Drug Target Identification Strategy

Genetics: Chr1 & Chr10



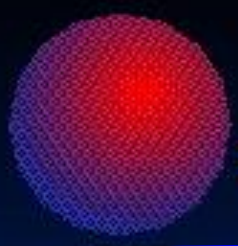
Pathways & Druggable Targets



Chr1- & Chr10-directed Biology

- Assessment of the independent contributions of Chr1 & Chr10 loci to AMD etiology has provided a refined understanding of AMD
 - Importantly, this approach has:
 - ✓ Provided robust evidence that AMD is multiple, distinct biological diseases
 - ✓ Allowed for the identification of critical pathways, targets & novel therapeutic strategies for the treatment of chromosome 1- & chromosome 10-mediated AMD

AMD is Multiple Distinct Diseases



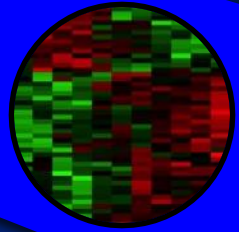
Ocular



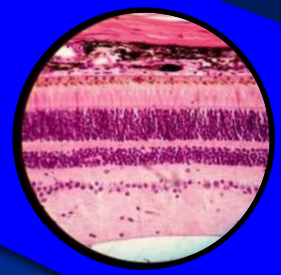
Genetic



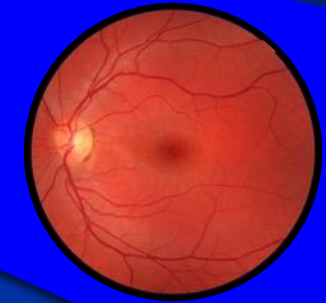
Mechanistic



Gene Expression



Histologic

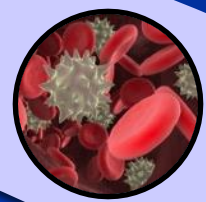


Clinical

Systemic



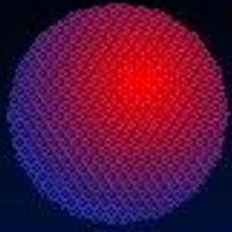
Biomarkers



Blood Cells



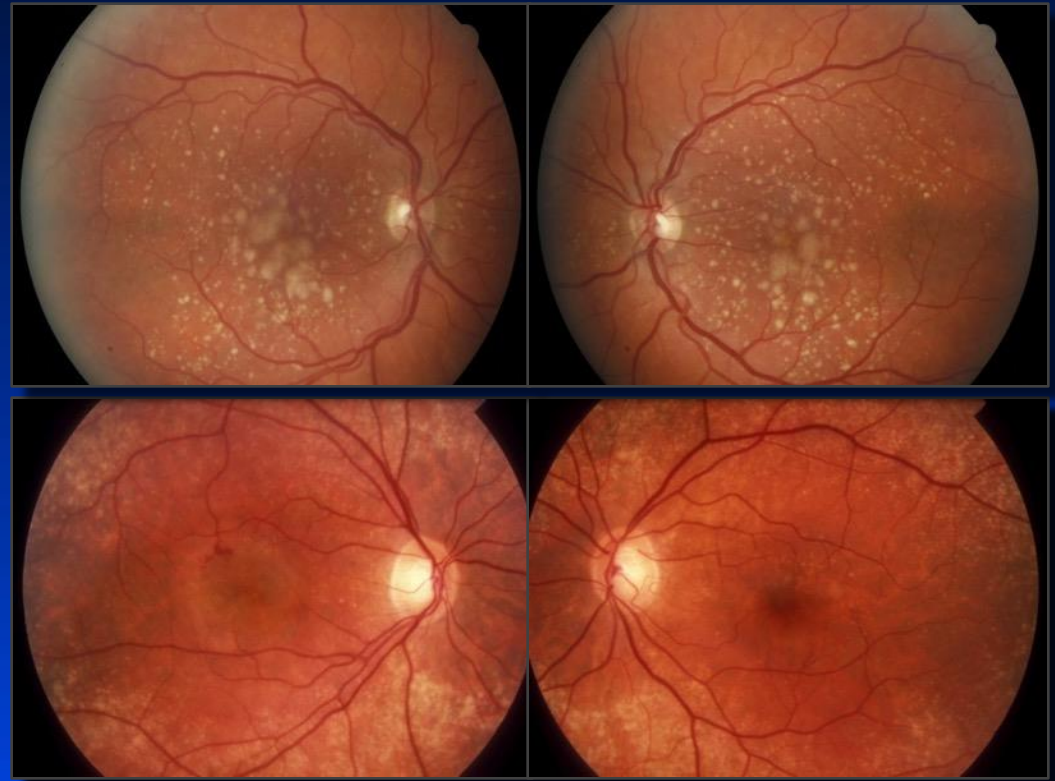
Co-segregating Diseases



Chr1- & Chr10-directed Phenotypes

Clinical

- Drusen
- Vasculature
- Retinal thickness
- Fluid distribution in exudative stages
(sub-RPE, subretinal & intraretinal)
- AVEGF treatment response



Clinical phenotypes of cases with Chr1- & Chr10-directed AMD exhibit distinct characteristics



Age-related Macular Degeneration

'Take Home' Messages

- We continue to gain fresh, new insights into the underpinning biology of AMD
 - Teamwork, dedication, resources & critical partnerships have been key game changers
- These game changers have allowed us to identify pathways that are manifest in AMD &, importantly, new targets upon which to develop drugs to treat this devastating disease



Thank You -- It Takes a Team!!

- *Prevent Blindness*
- *Eye donors & their families*
- *Study participants*

To those individuals with blindness, to their caregivers & their supporters -- please find some comfort with the knowledge that there are many working hard to find a cure for AMD & other blinding conditions



Our Vision Is Vision®

