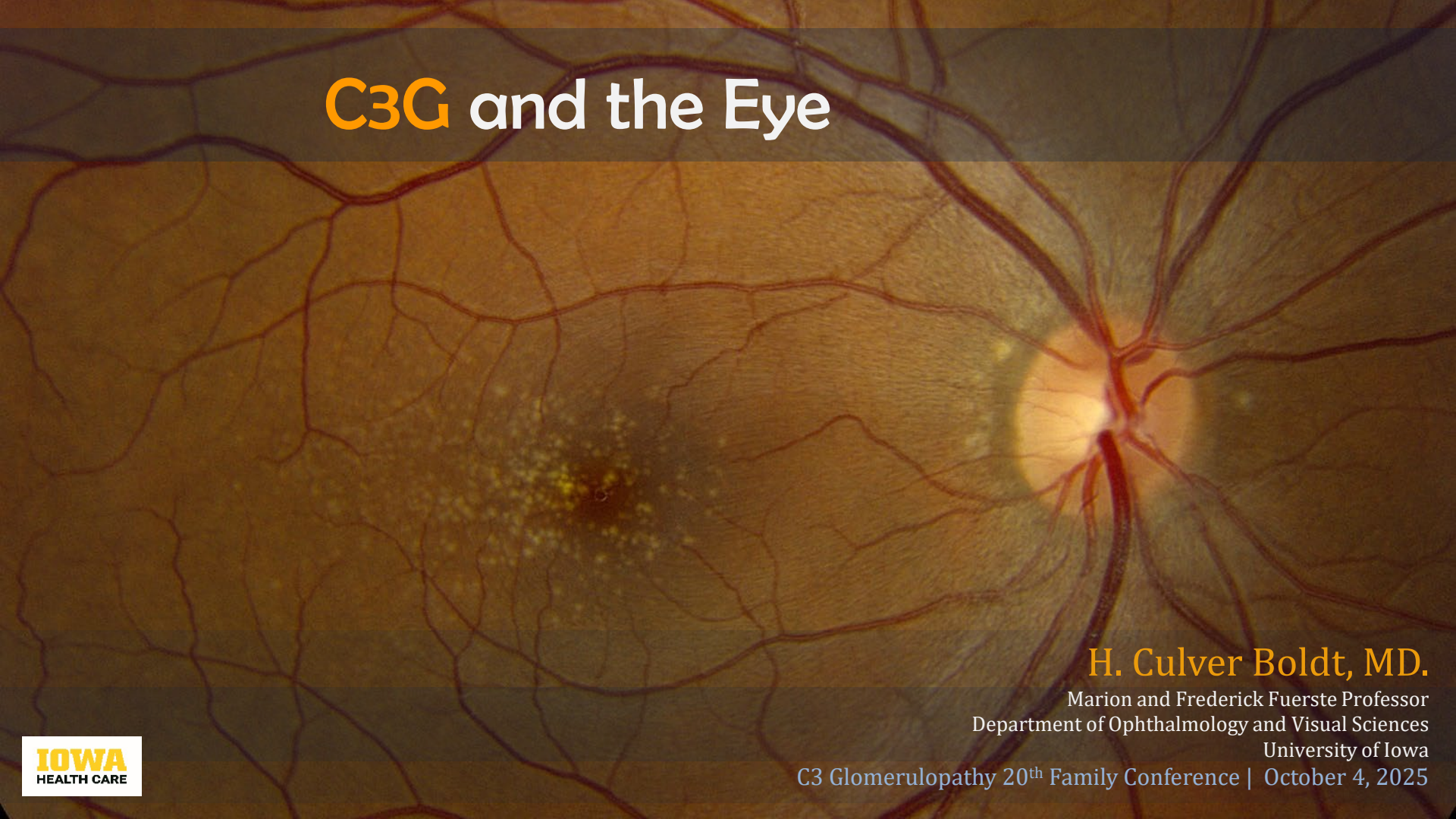
C3G and the Eye



H. Culver Boldt, MD.
Marion and Frederick Fuerste Professor
Department of Ophthalmology and Visual Sciences
University of Iowa

C3 Glomerulopathy 20th Family Conference | October 4, 2025

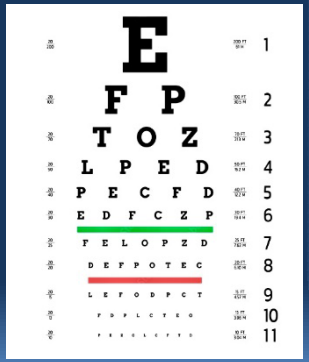
IOWA HEALTH CARE

Learning Objectives

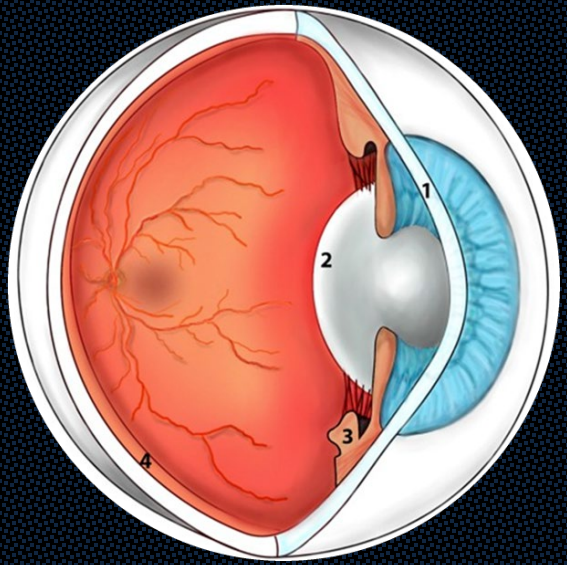
- To understand the anatomy of the eye
- To understand what drusen are and why they form in people with C3G
- To understand the vision changes you might see from C3G that require an urgent eye examination
- To understand how retina problems associated with C3G can be treated and what you can expect

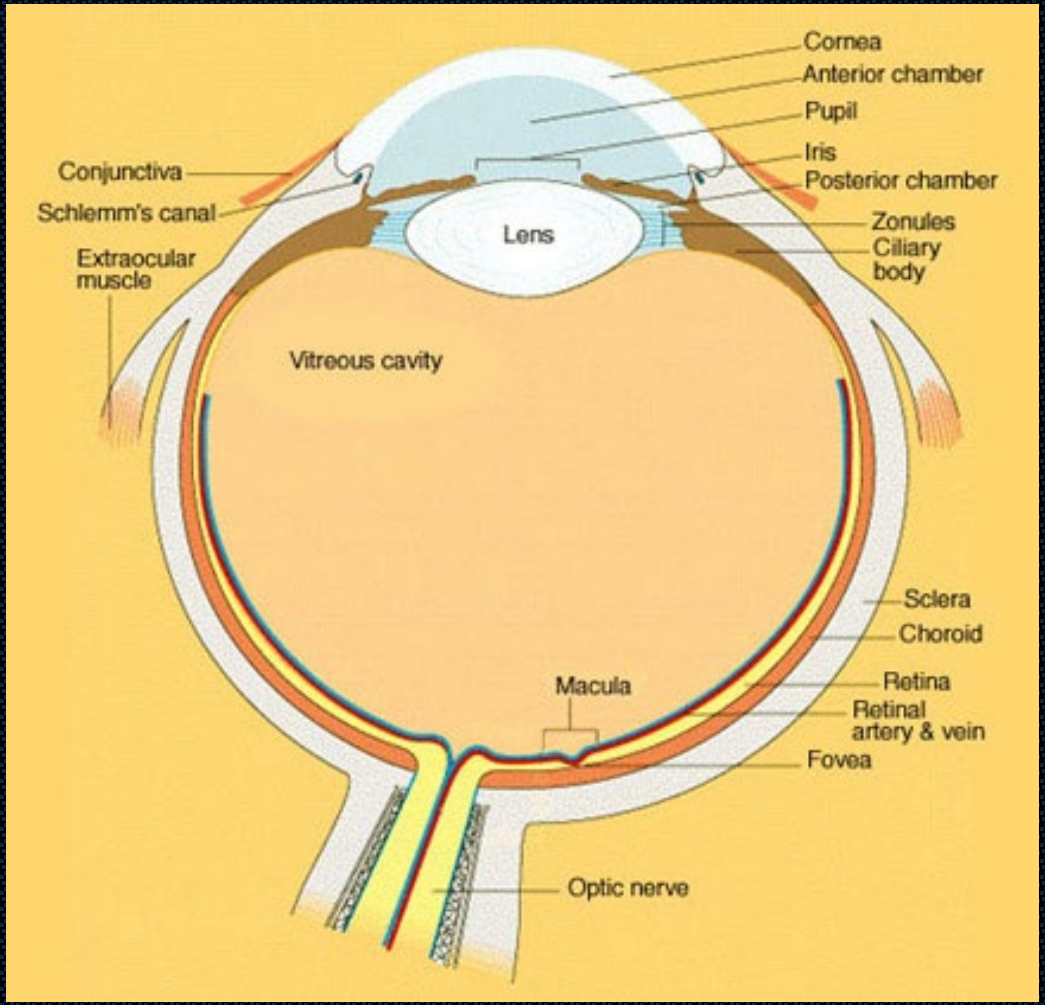
How Do we Measure Vision?

- Visual Acuity
  - Measures the smallest high contrast letters (black on white) you can see
  - Often expressed as a fraction (such as 20/20) for each eye
  - 20/20 vision: you see letters at 20 feet from eye chart that a person with “normal” vision sees at 20 feet from the chart.
  - 20/40 vision: you see letters at 20 feet from eye chart that a person with “normal” vision sees at 40 feet from the chart.
  - The big ”E” is 20/400
- Peripheral (“Side”) Vision:
  - Can only see large objects (Count Fingers vision)
  - Important for walking around a room, driving

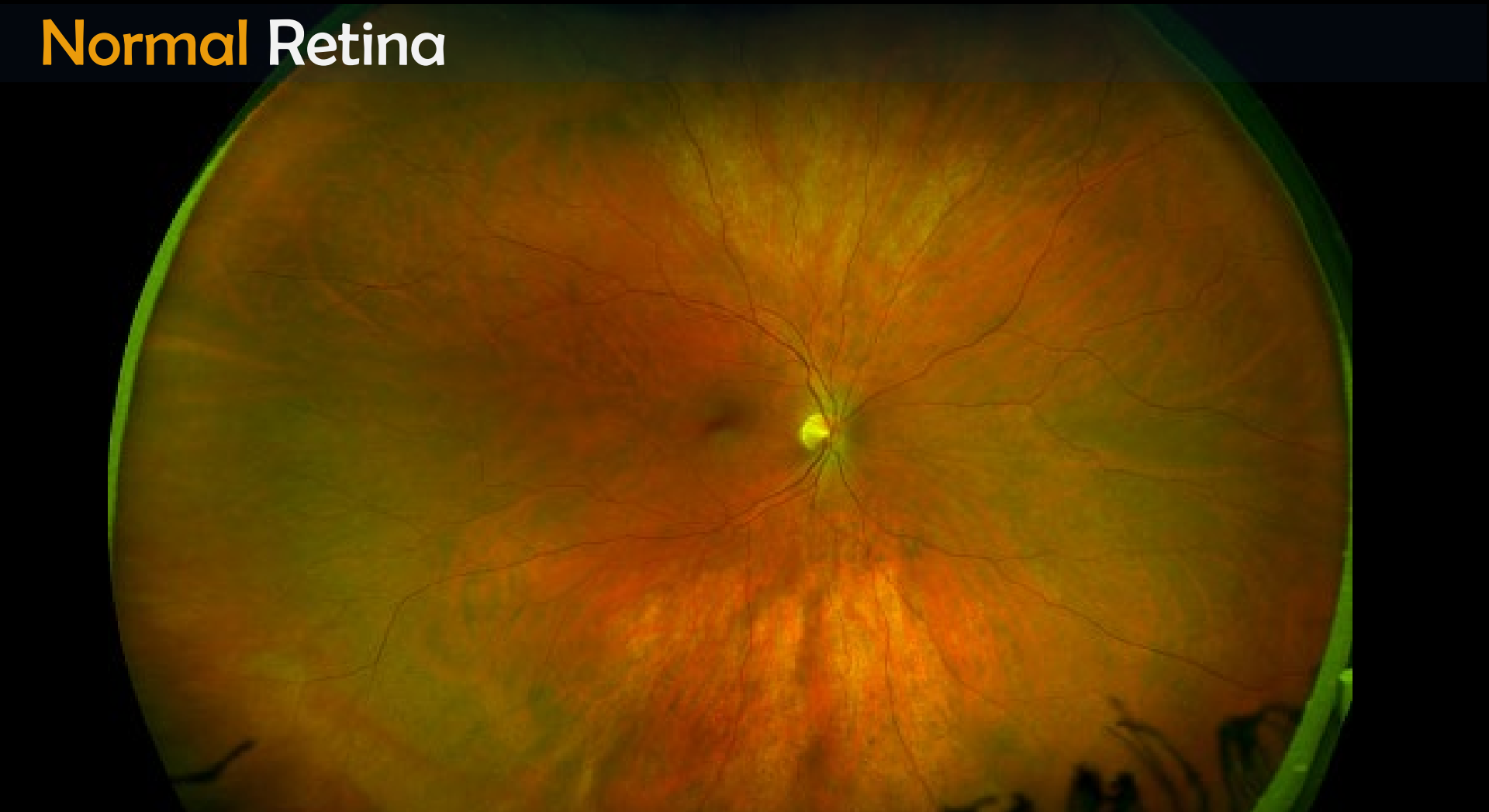


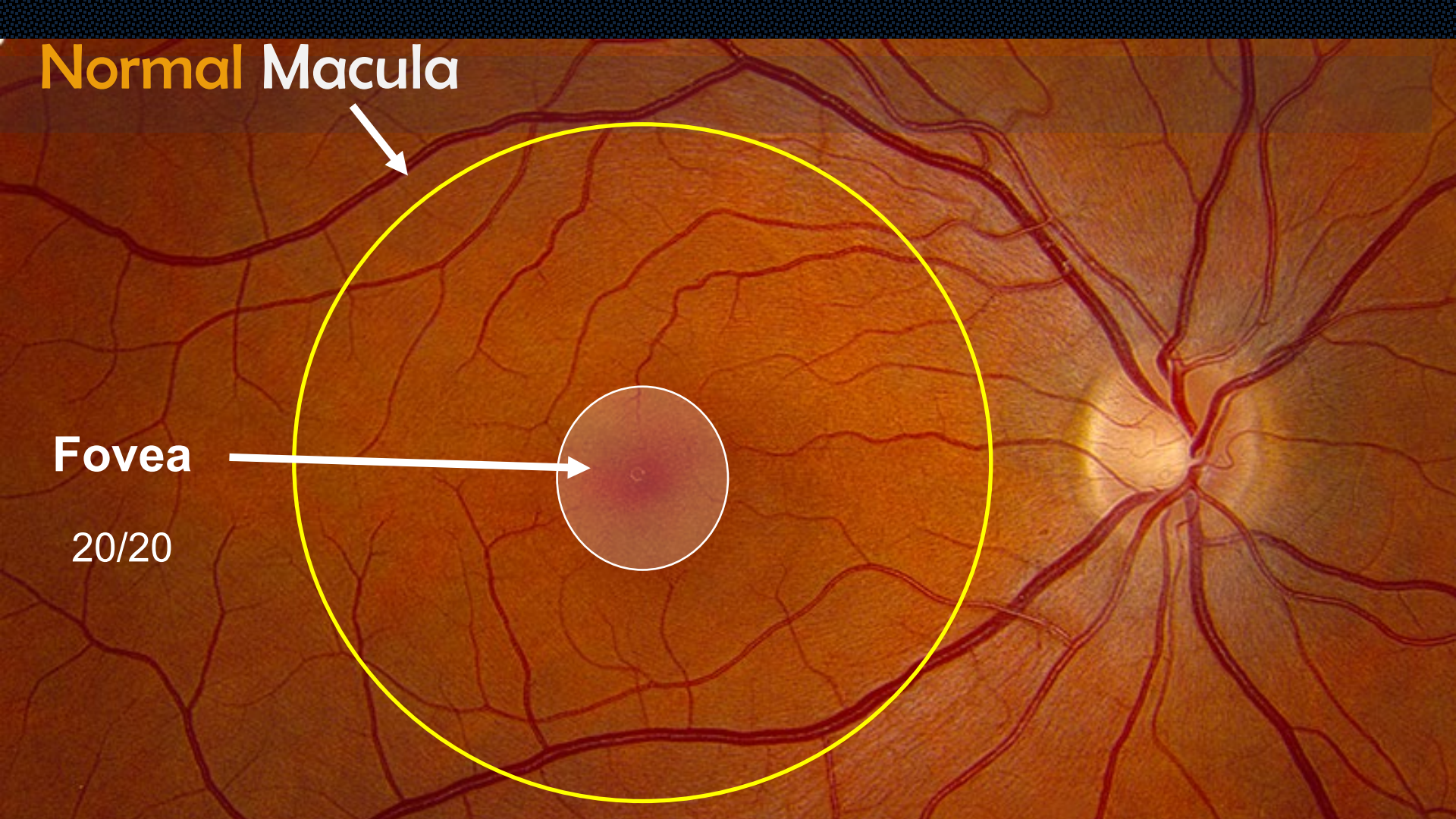
Eye Anatomy


1
2
3
4


Cornea
Anterior chamber
Pupil
Iris
Posterior chamber
Conjunctiva
Schlemm's canal
Lens
Zonules
Ciliary body
Extraocular muscle
Vitreous cavity
Sclera
Choroid
Retina
Macula
Retinal artery & vein
Fovea
Optic nerve

Normal Retina




Normal Macula
Fovea
20/20

Normal Retina

Count
Fingers

20/200
to
20/400

20/20
to
20/100

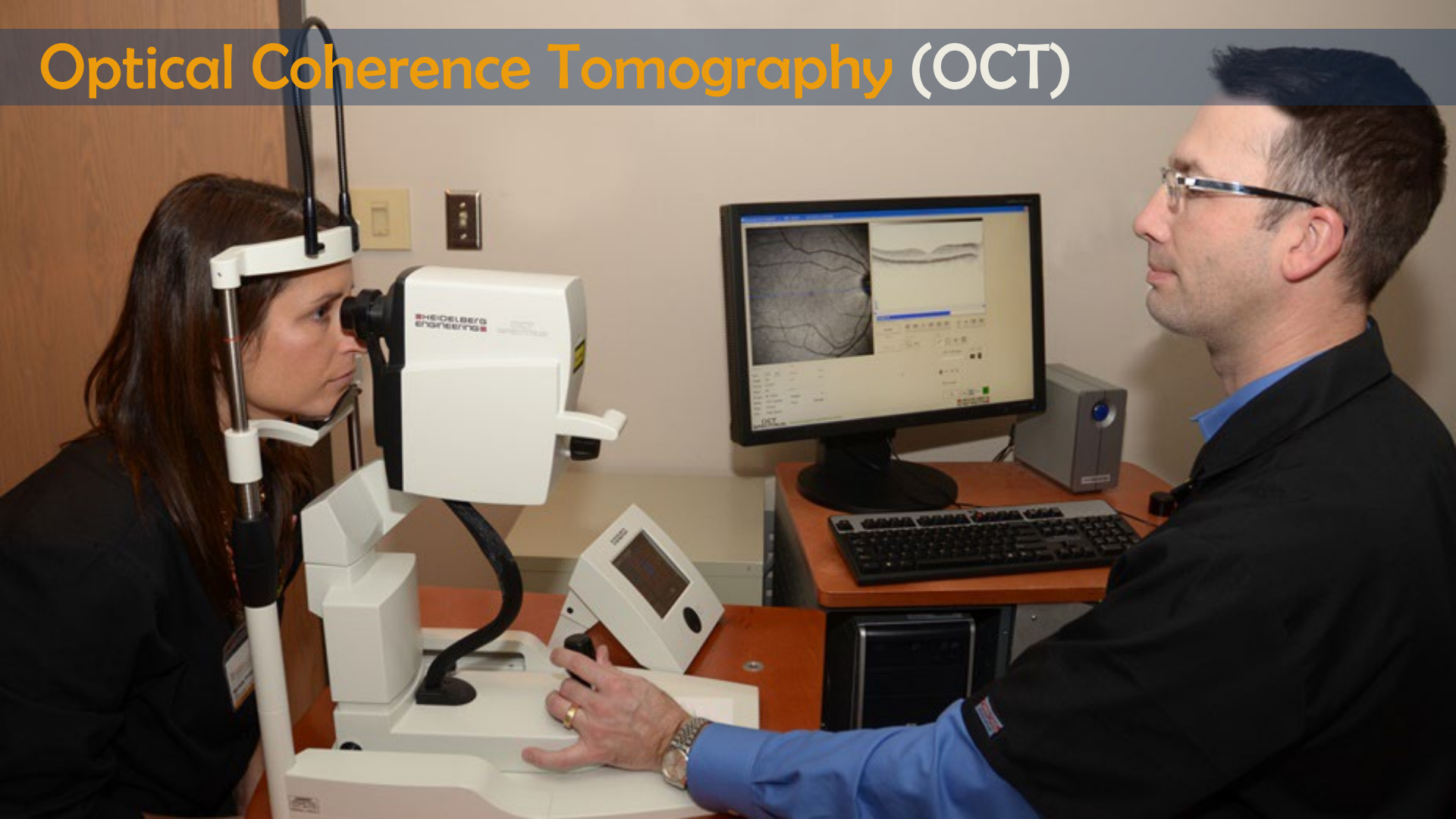
Normal Retina

Count
Fingers

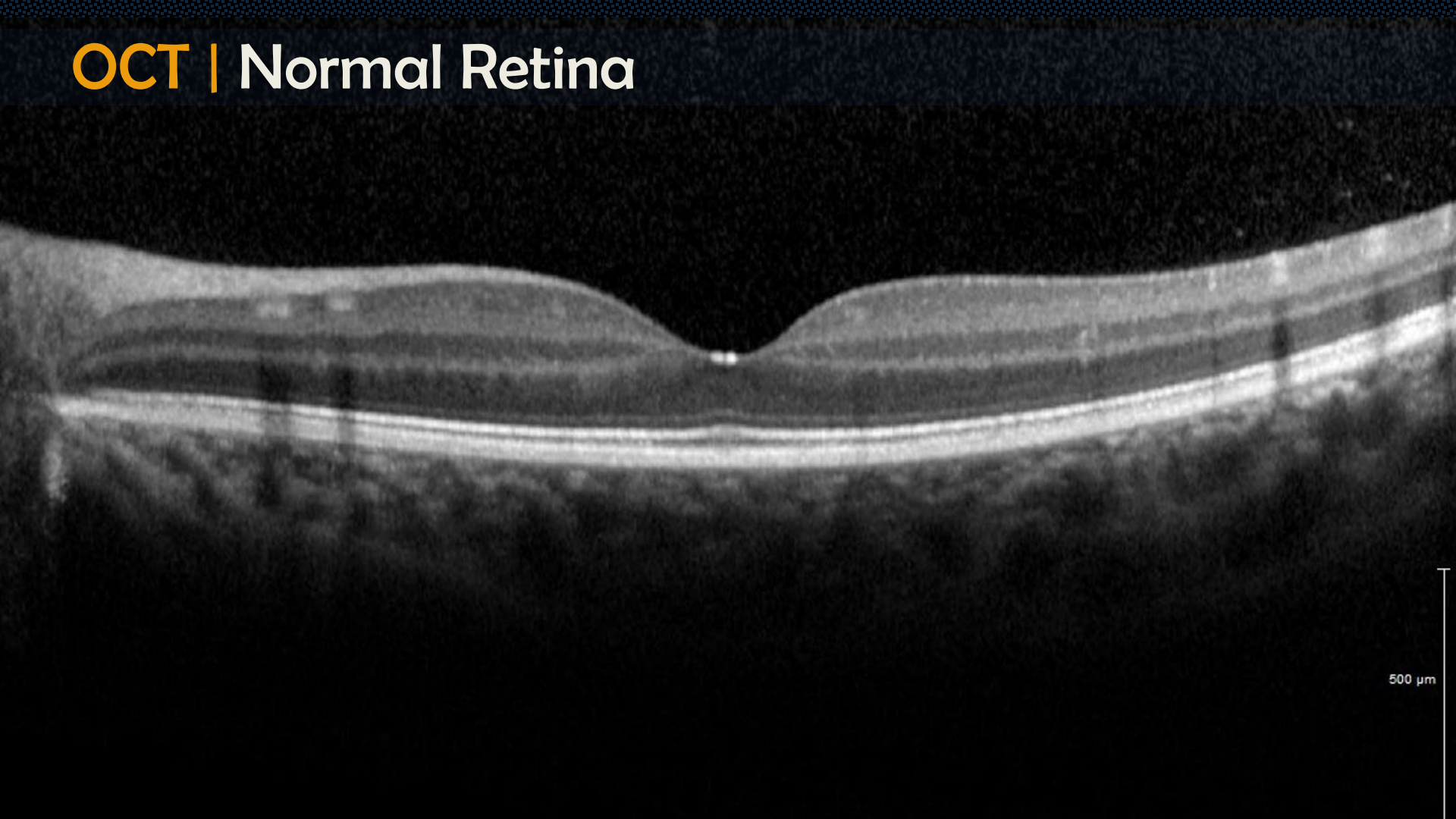
Fovea
Destroyed

20/200
to
20/400

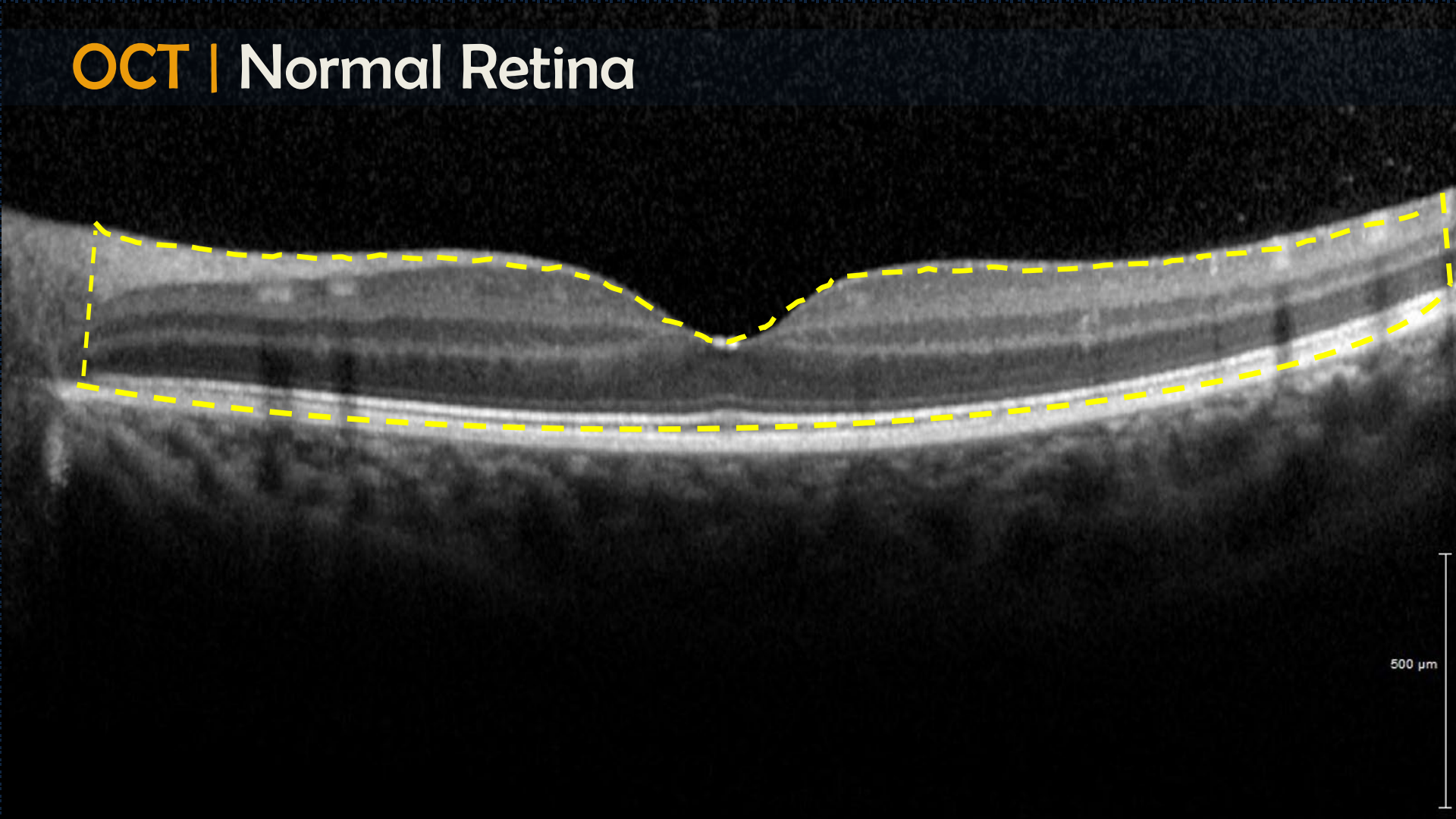
Optical Coherence Tomography (OCT)

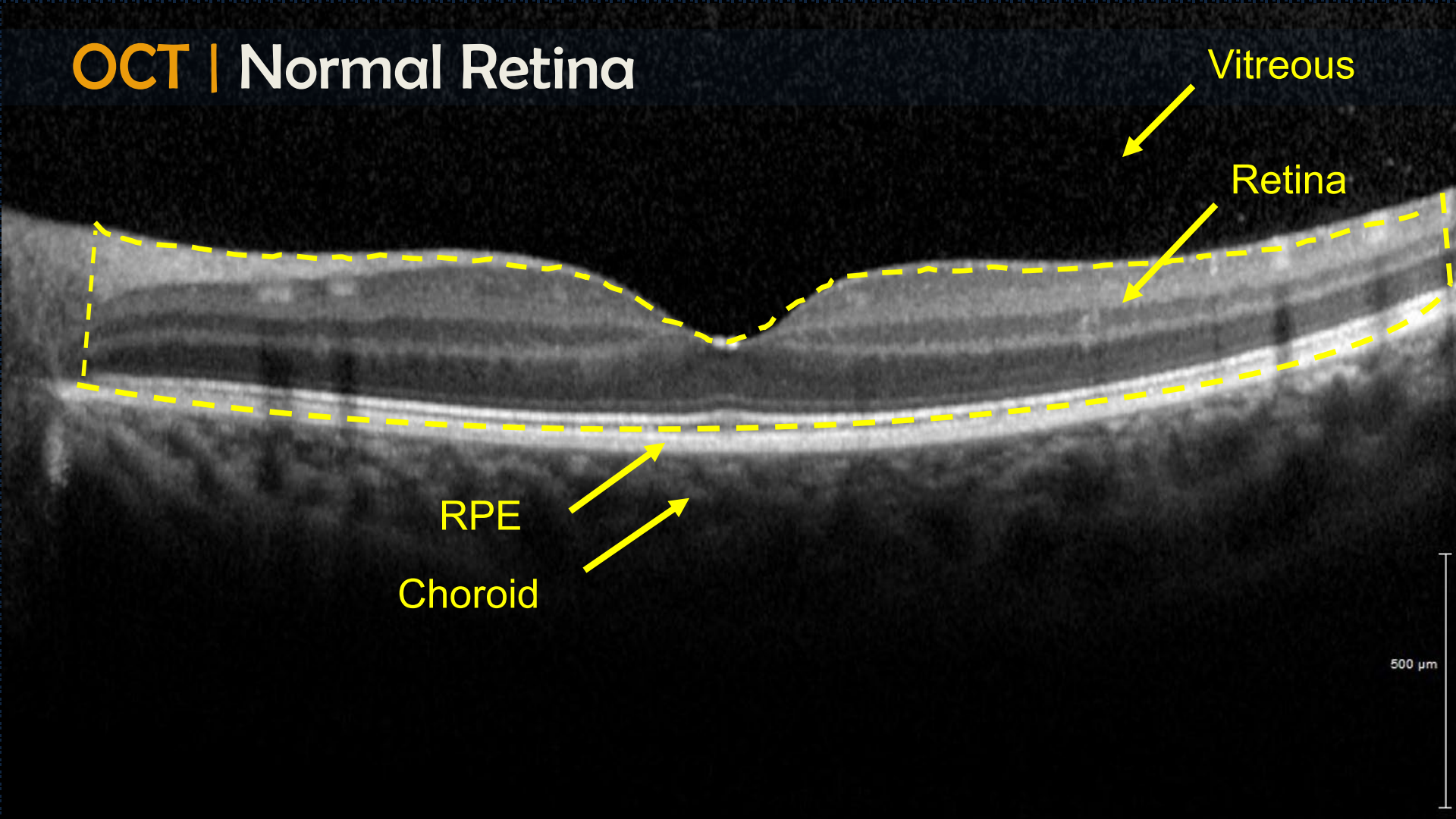


OCT | Normal Retina



OCT | Normal Retina

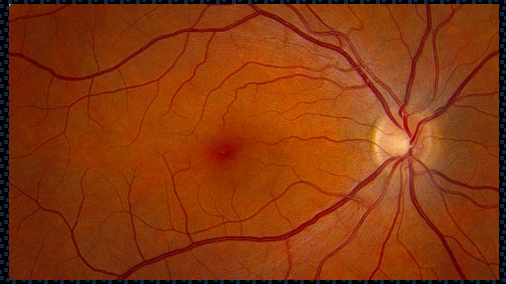



OCT | Normal Retina
Vitreous
Retina
RPE
Choroid
500 µm

What are Drusen?

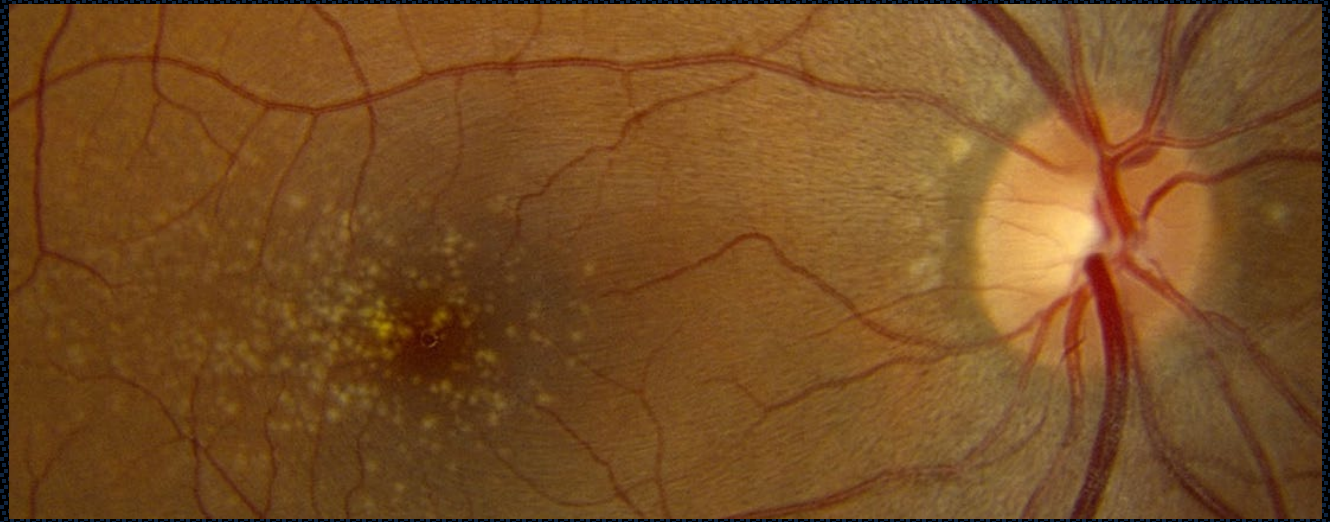
- ”Geode” or bump
- A “bump” of wear and tear yellow pigment beneath the retina in Bruch membrane, *a layer very similar to the membranes in kidney glomeruli that are damaged in C3G*
- Hallmark feature of Age-Related Macular Degeneration (AMD)
- Form in most patients with C3G
- Most of the Complement proteins in a normal eye are located in a small zone under the retina.
- Lots of complement proteins in drusen!
- Many similarities in the eyes of people with AMD and C3G

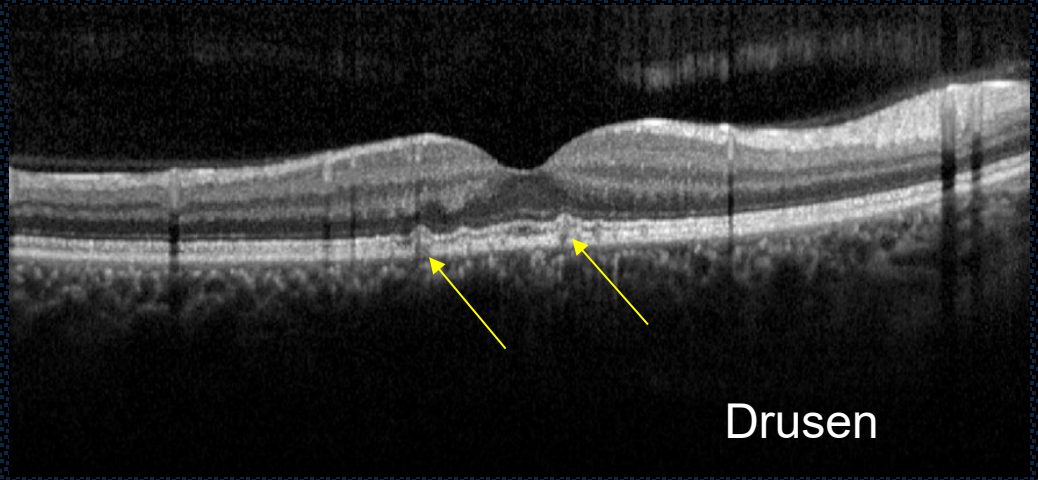
Drusen in AMD



- Hallmark feature
- AMD is very common (20 million people in US, most >50 yrs old)
- Advanced AMD in 1.5 mil
- Risk factors for AMD:
- Age
- White race
- Smoking
- Family History
- Genetics (CFH)
- Obesity
- Fatty Diet
- Hypertension, Heart Disease

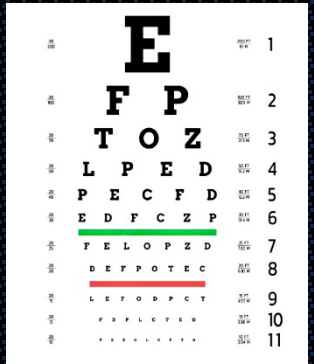
Drusen

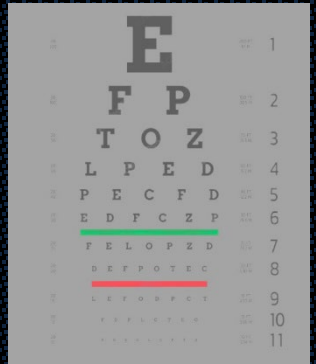




Drusen in AMD and C3G (MD)

- Symptoms in people with Drusen only:
  - Normal to Minimal blurring of vision
  - Slower adaption to light changes
  - Reduced contrast
- Drusen can come and go, but often become more numerous over time
- Risk for advanced MD higher if you have more/larger drusen

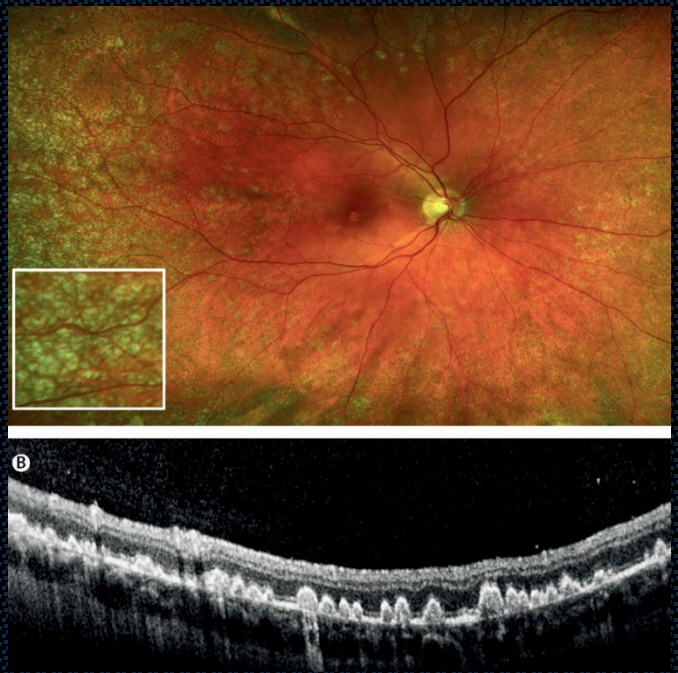




Drusen in C3G

- Commonly very seen in Complement-mediated GN
- Onset of drusen typically 10-40 yrs of age (avg 30) [compared to drusen onset in AMD after age 50}
  - Most people with drusen are asymptomatic, but some progress to Advanced forms (Wet or GA)
    - Wet form probably develops in about 1 in 10 people
    - Geographic Atrophy (GA) probably develops in about 1 in 20 people

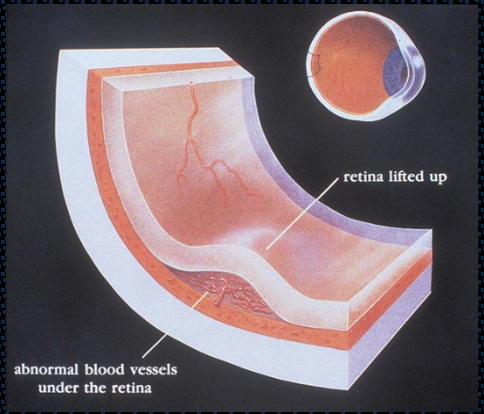
Drusen in C3G: Examples



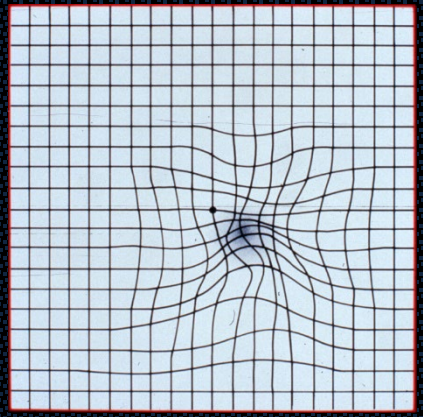
Center images from: Lent-Schochet D, YiuG. Drusen in dense deposit disease: not just age-related macular degeneration. *Lancet* 2020;395:1726

Advanced AMD: 2 Types

- Most people with significant vision loss have Advanced AMD.
- Can cause severe loss of vision.
- People with C3g can also progress from Drusen only to advanced Macular Degeneration

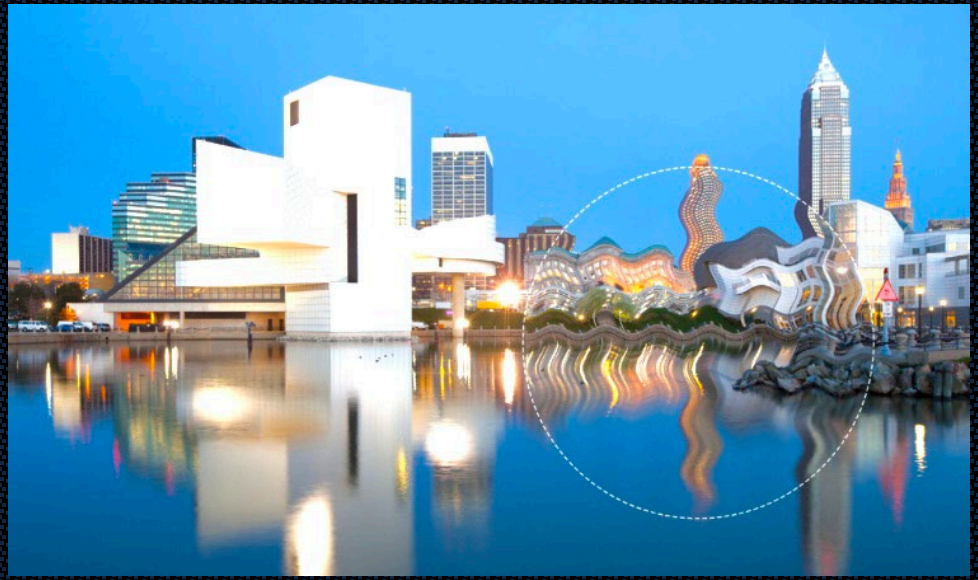


Amsler Grid

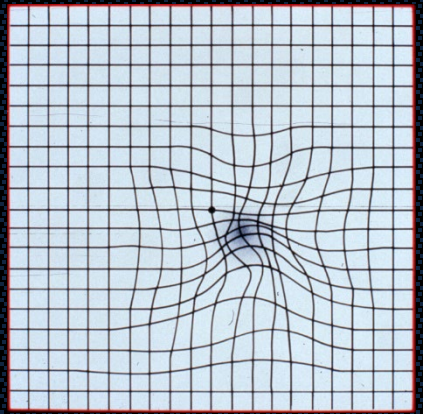


1. “Wet” AMD: Abnormal blood vessels growing under the retina that bleed and leak fluid. Progresses over wks to months.
    - Early Symptoms: Rapid onset of blurred central/close to center vision, often described as a dark fixed spot, blurry spot, faded spot, warped vision, color desaturation. Amsler Grid. Without treatment, symptoms worsen over days to months, with permanent vision loss.

Distortorted or Warped Vision (Metamorphopsia)



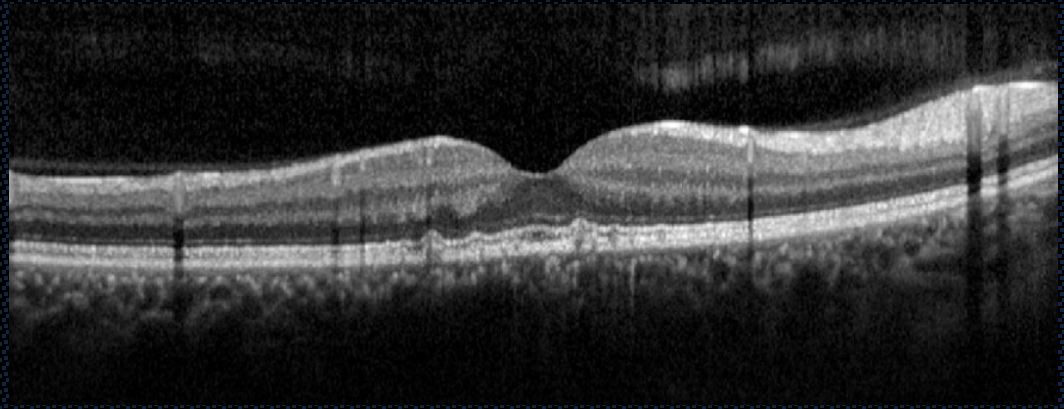
Amsler Grid



“Wet” AMD or C3G

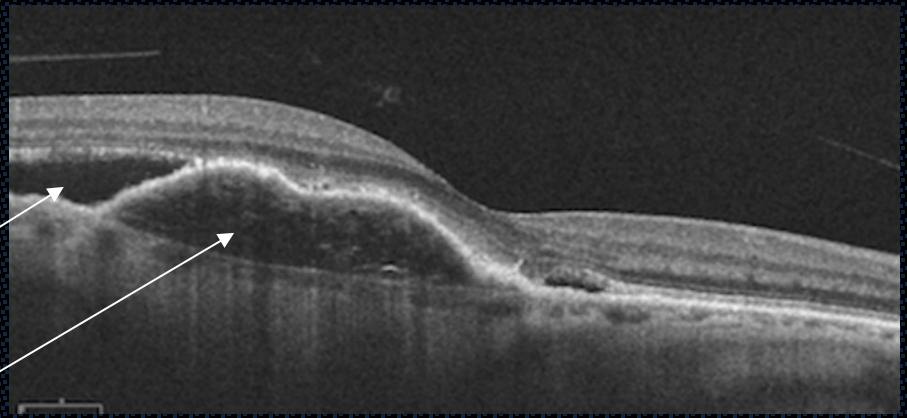
Central Blurring

OCT | "Wet" AMD (Choroidal Neovascularization)



Drusen

Wet AMD



Fluid

New Vessels

Advanced AMD: 2 Types

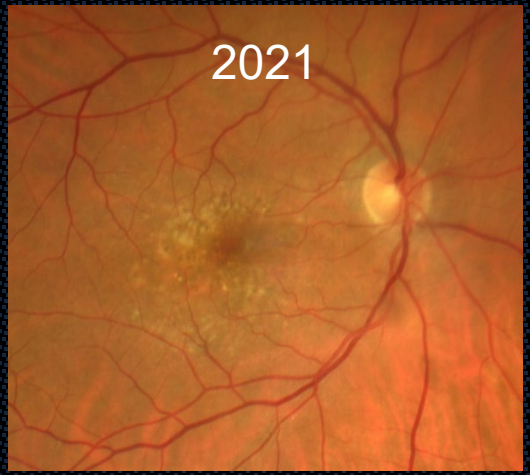
2. Geographic Atrophy: Less common than Wet AMD. Focal areas of withering of retina and layer beneath retina. Starts outside the center of vision but over time can spread into center.

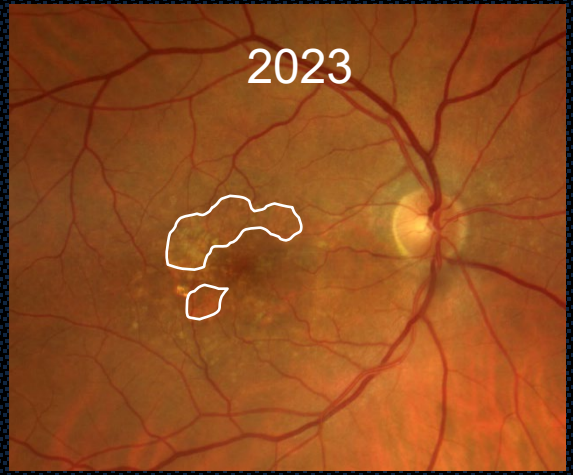
Early Symptoms: Usually none. Progresses over years. Once atrophy is closing in on foveal center, blurring starts. Often have trouble seeing all letters of longer words. Eventually, ends with a large blind spot centrally

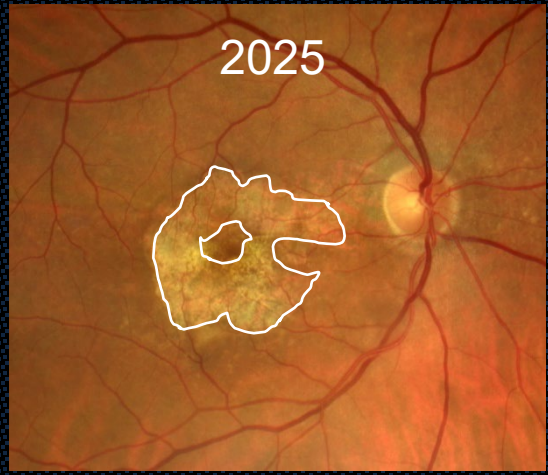
Advanced AMD: 2 Types

2. Geographic Atrophy: Less common than Wet AMD. Focal areas of withering of retina and layer beneath retina. Starts outside the center of vision but over time can spread into center.

Early Symptoms: Usually none. Progresses over years. Once atrophy is closing in on foveal center, blurring starts. Often have trouble seeing all letters of longer words. Eventually, ends with a large blind spot centrally







Severe Geographic Atrophy
Difficulty Reading Longer Words

Geographic Atrophy (GA) in AMD

- Overactive complement system plays a role in damaging the retina and RPE (cells beneath the retina), eventually causing severe vision loss.
- Defects in CFH and C3 genes are risk factors for developing GA in AMD, and are suspected to play a role in macular degeneration from C3G.

(avacincaptad
(avacincaptad

Management for intermediate Macular Degeneration (Moderate drusen)

- Regular eye exams with an ophthalmologist
- Eating a well-balanced diet + (AREDS2 supplements)
- Getting enough exercise
- Quit smoking

High levels of antioxidant vitamins and Zinc

(avacincaptad
(avacincaptad

Management for intermediate Macular Degeneration (Moderate drusen)

- Regular eye exams with an ophthalmologist
- Eating a well-balanced diet + (AREDS2 supplements)
- Getting enough exercise
- Quit smoking

High levels of antioxidant vitamins and Zinc

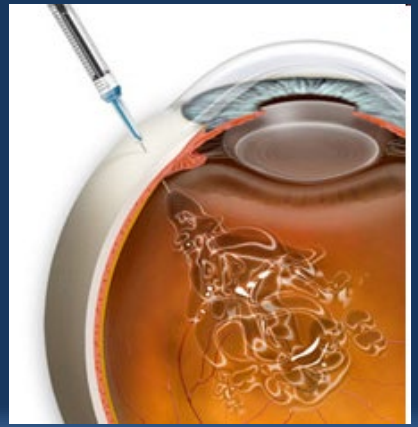
(avacincaptad

Treatments for Advanced Macular Degeneration

- Injection into the eye of various drugs that inhibit a growth factor called VEGF usually controls wet macular degeneration from AMD or C3G (but is off-label)
- Injections into the eye either of two complement inhibitors (pegcetacoplan or avacincaptad) can slow progression of GA in AMD (2023).

Intravitreal Injections

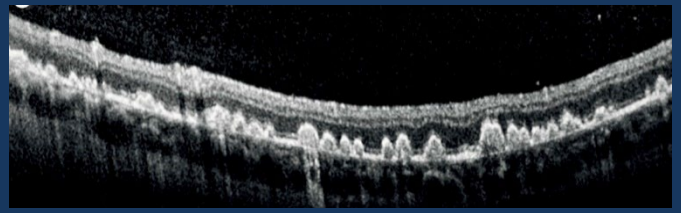
- Anesthetic and Betadine used before injection
- Uses a very thin needle to inject about1 drop of drug into the vitreous
- Usually painless or minimal pressure sensation
- Ocular Side Effects/ Complications rare: Small risk of bleeding, infection, cataract
- 4 to 12 week effective duration



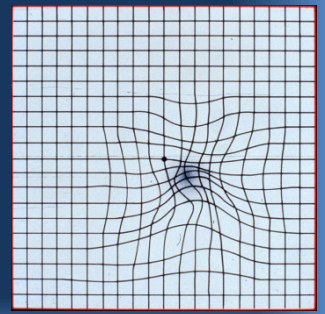
C3G and Eye

What should you do if you are diagnosed?

(My Recommendations)



- Obtain an eye exam with an ophthalmologist (retina specialist) familiar with C3G
- If no macular drusen, consider getting eye exams every 2 yrs
- If macular drusen present:
  - Yearly eye exams
  - Monitor central vision (one eye at a time, Amsler or other target)
  - Urgent eye exam if symptoms of Wet Macular Degeneration Develop (rapid blurring of central or paracentral vision, fixed blurry spot, wavy or distorted vision, color desaturation)
  - Discuss AREDS2 supplements with your eye doctor

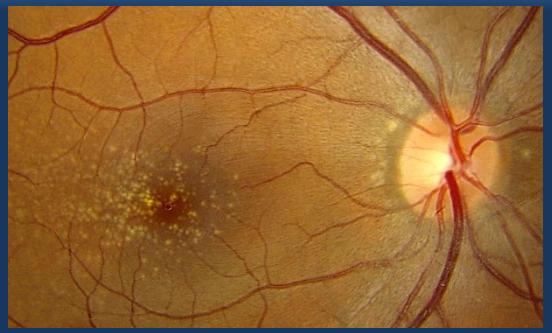


C3G and Macular Degeneration

Unanswered questions

1. Will the subcutaneous injections of pegcetacoplan for renal C3G slow or reverse drusen or prevent progression to wet disease or GA?
2. Could injection of complement inhibitors into the eye slow macular degeneration due to C3G? (NOT FDA approved, and may also have risks)

C3G and Eye
Summary



- Most of Complement in eyes is under the retina, in a membrane similar to the glomerular membranes damaged in C3G
- Complement plays a role in Drusen formation
- Drusen form in most people with C3G over time, and can cause mild vision loss
- A subset of people will progress to severe vision loss due to “Wet” macular degeneration or Geographic Atrophy
- Early detection and treatment of Wet Macular Degeneration can preserve vision in many people

Thanks!

Richard and Lynne, Celebrating the unofficial announcement of FDA approval of Empaveli (Pegcetacoplan) March 2025