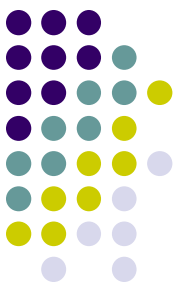


ARMD

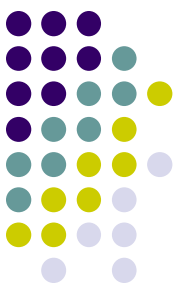


These are the key facts you need to know about ARMD. There's no need to try and memorize them at this juncture; rather, over the course of this slide-set we will unpack/drill down on each, hopefully allowing you to absorb them without having to explicitly commit them to memory!

- ARMD is the #1 cause of blindness in adults age 50+ in resource-rich nations
- Age is the strongest risk factor for ARMD
- The clinical hallmark of ARMD is the presence of *drusen* in the macula
- There are two types of ARMD: *Exudative* and *nonexudative*
- RPE and photoreceptor abnormalities are common findings in ARMD
- The pathogenesis of ARMD is not well understood, but the complement system is strongly implicated in it
- The DDx for exudative ARMD is extensive, but the three top conditions are ocular histoplasmosis, angioid streaks, and pathologic myopia
- VEGF plays a key role in exudative ARMD, and as a result, interdicting VEGF is key in managing it
- Nonexudative ARMD isn't treatable at present, but a major clinical trial found that micronutrient supplementation reduces the likelihood of conversion to exudative ARMD in at-risk pts

ARMD

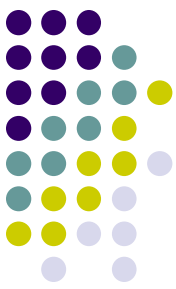
- **Key fact #1:** ARMD is the #1 cause of blindness in adults age 50+ in resource-rich nations

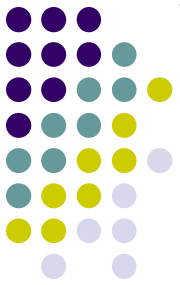


(Not much unpacking to do with this one—it is what it is. Memorize and move on!)

ARMD

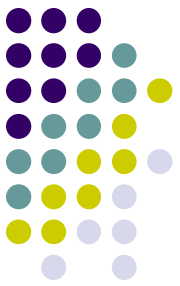
- Key fact #2: Age is the strongest risk factor for ARMD





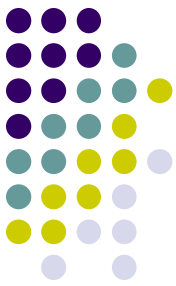
- **Key fact #2:** Age is the strongest risk factor for ARMD

Given its name, it should come as no surprise that *age is the strongest risk factor in ARMD*. It is estimated that 25% of Americans 75 and older have some degree of ARMD.



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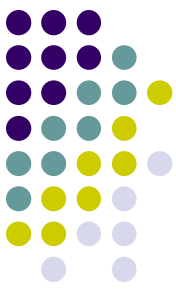


- **Key fact #2:** Age is the strongest risk factor for ARMD

Given its name, it should come as no surprise that *age is the strongest risk factor in ARMD*. It is estimated that 25% of Americans 75 and older have some degree of ARMD. **Other risk factors include race (non-Hispanic whites are at greatest risk; African-Americans, the lowest), family history, and light irides.** The strongest *modifiable* risk factor is **smoking**.

ARMD

- **Key fact #3:** The clinical hallmark of ARMD is the presence of *drusen* in the macula

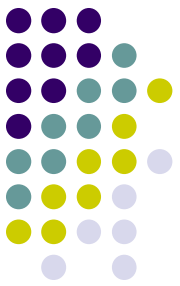


ARMD

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Drusen are focal accumulations of material within the layers of the outer retina. The material is composed of a variety of (mainly) proteins and lipids—waste shed by photoreceptors (PRs) as by-products of the visual cycle.





- **Key fact #3:** The clinical hallmark of ARMD is the presence of *drusen* in the macula

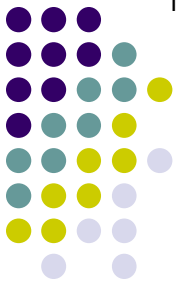
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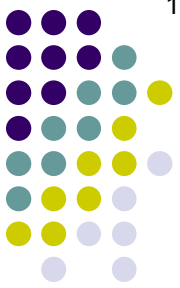
ARMD

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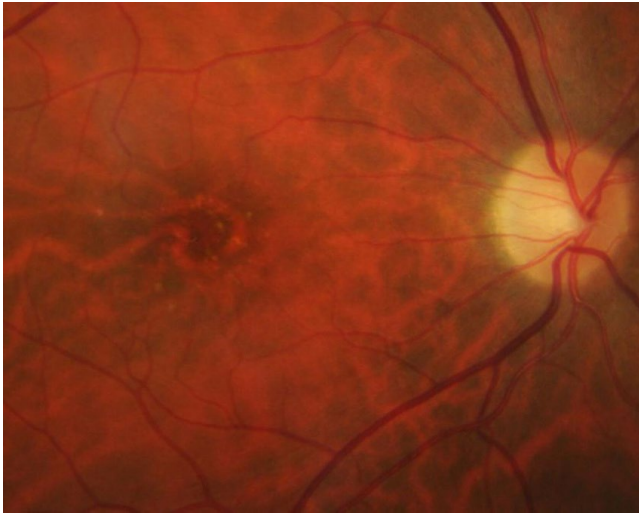
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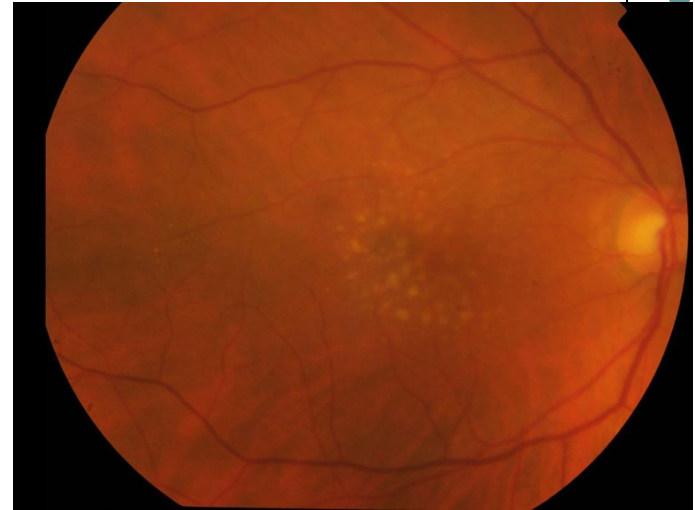
By **size** (Small, Intermediate; Large)



ARMD



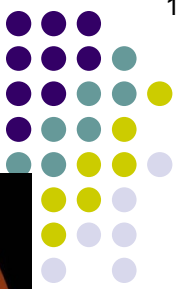
Small drusen



Intermediate drusen



Large drusen



ARMD

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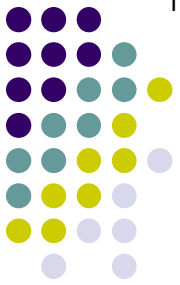
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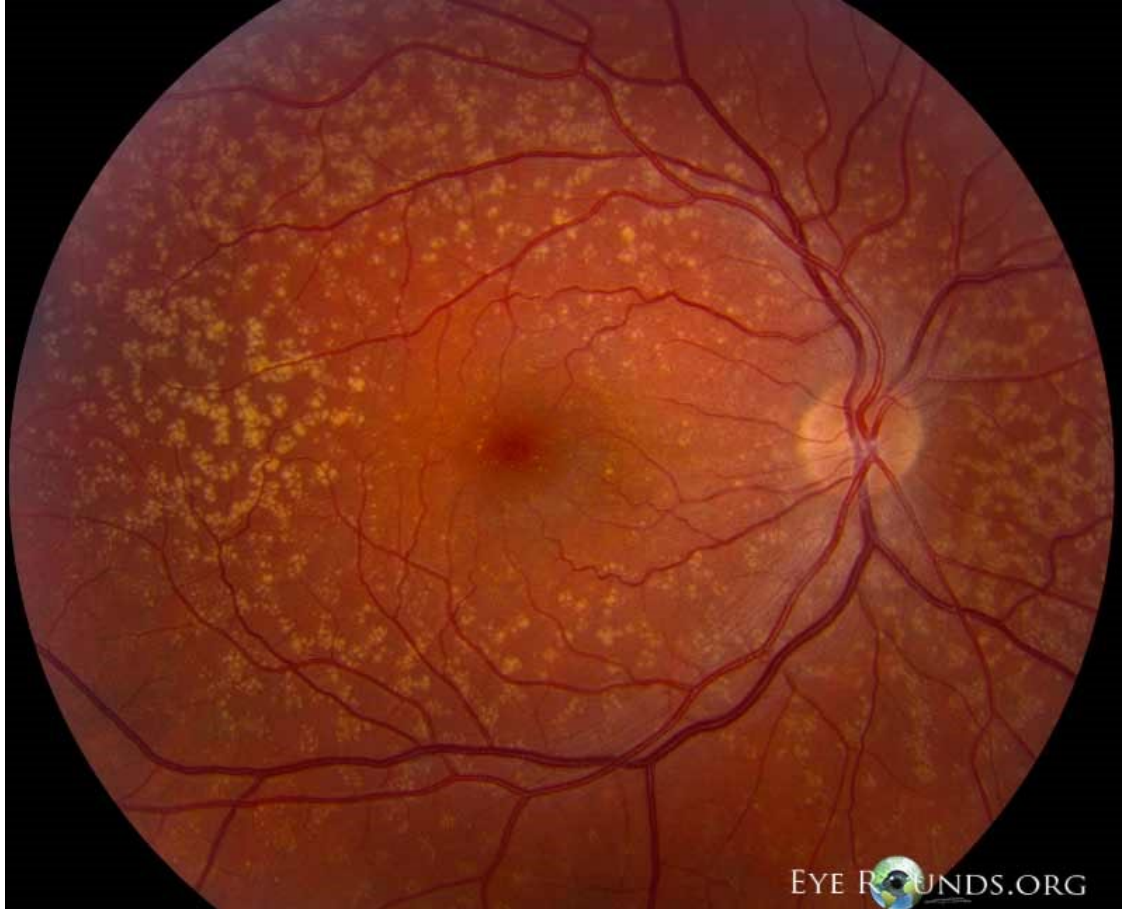
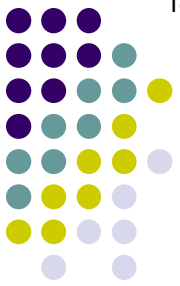
By the **nature/appearance of their boundaries:**

--'Hard' drusen (discrete, well demarcated boundaries)



ARMD

14



Hard drusen

ARMD

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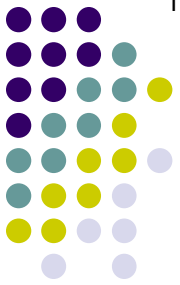
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By **size** (Small, Intermediate; Large)

By the **nature/appearance of their boundaries:**

--'Hard' drusen (discrete, well demarcated boundaries)

--'Soft' drusen (amorphous, poorly demarcated boundaries)



ARMD



Soft drusen

ARMD

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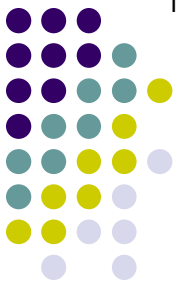
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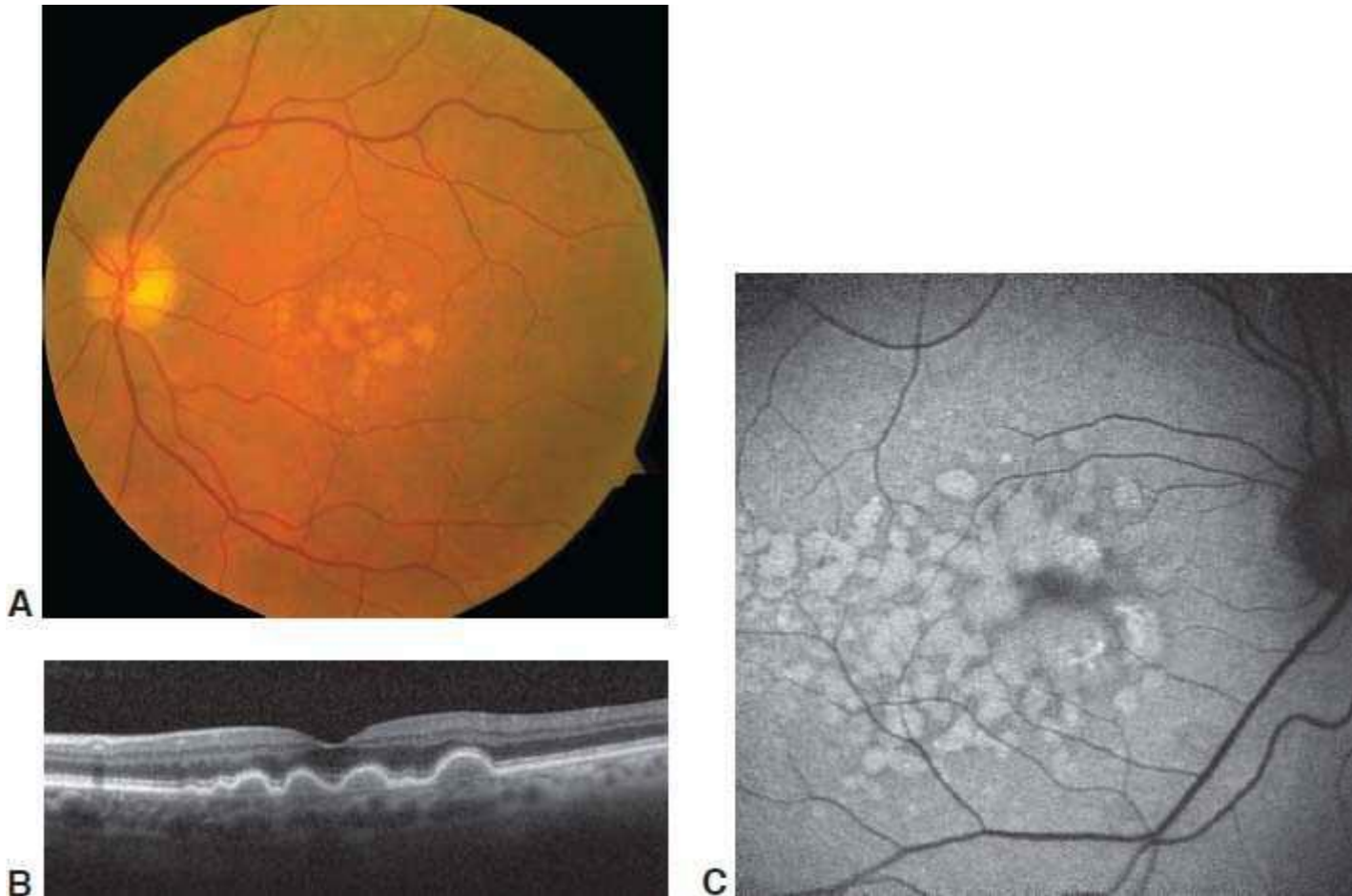
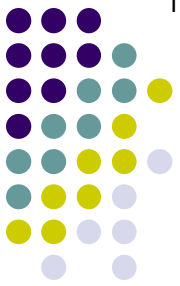
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- 'Confluent' drusen (contiguous drusen without clear boundaries)



ARMD



A, Color fundus photograph shows soft, **confluent**, large drusen in a patient with ARMD. **B**, Corresponding SD-OCT of the soft drusen. **C**, Autofluorescence image of an eye with areas of confluent drusen.

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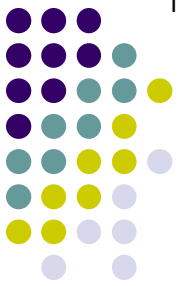
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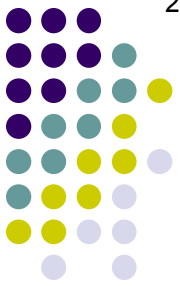
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By **where in the retina they are located**



ARMD



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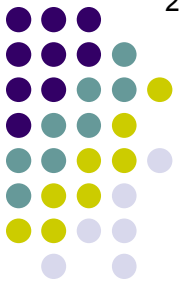
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By where in the retina they are located

Before we get into specific drusen locations, let's take a moment to review the anatomy of the outer retina

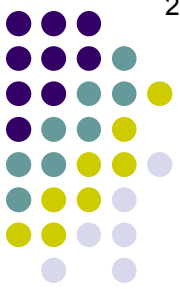
Quick review of ***outer retinal anatomy:***



We'll start with

Bruch's membrane

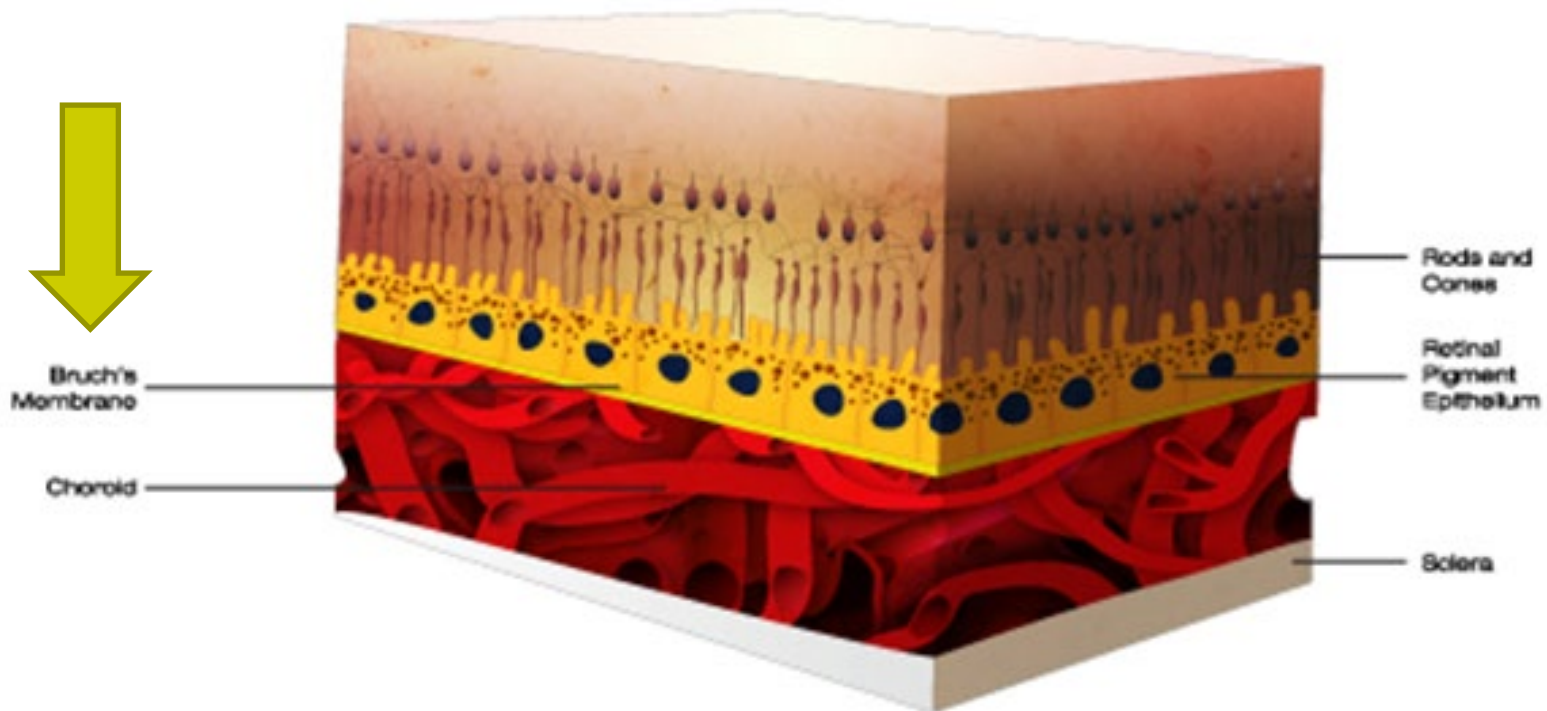
Quick review of *outer retinal anatomy*:



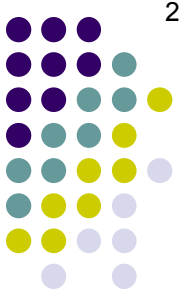
We'll start with

Bruch's membrane,

which is the structure that separates the retina from the choroid.



Quick review of **outer retinal anatomy**:



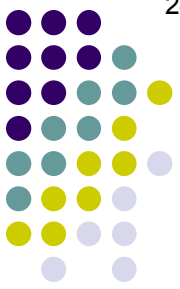
Bruch's membrane consists of 5 layers:



Innermost



Outermost



Bruch's membrane consists of 5 layers:

(Note: This line represents the RPE basement membrane)

- Bruch's membrane
- 1) Basement membrane of RPE
 - 2) Inner collagenous layer
 - 3) Elastic layer
 - 4) Outer collagenous layer
 - 5) Basement membrane of choriocapillaris

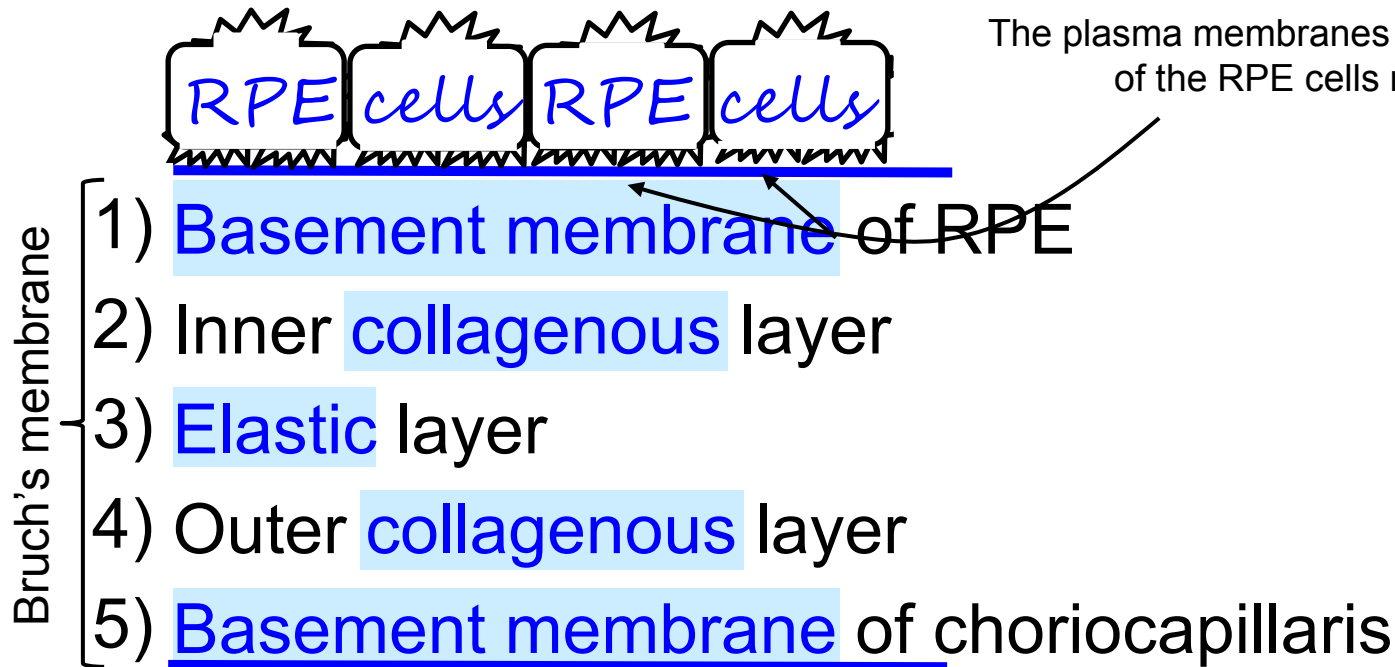
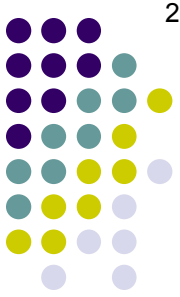
(Note: This line represents the c'capillaris basement membrane)

Innermost



Outermost

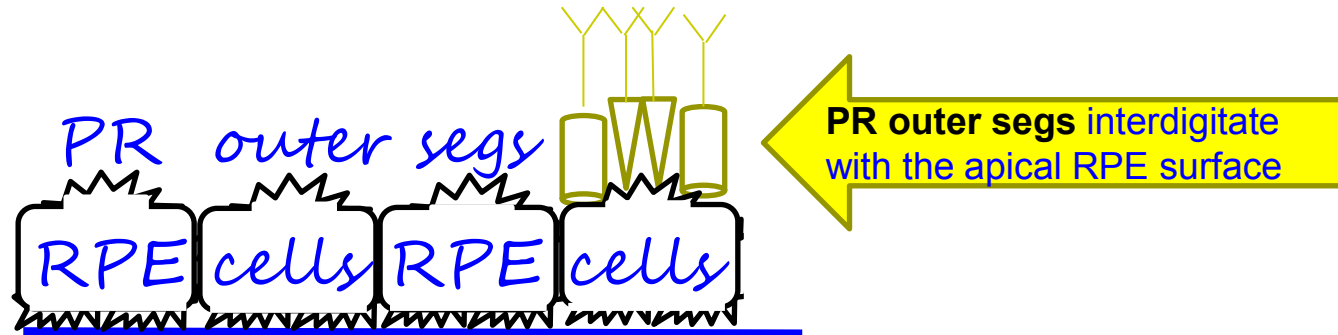
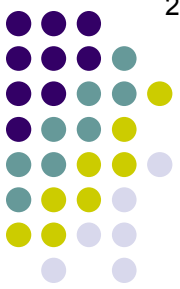
Quick review of **outer retinal anatomy**:



Innermost

Outermost

Quick review of **outer retinal anatomy**:



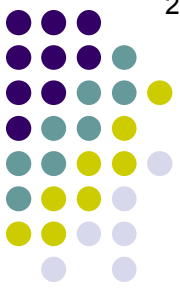
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Innermost



Outermost

Quick review of **outer retinal anatomy**:

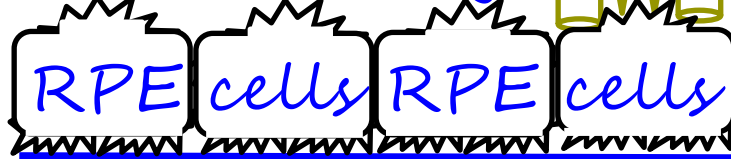


Bipolar cells

Bipolar cells synapse with the PRs

PR outer segs

PR outer segs interdigitate with the apical RPE surface

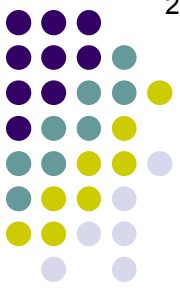


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Innermost

Outermost

Quick review of **outer retinal anatomy**:



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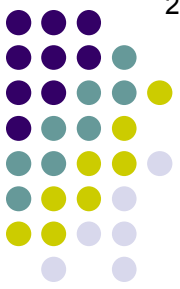
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 - 4) Outer collagenous layer
 - 5) Basement membrane of choriocapillaris
- Choriocapillaris*

Innermost

Outermost

Down here is the
choriocapillaris

Quick review of **outer retinal anatomy**:



Bipolar cells

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PR outer segs

PR outer segs interdigitate with the apical RPE surface



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Innermost

Outermost

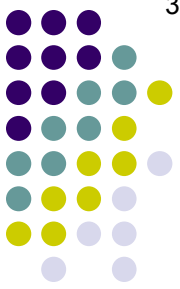
Choriocapillaris

Choroid

Down here is the choriocapillaris

And the choroid

Quick review of **outer retinal anatomy**:



Bipolar cells

Bipolar cells synapse with the PRs

PR outer segs

PR outer segs interdigitate with the apical RPE surface



- Bruch's membrane
- 1) Basement membrane of RPE
 - 2) Inner collagenous layer
 - 3) Elastic layer
 - 4) Outer collagenous layer
 - 5) Basement membrane of choriocapillaris

Innermost

Outermost

Choriocapillaris

Choroid

Sclera

Down here is the choriocapillaris

And the choroid

And the sclera

ARMD

- **Key fact #3:** The clinical hallmark of ARMD is the presence of *drusen* in the macula

Drusen are focal accumulations of material within the layers of the outer retina. The material is composed of a variety of (mainly) proteins and lipids—waste shed by photoreceptors (PRs) as by-products of the visual cycle. Drusen can alter the structural integrity of the outer retina in ways that produce local or widespread damage to PRs, resulting in significant vision loss.

Clinicians categorize drusen along several dimensions:

By **size** (Small, Intermediate; Large)

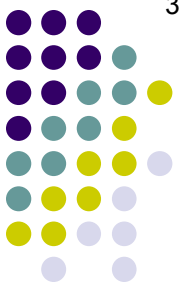


Now we're ready to discuss retinal location as it relates to various types of drusen

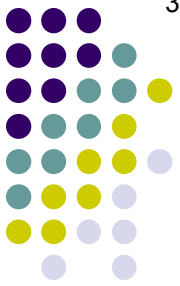


--'Soft' drusen (amorphous, poorly demarcated boundaries)
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By where in the retina they are located:



ARMD



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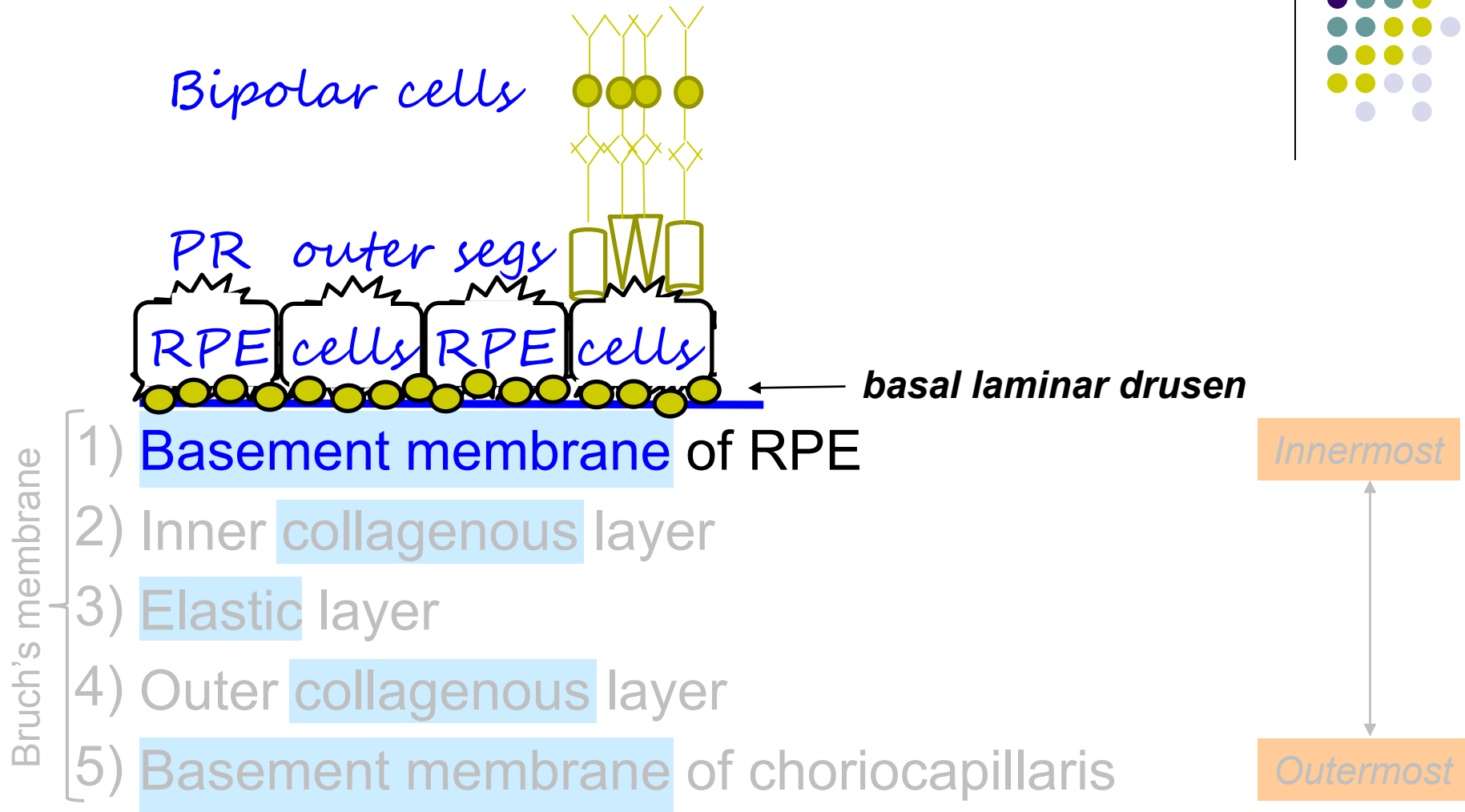
By **size** (Small, Intermediate; Large)

By the **nature/appearance of their boundaries**:

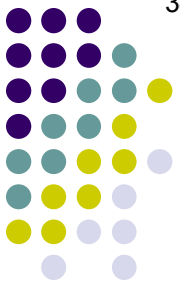
- 'Hard' drusen (discrete, well demarcated boundaries)
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By **where in the retina they are located**:

--*Basal laminar drusen* are between the RPE cells and their basement membrane



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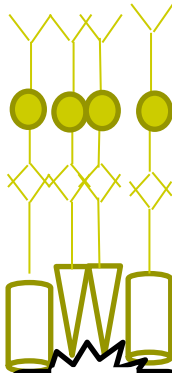
- Basal laminar drusen** are between the RPE cells and their basement membrane
- Basal linear drusen** are within the inner aspect of Bruch's membrane

ARMD

Bipolar cells

PR outer segs

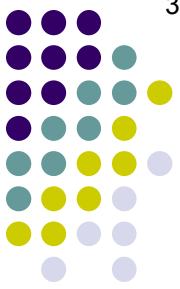
RPE cells RPE cells



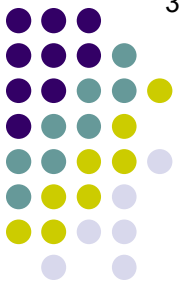
- Bruch's membrane
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- basal linear drusen*

Innermost

Outermost



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By **where in the retina they are located**:

- Basal laminar drusen** are between the RPE cells and their basement membrane
- Basal linear drusen** are within the inner aspect of Bruch's membrane
- Reticular pseudodrusen** are between the apical surface of the RPE cells and the overlying PRs

ARMD

Bipolar cells

PR outer segs

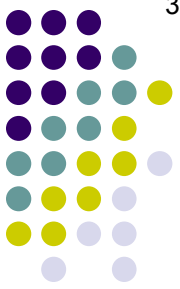
RPE cells RPE cells

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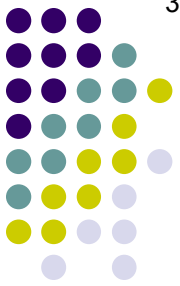
Innermost

Outermost



ARMD

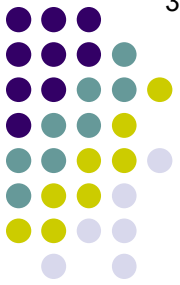
- **Key fact #4:** There are two types of ARMD: *Exudative* and *nonexudative*

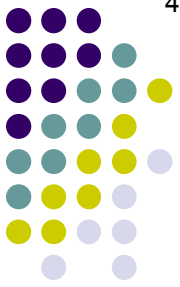


ARMD

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Bipolar cells

ARMD

PR outer segs



Basement membrane of RPE

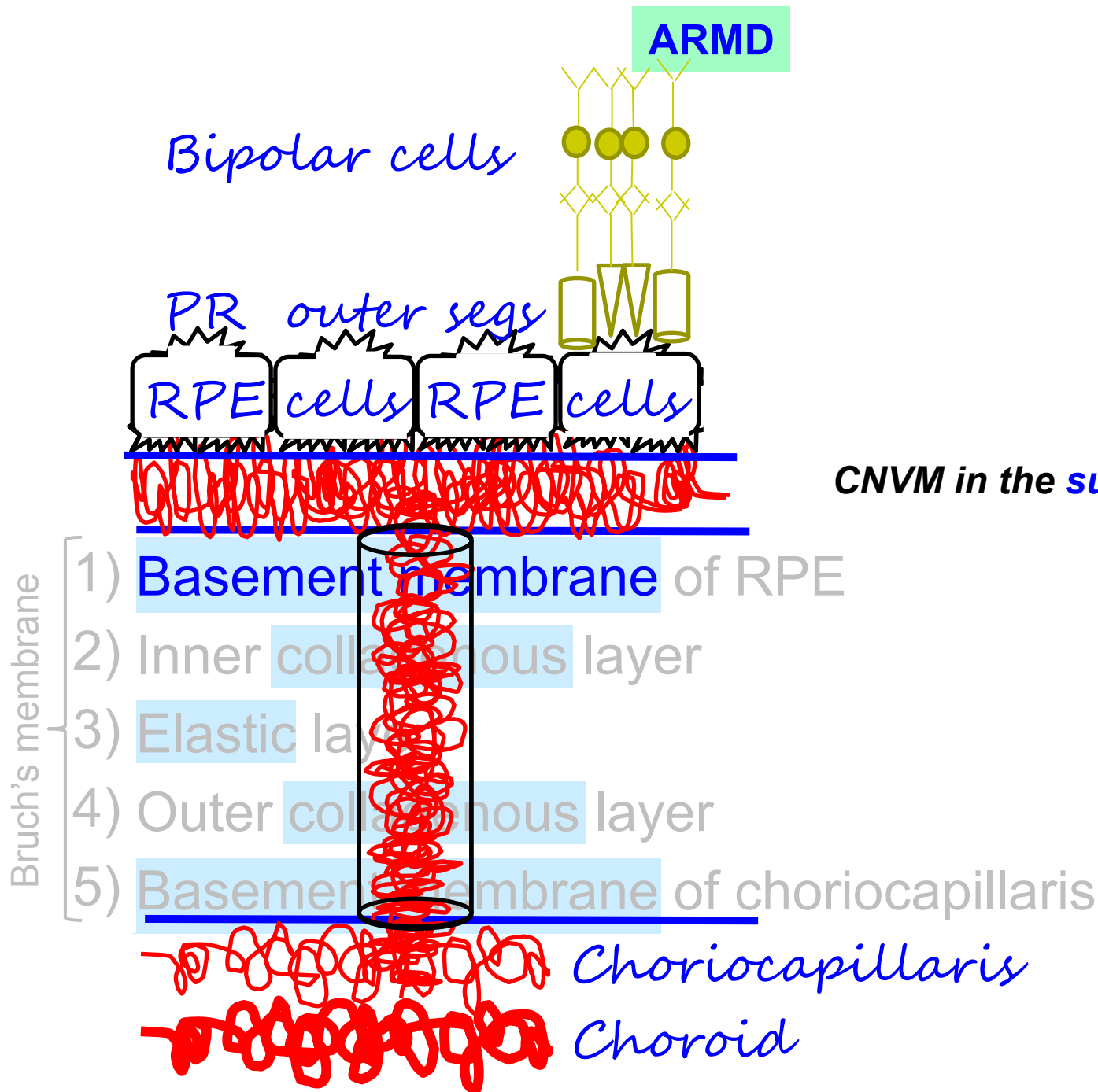
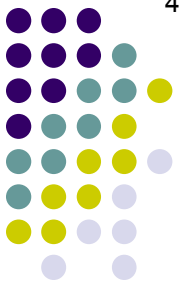
Bruch's membrane

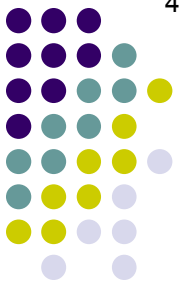
- 1) Inner collagenous layer
- 2) Inner collagenous layer
- 3) Elastic layer
- 4) Outer collagenous layer
- 5) Basement membrane of choriocapillaris

CNVM within Bruch's membrane

Choriocapillaris

Choroid





Bipolar cells

ARMD

CNVM in the *sub-retinal space*



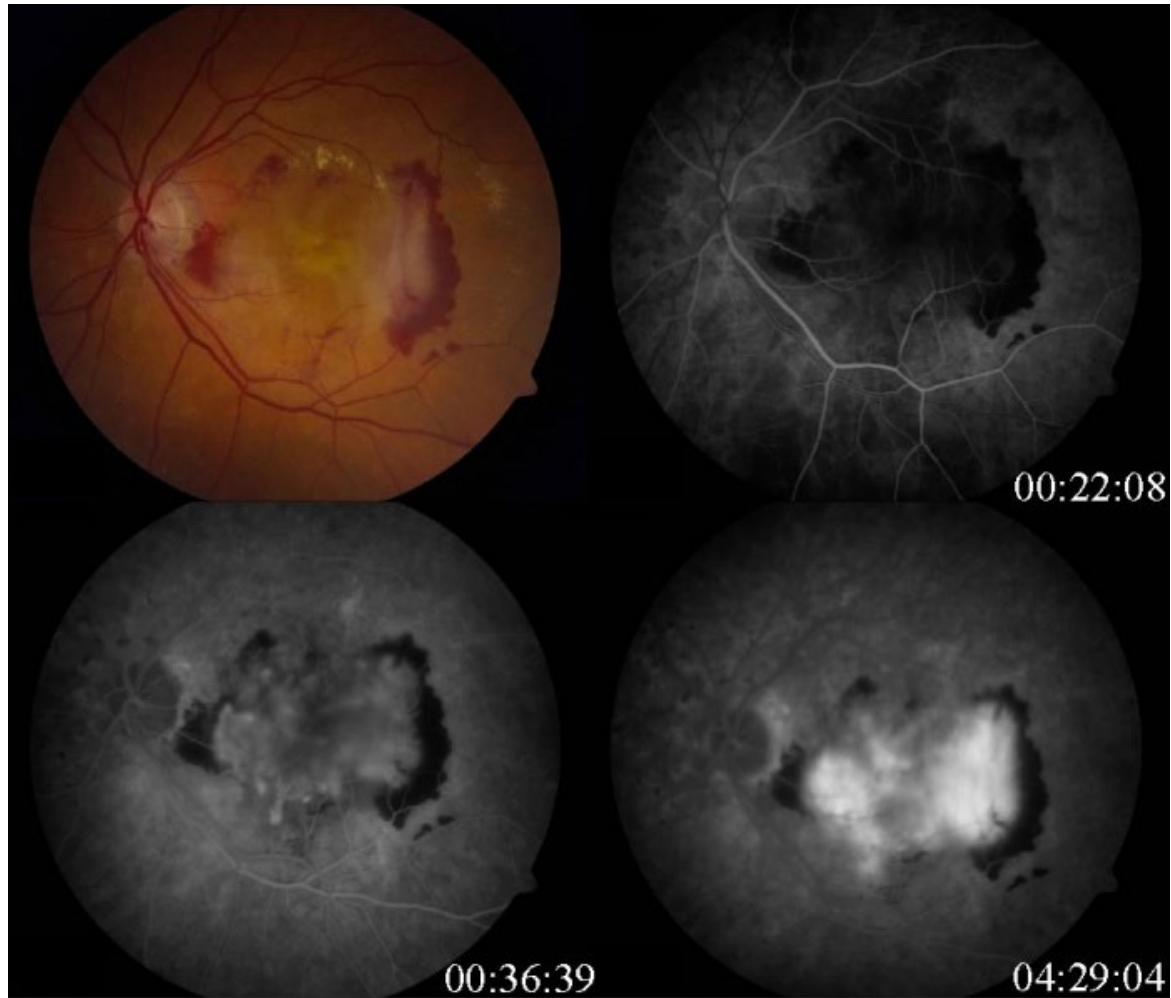
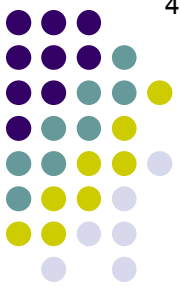
RPE cells RPE cells

- Bruch's membrane
- 1) Basement membrane of RPE
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 - 3) Elastic layer
 - 4) Outer collagenous layer
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Choriocapillaris

Choroid

ARMD

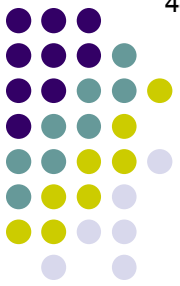


FP and FA of a CNVM in exudative ARMD

ARMD

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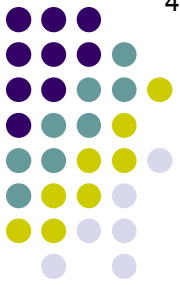


ARMD

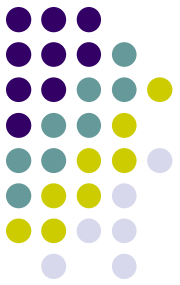
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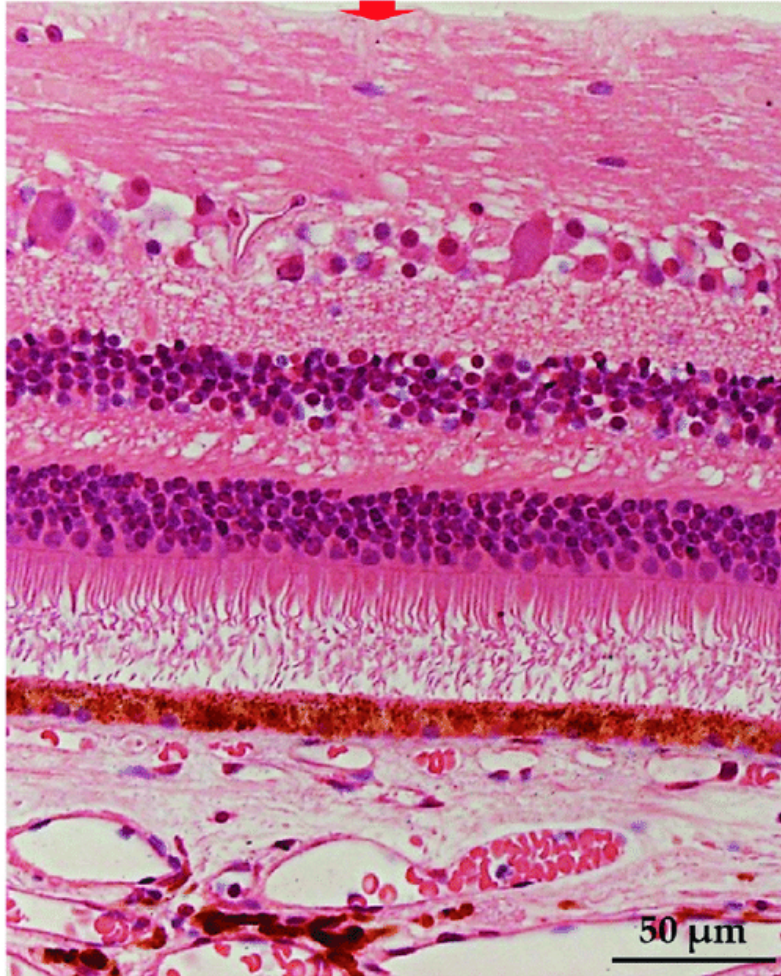
Let's take a moment to review the blood supply of the retina



ARMD



Light



Internal limiting membrane

Nerve fiber layer

Ganglion cell layer

Inner plexiform layer

Inner nuclear layer

Outer plexiform layer

Outer nuclear layer

Layer of Rods and Cones

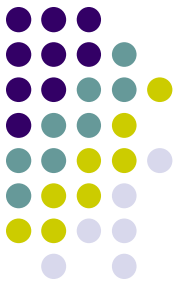
Retinal pigmented epithelium

Choroid

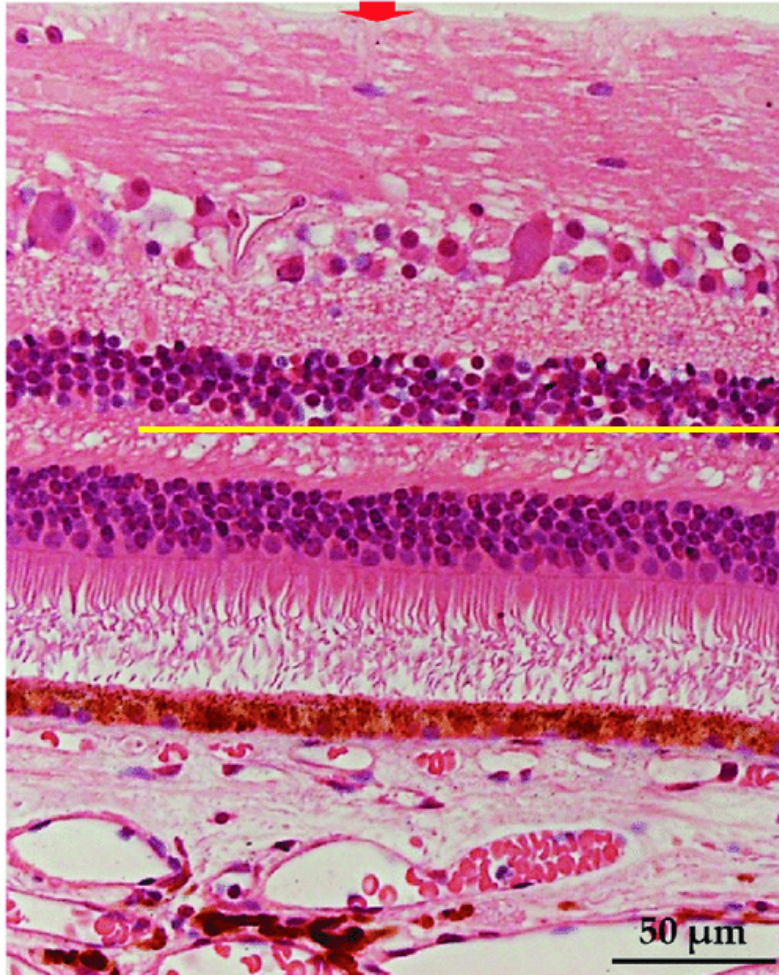
50 μm

Here is a micrograph of a normal human retina.

ARMD



Light



Internal limiting membrane

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Outer plexiform layer

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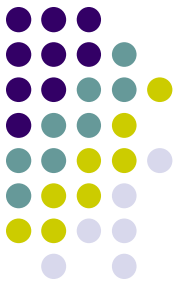
*Vascularized and oxygenated
by branches of the central
retinal artery (CRA)*

***Not** vascularized by the CRA
(or any other source).*

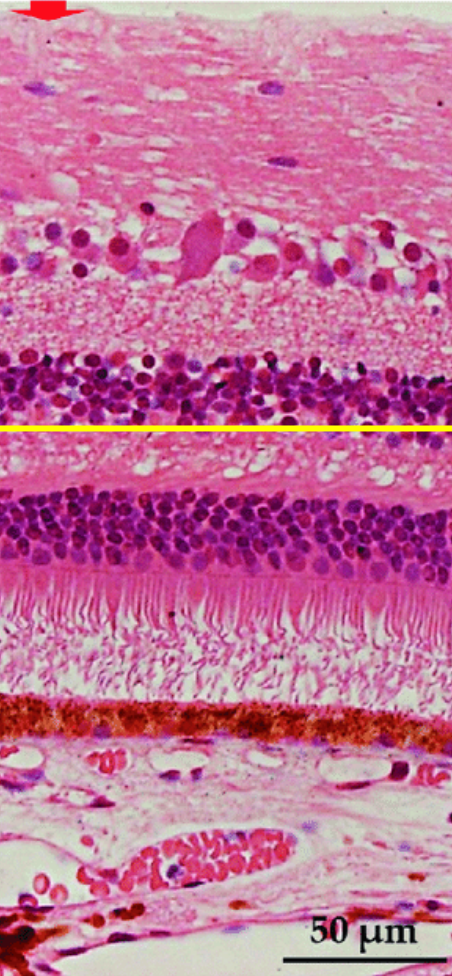
50 μm

Here is a micrograph of a normal human retina. The **yellow line** depicts the level below which retinal vessels do not pass.

ARMD



Light



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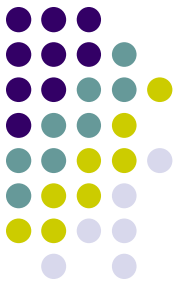
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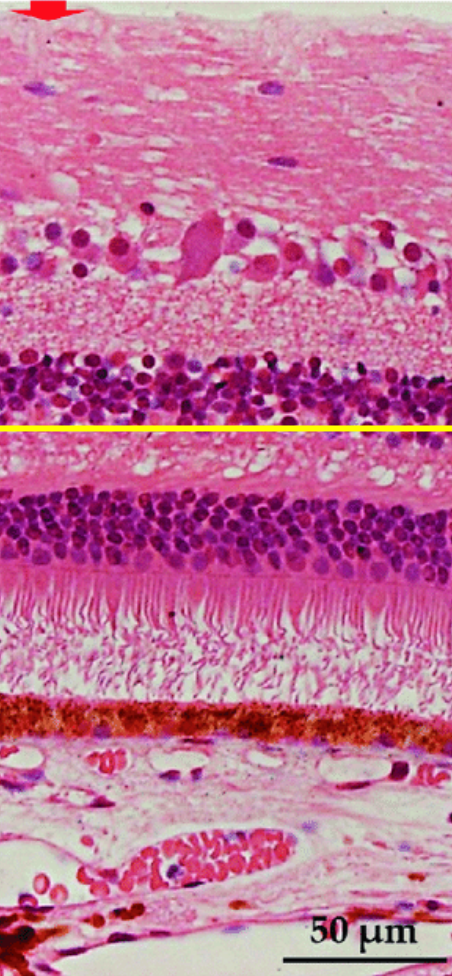
***Not** vascularized by the CRA
(or any other source).
Oxygenated via diffusion from
the choroidal circulation.*

Here is a micrograph of a normal human retina. The **yellow line** depicts the level below which retinal vessels do not pass. Instead, the outer-retina cells receive O_2 via diffusion from the choroid.

ARMD



Light



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Ganglion cell layer

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Inner nuclear layer

Outer plexiform layer

Outer nuclear layer

Layer of Rods and Cones

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Choroid

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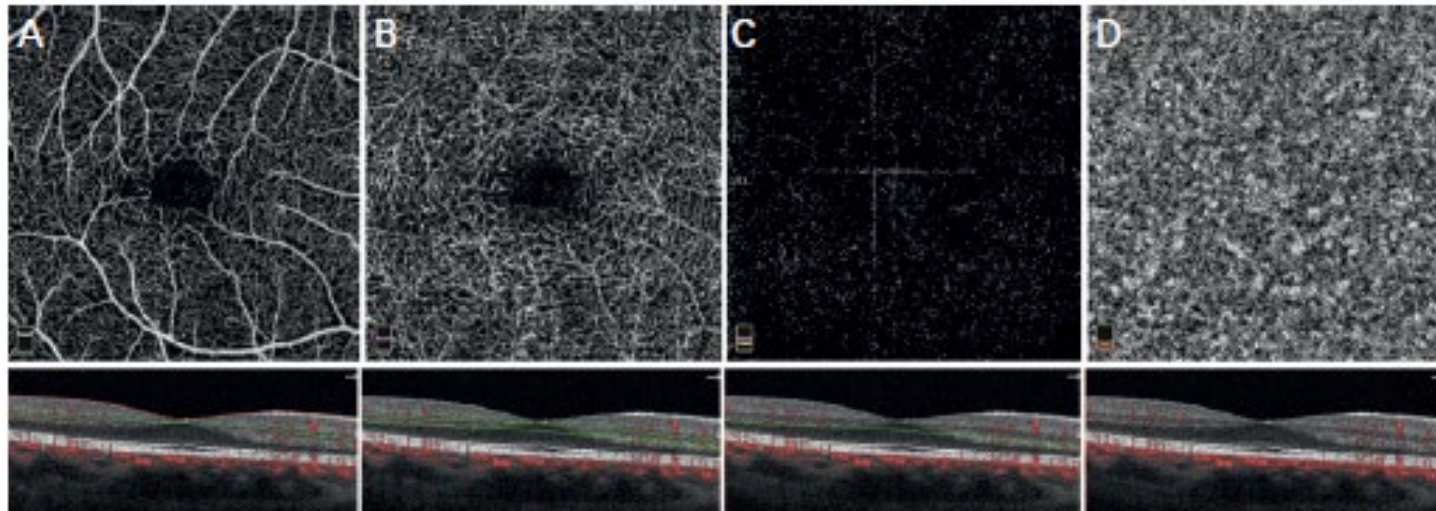
Here is a micrograph of a normal human retina. The **yellow line** depicts the level below which retinal vessels do not pass. Instead, the outer-retina cells receive O₂ via diffusion from the choroid.

Remember: The normal outer retina has no blood vessels!

ARMD

Figure 1: Optical Coherence Tomography Angiography of a Normal Eye

Very important—this is an OCTA of a normal eye

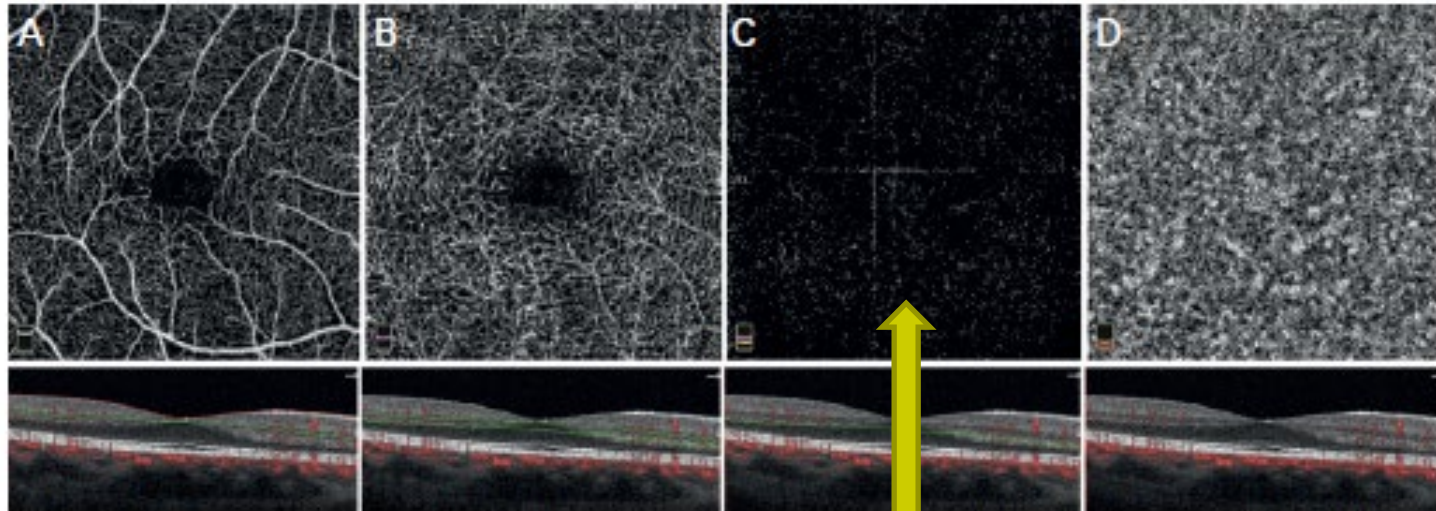


Optical coherence tomography (OCT) angiograms and corresponding OCT B-scans of the (A) superficial inner retina, (B) deep inner retina, (C) outer retina, (D) choriocapillaris. Note the regular ovoid foveal avascular zone, and homogeneity of vascular density of the retinal vasculature and choriocapillaris.

ARMD

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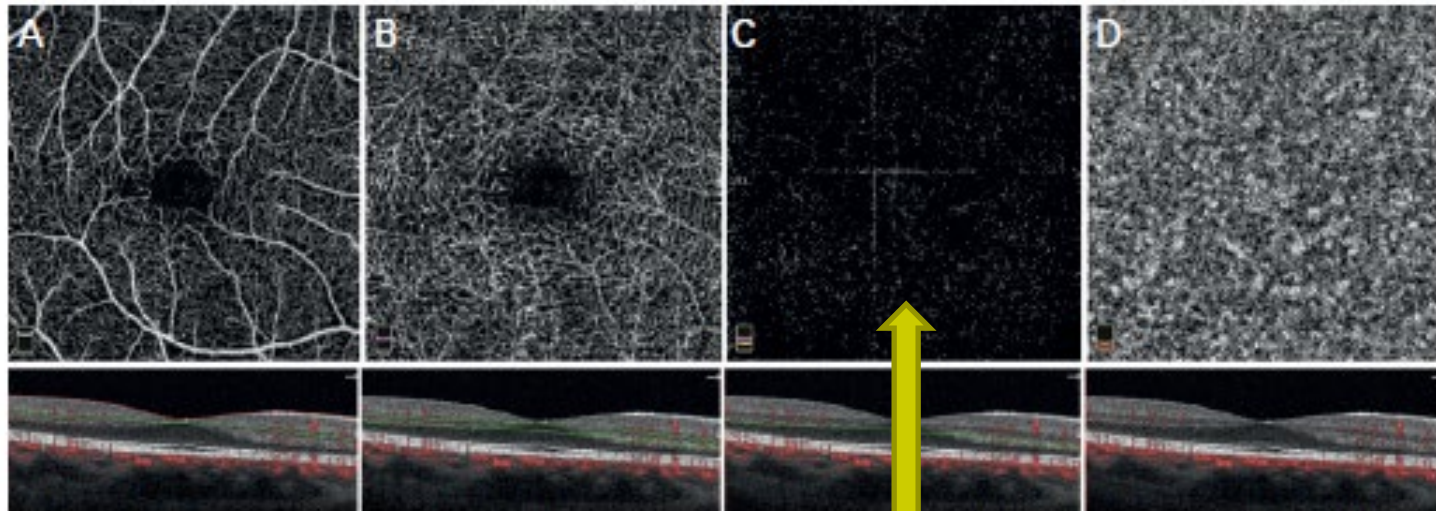
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Take special note of the **absence** of vascular structures within the outer retina.

ARMD

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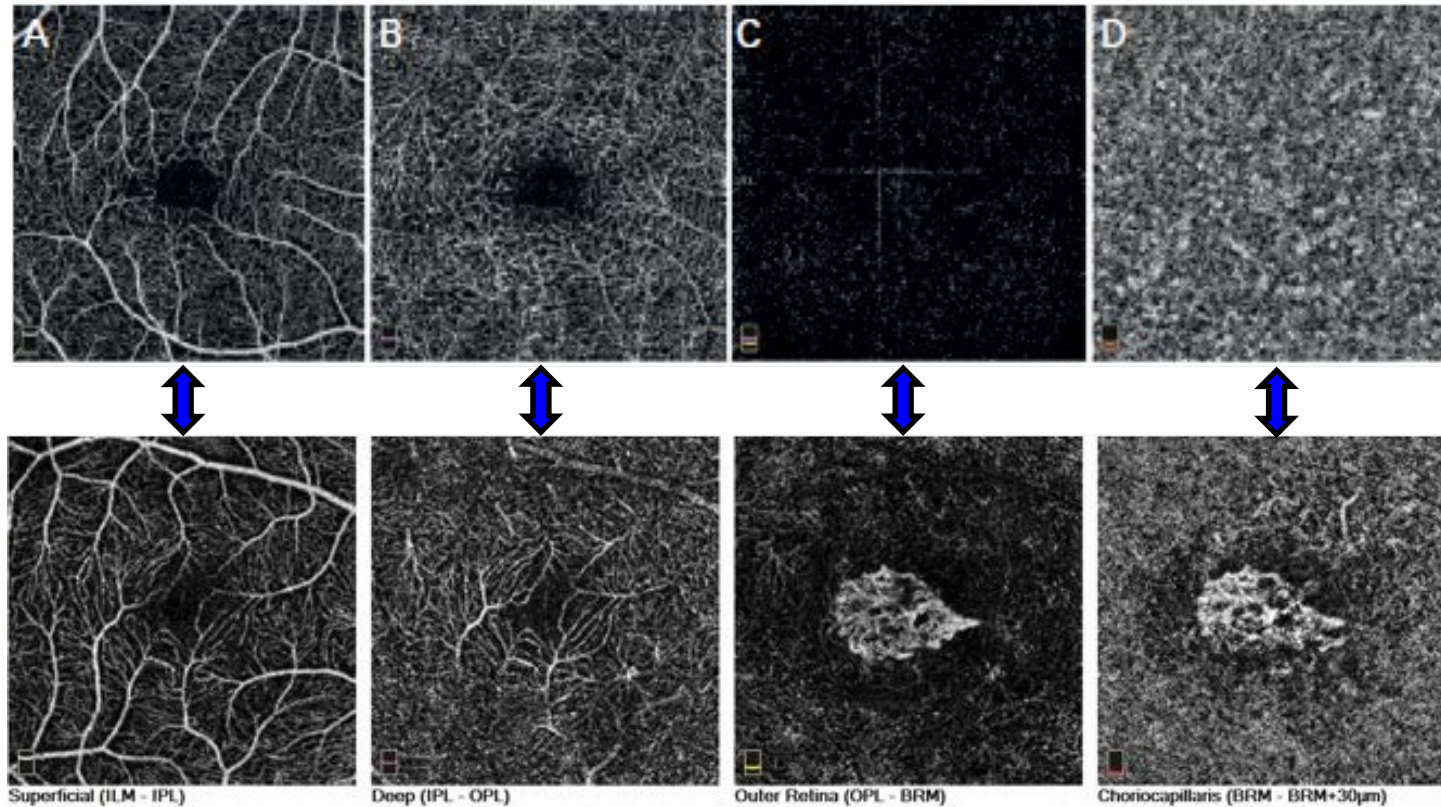


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Take special note of the **absence** of vascular structures within the outer retina. Again: This portion/layer of the retina is avascular under normal circumstances.

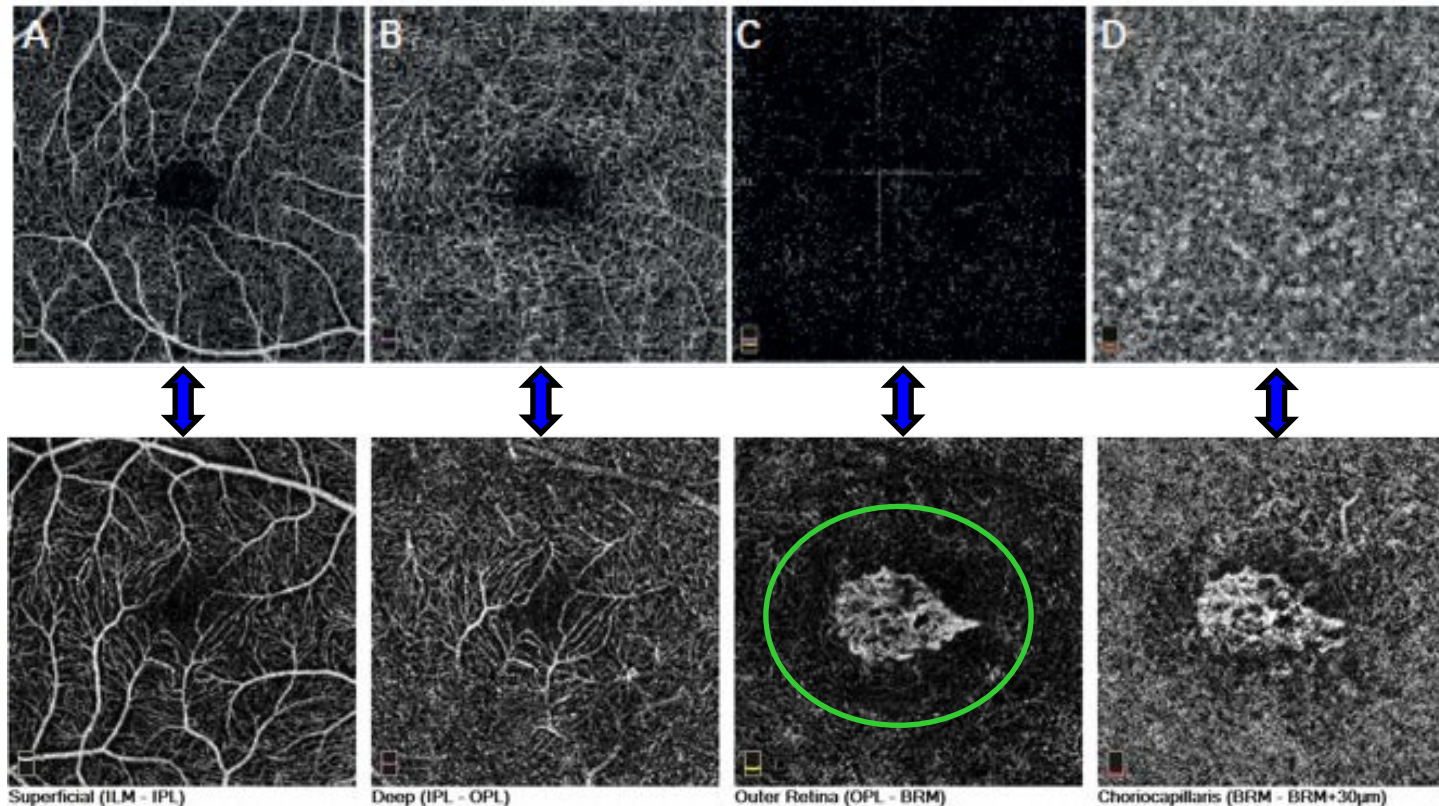


Figure 1: Optical Coherence Tomography Angiography of a Normal Eye



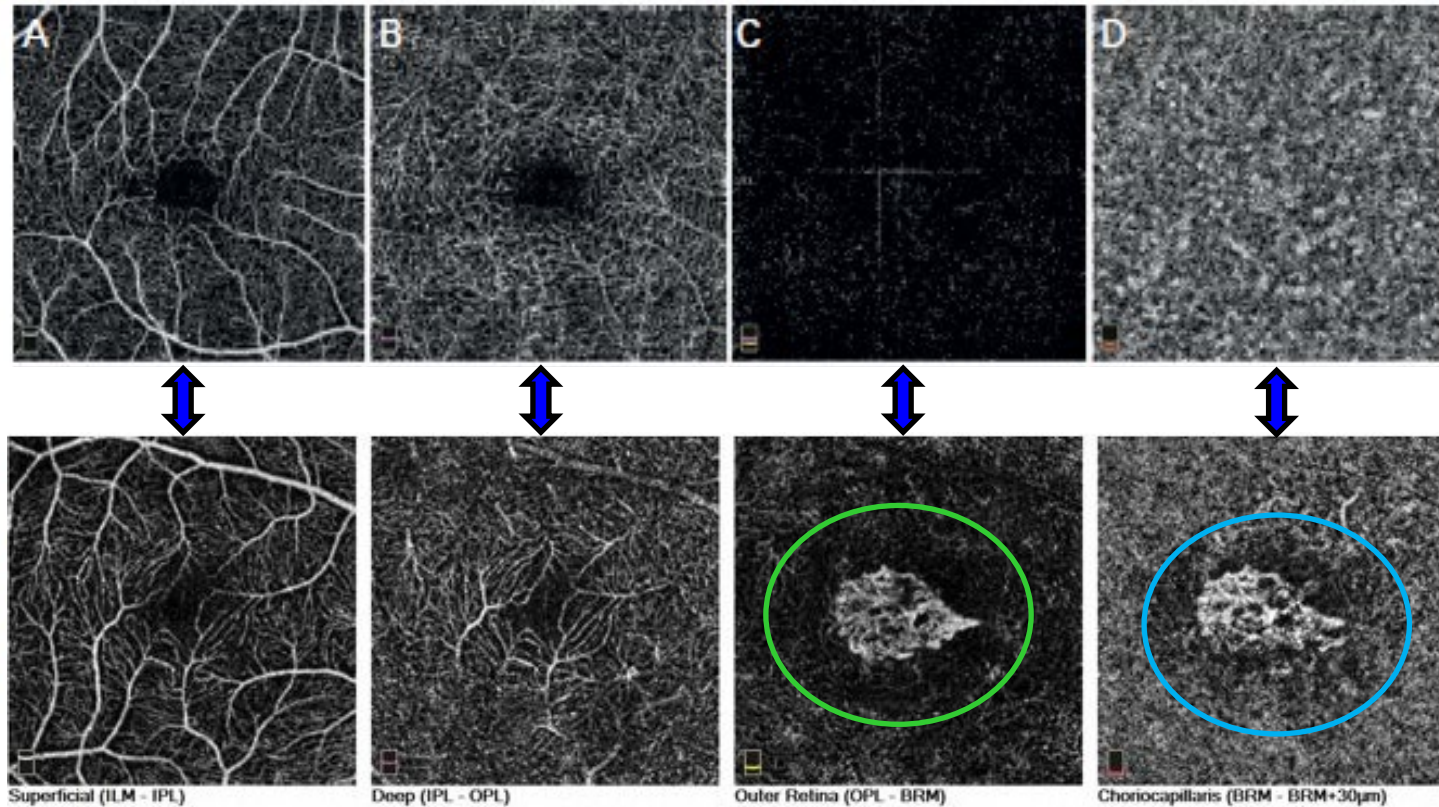
OCTA of the same layers, but in an eye with a CNVM

Figure 1: Optical Coherence Tomography Angiography of a Normal Eye

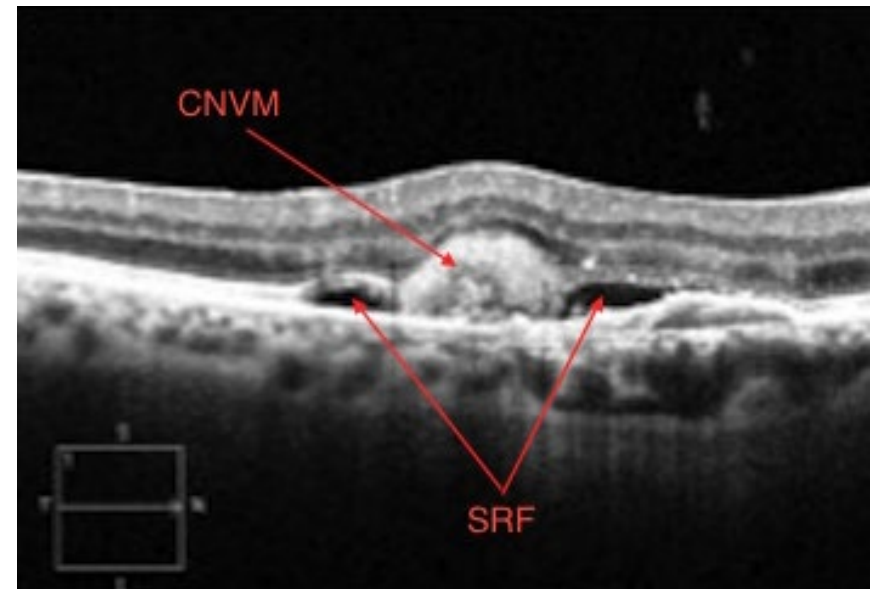
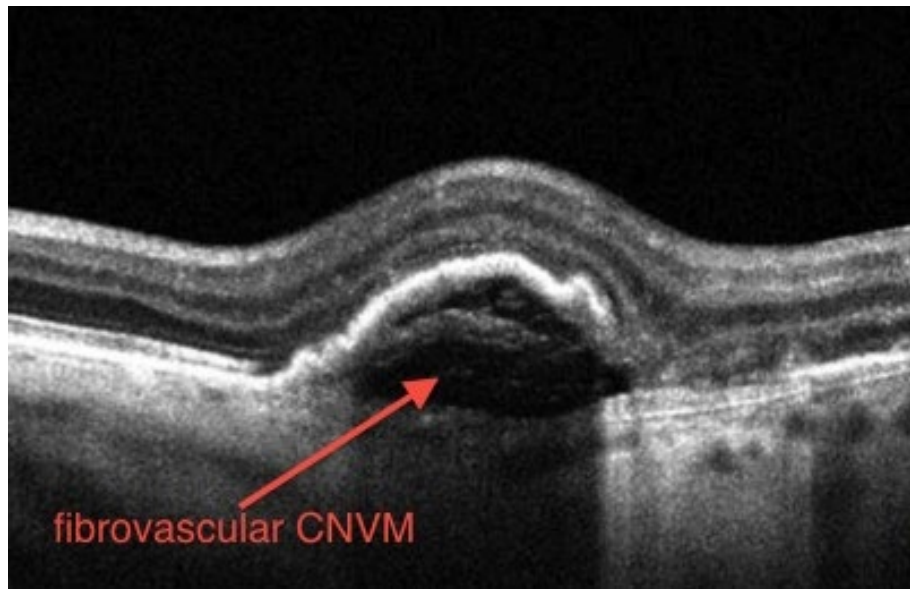
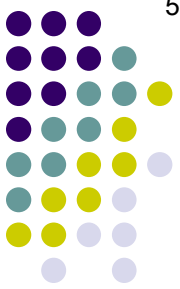


OCTA of the same layers, but in an eye with a CNVM. Note the presence of vasculature within the normally avascular outer retina (green circle). **This is a CNVM.**

Figure 1: Optical Coherence Tomography Angiography of a Normal Eye



OCTA of the same layers, but *in an eye with a CNVM*. Note the presence of vasculature within the normally avascular outer retina (green circle). This is a CNVM. You can see its origin in the choriocapillaris (blue circle).



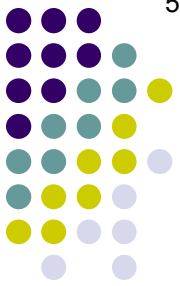
CNVM: OCT (*SRF* = subretinal fluid)

ARMD

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In contrast, *nonexudative* (aka *dry* or *non-neovascular*) ARMD is defined by the presence of drusen, RPE changes, and/or geographic atrophy (GA). In contrast with the sudden and severe loss of visual acuity (VA) associated with exudative dz, nonexudative ARMD is insidious, producing gradual VA loss of mild-to-moderate severity.

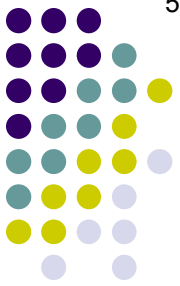


ARMD

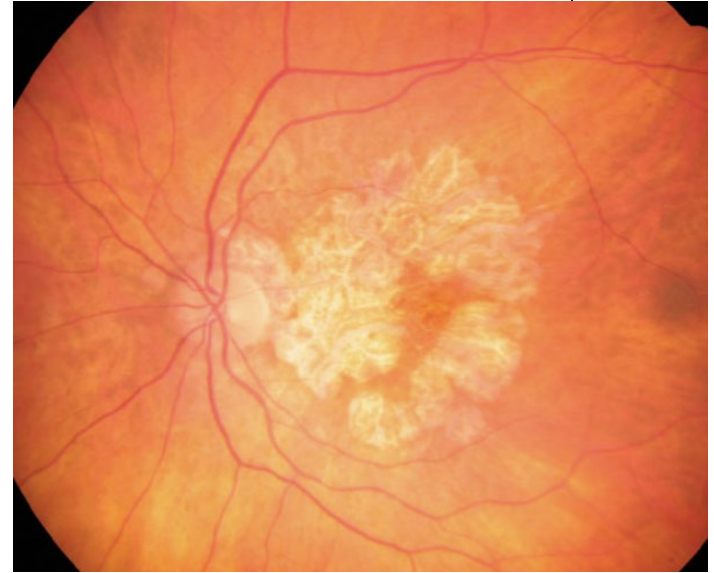
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ARMD



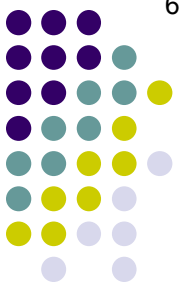
Geographic atrophy (GA)

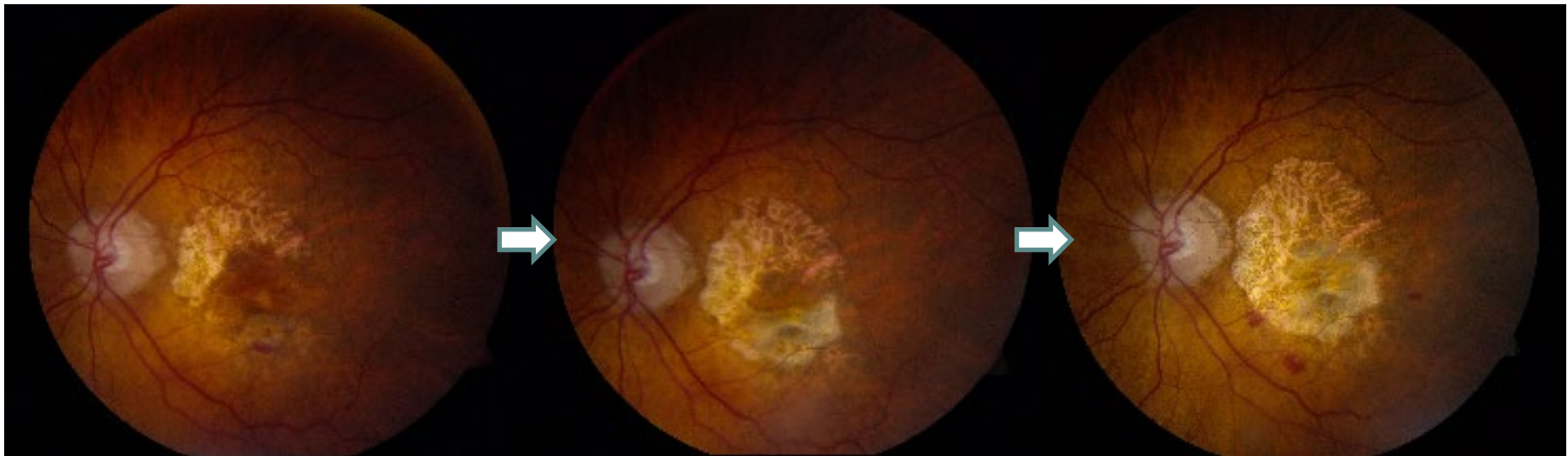
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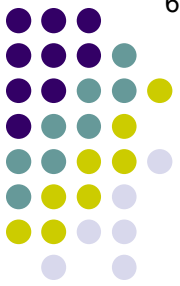
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Progression of GA over a 2.5 year period. Note the characteristic perifoveal→foveal-center pattern.

ARMD



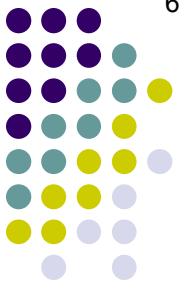
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ARMD



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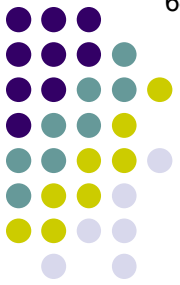
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ARMD

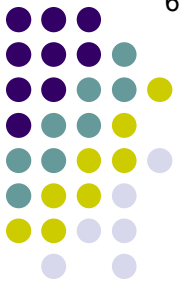
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ARMD

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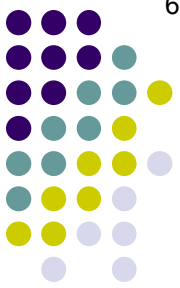
A tremendous amount is known about ARMD, but much more remains to be discovered. Part of the challenge is, most of the changes that occur in ARMD—RPE atrophy; PR loss—are also seen in the normal aging process.



ARMD

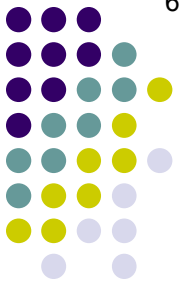
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A tremendous amount is known about ARMD, but much more remains to be discovered. Part of the challenge is, most of the changes that occur in ARMD—RPE atrophy; PR loss—are also seen in the normal aging process. **It is not yet clear why some aging eyes go on to develop clinical ARMD whereas others do not.**



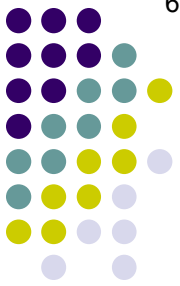
ARMD

- **Key fact #6:** The pathogenesis of ARMD is not well understood, but the *complement system* is strongly implicated in it



ARMD

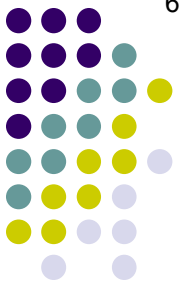
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There are two types of immune responses: *innate* (aka *natural*) and *adaptive* (aka *acquired*). The innate immune response relies on 'preprogrammed' immune cells (PMNs; macrophages) to recognize foreign material encountered in tissue or blood, whereas the adaptive response involves 'education,' with surveillance cells (T- and B-cells) learning to recognize and remember foreign antigens.

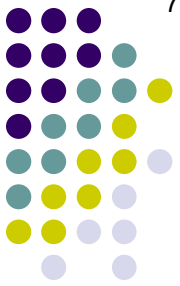
ARMD

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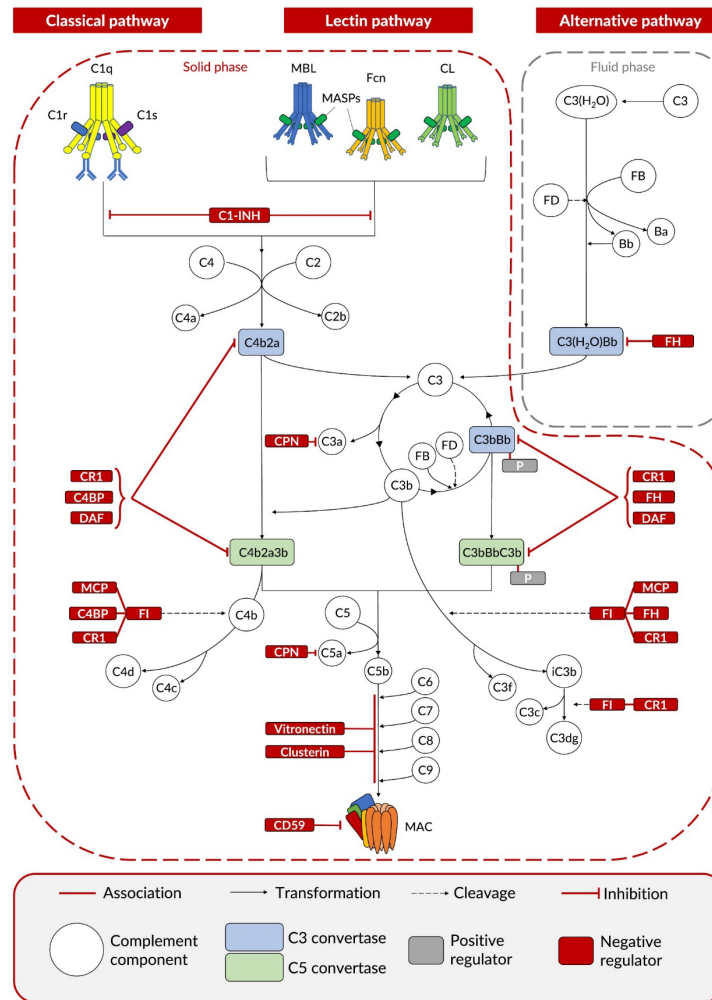
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ARMD



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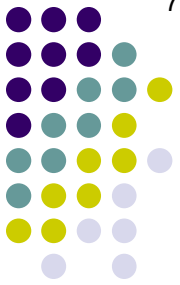
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Complement cascade. Give this Figure a brief once-over, then move on. (It's intended to do nothing more than reinforce the fact that the complement cascade is complex indeed.)

ARMD

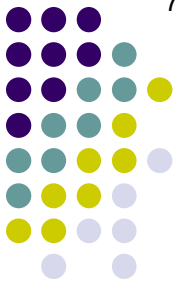
- **Key fact #7:** The DDx for exudative ARMD is extensive, but the three top conditions are ocular histoplasmosis, angioid streaks, and pathologic myopia

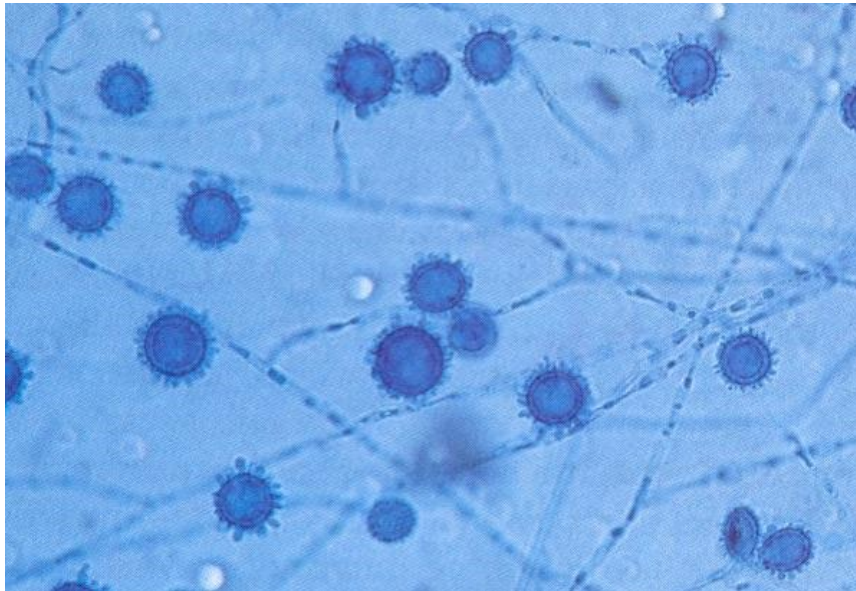
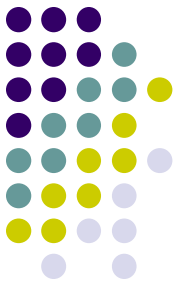


ARMD

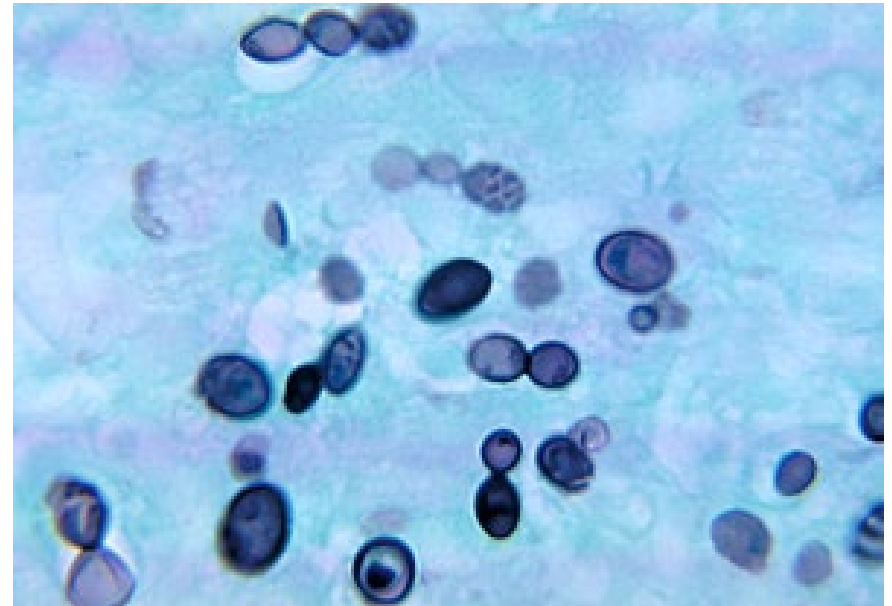
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H capsulatum: Mold (filamentous) form

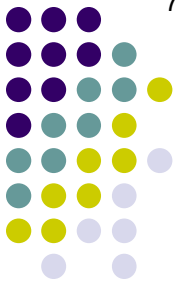


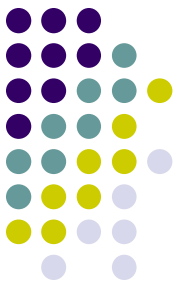
H capsulatum: Yeast form

ARMD

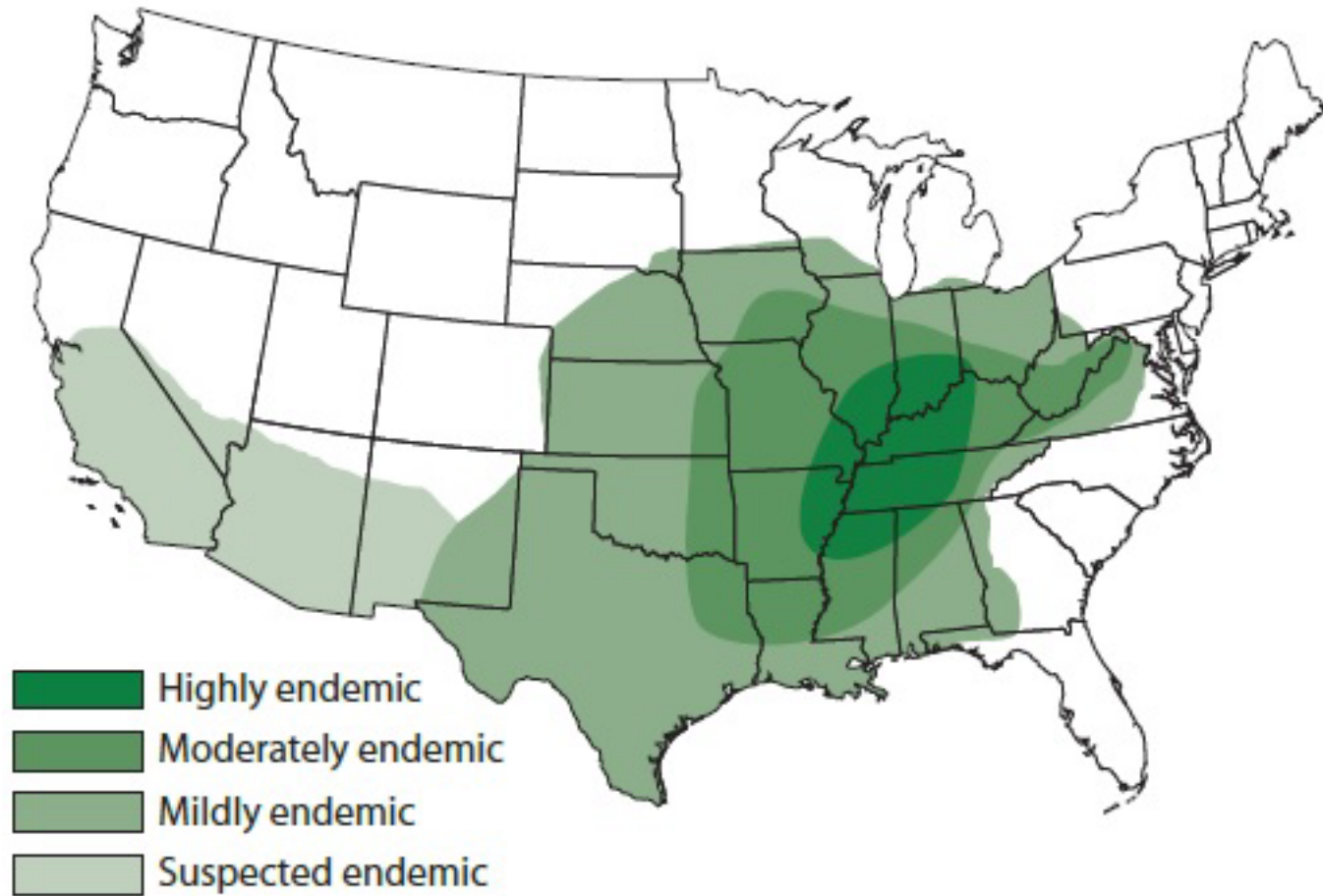
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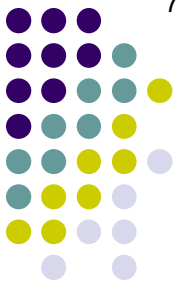
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Areas Endemic for Histoplasmosis



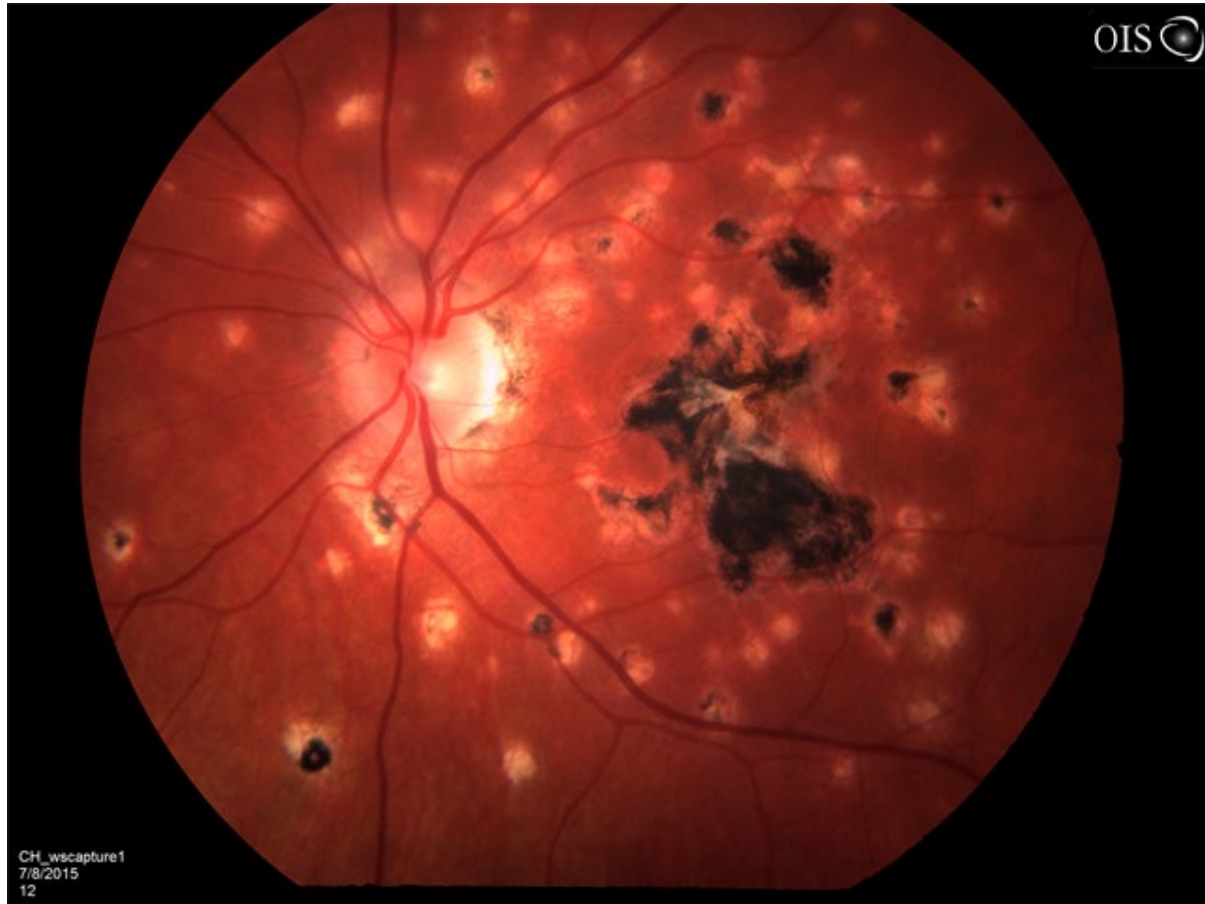
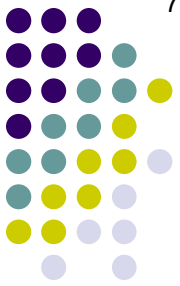


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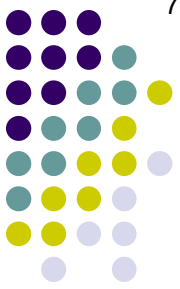
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- Histo spots
- Peripapillary atrophy
- Disciform CNVM lesions (either active or old/inactive)

ARMD



OHS: The classic triad



Active disciform lesion (ie, CNVM)



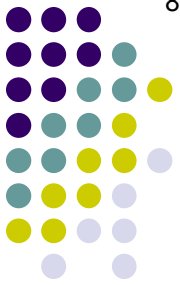
Inactive disciform lesion

OHS

ARMD

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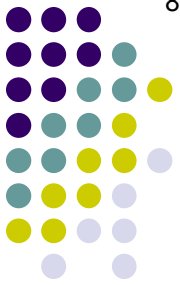
The pathologic hallmark of angioid streaks is a thickened and brittle Bruch's membrane. These abnormalities make Bruch's prone to breakage, which in turn allows the ingress of choriocapillaris vessels forming a CNVM.



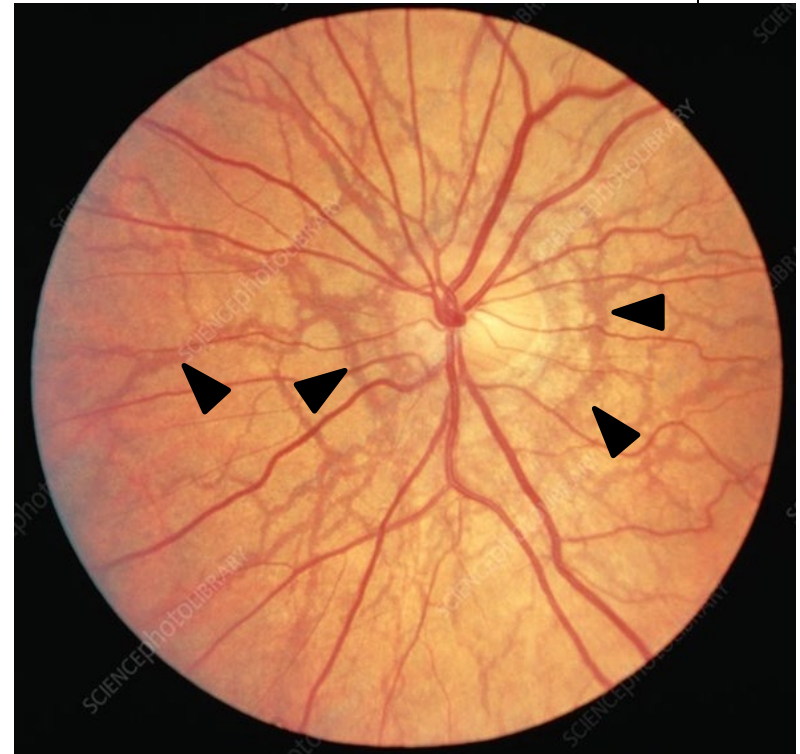
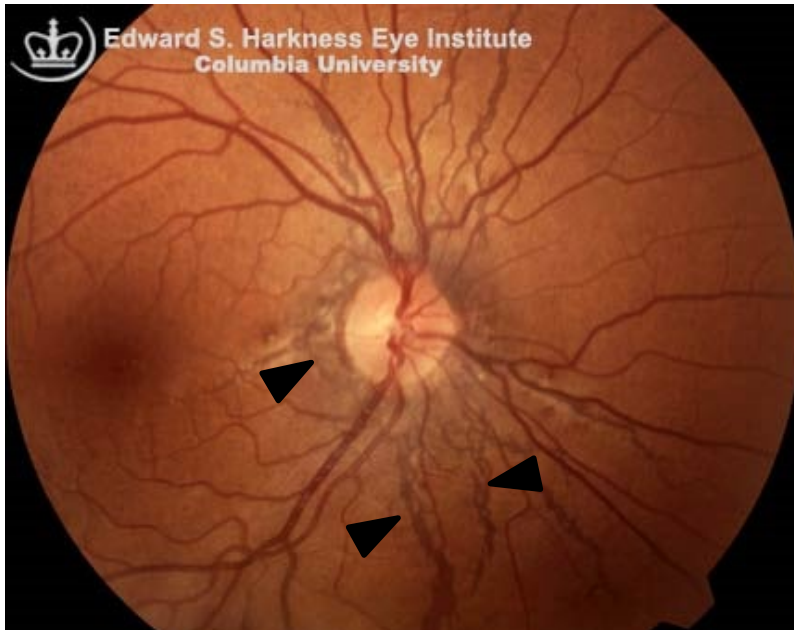
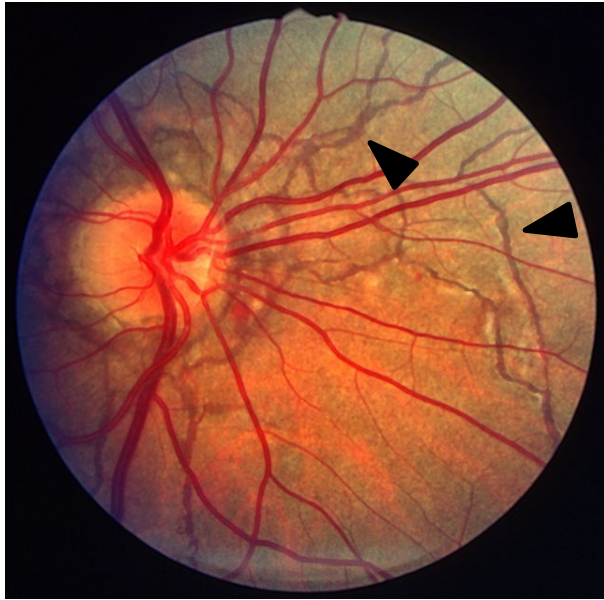
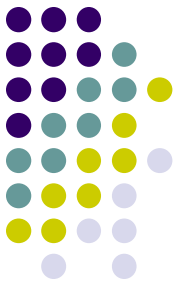
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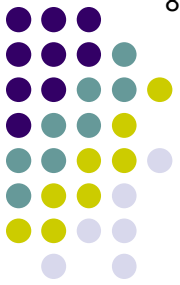


ARMD



Angioid streaks (arrowheads).
Note that only a few of the many
present have been marked.

ARMD



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Half of cases are idiopathic; the rest are associated with systemic abnormalities. The well-known mnemonic for angioid streak's associations is *PEPSI*:

Ppseudoxanthoma elasticum (PXE)

Ehlers-Danlos syndrome

Paget's disease of bone

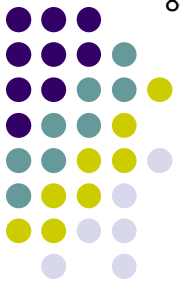
Sickle-cell disease

Idiopathic (ie, no association)

ARMD

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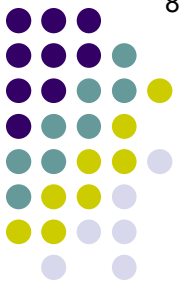
An axial length of 26.5 mm is the cutoff for defining pathologic myopia. The finding on DFE that puts high myopes at risk for CNVM are *lacquer cracks*. Like angioid streaks, lacquer cracks are breaks in Bruch's membrane that provide an opening for CNVM to enter the outer retina.



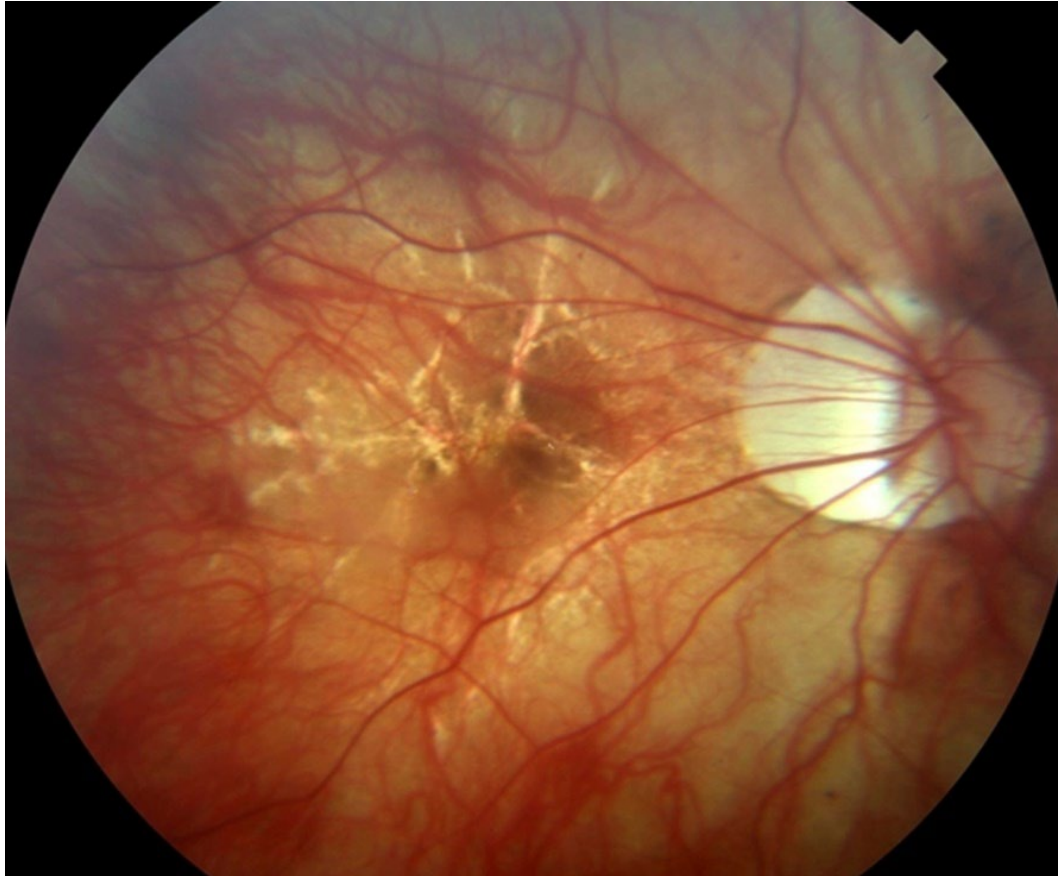
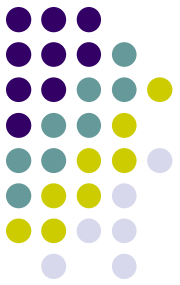
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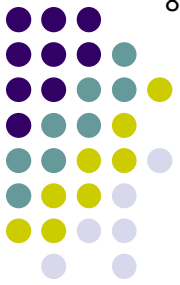
ARMD



Pathologic myopia: Lacquer cracks (note also the abnormal ONH appearance)

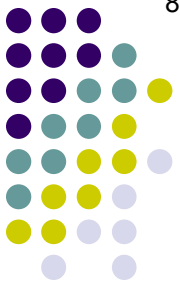
ARMD

- **Key fact #8:** VEGF plays a key role in exudative ARMD, and as a result, interdicting VEGF is key in managing it



ARMD

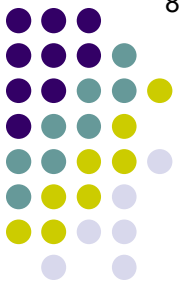
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Fundamentally, the CNVM that defines wet ARMD is a pathologic form of angiogenesis. *Angiogenesis* refers to the cascade of events involved in the formation of new blood vessels. Vascular endothelial growth factor (VEGF) is an extracellular signaling molecule integral to the angiogenesis cascade. Research indicates VEGF plays a causal role in the initiation of CNVM in wet ARMD.

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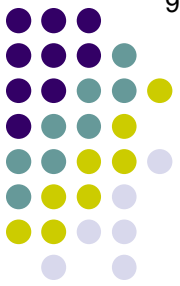


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Because of its importance in CNVM formation, VEGF presents a potent target for therapies intended to interdict CNVM. A number of highly effective anti-VEGF compounds have been developed (and more are in the therapeutic pipeline).

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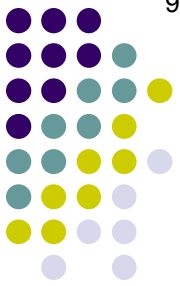


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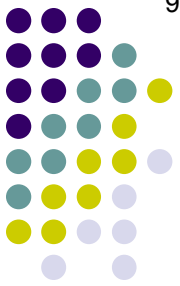


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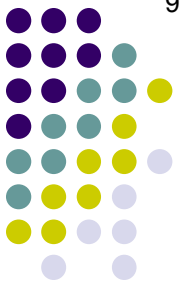
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ARMD



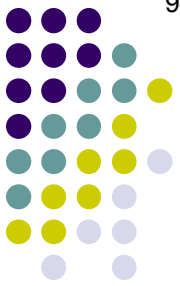
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ARMD

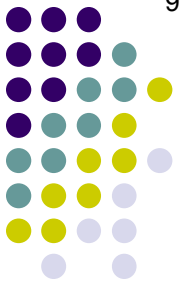
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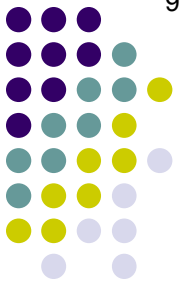
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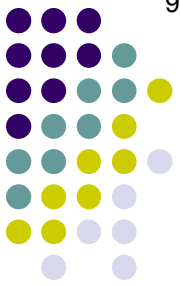
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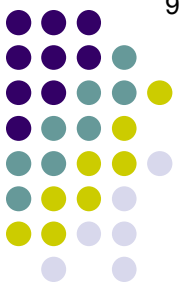
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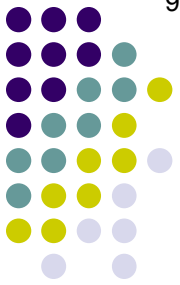
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Of note, β -carotene supplementation was associated with an increased risk of lung Ca in smokers. As smokers comprise a substantial proportion of ARMD pts, this is a significant finding. Happily, a follow-up study (AREDS2) found that for β -carotene could be replaced with xanthophylls (specifically, lutein and zeaxanthin) without loss of efficacy (and with no increased risk of lung Ca).





That's it! Go through this slide-set a couple of times (at least) until you feel like you have a handle on it. [When you're ready, do slide-set R69, which covers this material in a Q&A format \(and more detail\).](#)