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
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!)
Key fact #2: Age is the strongest risk factor for ARMD
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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.
Key fact #3: The clinical hallmark of ARMD is the presence of *drusen* in the macula
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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.
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Clinicians categorize drusen along several dimensions:
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Clinicians categorize *drusen* along several dimensions:

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

Intermediate drusen

Large drusen

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- **By the nature/appearance of their boundaries:**
  -- ’Hard’ drusen (discrete, well demarcated boundaries)
Hard drusen
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- By size (Small, Intermediate; Large)

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    - ‘Hard’ drusen (discrete, well demarcated boundaries)
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Soft drusen
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--'Hard' drusen (discrete, well demarcated boundaries)

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

--'Confluent' drusen (contiguous drusen without clear boundaries)
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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- **By where in the retina they are located**
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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:

1) Innermost
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Outermost
Bruch’s membrane consists of 5 layers:

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 RPE basement membrane)

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Bruch's membrane consists of 5 layers:

1. Basement membrane of RPE
2. Inner collagenous layer
3. Elastic layer
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The plasma membranes (aka the basal lamina) of the RPE cells rest directly on their BM
Quick review of outer retinal anatomy:

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

PR outer segs interdigitate with the apical RPE surface
Quick review of outer retinal anatomy:

- **Bipolar cells** synapse with the PRs
- **PR outer segs** interdigitate with the apical RPE surface

Bruch’s membrane layers:

1. **Basement membrane** of RPE
2. **Inner collagenous layer**
3. **Elastic layer**
4. **Outer collagenous layer**
5. **Basement membrane** of choriocapillaris

PR outer segs interdigitate with the apical RPE surface.

RPE cells

Bipolar cells
Quick review of outer retinal anatomy:

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
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- Bipolar cells synapse with the PRs
- PR outer segs interdigitate with the apical RPE surface

- Down here is the choriocapillaris
Quick review of outer retinal anatomy:

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
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Bipolar cells synapse with the PRs
PR outer segs interdigitate with the apical RPE surface

Bipolar cells
PR outer segs
RPE cells

Choriocapillaris
Choroid

Innermost
Outermost

Down here is the choriocapillaris
And the choroid
Quick review of outer retinal anatomy:

- Bipolar cells synapse with the PRs
- 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

Choriocapillaris
Choroid
Sclera

Down here is the choriocapillaris
And the choroid
And the sclera

Innermost
Outermost
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  - 'Soft' drusen (amorphous, poorly demarcated boundaries)
  - 'Confluent' drusen (contiguous drusen without clear boundaries)
- **By where in the retina they are located**:

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

By where in the retina they are located:
● **Key fact #3**: The clinical hallmark of ARMD is the presence of *drusen* in the macula

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By **where in the retina they are located**:
-- *Basal laminar drusen* are between the RPE cells and their basement membrane
Bruch's membrane

1) Basement membrane of RPE
2) Inner collagenous layer
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- 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
What are the five layers of Bruch's membrane?

- Baseline membrane of RPE
- Inner collagenous layer
- Elastic layer
- Outer collagenous layer
- Baseline membrane of choriocapillaris
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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
What are the five layers of Bruch's membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris
Key fact #4: There are two types of ARMD: Exudative and nonexudative.
Key fact #4: There are two types of ARMD: *Exudative* and *nonexudative*

To say a case of ARMD is *exudative* (aka wet or neovascular) is to say that a frond of fibrovascular tissue has grown into a space where none should be: within Bruch’s membrane, beneath the RPE, and/or in the subretinal space. Because they originate from choroidal vessels, these fronds are called *choroidal neovascular membranes* (CNVM).
1) Inner collagenous layer
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris

1) PR outer segs
2) Bipolar cells
3) RPE cells

CNVM within Bruch’s membrane

Bipolar cells

ARMD
What are the five layers:

1. Basement membrane of RPE
2. Inner collagenous layer
3. Elastic layer
4. Outer collagenous layer
5. Basement membrane of choriocapillaris

CNVM in the sub-RPE space
What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris
FP and FA of a CNVM in exudative ARMD
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Let’s take a moment to review the blood supply of the retina
Here is a micrograph of a normal human retina.
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Vascularized and oxygenated by branches of the central retinal artery (CRA)

Not vascularized by the CRA (or any other source).
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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.
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Remember: The normal outer retina has no blood vessels!
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.
Take special note of the absence of vascular structures within the outer retina.
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.
OCTA of the same layers, but in an eye with a CNVM
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.
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)
Key fact #4: There are two types of ARMD: Exudative and nonexudative

To say a case of ARMD is exudative (aka wet or neovascular) is to say that a frond of fibrovascular tissue has grown into a space where none should be: within Bruch’s membrane, beneath the RPE, and/or in the subretinal space. Because they originate from choroidal vessels, these fronds are called choroidal neovascular membranes (CNVM). CNVM break into or through Bruch’s membrane via drusen-induced defects within it. CNVM are highly prone to bleeding and/or leaking; when they do, pts usually experience the acute onset of a ‘gray spot’ in their vision. If untreated, subfoveal CNVM result in devastating, irreversible vision loss.

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.
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Geographic atrophy (GA)
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Progression of GA over a 2.5 year period. Note the characteristic perifoveal→foveal-center pattern.
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Note: ‘Advanced ARMD’ is defined by the presence of either CNVM…
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**Key fact #4:** There are two types of ARMD: *Exudative* and *nonexudative*.

*Note:* ‘Advanced ARMD’ is defined by the presence of either CNVM...or GA.
Key fact #5: RPE and photoreceptor abnormalities are common findings in 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.
● **Key fact #5:** RPE and photoreceptor abnormalities are common findings in ARMD

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

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. However, neither immune system is capable of producing an effective response on its own. Instead, both rely on inflammatory mediators—host-generated substances that act as force-multipliers for the immune response. Inflammatory mediators can be a single molecule, or a complex enzymatic process. The classic example of an enzymatic-cascade inflammatory mediator is the complement cascade. Activation of the complement cascade results in damage that is central in the pathogenesis of both dry and wet forms of ARMD. The complement cascade is indeed complex, with 30+ components comprising three different pathways. At present, research indicates that certain variants of complement factor H (CFH) are of particular significance in the development of ARMD. (If you remember nothing else from this slide, remember CFH.)
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.)
Key fact #7: The DDx for exudative ARMD is extensive, but the three top conditions are ocular histoplasmosis, angioid streaks, and pathologic myopia
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OHS is an infectious posterior uveitis caused by the dimorphic fungus *Histoplasma capsulatum*. Bats and various bird species are the reservoir; spores in their droppings become aerosolized, infecting humans via inhalation.
*H capsulatum*: Mold (filamentous) form

*H capsulatum*: Yeast form
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--- Histo spots
--- Peripapillary atrophy
--- Disciform CNVM lesions (either active or old/inactive)
OHS: The classic triad
Active disciform lesion (ie, CNVM)  

Inactive disciform lesion  

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

- Pseudoxanthoma elasticum (PXE)
- Ehlers-Danlos syndrome
- Paget’s disease of bone
- Sickle-cell disease
- Idiopathic (ie, no association)
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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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Pathologic myopia: Lacquer cracks (note also the abnormal ONH appearance)
Key fact #8: VEGF plays a key role in exudative ARMD, and as a result, interdicting VEGF is key in managing it.
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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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). *Bevacizumab* (brand name *Avastin*) is a recombinant monoclonal antibody against VEGF. Originally developed to treat metastatic cancer (by depriving it of its blood supply), bevacizumab is highly effective in causing both anatomic regression of CNVM as well as reversal of CNVM-induced VA loss.
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