Before you begin: This is a big topic, and big topics beget big slide-sets. There are natural breaks around slides 217 and 442; I placed a \textit{break time!} slides at those points to mark them.
Age-related macular degeneration is the #1 cause of blindness in adults age # in resource-rich nations.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

*What proportion of Americans 65+ have ARMD?*
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD?
10%
Age-related macular degeneration is the #1 cause of blindness in **adults age 50+** in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*

10%
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD? 75+?
10%. 25%!
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

What proportion of Americans 65+ have ARMD? 75+? 10%. 25%!

Speaking of demographics: Is ARMD risk related to ethnicity? Yes, ______ have the highest risk and ______ the lowest.
Age-related macular degeneration is the #1 cause of blindness in **adults age 50+** in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*
10%. 25%!

*Speaking of demographics: Is ARMD risk related to ethnicity?*
Yes, whites have the highest risk and AAs the lowest.
Age-related macular degeneration is the #1 cause of blindness in **adults age 50+** in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*
10%. 25%!

*Speaking of demographics: Is ARMD risk related to ethnicity?*
Yes, whites have the highest risk and AAs the lowest; and Asians and Hispanics fall in-between.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

*What proportion of Americans 65+ have ARMD? 75+?*
10%. 25%!

*Speaking of demographics: Is ARMD risk related to ethnicity?*
Yes, whites have the highest risk and AAs the lowest; Asians and Hispanics fall in-between.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. 

Age is the strongest risk factor for ARMD.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

*Age* is the strongest risk factor for ARMD.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

**Age** is the strongest risk factor for ARMD.

*What are the other ARMD risk factors?*

- Family history;
- Female;
- Light iris color;
- Age;
- Anglo (i.e., white ethnicity);
- Smoking; Sun exposure;
- Hyperopia; Hypercholesterolemia; High CRP.

The mnemonic is...
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

Age is the strongest risk factor for ARMD.

What are the other ARMD risk factors?

- F
- L
- Age
- S
- H

The mnemonic is... **FLASH**

- (two F’s)
- (another A)
- (two S’s)
- (three H’s)
What are the other ARMD risk factors?

- Family history; Female
- Light iris color
- Age; Anglo (i.e., white ethnicity)
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The mnemonic is... **FLASH**
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. **Age** is the strongest risk factor for ARMD.

**What are the other ARMD risk factors?**
- Family history; Female
- Light iris color
- Age; Anglo (ie, white ethnicity)
- Smoking; Sun exposure
- Hyperopia; Hypercholesterolemia; High CRP

*Of the modifiable ones, which is most impactful?*
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations. **Age** is the strongest risk factor for ARMD.

What are the other ARMD risk factors?

- Family history; Female
- Light iris color
- Age; Anglo (ie, white ethnicity)
- Smoking; Sun exposure
- Hyperopia; Hypercholesterolemia; High CRP

*Of the modifiable ones, which is most impactful? Smoking*
Age-related macular degeneration 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.
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The clinical hallmark of ARMD is the presence of drusen in the macula.

What are drusen?

Drusen are aggregates of material within the outer-retinal space.

What sorts of substances constitute the material?

Proteins and lipids—detritus shed by photoreceptors, mainly.

How are drusen categorized?

There are several ways:
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Drusen are categorized by their size?
Drusen are categorized by the boundaries?
Drusen are categorized by the retinal layer in which they’re located?

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  --?
  --?
  --?
  --?

- Drusen are categorized by their **boundaries**

- Drusen are categorized by the **retinal layer** in which they’re located
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  - Small
  - Intermediate
  - Large
  - Drusenoid PED

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**Age** is the strongest risk factor for ARMD.

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  - **Small:** \(<63 \mu m\) diameter
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- **Drusen are categorized by their boundaries**
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Small drusen
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There are several ways:

- *Drusen are categorized by their size:*
  - Small: <63 μm diameter
  - Intermediate: 63–124
  - Large
  - Drusenoid PED

- *Drusen are categorized by the retinal layer in which they’re located*

- *Drusen are categorized by their boundaries*
Intermediate drusen
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**How are drusen categorized?**
There are several ways:

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  - Large: ≥125
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There are several ways:

- **Drusen are categorized by their size:**
  - Small: <63 \( \mu \text{m} \) diameter
  - Intermediate: 63–124
  - Large: \( \geq 125 \)
  - Drusenoid PED

- Drusen are categorized by the retinal layer in which they’re located.

- Drusen are categorized by their boundaries.
Large drusen
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How are drusen categorized?
There are several ways:

- Drusen are categorized by their size:
  - Small: <63 µm diameter
  - Intermediate: 63–124
  - Large: ≥125

- Drusen are categorized by the retinal layer in which they're located:

- Drusen are categorized by their boundaries.

How the heck are you supposed to know the size of a druse in microns?

By comparing it to the size of a retinal vein as it crosses the border of the ONH (their diameter is about 124 µm there, and thus make a convenient reference).
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- **Boundaries**
- **Retinal layer** in which they're located

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Proteins and lipids—detritus shed by photoreceptors, mainly

**How are drusen categorized?**
There are several ways:

*Drusen are categorized by their size:*
- Small: <63 μm diameter
- Intermediate: 63–124
- Large: ≥125
- Drusenoid PED: ≥350

*Drusen are categorized by the retinal layer in which they’re located*

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Drusen are categorized by their boundaries.

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In this context, what does PED stand for?

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Drusen are categorized by their boundaries.

In this context, what does PED stand for?

Ped pigment epithelium detachment.

It means the RPE is no longer in direct contact with its basement membrane, or that the RPE/basement membrane complex is separated from the underlying structure.

Why is it a big deal if the RPE is separated from its BM, or deeper structures?
Recall that the RPE plays an indispensable role in the health of the photoreceptors.
Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris. Thus, a PED can lead to RPE dysfunction, death and atrophy. This in turn can lead to photoreceptor dysfunction, death and atrophy, which results in vision loss.

There are three basic forms of PED—what are the other two? Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?
- **Drusenoid**: Uniformly hyperreflective
- **Serous/hemorrhagic**: Solid with ‘clefts’
- **Fibrovascular**: Sub-RPE space ‘empty’
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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What does it mean to say the RPE is ‘detached’?
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Drusen are categorized by:
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Drusen are categorized by their boundaries:
- Inner: On RPE
- Outer: On photoreceptors

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In this context, what does PED stand for? Pigment epithelium detachment.

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Coalescence of large soft drusen over time to form a drusenoid PED with increasing accumulation of vitelliform material (red arrow) and overlying pigmentary changes, as seen on color fundus photograph (CFP) and OCT.

OCT: Drusenoid PED
Age-related macular degeneration (ARMD) is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Pigment epithelium detachment.

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What are drusen? Aggregates of material within the outer-retinal space.

What sorts of substances constitute the material? Proteins and lipids—detritus shed by photoreceptors, mainly.

How are drusen categorized? There are several ways:

- **Small**: <63 μm diameter
- **Intermediate**: 63–124
- **Large**: ≥125
- **DrusenoidPED**: >350

What do the terms 'size' and 'boundaries' refer to? Drusen are categorized by the retinal layer in which they're located. In this context, what does PED stand for? Pigment epithelium detachment.

What does it mean to say the RPE is 'detached'? It means the RPE is no longer in direct contact with its basement membrane, or that the RPE/basement membrane complex is separated from the underlying structure.

**Why is it a big deal if the RPE is separated from its BM, or deeper structures?** Recall that the RPE plays an indispensable role in the health of the photoreceptors. Recall further that the RPE meets its metabolic needs via blood supplied by the underlying choriocapillaris.
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**There are three basic forms of PED—what are the other two?**
- Drusenoid
- ?
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**There are three basic forms of PED—what are the other two?**

--Drusenoid
--Serous
--Fibrovascular
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There are three basic forms of PED—what are the other two? Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?

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**There are three basic forms of PED—what are the other two?**
Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?

- **Drusenoid**: Uniformly hyperreflective
- **Serous**
- **Fibrovascular**
Drusenoid PEDs have a uniform (aka ‘homogenous’), mildly hyper-reflective interior.
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There are three basic forms of PED—what are the other two? Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?
- Drusenoid: Uniformly hyperreflective
- Serous: Sub-RPE space ‘empty’
- Fibrovascular
Serous PEDs are seen on OCT as areas of smooth, sharply demarcated, dome-shaped RPE elevation, typically overlying a homogenously hyporeflective space.
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- **Drusenoid:** Uniformly hyperreflective
- **Serous:** Sub-RPE space ‘empty’
- **Fibrovascular:** Solid with ‘clefts’
Fibrovascular PEDs appear to be filled with solid layers of material of medium reflectivity separated by hyporeflective clefts.
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Drusen are categorized by the **retinal layer** in which they’re located

Drusen are categorized by their **boundaries**:
- ?
- ?
- ?
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*Drusen are categorized by the *retinal layer* in which they’re located*:

*Drusen are categorized by their boundaries:*
--Hard
--Soft
--Confluent
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Which are described as being…
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- Hard: Discrete, well demarcated
- Soft
- Confluent

**Drusen are categorized by the retinal layer in which they’re located**
Hard drusen
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**drusen**

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Drusen are categorized by their boundaries:
- Hard: Discrete, well demarcated
- Soft: Amorphous, poorly demarcated
- Confluent

Which are described as being...
Soft drusen
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*Which are described as being…*
**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.
Age-related macular degeneration (ARMD) is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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  -- **Hard**: Discrete, well demarcated  
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Which type(s) carry a greater risk of dz progression?
- Age-related macular degeneration 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.

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Which type(s) carry a greater risk of dz progression?

Soft for sure, and probably confluent as well.
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Drusen are categorized by their **size**:
- **Small**: <63 μm diameter
- **Intermediate**: 63–124
- **Large**: ≥125
- **Drusenoid PED**: >350

Drusen are categorized by the **retinal layer** in which they’re located:
- ?
- ?
- ?

Drusen are categorized by their **boundaries**:
- **Hard**: Discrete, well demarcated
- **Soft**: Amorphous, poorly demarcated
- **Confluent**: Contiguous drusen without clear boundaries
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Aggregates of material within the outer-retinal space.

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  - Reticular

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**Before identifying the location for each drusen, let’s review the anatomy of the outer retina**
But first:

What are the five layers of Bruch’s membrane?

Bruch’s membrane

1) (Start here)

2) 

3) 

4) 

5) 

Innermost

Outermost

ARMD
But first:

What are the five layers of Bruch’s membrane?

1) two words of RPE

1) Innermost

5) Outermost
But first:

What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE

(Note: This line represents the RPE basement membrane)
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) (next)
3) 
4) 
5)
But first:

What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) one word
4) 
5)
What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) (etc)
4)
5)
What are the five layers of Bruch’s membrane?

1) **Baseline membrane** of RPE
2) Inner **collagenous** layer
3) **diff one word** layer
4)
5)

**But first:**

ARMD
But first:

What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) 
5)
But first:

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) Inner **collagenous** layer
3) **Elastic** layer
4) Outer layer
5) **one familiar word**

**Bruch’s membrane**

**Innermost**

**Outermost**

**ARMD**
But first:

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)
**But first:**

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) **two familiar words** of choriocapillaris

*ARMD*
But first:

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

(Note: This line represents the c’capillaris basement membrane)
But first:

What are the five layers of Bruch’s membrane?

0) ?

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
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What (non-Bruch’s) structure goes here?

ARMD
What are the five layers of Bruch’s membrane?

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

What (non-Bruch’s) structure goes here? The RPE cells themselves
What are the five layers of Bruch’s membrane?

0) RPE cells RPE cells

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

So, the basal plasma membranes of the RPE cells…
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

But first:

So, the basal plasma membranes of the RPE cells… sit directly on their BM (as you would expect)
What are the five layers of Bruch’s membrane?

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

But first:

Foreshadowing alert: Another name for the basal plasma membrane of a cell is ‘basal lamina’
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

But first:

What (non-RPE) structures go here?

0) RPE cells
-1) ?

ARMD

Innermost

Outermost
What are the five layers of Bruch's membrane?

1. Basement membrane of RPE
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But first:

What (non-RPE) structures go here?
The photoreceptor outer segments

ARMD
What are the five layers of Bruch’s membrane?

1) Basement membrane of RPE
2) Inner collagenous layer
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But first:

0) RPE cells
1) PR outer segs

What cell type is this?

Bipolar cells

PR outer segs
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basal laminar drusen

ARMD

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Reticular pseudodrusen: Classic distribution in the superior macula
Reticular pseudodrusen can be seen as multiple areas of granular hyperreflectivity between the RPE and photoreceptors
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*Circling back to drusenoid PEDs for a moment...*
But first:

What are the five layers of Bruch's membrane?

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5. Basement membrane of choriocapillaris

So now we can see how basal laminar drusen, if extensive enough, can cause a drusenoid PED.

-2) Bipolar cells

-1) PR outer segs

0) RPE cells RPE cells

Bruch's membrane
Likewise, we can see that extensive basal linear drusen can also producing a drusenoid PED.
-2) **Bipolar cells**

**But first:**

-1) **PR outer segs**

0) **RPE cells**

### Bruch’s membrane

1) **Basement membrane** of RPE

2) **Inner collagenous layer**

3) **Elastic layer**

4) **Outer collagenous layer**

5) **Basement membrane** of choriocapillaris

However, *reticular pseudodrusen* do not separate the RPE from Bruch’s, so they cannot cause a PED.
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Nonexudative: ?
Exudative
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--?
--?
--?
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We have already discussed drusen, and will look at RPE change in detail a little later in the set.
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It is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris.
Geographic atrophy (GA)
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How large must the area of atrophy be to qualify as GA?

By definition, it must have a diameter of at least 175 µm.
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What is its typical pattern of progression?
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It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
Progression of GA over a 2.5 year period. Note the characteristic perifoveal→foveal center pattern.
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**What does GA look like on…**

- **FA?**
  - A well-circumscribed area of hyperfluorescence
- **Autofluorescence?**
  - Dense hypoautofluorescence with a ring of hypofluorescence
- **OCT?**
  - RPE loss; thinning/loss of the outer retinal layers
Age-related macular degeneration 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: **Nonexudative** and **exudative**.

**Nonexudative**: Nonneovascular ARMD; ‘dry’ ARMD

**Exudative**: Neovascular ARMD; ‘wet’ ARMD

By what two other names are each condition commonly known?

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Nonexudative: Nonneovascular ARMD; ‘dry’ ARMD

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--**Geographic atrophy**

What is geographic atrophy (GA)?

It is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris.

What does GA look like on...

**FA?** A well-circumscribed area of hypo- vs hyperfluorescence

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It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
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Geographic atrophy in ARMD: FA
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Nonexudative and exudative ARMD

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What is the typical pattern of progression of GA?
- It starts in the perifoveal region, expanding over time to eventually involve the foveal center.

Speaking generally: What are the four causes of hyperfluorescence on FA?
- Pooling
- Leaking
- Staining
- Window defect

What does GA look like on FA? A well-circumscribed area of hyperfluorescence
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Geographic atrophy. A, Fundus photo. B, On fluorescein angiography, there is a “window defect” during the early frames with transmission of choroidal fluorescence. C, Note the absence of leakage in later frames.
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Eventually involves the foveal center.
Geographic atrophy (GA). Top, Color fundus photographs of right (left panel) and left (right panel) eyes, demonstrating advanced GA. Bottom, Corresponding autofluorescent images of GA in the same patient with atrophic AMD. The areas of RPE atrophy are hypoautofluorescent (dark gray or black), the areas of “sick” RPE are hyperautofluorescent (brighter than background), and the areas of healthy RPE are gray.
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Eventually involve the fovea, leading to vision loss...
ARMD

- Age-related macular degeneration is the #1 cause of blindness in adults age \(50^+\) in resource-rich nations
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- **OCT**: RPE loss; thinning/loss of the outer retinal layers
OCT over the fovea in a patient with non-exudative AMD and geographic atrophy. There is loss of outer retinal layers and RPE.
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The presence of neovascularization.
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**Nonexudative**: Nonneovascular ARMD; ‘dry’ ARMD

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**Advanced ARMD**: Defined by the presence of either geographic atrophy or a neovascular membrane.

What about early and intermediate ARMD—how are they defined?

**Early ARMD**: ?

**Intermediate ARMD**

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**Exudative:** Neovascular ARMD; ‘wet’ ARMD

**Early ARMD:** Defined by the presence of small drusen +/- a “few” intermediate drusen

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**Advanced ARMD:** Defined by the presence of either geographic atrophy or a neovascular membrane.
Age-related macular degeneration is the #1 cause of blindness in adults older than 50 in the United States, which nations spend more than $9.5 billion a year treating this vision-threatening disease.

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What puts a dry ARMD pt at risk for wet ARMD? In a word, drusen. That is, the damage wrought to Bruch's membrane is felt to create a proangiogenic environment resulting in the development of a NVM.

What is the other form that defines advanced ARMD? The presence of neovascularization.
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By what two other names are each condition commonly known?

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What puts a dry ARMD pt at risk for wet ARMD?

In a word, **drusen.** The damage done to Bruch’s membrane by drusen produces a proangiogenic environment resulting in the development of a NVM.

What are the three hallmark findings in nonexudative ARMD?

--Drusen
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**Geographic atrophy** (GA)

What is one of two forms of advanced ARMD?

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You see a pt whose exam over time seems like typical ARMD. Initially she presents with drusen, which increase in number and size over time. This progresses to GA, and culminates in a CNVM.

When presented with what seems like ARMD in a pt far too young to have it, think Sorsby macular dystrophy. (See R52 for more on this rare condition.)
Age-related macular degeneration is the #1 cause of blindness in adults age 50+. ARMD is the strongest risk factor for ARMD.

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You see a pt whose exam over time seems like typical ARMD. Initially she presents with drusen, which increase in number and size over time. This progresses to GA, and culminates in a CNVM. Trouble is, she developed the drusen and GA in her 30s, and the CNVM at age 40 or so. What tops the DDx for a pt who seems to have ARMD, but is far too young for it?

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What puts a dry ARMD pt at risk for wet ARMD? In a word, drusen. The damage done to Bruch’s membrane by drusen produces a proangiogenic environment resulting in the development of a NVM.

You see a pt whose exam over time seems like typical ARMD. Initially she presents with drusen, which increase in number and size over time. This progresses to GA, and culminates in a CNVM. Trouble is, she developed the drusen and GA in her 30s, and the CNVM at age 40 or so. What tops the DDx for a pt who seems to have ARMD, but is far too young for it? When presented with what seems like ARMD in a pt far too young to have it, think Sorsby macular dystrophy.

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There are two types: Nonexudative and exudative ARMD.

By what two other names are each condition commonly known?

Nonexudative: Nonneovascular ARMD; ‘dry’ ARMD
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What are the three hallmark findings in nonexudative ARMD?

-- Drusen
-- RPE changes
-- Geographic atrophy

What is geographic atrophy (GA)? It is one of two forms of advanced ARMD. It is characterized by a sharply defined area in the posterior pole manifesting atrophy of the RPE, the overlying photoreceptors, and the underlying choriocapillaris.

What is its typical pattern of progression? It starts in the perifoveal region, expanding over time to eventually involve the foveal center.

What is the other form that defines advanced ARMD? The presence of neovascularization.

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**Nonexudative**: Nonneovascular ARMD; ‘dry’ ARMD

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Time to tackle exudative ARMD. But before doing so, we must familiarize ourselves with the vascular supply of the retina.
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

But first:

- PR outer segs
- Bipolar cells

RPE cells RPE cells

0) PR outer segs
1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris
6) Chorio capillaris

What structure is this?
What are the five layers of Bruch's membrane?

- Basement membrane of RPE
- Inner collagenous layer
- Elastic layer
- Outer collagenous layer
- Basement membrane of choriocapillaris

But first:

0) RPE cells

1) PR outer segs

2) Bipolar cells

3) Innermost

4) Outermost

What structure is this?
The choriocapillaris
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

But first:

0) RPE cells, RPE cells
-1) PR outer segs
-2) Bipolar cells

What structure is this?

The choroid

Choriocapillaris

ARMD
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
- 6) Choriocapillaris
- 7) Choroid

What structure is this? The choroid

But first:

- 0) RPE cells
- 1) PR outer segs
- 2) Bipolar cells

What is the outermost layer of Bruch’s membrane? The choroid
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

What is the deepest retinal layer in which branches of the retinal vasculature can be found?

- 1) PR outer segs
- 2) Bipolar cells

But first:

0) RPE cells

Retinal vessels

RPE cells

Choriocapillaris
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

But first:

0) RPE cells

- 1) PR outer segs

- 2) Bipolar cells

- 3) Retinal vessels

What is the deepest retinal layer in which branches of the retinal vasculature can be found? The inner nuclear layer (INL)
What are the five layers of Bruch’s membrane?

- 0) RPE cells
- 1) PR outer segs
- 2) Bipolar cells
- 3) Basement membrane of RPE
- 4) Inner collagenous layer
- 5) Elastic layer
- 6) Outer collagenous layer
- 7) Basement membrane of choriocapillaris

So, the retinal vessels supply the inner retinal layers…

But first:
0) RPE cells
- 1) PR outer segs
- 2) Bipolar cells

Retinal vessels

So, the retinal vessels supply the inner retinal layers…

Outermost

Choriocapillaris

Choroid
What are the five layers of Bruch’s membrane?

- 0) RPE cells

- 1) PR outer segs

- 2) Bipolar cells

- 3) Retinal vessels

- 4) Outer collagenous layer

- 5) Elastic layer

- 6) Basement membrane of choriod/choriocapillaris

- 7) Choroid

So, the retinal vessels supply the inner retinal layers…Whereas the choroid/choriocapillaris supply the outer retina and RPE.
Retinal Layers

- Internal limiting membrane
- Nerve fiber layer
- Ganglion cell layer
- Inner plexiform layer
- Inner nuclear layer
- Outer plexiform layer
- Outer nuclear layer
- External limiting membrane
- Rod & cone inner and outer segments

RPE

Bruch’s membrane

Blood supply:
- Central retinal artery

Which layers are supplied by each blood supply?

Blood supply:
- Choroid/Ch’capillaris
● **Retinal Layers**
  - Internal limiting membrane
  - Nerve fiber layer
  - Ganglion cell layer
  - Inner plexiform layer
  - Inner nuclear layer
  - Outer plexiform layer
  - Outer nuclear layer
  - External limiting membrane
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● **RPE**
● **Bruch’s membrane**

Blood supply: **Central retinal artery**

Blood supply: **Choroid/Ch’capillaris**

**Which layers are supplied by each blood supply?**
Age-related macular degeneration 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: **Nonexudative** and **exudative** ARMD.

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**Three types of neovascular membranes occur in ARMD—what are they called?**

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Three types of neovascular membranes occur in ARMD—what are they called?

-- Type 1
-- Type 2
-- Type 3

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--- Type 1: CNVM originates from the choriocapillaris and extends into Bruchs membrane and/or the sub-RPE space.

--- Type 2: CNVM originates from the choriocapillaris and extends into the sub-retinal space (ie, just above the RPE).

--- Type 3: NVM arises from the deep capillary plexus of the retina and grows down toward the RPE.

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--Type 2

--Type 3

Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma.
- 0) **RPE cells**
- 1) **Inner collagenous layer**
- 2) **Inner collagenous layer**
- 3) **Elastic layer**
- 4) **Outer collagenous layer**
- 5) **Basement membrane of choriocapillaris**
- 6) **Choriocapillaris**
- 7) **Choroid**

**Type 1 with the CNVM in Bruchs membrane**

- 1) **PR outer segs**
- 2) **Bipolar cells**

**ARMD**
What are the five layers:

- Basement membrane of RPE
- Inner collagenous layer
- Elastic layer
- Outer collagenous layer
- Basement membrane of choriocapillaris

Type 1 with the CNVM in the sub-RPE space
Type 1 CNVM with hyperreflective material visible in the PED. Note that the RPE can be seen to ride above the lesion.
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--- Type 3

Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma
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

Type 2 with the CNVM in the sub-retinal space
Type 2 CNVM located above the RPE with subretinal fluid (SRF) adjacent to the lesion. Note the RPE can be seen below the lesion.
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Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma
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

Type 3 with the NVM growing down from retinal vessels
- 1) PR outer segs
- 2) Bipolar cells
- 3) Retinal vessels
- 4) Type 3 with the NVM growing down from retinal vessels

1) Basement membrane of RPE
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*What does it mean to say ARMD is ‘exudative’?*

It means a neovascular membrane, (almost always choroidal in origin) is present.

*What vessels give rise to the neovascular membrane?*

The choriocapillaris (with one exception, to be discussed later).

*What will a pt c/o if a CNVM develops?*

Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma

*What vessels give rise to the neovascular membrane?*

The choriocapillaris (with one exception, to be discussed later).

*Type 3 is the exception to the statement ‘CNVM originate in the choriocapillaris’ referred to a few slides ago.*

---Type 3: **NVM arises from the deep capillary plexus of the retina**
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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So we’re referring to something as a ‘choroidal’ NVM when it doesn’t originate in the choroid? Make it make sense.

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I can’t, and the BCSC no longer tries.

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--Type 2: CNVM originates from the choriocapillaris and extends into the sub-retinal space (ie, just above the RPE).
--Type 3: NVM arises from the deep capillary plexus of the retina and grows down toward the RPE.
Age-related macular degeneration 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.

So we’re referring to something as a ‘choroidal’ NVM when it doesn’t originate in the choroid? Make it make sense.

I can’t, and the BCSC no longer tries. Instead, they now prefer *macular neovascularization* (MNV) as the general term for neovascularization associated with ARMD.

---

**Type 3 is the exception to the statement ‘CNVM originate in the choriocapillaris’ referred to a few slides ago**

*What vessels give rise to the neovascular membrane?*

*The choriocapillaris (with one exception, to be discussed later)*

---

*What will a pt c/o if a CNVM develops?*

*Blurry vision, metamorphopsia and/or a paracentral scotoma*

---

*Type 3: NVM arises from the deep capillary plexus of the retina*
Age-related macular degeneration (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: Nonexudative and Exudative.

By what two other names are each condition commonly known?

Nonexudative: Nonneovascular ARMD; ‘dry’ ARMD

Exudative: Neovascular ARMD; ‘wet’ ARMD

What does it mean to say ARMD is ‘exudative’?

It means a neovascular membrane, (almost always choroidal in origin), is present.

What vessels give rise to the neovascular membrane?

The choriocapillaris (with one exception, to be discussed later).

What will a pt c/o if a CNVM develops?

Blurry vision, metamorphopsia and/or a paracentral scotoma.

Three types of neovascular membranes occur in ARMD—what are they called? What are the defining features of each?

--Type 1: CNVM originates from the choriocapillaris and extends into Bruchs membrane and/or the sub-RPE space.

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--Type 3: NVM arises from the deep capillary plexus of the retina and grows down toward the RPE.

Of the three, which occurs most frequently in ARMD?

Type 1

Type 2 CNVM is strongly associated with what condition (it’s not ARMD)?

Ocular histoplasmosis

By what other name is Type 3 known?

Retinal angiomatous proliferation (RAP)
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**What are the defining features of each type?**

- **Type 1**: CNVM originates from the choriocapillaris and extends into Bruchs membrane and/or the sub-RPE space.
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Ocular histo is high on the DDx for CNVM. What other non-ARMD conditions are important causes of CNVM?

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Ocular histo is high on the DDx for CNVM. What other non-ARMD conditions are important causes of CNVM?

Coming in hot…
(This is a good point in the set to take a break)
**CNVM DDx:**

- **ARMD**
- **OHS**
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?

*Other than these two, what is the DDx for causes of CNVM?*
**CNVM DDx:**

- **ARMD** *Other than these two, what is the DDx for causes of CNVM?*
- **OHS**
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
CNVM DDx:

- ARMD
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Let me stress, these are all important clinical alternatives that must come to mind when contemplating CNVM.

No question—advance when ready
Let me stress, these are all important clinical alternatives that must come to mind when contemplating CNVM. That being said, three are discussed in detail in the ARMD chapter of the Retina book, and thus are probably deserving of special attention. Which three?

(Sorsby, discussed earlier, is not one of them)
Let me stress, these are all important clinical alternatives that must come to mind when contemplating CNVM. That being said, three are discussed in detail in the ARMD chapter of the Retina book, and thus are probably deserving of special attention. Which three?
Is there a racial predilection in OHS?

Yes, OHS occurs almost exclusively among whites of Northern European heritage.

Is there a geographic predilection?

Yes, the majority of cases are found in people who reside in the Mississippi/Ohio River valleys of the US.

Does OHS manifest unilaterally, or bilaterally?

Bilaterally (although it can be somewhat asymmetric).

Is OHS associated with vitritis?

Never. If vitritis is present, it's not OHS.

What about AC cell?

Never. If AC cell is present, it's not OHS.
CNVM DDx:

- ARMD
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ARMD

OHS

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**ARMD**

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**What about AC cell?**
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**Never.** If vitritis is present, it’s not OHS.

*What about AC cell?*
**Never.** If AC cell is present, it’s not OHS.
How is the diagnosis of OHS made?

It is a clinical diagnosis based on DFE findings.

What are you looking for on DFE?

The so-called 'classic triad' of OHS:

-- Histo spots
-- Peripapillary atrophy
-- Disciform macular lesion(s)

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OHS: The classic triad
OHS: The classic triad

For more on OHS, see slide-set U21
CNVM DDx:

- ARMD
- OHS
- **Angioid streaks**

What is the classic DFE appearance of angioid streaks?

Adult-onset vitelliform dystrophy
What is the classic DFE appearance of angioid streaks?

Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in retinal structure.
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane
Angioid streaks (arrowheads). Note that only a few of the many present have been marked.
CNVM DDx:

- ARMD
- OHS
- Angioid streaks

What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).
### CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

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**What is the classic DFE appearance of angioid streaks?**

Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

**What proportion of angioid streaks are associated with systemic abnormalities?**

About half.
**CNVM DDx:**

- ARMD
- OHS
- **Angioid streaks**

What is the classic DFE appearance of angioid streaks?

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About half.

What is the well-known mnemonic for angioid streak’s associations?

- P
- E
- P
- S
- I
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What is the well-known mnemonic for angioid streak’s associations? PEP S I

Adult-onset vitelliform dystrophy
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What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? P E P S I.
Angioid streaks

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What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association).

Adult-onset vitelliform dystrophy
What is the classic DFE appearance of angioid streaks? 
**Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations? 
- Pseudoxanthoma elasticum (PXE) 
- Ehlers-Danlos syndrome 
- Paget’s disease of bone 
- Sickle-cell disease 
- Idiopathic (ie, no association) 

~# of cases are associated with one of these 
~# of cases have no known systemic association.

Adult-onset vitelliform dystrophy
**CNVM DDx:**

- **ARMD**

**OHS**

**Angioid streaks**

What is the classic DFE appearance of angioid streaks?
**Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities?
About half.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
- **P**seudoxanthoma elasticum (PXE)
- **E**hlers-Danlos syndrome
- **P**aget’s disease of bone
- **S**ickle-cell disease
- **I**diopathic (ie, no association)

~50% of cases are associated with one of these
~50% of cases have no known systemic association

- **Adult-onset vitelliform dystrophy**
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane

What proportion of angioid streaks are associated with systemic abnormalities?
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Pseudoxanthoma elasticum (PXE)?
Ehlers-Danlos syndrome?
Paget’s disease of bone?
Sickle-cell disease?
Idiopathic (ie, no association)

Which condition has the strongest association with angioid streaks?
What is the classic DFE appearance of angioid streaks? **Reddish-brown** lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

What proportion of angioid streaks are associated with systemic abnormalities? About half.

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Which condition has the strongest association with angioid streaks? **PXE**, by a mile.
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What other organ-systems are affected in PXE? Eye.

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Which condition has the strongest association with angioid streaks? PXE, by a mile.

What other organ-systems are affected in PXE?
--Skin
--Vascular system
--GI tract
--Eye

Adult-onset vitelliform dystrophy
**CNVM DDx:**

- ARMD

**Angioid streaks**

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Which condition has the strongest association with angioid streaks? 
PXE, by a mile

What is the appearance of affected skin? 
An area of waxy-yellow, papule-like lesions. Known as ‘chicken skin’.

**Adult-onset vitelliform dystrophy**
**CNVM DDx:**

- ARMD
- OHS

**Angioid streaks**

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  - An area of waxy-yellow, papule-like lesions.

- What other organ-systems are affected in PXE?
  - Skin
  - Vascular
  - GI tract
  - Eye

- What is the classic informal descriptor for this appearance?
  - 'Chicken skin'
Angioid streaks

What is the classic DFE appearance of angioid streaks? Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch’s membrane.

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Adult-onset vitelliform dystrophy
- **CNVM DDx:**
  - ARMD
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PXE skin
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**Angioid streaks**

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Which condition has the strongest association with angioid streaks? PXE, by a mile.

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?

--- Angioid streaks
--- ?
--- ?

- Skin
- Vascular system
- GI tract
- Eye

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Angioid streaks

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There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?

- Angioid streaks
- RPE mottling
- Optic disc drusen

Which condition has the strongest association with angioid streaks? PXE, by a mile.
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

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What other organ-systems are affected in PXE?
- Skin
- Vascular system
- GI tract
- Eye

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?
- Angioid streaks
- RPE mottling
- Optic disc drusen

What mellifluous name is used to describe the RPE mottling?
Peau d’orange.

Which condition has the strongest association with angioid streaks? PXE, by a mile.
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks

What is the classic DFE appearance of angioid streaks?
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What is the well-known mnemonic for angioid streak’s associations? What are these associations?
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Which condition has the strongest association with angioid streaks?
PXE, by a mile.

What mellifluous name is used to describe the RPE mottling?
Peau d’orange.

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?
RPE mottling, Optic disc drusen.

What other organ-systems are affected in PXE?
--Skin
--Vascular system
--GI tract
--Eye

There are three classic eye findings in PXE, one of which is angioid streaks. What are the other two?
RPE mottling, Optic disc drusen.

What is the well-known mnemonic for angioid streak’s associations? What are these associations?
Pseudoxanthoma elasticum (PXE), Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association), Central serous chorioretinopathy, Pattern dystrophy, Adult-onset vitelliform dystrophy.
PXE: *Peau d’orange* fundus
PXE: Peau d’orange fundus

For more on angioid streaks, see slide-set R61
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - Central serous chorioretinopathy
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

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*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*
CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia? 26.5 mm
• **CNVM DDx:**
  - ARMD
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*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*
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*What is the classic finding on DFE that puts high myopes at risk for CNVM?*
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - Central serous chorioiditis
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

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*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*

26.5 mm

*What is the classic finding on DFE that puts high myopes at risk for CNVM?*

Lacquer cracks
**CNVM DDx:**

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
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*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*

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*What is the classic finding on DFE that puts high myopes at risk for CNVM?*

Lacquer cracks

*What are lacquer cracks?*
CNVM DDx:
- ARMD
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- Pattern dystrophy
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Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?
- 26.5 mm

What is the classic finding on DFE that puts high myopes at risk for CNVM?
- Lacquer cracks

What are lacquer cracks?
- Breaks in Bruch’s membrane, in color, usually found in the retinal area.
CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - Central serous choroiditis
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

*Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia?*
26.5 mm

*What is the classic finding on DFE that puts high myopes at risk for CNVM?*
Lacquer cracks

*What are lacquer cracks?*
Breaks in Bruch’s membrane, yellowish in color, usually found in the macula.
Lacquer cracks
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous choroidopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Per the Retina book, what axial length serves as a useful cutoff for defining pathologic myopia? 26.5 mm

What is the classic finding on DFE that puts high myopes at risk for CNVM? Lacquer cracks

What are lacquer cracks? Breaks in Bruch’s membrane, yellowish in color, usually found in the macula. These breaks are the nidus for CNVM ingress in pathologic myopia.
CNVM DDx:

- ARMD
- OHS?
- Angioid streaks?
- Pathologic myopia?
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- Sorsby macular dystrophy?
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- Central serous chorioretinopathy?
- Pattern dystrophy?
- Adult-onset vitelliform dystrophy?

The ARMD chapter of the Retina book mentions one of these as being particularly likely to be misdiagnosed as CNVM, ie, to produce the impression that a CNVM is present when it isn’t—which one?
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In two words, what is the underlying cause of CSC?

Central serous chorioretinopathy

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
- Choroidal hyperpermeability

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
- Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?

🌟 Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

*To be clear: Is CNVM associated with CSC?*  
**Yes**—2ndry CNVM can and does occur in CSC, albeit uncommonly.

**Central serous chorioretinopathy**  
- Pattern dystrophy  
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM and masquerade as it.

Central serous chorioretinopathy
- Pattern dystrophy
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For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?

Central serous chorioretinopathy

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?

Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM *and* masquerade as it.

For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?
The presence of SRF on OCT

**Central serous chorioretinopathy**

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
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The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?

★ **Central serous chorioretinopathy**
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For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?
The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

**Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability *(choriocapillaris hyperpermeability is correct as well, and may even be preferred)*

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The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?

In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

**Central serous chorioretinopathy**

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
**ARMD**: PED (Δ) and SRF (↓), along with subretinal hemorrhage (*)

**CSC**: PED and SRF, but no hemorrhage
In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?

Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
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For the CSC cases in which no CNVM is present: What clinical finding.

There is another important OCT finding that distinguishes CSC from ARMD—what is it?

Central serous chorioretinopathy

• Pattern dystrophy
• Adult-onset vitelliform dystrophy
CNVM DDx:

In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

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For the CSC cases in which no CNVM is present: What clinical finding.
There is another important OCT finding that distinguishes CSC from ARMD—what is it?
The thickness of the choroid

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What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

There is another important OCT finding that distinguishes CSC from ARMD—what is it?
The thickness of the choroid. It tends to be normal or thinned in ARMD, but thickened in CSC.

Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy
ARMD

CNVM DDx:

In two words, what is the underlying cause of CSC?
Choroidal hyperpermeability (choriocapillaris hyperpermeability is correct as well, and may even be preferred)

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For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?
The presence of SRF on OCT

What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage, whereas this will not be present in CSC (absent a 2ndry CNVM)

There is another important OCT finding that distinguishes CSC from ARMD—what is it?
The thickness of the choroid. It tends to be normal or thinned in ARMD, but thickened in CSC.

Central serous chorioretinopathy

Pattern dystrophy
Adult-onset vitelliform dystrophy
The choroid is seen in cross section. Subfoveal choroidal thickness was measured vertically from the outer border of the RPE to the inner border of the sclera (*brackets*) in a healthy eye in a 55-year-old man (A) and in 3 representative eyes with CSC: in a 44-year-old man (B), a 57-year-old man (C), and a 63-year-old man (D).
**ARMD**

**CNVM DDx:**

In two words, what is the underlying cause of CSC?

Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)

To be clear: Is CNVM associated with CSC?

Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.

The takeaway point: CSC can both cause CNVM and masquerade as it.

For the CSC cases in which no CNVM is present: What clinical finding, common to both wet ARMD and CSC, is responsible for the misdiagnosis?

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Choroidal thickness may not be readily interpretable on spectral-domain OCT (SD-OCT). What OCT modality is preferred for assessing the choroid?

**Central serous chorioretinopathy**

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
ARMD

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In two words, what is the underlying cause of CSC?
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Choroidal thickness may not be readily interpretable on spectral-domain OCT (SD-OCT).
What OCT modality is preferred for assessing the choroid?
Enhanced-depth imaging OCT (EDI-OCT)

Central serous chorioretinopathy

Pattern dystrophy
Adult-onset vitelliform dystrophy
Dry ARMD

CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

Regarding conditions that can be misdiagnosed as dry ARMD—what feature do they have in common?

Abnormalities of the RPE
Dry ARMD

CNVM

DDx:

- ARMD
- OHS
- Angioid streaks
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Regarding conditions that can be misdiagnosed as dry ARMD—what feature do they have in common?
Abnormalities of the RPE
The ARMD chapter of the Retina book mentions three of these as being particularly likely to produce a misdiagnosis of dry ARMD—which three?
Dry ARMD

The ARMD chapter of the Retina book mentions three of these as being particularly likely to produce a misdiagnosis of dry ARMD—which three?

(Yes, CSC is a prominent member of the DDx for both wet and dry ARMD!)

★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy
Dry ARMD

DNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

How does CSC—a choroidal condition that produces serous detachments—acquire the RPE abnormalities that characterize dry ARMD masqueraders?
Dry ARMD

- CNVM
- DDx:
  - ARMD
  - OHS
  - Angioid streaks
  - Pathologic myopia
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
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  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

How does CSC—a choroidal condition that produces serous detachments—acquire the RPE abnormalities that characterize dry ARMD masqueraders? If the SRF is chronic, it can produce RPE mottling.
CSC: RPE mottling
\begin{itemize}
\item ARMD
\item OHS
\item Angioid streaks
\item Pathologic myopia
\item Idiopathic
\item Sorsby macular dystrophy
\item Traumatic choroidal rupture
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\item Central serous chorioretinopathy
\end{itemize}

**Central serous chorioretinopathy**

★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy

---

**Dry ARMD**

How does CSC—a choroidal condition that produces serous detachments—acquire the RPE abnormalities that characterize dry ARMD masqueraders?

If the SRF is chronic, it can produce RPE mottling

Because SRF is subject to gravity-induced downward migration, the RPE changes often demonstrate a particular pattern. What are the formal and informal names for this pattern?
**Dry ARMD**

- ARMD
- OHS
- Angioid streaks

**Central serous chorioretinopathy**

- Pattern dystrophy
- Adult-onset vitelliform dystrophy
CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.
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For more on CSC, see slide-set R47
Dry ARMD

**Pattern dystrophy**

★ Adult-onset vitelliform dystrophy

Briefly, what is a pattern dystrophy?

An inherited macular dystrophy that has a characteristic appearance (ie, a particular "pattern")

What is the inheritance pattern?

AD

Are pattern dystrophies associated with severe vision loss?

Generally no—vision is only slightly affected

Do the macular 'patterns' appear early in life?

Generally no—they usually show up in middle adulthood

The BCSC Retina book identifies four pattern dystrophies by name—what are they?

-- Butterfly dystrophy

-- Adult-onset foveomacular vitelliform dystrophy

-- Reticular dystrophy

-- Fundus pulverulentus
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Adult-onset vitelliform dystrophy
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Dry ARMD

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The mnemonic is…

Pattern dystrophy

Adult-onset vitelliform dystrophy
Dry ARMD

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-B
-A
-R
-F

The mnemonic is…BARF?

Pattern dystrophy
Adult-onset vitelliform dystrophy
Dry ARMD

**ARMD**

**CNVM DDx:**

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--Butterfly dystrophy
--Adult-onset foveomacular vitelliform dystrophy
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**Pattern dystrophy**
★ Adult-onset vitelliform dystrophy
Butterfly dystrophy

Adult-onset foveomacular vitelliform dystrophy

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Dry ARMD

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These terms are awfully similar…Do they refer to the same, or different conditions?

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--Fundus pulverulentus

These terms are awfully similar…Do they refer to the same, or different conditions?
The same (the Retina book uses both)
At what age do AOVD lesions appear?

30s to 50s

What do pts c/o initially?

Not much—maybe a little blurring or metamorphopsia

What does DFE reveal?

Bilateral vitelliform (which means egg-yolk like) lesions

How might such a lesion lead to a misdiagnosis of dry ARMD?

Its DFE and OCT appearance could be misinterpreted as representative of a drusenoid PED

Adult-onset vitelliform dystrophy
Dry ARMD

CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic

★ Central serous chorioretinopathy
★ Pattern dystrophy
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Pattern dystrophy

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Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:
--Color?
Yellow(ish)

--Shape?
Round

--Contour?
Domed
Dry ARMD

CNVM

ARMD
OHS
Angioid streaks
Pathologic myopia
Idiopathic
Sorsby macular dystrophy
Traumatic choroidal rupture
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**Dry ARMD**

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  - ARMD
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  - Traumatic choroidal rupture
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- Pattern dystrophy

**Adult-onset vitelliform dystrophy**

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**Because they're egg-yolk-like, what can you infer about the vitelliform lesion’s:**
- **Color?** Yellow(ish)
- **Shape?** Round

---

**ARMD**
Typical round, yellow lesion of AOVD
Dry ARMD

CNVM DDx:

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- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
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- Central serous chorioretinopathy
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What does DFE reveal?
Bilateral vitelliform (which means 'egg-yolk-like') lesions

Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:

--Color? Yellow(ish)
--Shape? Round
--Contour?
Dry ARMD

At what age do AOVD lesions appear? 30s to 50s

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What does DFE reveal? Bilateral vitelliform (which means 'egg-yolk-like') lesions

Because they’re egg-yolk-like, what can you infer about the vitelliform lesion’s:

--Color? Yellow(ish)
--Shape? Round
--Contour? Domed

---central serous chorioretinopathy
---Pattern dystrophy
---Adult-onset vitelliform dystrophy
OCT showing dome-like lesion in AOVD
Dry ARMD

CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
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**Dry ARMD**

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- ARMD
- OHS
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- Traumatic choroidal rupture
- Iatrogenic

**Central serous chorioretinopathy**

**Pattern dystrophy**

**Adult-onset vitelliform dystrophy**

---

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What does DFE reveal?

Bilateral vitelliform (which means *egg-yolk like*) lesions

How might such a lesion lead to a misdiagnosis of dry ARMD?

Its DFE and OCT appearance could be misinterpreted as representative of a drusenoid PED
Here's a clinical challenge: AOVD in a patient with extensive drusen. Fundus photo demonstrates drusen, and an ill-defined vitelliform lesion. OCT shows the material over the soft drusen (yellow arrow) that could be misinterpreted as a CNVM related to wet ARMD.
Here’s a clinical challenge: AOVD in a patient with extensive drusen. Fundus photo demonstrates drusen, and an ill-defined vitelliform lesion. OCT shows the material over the soft drusen (yellow arrow) that could be misinterpreted as a CNVM related to wet ARMD.

For more on the pattern dystrophies, see slide-set R11.
Dry ARMD

CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Vitelliform dystrophy

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

CNVM DDx:

- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic

★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Vitelliform dystrophy
★ Drug toxicity

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

**CNVM**

**DDx:**
- ARMD
- OHS
- Angioid streaks
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- Sorsby macular dystrophy
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★ Central serous chorioretinopathy
★ Pattern dystrophy
★ Vitelliform dystrophy
★ **Drug toxicity, especially…**

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

ARMD

OHS

Angioid streaks

Pathologic myopia

Idiopathic

Sorsby macular dystrophy

Traumatic choroidal rupture

Iatrogenic

Central serous chorioretinopathy

Pattern dystrophy

Vitelliform dystrophy

Drug toxicity, especially...hydroxychloroquine

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?
Dry ARMD

- CNVM
- DDx:
  - ARMD
  - OHS
  - Angioid streaks
  - Pathologic myopia

Finally: The book emphasizes another condition (not on this list—yet) as being high on the DDx for dry ARMD—what is it?

Plaquenil maculopathy is covered in slide-set R25

- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Iatrogenic
- Central serous chorioretinopathy
- Pattern dystrophy
- Vitelliform dystrophy
- Drug toxicity, especially...hydroxychloroquine
Age-related macular degeneration 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: Nonexudative and exudative

Abnormalities in ARMD are typical
Age-related macular degeneration 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: *Nonexudative* and *exudative*.
- RPE abnormalities in ARMD are typical.
Age-related macular degeneration 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: Nonexudative and exudative.

RPE abnormalities in ARMD are typical.

The two RPE changes most typical of ARMD are:
--Atrophy (we knew this one already because of GA)
--Focal
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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*The two RPE changes most typical of ARMD are:*
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ARMD: RPE hyperpigmentation
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

- **Age** is the strongest risk factor for ARMD.
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- in ARMD are abnormal as well.
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What’s abnormal about the photoreceptors (PRs) in ARMD?
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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What’s abnormal about the photoreceptors (PRs) in ARMD? They are reduced in density (ie, they die off).
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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There are two types: 

- Nonexudative
- Exudative

RPE abnormalities in ARMD are typical.

Photoreceptors in ARMD are abnormal as well.

What’s abnormal about the photoreceptors (PRs) in ARMD?  
They are reduced in density (ie, they die off).

Do the RPE abnormalities cause the PR abnormalities?
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Do the RPE abnormalities cause the PR abnormalities?
I’s not clear how changes in the RPE and PR are causally linked to one another.
Age-related macular degeneration 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: Nonexudative and exudative.

RPE abnormalities in ARMD are typical.

Photoreceptors in ARMD are abnormal as well.

What’s abnormal about the photoreceptors (PRs) in ARMD?
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Speaking of being unsure about causality in ARMD…
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So, changes in ARMD include:
--Basal laminar/linear deposits accumulate
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So, changes in ARMD include:
--Basal laminar/linear deposits accumulate
--Ultrastructural changes in the pigment epithelium include loss of melanin granules, formation of lipofuscin granules, and accumulation of residual bodies.

No question—advance when ready.
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All of them. This is one of the challenges of ARMD—finding a bright line between its pathologic changes and those associated with normal aging.
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*Which if any of these can occur as part of the normal aging process? All of them.* This is one of the challenges of ARMD—finding a bright line between its pathologic changes and those associated with normal aging. Normal aging changes can be observed in the outer retina, RPE, Bruch’s membrane, and choriocapillaris, and many of these changes are difficult to separate from those seen in ARMD.
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What is the complement system?
To answer this, we need to unpack the notion of the immune response...
What are the two fundamental immune responses?
What are the two fundamental immune responses?
Immune response

Innate
aka... immunity

Adaptive
aka... immunity

What word is used to capture the essence of each?
Immune response

Innate
aaka...natural immunity

Adaptive
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Immune response

Innate
aka...**natural** immunity
provide immediate protection

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*Which provides immediate protection against antigens deemed threatening?*
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*Which must have previous experience with an antigen to gain the capacity to neutralize it?*
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<th><strong>Innate</strong></th>
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**What would be an example of a single-molecule inflammatory mediator?**

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Let's drill down on VEGF for a bit...
What does VEGF stand for?

VEGF-A$_{165}$
What does VEGF stand for?
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What is a growth factor?
One of a diverse group of proteins that affect cell function, including cell proliferation and tissue differentiation.

What are some other growth factors of note regarding ocular development and health?
-- Epidermal growth factor
-- Fibroblast growth factor(s)
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2) 
3) 
4) 
5) 
6) 

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1) Reis-Bücklers
2) Thiel-Behnke
3) Lattice, type 1
4) Lattice, variant types (III, IIIA, I/IIIA, IV)
5) Granular type 1
6) Granular type 2
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In a nutshell, what sort of structure is the VEGFR?

Are there multiple subtypes of VEGFRs?
Yes. VEGF-A binds to two: VEGFR-1 and VEGFR-2.

Is one of these more important in the pathogenesis of ARMD?
Yes, VEGFR-2 seems to be responsible for all of the findings in ARMD.
The function of VEGFR-1 is unclear at this time.
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Vascular endothelial growth factor

Broadly speaking, what is VEGF?
An extracellular signaling protein involved in vascular development

How does VEGF work?
Extracellular VEGF binds to VEGF receptors (VEGFR) on target cells

In a nutshell, what sort of structure is the VEGFR?
It is a so-called ‘transmembrane receptor tyrosine kinase structures’ (if nothing else, make sure you hold onto the term tyrosine kinase in connection to the VEGFRs)

Are there multiple subtypes of VEGFRs?
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Is one of these more important in the pathogenesis of ARMD?
Yes, VEGFR-2 seems to be responsible for all of the findings in ARMD.
The function of VEGFR-1 is unclear at this time.
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**What does 165 signify?**
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**What does VEGF-A 165 signify?**
VEGF-A is not a single entity either. At least 4 isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.
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**Why focus on isoform 165?**
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VEGF-A_{165}

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How strong is the evidence implicating VEGF in ARMD?
Very. Elevated VEGF levels are found within the RPE and vitreous of eyes with early ARMD, and within excised choroidal neovascular membranes. The Retina book goes so far as to say the evidence suggests “a causal role for VEGF in the initiation of neovascularization” in ARMD.

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ARMD
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Why focus on isoform 165? It seems to be the most important with respect to pathologic angiogenesis in the human eye.
Age-related macular degeneration (ARMD) affects 1 million Americans ages 65 and older and is the leading cause of adult blindness. The most significant risk factor is age, with the risk increasing as individuals age. The first symptom usually involves the presence of drusen in the macula, the central part of the retina that controls central vision. There are two types of ARMD: nonexudative and exudative. Nonexudative ARMD is more common and can cause vision loss over time, while exudative ARMD is less common but can cause sudden vision loss. Retinal pigment epithelium (RPE) abnormalities and photoreceptor abnormalities are typical in ARMD. The pathogenesis of ARMD is not well understood, but the complement system and vascular endothelial growth factor (VEGF) play important roles. Interdicting VEGF is key in managing exudative ARMD.
Age-related macular degeneration 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: *Nonexudative* and *exudative*

RPE abnormalities in ARMD are typical

Photoreceptors in ARMD are abnormal as well

The pathogenesis of ARMD is not well understood; that said, the *complement* system is strongly implicated in it

**VEGF** plays a key role in exudative ARMD; likewise, interdicting **VEGF** is key in managing it
(This is a good point in the set to take a break)
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Next let’s drill down on anti-VEGF therapy…
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
Ranibizumab *is a* recombinant, humanized, affinity-matured, monoclonal antibody fragment.
Ranibizumab is the generic, nonproprietary name. What is the brand name for this drug?

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What does recombinant mean?

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What does recombinant mean? That the substance was produced via recombinant DNA; i.e., DNA created by re-combining portions of 2+ different DNA molecules.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

**What does recombinant mean?**
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**What does humanized mean?**
Like many monoclonal antibodies, the parent molecule of ranibizumab was derived from mouse cells. Such murine antibodies would be recognized as foreign by the human immune system and attacked as such. To preclude this, a portion of the mouse antibody is replaced with its human counterpart via recombinant DNA techniques.
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What does the suffix –mab indicate? That the drug is a monoclonal antibody.

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Next we will take a deep dive into the key clinical trials that established the safety and effectiveness of ranibizumab in the tx of wet ARMD.
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**Next we will take a deep dive into the key clinical trials that established the safety and effectiveness of ranibizumab in the tx of wet ARMD. Dr Flynn, are we expected (by the authors of the OKAP, WQE and Boards) to know these trial by name?** Yes you are. **Are we expected to be familiar with their outcomes, as well as the implications of those outcomes?** Yes you are.
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?
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MARINA

What does MARINA stand for?

ANCHOR

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What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

What does MARINA stand for? Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration

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What was the dosing schedule?

ARMD
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What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

**MARINA**

What does MARINA stand for? Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration

One injection every month for 24 months

What was the dosing schedule?

Was another intervention involved?

**ANCHOR**

What does ANCHOR stand for? ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in Age-Related Macular Degeneration

One injection every month for 24 months

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No (other than a sham inj group)

Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections
## MARINA

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<th>Intervention</th>
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## ANCHOR

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No (other than a sham inj group)

Proportion of patients losing <15 ETDRS letters

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*What was the primary outcome measure?*

*What was the secondary outcome measure?*

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YEAR ONE

**RESULTS**

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ARMD
### MARINA

Evaluated ranibizumab for the treatment of minimally classic/occult CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months.

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### ANCHOR

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Loss <15 letters 95% 95% 62%

Gained >15 letters

Note: Only 1 in 20 tx’d pts lost >15 letters of VA

Anchor evaluated ranibizumab for the treatment of predominantly classic CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or PDT). One injection every month for 24 months. 0.3 mg 0.5 mg PDT

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ARMD
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0.3 mg 0.5 mg PDT
Loss <15 letters 94% 96% 64%
Gained >15 letters 36% 40% 6%

Evaluated ranibizumab for the treatment of minimally classic/occult CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections). One injection every month for 24 months.

0.3 mg 0.5 mg Sham
Loss <15 letters 95% 95% 62%
Gained >15 letters 25% 34% 5%
MARINA RESULTS ANCHOR

**ARMD**

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<tr>
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<td></td>
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**Note:**
--30 to 40% of (0.5) pts gained 15+ letters of VA, compared to only ~5% of sham/PDT pts
Marina Anchor evaluated ranibizumab for the treatment of minimally classic/occult and predominantly classic CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections) with one injection every month for 24 months.

### Results

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**YEAR TWO**

**ARMD**
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**Note:**
--The vast majority of ranibizumab-tx’d pts still hadn’t lost >15 letters at the 24-month mark
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ARMD

MARINA

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Note: --And the (0.5) pts maintained their VA gains

ARMD
MARINA and ANCHOR tl;dr:
1) Both were strong Phase III clinical trials
2) Both evaluated monthly injections of ranibizumab for 2 years
3) The studies found that only 1 in 20 (5%) of treated pts lost more than 15 letters of VA at 1 yr, and 1 in 10 (10%) at 2 yrs
4) 30-40% of treated pts gained 15+ letters
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

MARINA

What does MARINA stand for?
Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab In the Treatment of Neovascular Age-Related Macular Degeneration

What significant ocular and/or systemic safety issues manifested in the MARINA and/or ANCHOR trials?
Nothing too concerning. The rates of endophthalmitis, RD, uveitis, etc., were comparable between the ranibizumab and sham groups, although there was a trend toward higher rates with ranibizumab. The same was true of possible systemic side effects: There was a trend toward higher rates of HTN, CVA and MI, but these differences were not significant either.

ANCHOR

What does ANCHOR stand for?
ANti-VEGF Antibody for the Treatment of Predominantly Classic CHORoidal Neovascularization in Age-Related Macular Degeneration

What was the primary outcome measure?
Proportion of patients losing <15 ETDRS letters

What was the secondary outcome measure?
Proportion of patients gaining >15 ETDRS letters

One injection every month for 24 months

Did another intervention involve?
Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections

Proportion of patients losing <15 ETDRS letters
Proportion of patients gaining >15 ETDRS letters
What were the 2 key clinical trials demonstrating the safety and efficacy of ranibizumab in the treatment of ARMD?

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gaining >15 ETDRS letters

outcome measure?

gaining >15 ETDRS letters
What are 2 key studies addressing the **dosing schedule** of ranibizumab in the treatment of ARMD?
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(Other acceptable answers: SAILOR; SUSTAIN; HORIZON; HARBOR)
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What does PIER stand for?

What does PrONTO stand for?
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**Phase IIIb, Multicenter, Randomized, Double-Masked, Sham-Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization with or without Classic CNV Secondary to Age-Related Macular Degeneration**

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One injection every month for 3 months, then PRN as indicated by OCT, VA and DFE findings at monthly exams.

One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?
One injection every month for 3 months, then every 3 months to 12 months.

**What were the dosing schedules?**

**Three Months**

<table>
<thead>
<tr>
<th>0.3 mg</th>
<th>0.5 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
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</table>

Average VA change (ETDRS letters)

(Note the different outcome variable)

**What were the three-month results?**

Focus your attention on the 0.5 outcome.
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

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<tr>
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<td>↓8.7</td>
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Consistent with MARINA and ANCHOR, monthly ranibizumab injections led to improved visual acuity.
One injection every month for 3 months, then every 3 months to 12 months

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What were the three-month results?
Consistent with MARINA and ANCHOR, monthly ranibizumab injections led to improved visual acuity. Which makes sense, because the first three months of PIER were identical to the first three months of MARINA and ANCHOR (ie, a shot every month).
PIER: Results at 3 months
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

<table>
<thead>
<tr>
<th>One Year</th>
<th>0.3 mg</th>
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<th>Sham</th>
</tr>
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<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↓1.6</td>
<td>?</td>
<td>↓16.3</td>
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What about the one-year results?
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

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<tr>
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What about the one-year results?
These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels.
PIER: Results at 12 months
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

What about the one-year results? These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels. So while better than no treatment (ie, the sham arm), this was a dramatically worse outcome than what was achieved via monthly injections in MARINA and ANCHOR.

No question—advance when ready.
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

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These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels. So while better than no treatment (ie, the sham arm), this was a dramatically worse outcome than what was achieved via monthly injections in MARINA and ANCHOR. Clearly, a q3 month schedule was not going to be acceptable.

No question—advance when ready.
What were the dosing schedules?

One injection every month for 3 months, then PRN as indicated by OCT, VA and DFE findings at monthly exams.

So if the PIER schedule isn’t effective, what about the PRN PrONTO schedule? Recall these pts received a monthly injection x 3, after which they were examined (not injected!) monthly, receiving an injection only if evidence of worsening was found.
For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials.

<table>
<thead>
<tr>
<th></th>
<th>PrONTO RESULTS</th>
<th>MARINA/ANCHOR RESULTS</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Year One</td>
<td>MARINA</td>
</tr>
<tr>
<td>Lost &lt;15 letters</td>
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<td>96%</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>35%</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td>Mean ↑ in letters</td>
<td>9.3</td>
<td>7.2</td>
<td>11.3</td>
</tr>
<tr>
<td>Mean # of injections</td>
<td>5.6</td>
<td>13</td>
<td>13</td>
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What doses of ranibizumab were used? What is the dosing schedule? Is another intervention involved? What is the primary outcome measure? What is the secondary outcome measure?

### MARINA ANCHOR

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### PRONTO RESULTS

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Enter the treat-and-extend approach. While specifics vary among clinicians, most do something along these lines: First, the pt is treated monthly until the macula is ‘dry.’ Once dryness has been achieved, the time until the next visit is extended to 6 weeks. At the 6-week visit the pt is both evaluated and injected. If the 6-week evaluation revealed that the macula remained dry, the interval until the next visit is extended to 8 weeks. Again, at the 8-week visit the pt is both evaluated and injected, and if the eval indicates she remained dry, the interval until the next visit is extended by another 2 weeks to 10.
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Anti-VEGF injection scheduling tl;dr

- **Continuous**: Pt evaluated and treated monthly
- **PRN**: Pt evaluated monthly, treated if evidence active dz
- **Treat and extend**: After dz resolution achieved, interval between eval/tx visits gradually increased to the max the pt can sustain w/o recurrence (or 12 weeks, whichever comes first)

*But that’s a topic for another slide-set*
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

What does recombinant mean? That the substance was produced via recombinant DNA; i.e., DNA created by re-combining portions of 2+ different DNA molecules.

What does humanized mean? Like many monoclonal antibodies, the parent molecule of ranibizumab was derived from mouse cells. Such murine antibodies would be recognized as foreign by the human immune system and attacked as such. To preclude this, a portion of the mouse antibody is replaced with its human counterpart via recombinant DNA techniques.

What is a monoclonal antibody? Antibodies produced by a set of immune cells that all derived from (i.e., clones of) the same parent cell.

What is the ‘parent’ antibody from which the ranibizumab fragment is derived? Bevacizumab.

What does fragment mean in this context? Ranibizumab is not a complete antibody; rather, it consists of a portion—or fragment—of an antibody.
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Note: Different drug!

Bevacizumab
Bevacizumab is the generic, nonproprietary name. What is the brand name for this drug?

**Bevacizumab**

*Ranibizumab* is a **recombinant**, **humanized**, **affinity-matured**, **monoclonal antibody** fragment.

ARMD
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

Bevacizumab is the generic, nonproprietary name. What is the brand name for this drug? Avastin
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

You know bevacizumab is humanized because of the infix, Bevacizumab.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.

You know bevacizumab is humanized because of the infix.

You know it is a monoclonal antibody because of the suffix.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment. Why did we lose the term affinity matured?

Bevacizumab is also a recombinant, humanized, monoclonal antibody fragment. Unlike ranibizumab, bevacizumab was not affinity-matured for VEGF-A.
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Unlike ranibizumab, which consists of an antibody fragment, bevacizumab is a full-length antibody.

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Because it is smaller, ranibizumab clears faster than bevacizumab. What are their systemic half-lives?
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Bevacizumab

Why did we lose the term affinity matured? Unlike ranibizumab, bevacizumab was not affinity-matured for VEGF-A.

Why go to the trouble of engineering an antibody fragment in the first place?

Because it is smaller, ranibizumab clears faster than bevacizumab. What are their systemic half-lives? Bevacizumab’s is about 21 days, whereas ranibizumab’s is only 2.1 hours.
Why did we lose the term affinity matured? Unlike ranibizumab, bevacizumab was not affinity-matured for VEGF-A.

Why go to the trouble of engineering an antibody fragment in the first place? Researchers initially believed that the full-length bevacizumab molecule was too large to pass through the ILM and enter the sub-retinal space.

Why did we lose the word fragment? Unlike ranibizumab, which consists of an antibody fragment, bevacizumab is a full-length antibody.

Because it is smaller, ranibizumab clears faster than bevacizumab. What are their systemic half-lives? Bevacizumab’s is about 21 days, whereas ranibizumab’s is only 2.1 hours.
Which drug was created first—ranibizumab, or bevacizumab?

Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
Which drug was created first—ranibizumab, or bevacizumab?

Bevacizumab

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Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment.
What were the key clinical trials demonstrating the safety and efficacy of bevacizumab in the treatment of ARMD?
To date there have been NO randomized, prospective clinical trials of intravitreal bevacizumab for the treatment of wet ARMD.
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To date there have been NO randomized, prospective clinical trials of intravitreal bevacizumab for the treatment of wet ARMD.

For that matter, there weren’t even any animal trials of intravitreal bevacizumab prior to its use in humans. Clinicians started using it off-label based on what they knew about its ‘next-of-kin’ (ranibizumab).
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?
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What does CATT stand for?
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?

What does CATT stand for? Comparison of Age-related Macular Degeneration Treatments Trial
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?

What doses of each were used?

Ranibizumab: Bevacizumab: 0.5 mg

What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?

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What were the two dosing schedules?
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Was another intervention involved?

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Was another intervention involved?

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What was the primary outcome measure?
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Was another intervention involved?

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What doses of each were used?
- Ranibizumab: 0.5 mg
- Bevacizumab: 1.25 mg

What were the two dosing schedules?
- Continuous
- PRN

Was another intervention involved?
- No

What was the primary outcome measure?
- Mean change in VA

What was the secondary outcome measure?
What study 1) compared the safety and efficacy of bevacizumab vs ranibizumab, and 2) evaluated dosing schedule of these meds in the treatment of ARMD?

What doses of each were used?
Bevacizumab: 1.25 mg
Ranibizumab: 0.5 mg

What were the two dosing schedules?
Continuous, and PRN

Was another intervention involved?
No

What was the primary outcome measure?
Mean change in VA

What was the secondary outcome measure?
Number of treatments
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What were the two dosing schedules?

Continuous, and PRN

Was another intervention involved?

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Mean change in VA

What was the secondary outcome measure?

Number of treatments

What was another oft-discussed secondary outcome measure?
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What doses of each were used?
Ranibizumab: 0.5 mg
Bevacizumab: 1.25 mg

What were the two dosing schedules?
Continuous, and PRN

Was another intervention involved?
No

What was the primary outcome measure?
Mean change in VA

What was the secondary outcome measure?
Number of treatments

What was another oft-discussed secondary outcome measure?
Incidence of adverse events
## CATT RESULTS

*Average Number of Letters Gained at One Year*

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th>Bevacizumab</th>
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<tbody>
<tr>
<td><strong>Every Month Dosing</strong></td>
<td>?</td>
<td>?</td>
</tr>
<tr>
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**ARMD**
# CATT RESULTS

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*These are statistically equivalent*
## CATT RESULTS

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<table>
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**ARMD**
**CATT RESULTS**

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## CATT RESULTS

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However, PRN bevacizumab yielded a significantly lower average gain when compared to monthly bevacizumab…
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However, PRN bevacizumab yielded a significantly lower average gain when compared to monthly bevacizumab… or when compared to monthly ranibizumab.
CATT RESULTS

Average Number of Letters Gained at One Year (and average number of injections)

<table>
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<tr>
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<tbody>
<tr>
<td><strong>Every Month Dosing</strong></td>
<td>8.5(12)</td>
<td>8.0(12)</td>
</tr>
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<td><strong>PRN Dosing</strong></td>
<td>6.8(?)</td>
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Another important issue concerns the number of injections needed. The fixed-schedule pts received 12 monthly injections over the first year (obviously), but what about in the PRN-dosing conditions?
**CATT RESULTS**

*Average Number of Letters Gained at One Year (and average number of injections)*

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Another important issue concerns the number of injections needed. The fixed-schedule pts received 12 monthly injections over the first year (obviously), but what about in the PRN-dosing conditions? On average, the PRN ranibizumab and PRN bevacizumab pts received 7 and 8 injections respectively.
What about adverse events?

In terms of these events, no differences obtained between the bevacizumab and the ranibizumab cohorts. However, post hoc analysis of the rates of other adverse events (eg, hospitalization) suggested an association between these events and bevacizumab. Is this finding concerning enough to warrant using ranibizumab preferentially? Probably not. As of this writing, the opinion seems to be that the increased adverse effects were probably happenstance. This opinion is based on two facts:

1) The reported adverse events have not been found in studies involving the systemic administration of bevacizumab. If these events were triggered by the minute amounts of bevacizumab that might have entered the systemic circulation after intravitreal injection, the thinking goes, surely they would have occurred during systemic bevacizumab trials in which systemic concentrations were at least 500 times greater.

2) The reported adverse events did not correlate with bevacizumab dosing, as would be expected if a causal relationship held.
What about adverse events?
Certain events were identified a priori to be tracked; these included MI, CVA and death. In terms of these events, no differences obtained between the bevacizumab and the ranibizumab cohorts.
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Next we drill down on a third drug that has come to play a vital role in the management of wet ARMD.
Aflibercept is a recombinant fusion protein.
Aflibercept is a *recombinant* fusion protein
Aflibercept is a recombinant fusion protein

What is a fusion protein?
Afiblercept is a **recombinant fusion protein**

**What is a fusion protein?**
A novel protein constructed by joining (fusing) the genetic information coding for two other proteins.
Aflibercept is the generic, nonproprietary name. What is the brand name for this drug?

Aflibercept is a recombinant fusion protein.
Aflibercept is the generic, nonproprietary name. What is the brand name for this drug? Eylea

Aflibercept *is a recombinant fusion protein*
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What does the suffix –cept indicate?
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That the drug functions by mimicking a receptor molecule

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What does the infix –ber- indicate?
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ARMD
Aflibercept is a recombinant fusion protein

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ARMD

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Afibl**ercept** is a recombinant fusion protein

**What does the suffix –cept indicate?**
That the drug functions by mimicking a receptor molecule

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Spell it out for me—what does it mean to say aflibercept ‘mimics the VEGF receptor’?
Put another way: How does aflibercept work?
Afib**lercept** is a recombinant fusion protein

What does the suffix –**cept** indicate?
That the drug functions by mimicking a receptor molecule

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Put another way: How does aflibercept work?
Aflibercept is a **decoy receptor** that locks up unbound VEGF in the retinal space before it (the VEGF) can find an actual VEGF receptor on a target structure.
Afli\textit{bercept} is a recombinant fusion protein

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Afib\(\text{lercept}\) is a recombinant fusion protein

**What does the suffix **–cept** indicate?**
That the drug functions by mimicking a **receptor molecule**

**Afib\(\text{lercept}\) is a recombinant fusion protein**

**What does the infix **–ber**- indicate?**
That the mimicked receptor is the **VEGF receptor**

*Spell it out for me—what does it mean to say aflibercept ‘mimics the VEGF receptor’?*
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Afib\(\text{lercept}\) is a **decoy receptor** that locks up unbound VEGF in the retinal space before it (the VEGF) can find an actual VEGF receptor on a target structure. **This strategy is referred to as ‘VEGF trap.’**
Aflibercept is a recombinant fusion protein.

Which isoforms of VEGF-A does aflibercept bind?

Of bevacizumab, ranibizumab and aflibercept, which binds VEGF-A with the greatest affinity?

Aflibercept

In addition to VEGF-A, aflibercept binds another protein implicated in the pathogenesis of CNVM—what is it?

Placental growth factor (PLGF)
Aflibercept is a **recombinant fusion protein**

Which isoforms of VEGF-A does aflibercept bind?
All of them
Afiblercept is a recombinant fusion protein

**Which isoforms of VEGF-A does afiblercept bind?**
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Aflibercept

This ability to bind PLGF may account for the fact that aflibercept is effective in some cases of **ranibizumab-refractory CNVM**—a pathogenesis of CNVM—what is it?
**Placental growth factor (PLGF)**
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?
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Technically, there were two VIEW trials--**VIEW1** was conducted in the US and Canada, **VIEW2** overseas. However, because the results of the two studies were essentially identical, for simplicity's sake we will treat them as if they were a single study.
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

What does VIEW stand for?

VIEW stands for "VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet ARMD".
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

What does VIEW stand for?
The **VEGF Trap-Eye**: **I**nvestigation of **E**fficacy and Safety in **W**et ARMD
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What doses of aflibercept were used?
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What doses of aflibercept were used?

Either 0.5 or 2 mg by intravitreal injection.
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What was the dosing schedule?
What were the key clinical trials demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

**What doses of aflibercept were used?**

Either 0.5 or 2 mg by intravitreal injection.

**What was the dosing schedule?**

There were 3:

a) 0.5 mg every 4 weeks, or
b) 2 mg every 4 weeks, or

c) 2 mg every 8 weeks after three q4 week loading doses.
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

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Take note of the q8 week condition. Remember, one of the drawbacks of ranibizumab is its q4 week dosing requirement, which places tremendous financial and structural strain on the healthcare system. (Consider: In 2003, prior to the advent of intravitreal anti-VEGF meds, Medicare was billed for ~3000 intravitreal injections. In 2010, it was billed for over a MILLION.) Thus there was considerable interest in whether a q8 week dosing schedule would work.
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

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Was another intervention involved?
A control group received ranibizumab 0.5 mg every 4 weeks
The VIEW was a *noninferiority trial*, meaning the efficacy/safety of a new treatment was being compared to that of a ‘gold standard’ treatment. In other words, the VIEW had to demonstrate that aflibercept was *at least* as good and *at least* as safe as ranibizumab in order to gain approval.

**Was another intervention involved?**

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The VIEW was a noninferiority trial, meaning the efficacy/safety of a new treatment was being compared to that of a ‘gold standard’ treatment. In other words, the VIEW had to demonstrate that aflibercept was at least as good and at least as safe as ranibizumab in order to gain approval. To do so required:
1) the presence of a ranibizumab arm in the study, and
2) that patients in the VIEW have lesions similar to those of the participants in the studies used to prove the safety and efficacy of ranibizumab in the first place (ie, the MARINA and ANCHOR studies).

Was another intervention involved?
A control group received ranibizumab 0.5 mg every 4 weeks
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

What doses of aflibercept were used?

Either 0.5 or 2 mg by intravitreal injection

What was the dosing schedule?

There were 3:
  a) 0.5 mg every 4 weeks, or
  b) 2 mg every 4 weeks, or
  c) 2 mg every 8 weeks after three q4 week loading doses

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Proportion of patients losing <15 ETDRS letters

What was the secondary outcome measure?

Proportion of patients maintaining (i.e., losing zero ETDRS letters) or gaining ETDRS letters
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Year One Results

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ARMD
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| Mean gain in ETDRS letters read | 8.3 | 9.2 | 8.4 | 8.7 |

**VIEW study:**  
**Year Two Results**

The VIEW was carried into a second year. The basic Year 2 study criteria were:
1) Participants remained in the same treatment condition
2) Participants were evaluated monthly and treated PRN
3) All participants were treated at least every 12 weeks
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As with the Year One data, the key finding is that q8 weeks aflibercept worked **just as well** as monthly ranibizumab.
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Also of note is the fact that the Year Two results are similar to those of Year One.
Another much-anticipated outcome concerned the **average number of treatments** required in the q8 week aflibercept vs ranibizumab conditions.
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<tr>
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<td>12</td>
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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: Nonexudative and exudative.

RPE abnormalities in ARMD are typical.

Photoreceptors in ARMD are abnormal as well.

The pathogenesis of ARMD is not well understood; that said, the complement system is strongly implicated in it.

VEGF plays a key role in exudative ARMD; likewise, interdicting VEGF is key in managing it.

Nonexudative ARMD is treatable at present.
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ARMD: The AREDS

AREDS is the...
ARMD: The AREDS

- AREDS is the Age-Related Eye Disease Study
ARMD: The AREDS

- AREDS is the Age-Related Eye Disease Study
- Looked at dietary supplements and ARMD:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene 15 mg
  - Zinc 80 mg
  - Cupric oxide 2 mg
- Findings:
  - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
  - Patients with no/early ARMD: No benefit

Note: Don't give AREDS supplements to smokers (β-carotene increases the risk of lung Ca in these patients)
ARMD: The AREDS

AREDS is the Age-Related Eye Disease Study

Looked at dietary supplements and ARMD:

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- Vitamin E
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**Antioxidants**

**Minerals**
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ARMD: The AREDS

AREDS is the Age-Related Eye Disease Study

Looked at dietary supplements and ARMD:

- **Vitamin C** 500 mg
- **Vitamin E** 400 IU
- **β-carotene** 15 mg
- **Zinc** 80 mg
- **Cupric oxide** 2 mg

**Study findings:**

- Patients with **intermediate/advanced dry** ARMD had a **25%** reduced risk of advanced disease and vision loss
- Patients with **no/early** ARMD: No benefit

Note: Don’t give AREDS supplements to smokers (β-carotene increases the risk of lung Ca in these patients)
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- **ARMD: The AREDS**
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C: 500 mg
    - Vitamin E: 400 IU
    - β-carotene: 15 mg
    - Zinc: 80 mg
    - Cupric oxide: 2 mg
    - *Antioxidants*
    - *Minerals*
  - Study findings:
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit
  - Note: Don’t give AREDS supplements to smokers
    - an AREDS anti-ox increases the risk of lung Ca in these patients
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*Next, let’s drill down on the AREDS2*
ARMD: The AREDS2

Follow-up to the AREDS

- **Vitamin C**: 500 mg
- **Vitamin E**: 400 IU
- **β-carotene**: 15 mg
- **Zinc**: 80 mg
- **Cupric oxide**: 2 mg
**ARMD: The ARED S2**

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene

- **Vitamin C** 500 mg
- **Vitamin E** 400 IU
- **β-carotene** ? & ?
- **Zinc** 80 mg
- **Cupric oxide** 2 mg
**ARMD: The AREDS 2**
- Follow-up to the AREDS
- Subbed **xanthophylls** for β-carotene
  - **Vitamin C** 500 mg
  - **Vitamin E** 400 IU
  - **β-carotene** *Lutein & Zeaxanthin* (These are the two xanthophylls employed)
  - **Zinc** 80 mg
  - **Cupric oxide** 2 mg
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added
  - Vitamin C  500 mg
  - Vitamin E  400 IU
  - β-carotene  (Lutein & Zeaxanthin)
  - Zinc   80 mg
  - Cupric oxide  2 mg
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene
  - Zinc 80 mg
  - Cupric oxide 2 mg

Lutein & Zeaxanthin

Omega-3 fatty acids
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C  500 mg
  - Vitamin E  400 IU
  - β-carotene  Lutein & Zeaxanthin
  - Zinc  80 mg
  - Cupric oxide  2 mg

- Study findings:
  - Reaffirmed vs Disputed results of the AREDS
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C  500 mg
  - Vitamin E  400 IU
  - β-carotene
  - Zinc   80 mg
  - Cupric oxide 2 mg

- Study findings:
  - Reaffirmed results of the AREDS
**ARMD: The AREDS 2**

- Follow-up to the AREDS
- Subbed **xanthophylls** for β-carotene; added **O3FAs**:
  - **Vitamin C** 500 mg
  - **Vitamin E** 400 IU
  - **β-carotene** (Lutein & Zeaxanthin)
  - **Zinc** 80 mg
  - **Cupric oxide** 2 mg

**Study findings:**
- **Reaffirmed** results of the AREDS
- **Xanthophylls** effective vs ineffective substitute for β-carotene
ARMD: The AREDS\textsuperscript{2}

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene
  - Zinc 80 mg
  - Cupric oxide 2 mg

- Study findings:
  - Reaffirmed results of the AREDS
  - Xanthophylls suitable substitute for β-carotene
**ARMD: The AREDS2**
- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added **O3FAs**:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene
  - Zinc 80 mg
  - Cupric oxide 2 mg
- **Study findings:**
  - Reaffirmed results of the AREDS
  - Xanthophylls **suitable** substitute for β-carotene

*Why is this important?*
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene
  - Lutein & Zeaxanthin
  - Zinc 80 mg
  - Cupric oxide 2 mg
- Study findings:
  - Reaffirmed results of the AREDS
  - Xanthophylls suitable substitute for β-carotene

Why is this important? Because it means β-carotene can be dropped, obviating this concern.

- Note: Don’t give AREDS supplements to smokers
  - β-carotene increases the risk of lung Ca in these patients
ARMD: The AREDS2

- Follow-up to the AREDS
- Subbed **xanthophylls** for β-carotene; added **O3FAs:**
  - Vitamin C 500 mg
  - Vitamin E 400 IU
  - β-carotene
  - Lutein & Zeaxanthin
  - Zinc 80 mg
  - Cupric oxide 2 mg

- **Study findings:**
  - **Reaffirmed** results of the AREDS
  - Xanthophylls **suitable** substitute for β-carotene
  - O3FAs **effective vs ineffective** at reducing risk of progression
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- Follow-up to the AREDS
- Subbed xanthophylls for β-carotene; added O3FAs:
  - Vitamin C 500 mg
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  - β-carotene
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- Study findings:
  - Reaffirmed results of the AREDS
  - Xanthophylls suitable substitute for β-carotene
  - O3FAs ineffective at reducing risk of progression