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.
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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 have 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 (ie, 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**
- **A**ge
- **S**moking
- **H**yperopia
- **H**ypercholesterolemia
- **H**igh CRP

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 (ie, white ethnicity)**
- **Smoking; Sun exposure**
- **Hyperopia; Hypercholesterolemia; High CRP**

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.

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- **Family history; Female**
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- **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

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**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

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

**Age-related macular degeneration (ARMD)**

Age is the strongest risk factor for ARMD.

The clinical hallmark of ARMD is the presence of drusen in the macula.

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

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

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- Drusen are categorized by their boundaries.

**drusen**
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  - Large
  - Drusenoid PED

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- **Drusen are categorized by their boundaries**
Small drusen
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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The clinical hallmark of ARMD is the presence of *drusen* in the macula.

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There are several ways:

- **Drusen are categorized by their size:**
  - Small: <63 μm diameter
  - Intermediate: 63–124
  - Large
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- **Drusen are categorized by the retinal layer in which they’re located**

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

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  - Large: ≥125
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Drusen are categorized by their boundaries.
Large drusen
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**How the heck are you supposed to know the size of a druse in microns?**

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**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).

Drusenoid PED
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- **By boundaries:**

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Drusen are categorized by their size:
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In this context, what does PED stand for?

Drusen are categorized by their size:
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Drusen are categorized by their boundaries:

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. 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:
- Drusenoid: Uniformly hyperreflective
- Serous/hemorrhagic: Solid with 'clefts'
- Fibrovascular: Sub-RPE space 'empty'
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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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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
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- **Boundaries**

- **Retinal layer**

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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.

What are drusen?
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Drusen are categorized by their size:
- Small: <63 μm diameter
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- Drusenoid PED: >350

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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?** Each is identifiable via the appearance of the sub-RPE space on OCT. What is this appearance for each?
--Drusenoid: ?
--Serous
--Fibrovascular

Drusen are categorized by:
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Drusen are categorized by:
--Boundaries
--Retinal layer in which they're located

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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
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---

**Drusen are categorized by:**

- **Size:**
  - Small: <63 μm diameter
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- **Boundaries:**
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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
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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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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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: 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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  - Small: <63 μm diameter
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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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**Drusen are categorized by the retinal layer in which they’re located**

**Drusen are categorized by their boundaries:**
--Hard: ?
--Soft
--Confluent

Which are described as being...
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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  - Hard: Discrete, well demarcated
  - Soft
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Which are described as being...
Hard drusen
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  - Soft: ?
  - Confluent

Which are described as being…
Age-related macular degeneration (ARMD)

- Age is the strongest risk factor.
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- **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

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

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--Confluent: ?

*Drusen are categorized by the *retinal layer* in which they’re located*
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Drusen are categorized by their boundaries:
--Hard: Discrete, well demarcated
--Soft: Amorphous, poorly demarcated
--Confluent: Contiguous drusen without clear boundaries

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

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.
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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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  -- Hard: Discrete, well demarcated  
  -- Soft: Amorphous, poorly demarcated  
  -- Confluent: Contiguous drusen without clear boundaries

Which type(s) carry a greater risk of disease progression? Soft for sure, and probably confluent as well.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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- ?
- ?
- ?

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

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*Drusen are categorized by the retinal layer in which they're located:*
  --Basal laminar
  --Basal linear
  --Reticular pseudodrusen

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  --Hard: Discrete, well demarcated
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  - Basal laminar:
  - Basal linear:
  - Reticular pseudodrusen:

- Drusen are categorized by their size:
  - Small: <63 μm diameter
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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

\[
\begin{array}{c}
1) \quad \text{(Start here)} \\
2) \\
3) \\
4) \\
5)
\end{array}
\]

**Innermost**

**Outermost**
But first:

What are the five layers of Bruch’s membrane?

1) Innermost
2) two words of RPE
3) 
4) 
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 layer
3)
4)
5)
But first:

What are the five layers of Bruch’s membrane?

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

What are the five layers of Bruch’s membrane?

1) **Basement membrane** of RPE
2) Inner **collagenous** layer
3) layer
4) 
5) 

**Innermost**

**Outermost**
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)  

**Innermost**

**Outermost**
**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. **one familiar word**
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

**Innermost**

**Outermost**
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)
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-Bruch’s) structure goes here?

0) ?
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

What (non-Bruch’s) structure goes here? The RPE cells themselves
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

So, the basal plasma membranes of the RPE cells…

[Diagram showing the five layers of Bruch’s membrane with RPE cells at the top and ARMD mentioned nearby.]
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... sit directly on their BM (as you would expect)
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

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:

0) RPE cells RPE cells

What (non-RPE) structures go here?
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

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
3. Elastic layer
4. Outer collagenous layer
5. Basement membrane of choriocapillaris

What cell type is this?

But first:

PR outer segs

RPE cells RPE cells

Basement membrane of RPE

Innermost

Outermost

ARMD

0) RPE cells RPE cells

1) PR outer segs

2) ?

3) RPE cells RPE cells

4) RPE cells RPE cells

5) Basement membrane of choriocapillaris
Bruch’s membrane

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

0) RPE cells

1) PR outer segs

-2) Bipolar cells

But first:

What cell type is this? Bipolar cells

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.

**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:

- 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:
  - Basal laminar
  - Basal linear
  - Reticular pseudodrusen

- Drusen are categorized by their **boundaries**:
  - Hard: Discrete, well demarcated
  - Soft: Amorphous, poorly demarcated
  - Confluent: Contiguous drusen without clear boundaries
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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

-PR outer segs
-2) Bipolar cells

**ARMD**

**basal laminar drusen**
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  - **Small:** \(<63 \text{ \mu m}\) diameter
  - **Intermediate:** 63–124
  - **Large:** \(\geq125\)
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- **Drusen are categorized by the retinal layer in which they’re located:**
  - **Basal laminar:** Between RPE cells and their BM
  - **Basal linear:** Within inner aspect of Bruchs membrane
  - **Reticular pseudodrusen**

- **Drusen are categorized by their boundaries:**
  - **Hard:** Discrete, well demarcated
  - **Soft:** Amorphous, poorly demarcated
  - **Confluent:** Contiguous drusen without clear boundaries
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**

- **-2) Bipolar cells**

- **-1) PR outer segs**

- **1) **Basement membrane of RPE** **innermost**

- **2) Inner collagenous layer**

- **3) Elastic layer**

- **4) Outer collagenous layer**

- **5) Basement membrane of choriocapillaris** **outermost**

*ARMD*
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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?
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--Small: <63 μm diameter
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- **Drusen are categorized by the retinal layer in which they’re located:**
  - Basal laminar: Between RPE cells and their BM
  - Basal linear: Within inner aspect of Bruchs membrane
  - Reticular pseudodrusen: Between the apical surface of the RPE cells and the overlying photoreceptors

- **Drusen are categorized by their boundaries:**
  - Hard: Discrete, well demarcated
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What are the five layers of Bruch’s membrane?

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

ARMD
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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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

So now we can see how basal laminar drusen, if extensive enough, can cause a drusenoid PED.
Likewise, we can see that extensive basal linear drusen can also producing a drusenoid PED.
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

However, reticular pseudodrusen do not separate the RPE from Bruch's, so they cannot cause a PED.

But first:

- Bipolar cells
- PR outer segs
- RPE cells

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

Innermost

Outermost
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**
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 and exudative.

By what two other names are each condition commonly known?

Nonexudative: ?
Exudative
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Nonexudative: Nonneovascular ARMD; ‘dry’ ARMD
Exudative: ?
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*By what two other names are each condition commonly known?*

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What are the three hallmark findings in nonexudative ARMD?

--?

--?

--?
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What are the three hallmark findings in nonexudative ARMD?

--Drusen
--RPE changes
--Geographic atrophy
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What are the three hallmark findings in nonexudative ARMD?

- **Drusen**
- **RPE changes**
- **Geographic atrophy**

We have already discussed drusen, and will look at RPE change in detail a little later in the set.
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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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. It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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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.
- 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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What is its typical pattern of progression?
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**What is its typical pattern of progression?**

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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--**Geographic atrophy**

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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.

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-- RPE changes

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What does GA look like on…

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

**Autofluorescence?** Dense hypoautofluorescence with a ring of hypautofluorescence

**OCT?** RPE loss; thinning/loss of the outer retinal layers

Eventually involves the fovea itself.
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. By what two other names are each condition commonly known? **Nonexudative**: Nonneovascular ARMD; ‘dry’ ARMD. **Exudative**: Neovascular ARMD; ‘wet’ ARMD. 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 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
Geographic atrophy in ARMD: FA
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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What is its typical pattern of progression?

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?

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

Which one of these accounts for the hyperfluorescence of GA?

Window defect

What does GA look like on FA?

A well-circumscribed area of hyperfluorescence

What does GA look like on Autofluorescence?

Dense hypoautofluorescence with a ring of hypofluorescence

What does GA look like on 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.

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

GA 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.

It starts in the perifoveal region, expanding over time to eventually involve the foveal center.
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.

By what two other names are each condition commonly known?

Nonexudative: Nonneovascular ARMD; 'dry' ARMD
Exudative: Neovascular ARMD; 'wet' ARMD

What are the three hallmark findings in nonexudative ARMD?

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

Which one of these accounts for the hyperfluorescence of GA?

---Geographic atrophy

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
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Speaking generally: What are the four causes of hyperfluorescence on FA?
-- Pooling
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Which one of these accounts for the hyperfluorescence of GA?
Window defect
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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**What does GA look like on…**

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

**Autofluorescence?** Dense hypoauflorescence with a ring of hyperautofluorescence

Eventually involves the foveal center.
FAF: Normal retina for comparison

FAF: GA
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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What does GA look like on...

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What does GA look like on...

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- **Autofluorescence?** Dense hypoautofluorescence with a ring of hyperautofluorescence
- **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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**Exudative**:
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**Nonexudative**:
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- **Nonexudative**
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**Advanced ARMD**: Defined by the presence of either geographic atrophy or a neovascular membrane.

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

The presence of neovascularization 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**

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

- **Early ARMD**:
  - The presence of small drusen +/- a few intermediate drusen

- **Intermediate ARMD**:
  - Characterized by extensive intermediate drusen, or the presence of any large drusen

What are the three hallmark findings in nonexudative ARMD?

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- RPE changes
- Geographic atrophy

What is geographic atrophy (GA)?

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There are two types: **nonexudative** and **exudative** ARMD.

**Nonexudative** ARMD:
- Non-neovascular ARMD; 'dry' ARMD

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

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

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

- **Intermediate ARMD**

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- The presence of neovascularization.
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There are two types: nonexudative and exudative.

**Nonexudative (‘dry’ ARMD)**: Defined by the presence of small drusen +/- a “few” intermediate drusen.

**Exudative (‘wet’ ARMD)**: Neovascular ARMD.

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

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

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- Drusen
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It starts in the perifoveal region, expanding over time to eventually involve the foveal center.

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The presence of neovascularization.
Age-related macular degeneration (ARMD) is the #1 cause of blindness in adults age 50 and older in resource-rich nations. The strongest risk factor for ARMD is age. The clinical hallmark of ARMD is the presence of drusen in the macula.

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 about early and intermediate ARMD—how are they defined?

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

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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 neovascular membrane.

What about early and intermediate ARMD—how are they defined?
- Early ARMD: Defined by the presence of small drusen +/- a “few” intermediate drusen
- Intermediate ARMD: Characterized by extensive intermediate drusen, or the presence of any large drusen
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What are the three hallmark risk factors in nonexudative ARMD?
- Drusen
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- What are the three hallmark findings in nonexudative ARMD?
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- What is geographic atrophy (GA)?
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  **Nonexudative (‘dry’ ARMD)**:
  - By what two other names are each condition commonly known?
  - Exudative (‘wet’ ARMD): Neovascular ARMD

  **What are the three hallmark findings in nonexudative ARMD?**
  - Drusen
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  - It starts in the perifoveal region, expanding over time to eventually involve the foveal center.

  **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.

- Early ARMD: Defined by the presence of small drusen +/- a “few” intermediate drusen
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**Exudative**: Neovascular ARMD; ‘wet’ ARMD

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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. (See R52 for more on this rare condition.)

No question yet—advance when ready
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By what two other names are each condition commonly known?

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

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

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?

- 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

What structure is this?
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

1. PR outer segs
2. Bipolar cells
3. RPE cells
4. RPE cells

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
- 6) Choriocapillaris
- 7) ?

What structure is this?

The choroid

ARMD

But first:

0) RPE cells
1) PR outer segs
2) Bipolar cells
3) ?
4) ?
5) ?
6) ?
7) ?

Innermost

Outermost
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

Innermost: RPE cells

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

Outermost: Choriocapillaris

What structure is this?
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
- 3) Retinal vessels
- 4) Choriocapillaris
- 5) Choroid
What are the five layers of Bruch’s membrane?

-1) PR outer segs
-2) Bipolar cells
-3) Retinal vessels
-4) Ongoing...
What are the five layers of Bruch's membrane?

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

But first:

0) RPE cells

1) PR outer segs

So, the retinal vessels supply the inner retinal layers…
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

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
- Rod & cone inner and outer segments

RPE

Bruch’s membrane

Blood supply:
- Central retinal artery
- Choroid/Ch’capillaris

Which layers are supplied by each blood supply?

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.

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’?
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By what two other names are each condition commonly known?

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

--?

--?

--?

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

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

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

*Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma.*
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--Type 2

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--Type 3

Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma.
-2) Bipolar cells

-1) PR outer segs

0) RPE cells 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
What are the five layers:

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

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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There are two types: Nonexudative and exudative.

By what two other names are each condition commonly known?
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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 Bruch’s membrane and/or the sub-RPE space
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--Type 3: Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma
ARMD

- Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations
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--Type 3 NVM arises from the deep capillary plexus of the retina and grows down toward the RPE

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

- Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations
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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 Bruch’s membrane and/or the sub-RPE space.
- **Type 2**: CNVM originates from the choriocapillaris and extends into the sub-retinal space (i.e., just above the RPE).
- **Type 3**

Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma.
What are the five layers of Bruch's membrane?

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

**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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Type 3: ?

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

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
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
ARMD

- 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 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.

**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).

**Type 3: NVM arises from the deep capillary plexus of the retina.**

Blurry vision, metamorphopsia, and/or a paracentral scotoma.
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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So we’re referring to something as a ‘choroidal’ NVM when it doesn’t originate in the choroid? Make it make sense.

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

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

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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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What vessels give rise to the neovascular membrane?

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

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

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*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 (OHS)
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

By what two other names are each condition commonly known?

Nonexudative: Nonneovascular ARMD; ‘dry’ ARMD

Exudative: Neovascular ARMD; ‘wet’ ARMD

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 (OHS)

By what other name is Type 3 known?

Retinal angiomatous proliferation (RAP)
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There are two types: **Nonexudative** and **exudative**.

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**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.

Of the three, which occurs most frequently in ARMD?

Type 1

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

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

Blurry vision, metamorphopsia and/or a paracentral scotoma.

Of the three, which occurs most frequently in ARMD?

Type 1.

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Ocular histoplasmosis.

Type 3: NVM arises from the deep capillary plexus of the retina and grows 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).

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

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)

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

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

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)
CNVM DDx:

- ARMD
- OHS ★
- Angioid streaks ★
- Pathologic myopia ★
  - Idiopathic
  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
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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?
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*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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How is the diagnosis of OHS made?

- 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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ARMD
OHS: The classic triad
For more on OHS, see slide-set U21

OHS: The classic triad
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**

*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 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
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- **S**ickle-cell disease
- **I**diopathic (ie, no association)
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.
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?

Adult-onset vitelliform dystrophy
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P E P S I

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- Adult-onset vitelliform dystrophy
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Psuedoxanthoma elasticum (PXE)
Ehlers-Danlos syndrome
Paget’s disease of bone
Sickle-cell disease
Idiopathic (ie, no association)

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

- ARMD
- OHS

**Angioid streaks**

<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
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$\bullet$ Iatrogenic

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

$\bullet$ Idiopathic (ie, no association) $\sim$ # of cases have no known systemic association
What is the classic DFE appearance of angioid streaks?
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About half

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- Pseudoxanthoma elasticum (PXE)
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~50% of cases are associated with one of these
~50% of cases have no known systemic association

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Which condition has the strongest association with angioid streaks?

Adult-onset vitelliform dystrophy.
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PXE, by a mile

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

What other organ-systems are affected in PXE?
--Eye.
**CNVM DDx:**
- ARMD
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**Angioid streaks**

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

Other organ-systems affected in PXE:
- Skin
- Vascular system
- GI tract
- Eye

Adult-onset vitelliform dystrophy
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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. The classic informal descriptor for this appearance is 'Chicken skin'.

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?* 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?* PXE, by a mile.

*What is the appearance of affected skin?* An area of waxy-yellow, papule-like lesions.

*About how many organ-systems are affected in PXE?* Skin, vascular system, 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?**
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**About how many angioid streaks are associated with systemic abnormalities?**
About half.

**What is the well-known mnemonic for angioid streak’s associations?**
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?**
PXE, by a mile.

**What is the appearance of affected skin?**
An area of waxy-yellow, papule-like lesions.

**What is the classic informal descriptor for this appearance?**
'Chicken skin'.
**CNVM DDx:**
- ARMD
- OHS

**Angioid streaks**

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  - 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 are these associations?
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- What is the appearance of affected skin?
  - An area of waxy-yellow, papule-like lesions

- What is the classic informal descriptor for this appearance?
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**CNVM DDx:**

- ARMD
- OHS

**Angioid streaks**

- What is the classic DFE appearance of angioid streaks?
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- What proportion of angioid streaks are associated with systemic abnormalities?
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- What is the well-known mnemonic for angioid streak’s associations? What are these associations?
  - Suspicious associations:
    - Pseudoxanthoma elasticum (PXE)
    - Ehlers-Danlos syndrome
    - Paget’s disease of bone
    - Sickle-cell disease
    - Idiopathic (ie, no association)

**Pseudoxanthoma elasticum (PXE)**

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

- 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

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

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

- ARMD
- OHS

**Angioid streaks**

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**Which condition has the strongest association with 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

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- 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
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**CNVM DDx:**
- ARMD
- OHS

★ **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.

- What mellifluous name is used to describe the RPE mottling?
  - Peau d’orange.
CNVM DDx:
- ARMD
- OHS
- Angioid streaks
- Pathologic myopia
- Idiopathic
- Sorsby macular dystrophy
- Traumatic choroidal rupture
- Adult-onset vitelliform dystrophy

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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.

What is the well-known mnemonic for angioid streak’s associations? PEAPS (Pseudoxanthoma elasticum, Ehlers-Danlos syndrome, Paget’s disease of bone, Sickle-cell disease, Idiopathic (ie, no association)).
PXE: *Peau d’orange* fundus
For more on angioid streaks, see slide-set R61

PXE: Peau d’orange fundus
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
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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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- Angioid streaks
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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?
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

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
  - Sorsby macular dystrophy
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  - Central serous chorioretinopathy
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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?*
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- ARMD
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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, yellowish in color, usually found in the retinal area.
**CNVM DDx:**

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

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
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?
- Idiopathic?
- Sorsby macular dystrophy?
- Traumatic choroidal rupture?
- Iatrogenic?
- 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?
CNVM DDx:

- ARMD
- OHS
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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?
**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?*
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
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In two words, what is the underlying cause of CSC?

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

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The presence of SRF on OCT

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

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

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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. 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

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.

Choroidal thickness may not be readily interpretable on standard (SD) OCT. What OCT modality is preferred for assessing the choroid?
Enhanced-depth imaging OCT (EDI-OCT)
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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The thickness of the choroid

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)

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

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Central serous chorioretinopathy

- Pattern dystrophy
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In two words, what is the underlying cause of CSC?
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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.
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).
**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

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.

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
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
- 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
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

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

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

Central serous chorioretinopathy

Pattern dystrophy

Adult-onset vitelliform dystrophy
CSC: RPE mottling
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?

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? 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?

Descending tracts, aka ‘guttering’

Central serous chorioretinopathy

Pattern dystrophy

Adult-onset vitelliform dystrophy
CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.
CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.

For more on CSC, see slide-set R47
**Pattern dystrophy**

- Adult-onset vitelliform dystrophy
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’)
**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?
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

Pattern dystrophy
Adult-onset vitelliform dystrophy
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’)

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AD

are pattern dystrophies associated with severe vision loss?
Generally no--vision is only slightly affected

pattern dystrophy

adult-onset vitelliform dystrophy
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Generally no--vision is only slightly affected

Do the macular ‘patterns’ appear early in life?

Pattern dystrophy
★ Adult-onset vitelliform dystrophy
**Dry ARMD**

- CNVM

**DDx:**

Briefly, what is a pattern dystrophy?
An inherited macular dystrophy that has a characteristic appearance (ie, a particular ‘pattern’)

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Generally no--vision is only slightly affected

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Generally no--they usually show up in middle adulthood

★ **Pattern dystrophy**

★ Adult-onset vitelliform dystrophy
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Generally no--they usually show up in middle adulthood

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

★ 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?
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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?
--
--
--

The mnemonic is…

Pattern dystrophy
Adult-onset vitelliform dystrophy
Dry ARMD

**CNVM DDx:**

_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?_
--B
--A
--R
--F

_The mnemonic is…BARF?_

★ **Pattern dystrophy**
★ **Adult-onset vitelliform dystrophy**
Briefly, what is a pattern dystrophy?
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The BCSC Retina book identifies four pattern dystrophies by name--what are they?
--Butterfly dystrophy
--Adult-onset foveomacular vitelliform dystrophy
--Reticular dystrophy
--Fundus pulverulentus

★ Pattern dystrophy
★ Adult-onset vitelliform dystrophy
Butterfly dystrophy

Reticular dystrophy

Adult-onset foveomacular vitelliform dystrophy

Fundus pulverulentus
**Dry ARMD**

**CNVM**

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

- CNVM
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*These terms are awfully similar…Do they refer to the same, or different conditions?*
The same (the *Retina* book uses both)
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

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
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Dry ARMD

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Adult-onset vitelliform dystrophy
Dry ARMD

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two-words
Dry ARMD

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- 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

**egg-yolk like**
**Dry ARMD**

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```
egg-yolk like
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Typical round, yellow lesion of AOVD
**Dry ARMD**

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- **CNVM**

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OCT showing dome-like lesion in AOVD
**Dry ARMD**

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Adult-onset vitelliform dystrophy
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.
Dry ARMD

CNVM\textsuperscript{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
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★ 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

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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

CNVM

DDx:

- ARMD
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★ Central serous chorioretinopathy
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★ 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
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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

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**RPE** abnormalities in ARMD are typical
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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**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:

-- Atrophy (we knew this one already because of GA)
-- Focal hyperpigmentation
ARMD: RPE hyperpigmentation
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Photoreceptors in ARMD are abnormal as well.

What’s abnormal about the photoreceptors (PRs) in ARMD?
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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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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

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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 (ARMD) 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?
It’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.

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I’s not clear how changes in the RPE and PR are causally linked to one another. That is, we don’t know for certain whether RPE damage leads to PR damage, or PR to RPE, or whether both result from some other cause.

Speaking of being unsure about causality in ARMD…
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations

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So, changes in ARMD include:
--Basal laminar/linear deposits accumulate

No question—advance when ready
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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Which if any of these can occur as part of the normal aging process?
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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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.
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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.
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

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- The pathogenesis of ARMD is not well understood; that said, the **complement** system is strongly implicated in it
Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations.

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*What is the complement system?*
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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

I:\nate
aka... immunity

A:\nate
aka... immunity

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

Innate
aka…natural immunity

Adaptive
aka…acquired immunity

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

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

**Adaptive**
aka...acquired immunity
provide immediate protection

Which provides immediate protection against antigens deemed threatening?
Immune response

**Innate**
aka…natural immunity
Does provide immediate protection

**Adaptive**
aka…acquired immunity
Does not provide immediate protection

Which provides immediate protection against antigens deemed threatening?
Immune response

**Innate**
aka...natural immunity
Does not provide immediate protection
Does not require previous contact with the threat

**Adaptive**
aka...acquired immunity
Does not provide immediate protection
Does not require previous contact with the threat

Which must have previous experience with an antigen to gain the capacity to neutralize it?
### Immune response

**Innate**
- aka... **natural** immunity
- Does **not** provide immediate protection
- Does **not** require previous contact with the threat

**Adaptive**
- aka... **acquired** immunity
- Does **not** provide immediate protection
- Does require previous contact with the threat

*Which must have previous experience with an antigen to gain the capacity to neutralize it?*
Immune response

**Innate**
aka…natural immunity

Does provide immediate protection

Does not require previous contact with the threat

Primary effector cells:
--?
--?

**Adaptive**
aka…acquired immunity

Does not provide immediate protection

Does require previous contact with the threat

Primary effector cells:
--?
--?

*What are the primary effector cells for each?*
# Immune response

## Innate

**aka… natural immunity**

- **Does** provide immediate protection
- **Does not** require previous contact with the threat

Primary effector cells:
- --PMNs
- --Monocytes/macrophages

## Adaptive

**aka… acquired immunity**

- **Does not** provide immediate protection
- **Does** require previous contact with the threat

Primary effector cells:
- --T cells
- --B cells

*What are the primary effector cells for each?*
The innate (or natural) immune response relies on ‘preprogrammed’ immune cells to recognize foreign material encountered in tissue or blood, whereas the adaptive (or acquired) immune response involves ‘education,’ with surveillance cells learning to recognize and remember foreign material.

**Primary effector cells:**
- PMNs
- Monocytes/macrophages

**Primary effector cells:**
- T cells
- B cells
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What would be an example of a single-molecule inflammatory mediator?

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PMNs

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**What would be an example of a single-molecule inflammatory mediator?**

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--Cytokines
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What would be an example of a single-molecule inflammatory mediator?

What is the classic example of a complex, enzymatic-cascade inflammatory mediator (and the reason for this long detour on our ARMD journey)?
Immune response

Innate  aka…natural immunity

Adaptive  aka…acquired immunity

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The complement cascade
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The complement cascade is indeed complex, with components comprising different pathways.
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Complement factor H (CFH)
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. 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.
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VEGF plays a key role in exudative ARMD

Let's drill down on VEGF for a bit...
What does VEGF stand for?
What does VEGF stand for?
Vascular endothelial growth factor
What does VEGF stand for?
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What is a growth factor?

What are some other growth factors of note regarding ocular development and health?
-- Epidermal growth factor
-- Fibroblast growth factor(s)
-- Transforming growth factor \( \beta \) (s)
-- Insulin-like growth factor(s)
What does VEGF stand for?
Vascular endothelial growth factor

What is a growth factor?
One of a diverse group of proteins that affect cell function, including cell proliferation and tissue differentiation

---

ARMD

VEGF-A_{165}
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When you hear ‘transforming growth factor β,’ a particular type of condition should spring to mind.

hint
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Corneal dystrophy, specifically, the so-called transforming growth factor β-induced (TGFBI) dystrophies

There are # TGFBI dystrophies
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There are six TGFBI dystrophies—what are they? (Note: The Cornea book treats four subtypes as a single dystrophy, and they are treated the same way in the list below.)
1) ?
2) ?
3) ?
4) ?
5) ?
6) ?
What does VEGF stand for?
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**growth factor**

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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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Vascular endothelial growth factor

Broadly speaking, what is VEGF?
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Broadly speaking, what is VEGF?
An extracellular signaling protein involved in vascular development
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Does VEGF do anything besides grow new blood vessels?
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as *vascular permeability factor*).
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Does VEGF do anything besides grow new blood vessels?
Yes, it also is a potent vasodilator (it was known originally as vascular permeability factor). This property is important in the development of diabetic macular edema, which explains the effectiveness of anti-VEGF therapies in the treatment of this condition.
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How does VEGF work?
What does VEGF stand for?
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How does VEGF work?
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In a nutshell, what sort of structure is the VEGFR?
It is a so-called ‘transmembrane receptor tyrosine kinase structures’

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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What does the A signify?
VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through **VEGF-A**.
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Vascular endothelial growth factor

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What does the A signify?
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VEGF-A165
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Vascular endothelial growth factor

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What does 165 signify?

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**What does 165 signify?**
VEGF-A is not a single entity either. At least # isoforms exist; these differ in the number of peptides they contain, and that number is used as a subscript to identify specific isoforms.

**VEGF-A**

**ARMD**
**VEGF** stands for **Vascular endothelial growth factor**

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**VEGF-A**

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**Why focus on isoform 165?**
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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
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Extracellular VEGF binds to VEGF receptors on target cells

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.

What does the A signify?
VEGF is not a single entity—a number of similar-but-different proteins comprise the ‘VEGF family.’ These are differentiated as VEGF-A through VEGF-F. (One family member, placental growth factor [PlGF], is the exception to the naming rule.) When the term VEGF is used in the ophthalmology literature without a sub-family designation, it is understood to mean VEGF-A.

What does 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.

Why focus on isoform 165?
It seems to be the most important with respect to pathologic angiogenesis in the human eye.
What does VEGF stand for? Vascular endothelial growth factor

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

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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.

RPE abnormalities in ARMD are typical.

Photoreceptors in ARMD are abnormal as well.

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Next let’s drill down on anti-VEGF therapy…
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What does MARINA stand for?

What does ANCHOR stand for?
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Either 0.3 and 0.5 mg by intravitreal injection (or sham injections)
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0.3 mg 0.5 mg Sham
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YEAR ONE
RESULTS

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<tr>
<th></th>
<th>0.3 mg</th>
<th>0.5 mg</th>
<th>PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss &lt;15 letters</td>
<td>94%</td>
<td>96%</td>
<td>64%</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>
Evaluated ranibizumab for the treatment of predominantly classic 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 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%

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

- Loss <15 letters: 95% (0.3 mg), 95% (0.5 mg), 62% (Sham)
- Gained >15 letters: 25% (0.3 mg), 34% (0.5 mg), 5% (Sham)

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

- Loss <15 letters: 95% (0.3 mg), 95% (0.5 mg), 62% (Sham)
- Gained >15 letters: 25% (0.3 mg), 34% (0.5 mg), 5% (Sham)

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 CNVM
Either 0.3 and 0.5 mg by intravitreal injection (or sham injections)
One injection every month for 24 months

Proportion of patients losing <15 ETDRS letters
Proportion of patients gaining >15 ETDRS letters

<table>
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<td>36%</td>
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</tr>
</tbody>
</table>

RESULTS

YEAR ONE

YEAR TWO

<table>
<thead>
<tr>
<th></th>
<th>0.3 mg</th>
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</tr>
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<td>?</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>34%</td>
<td>41%</td>
<td>6%</td>
</tr>
</tbody>
</table>
MARINA

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

<table>
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<td>25%</td>
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<td>5%</td>
</tr>
</tbody>
</table>

ANCHOR

Evaluated ranibizumab for the treatment of predominantly classic CNVM. Either 0.3 and 0.5 mg by intravitreal injection (or sham injections) for 24 months.

<table>
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<tr>
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<th>PDT</th>
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<tbody>
<tr>
<td>Loss &lt;15 letters</td>
<td>92%</td>
<td>90%</td>
<td>53%</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>34%</td>
<td>41%</td>
<td>6%</td>
</tr>
</tbody>
</table>

### RESULTS

**YEAR ONE**

- **Proportion of patients losing <15 ETDRS letters:**
  - 0.3 mg: 95%
  - 0.5 mg: 95%
  - Sham: 62%

- **Proportion of patients gaining >15 ETDRS letters:**
  - 0.3 mg: 25%
  - 0.5 mg: 34%
  - Sham: 5%

**YEAR TWO**

- **Proportion of patients losing <15 ETDRS letters:**
  - 0.3 mg: 92%
  - 0.5 mg: 90%
  - Sham: 53%

- **Proportion of patients gaining >15 ETDRS letters:**
  - 0.3 mg: 34%
  - 0.5 mg: 41%
  - Sham: 6%
MARINA

RESULTS

ANCHOR

<table>
<thead>
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<tr>
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<td></td>
<td>40%</td>
<td>6%</td>
</tr>
</tbody>
</table>

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

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<td>41%</td>
<td>6%</td>
</tr>
</tbody>
</table>

YEAR ONE

YEAR TWO

ARMD
Evaluated ranibizumab for the treatment of minimally classic/occult CNVM and predominantly classic CNVM.

- Either 0.3 and 0.5 mg by intravitreal injection (or sham injections) for 24 months.

### RESULTS

<table>
<thead>
<tr>
<th>Year</th>
<th>0.3 mg</th>
<th>0.5 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loss &lt;15 letters</td>
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**YEAR ONE**

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**YEAR TWO**

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</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

**Proportion of patients losing <15 ETDRS letters**
- 0.3 mg: 94%, 96%, 64%
- 0.5 mg: 96%, 90%, 53%
- Sham: 62%, 53%, 5%

**Proportion of patients gaining >15 ETDRS letters**
- 0.3 mg: 36%, 40%, 6%
- 0.5 mg: 40%, 36%, 6%
- Sham: 5%, 5%, 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.

Proportion of patients losing <15 ETDRS letters:
- 0.3 mg: 94% 90% 92%
- 0.5 mg: 96% 90% 90%
- Sham: 64% 66% 66%

Proportion of patients gaining >15 ETDRS letters:
- 0.3 mg: 36% 34% 26%
- 0.5 mg: 40% 33% 33%
- Sham: 6% 6% 6%
MARINA ANCHOR

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.

Proportion of patients losing <15 ETDRS letters:

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Proportion of patients gaining >15 ETDRS letters:

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<tbody>
<tr>
<td>Loss &lt;15 letters</td>
<td>90%</td>
<td>90%</td>
<td>53%</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>26%</td>
<td>33%</td>
<td>4%</td>
</tr>
</tbody>
</table>

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

RESULTS

YEAR ONE

YEAR TWO

ARMD
MARINA

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

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

ANCHO terribly long version:

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

Was another intervention involved?
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 was the primary outcome measure?

What was the secondary outcome measure?

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?

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 does ANCHOR stand for?
ANTI-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in 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.

Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

What was the primary outcome measure?

What was the secondary outcome measure?

Proportion of patients losing <15 ETDRS letters

Proportion of patients gaining >15 ETDRS letters

Was another intervention involved?
Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections.
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

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

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.

What was the dosing schedule?
One injection every month for 24 months

Was another intervention involved?
Yes—PDT. Participants received either sham injections + real PDT or sham PDT + real injections.
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

One injection every month for 24 months

What was the dosing schedule?

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

The MARINA and ANCHOR trials left little doubt re the safety and efficacy of ranibizumab therapy for wet ARMD. But what was in doubt was the treatment schedule, ie, was it really necessary to inject every month?

gaining >15 ETDRS letters

outcome measure?

gaining >15 ETDRS 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

- One injection every month for 24 months

**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

The MARINA and ANCHOR trials left little doubt re the safety and efficacy of ranibizumab therapy for wet ARMD. But what was in doubt was the treatment schedule, ie, was it really necessary to inject every month? Clearly, a monthly continuous schedule such as this was not sustainable indefinitely—the burden imposed (both in cost and labor) would overwhelm the resources of any healthcare system. To address this very important issue, several clinical trials were initiated, including…

- Proportion of patients losing <15 ETDRS letters
- Proportion of patients gaining >15 ETDRS letters

What was the dosing schedule?

- One injection every month for 24 months
What are 2 key studies addressing the *dosing schedule* of ranibizumab in the treatment of ARMD?
What are 2 key studies addressing the **dosing schedule** of ranibizumab in the treatment of ARMD?

(Other acceptable answers: SAILOR; SUSTAIN; HORIZON; HARBOR)
What are 2 key studies addressing the *dosing schedule* of ranibizumab in the treatment of ARMD?

What does PIER stand for?

What does PrONTO stand for?
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

What does PIER stand for?
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

What does PrONTO stand for?
Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

PIER

What does PIER stand for?
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

PrONTO

What does PrONTO stand for?
Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab

What were the dosing schedules?
What are 2 key studies addressing the dosing schedule of ranibizumab in the treatment of ARMD?

What does PIER stand for?
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

What does PrONTO stand for?
Prospective Optical Coherence Tomography Imaging of Patients with Neovascular AMD Treated with Intra-Ocular Ranibizumab

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 PRN as indicated by OCT, VA and DFE findings at monthly exams
What were the dosing schedules?

Three Months

<table>
<thead>
<tr>
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<th>0.3 mg</th>
<th>0.5 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

(Note the different outcome variable)

Focus your attention on the 0.5 outcome

What were the three-month results?

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

What were the three-month results?
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

### Three Months

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↑2.9</td>
<td>↑4.3</td>
<td>↓8.7</td>
</tr>
</tbody>
</table>

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

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

What were the dosing schedules?

<table>
<thead>
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<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↑2.9</td>
<td>↑4.3</td>
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</table>

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>
<th>0.5 mg</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↓1.6</td>
<td>?</td>
<td>↓16.3</td>
</tr>
</tbody>
</table>

What about the one-year results?

ARMD
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.

<table>
<thead>
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<th>Sham</th>
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</thead>
<tbody>
<tr>
<td>Average VA change (ETDRS letters)</td>
<td>↓1.6</td>
<td>↓0.2</td>
<td>↓16.3</td>
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</table>
PIER: Results at 12 months
One injection every month for 3 months, then every 3 months to 12 months.

What were the dosing schedules?

<table>
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<td>↓1.6</td>
<td>↓0.2</td>
<td>↓16.3</td>
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</table>

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?

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. Clearly, a q3 month schedule was not going to be acceptable.

No question—advance when ready
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>Year One</th>
<th>MARINA</th>
<th>ANCHOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lost &lt;15 letters</td>
<td>95%</td>
<td>96%</td>
</tr>
<tr>
<td>Gained &gt;15 letters</td>
<td>34%</td>
<td>40%</td>
</tr>
<tr>
<td>Mean ↑ in letters</td>
<td>7.2</td>
<td>11.3</td>
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What doses of ranibizumab were used?
What is the dosing schedule?
Is another intervention involved?
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<table>
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<tr>
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<th>Year One</th>
<th>MARINA</th>
<th>ANCHOR</th>
</tr>
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<tbody>
<tr>
<td>Lost &lt;15 letters</td>
<td>95%</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>
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</tr>
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For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials. Note that the PrONTO protocol (3 monthly injections, then PRN) produced results essentially identical to those of MARINA and ANCHOR (monthly injections)…
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<td>5.6</td>
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At present, most clinicians employ some version of treat-and-extend with most of their pts.

Anti-VEGF injection scheduling tl;dr

Continuous: Pt evaluated and treated monthly
PRN: Pt evaluated monthly, treated if evidence of 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)

Next we will turn our attention to another drug that has proven to be hugely important in the management of wet ARMD (and other conditions*)

*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 identical 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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What is a monoclonal antibody? Antibodies produced by a set of clones of the same immune cells.

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Note: Different drug!

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

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.
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.
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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.

Bevacizumab

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

Why did we lose the term affinity matured? Unlike ranibizumab, bevacizumab was not affinity-matured for VEGF-A.
Ranibizumab is a recombinant, humanized, affinity-matured, monoclonal antibody fragment. Unlike ranibizumab, which consists of an antibody fragment, bevacizumab is a full-length antibody.

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

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Bevacizumab's is about 21 days, whereas ranibizumab's is only 2.1 hours.

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.
Which drug was created first—ranibizumab, or bevacizumab?

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

Bevacizumab
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Was bevacizumab developed to treat ARMD?

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Was bevacizumab developed to treat ARMD?
No, it was developed and FDA-approved to treat cancer.

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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
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What doses of each were used?

- Ranibizumab:
- Bevacizumab:
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  - No

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- **What was the secondary outcome measure?**
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Was another intervention involved?
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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>
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<tr>
<th></th>
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<tr>
<td><strong>Every Month Dosing</strong></td>
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**ARMD**
CATT RESULTS

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*These are statistically equivalent*
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*These are statistically equivalent as well*
CATT RESULTS

Average Number of Letters Gained at One Year

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## CATT RESULTS

**Average Number of Letters Gained at One Year**

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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)

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<tr>
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<tr>
<td>PRN Dosing</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
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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?

CATT RESULTS

What about adverse events?
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.

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.
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Is this finding concerning enough to warrant using ranibizumab preferentially?
CATT RESULTS

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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 for ARMD.
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?

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Aflibercept *is a recombinant fusion protein*
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What does the suffix –cept indicate?

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

Aflibercept is a recombinant fusion protein.
Afli\textbf{bercept} is a recombinant fusion protein

\textbf{What does the suffix –cept indicate?}
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\textbf{What does the infix –ber- indicate?}
Afiblercept is a recombinant fusion protein

What does the suffix –cept indicate?
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What does the infix –ber- indicate?
That the mimicked receptor is the VEGF receptor
Afib**l**e**r**cept is a recombinant fusion protein

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

**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 afib**l**e**r**cept ‘mimics the VEGF receptor’? Put another way: How does afib**l**e**r**cept work?
Afli\textit{bercept} is a recombinant fusion protein

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\textit{Aflibercept} is a \textit{recombinant fusion protein}

\textit{Spell it out for me—what does it mean to say aflibercept \textquoteleft mimics the VEGF receptor\textquoteleft?}
\textit{Put another way: How does aflibercept work?}
Aflibercept is a \textit{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.
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Afli
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Afiblercept is a recombinant fusion protein

Which isoforms of VEGF-A does afiblercept bind?
Aflibercept is a recombinant fusion protein

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

Which isoforms of VEGF-A does aflibercept bind?
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Of bevacizumab, ranibizumab and aflibercept, which binds VEGF-A with the greatest affinity?
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In addition to VEGF-A, aflibercept binds another protein implicated in the pathogenesis of CNVM—what is it?
Afiblercept is a **recombinant fusion protein**

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

*In addition to VEGF-A, afiblercept 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?
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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?
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The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet ARMD
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Either 0.5 or 2 mg by intravitreal injection
ARMD

What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

What doses of aflibercept were used?

What was the dosing schedule?

VIEW

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There were 3:

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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.
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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.
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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).

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What was the primary outcome measure?

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
**VIEW study:**
Year One Results

<table>
<thead>
<tr>
<th></th>
<th>0.5 mg q4 week</th>
<th>2.0 mg q4 week</th>
<th>2.0 mg q8 week</th>
<th>Ran-bizumab</th>
</tr>
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<tr>
<td><strong>Lost &lt;15 letters</strong></td>
<td>?%</td>
<td>?%</td>
<td>?%</td>
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<tr>
<td><strong>Mean gain in ETDRS letters read</strong></td>
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| Mean gain in ETDRS letters read | ? | ? | ? | ? |
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The key finding is that **q8 weeks** aflibercept worked just as well as **monthly** ranibizumab.
**VIEW study:**

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**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
**VIEW study: Year One Results**

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## VIEW study: Year Two Results

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<tr>
<th></th>
<th>0.5 mg q4 week</th>
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<th>2.0 mg q8 week</th>
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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.
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- **Mean gain in ETDRS letters read**: 8.3, 9.2, 8.4, 8.7
- **Mean number of treatments**: Question mark

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- **Mean gain in ETDRS letters read**: 6.6, 7.6, 7.6, 7.9
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Another much-anticipated outcome concerned the **average number of treatments** required in the q8 week aflibercept vs ranibizumab conditions.
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Another much-anticipated outcome concerned the **average number of treatments** required in the q8 week aflibercept vs ranibizumab conditions.
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.

**Nonexudative ARMD** is treatable at present.
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- 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
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  - 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)
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*Antioxidants* and *minerals*
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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 AREDS2

- 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

Zinc 80 mg
Cupric oxide 2 mg
ARMD: The AREDS2

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

(These are the two xanthophylls employed)
● **ARMD: The AREDS2**

  ● Follow-up to the AREDS
  
  ● Subbed **xanthophylls** for β-carotene; added

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

  ![Lutein & Zeaxanthin](image)
**ARMD: The AREDS**

- 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:
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- Study findings:
  - Reaffirmed vs Disputed results of the AREDS
ARMD: The AREDS2
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- Subbed xanthophylls for β-carotene; added O3FAs:
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- **Study findings:**
  - **Reaffirmed** results of the AREDS
  - Xanthophylls **effective vs ineffective** substitute for β-carotene
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- Subbed **xanthophylls** for β-carotene; added **O3FAs**: 
  - **Vitamin C** 500 mg
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- **Study findings:**
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  - Xanthophylls **suitable** substitute for β-carotene
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Why is this important?
ARMD: The AREDS2

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  - Vitamin C 500 mg
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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**

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- Subbed **xanthophylls** for β-carotene; added **O3FAs**:
  - Vitamin C 500 mg
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**Study findings:**

- **Reaffirmed** results of the AREDS
- Xanthophylls **suitable** substitute for β-carotene
- O3FAs **effective vs ineffective** at reducing risk of progression
ARMD: The AREDS\textsuperscript{2}

- Follow-up to the AREDS
- Subbed xanthophylls for $\beta$-carotene; added O3FAs:
  - Vitamin C 500 mg
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  - $\beta$-carotene
  - Lutein & Zeaxanthin
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- Study findings:
  - Reaffirmed results of the AREDS
  - Xanthophylls suitable substitute for $\beta$-carotene
  - O3FAs ineffective at reducing risk of progression