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 *break time!* slides at those points to mark them.

ARMD

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

ARMD

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

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?

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%

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? 75+?
10%

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? 75+?
10%. 25%!

ARMD

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

Speaking of demographics: Is ARMD risk related to ethnicity?
Yes, have the highest risk and the lowest

ARMD

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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

ARMD

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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 fall in-between

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? 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

ARMD

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

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

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?

-
-
- ***A***ge
-
-

The mnemonic is…

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?

- ***F*** ***F*** ← *(two* F's*)*
- ***L***
- ***A***ge ***A*** ← *(another* A*)*
- ***S*** ***S*** ← *(two* S's*)*
- ***H*** ***H*** ***H*** ← *(three* H's*)*

The mnemonic is…***FLASH***

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?

- ***F***amily history; ***F***emale ← *(two* F's*)*
- ***L***ight iris color
- ***A***ge; ***A***nglo (ie, white ethnicity) ← *(another* A*)*
- ***S***moking; ***S***un exposure ← *(two* S's*)*
- ***H***yperopia; ***H***ypercholesterolemia; ***H***igh CRP ← *(three* H's*)*

The mnemonic is…***FLASH***

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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**

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Of the modifiable ones, which is most impactful?

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Of the modifiable ones, which is most impactful?
Smoking

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 in the macula

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

ARMD

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

What are drusen*?*

drusen

ARMD

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

drusen

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There are several ways:

drusen

Drusen are categorized by their ***?***

Drusen are categorized by the ***?*** *in which they're located*

Drusen are categorized by their ***?***

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Drusen are categorized by their ***size***

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Drusen are categorized by their ***boundaries***

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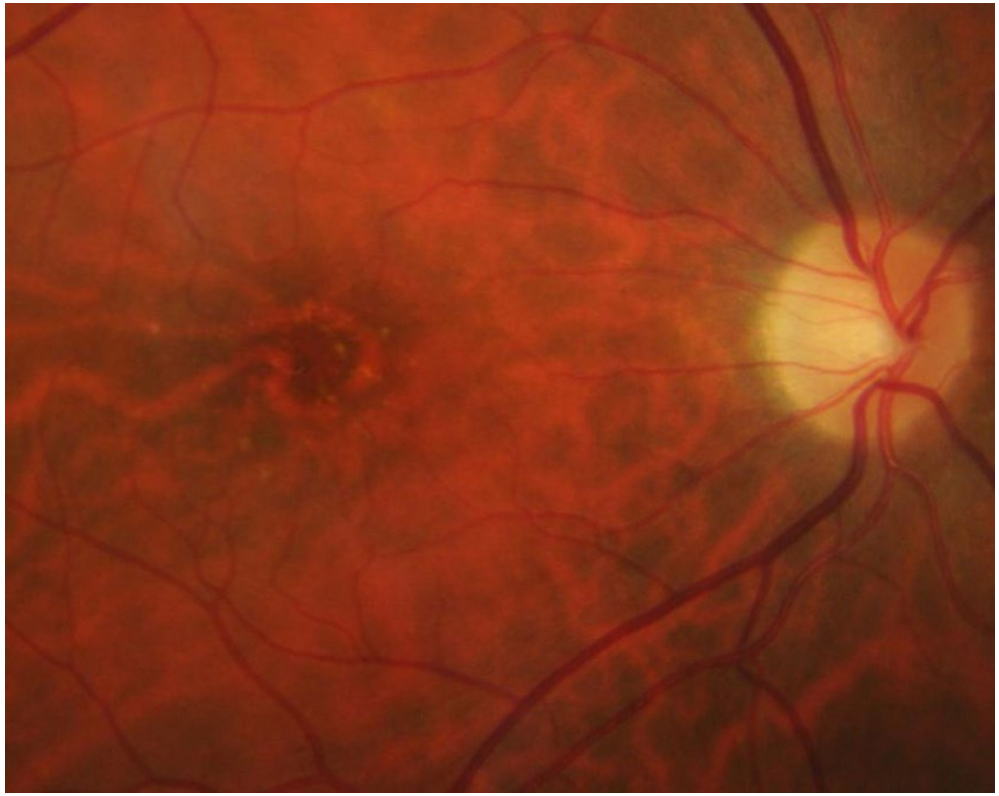
ARMD



Small drusen

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--**Intermediate**: 63–124
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ARMD

Intermediate drusen

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ARMD

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

lotsa words

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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

*Drusen are categorized by their **boundaries***

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(their diameter is about 124 µm there, and thus make a convenient reference)

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--**Drusenoid PED**: >350

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In this context, what does PED *stand for?*

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Druser

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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

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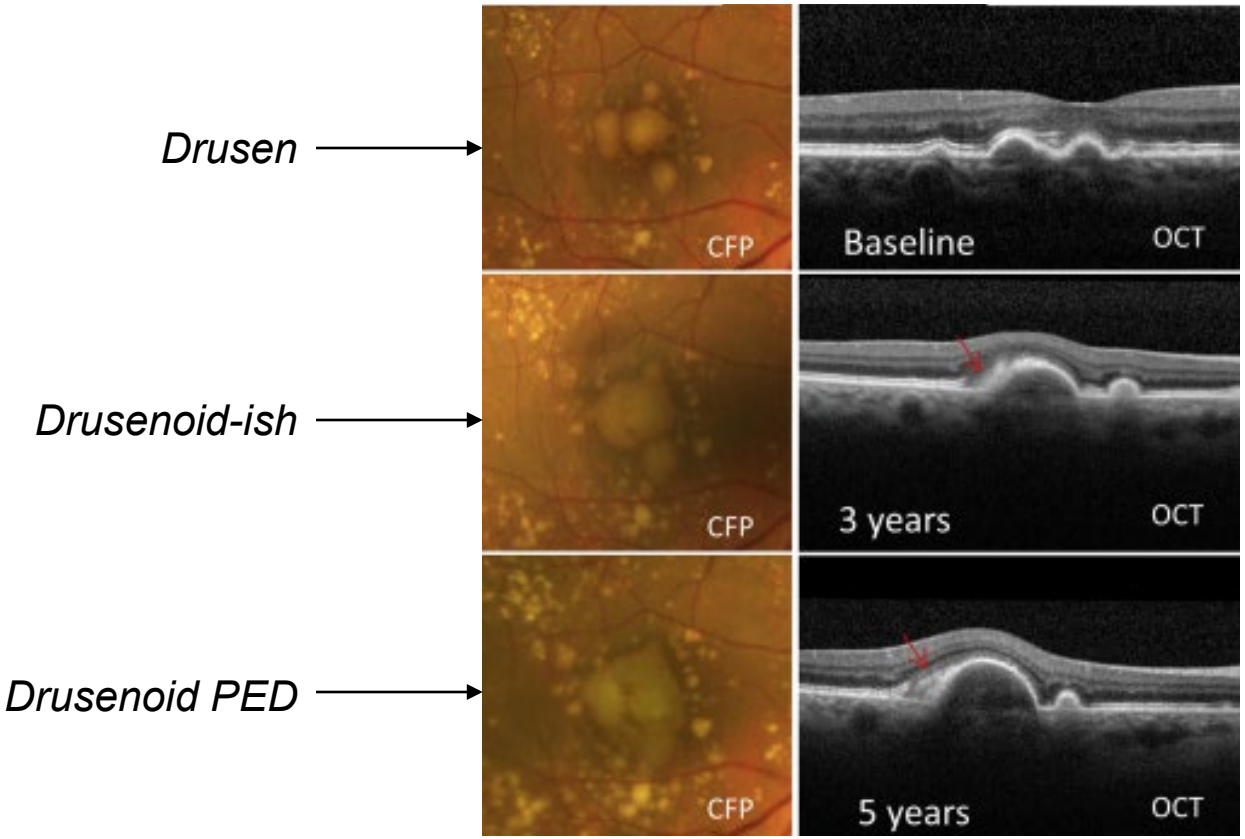
ARMD



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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Why is it a big deal if the RPE is separated from its BM, or deeper structures?

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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 [redacted].

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There are three basic forms of PED—what are the other two?

--Drusenoid
--*?*
--*?*

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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, resulting in vision loss.

There are three basic forms of PED—what are the other two?

--Drusenoid
--Serous
--Fibrovascular

Drusen are categori
--**Small**: <63 µm d
--**Intermediate**: 63–
--**Large**: ≥125
--**Drusenoid**

PED

Druser

ARMD

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

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

What sorts of substances constitute the material?

drusen

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

What does it mean to say the RPE is 'detached'?
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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
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PED

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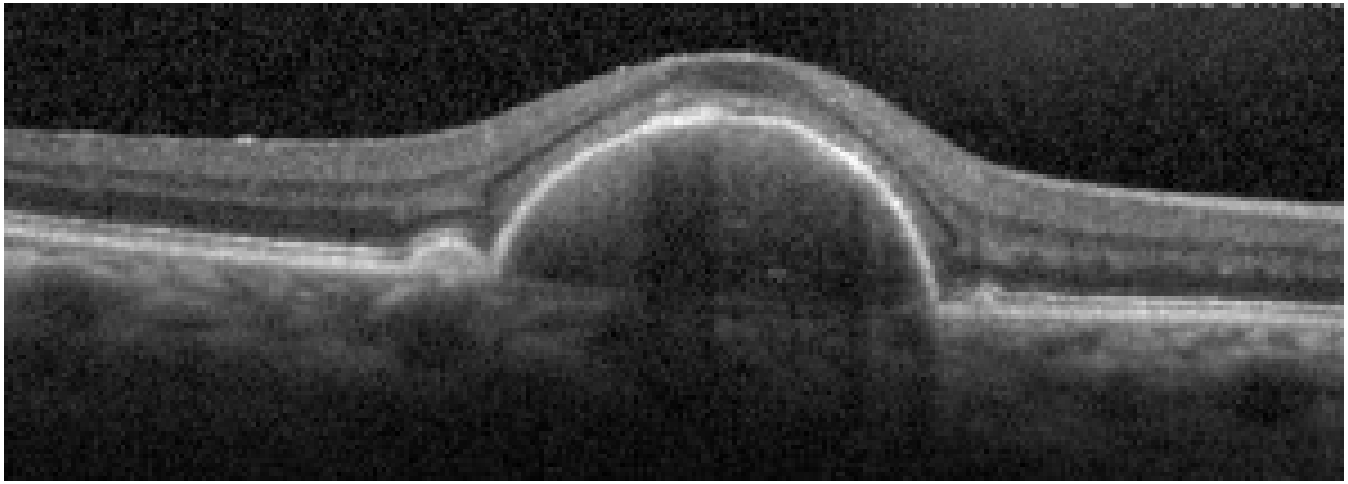
ARMD



Drusenoid PEDs have a uniform (aka ‘homogenous’), mildly hyper-reflective interior

Drusenoid PED

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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

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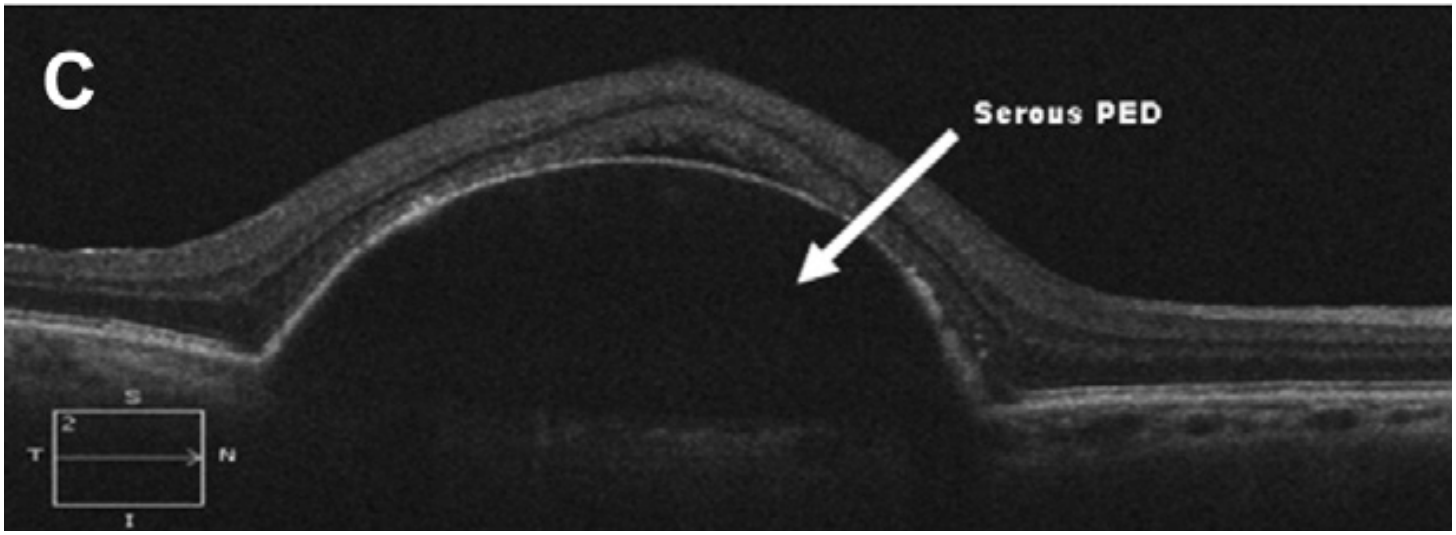
PED

Druser

ARMD



Serous PEDs are seen on OCT as areas of smooth, sharply demarcated, dome-shaped RPE elevation, typically overlying a homogenously hyporeflective space

Serous PED

ARMD

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--Serous: Sub-RPE space 'empty'
--Fibrovascular: ***?***

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--Drusenoid: Uniformly hyperreflective
--Serous: Sub-RPE space 'empty'
--Fibrovascular: Solid with 'clefts'

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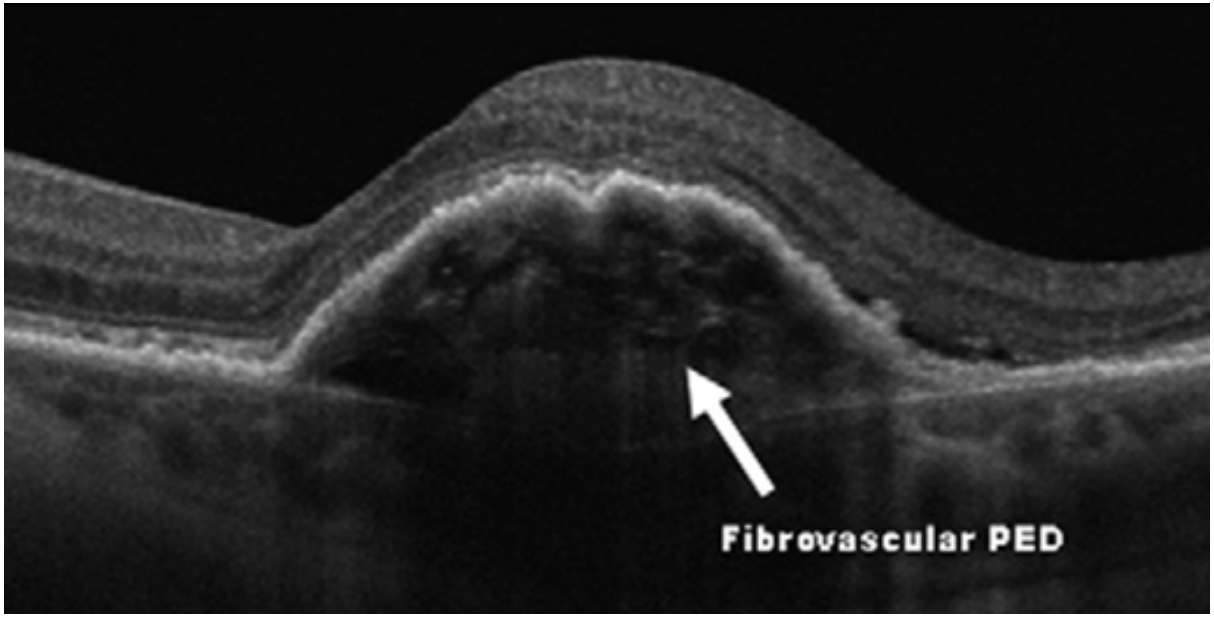
PED

Druser

ARMD



Fibrovascular PEDs appear to be filled with solid layers of material of medium reflectivity **separated by hyporeflective clefts**

Fibrovascular PED

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?
There are several ways:

drusen

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

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

Drusen are categorized by their ***boundaries****:*
--***?***
--***?***
--***?***

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--**Hard**
--**Soft**
--**Confluent**

ARMD

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Which are described as being…

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--**Hard**: Discrete, well demarcated ← *Which are described as being…*
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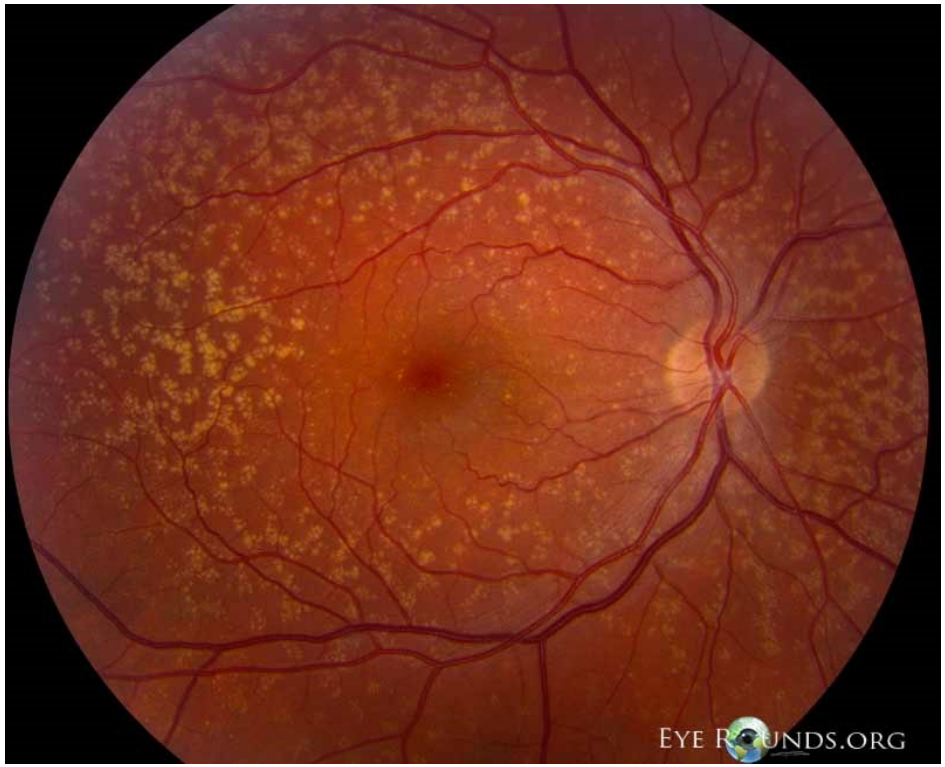
ARMD



Hard drusen

ARMD

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--**Soft**: Amorphous, poorly demarcated ← *Which are described as being…*
--**Confluent**

ARMD

Soft drusen

ARMD

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Which are described as being…

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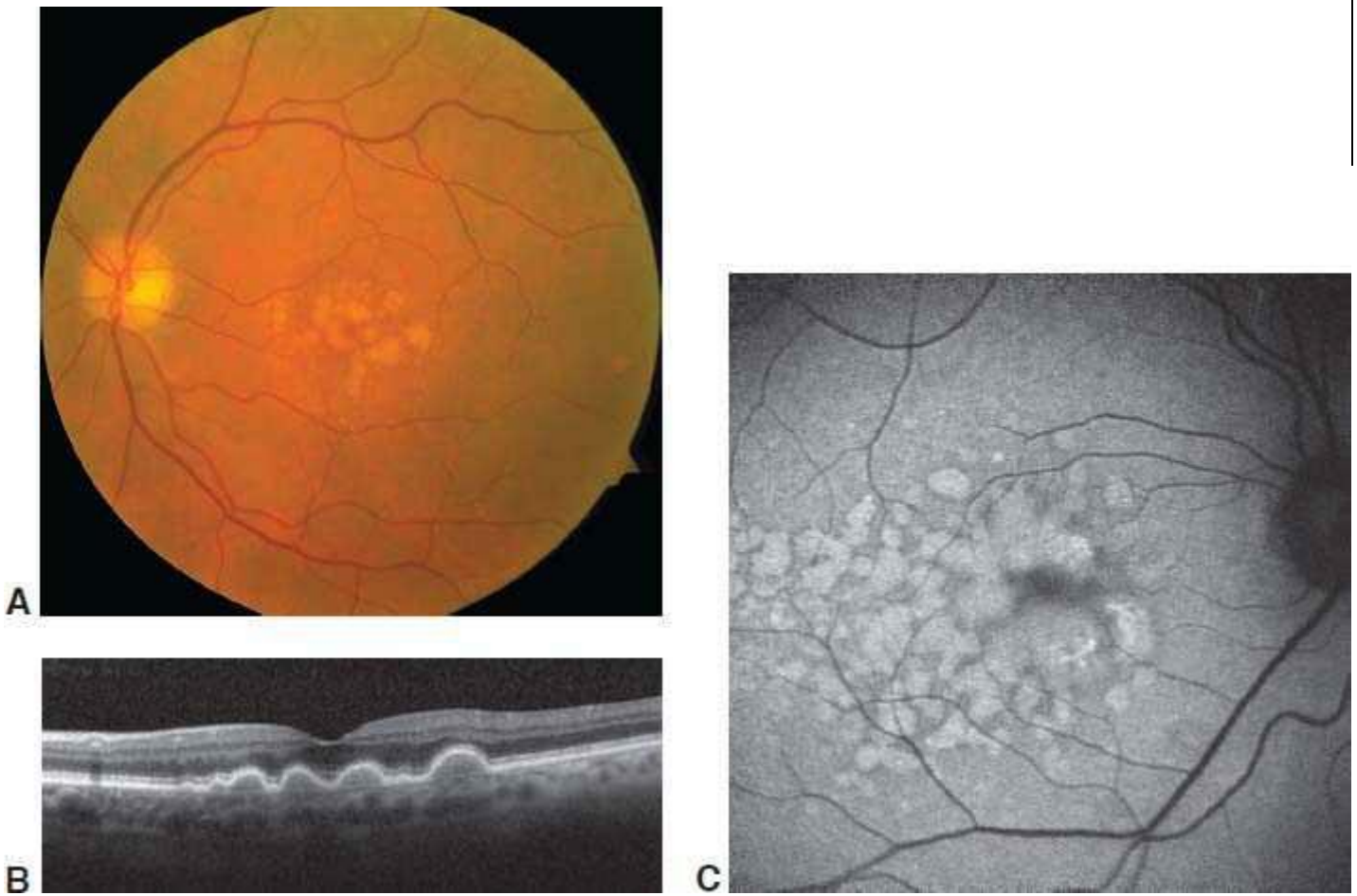

A, Color fundus photograph shows soft, **confluent**, large drusen in a patient with ARMD. **B,** Corresponding SD-OCT of the soft drusen. **C,** Autofluorescence image of an eye with areas of confluent drusen.

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

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

ARMD

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--**Hard**: Discrete, well demarcated
--**Soft**: Amorphous, poorly demarcated
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Which type(s) carry a greater risk of dz progression?
Soft for sure, and probably confluent as well

ARMD

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

Drusen are categorized by their ***boundaries****:*
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--**Soft**: Amorphous, poorly demarcated
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*Drusen are categorized by the **retinal layer** in which they're located:*
--**Basal laminar**
--**Basal linear**
--**Reticular pseudodrusen**

*Drusen are categorized by their **boundaries**:*
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There are several ways:

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Before identifying the location for each drusen, let's review the anatomy of the outer retina

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--**Basal laminar**: ?
--**Basal linear**: ?
--**Reticular pseudodrusen**: ?

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--**Hard**: Discrete, well demarcated
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ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

1) *(Start here)*
2)
3)
4)
5)

Innermost

↕

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

1) two words of RPE
2)
3)
4)
5)

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

★ (***Note***: *This line represents the RPE basement membrane*) ★

Bruch's membrane

1) Basement membrane of RPE
2)
3)
4)
5)

Innermost

↕

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

1) Basement membrane of RPE
2) Inner [one word] layer
3)
4)
5)

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

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

ARMD

But first:

What are the five layers of Bruch's membrane?

Bruch's membrane

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

Innermost

Outermost

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

ARMD

But first:

What are the five layers of Bruch's membrane?

0) ?

What (non-Bruch's) structure goes here?

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

0) RPE cells

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

Bruch's membrane

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

Innermost

Outermost

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But first:

What are the five layers of Bruch's membrane?

0) RPE cells RPE cells

So, the basal plasma membranes of the RPE cells…

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

0) RPE cells RPE cells

So, the basal plasma membranes of the RPE cells…
sit directly on their BM
(as you would expect)

Bruch's membrane

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

Innermost

Outermost

ARMD

But first:

What are the five layers of Bruch's membrane?

0) RPE cells RPE cells

Foreshadowing alert: Another name for the basal plasma membrane of a cell is 'basal ***lamina***'

Bruch's membrane

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

Outermost

ARMD

But first:

What are the five layers of

-1) ?

0) RPE cells RPE cells

What (non-RPE) structures go here?

Bruch's membrane

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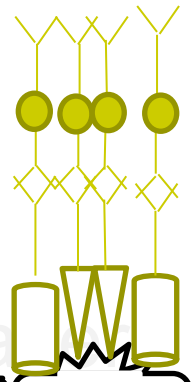
Innermost

Outermost

ARMD



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

But first:

What are the five layers of

-1) PR outer segs

0) RPE cells RPE cells

Bruch's membrane

1) Basement membrane of RPE
2) Inner collagenous layer
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Innermost

Outermost

ARMD

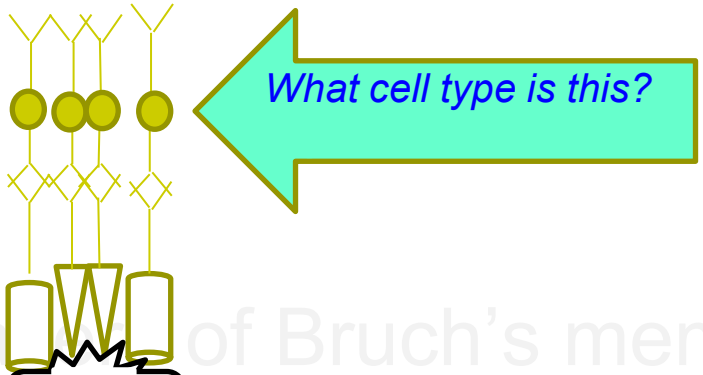
-2) ?

But first:

-1) PR outer segs

What are the layers of Bruch's membrane?

0) RPE cells RPE cells



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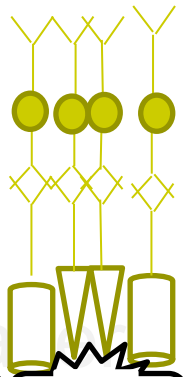
Outermost

ARMD

-2) Bipolar cells



What cell type is this?
Bipolar cells

But first:

-1) PR outer segs

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Bruch's membrane

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Innermost

Outermost

ARMD

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

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

*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**

Next question

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

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ARMD

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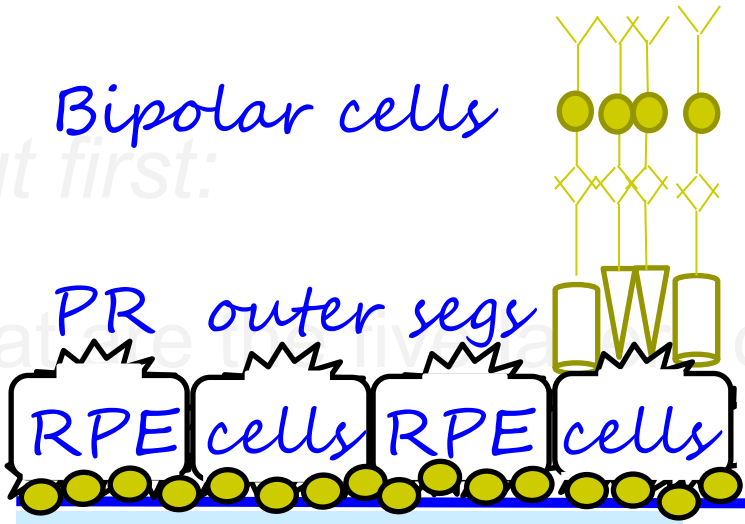

basal laminar drusen

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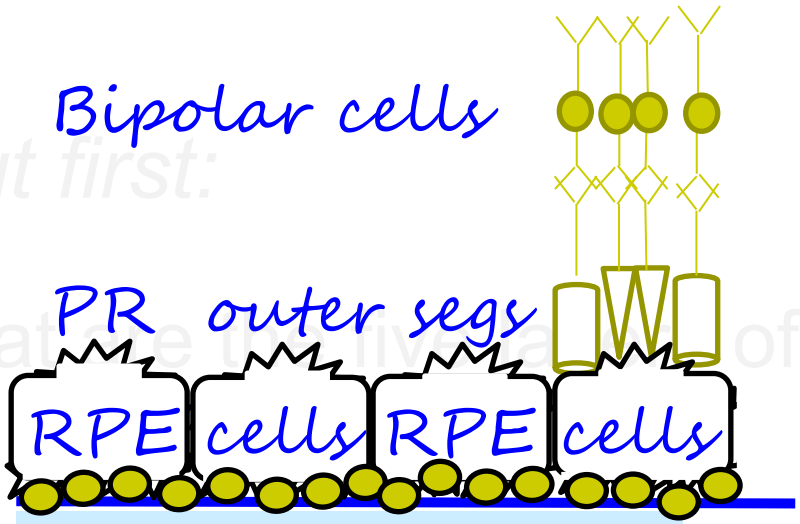

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basal linear drusen

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ARMD

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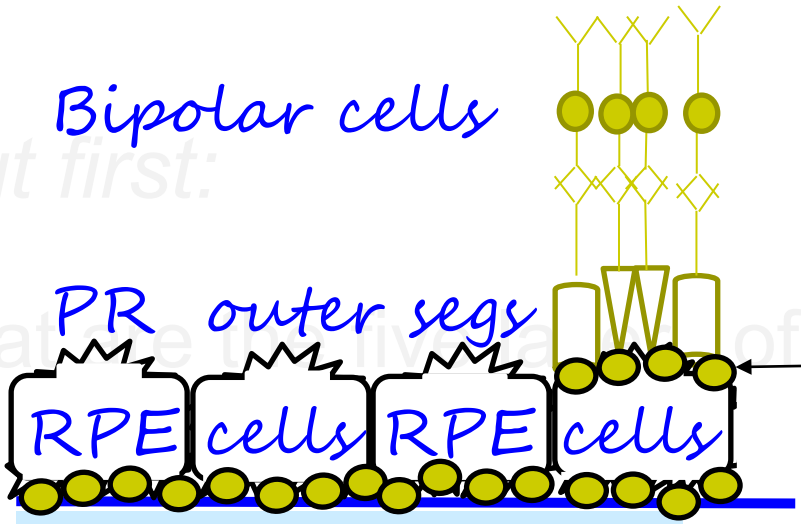

Reticular pseudodrusen

Bruch's membrane

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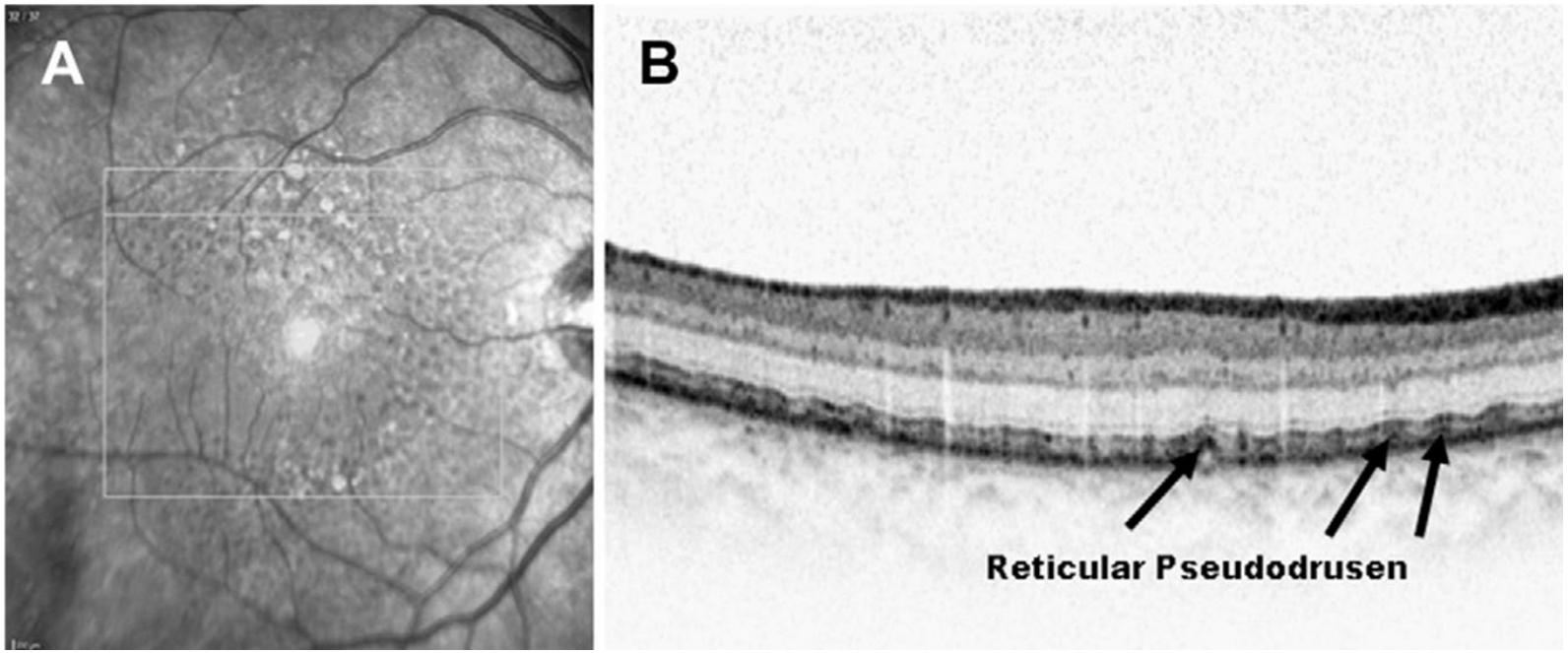
Innermost

Outermost

ARMD

Reticular pseudodrusen: Classic distribution in the superior macula

ARMD



Reticular pseudodrusen can be seen as multiple areas of granular hyperreflectivity between the RPE and photoreceptors

ARMD

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Circling back to drusenoid PEDs for a moment…

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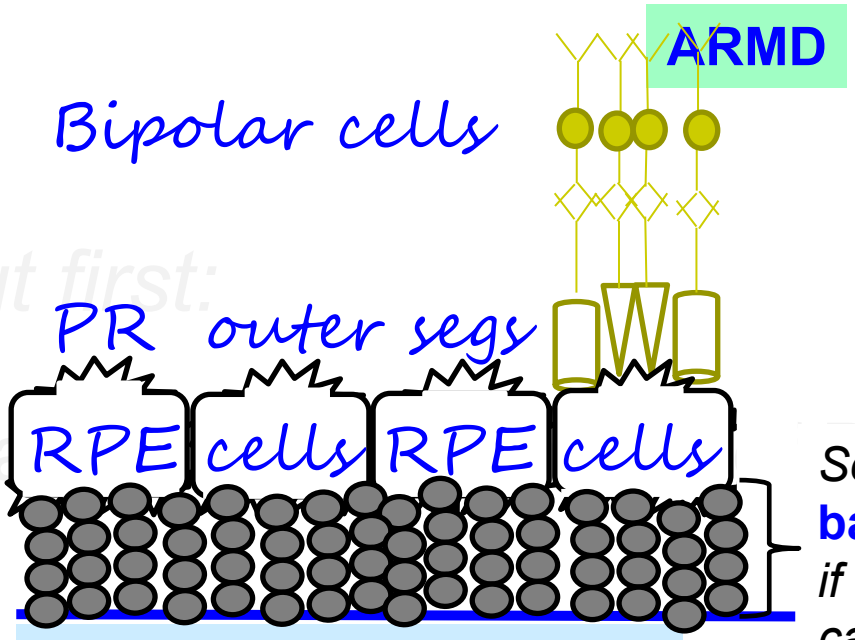


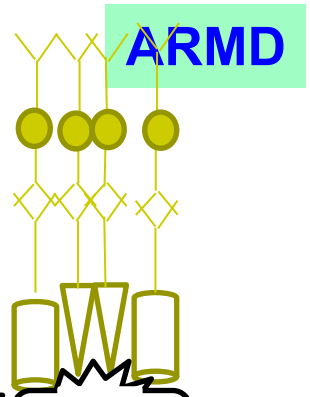
So now we can see how **basal laminar drusen,** *if extensive enough, can cause a drusenoid PED*

Bruch's membrane

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

Innermost

Outermost



-2) Bipolar cells

But first:

-1) PR outer segs

0) RPE cells RPE cells

Basement membrane of RPE

Bruch's membrane

1) Inner collagenous layer

2) Inner collagenous layer

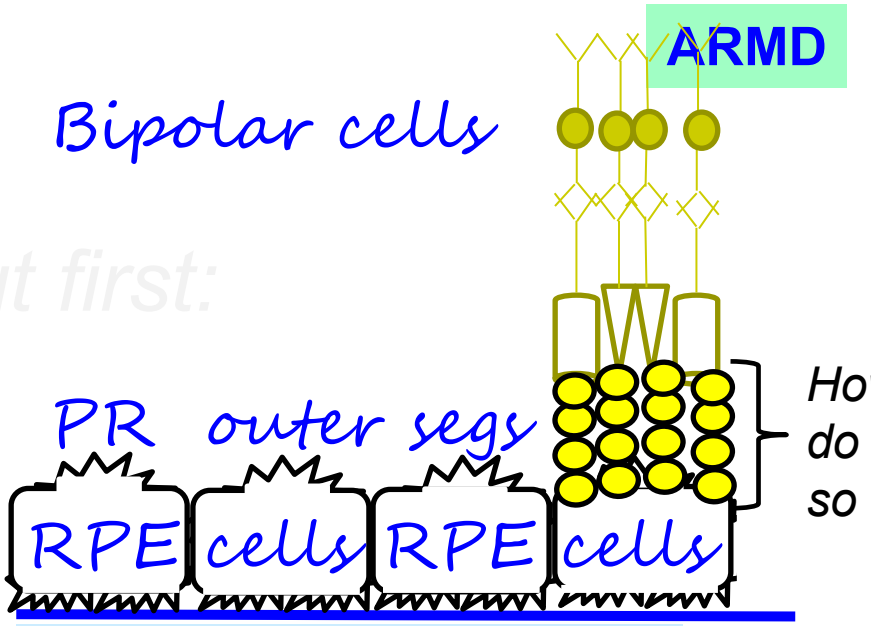
Likewise, we can see that extensive **basal *linear* drusen** *can* **also** *producing a drusenoid PED*

3) Elastic layer

4) Outer collagenous layer

5) Basement membrane of choriocapillaris

Outermost



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

Bruch's membrane

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

Innermost

Outermost

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: _____ and _____

ARMD

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By what two other names are each condition commonly known?
Nonexudative: ***?***
Exudative

ARMD

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Nonexudative: Nonneovascular ARMD; 'dry' ARMD
Exudative: ***?***

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What are the three hallmark findings in nonexudative ARMD?

--?

--?

--?

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--Drusen

--RPE changes

--Geographic atrophy

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--**RPE changes**

--Geographic atrophy

We have already discussed drusen, and will look at RPE change in detail a little later in the set

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What is geographic atrophy *(GA)?*

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It is one of # forms of advanced ARMD

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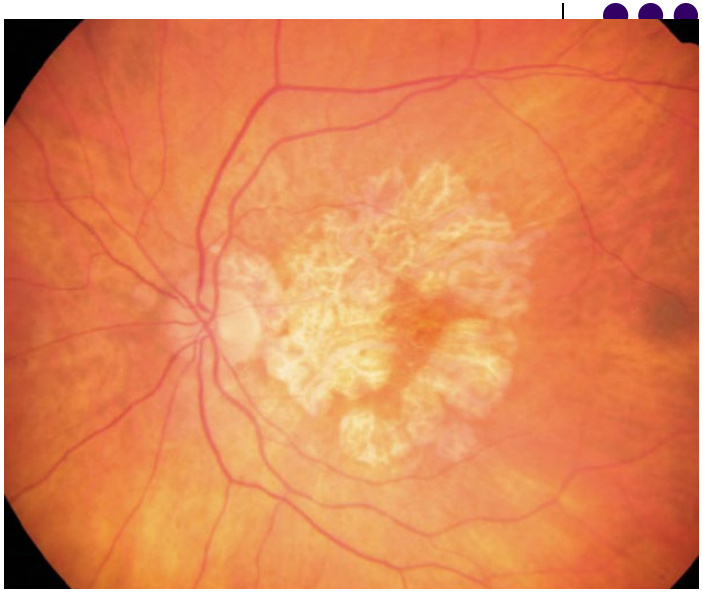
ARMD



Geographic atrophy (GA)

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How large must the area of atrophy be to qualify as GA?

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By definition, it must have a diameter of at least 175 μm

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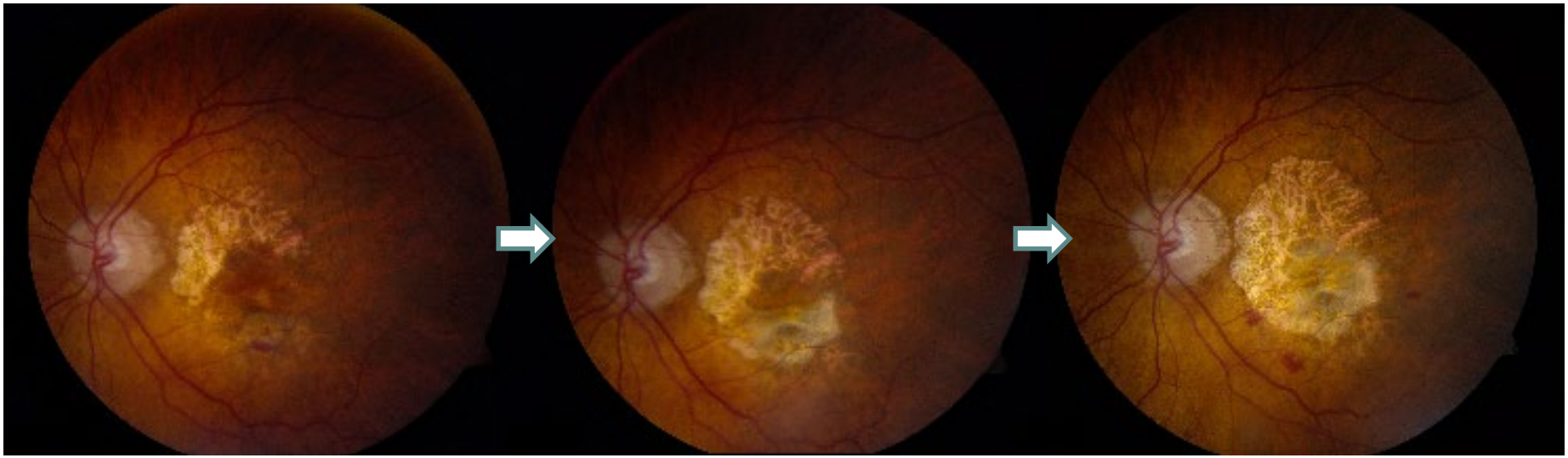
It starts in the perifoveal region, expanding over time to eventually involve the foveal center

ARMD



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

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me to

What does GA look like on…

FA?

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[illegible]me to eventually involve the foveal center.

What does GA look like on…

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

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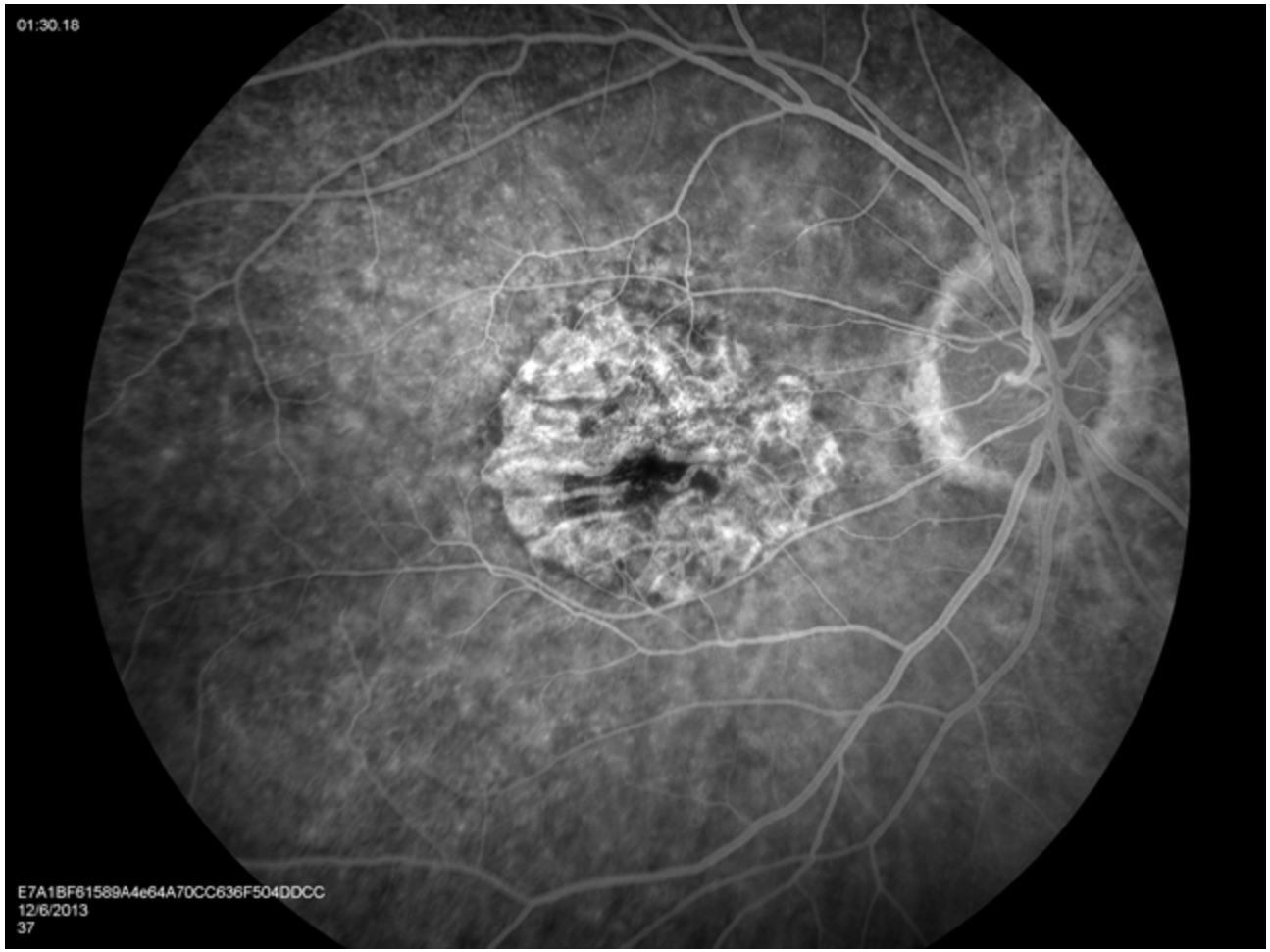

Geographic atrophy in ARMD: FA

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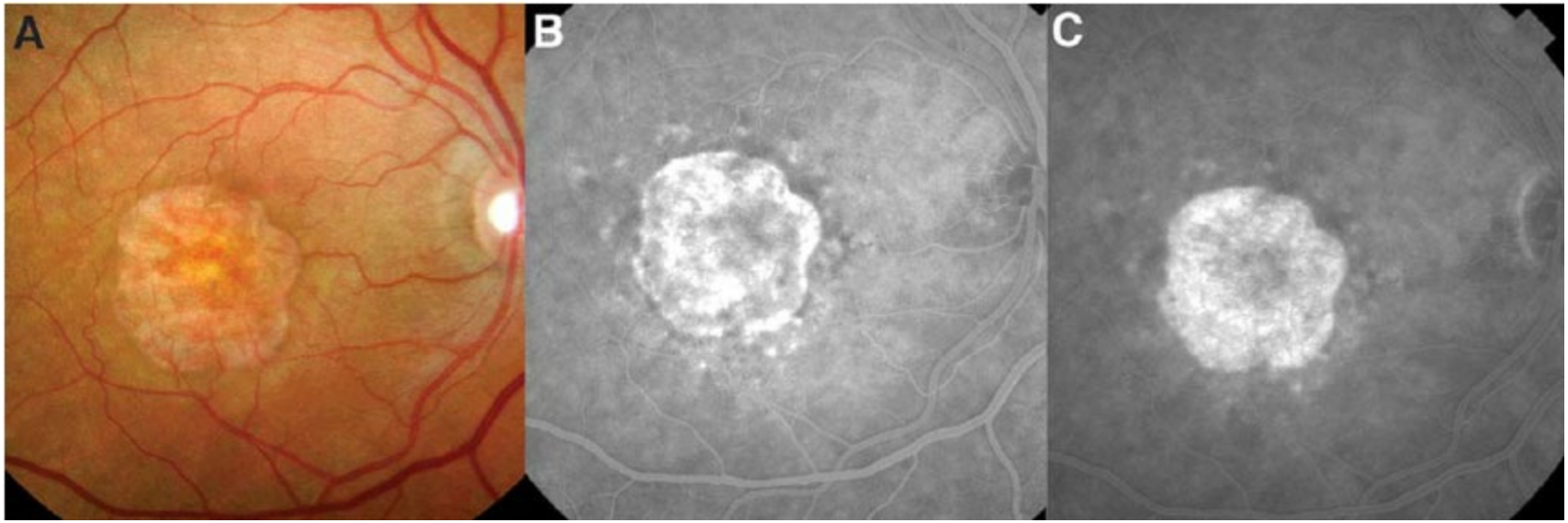

Geographic atrophy. **A**, Fundus photo. **B**, On fluorescein angiography, there is a "window defect" during the early frames with transmission of choroidal fluorescence. **C**, Note the absence of leakage in later frames.

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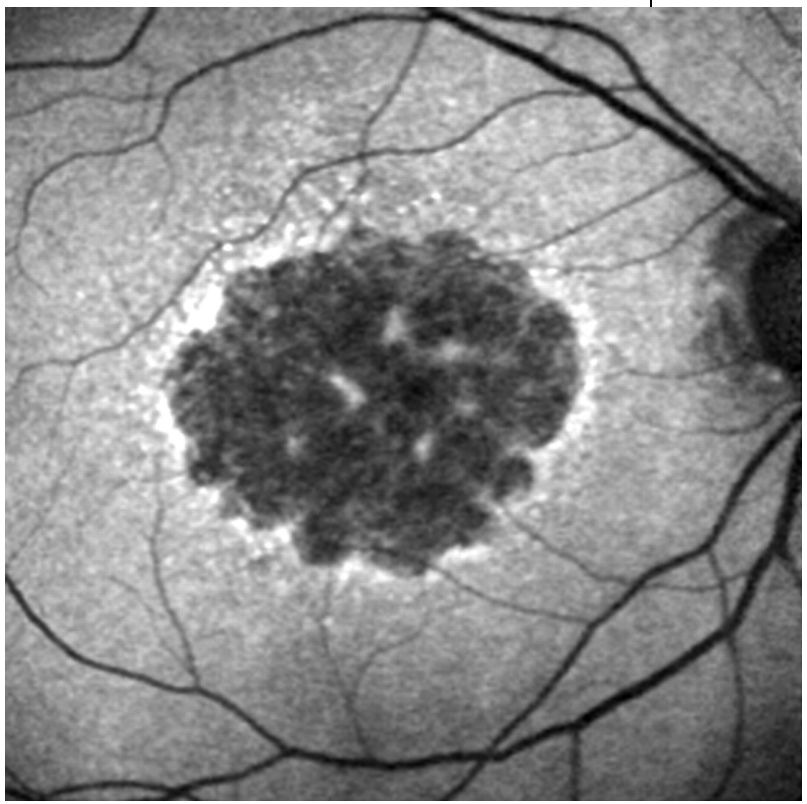
FAF: Normal retina for comparison



FAF: GA

ARMD

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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OCT?

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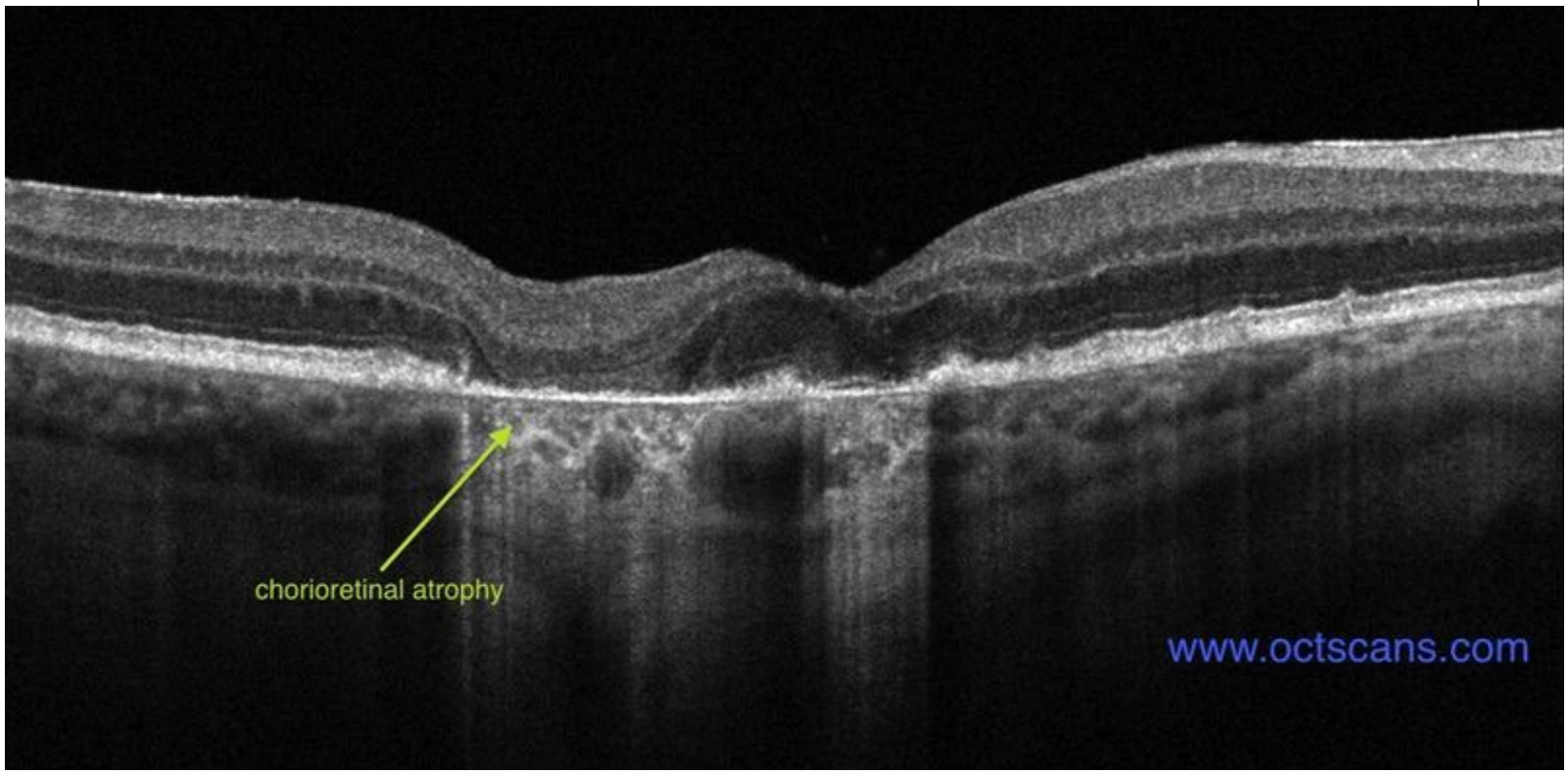
Autofluorescence? Dense hyp**o**autofluorescence with a ring of hyp**er**autofluorescence

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

ARMD



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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No question yet—advance when ready

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

ARMD

But first:

What are the layers of Bruch's membrane?

-2) Bipolar cells

-1) PR outer segs

0) RPE cells RPE cells

Bruch's membrane

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
4) Outer collagenous layer
5) Basement membrane of choriocapillaris
6) ?

Innermost

Outermost

What structure is this?

ARMD

But first:

What are the layers of Bruch's membrane?

-2) Bipolar cells

-1) PR outer segs

0) RPE cells RPE cells

Bruch's membrane

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

Innermost

Outermost

What structure is this?
The choriocapillaris

ARMD

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But first:

-1) PR outer segs

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7) ?

Innermost

Outermost

What structure is this?

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7) Choroid

Innermost

Outermost

What structure is this?
The choroid

-3) Retinal vessels

-2) Bipolar cells

-1) PR outer segs

0) RPE cells RPE cells

Bruch's membrane

1) Basement membrane of RPE
2) Inner collagenous layer
3) Elastic layer
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Retinal vessels

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

But first:

What are the layers of Bruch's membrane?

Innermost

Outermost

Retinal vessels

-3) Retinal vessels

-2) Bipolar cells

What is the deepest retinal layer in which branches of the retinal vasculature can be found?
The inner nuclear layer (INL)

But first:

-1) PR outer segs

What are the layers of Bruch's membrane?

0) RPE cells RPE cells

Bruch's membrane

1) Basement membrane of RPE
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Innermost

Outermost

6) Choriocapillaris
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-3) Retinal vessels

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So, the retinal vessels supply the **inner** *retinal layers…*

Outermost

-3) Retinal vessels

-2) Bipolar cells

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Bruch's membrane

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

Outermost

ARMD

- **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

ARMD

- **Retinal Layers**
  - Internal limiting membrane
  - Nerve fiber layer
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  - Outer plexiform layer
  - Outer nuclear layer
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  - Rod & cone inner and outer segments
- **RPE**
- **Bruch's membrane**

Inner 2/3 of INL on in

Blood supply:
Central retinal artery

Which layers are supplied by each blood supply?

Outer 1/3 of INL on out

Blood supply:
Choroid/Ch'capillaris

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

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What does it mean to say ARMD is 'exudative'?

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--?

--?

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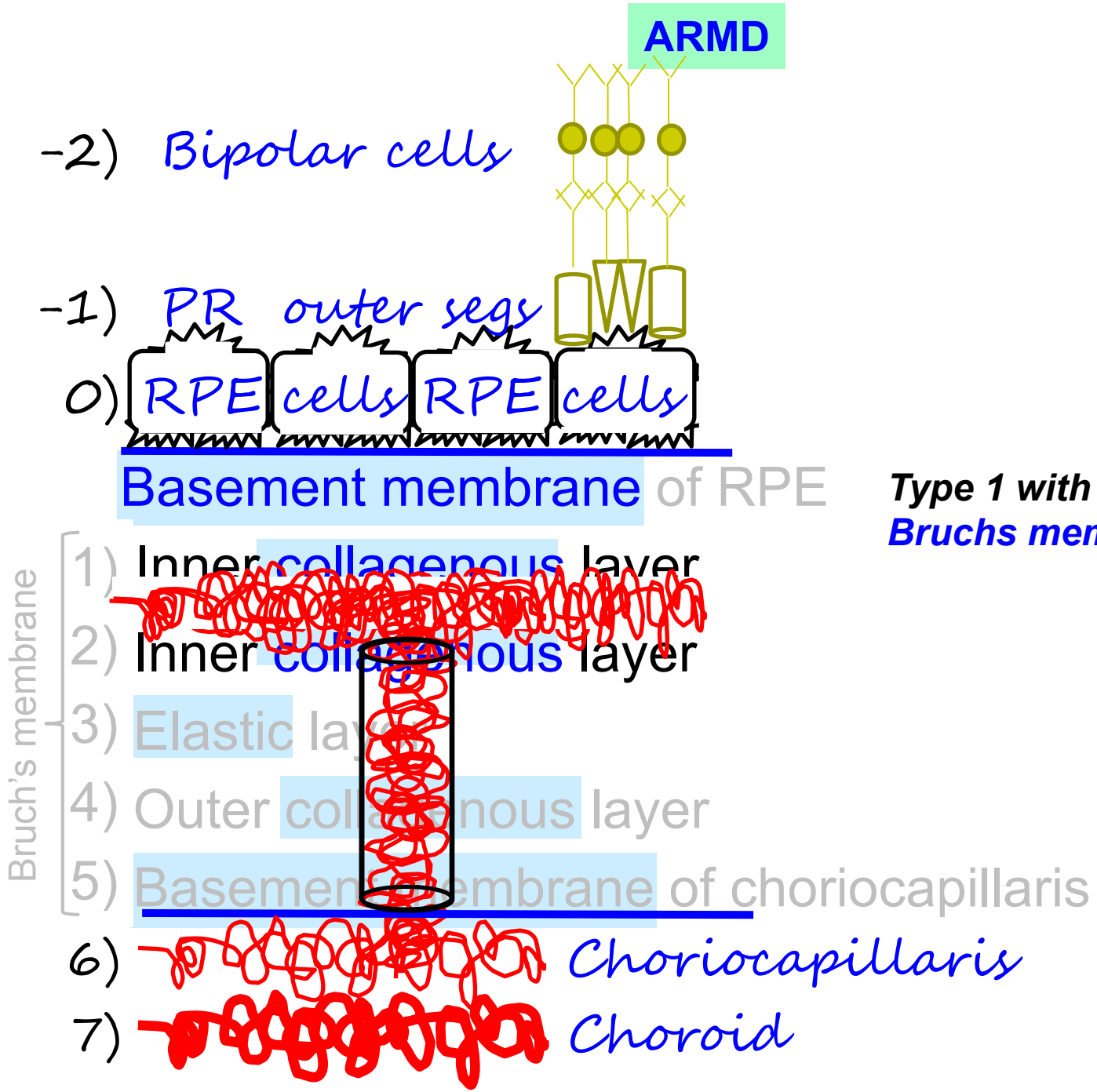
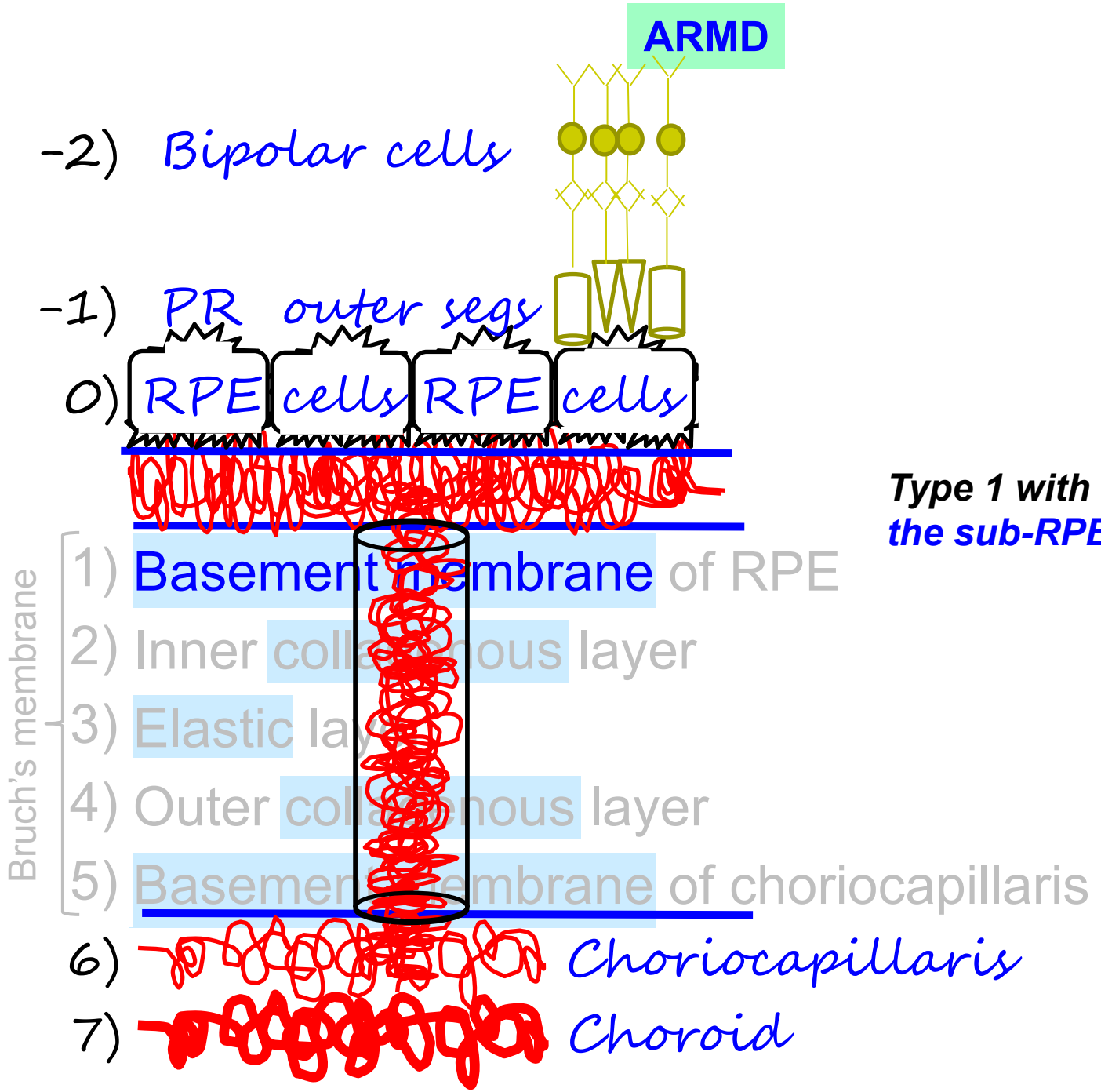
Sudden decrease in vision, metamorphopsia, and/or a paracentral scotoma

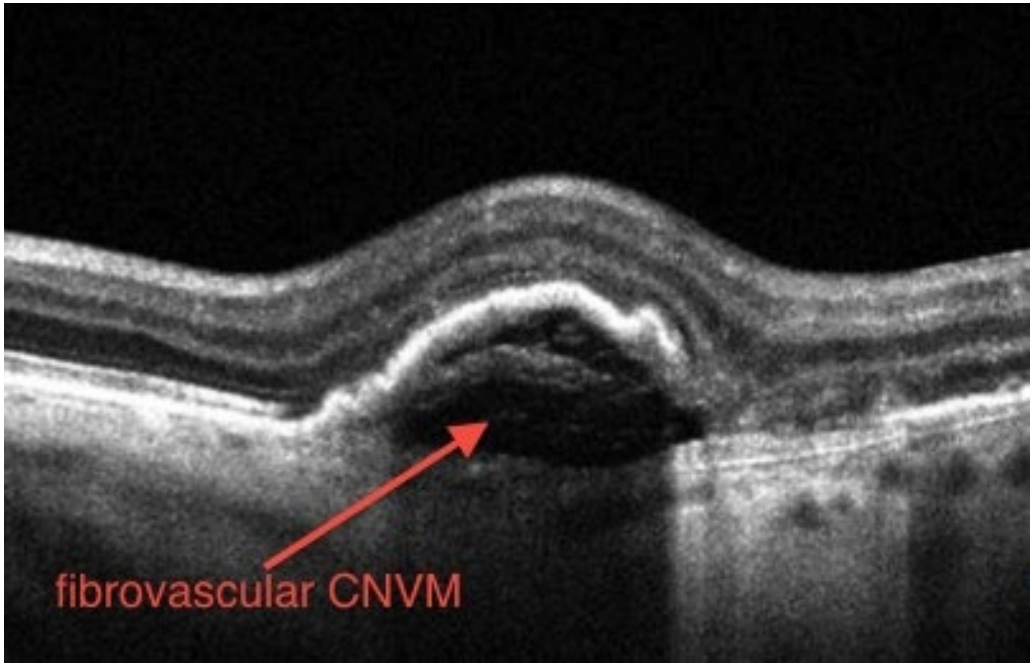


Type 1 with the CNVM in Bruchs membrane



Type 1 with the CNVM in the sub-RPE space

ARMD



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

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--Type 3

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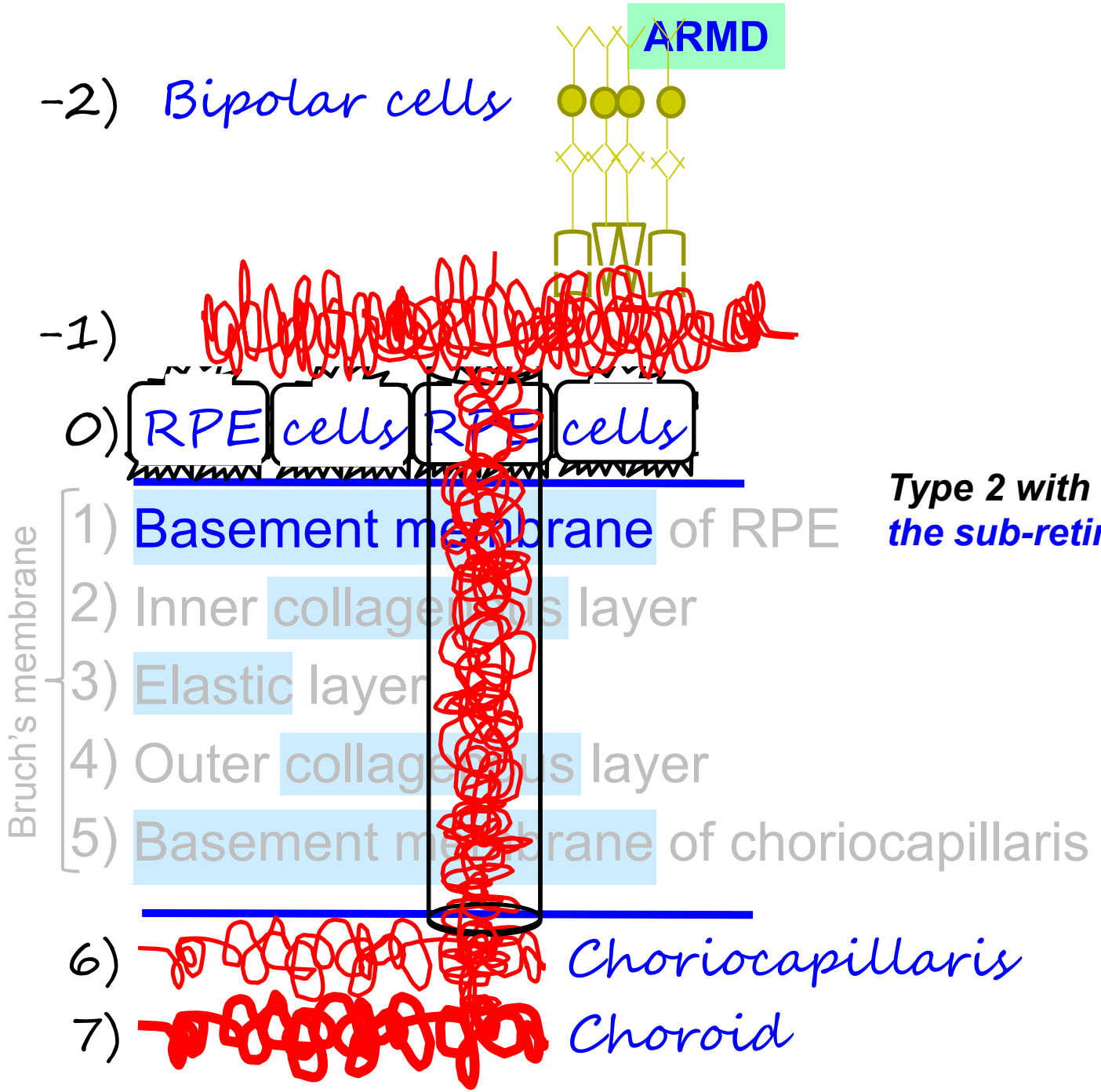
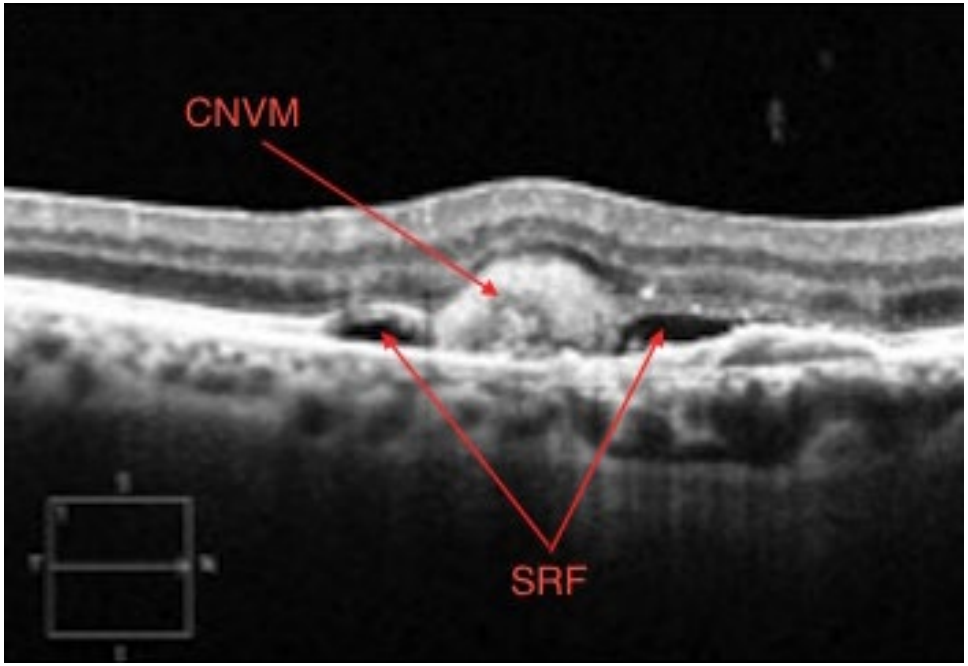
--Type 3

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



Type 2 with the CNVM in the sub-retinal space

ARMD



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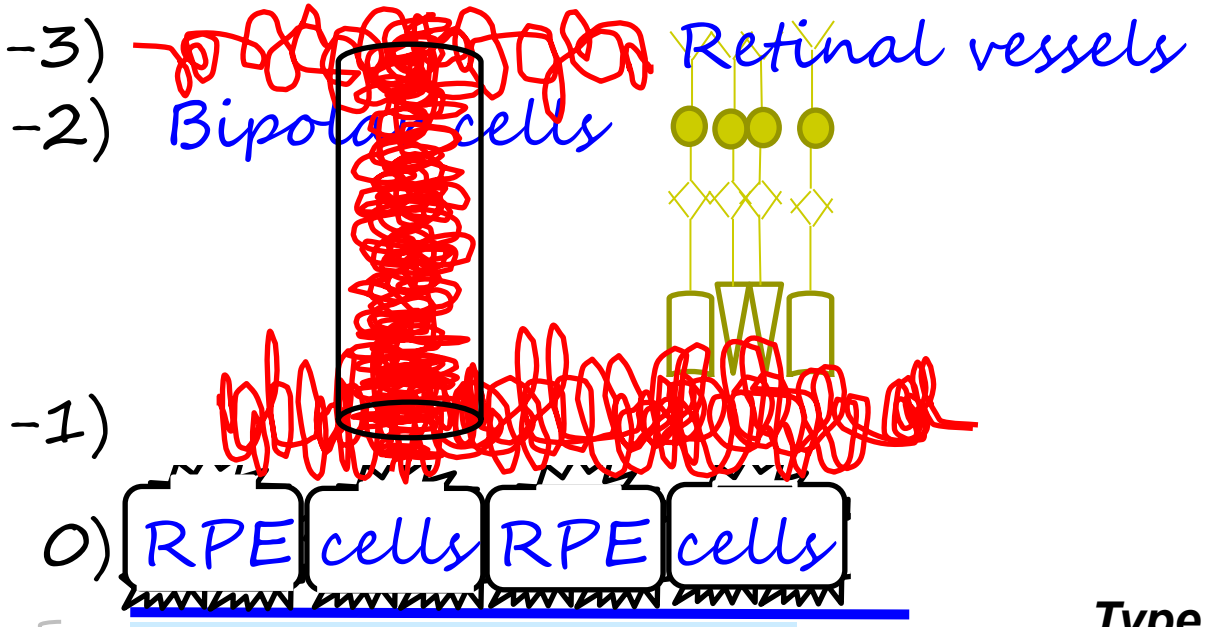
--Type 3: NVM arises from the deep capillary plexus of the retina and grows *down* toward the RPE

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



Type 3 with the NVM growing down from retinal vessels

Bruch's membrane

1) Basement membrane of RPE
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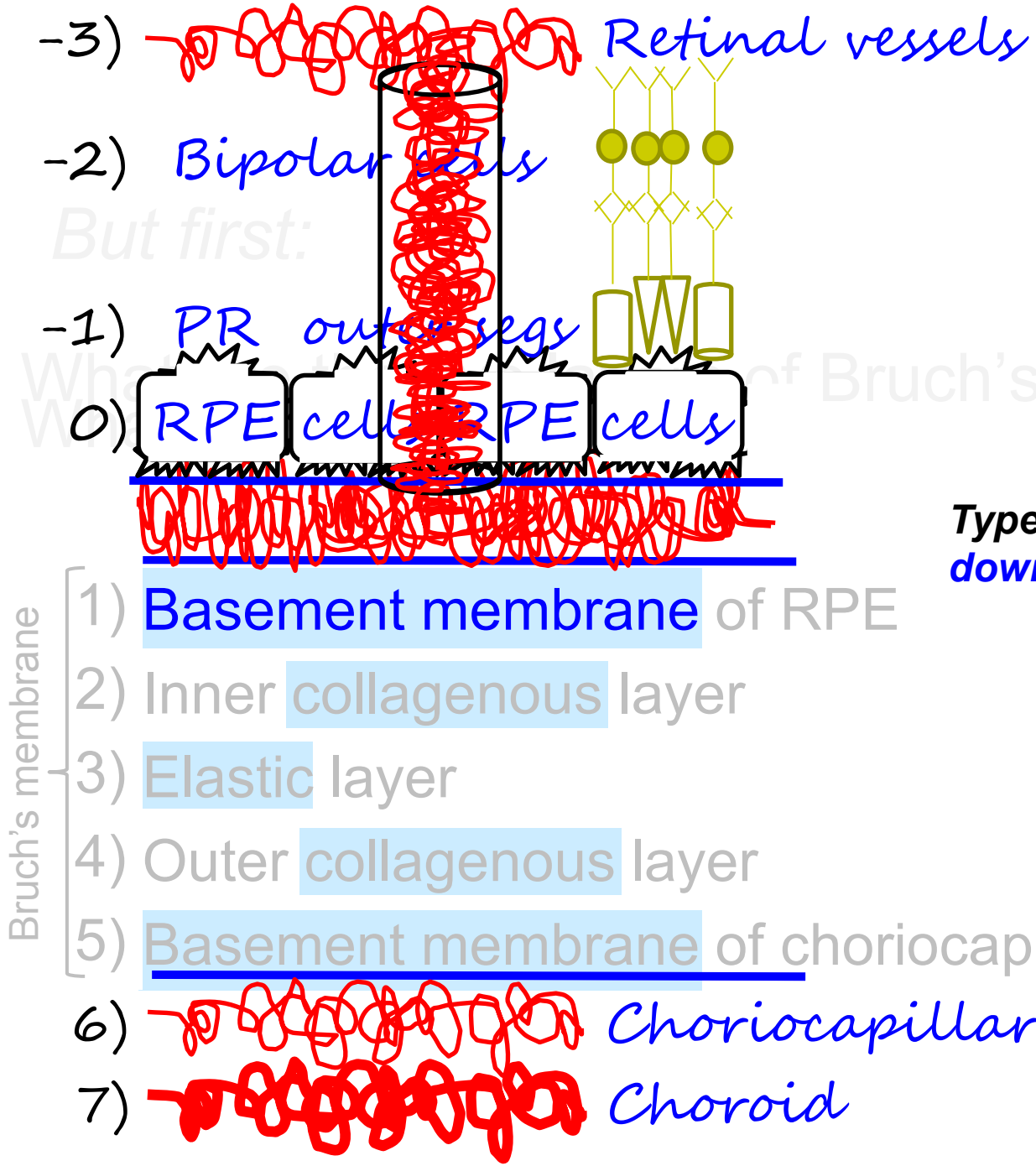

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What vessels give rise to the neovascular membrane?
The choriocapillaris (with one exception, to be discussed later)

What will a pt c/o if a CNVM develops?
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Three ... defining features ...
--Type ... or the sub-RP...
--Type 2 ... e, just *above the RPE)*
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Of the three, which occurs most frequently in ARMD?

Three types of neov *? What are the defining features of*

--Type 1: CNVM orig *embrane and/or the sub-RPE space*

--Type 2: CNVM orig *tinal space (ie, just above the RPE)*

--Type 3: NVM arise *wn toward the RPE*

Blurry

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- 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

Three types of neov *? What are the defining features of*
--**Type 1**: CNVM ori *embrane and/or the* sub-RPE space
--Type 2: CNVM ori *etinal* space (ie, just *above* the RPE)
--Type 3: NVM arise *wn* toward the RPE

Blurry

ARMD

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ARMD

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By what other name is Type 3 known?
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ARMD

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

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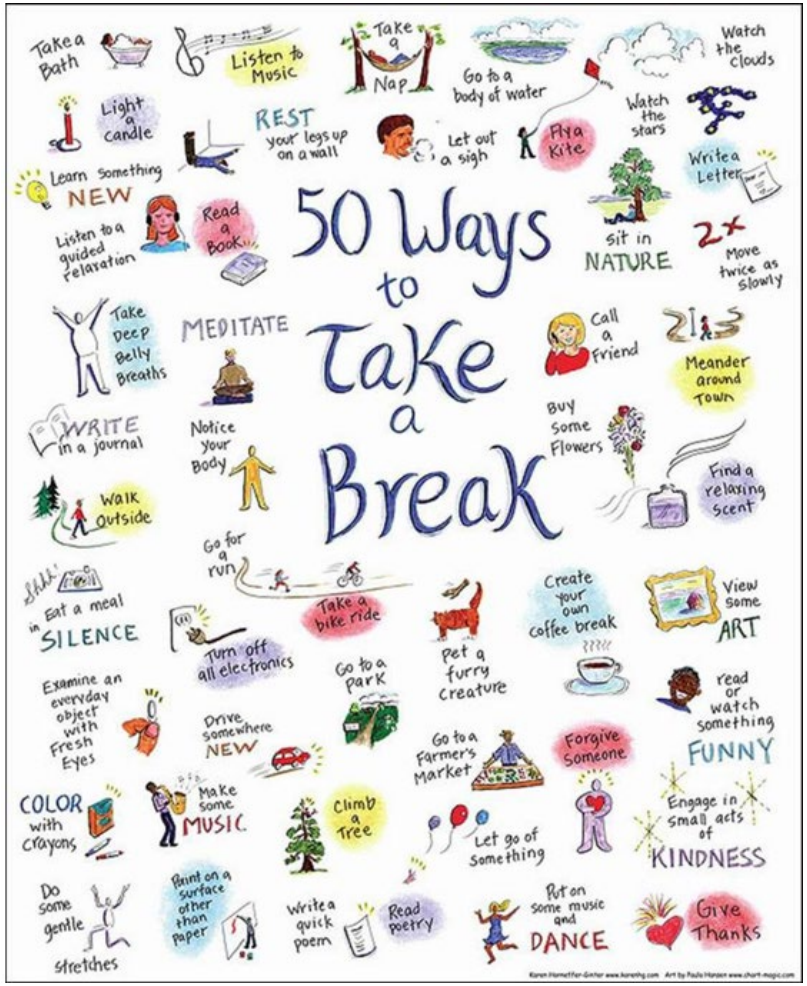
Coming in hot…



(This is a good point in the set to take a break)

ARMD

- CNVM DDx:
  - ARMD
  - OHS
  - ?
  - ?
  - ?
  - ?
  - ?
  - ?
  - ?
  - ?
  - ?

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

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

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ARMD

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  - ARMD
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  - 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.

No question—advance when ready

ARMD

- CNVM DDx:
  - ARMD
  - *OHS?*
  - *Angioid streaks?*
  - *Pathologic myopia?*
  - *Idiopathic?*
  - Sorsby macular dystrophy (Sorsby, discussed earlier, is **not** one of them)
  - *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?*

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ Angioid streaks
  - ★ Pathologic myopia
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  - Sorsby macular dystrophy
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ARMD

- CNVM DDx:
  - ARMD
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  - ☆ Patholo
  - Idiopath
  - Sorsby
  - Trauma
  - Iatroger
  - Central serous chorioretinopathy
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Is there a racial predilection in OHS?

ARMD

- CNVM DDx:
  - ARMD
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Is there a racial predilection in OHS?
Yes, OHS occurs almost exclusively among ethnicity of geographic area heritage

ARMD

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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 two rivers valleys of the US

ARMD

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Does OHS manifest unilaterally, or bilaterally?

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How is the diagnosis of OHS made?
It is a clinical diagnosis based on DFE findings

What are you looking for on DFE?
The so-called 'classic triad' of OHS:
--?
--?
--?

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How is the diagnosis of OHS made?
It is a clinical diagnosis based on DFE findings

What are you looking for on DFE?
The so-called 'classic triad' of OHS:
--Histo spots
--Peripapillary atrophy
--Disciform macular lesion(s)

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Bilaterally (although it can be somewhat asymmetric)

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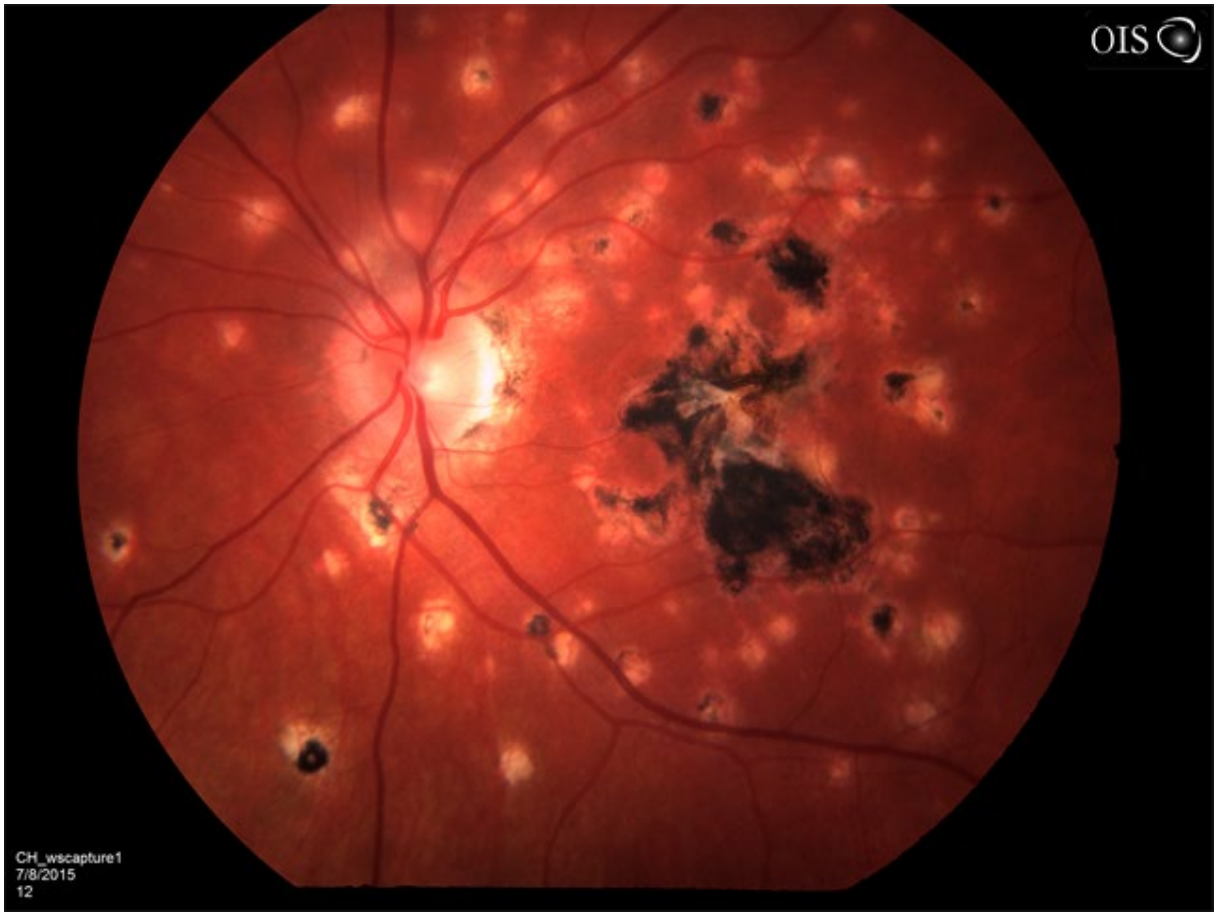
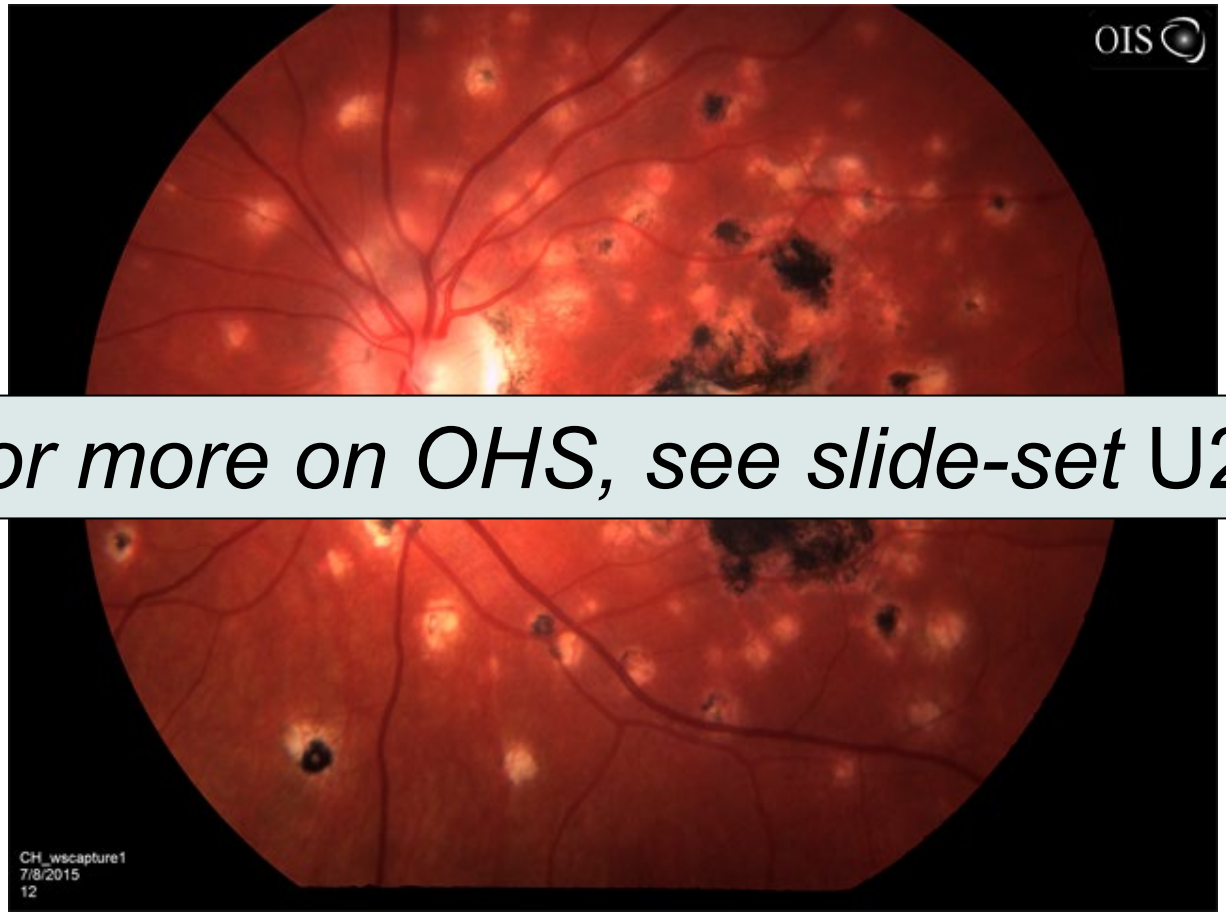
ARMD



OHS: The classic triad

ARMD



For more on OHS, see slide-set U21

ARMD

- CNVM DDx:
  - ARMD
  - OHS
  - **Angioid streaks**

What is the classic DFE appearance of angioid streaks?

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - OHS
  - **Angioid streaks**

What is the classic DFE appearance of angioid streaks?

color-color

retinal structure

lines radiating out from the peripapillary region; these lines represent breaks in

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - OHS
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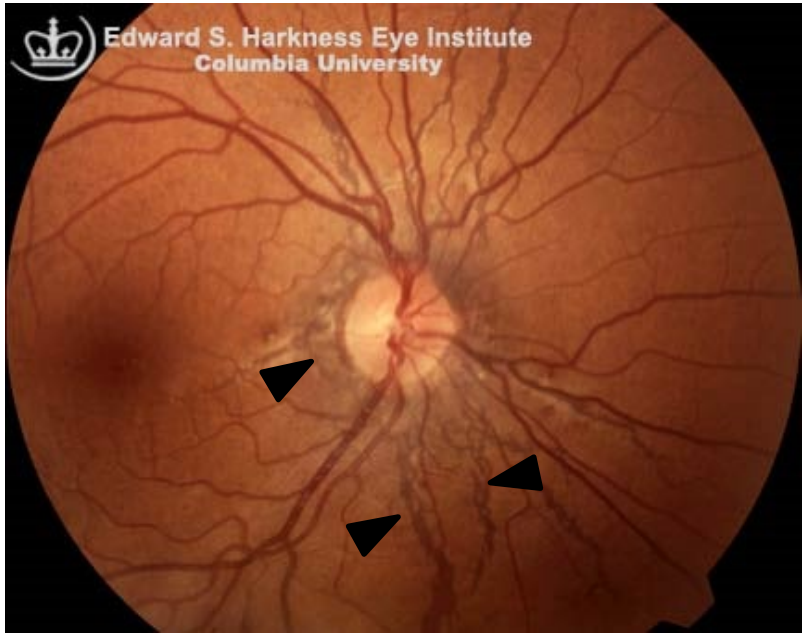
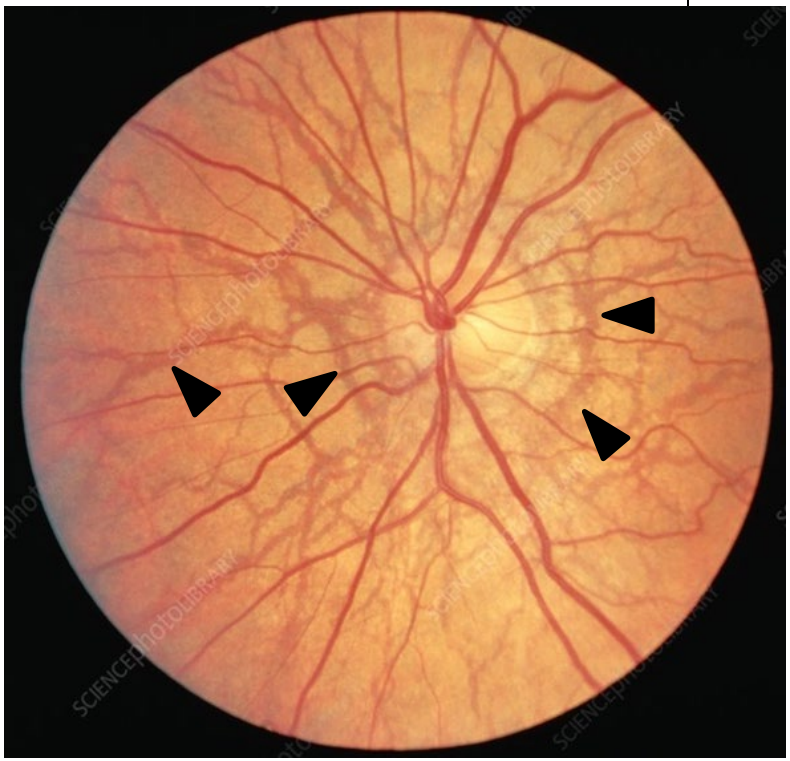
What is the classic DFE appearance of angioid streaks?
Reddish-brown lines radiating out from the peripapillary region; these lines represent breaks in Bruch's membrane

  - Adult-onset vitelliform dystrophy

ARMD





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

ARMD

- 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?

  - Adult-onset vitelliform dystrophy

ARMD

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

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About half

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

  - Adult-onset vitelliform dystrophy

ARMD

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P
E
P
S
I

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ARMD

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  - ARMD
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P
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About half

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

  - Adult-onset vitelliform dystrophy

ARMD

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Pseudoxanthoma elasticum (PXE)
Ehlers-Danlos syndrome
Paget's disease of bone
Sickle-cell disease
Idiopathic (ie, no association)

~ # of cases are associated with one of these

~ # of cases have no known systemic association

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
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Pseudoxanthoma elasticum (PXE)
Ehlers-Danlos syndrome
Paget's disease of bone
Sickle-cell disease
Idiopathic (ie, no association)

~50% of cases are associated with one of these

~50% of cases have no known systemic association

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

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

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

What is the well-known mnemonic for angioid streak's associations? What are these associations?

***P**seudoxanthoma elasticum (PXE)?*
***E**hlers-Danlos syndrome?*
***P**aget's disease of bone?*
***S**ickle-cell disease?*
Idiopathic (ie, no association)

Which condition has the strongest association with angioid streaks?

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

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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

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

What is the classic DFE appearance of angioid streaks?
Reddis these lines represent breaks in Bruch's

What p abnormalities?
About h

What other organ-systems are affected in PXE?
--?
--?
--?
--Eye

What is the well-known mnemonic for angioid streak's associations? What are these associations?

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ARMD

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  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

What is the classic DFE appearance of angioid streaks?
Reddis these lines represent breaks in Bruch's

What p *abnormalities?*
About h

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? What are these associations?

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ARMD

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  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

What is the classic DFE appearance of angioid streaks?

Reddis ... present breaks in Bruch's ...

What p ...

About h ...

What is the appearance of affected skin?

What ot ...

Skin

--Vascu ...

--GI trac ...

--Eye

What is the well-known mnemonic for angioid streak's associations? What are these associations?

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About h ...

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Ehlers-Danlos syndrome
Paget's disease of bone
Sickle-cell disease
Idiopathic (ie, no association)

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

Skin
--Vascu
--GI trac
--Eye

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

- Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
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What p ...
About h ...

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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?
PXE, by a mile

Skin

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

What is the classic informal descriptor for this appearance?

- Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

What is the classic DFE appearance of angioid streaks?

Reddis ... present breaks in Bruch's ...

What p ...
About h ...

What is the well-known mnemonic for angioid streak's associations? What are these associations?

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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?
PXE, by a mile

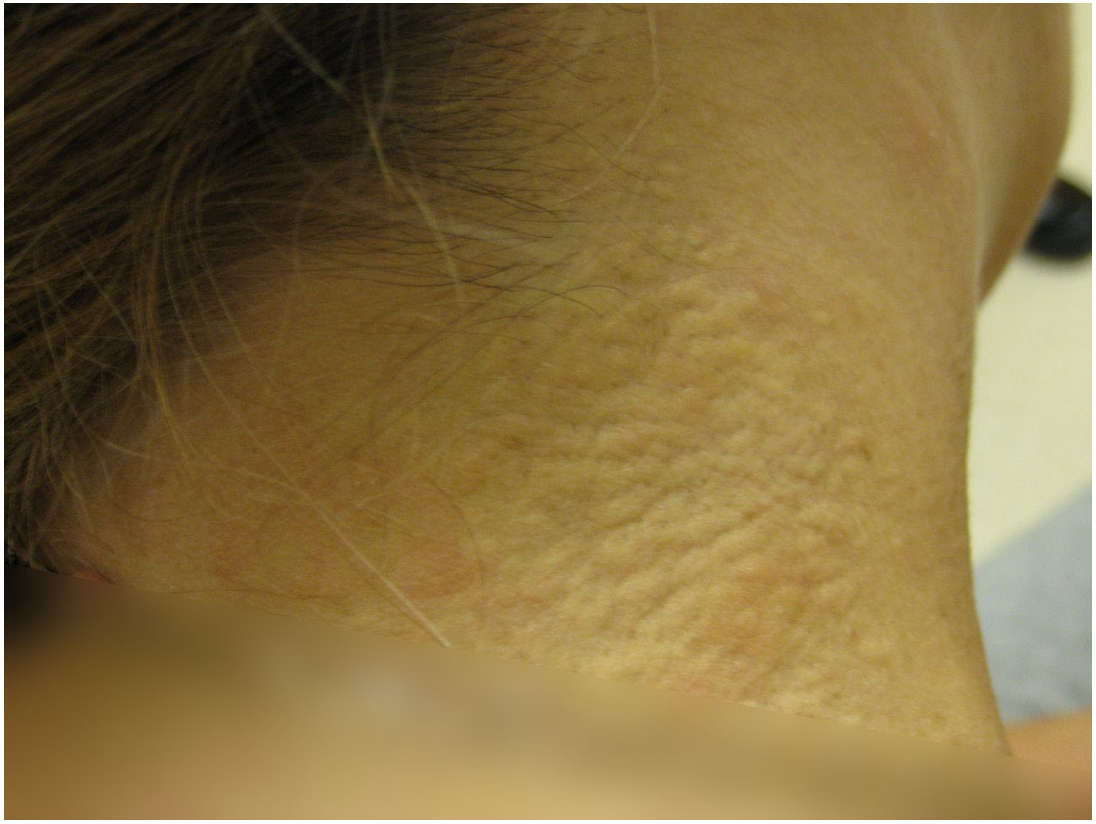
Skin

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'

- Adult-onset vitelliform dystrophy

ARMD



PXE skin

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

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What p *malities?*
About h

What is the well-known mnemonic for angioid streak's associations? What are these associations?

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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?
PXE, by a mile

What other organ-systems are affected in PXE?
--Skin
--Vasc
--GI tra

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

ARMD

- 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?
PXE, by a mile

What other organ-systems are affected in PXE?
--Skin
--Vasc
--GI tra

Eye

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

  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ **Angioid streaks**

What is the classic DFE appearance of angioid streaks?
Reddis these lines represent breaks in Bruch's

What p
About h

What other organ-systems are affected in PXE?
--Skin
--Vasc
--GI tra

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

Eye

What mellifluous name is used to describe the RPE mottling?

What is the well-known mnemonic for angioid streak's associations? What are these associations?

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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?
PXE, by a mile

- Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
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What is the classic DFE appearance of angioid streaks?
Reddis these lines represent breaks in Bruch's

What p
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What other organ-systems are affected in PXE?
--Skin
--Vasc
--GI tra

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

Eye

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

What is the well-known mnemonic for angioid streak's associations? What are these associations?

Pseudoxanthoma elasticum (PXE)
Ehlers-Danlos syndrome
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Idiopathic (ie, no association)

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

- Adult-onset vitelliform dystrophy

ARMD

PXE: *Peau d'orange* fundus

ARMD

For more on angioid streaks, see slide-set R61

PXE: *Peau d'orange* fundus

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ Angioid streaks
  - ★ **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dyst
  - Traumatic choroidal
  - Iatrogenic
  - Central serous chori
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

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

ARMD

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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

ARMD

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

ARMD

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

ARMD

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  - ARMD
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  - ★ **Pathologic myopia**
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What are lacquer cracks*?*

ARMD

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26.5 mm

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

What are lacquer cracks*?*
Breaks in Bruch's membrane, _____ in color, usually found in the retinal area

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ Angioid streaks
  - ★ **Pathologic myopia**
  - Idiopathic
  - Sorsby macular dyst
  - Traumatic choroidal
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  - Central serous chori
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Per the Retina *book, what axial length serves as a useful cutoff for defining pathologic myopia?*
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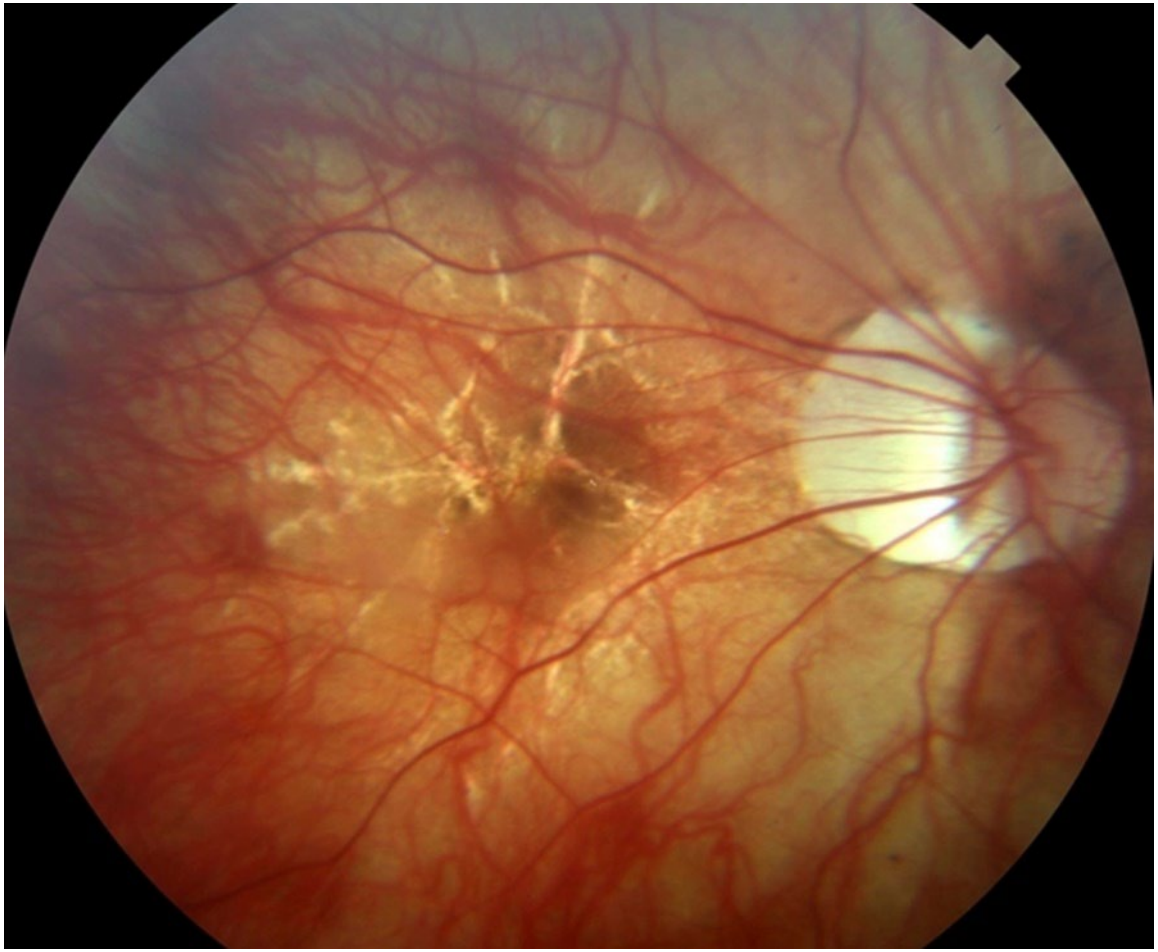
What is the classic finding on DFE that puts high myopes at risk for CNVM?
Lacquer cracks

What are lacquer cracks*?*
Breaks in Bruch's membrane, yellowish in color, usually found in the macula .

ARMD



Lacquer cracks

ARMD

- CNVM DDx:
  - ARMD
  - ★ OHS
  - ★ Angioid streaks
  - ★ **Pathologic myopia**
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  - Adult-onset vitelliform dystrophy

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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*?*
Breaks in Bruch's membrane, yellowish in color, usually found in the macula . <u>These breaks are the nidus for CNVM ingress in pathologic myopia.</u>

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 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?*

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
  - 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?*

ARMD

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

ARMD

- CNVM DDx:
  - *In two words, what is the underlying cause of CSC?*
    Choroidal hyperpermeability
  -
  -
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  -
  - ★ **Central serous chorioretinopathy**
  - Pattern dystrophy
  - Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - *In two words, what is the underlying cause of CSC?*
    Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)
  -
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  - ★ **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?*
  -
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  -
  -
  - ★ **Central serous chorioretinopathy**
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ARMD

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  - *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

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.

★ **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?

- ★ **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

- ★ **Central serous chorioretinopathy**
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ARMD

- CNVM DDx:

In two words, what is the underlying cause of CSC?
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To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
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The presence of SRF on OCT

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

- ★ **Central serous chorioretinopathy**
- Pattern dystrophy
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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
  - *What distinguishes SRF seen on OCT in CNVM from that seen in CSC?*
    In CNVM there is usually a concomitant [two words], whereas this will not be present in CSC (absent a 2ndry CNVM)
  - ★ **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)

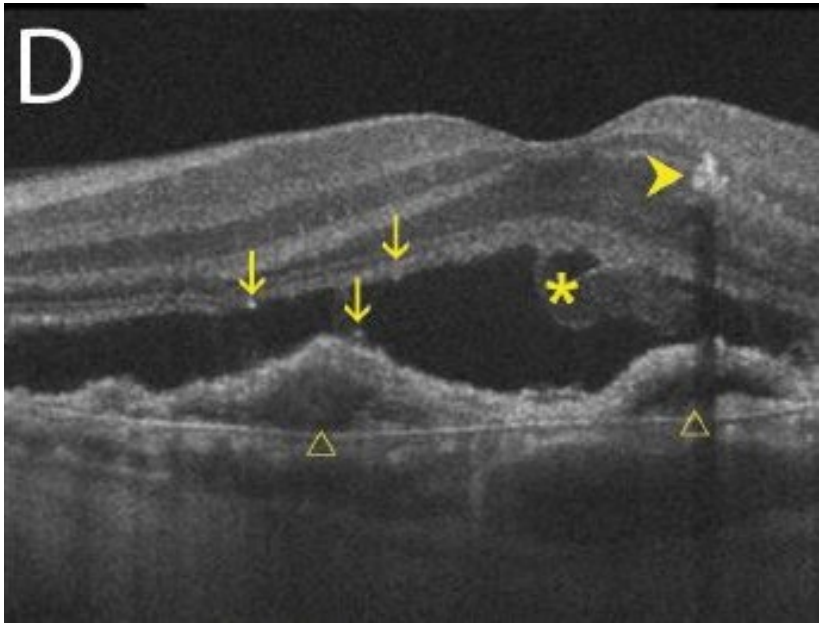
To be clear: Is CNVM associated with CSC?
Yes—2ndry CNVM can and does occur in CSC, albeit uncommonly.
The takeaway point: CSC can both cause CNVM ***and*** masquerade as it.

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

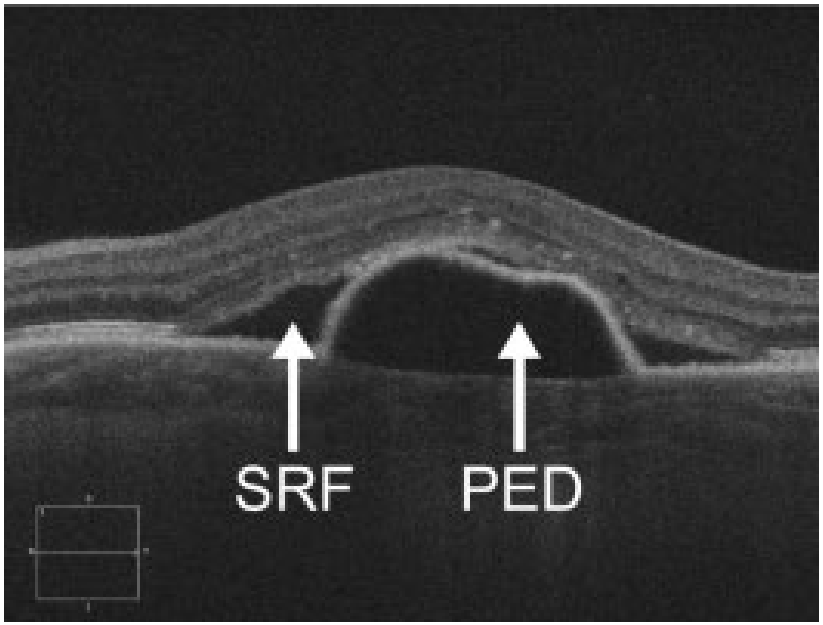
What distinguishes SRF seen on OCT in CNVM from that seen in CSC?
In CNVM there is usually a concomitant subretinal hemorrhage , whereas this will not be present in CSC (absent a 2ndry CNVM)

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

ARMD



ARMD: PED (Δ) and SRF (↓), along with subretinal hemorrhage (*)



CSC: PED and SRF, but no hemorrhage

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,*
  - *There is another important OCT finding that distinguishes CSC from ARMD—what is it?*
  -
  -
  -
  - ★ **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?*
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  -
  - *For the CSC cases in which no CNVM is present: What clinical finding,*
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  - The thickness of the choroid
  -
  -
  -
- ★ **Central serous chorioretinopathy**
- Pattern dystrophy
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ARMD

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  - *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*
  - *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 [redacted] in ARMD, but [redacted] in CSC.
  -
  -
  -
- ★ **Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - *In two words, what is the underlying cause of CSC?*
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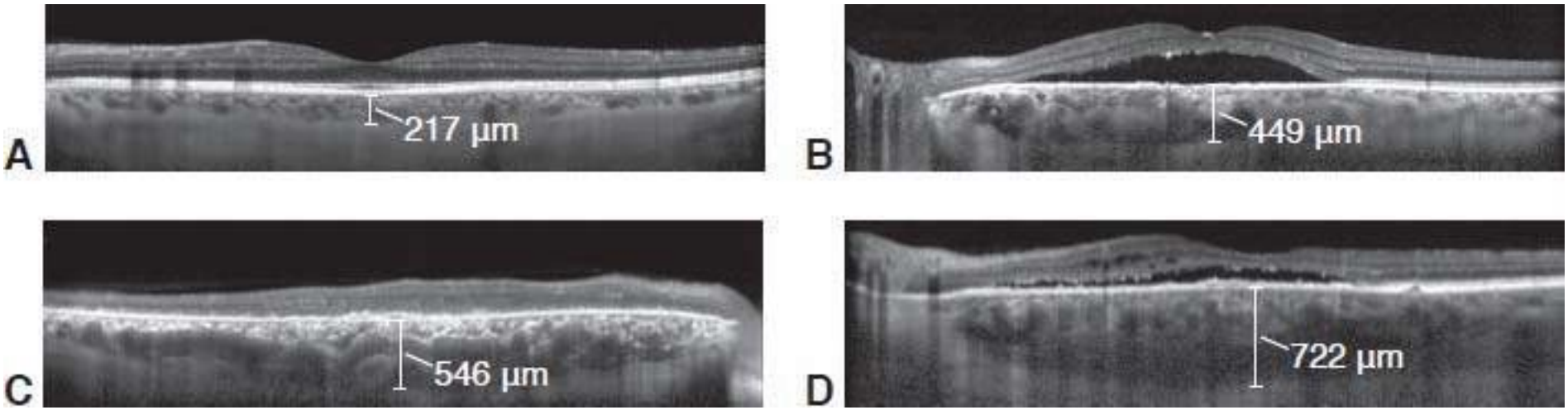
  - *For the CSC cases in which no CNVM is present: What clinical finding,*
  - *There is another important OCT finding that distinguishes CSC from ARMD—what is it?*
  - The thickness of the choroid. It tends to be normal or thinned in ARMD, but thickened in CSC.
  -
  -
- ★ **Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

ARMD



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

ARMD

- CNVM DDx:
  - *In two words, what is the underlying cause of CSC?*
  - Choroidal hyperpermeability (*choriocapillaris hyperpermeability* is correct as well, and may even be preferred)
  -
  - *To be clear: Is CNVM associated with CSC?*
  - **Yes**—2ndry CNVM can and does occur in CSC, albeit uncommonly. The takeaway point: CSC can both cause CNVM ***and*** masquerade as it.
  -
  - *For the CSC cases in which no CNVM is present: What clinical finding*
  - *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?*
  -
- ★ **Central serous chorioretinopathy**
- Pattern dystrophy
- Adult-onset vitelliform dystrophy

ARMD

- CNVM DDx:
  - *In two words, what is the underlying cause of CSC?*
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  - *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*
  - *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

ARMD

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

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

ARMD

Regarding conditions that can be misdiagnosed as **dry** *ARMD—what feature do they have in common?*
Abnormalities of the RPE

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

ARMD

- ~~CNVM~~ Dry ARMD 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?*

ARMD

- ~~CNVM~~ Dry ARMD 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!)*

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARMD
  - OHS
  - Angioid streaks
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - ★ **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?

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARMD
  - OHS
  - Angioid streaks
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - ★ **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

ARMD

CSC: RPE mottling

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARMD
  - OHS
  - Angioid streaks
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - ★ **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?

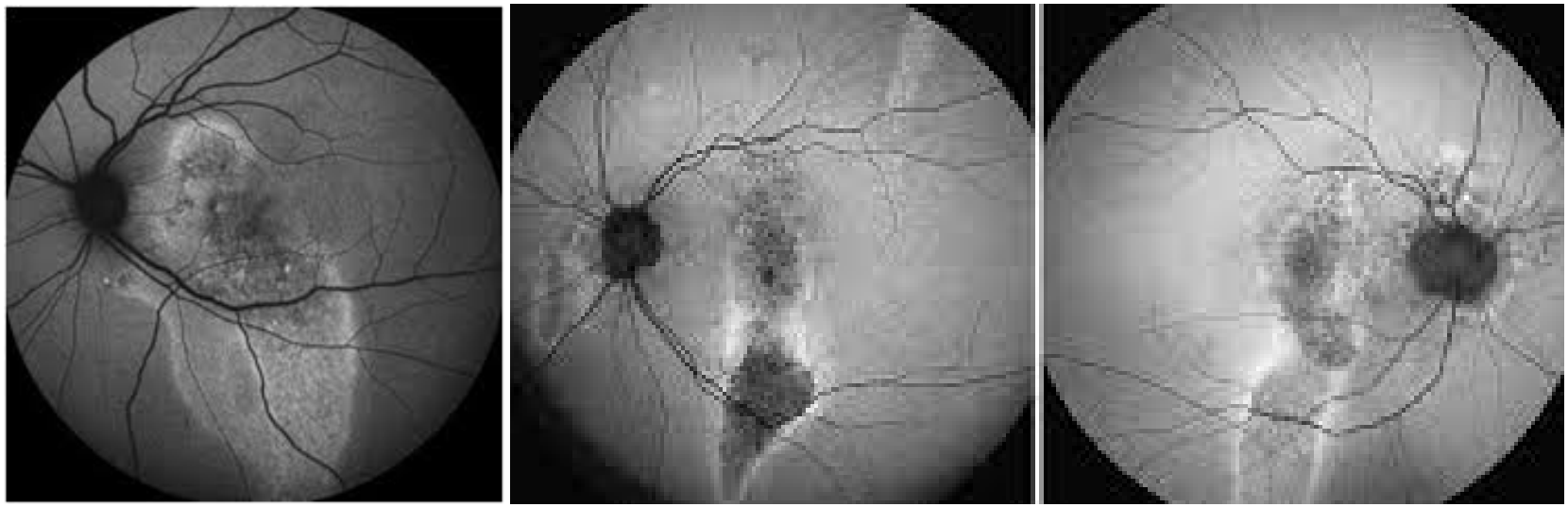
ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARMD
  - OHS
  - Angioid streaks
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - [illegible]
  - ★ **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

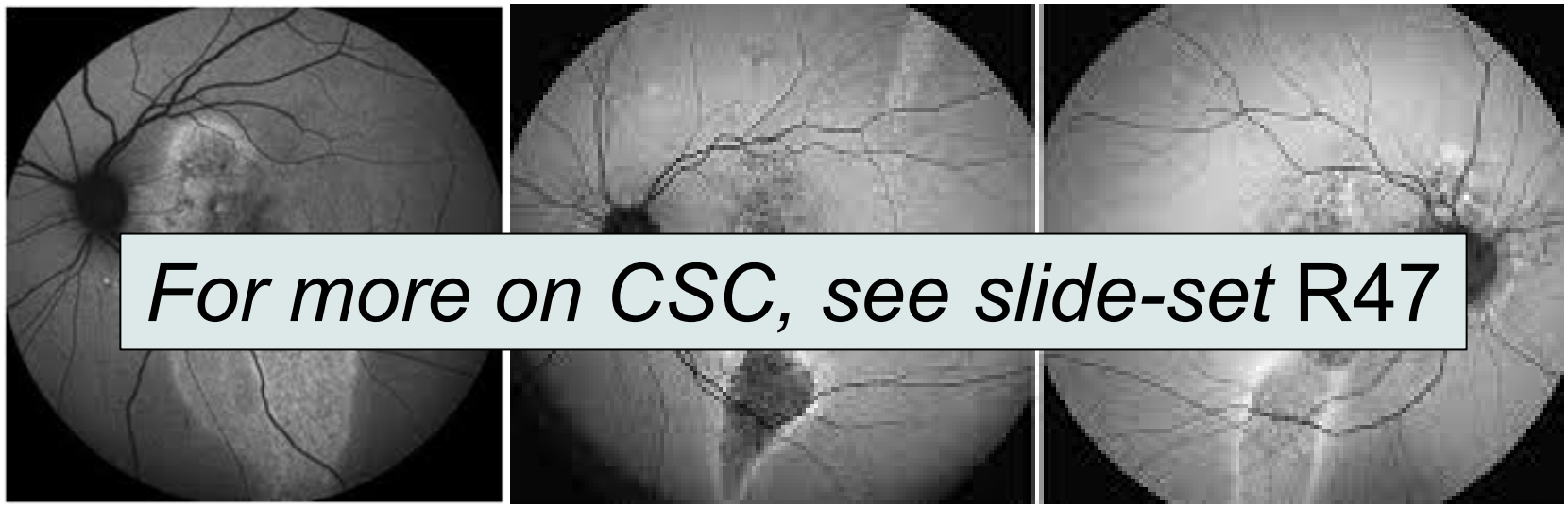
Because SRF is subject to gravity-induced downward migration, the RPE changes often demonstrate a particular pattern. What are the formal and informal names for this pattern?
Descending tracts, aka ‘guttering’

ARMD



CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.

ARMD



For more on CSC, see slide-set R47

CSC: Descending tracts. These are best seen via fundus autofluorescence imaging.

ARMD

- ~~CNVM~~ Dry ARMD DDx:

Briefly, what is a pattern dystrophy*?*

★ **Pattern dystrophy**

☆ Adult-onset vitelliform dystrophy

ARMD

- ~~CNVM~~ Dry ARMD DDx:

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

ARMD

- ~~CNVM~~ Dry ARMD DDx:

Briefly, what is a pattern dystrophy*?*
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What is the inheritance pattern?

★ **Pattern dystrophy**

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ARMD

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AD

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Are pattern dystrophies associated with severe vision loss?

★ **Pattern dystrophy**

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Generally no--vision is only slightly affected

★ **Pattern dystrophy**

☆ Adult-onset vitelliform dystrophy

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Do the macular 'patterns' appear early in life?

★ **Pattern dystrophy**

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

★ **Pattern dystrophy**

☆ Adult-onset vitelliform dystrophy

ARMD

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--
--
--

The mnemonic is…

★ **Pattern dystrophy**

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ARMD

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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

ARMD

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--**B**utterfly dystrophy
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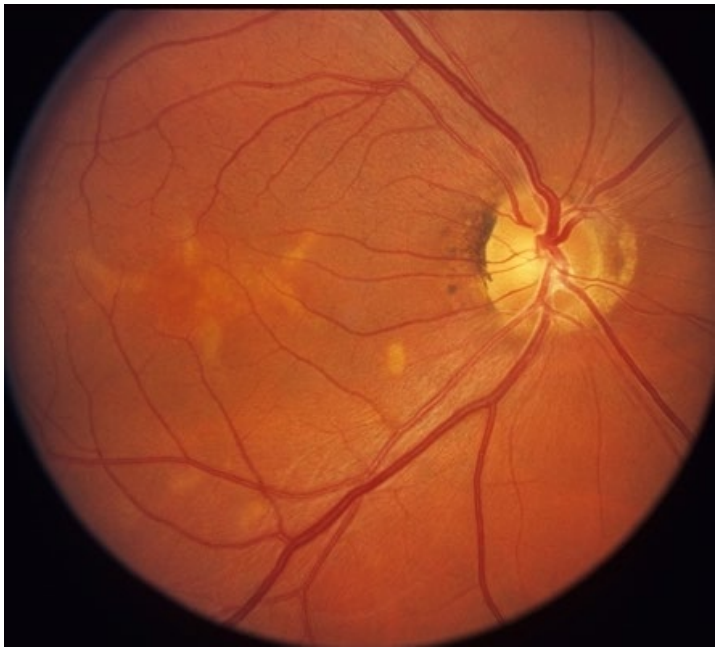
--**R**eticular dystrophy
--**F**undus pulverulentus

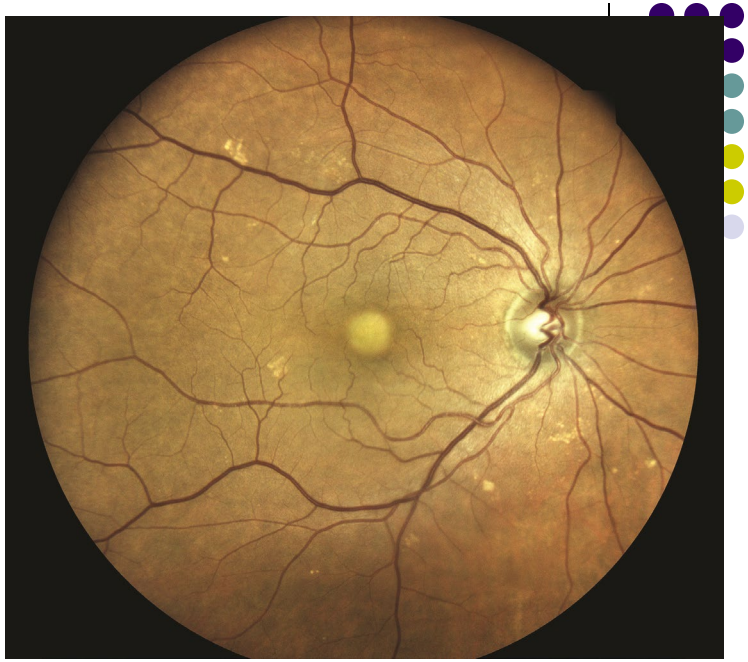
★ **Pattern dystrophy**

☆ Adult-onset vitelliform dystrophy

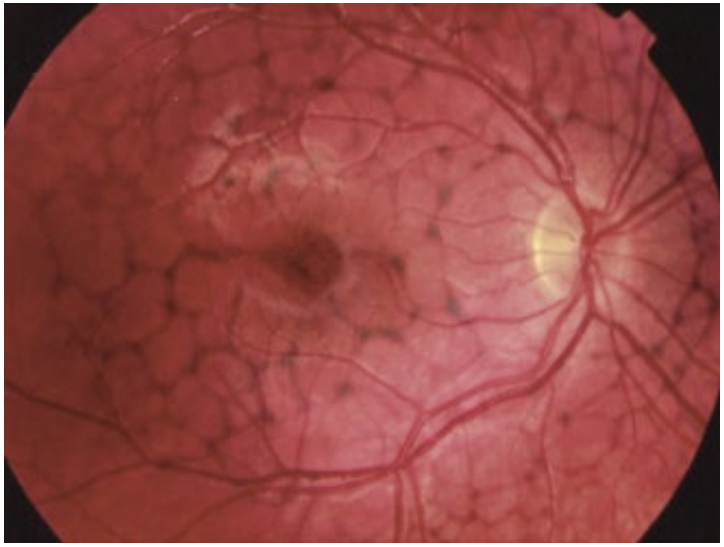
ARMD



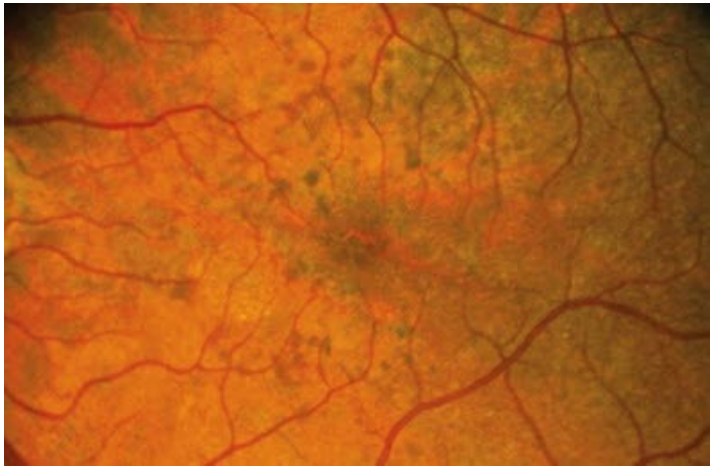
Butterfly dystrophy



Adult-onset foveomacular vitelliform dystrophy



Reticular dystrophy



Fundus pulverulentus

ARMD

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

☆ Pattern dystrophy

★ **Adult-onset vitelliform dystrophy**

ARMD

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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)

☆ Pattern dystrophy

★ **Adult-onset vitelliform dystrophy**

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARM
  - OHS
  - Ang
  - Path
  - Idiop
  - Sors
  - Trau
  - Iatrogenic
  - ☆ Central serous chorioretinop thy
  - ☆ Pattern dystrophy
  - ★ **Adult-onset vitelliform dystrophy**

At what age do AOVD lesions appear?

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARM
  - OHS
  - Ang
  - Path
  - Idiop
  - Sors
  - Trau
  - Iatrogenic
  - ☆ Central serous chorioretinop thy
  - ☆ Pattern dystrophy
  - ★ **Adult-onset vitelliform dystrophy**

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

ARMD

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  - ☆ Pattern dystrophy
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At what age do AOVD lesions appear?
30s to 50s

What do pts c/o initially?

ARMD

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

What do pts c/o initially?
Not much—maybe a little blurring or metamorphopsia

ARMD

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  - OHS
  - Ang
  - Path
  - Idiop
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What do pts c/o initially?
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What does DFE reveal?

ARMD

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  - ARM
  - OHS
  - Ang
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At what age do AOVD lesions appear?
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What do pts c/o initially?
Not much—maybe a little blurring or metamorphopsia

What does DFE reveal?
Bilateral vitelliform (which means two-words *like*) lesions

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARM
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At what age do AOVD lesions appear?
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Not much—maybe a little blurring or metamorphopsia

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

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARM
  - OHS
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  - Path
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  - Trau
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  - ☆ Pattern dystrophy
  - ★ **Adult-onset vitelliform dystrophy**

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

What do pts
Not much—r

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

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

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARM
  - OHS
  - Ang
  - Path
  - Idiop
  - Sors
  - Trau
  - Iatrogenic
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At what age do AOVD lesions appear?
30s to 50s

What do pts
Not much—r

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

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

ARMD

- ~~CNVM~~ Dry ARMD DDx:
  - ARM
  - OHS
  - Ang
  - Path
  - Idiop
  - Sors
  - Trau
  - Iatrogenic
  - ☆ Central serous chorioretinop thy
  - ☆ Pattern dystrophy
  - ★ **Adult-onset vitelliform dystrophy**

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

What do pts
Not much—r

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

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

ARMD

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  - ARM
  - OHS
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  - Iatrogenic
  - ☆ Central serous chorioretinop thy
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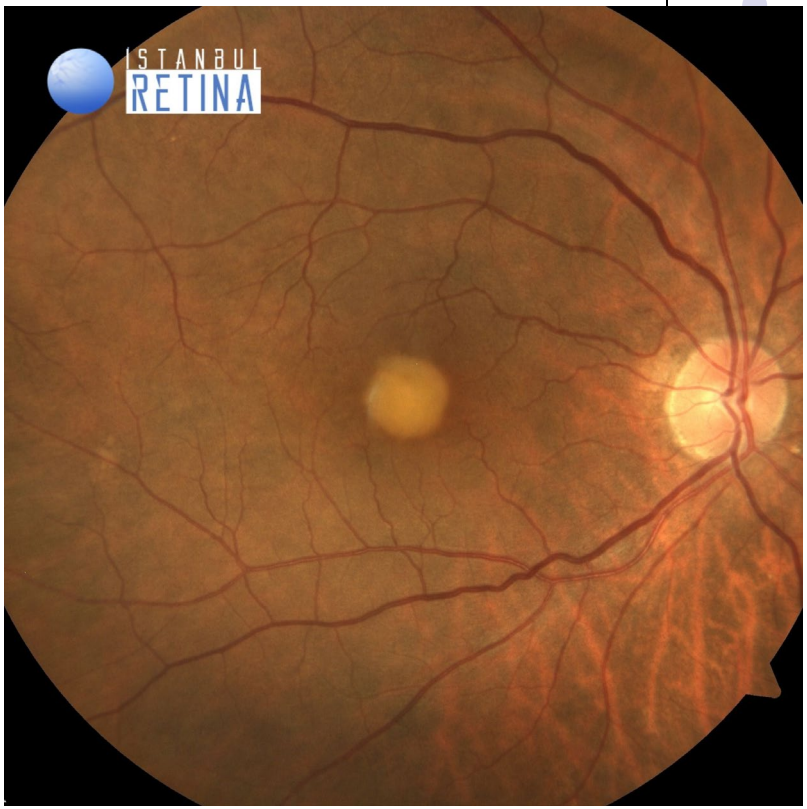
At what age do AOVD lesions appear?
30s to 50s

What do pts
Not much—r

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

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

ARMD



Typical round, yellow lesion of AOVD

ARMD

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  - ARM
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  - Path
  - Idiop
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At what age do AOVD lesions appear?
30s to 50s

What do pts
Not much—r

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

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

ARMD

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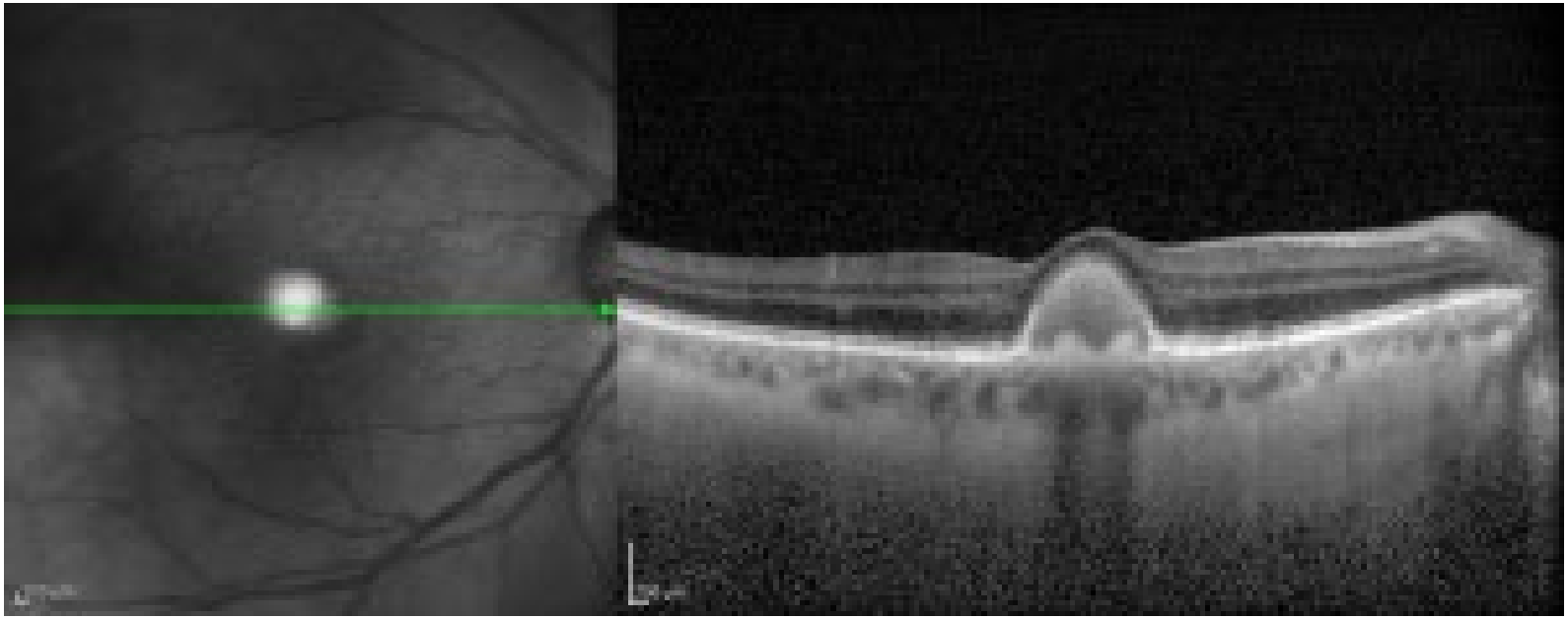
ARMD



OCT showing dome-like lesion in AOVD

ARMD

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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?

ARMD

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  - ☆ Central serous chorioretinop thy
  - ☆ Pattern dystrophy
  - ★ **Adult-onset vitelliform dystrophy**

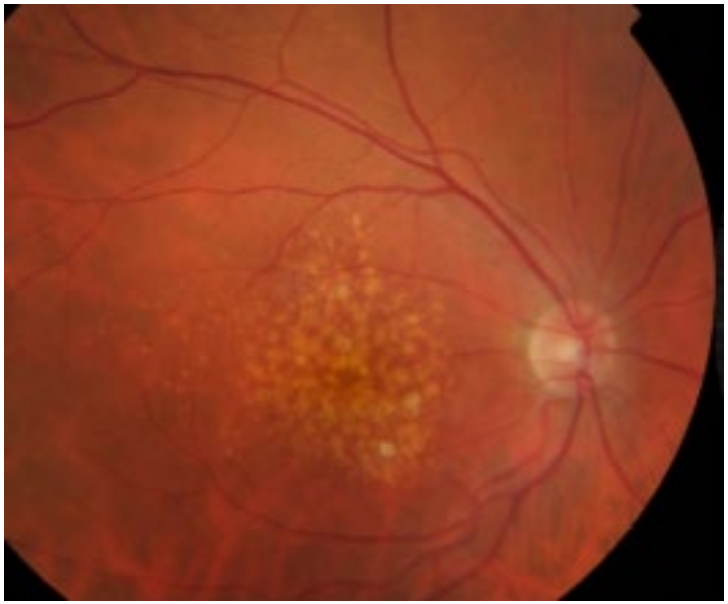
At what age do AOVD lesions appear?
30s to 50s

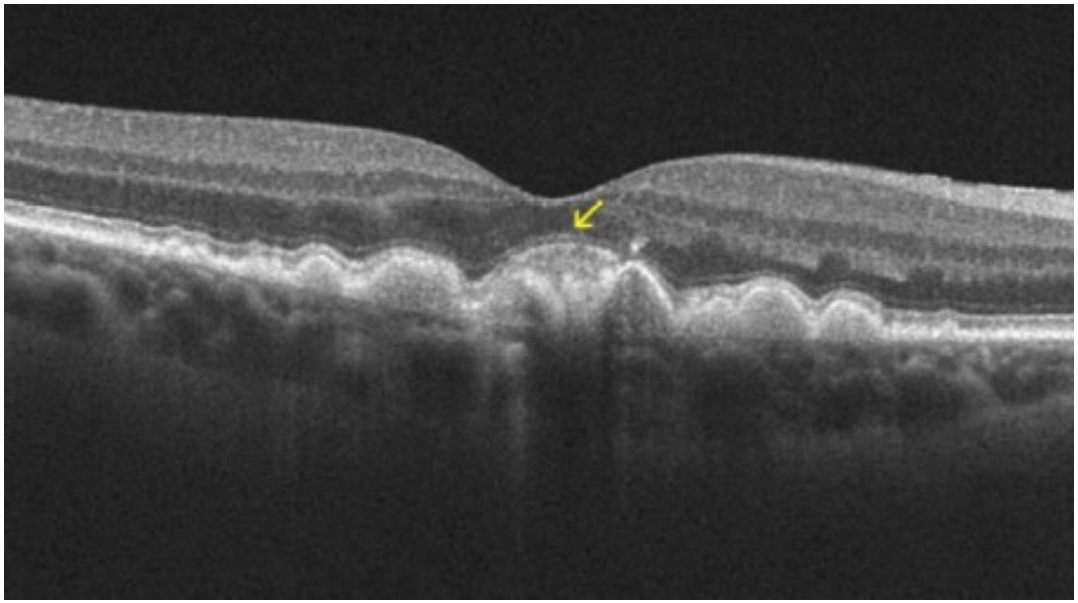
What do pts c/o initially?
Not much—maybe a little blurring or metamorphopsia

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

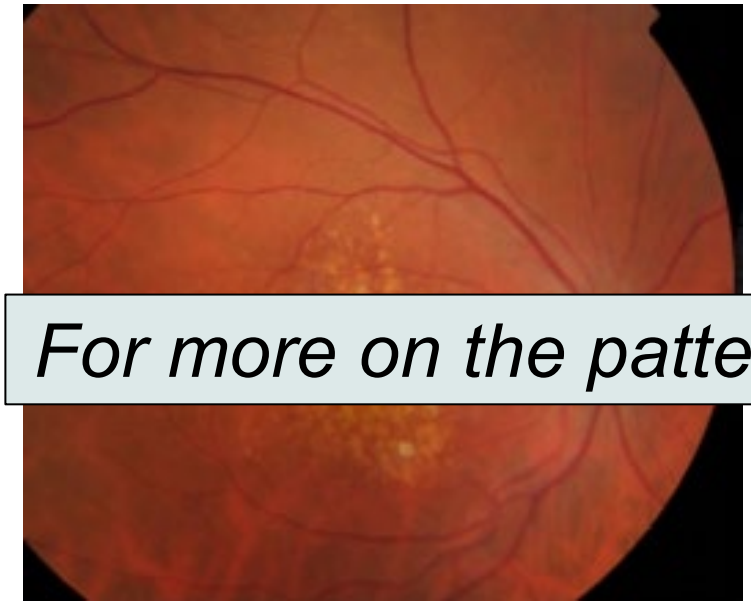
ARMD

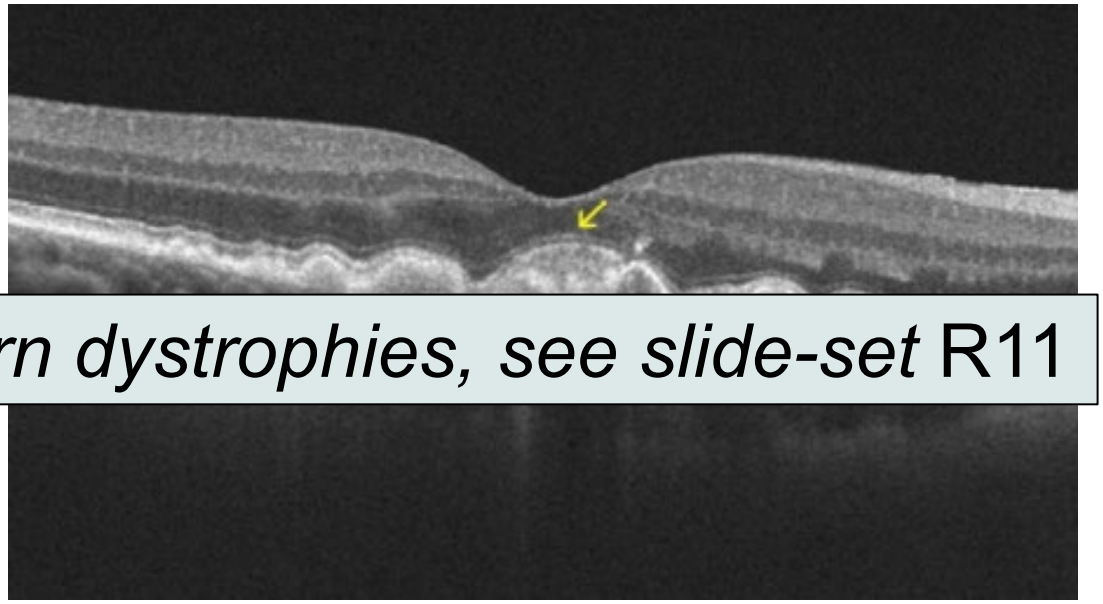




Here's a clinical challenge: AOVD in a patient with extensive drusen. Fundus photo demonstrates drusen, and an ill-defined vitelliform lesion. OCT shows the material *over* the soft drusen (yellow arrow) that could be misinterpreted as a CNVM related to **wet** ARMD.

ARMD





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

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ARMD

- ~~CNVM~~ Dry ARMD 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?

ARMD

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  - ★ **Drug toxicity**

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ARMD

Dry ARMD

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

Plaquenil maculopathy is covered in slide-set R25

  - Sorsby macular dystrophy
  - Traumatic choroidal rupture
  - Iatrogenic
  - ★ Central serous chorioretinopathy
  - ★ Pattern dystrophy
  - ★ Vitelliform dystrophy
  - ★ **Drug toxicity, especially…hydroxychloroquine**

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*
- abb. abnormalities in ARMD are typical

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The two RPE changes most typical of ARMD are:
--Atrophy (we knew this one already because of GA)
--Focal

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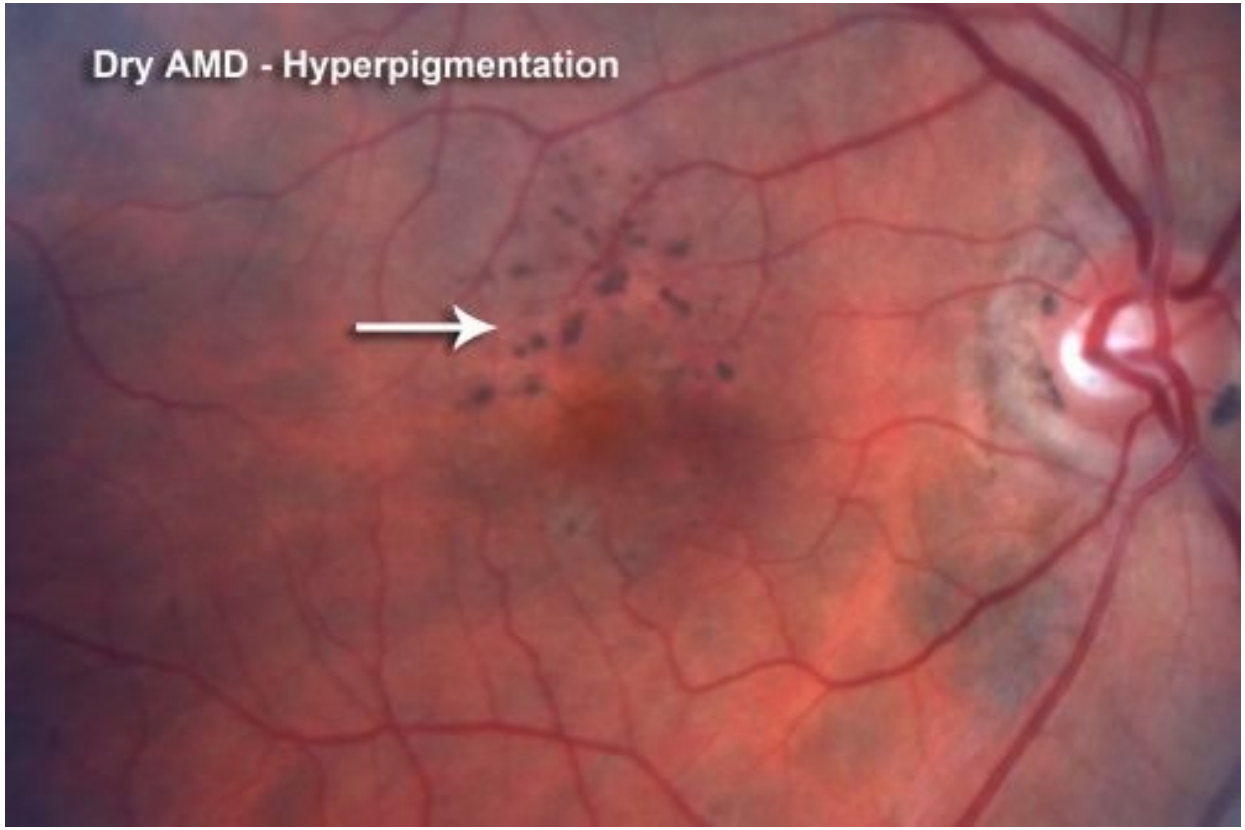

ARMD: RPE hyperpigmentation

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Speaking of being unsure about causality in ARMD…

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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*…

ARMD

Immune response

? ***?***

What are the two fundamental immune responses?

ARMD

Immune response

Innate **Adaptive**

What are the two fundamental immune responses?

ARMD

Immune response

Innate

aka.. _____ immunity

Adaptive

aka… _____ immunity

What word is used to capture the essence of each?

ARMD

Immune response

Innate

aka…**natural** immunity

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[redacted] provide immediate protection

Adaptive

aka…**acquired** immunity

[redacted] provide immediate protection

Which provides immediate protection against antigens deemed threatening?

ARMD

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Adaptive

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Does **not** provide immediate protection

Which provides immediate protection against antigens deemed threatening?

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aka…**natural** immunity

Does provide immediate protection

[redacted] require previous contact with the threat

Adaptive

aka…**acquired** immunity

Does **not** provide immediate protection

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

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Primary effector cells:
--***?***
--***?***

Adaptive

aka…**acquired** immunity

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Primary effector cells:
--***?***
--***?***

What are the primary effector cells for each?

ARMD

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

Adaptive

aka…**acquired** immunity

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

What are the primary effector cells for each?

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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**

No question—advance when ready

ARMD

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Primary effector
--**PMNs**
--**Monocytes/ma**

What would be an example of a single-molecule inflammatory mediator?
--***?***
--***?***
--***?***
(list not exhaustive obv)

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Primary effector
--**PMNs**
--**Monocytes/ma**

What would be an example of a single-molecule inflammatory mediator?
--Histamine
--Cytokines
--PMN degranulation products
(list not exhaustive obv)

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Primary effector

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

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The complement cascade is indeed complex, with # *components comprising* # *different pathways.*

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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. All that said, *neither* response type is adequate in and of itself to produce an effective immune response. Instead, both rely on **inflammatory mediators**—host-generated substances that act as force-multipliers for innate and/or adaptive immune responses. **Inflammatory mediators can be a single molecule**, or a **complex enzymatic cascade**

Primary effector

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)?

The complement cascade. Activation of the complement cascade results in cellular damage that is central in the pathogenesis of both dry and wet forms of ARMD.

The complement cascade is indeed complex, with 30+ components comprising three different pathways.

ARMD

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Complement factor H (CFH)

ARMD

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Let's drill down on VEGF for a bit…

ARMD

What does **VEGF** *stand for?*

VEGF-A$_{165}$

ARMD

What does **VEGF** *stand for?*
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What are some other growth factors of note regarding ocular development and health?
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hint

When you hear 'transforming growth factor β,' a particular type of condition should spring to mind.

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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) ***?***

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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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Does VEGF do anything besides grow new blood vessels?

$VEGF\text{-}A_{165}$

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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*).

VEGF-A $_{165}$

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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.

VEGF-A $_{165}$

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How does VEGF *work?*

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In a nutshell, what sort of structure is the VEGFR?

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Is one of these more important in the pathogenesis of ARMD?

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VEGF-A$_{165}$

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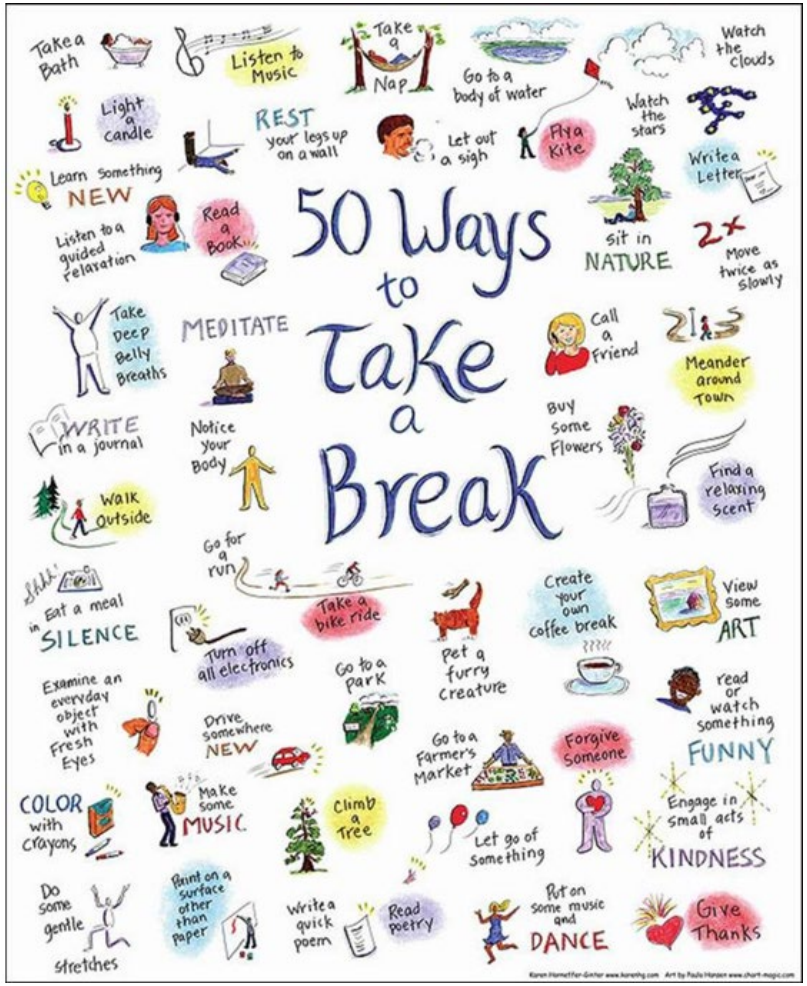

(This is a good point in the set to take a break)

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

Next let's drill down on anti-VEGF therapy…

ARMD

Ranibizumab *is a* one word (adj.), one word (adj.), hyphened-term, three words (two-word adj. and final noun)

ARMD

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

ARMD

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

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ARMD

What does recombinant *mean?*

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

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ARMD

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

ARMD

MARINA

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ANCHOR

ARMD

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ANCHOR

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ARMD

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

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

ARMD

RESULTS

MARINA

	0.3 mg	0.5 mg	Sham
Loss <15 letters	?	?	?
Gained >15 letters			

YEAR **ONE**

ANCHOR

	0.3 mg	0.5 mg	PDT
Loss <15 letters	?	?	?
Gained >15 letters			

ARMD

RESULTS

MARINA

	0.3 mg	0.5 mg	Sham
Loss <15 letters	**95%**	**95%**	**62%**
Gained >15 letters			

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

ARMD

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Note:
--30 to 40% of (0.5) pts **gained** 15+ letters of VA, compared to only ~5% of sham/PDT pts

ARMD

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YEAR ONE

YEAR TWO

	0.3 mg	0.5 mg	Sham
Loss <15 letters	?	?	?
Gained >15 letters			

	0.3 mg	0.5 mg	PDT
Loss <15 letters	?	?	?
Gained >15 letters	34%	41%	6%

ARMD

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YEAR TWO

	0.3 mg	0.5 mg	Sham
Loss <15 letters	92%	90%	53%
Gained >15 letters			

	0.3 mg	0.5 mg	PDT
Loss <15 letters	90%	90%	66%
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			40%	6%

YEAR ONE

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

YEAR TWO

	0.3 mg	0.5 mg	Sham
Loss <15 letters	92%	90%	53%
Gained >15 letters			

	0.3 mg	0.5 mg	PDT
Loss <15 letters	90%	90%	66%
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Gained >15 letters	26%	33%	4%

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YEAR ONE

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

YEAR TWO

	0.3 mg		
Loss <15 letters	92%	90%	53%
Gained >15 letters	26%	33%	4%

		0.5 mg	PDT
Loss <15 letters	[illegible]	90%	66%
Gained >15 letters	34%	41%	6%

ARMD

MARINA

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

ANCHOR

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Minimally Classic/Occult Trial of the
Anti-VEG
In the Tre
Age-Rela

What does ANCHOR *stand for?*
ANti-VEGF Antibody for the Treatment
ORoidal
lated

MARINA and ANCHOR tl;dr:
1) Both were strong **Phase III clinical trials**
2) Both evaluated **monthly injections of ranizumab** 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**

One

nth

No

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

*What was the **primary** outcome measure?*

Proportion of patients losing <15 ETDRS letters

Proportion of patients **gaining** >15 ETDRS letters

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Age-

What does ANCHOR *stand for?*
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of Predominantly Classic **CHOR**oidal
elated

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.

onth

intervention involved?

eceived
either sham injections + real PDT
or sham PDT + real injections

Proportion of patients losing <15 ETDRS letters

*What was the **primary** outcome measure?*

Proportion of patients losing <15 ETDRS letters

Proportion of patients **gaining** >15 ETDRS letters

*What was the **secondary** outcome measure?*

Proportion of patients **gaining** >15 ETDRS letters

ARMD

MARINA

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

ANCHOR

What does MARINA *stand for?*
Minimally Classic/Occult Trial of the
Anti-VEGF Antibody **R**anibizumab
In the
Age-

What does ANCHOR *stand for?*
ANti-VEGF Antibody for the Treatment
of Predominantly Classic **CHOR**oidal
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ARMD

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One injection every month for 24 months

What was the dosing schedule?

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***?

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outcome measure?

gaining >15 ETDRS letters

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gaining >15 ETDRS letters

outcome measure?

gaining >15 ETDRS letters

ARMD

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

ARMD

PIER

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

PrONTO

(Other acceptable answers: *SAILOR; SUSTAIN; HORIZON; HARBOR)*

ARMD

PIER

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PrONTO

What does PIER *stand for?*

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ARMD

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ARMD

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ARMD

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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

ARMD

PIER

Focus your attention on the 0.5 outcome

Three Months	0.3 mg	0.5 mg	Sham
Average VA change (ETDRS letters)	?	?	?

(Note the different outcome variable)

*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?

ARMD

PIER

Three Months	0.3 mg	0.5 mg	Sham
Average VA change (ETDRS letters)	↑2.9	↑**4.3**	↓8.7

*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?

ARMD

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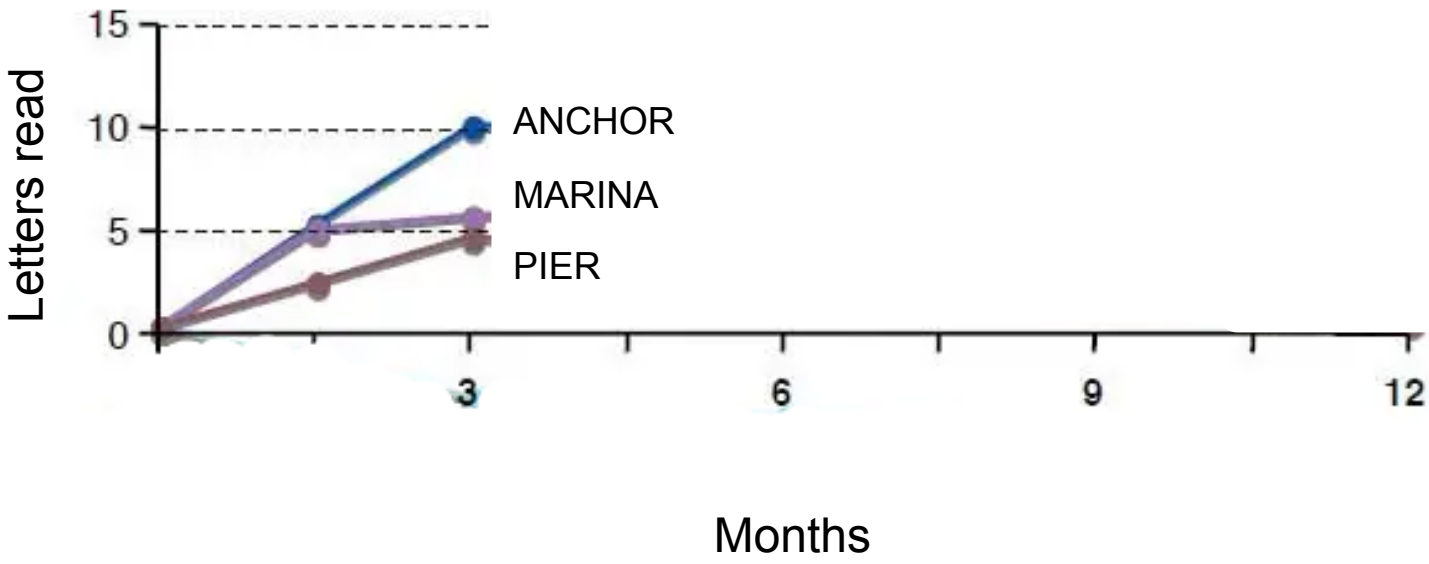
Average VA change (ETDRS letters)	↑2.9	↑**4.3**	↓8.7

*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).

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

What were the dosing schedules?

ARMD



PIER: Results at 3 months

ARMD

PIER

One Year	0.3 mg	0.5 mg	Sham
Average VA change (ETDRS letters)	↓1.6	?	↓16.3

*What about the **one-year results**?*

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

What were the dosing schedules?

ARMD

PIER

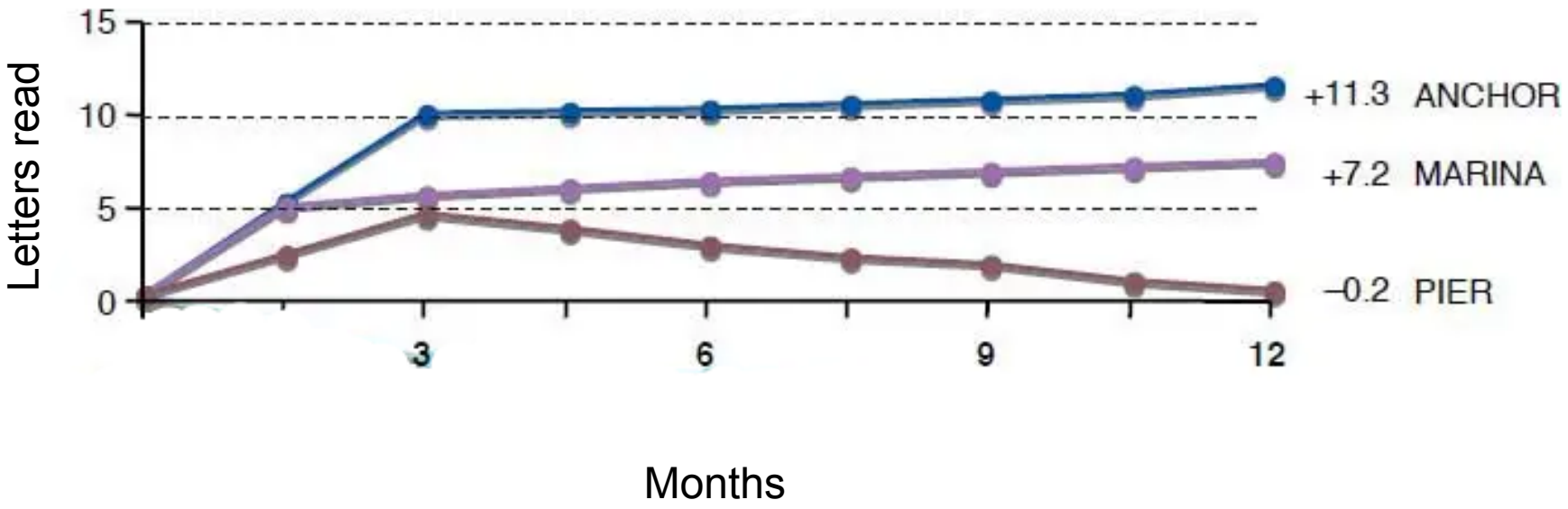
One Year	0.3 mg	0.5 mg	Sham
Average VA change (ETDRS letters)	↓1.6	↓**0.2**	↓16.3

*What about the **one-year results**?*
These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels.

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

What were the dosing schedules?

ARMD



PIER: Results at 12 months

ARMD

PIER

One Year	0.3 mg	0.5 mg	Sham
Average VA change (ETDRS letters)	↓1.6	↓**0.2**	↓16.3

*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.

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

What were the dosing schedules?

No question—advance when ready

ARMD

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One Year	0.3 mg	0.5 mg	Sham
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*What about the **one-year results**?*

These are much less encouraging—after dropping to q3-month injections, VA had returned to baseline levels. 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.**

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

What were the dosing schedules?

No question—advance when ready

ARMD

PrONTO

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.

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

ARMD

PrONTO RESULTS

MARINA/ ANCHOR RESULTS

PrONTO

	Year One		*MARINA*	*ANCHOR*
Lost <15 letters	?		95%	96%
Gained >15 letters	?		34%	40%
Mean ↑ in letters	?		7.2	11.3

For comparison purposes, here are the year-one results from the MARINA and ANCHOR trials.

ARMD

PrONTO RESULTS

MARINA/ ANCHOR RESULTS

PrONTO

	Year One		*MARINA*	*ANCHOR*
Lost <15 letters	**95%**		**95%**	**96%**
Gained >15 letters	**35%**		**34%**	**40%**
Mean ↑ in letters	**9.3**		**7.2**	**11.3**

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*)…

ARMD

PrONTO RESULTS

MARINA/ ANCHOR RESULTS

PrONTO

	Year One		*MARINA*	*ANCHOR*
Lost <15 letters	**95%**		**95%**	**96%**
Gained >15 letters	**35%**		**34%**	**40%**
Mean ↑ in letters	**9.3**		**7.2**	**11.3**
Mean # of injections	**5.6**		**13**	**13**

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*)… but **with fewer than *half* the number of injections!**

ARMD

The PIER and PrONTO studies (and others) were undertaken to explore alternative tx schedules to the effective-but-impractical ‘continuous monthly’ schedule employed in MARINA and ANCHOR.

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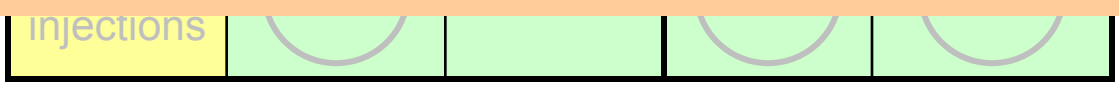

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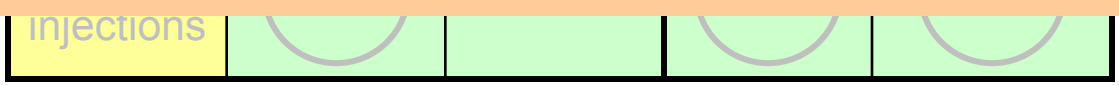

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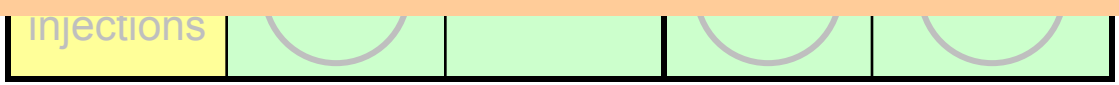

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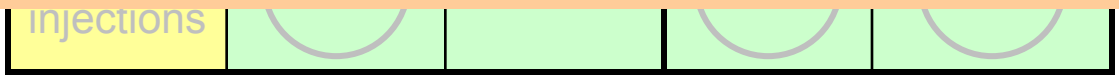

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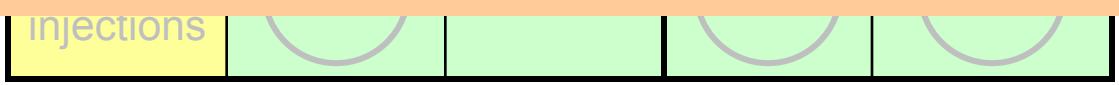

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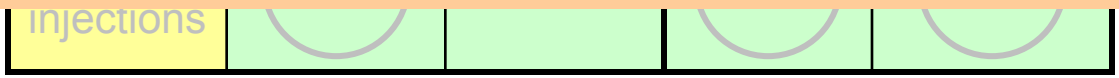
Enter the *treat-and-extend* approach.



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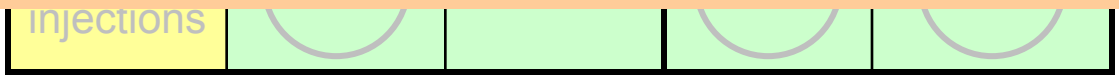
Enter the *treat-and-extend* approach. While specifics vary among clinicians, most do something along these lines: First, the pt is treated monthly until the macula is 'dry.' Once dryness has been achieved, the time until the next visit is extended to 6 weeks. At the 6-week visit the pt is both ***evaluated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



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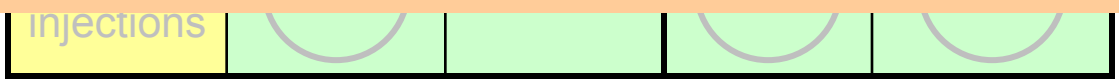

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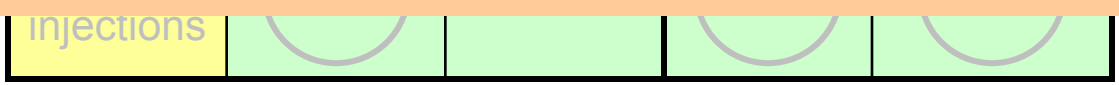
At present, most *clinicians employ some version of treat-and-extend with* most *of their pts.*



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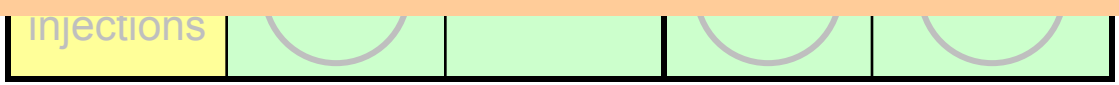
At present, most *clinicians employ some version of treat-and-extend with* most *of their pts.*

<u>Anti-VEGF injection scheduling tl;dr</u>

Continuous: Pt evaluated **and** treated monthly

PRN*:* Pt evaluated monthly, treated **if** evidence active dz

Treat and extend: After dz resolution achieved, interval between eval/tx visits gradually increased to the max the pt can sustain w/o recurrence (or 12 weeks, whichever comes first)



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Anti-VEGF injection scheduling tl;dr

Continuous: Pt evaluated **and** treated monthly

PRN: Pt evaluated monthly, treated **if** evidence active dz

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)*

En so dryn ek visit the pt is both **evaluated *and injected***. If the 6-week evaluation revealed that the macula remained dry, the interval until the next visit is extended to 8 weeks. Again, at the 8-week visit the pt is both **evaluated *and injected***, and if the eval indicates she remained dry, the interval until the next visit is extended by another 2 weeks to 10. If at any point the evaluation revealed the return of edema/heme, the pt's inter-tx interval is rolled back to whatever was the longest progression-free interval they had achieved. (Many clinicians use an inter-tx interval of 12 weeks as a cap, ie, they don't try to extend beyond it.)

At present, most *clinicians employ some version* d

injections

*But that's a topic for another slide-set

ARMD

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.

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

What is a monoclonal antibody?
Antibodies produced by a set of

What
Affinity
which
repeatedly exposed to the antigen of interest, resulting in antibody crops with progressively greater affinity for the antigen

What is the 'parent' antibody from which the ranibizumab fragment is derived?

What does fragment *mean in this context?*
Ranibizumab is *not* a complete antibody; rather, it consists of a portion—or *fragment*—of an antibody

ARMD

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

What is a monoclonal antibody?
Antibodies produced by a set of

What c
Affinity
which
repeatedly exposed to the antigen of interest, resulting in antibody crops with progressively greater affinity for the antigen

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

ARMD

Note: Different drug!

Bevacizumab

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

ARMD

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

Bevacizumab

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

ARMD

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

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

ARMD

You know bevacizumab is **humanized** because of the infix

*Bevaci**zu**mab*

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You know it is a **monoclonal antibody** because of the suffix

ARMD

Bevacizumab

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

Why did we lose the term affinity matured?

ARMD

Bevacizumab

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

ARMD

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Why did we lose the word fragment*?*

ARMD

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

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

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

ARMD

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ARMD

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

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ARMD

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

Bevacizumab

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ARMD

Which drug was created first—ranibizumab, or bevacizumab?

Bevacizumab

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Was bevacizumab developed to treat ARMD?

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Bevacizumab

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

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ARMD

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

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

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

ARMD

What were the key clinical trials demonstrating the safety and efficacy of **bevacizumab** *in the treatment of ARMD?*

ARMD

ZILCH

What were the key clinical trials demonstrating the safety and efficacy of **bevacizumab** *in the treatment of ARMD?*

NADA

To date there have been NO randomized, prospective clinical trials of intravitreal bevacizumab for the treatment of wet ARMD.

ARMD

ZILCH

What were the key clinical trials demonstrating the safety and efficacy of **bevacizumab** *in the treatment of ARMD?*

NADA

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).

ARMD

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?

ARMD

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?

CATT

ARMD

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CATT

What does CATT *stand for?*

ARMD

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CATT

What does CATT *stand for?*
***C**omparison of **A**ge-related Macular Degeneration **T**reatments **T**rial*

ARMD

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CATT

What doses of each were used?

Ranibizumab:
Bevacizumab:

ARMD

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CATT

What doses of each were used?

Ranibizumab: 0.5 mg
Bevacizumab: 1.25 mg

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What were the two dosing schedules?

Continuous, and PRN

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Was another intervention involved?

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*What was the **secondary** outcome measure?*	

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Was another intervention involved?	No
*What was the **primary** outcome measure?*	Mean change in VA
*What was the **secondary** outcome measure?*	Number of treatments
*What was **another** oft-discussed secondary outcome measure?*	Incidence of adverse events

ARMD

CATT RESULTS

Average Number of Letters Gained at One Year

	Ranibizumab	Bevacizumab
Every Month Dosing	*?*	*?*
PRN Dosing		

ARMD

CATT RESULTS

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	Ranibizumab	Bevacizumab
Every Month Dosing	**8.5**	**8.0**
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ARMD

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These are statistically equivalent

ARMD

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ARMD

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ARMD

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These are statistically equivalent as well

ARMD

CATT RESULTS

Average Number of Letters Gained at One Year

	Ranibizumab	Bevacizumab
Every Month Dosing	**8.5**	**8.0**
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However, PRN bevacizumab yielded a significantly lower average gain when compared to monthly bevacizumab…

ARMD

CATT RESULTS

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Every Month Dosing	**8.5**	**8.0**
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However, PRN bevacizumab yielded a significantly lower average gain when compared to monthly bevacizumab… or when compared to monthly ranibizumab.

ARMD

CATT RESULTS

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

	Ranibizumab	Bevacizumab
Every Month Dosing	**8.5(12)**	**8.0(12)**
PRN Dosing	**6.8(?)**	**5.9(?)**

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?

ARMD

CATT RESULTS

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

	Ranibizumab	Bevacizumab
Every Month Dosing	**8.5(12)**	**8.0(12)**
PRN Dosing	**6.8(7)**	**5.9(8)**

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.

ARMD

CATT RESULTS

What about adverse events?

ARMD

CATT RESULTS

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.

ARMD

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Is this finding concerning enough to warrant using ranibizumab preferentially?

ARMD

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Is this finding concerning enough to warrant using ranibizumab preferentially?
Probably not. As of this writing, the opinion seems to be that the increased adverse effects were probably happenstance. This opinion is based on two facts:
1)

2)

ARMD

CATT RESULTS

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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** bavacizumab trials (in which systemic concentrations were at least 500 times greater).
2)

ARMD

CATT RESULTS

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2) The reported adverse events did not correlate with bevacizumab dosing, as would be expected if a causal relationship held.

ARMD

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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

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ARMD

Aflibercept *is a* one word (adj.) two words (adj. and final noun)

ARMD

Aflibercept *is a recombinant fusion protein*

ARMD

Aflibercept *is a recombinant fusion protein*

What is a fusion protein*?*

ARMD

Aflibercept *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

ARMD

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

Aflibercept *is a recombinant fusion protein*

ARMD

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

Aflibercept *is a recombinant fusion protein*

ARMD

*What does the suffix –**cept** indicate?*

Afliber**cept** *is a recombinant fusion protein*

ARMD

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

Afliber**cept** *is a recombinant fusion protein*

ARMD

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

Afli**ber**cept *is a recombinant fusion protein*

What does the infix –**ber**- *indicate?*

ARMD

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

Afli**ber**cept *is a recombinant fusion protein*

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

ARMD

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

Aflibercept *is a recombinant fusion protein*

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

Spell it out for me—what does it mean to say aflibercept 'mimics the VEGF receptor'?
Put another way: How does aflibercept work?

ARMD

What does the suffix –**cept** *indicate?*
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Spell it out for me—what does it mean to say aflibercept 'mimics the VEGF receptor'?
Put another way: How does aflibercept work?
Aflibercept is a **decoy receptor** that locks up unbound VEGF in the retinal space before it (the VEGF) can find an actual VEGF receptor on a target structure.

ARMD

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ARMD

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That the drug functions by mimicking a **receptor molecule**

Aflibercept *is a recombinant fusion protein*

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Spell it out for me—what does it mean to say aflibercept 'mimics the VEGF receptor'?
Put another way: How does aflibercept work?
Aflibercept is a **decoy receptor** that locks up unbound VEGF in the retinal space before it (the VEGF) can find an actual VEGF receptor on a target structure. This strategy is referred to as '**VEGF trap**.'

ARMD

Aflibercept *is a recombinant fusion protein*

Which isoforms of VEGF-A does aflibercept bind?

ARMD

Aflibercept *is a recombinant fusion protein*

Which isoforms of VEGF-A does aflibercept bind?

All of them

ARMD

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

ARMD

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

ARMD

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Placental growth factor (PLGF)

ARMD

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All of them

Of bevacizumab, ranibizumab and aflibercept, which binds VEGF-A with the greatest affinity?
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This ability to bind PLGF may account for the fact that aflibercept is effective in some cases of *ranibizumab-refractory CNVM*

e
pathogenesis of CNVM—what is it?
Placental growth factor (PLGF)

ARMD

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

?

ARMD

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

VIEW

ARMD

What ~~was~~ were the key clinical trials demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?

VIEW1

VIEW2

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.

ARMD

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

VIEW

What does VIEW *stand for?*

ARMD

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

VIEW

What does VIEW *stand for?*
The **V**EGF Trap-Eye:
Investigation of **E**fficacy
and Safety in **W**et ARMD

ARMD

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

VIEW

What doses of aflibercept were used?

ARMD

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

VIEW

What doses of aflibercept were used?

Either 0.5 or 2 mg
by intravitreal injection

ARMD

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ARMD

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VIEW

What doses of aflibercept were used?

Either 0.5 or 2 mg
by intravitreal injection

What was the dosing schedule?

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

ARMD

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

ARMD

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by intravitreal injection

What was the dosing schedule?

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

Was another intervention involved?

ARMD

	VIEW
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?	
What doses of aflibercept were used?	Either 0.5 or 2 mg by intravitreal injection
What was the dosing schedule?	There were 3: a) 0.5 mg every 4 weeks, **or** b) 2 mg every 4 weeks, **or** c) 2 mg every 8 weeks after three q4 week loading doses
Was another intervention involved?	A control group received ranibizumab 0.5 mg every 4 weeks

ARMD

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

VIEW

The VIEW was a *noninferiority trial*, meaning the efficacy/safety of a new treatment was being compared to that of a 'gold standard' treatment. In other words, the VIEW had to demonstrate that aflibercept was *at least* as good and *at least* as safe as ranibizumab in order to gain approval.

Was another intervention involved?

A control group received ranibizumab 0.5 mg every 4 weeks

ARMD

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VIEW

The VIEW was a *noninferiority trial*, meaning the efficacy/safety of a new treatment was being compared to that of a 'gold standard' treatment. In other words, the VIEW had to demonstrate that aflibercept was *at least* as good and *at least* as safe as ranibizumab in order to gain approval. To do so required:

1) the presence of a ranibizumab arm in the study, and
2) that patients in the VIEW have lesions similar to those of the participants in the studies used to prove the safety and efficacy of ranibizumab in the first place (ie, the MARINA and ANCHOR studies).

Was another intervention involved?

A control group received ranibizumab 0.5 mg every 4 weeks

ARMD

	VIEW
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?	
What doses of aflibercept were used?	Either 0.5 or 2 mg by intravitreal injection
What was the dosing schedule?	There were 3: a) 0.5 mg every 4 weeks, **or** b) 2 mg every 4 weeks, **or** c) 2 mg every 8 weeks after three q4 week loading doses
Was another intervention involved?	A control group received ranibizumab 0.5 mg every 4 weeks
*What was the **primary** outcome measure?*	

ARMD

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What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?	
What doses of aflibercept were used?	Either 0.5 or 2 mg by intravitreal injection
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Was another intervention involved?	A control group received ranibizumab 0.5 mg every 4 weeks
*What was the **primary** outcome measure?*	Proportion of patients **losing** <15 ETDRS letters

ARMD

	VIEW
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?	
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What was the dosing schedule?	There were 3: a) 0.5 mg every 4 weeks, **or** b) 2 mg every 4 weeks, **or** c) 2 mg every 8 weeks after three q4 week loading doses
Was another intervention involved?	A control group received ranibizumab 0.5 mg every 4 weeks
*What was the **primary** outcome measure?*	Proportion of patients **losing** <15 ETDRS letters
*What was the **secondary** outcome measure?*	

ARMD

	VIEW
What was the key clinical trial demonstrating the safety and efficacy of aflibercept in the treatment of ARMD?	
What doses of aflibercept were used?	Either 0.5 or 2 mg by intravitreal injection
What was the dosing schedule?	There were 3: a) 0.5 mg every 4 weeks, **or** b) 2 mg every 4 weeks, **or** c) 2 mg every 8 weeks after three q4 week loading doses
Was another intervention involved?	A control group received ranibizumab 0.5 mg every 4 weeks
*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

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	*?%*	*?%*	*?%*	*?%*
Mean gain in ETDRS letters read				

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
Mean gain in ETDRS letters read				

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
Mean gain in ETDRS letters read	?	?	?	?

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
Mean gain in ETDRS letters read	**8.3**	**9.2**	**8.4**	**8.7**

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	96%	95%	**95%**	**94%**
Mean gain in ETDRS letters read	8.3	9.2	**8.4**	**8.7**

The key finding is that **q8 weeks** aflibercept worked just as well as **monthly** ranibizumab.

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
Mean gain in ETDRS letters read	**8.3**	**9.2**	**8.4**	**8.7**

VIEW study: Year Two Results

The VIEW was carried into a second year. The basic Year 2 study criteria were:

1) Participants remained in the same treatment condition
2) Participants were evaluated monthly and treated PRN
3) All participants were treated at least every 12 weeks

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
Mean gain in ETDRS letters read	**8.3**	**9.2**	**8.4**	**8.7**

VIEW study: Year Two Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	***?%***	***?%***	***?%***	***?%***
Mean gain in ETDRS letters read				

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
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VIEW study: Year Two Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**91%**	**92%**	**92%**	**92%**
Mean gain in ETDRS letters read				

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
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Lost <15 letters	**91%**	**92%**	**92%**	**92%**
Mean gain in ETDRS letters read	***?***	***?***	***?***	***?***

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**96%**	**95%**	**95%**	**94%**
Mean gain in ETDRS letters read	**8.3**	**9.2**	**8.4**	**8.7**

VIEW study: Year Two Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	**91%**	**92%**	**92%**	**92%**
Mean gain in ETDRS letters read	**6.6**	**7.6**	**7.6**	**7.9**

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
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	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	91%	92%	**92%**	**92%**
Mean gain in ETDRS letters read	6.6	7.6	**7.6**	**7.9**

As with the Year One data, the key finding is that q8 weeks aflibercept worked **just as well** as monthly ranibizumab.

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	96%	95%	**95%**	**94%**
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	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost <15 letters	91%	92%	**92%**	**92%**
Mean gain in ETDRS letters read	6.6	7.6	**7.6**	**7.9**

Also of note is the fact that the Year Two results are similar to those of Year One

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost lett				
Mean gain in ETDRS letters read	8.3	9.2	8.4	8.7
Mean number of treatments			?	?

(Determined by study protocol)

VIEW study: Year Two Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost lette				
Mean gain in ETDRS letters read	6.6	7.6	7.6	7.9
Mean number of treatments			?	?

(Determined by drug efficacy)

Another much-anticipated outcome concerned the **average number of treatments** required in the q8 week aflibercept vs ranibizumab conditions.

ARMD

VIEW study: Year One Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost lett				
Mean gain in ETDRS letters read	8.3	9.2	8.4	8.7
Mean number of treatments			**7**	**12**

(Determined by study protocol)

VIEW study: Year Two Results

	0.5 mg q4 week	2.0 mg q4 week	2.0 mg q8 week	Ran-bizu-mab
Lost lette				
Mean gain in ETDRS letters read	6.6	7.6	7.6	7.9
Mean number of treatments			**4.2**	**4.7**

(Determined by drug efficacy)

Another much-anticipated outcome concerned the **average number of treatments** required in the q8 week aflibercept vs ranibizumab conditions

ARMD

- Age-related macular degeneration is the #1 cause of blindness in adults age 50+ in resource-rich nations
- Age is the strongest risk factor for ARMD
- The clinical hallmark of ARMD is the presence of drusen in the macula
- There are two types: *Nonexudative* and *exudative*
- RPE abnormalities in ARMD are typical
- Photoreceptors in ARMD are abnormal as well
- The pathogenesis of ARMD is not well understood; that said, the complement system is strongly implicated in it
- VEGF plays a key role in exudative ARMD; likewise, interdicting VEGF is key in managing it
- Nonexudative ARMD is vs isn't treatable at present

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- Nonexudative ARMD isn't treatable at present
- The AREDS found that micronutrient supplementation reduces the likelihood of exudative ARMD in at-risk pts

Q

ARMD

- *ARMD: The AREDS*
  - AREDS is the

write it out

A

ARMD

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

Q

ARMD

- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - ?
    - ?
    - ?
    -
    -

antioxidants

minerals

A

ARMD

- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C
    - Vitamin E
    - β-carotene
    -
    -

antioxidants

minerals

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- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
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    - Vitamin E *dose?*
    - β-carotene *dose?*
    -
    -

antioxidants

minerals

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ARMD

- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - β-carotene 15 mg

    } ***antioxidants***
    -
    -

    } *minerals*

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    - ?
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    } *antioxidants*
    - Zinc
    - Cupric oxide

    } ***minerals***

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    } *antioxidants*
    - Zinc *dose?*
    - Cupric oxide *dose?*

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    } *antioxidants*
    - Zinc 80 mg
    - Cupric oxide 2 mg

    } ***minerals***

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    - Vitamin C 500 mg
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    - β-carotene 15 mg

    } *antioxidants*
    - Zinc 80 mg
    - Cupric oxide 2 mg

    } *minerals*
  - **Study findings:**
    - Patients with [severity of dz] ARMD had a [%] reduced risk of advanced disease and vision loss

A

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- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
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    - Zinc 80 mg
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    minerals
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss

Q

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- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
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    antioxidants
    - Zinc 80 mg
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    minerals
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with severity ARMD: No benefit

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    - Vitamin C 500 mg
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    - Zinc 80 mg
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    } *minerals*
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit

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    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - β-carotene 15 mg

    antioxidants
    - Zinc 80 mg
    - Cupric oxide 2 mg

    minerals
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit
  - Note: Don't give AREDS supplements to pt population

Q

ARMD

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  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - β-carotene 15 mg

    antioxidants
    - Zinc 80 mg
    - Cupric oxide 2 mg

    minerals
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit
  - Note: Don't give AREDS supplements to smokers

A

ARMD

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  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - β-carotene 15 mg

    } *antioxidants*
    - Zinc 80 mg
    - Cupric oxide 2 mg

    } *minerals*
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit
  - Note: Don't give AREDS supplements to smokers
    - an AREDS anti-ox increases the risk of lung Ca in these patients

A

ARMD

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  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - β-carotene 15 mg

    antioxidants
    - Zinc 80 mg
    - Cupric oxide 2 mg

    minerals
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit
  - Note: Don't give AREDS supplements to smokers
    - β-carotene increases the risk of lung Ca in these patients

ARMD

- *ARMD: The AREDS*
  - AREDS is the Age-Related Eye Disease Study
  - Looked at dietary supplements and ARMD:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - β-carotene 15 mg
    - Zinc
    - Cupric oxide 2 mg

    antioxidants

    minerals

    Next, let's drill down on the AREDS2
  - **Study findings:**
    - Patients with intermediate/advanced dry ARMD had a 25% reduced risk of advanced disease and vision loss
    - Patients with no/early ARMD: No benefit
  - Note: Don't give AREDS supplements to smokers
    - β-carotene increases the risk of lung Ca in these patients

ARMD

- *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

Q

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed [ ] for β-carotene
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ ? & ?
    - Zinc 80 mg
    - Cupric oxide 2 mg

A

ARMD

- *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 *(These are the two xanthophylls employed)*
    - Zinc 80 mg
    - Cupric oxide 2 mg

Q

ARMD

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

?

A

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

Q

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

  - **Study findings:**
    - Reaffirmed vs Disputed results of the AREDS

A

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

  - **Study findings:**
    - Reaffirmed results of the AREDS

Q

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

  - **Study findings:**
    - Reaffirmed results of the AREDS
    - Xanthophylls [effective vs ineffective] substitute for β-carotene

A

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

  - **Study findings:**
    - Reaffirmed results of the AREDS
    - Xanthophylls suitable substitute for β-carotene

Q

ARMD

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

Omega-3 fatty acids

  - **Study findings:**
    - Reaffirmed results of the AREDS
    - **Xanthophylls suitable substitute for β-carotene**

*Why is **this** important?*

A

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ *Lutein & Zeaxanthin*
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

  - **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

Q

ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

  - **Study findings:**
    - Reaffirmed results of the AREDS
    - Xanthophylls suitable substitute for β-carotene
    - O3FAs effective vs ineffective at reducing risk of progression

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ARMD

- *ARMD: The AREDS2*
  - Follow-up to the AREDS
  - Subbed xanthophylls for β-carotene; added O3FAs:
    - Vitamin C 500 mg
    - Vitamin E 400 IU
    - ~~β-carotene~~ Lutein & Zeaxanthin
    - Zinc 80 mg
    - Cupric oxide 2 mg

Omega-3 fatty acids

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