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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Click Next button to begin module

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Objectives

Retinal imaging technology has allowed us to identify and analyse biomarkers that can be used to predict disease progression as well as response to therapy.

This module explores the use of OCT imaging technology to image, identify and analyse biomarkers in exudative AMD, as well as what they can tell us about the status of the disease.

Having completed this module, you will be able to:

- ✓ Identify the key purposes and benefits of identifying and using imaging biomarkers in exudative AMD
- ✓ List some of the important fluid and morphology candidates for biomarkers, and describe their role in managing exudative AMD
- ✓ Identify some of the potential future applications for SD-OCT in identifying and utilising biomarkers for exudative AMD

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Outline

This module is divided into the topics listed below; each is followed by a quiz if you chose this option on the first screen. Click next to begin. Revisit any section by clicking it here.

Click the buttons above to visit a specific topic or the next button below to visit all topics in order

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Exudative AMD: Biomarkers of Disease & Therapy

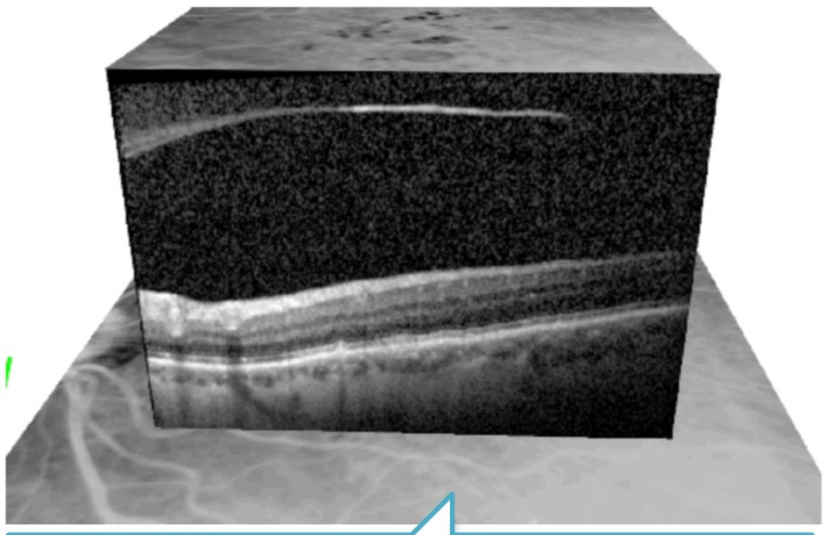
Multimodal OCT: Research to Routine

Introduction: Biomarkers in Retinal Disease

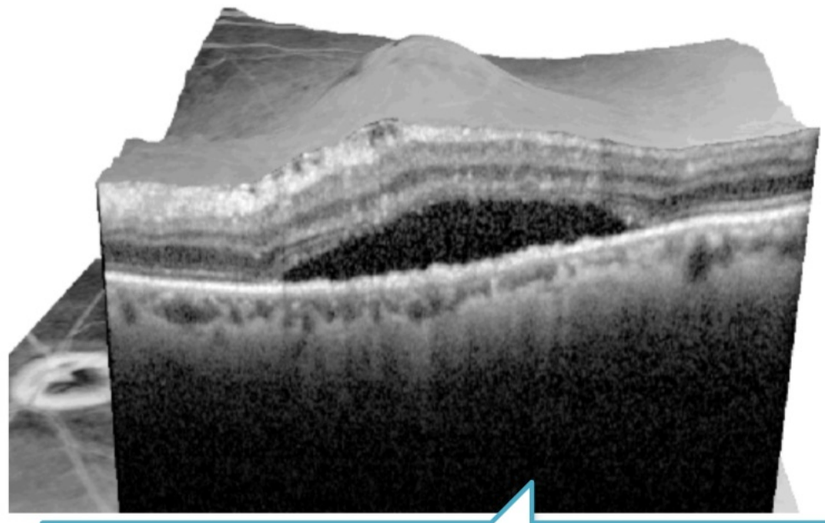
The development of imaging technology and techniques has allowed us to image, identify and analyse biomarkers of retinal disease.

Why is this important?
Consider these examples:

- What can we learn from these two different appearances?
- Can the interpretation of OCT morphology help us to capture the characteristics of the disease and to guide our treatment decisions?



Intraretinal cystoid fluid (IRC) and vitreomacular adhesion (VMA)



Pigment epithelial detachment (PED) and subretinal fluid (SRF).

Do you think these different morphologies of exudative AMD will lead to different outcomes?

- ○ Yes, different morphologies will have different effects
- ○ No, while they appear differently, the effects are similar

Submit

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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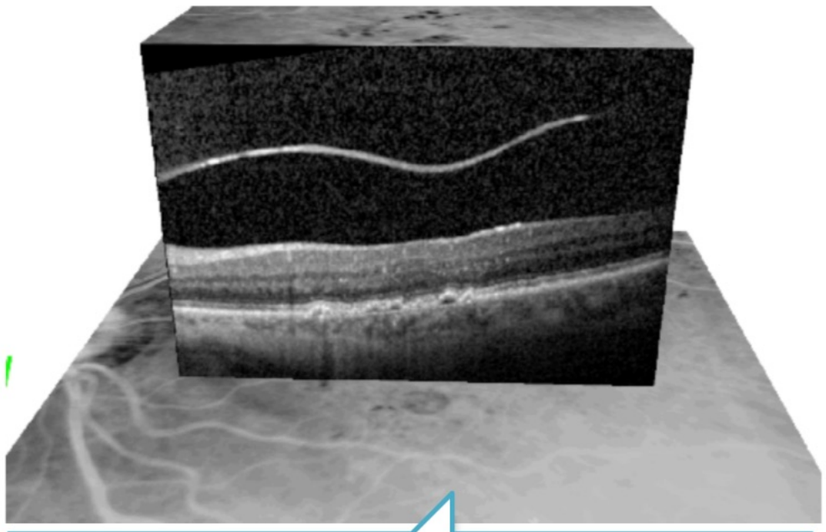
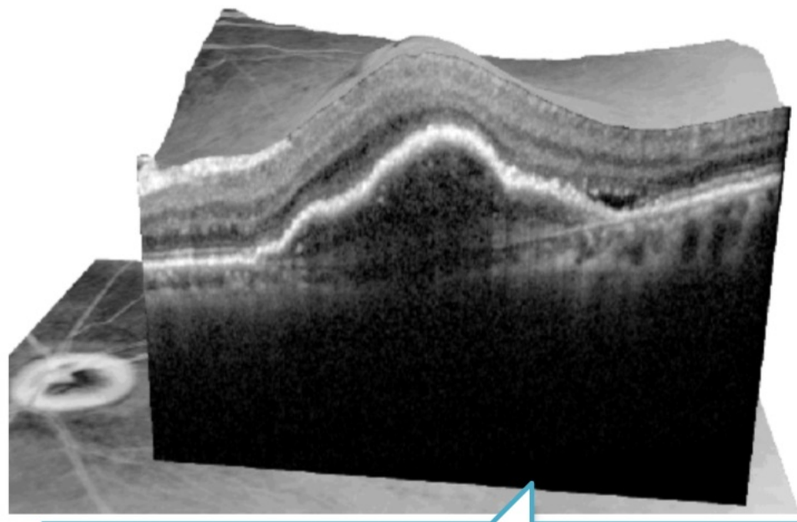


Intraretinal cystoid fluid (IRC) and vitreomacular adhesion (VMA)



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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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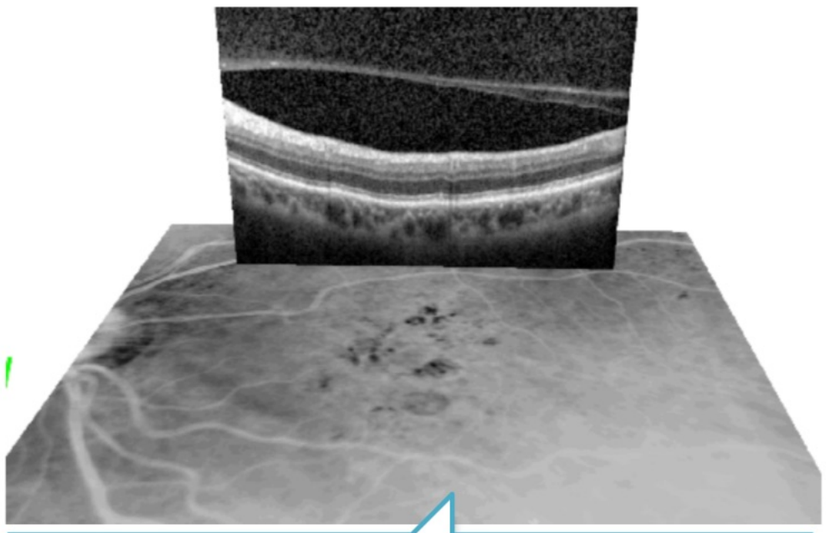
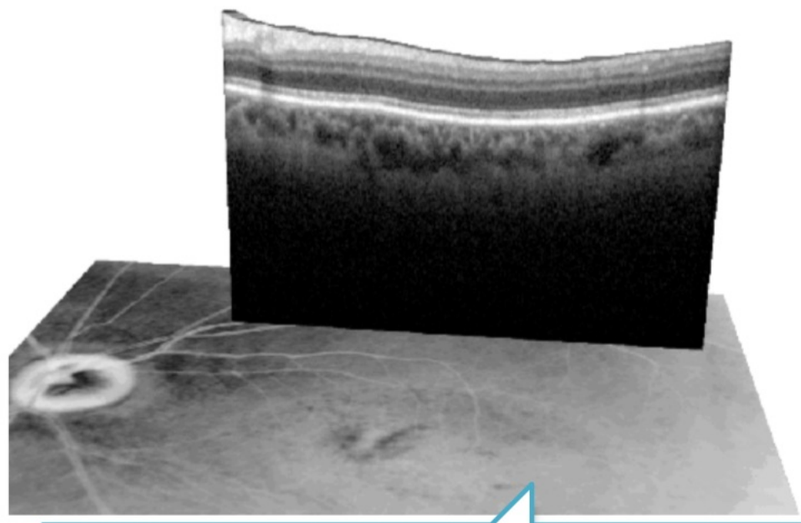


Intraretinal cystoid fluid (IRC) and



Pigment epithelial detachment (PED)
nal fluid (SRF).

Do you think these di

Y

N

That's right.

These different morphologies can lead to very different outcomes. In this module, we will explore:

- what we can learn from these differing appearances
- the interpretation of OCT morphology to capture characteristics of disease and guide treatment decisions

Continue

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

What are the Imaging Biomarkers in OCT?

There is a long list of biomarker candidates in OCT (i.e. what we look for), and also a number of targets (i.e. what the candidates will tell you about). This module will consider the candidates and targets listed below.

Candidates (What we look for)

Fluid

- Central retinal thickness
- Fluid
  - intraretinal
  - subretinal
  - sub-RPE

Morphology

- Subretinal hyperreflective material
- Photoreceptor status
- Vitreous

Targets (What we want to anticipate)

Function

- Visual function
  - Visual acuity
  - At presentation
  - During therapy

Treatment

- Treatment requirements
- Treatment regimens

Damage

- Development of atrophy / fibrosis

Why do you think predicting visual function and treatment response from retinal morphology is important?

- ○ There is prognostic value
- ○ More effective trial design
- ○ Efficient distribution of resources
- ○ All of these

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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Function

- Visual function
  - Visual acuity
  - At presentation
  - During therapy

Treatment

Damage

Why do you thin ant?

That's right.

Imaging biomarkers to predict visual function and treatment response from retinal morphology offers all of these benefits:

- **Prognostic value**
  - For patients and physicians
  - Managing expectations
- **Efficient distribution of resources**
  - The right treatment for the right patient
- **Effective trial design**
  - More precise endpoints

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

What Role do these Imaging Biomarkers Play?

The imaging biomarkers discussed in this module have been shown to have use in the roles listed below. Over the course of the module, we will explore how the candidates can be identified, and the hypotheses for their effectiveness in playing their roles.

Candidates (What we look for)	Role (What the candidate is predictive of)
• Central retinal thickness →	Limited value in prognosis

Fluid

• Fluid →	Visual function
• intraretinal →	Poor BCVA (gains)
• subretinal →	Better VA, less GA, stable disease, less treatment
• sub-RPE →	Not relevant for VA, at risk during PRN treatment

Morphology

• Subretinal hyperreflective material (SRHM) →	Poorer BCVA, poorer contrast sensitivity
• Outer retinal tubulations (ORT) →	Poorer BCVA, advanced tissue damage
• Photoreceptor status →	Predictive of baseline VA
• Vitreous →	PVD: less treatment, VMA: more treatment

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Module Progress:

Fluid Biomarkers in AMD

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Exudative AMD: Biomarkers of Disease & Therapy

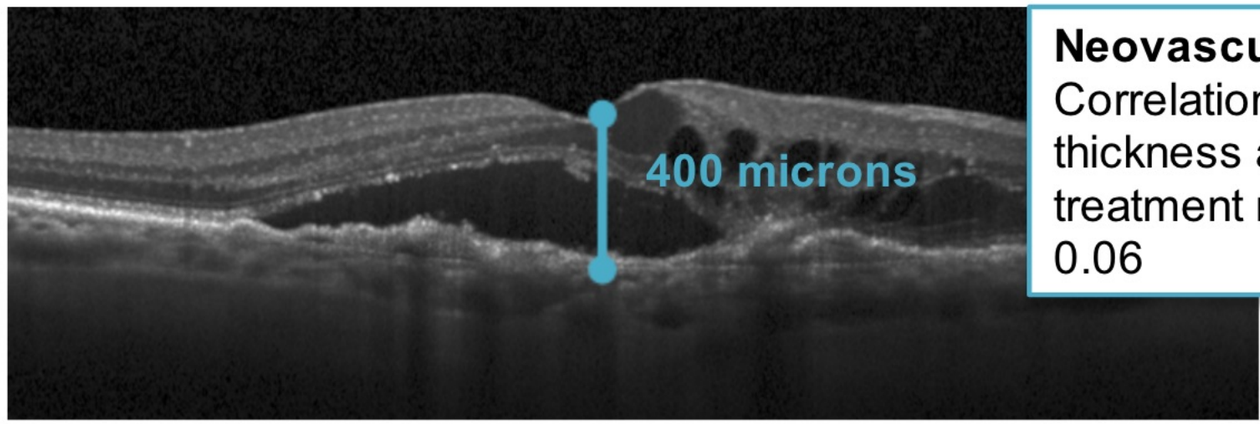
Multimodal OCT: Research to Routine

Introduction: Central Retinal Thickness vs Fluid Compartments

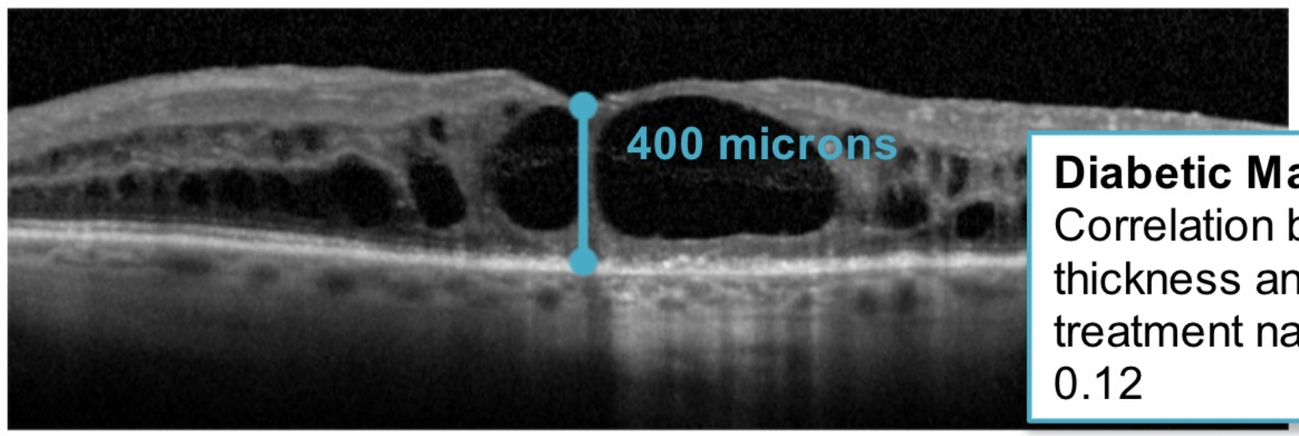
Central retinal thickness is not very useful as a biomarker in exudative AMD. It has a poor correlation to VA (6%). While diabetic macular edema is better, it is still not very useful.

As we will see, intraretinal cystoid fluid (IRC) and subretinal fluid (SRF) have very different effects on vision.

Therefore, they cannot be "summed up" in one measurement (central retinal thickness) .



Neovascular AMD: Correlation between retinal thickness and VA in treatment naive eyes: R^2 = 0.06



Diabetic Macular Edema: Correlation between retinal thickness and VA in treatment naive eyes: R^2 = 0.12

Do you think central retinal thickness has any role in the management of exudative AMD?

- Yes, it is useful to judge the response to therapy
- No, one should always measure individual fluid compartments instead

Submit

Central retinal thickness still has a role in judging response to therapy.

However, to better understand what is happening, one should consider the individual changes that occur in - or under - the retina.

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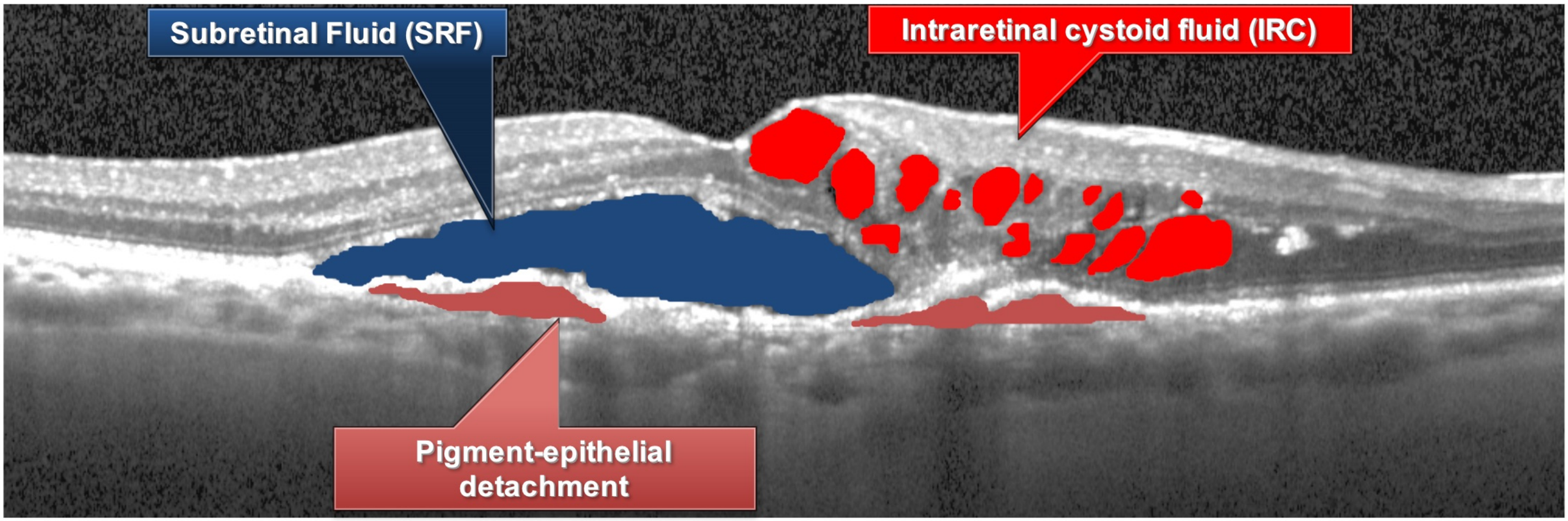
Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Fluid Compartments as Biomarkers

So, how do the different fluid compartments affect vision, and what can they tell us as biomarkers? In this topic, we will explore each in more detail.



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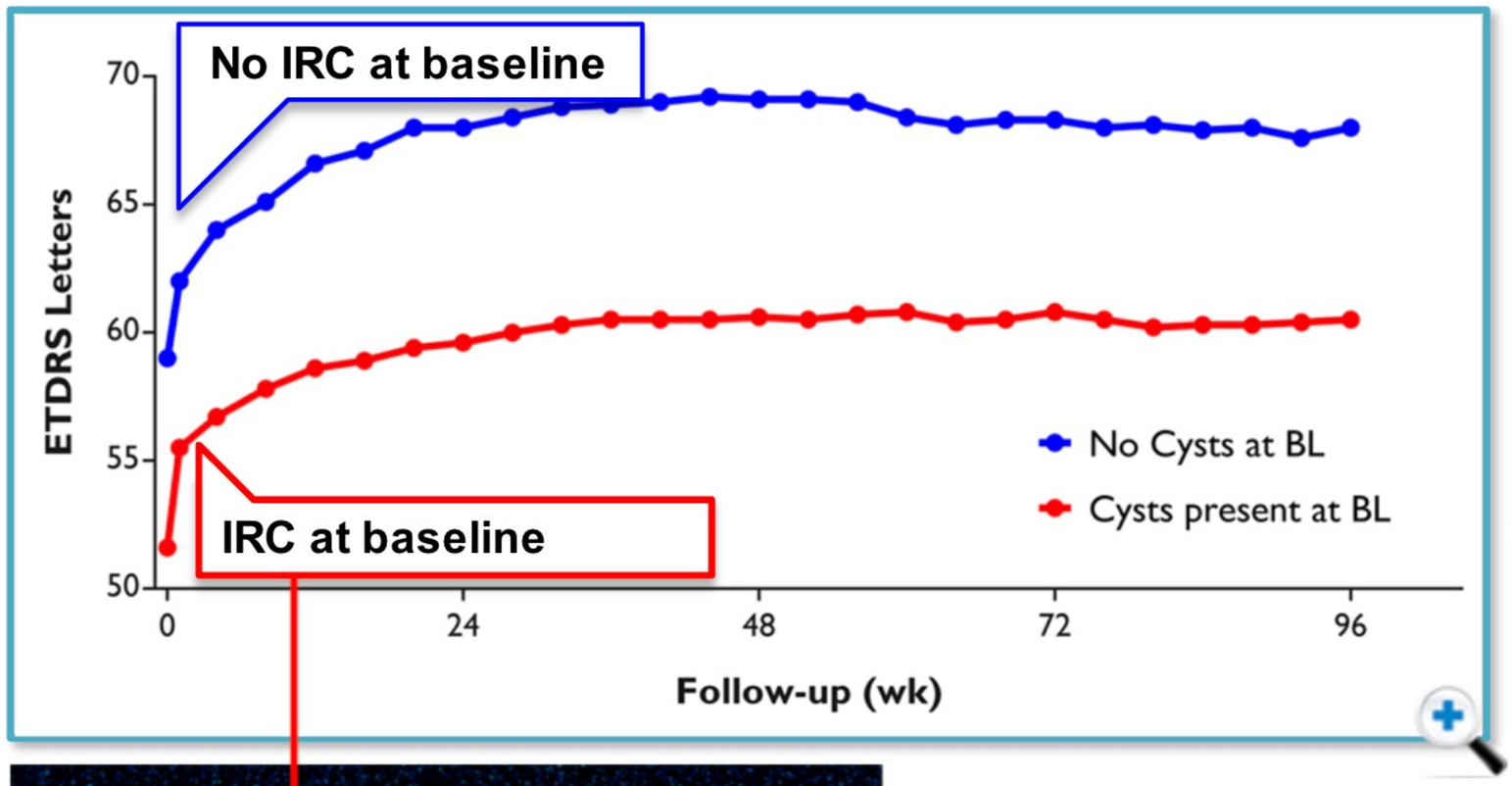
Multimodal OCT: Research to Routine

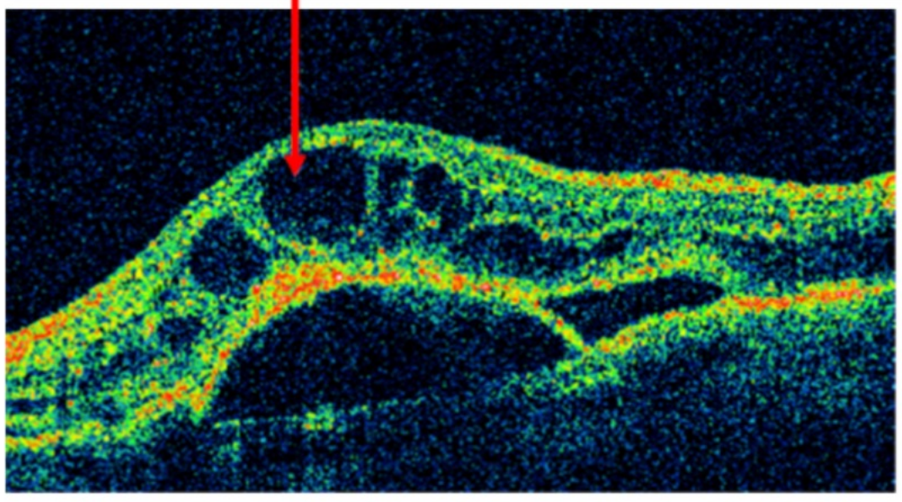
Intraretinal Cystoid Fluid (IRC)

Intraretinal fluid appears to be the most important of the fluid compartments.

Post-hoc analysis of large randomised clinical trials (where reading centres evaluate images in a standardised way) show patients who have **intraretinal cystic changes at baseline have 1 line less of visual acuity**, compared to patients without intraretinal changes.

This **relative loss of vision is maintained during the treatment phase**: these patients gain vision, but not as much as they would gain if they didn't have IRC.





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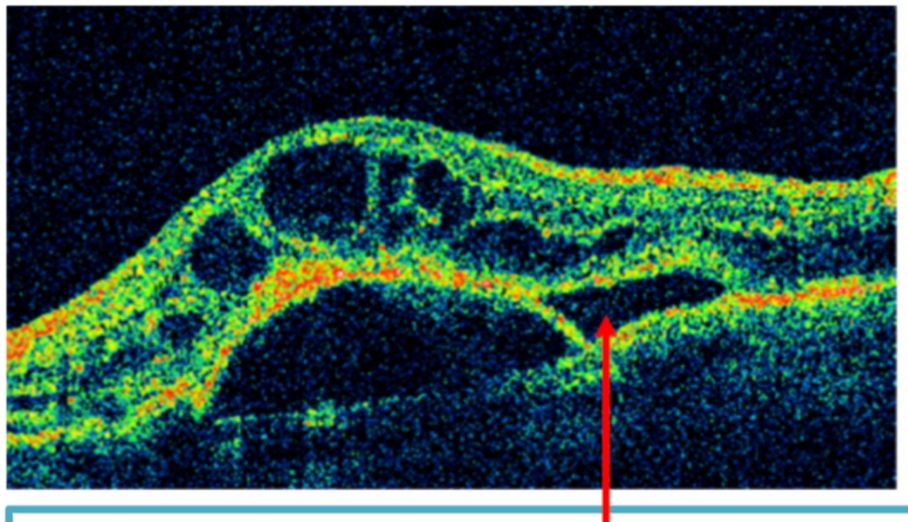
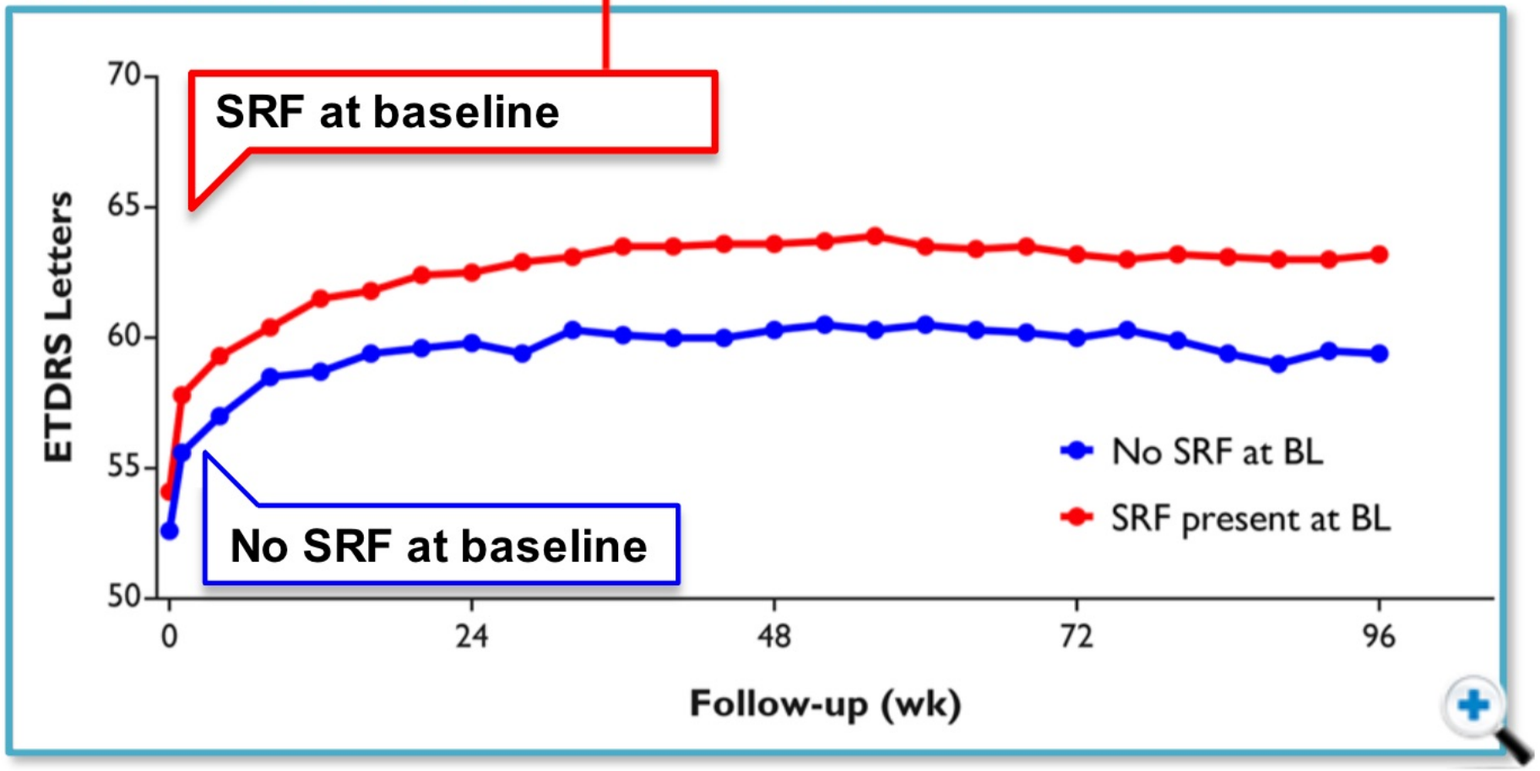
Subretinal Fluid

Subretinal fluid has a completely different effect than IRC.

As can be seen from the graph (perhaps surprisingly), patients with SRF at baseline had:

- slightly better vision at baseline
- much better vision gains during therapy





SRF in the EXCITE Trial

SRF: A "Protective" Factor?

Click the tabs to learn more about the effect of SRF on vision

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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SRF in the EXCITE Trial

SRF: A "Protective" Factor?

No SRF at baseline, frequent treatment arm (n=23)

No SRF at baseline, infrequent treatment arm (n=59)

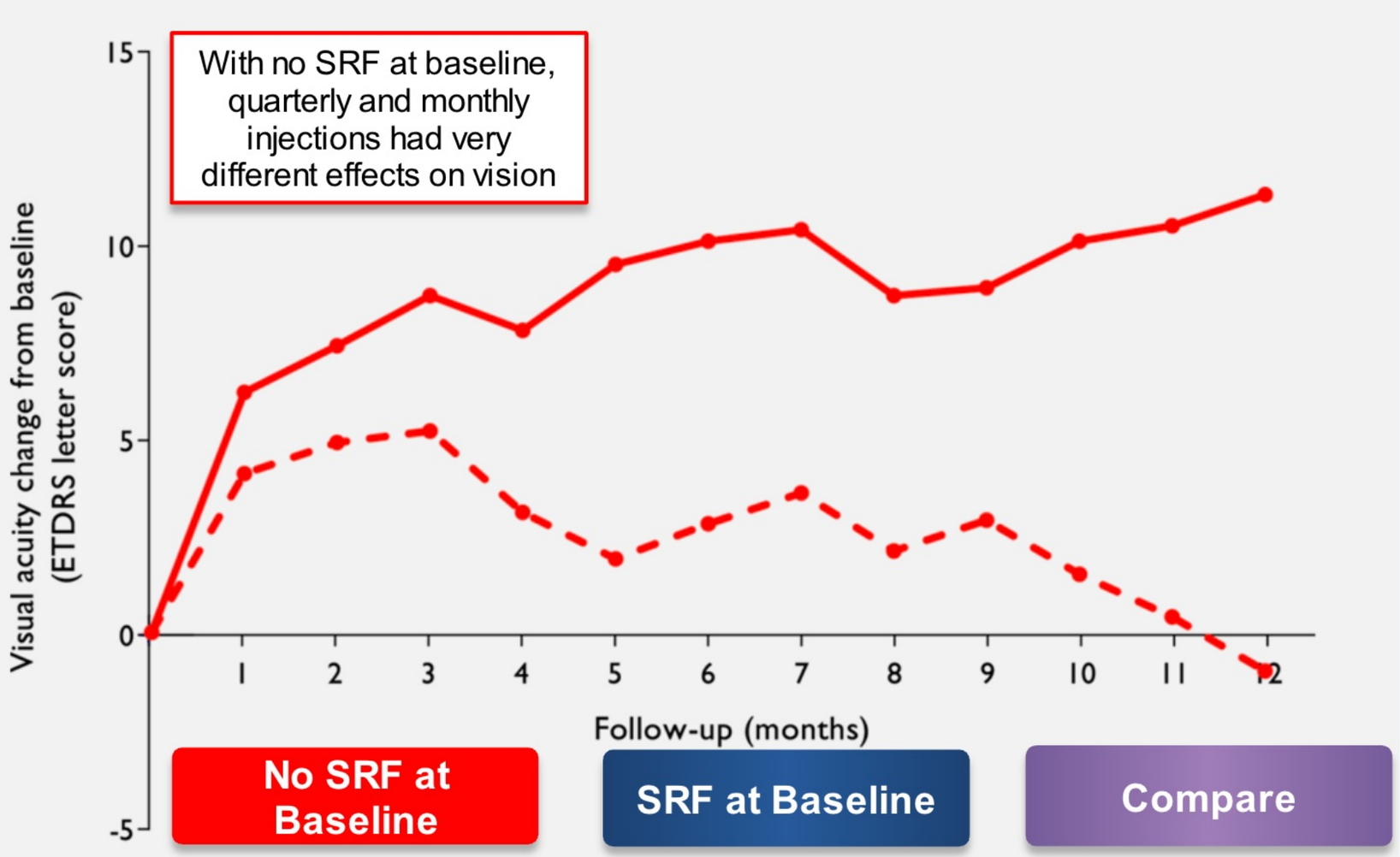
SRF at baseline, frequent treatment arm (n=71)

SRF at baseline, infrequent treatment arm (n=138)

Post Hoc Analysis: The EXCITE Trial

One aspect of the EXCITE trial was to compare vision of patients treated monthly with those treated quarterly. As can be seen in the graph, those treated monthly had much better results than those treated quarterly.

However, a different pattern emerges, when post-hoc analysis of those patients who had SRF is performed. Click the buttons below to learn more.



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Multimodal OCT: Research to Routine

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SRF in the EXCITE Trial

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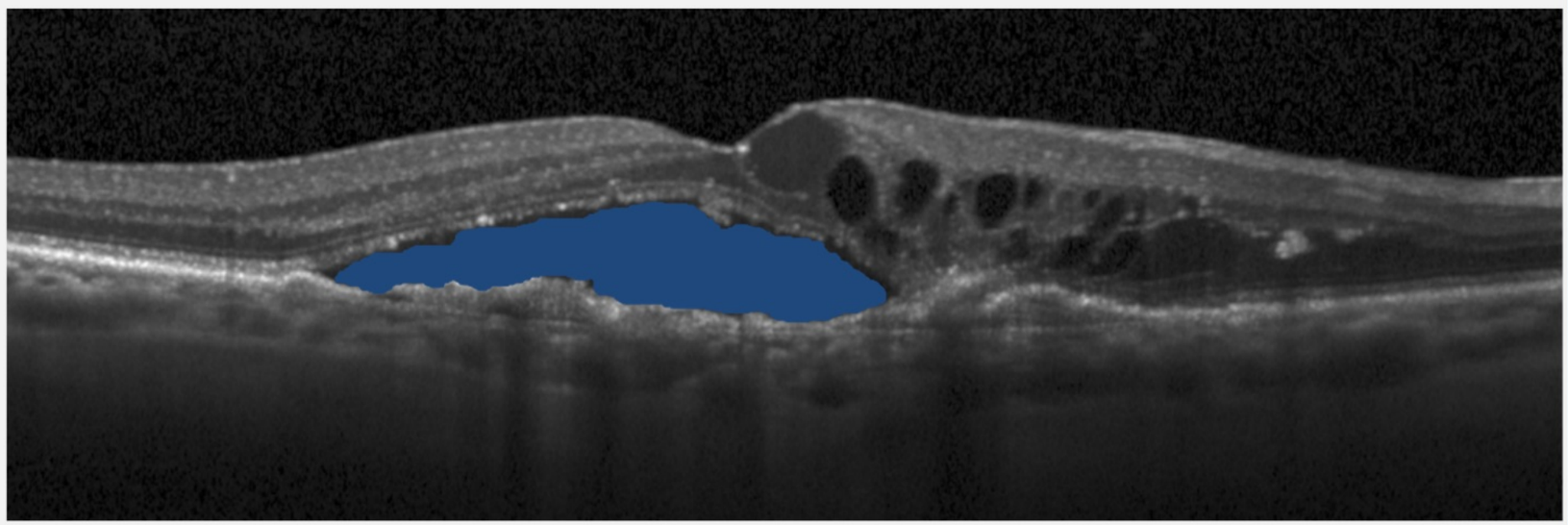
SRF: A "Protective" Factor?

Other findings may show subretinal fluid has some kind of a "protective" role. For example:
In the HARBOR trial, **eyes that had subretinal fluid at baseline had less development of geographic atrophy**.

In a recent study, **refractory subretinal fluid was not associated with vision loss**.

So we have to ask ourselves: could SRF may be a good sign - a sign of a **CNV that is still "perfused" to some extent** (such that it does not cause functional damage, but provides nutritional factors to the retina)?



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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Pigment Epithelial Detachment (PED)

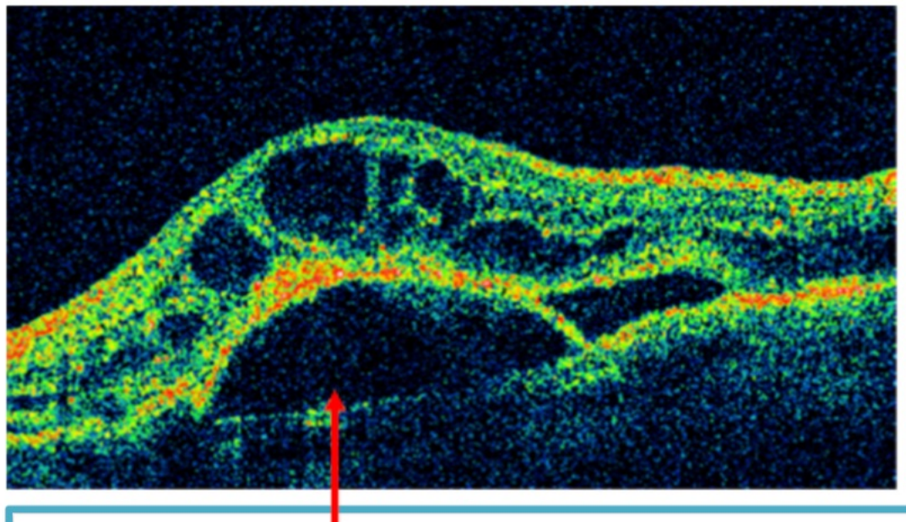
As can be seen in this graph, pigment epithelial detachment is observed to be not really relevant to a patients vision.

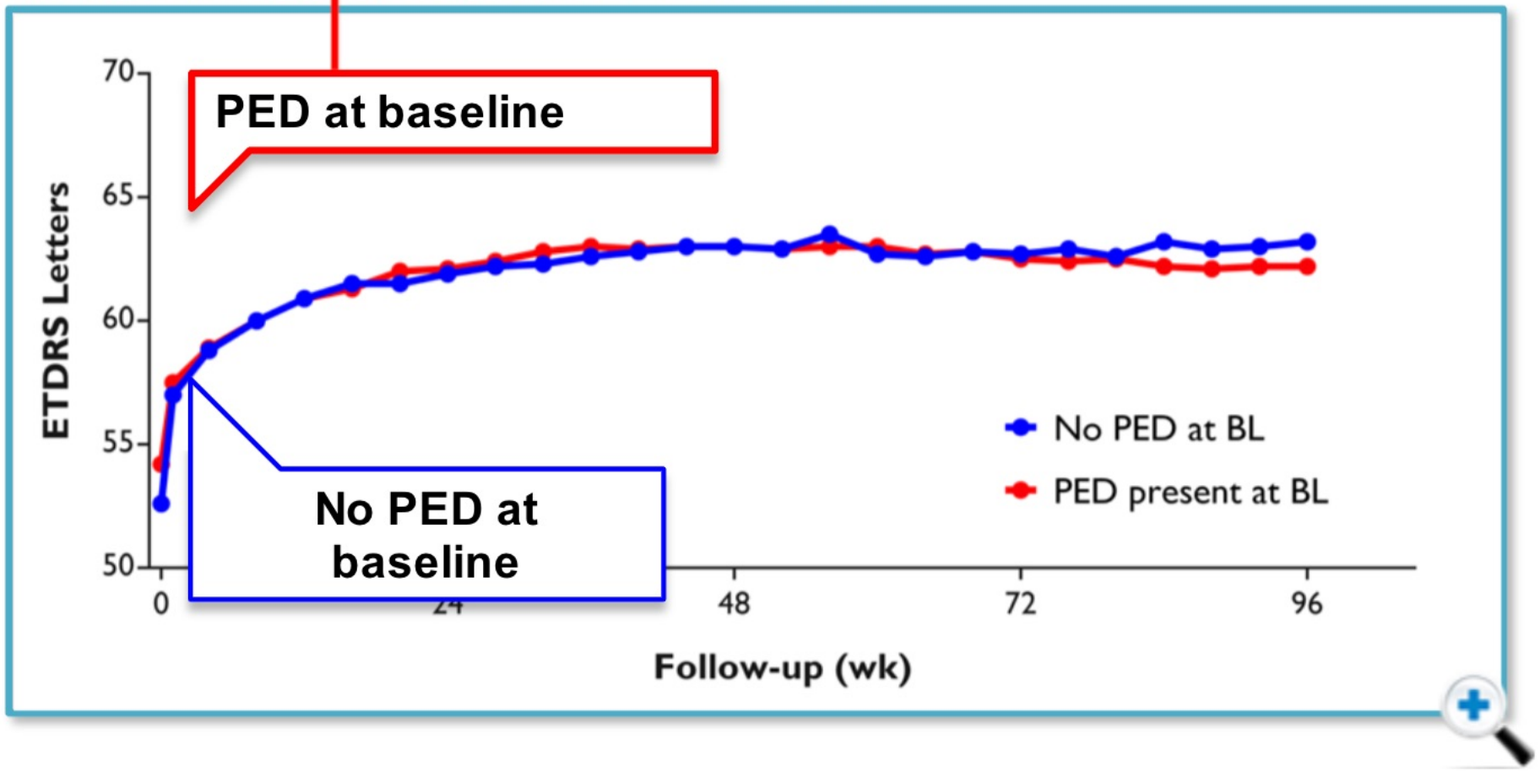
However, the **VIEW trial** (in which patients were dosed regularly in Year 1, then PRN in Year 2) found the only **patients to lose vision were those who had PED at baseline, and they lost vision in Year 2** (during PRN dosing).

So, what is happening here? Click the tabs to learn more.

PED in the VIEW Trial

PED & Vision: Pathophysiology





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Multimodal OCT: Research to Routine

- *No cysts, no PED*
- *No cysts, PED present*
- *Cysts present, no PED*
- *Cysts and PED present*

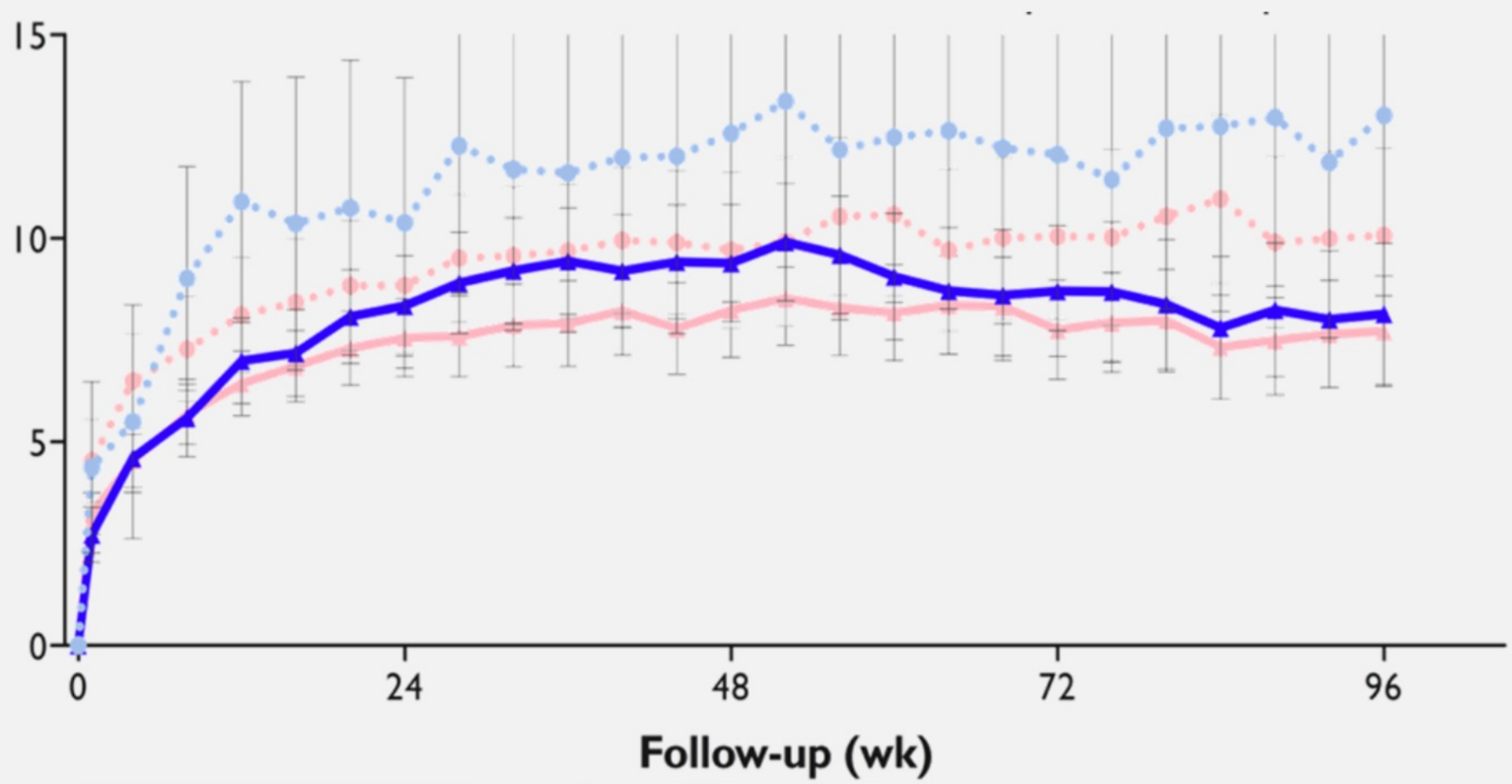
So, what is happening here? Click the tabs to learn more.

PED in the VIEW Trial

PED & Vision: Pathophysiology

BCVA change by OCT Morphology in VIEW

In the VIEW trial, it can be observed that only the group of patients who had PED at baseline lost vision - and this was in the second year (during PRN dosing).



IRC +/- PED at Baseline

PED vs PED with IRC Developing

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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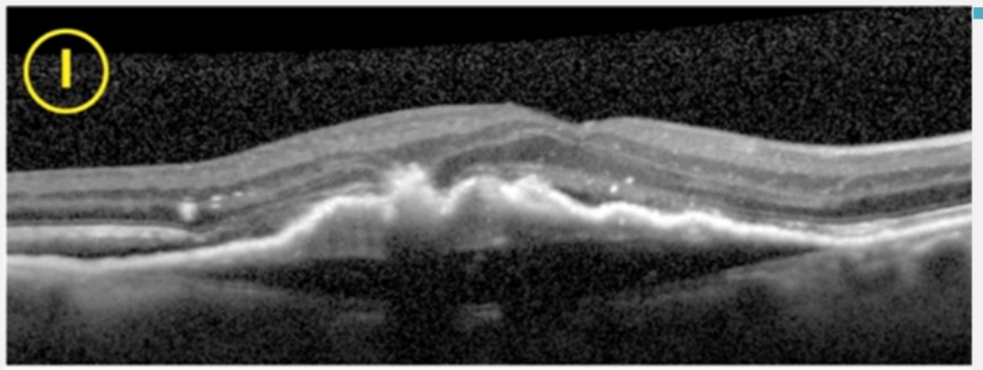
PED in the VIEW Trial

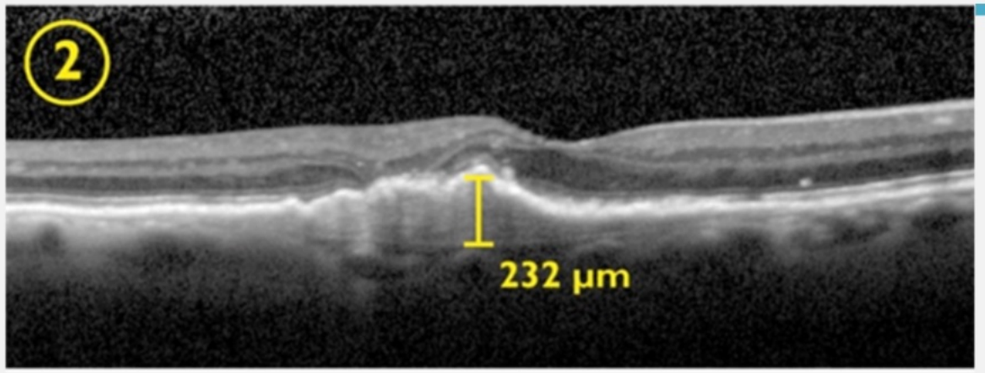
PED & Vision: Pathophysiology

What is the Hypothesis for PED leading to Vision Loss?

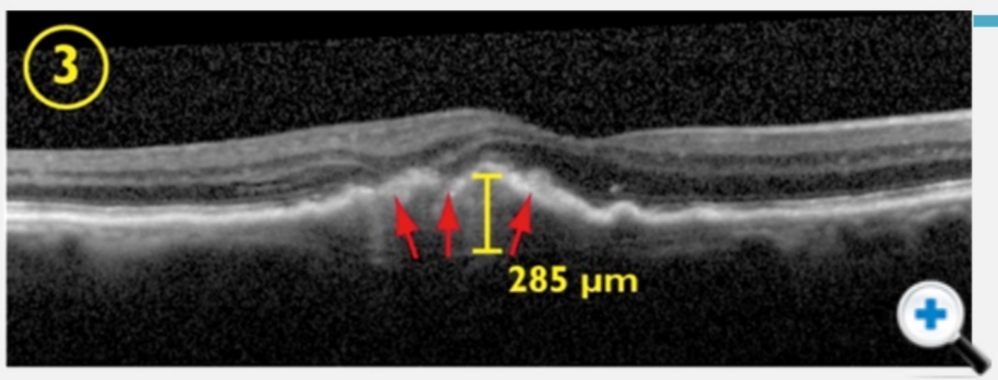
The following series of images outlines a hypothesis for this pathophysiology.



This patient has fixed-interval treatment.



At this point, the retina is dry (No IRC, no SRF). Note, however, the PED does not resolve. Fixed-interval treatment is stopped, and the patient observed.



The PED may start growing again. This may go unnoticed, as PED is not usually measured in follow up.

What happens next?

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Multimodal OCT: Research to Routine

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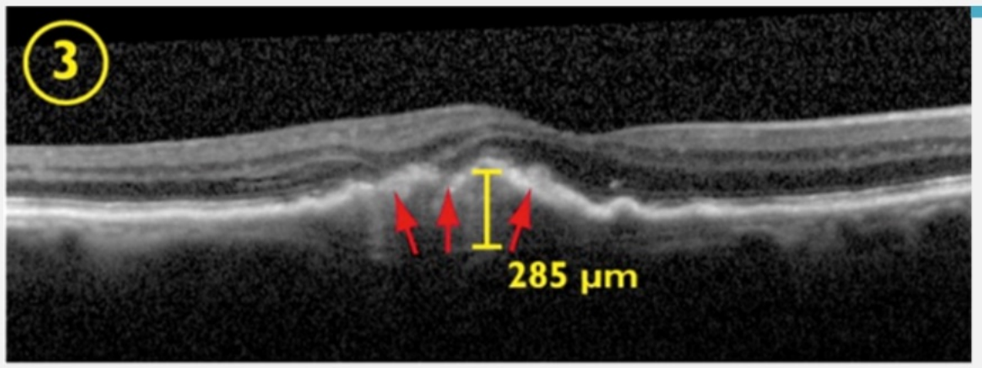
So, what is happening here? Click the tabs to learn more.

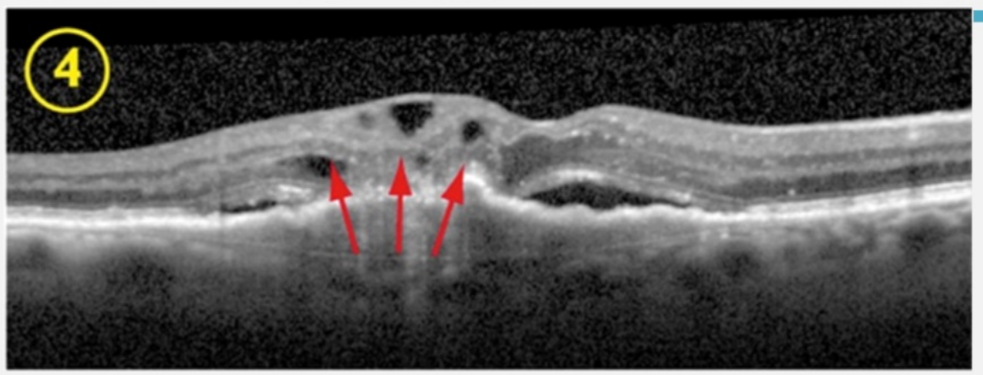
PED in the VIEW Trial

PED & Vision: Pathophysiology

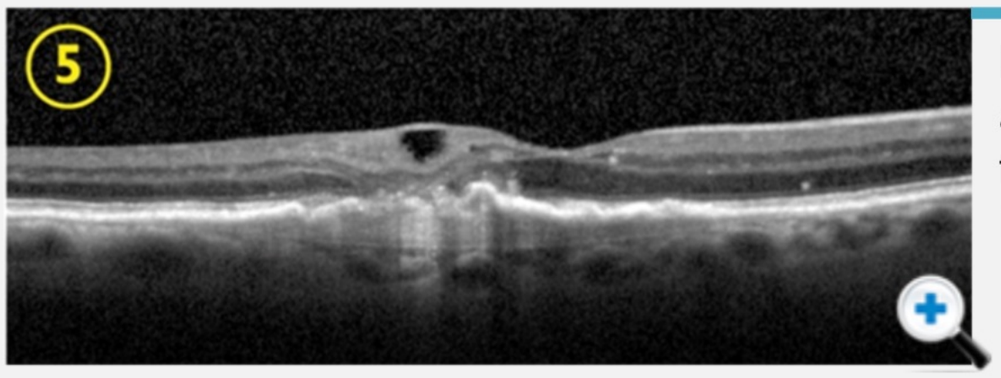
What is the Hypothesis for this PED Pathophysiology?



Without closely monitoring the PED, this growth may go unnoticed. The retina is dry, so observation continues.



At some point, IRC and SRF appear again. Treatment is re-initiated. However, even at this point it may be too late to prevent irreversible damage.



Even if the retina were dry after starting treatment again, there could still be irreversible damage.

Back

Exploring Pathophysiology

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Multimodal OCT: Research to Routine

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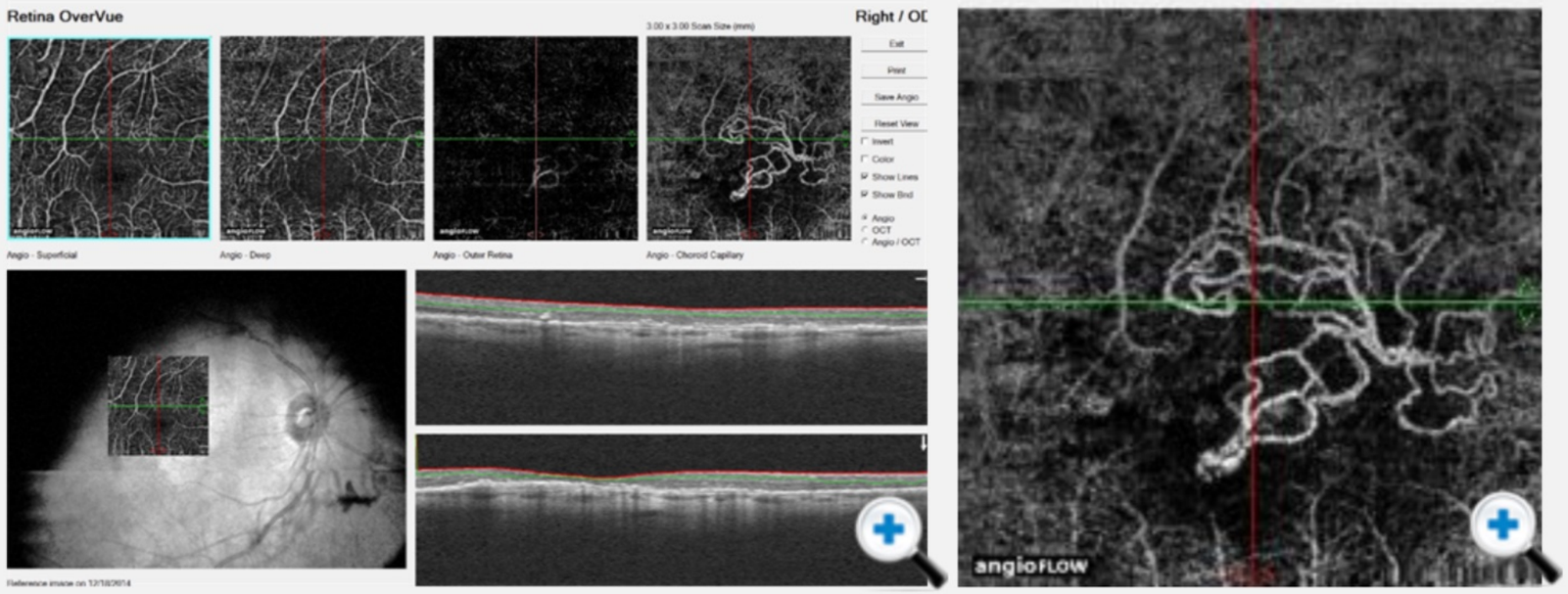
PED in the VIEW Trial

PED & Vision: Pathophysiology

PED May Harbour Primary CNV Lesion

OCT angiography now gives us the opportunity to look beneath the PED and this can often visualise the neovascular network that remains there.

Even if these vessels have a mature shape, stopping treatment may cause reactivation of the lesion, PED growth and secondary retinal exudation.



This example is a female patient (87 years) with initially occult choroidal neovascularisation (CNV) showing a vascular loop configuration (TVC) in the choriocapillaris penetrating the outer retina.

25 injections: 25; Duration of disease: 2592 days (7.1 years); BCVA: 0.16 Snellen.

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Module Progress:

Morphology Biomarkers in Exudative AMD

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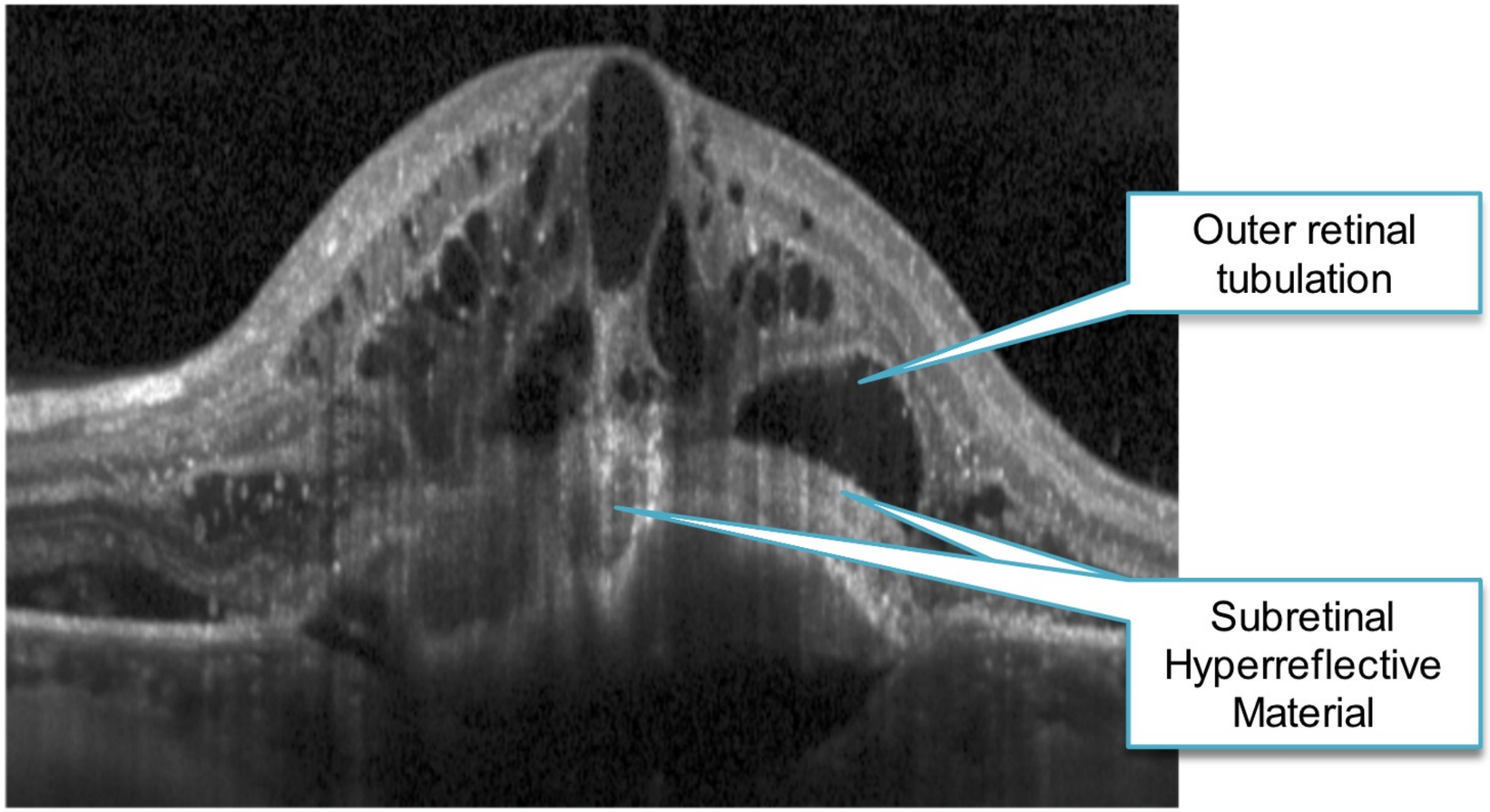
Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Introduction: Morphological Changes

Beyond fluid, morphology changes in AMD can also be used as biomarkers.

- **Outer retinal tubulation (ORT)** ORT can be misdiagnosed as subretinal fluid, but they have a hyper-reflective border.
- **Subretinal hyperreflective material (SRHM)**



Do you think these morphological changes will resolve after treatment?

- ○ No, even after treatment, these morphological changes will remain
- ○ Yes, these changes can regress, once the correct treatment path is taken

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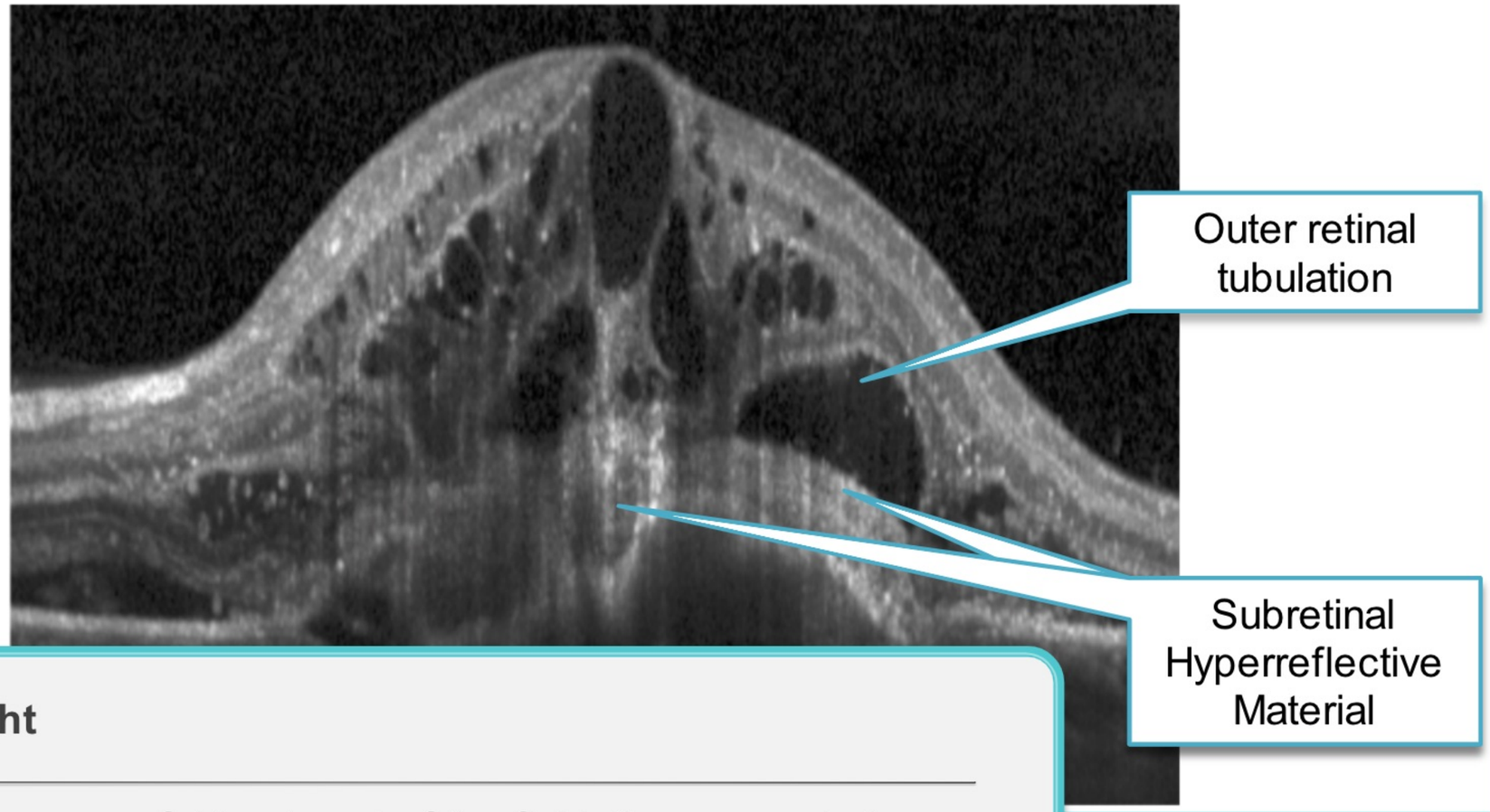
Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Introduction: Morphological Changes

Beyond fluid, morphology changes in AMD can also be used as biomarkers.

- **Outer retinal tubulation (ORT)**
  ORT can be misdiagnosed as subretinal fluid, but they have a hyper-reflective border.
- **Subretinal hyperreflective material (SRHM)**



Do you think thes

No, e

Yes,

That's right

Even after successful treatment of the fluid, these morphology changes will remain.

Close

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Multimodal OCT: Research to Routine

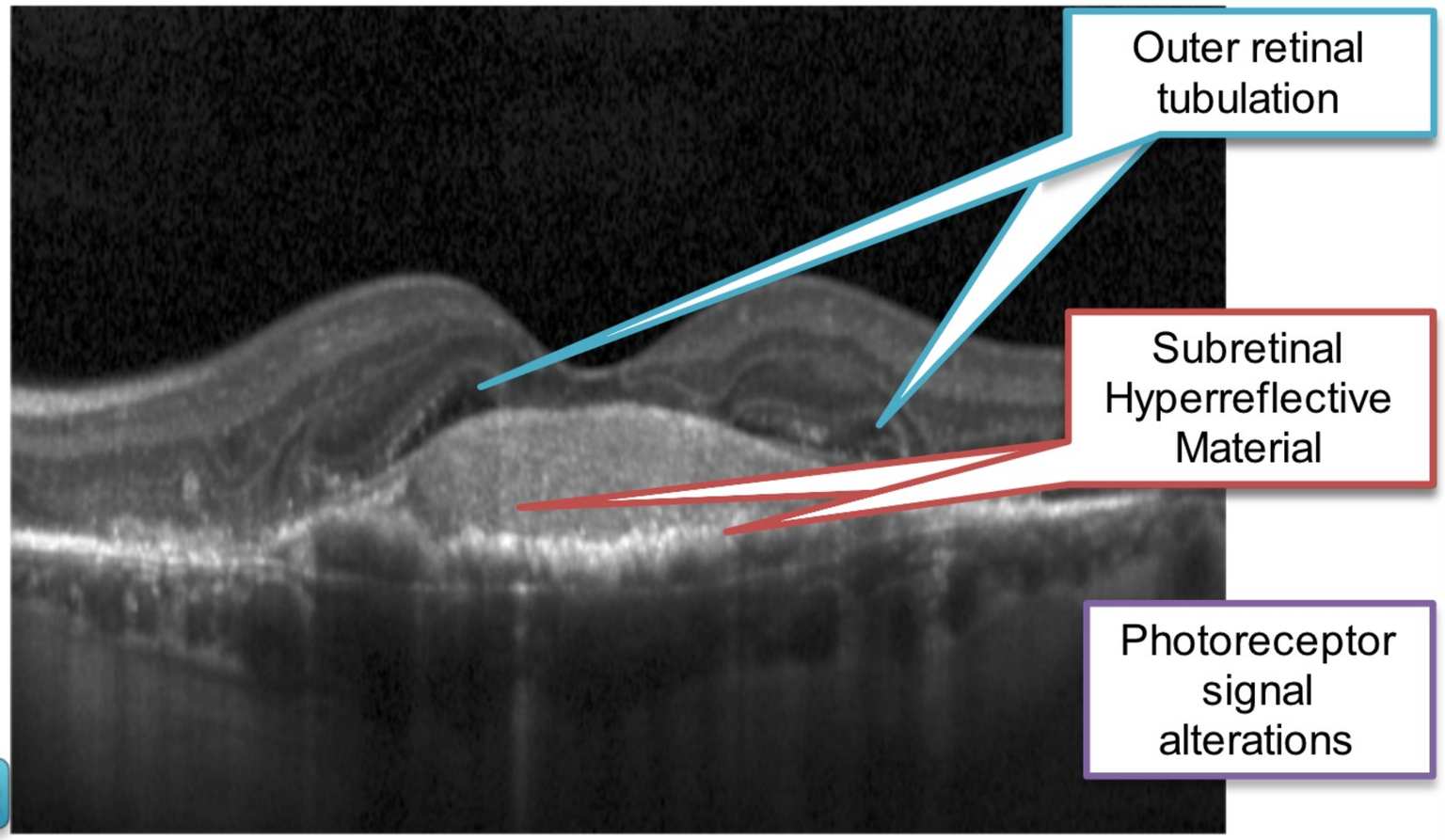
Morphology Biomarkers

This is the same case from the previous screen. Treatment has resolved the fluid, but the morphology changes remain.

These are signs of **extensive structural damage**. They often **remain over time** and are **not modified by treatment**.

Treatments are in development that try to target morphology changes. These biomarkers will be useful. For example, in the development of fibrosis, subretinal hyperreflective material may be an important end point.

Click the labels to learn more about what these changes can tell us.



See Pre-Treatment

SD-OCT can also help us image the vitreomacular interface. Do you think this can provide useful information as a biomarker of retinal disease?

- No, while the vitreomacular interface is of interest, it isn't a biomarker for retinal disease
- Yes, the vitreomacular interface can be a biomarker of retinal disease

Submit

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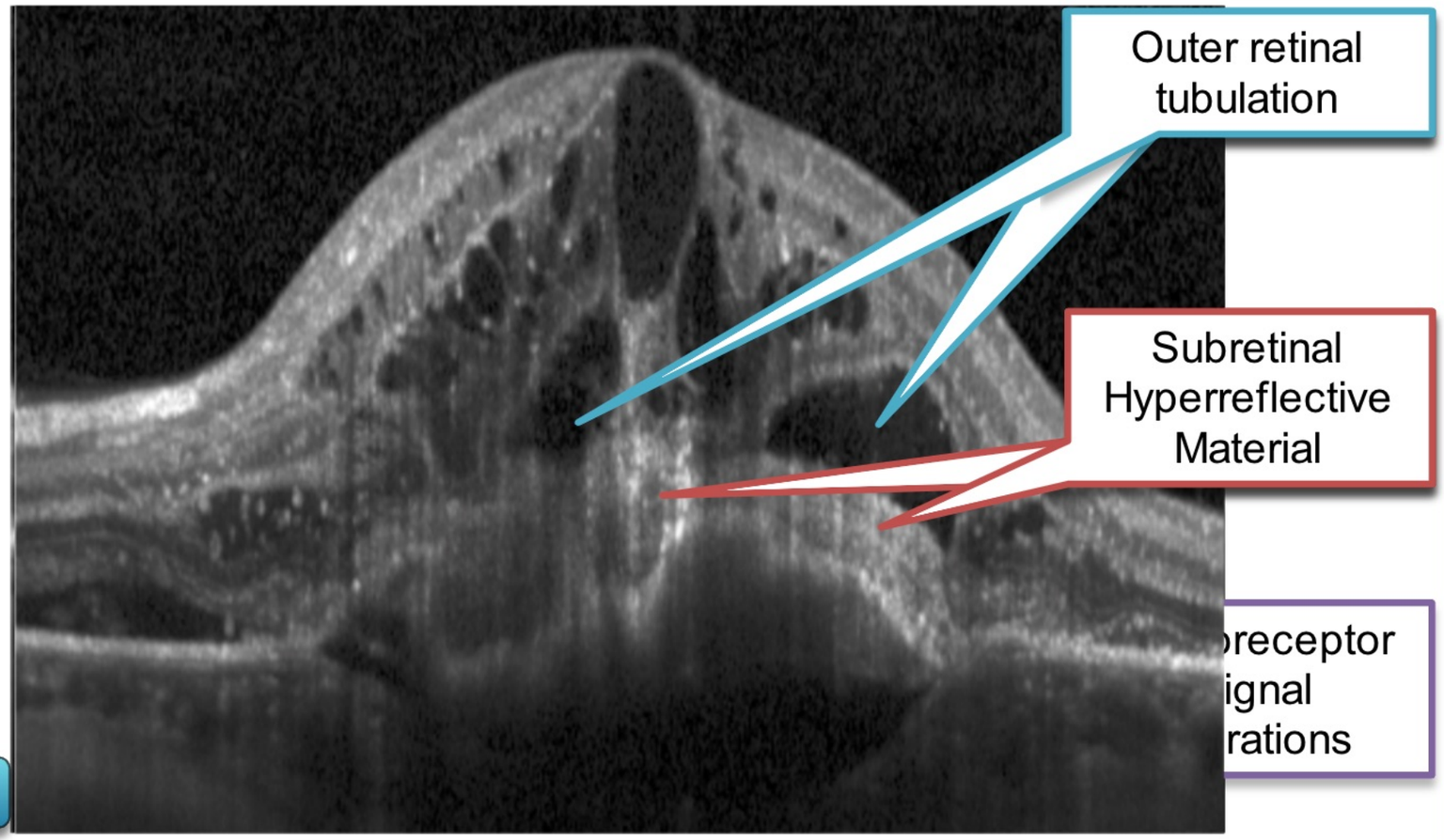

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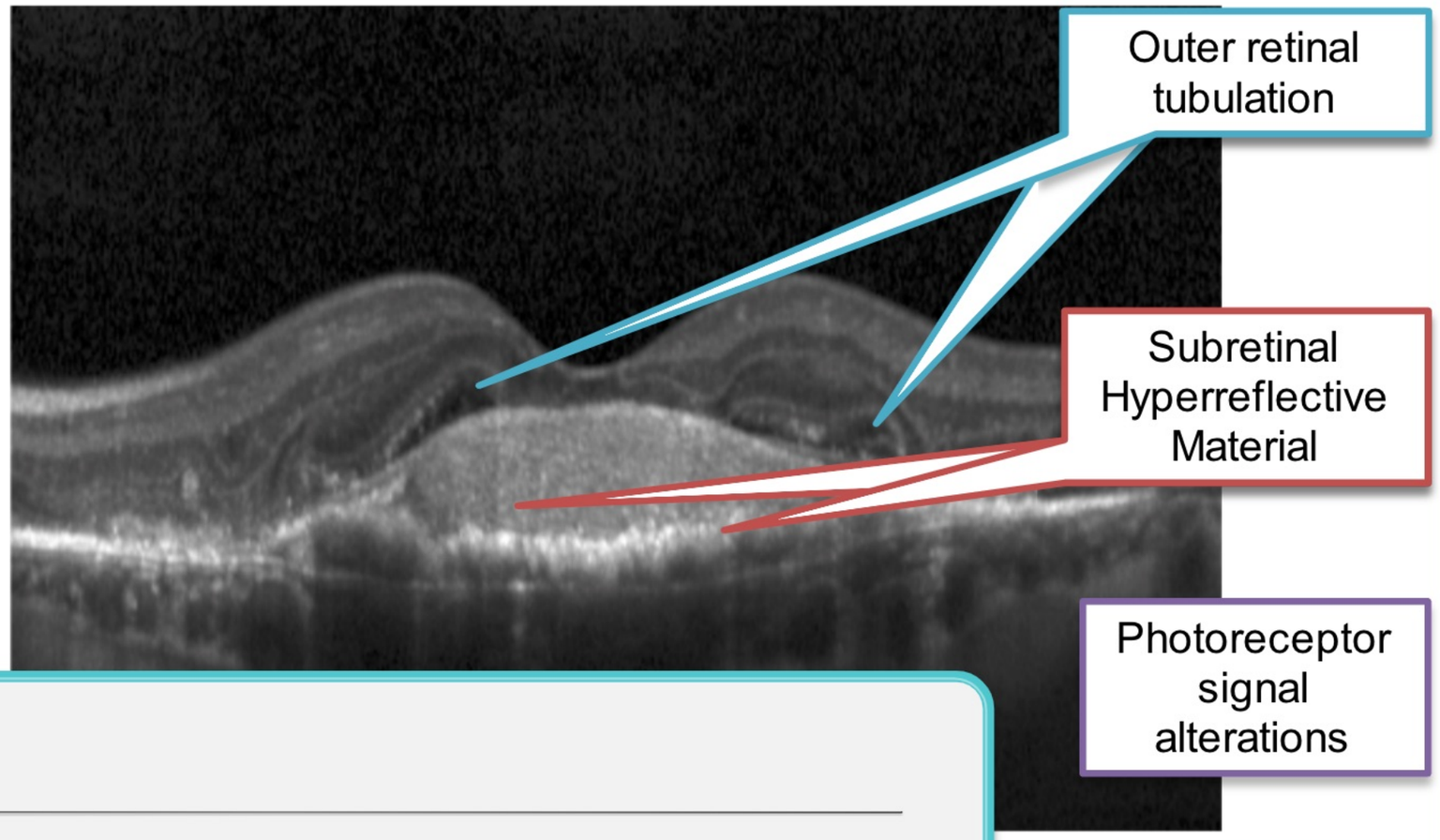

SD-OCT can also … information as a …

- No, … disea…
- Yes, …

…vide useful

That's not it

The vitreomacular interface is a useful biomarker in retinal disease: not just for the physical changes at the interface, but because the vitreous is where the drug is delivered.

Close

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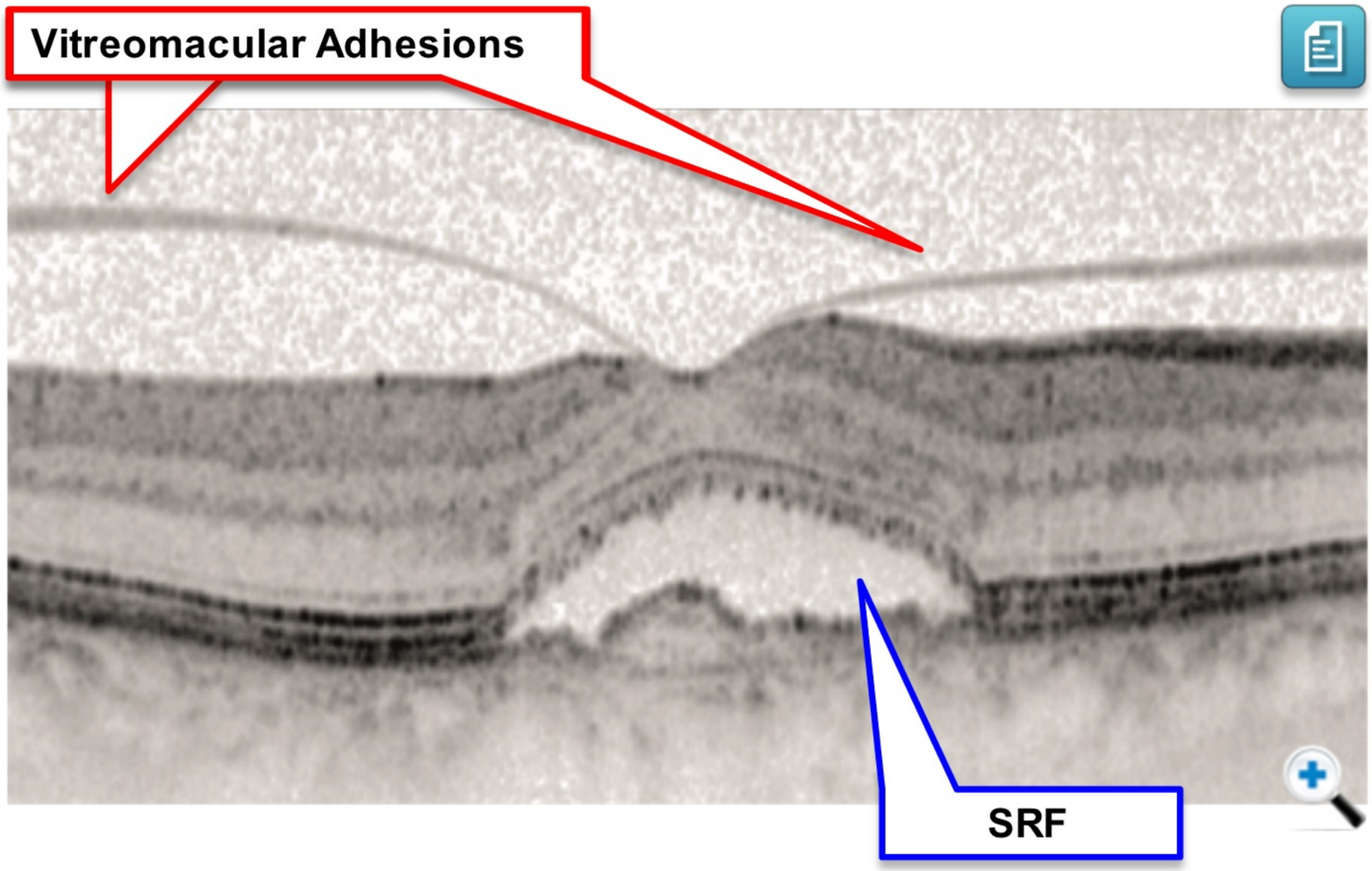
Vitreomacular Adhesion

this patient has SRF only, but there is also vitreomacular adhesion

Remember, the vitreous is the compartment where the drug is being delivered so - this may actually play a role for the efficacy of the treatment.



Vitreous in nAMD

VMA/PVD: Effect on Therapy

Click the tabs to learn more about the effect of vitreous status on vision and therapy decisions.

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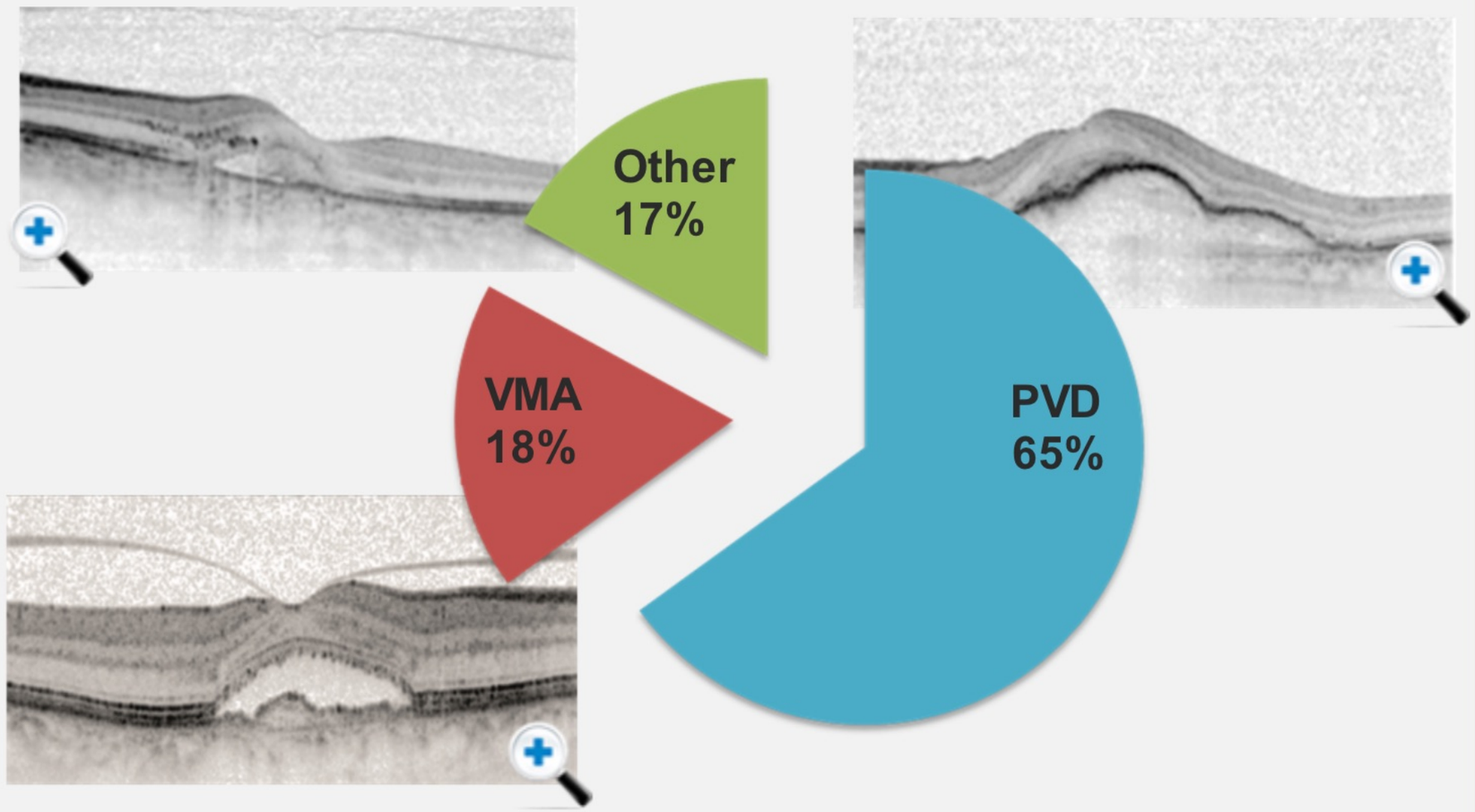
Vitreous condition in nAMD eyes

- VMA is twice as likely in nAMD eyes (compared with normal)
- PVD 0.77 times as likely in nAMD eyes (compared with normal)
- Intravitreal injections may (rarely) induce PVD

The vitreous conditions often seen in exudative AMD are outlined in this chart.



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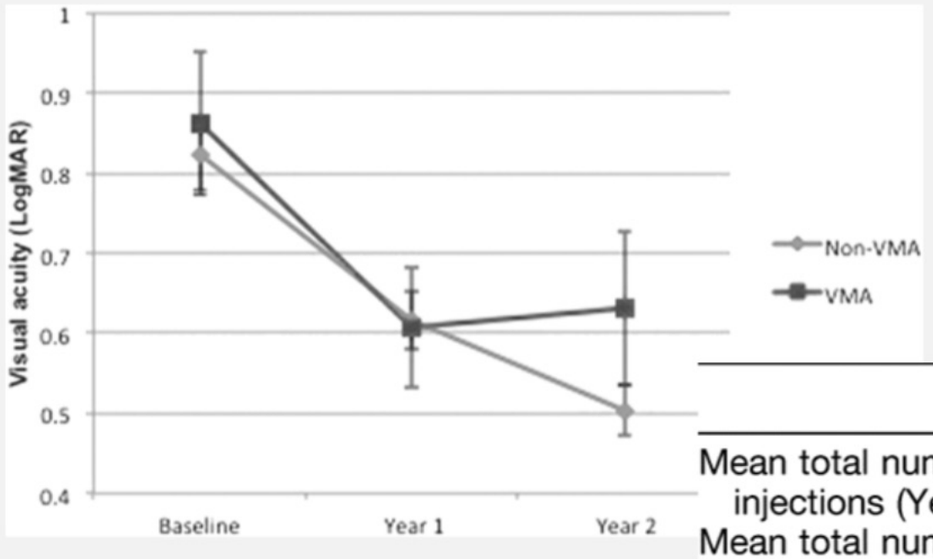
Impact of VMA therapy

Studies have shown that **vitreomacular adhesion (VMA) is does not affect vision in a treat and extend regimen** (during year one). All patients gain vision.

However, the number of treatments patients received was significantly different: **patients with VMA required more treatments**, while those without VMA needed less.



	Non-VMA	VMA	*P*
Mean total number of injections (Year 1) (SD)	7.37 (1.81)	8.35 (1.79)	0.001
Mean total number of injections (Year 2) (SD)	5.52 (1.84)	6.67 (2.32)	0.027
Mean longest extension (Year 1) (SD)	11.81 (4.95)	10.08 (3.12)	0.005
Mean longest extension (Year 2) (SD)	14.08 (6.09)	11.89 (3.82)	0.041

Effect of PVD on therapy

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Vitreous in nAMD

VMA/PVD: Effect on Therapy

No PVD at baseline, monthly treatment arm (n=36)

No PVD at baseline, quarterly treatment arm (n=70)

PVD at baseline, monthly treatment arm (n=62)

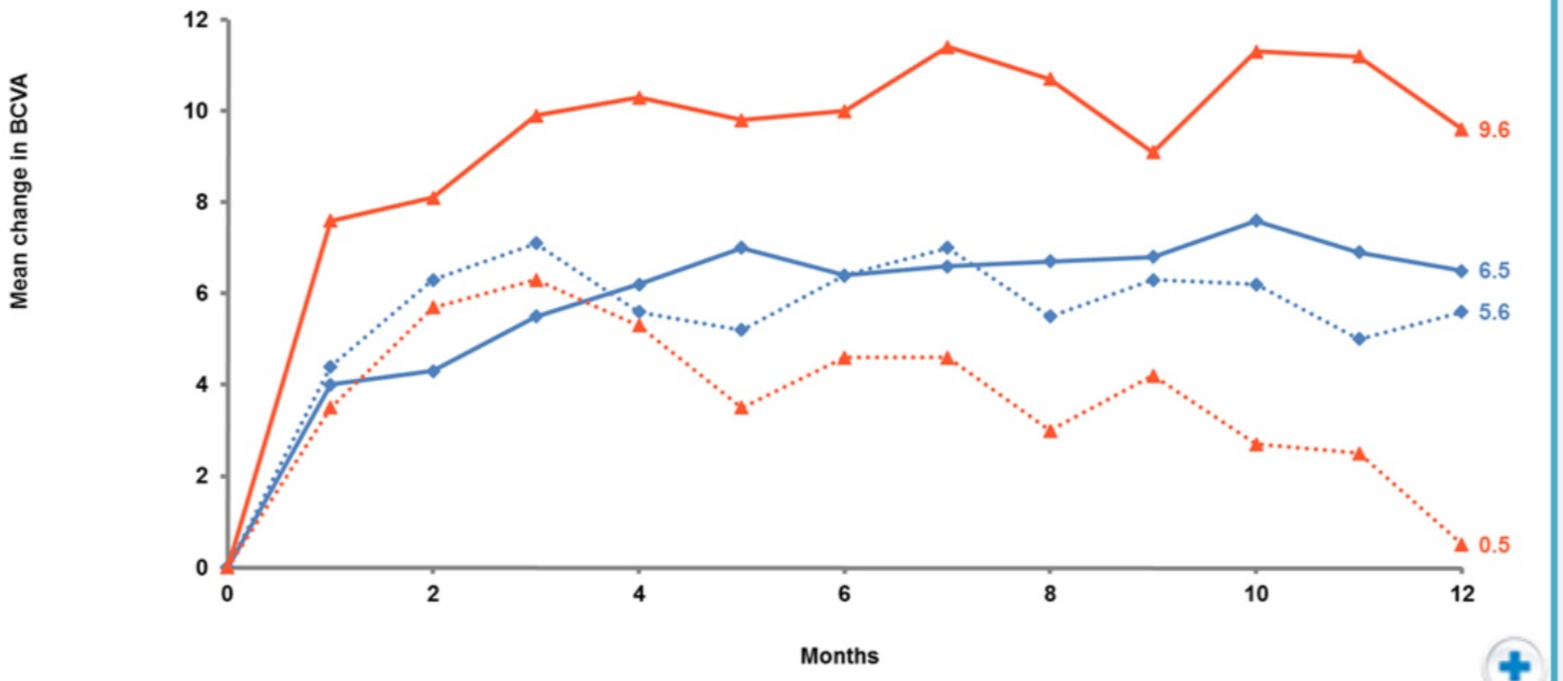
PVD at baseline, quarterly treatment arm (n=126)

Impact of PVD on nAMD therapy

In the EXCITE trial, patients that showed posterior vitreous detachment had very stable disease, regardless of injection frequency.

Patients that did not show posterior vitreous detachment did very well in monthly treatment and very poorly on quarterly treatment.

This is similar behaviour to subretinal fluid (discussed earlier).



Impact of VMA on therapy

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Module Progress:

Imaging Biomarkers: Into the Future

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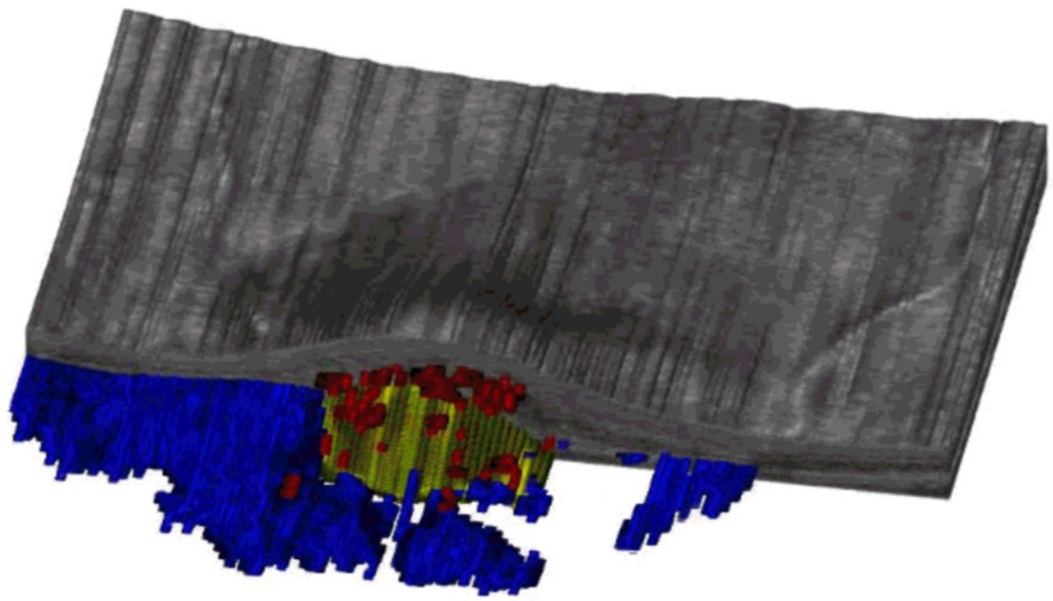
Multimodal OCT: Research to Routine

Introduction: Future Outlook

The data discussed in this module was based on binary classification: *was a component present or not*?

Imaging technology is still developing: SD-OCTs can now provide volume information, so each components can be quantified very effectively.



What do you think is the key benefit provided by quantifying each compartment in retinal disease?

- Ability to learn about the development of fluid in retinal disease
- Ability to study retinal morphology in more detail (e.g. IRC, SRF, PED) over time

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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

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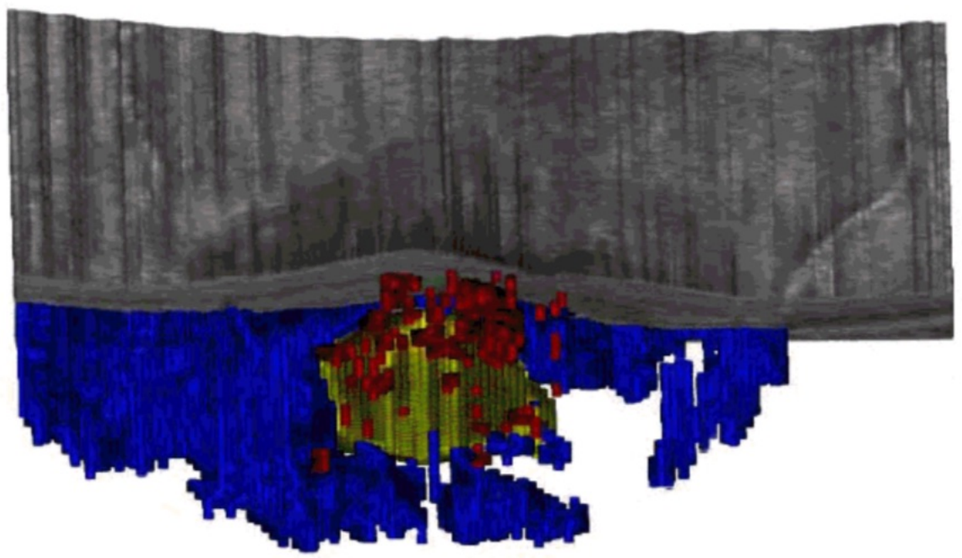

What do you thinl **inal disease?**

Abilit

Abilit

That's right

Volume information will allow us to monitor each compartment (IRC, SRF, PED) of retinal disease in more detail over time.

Close

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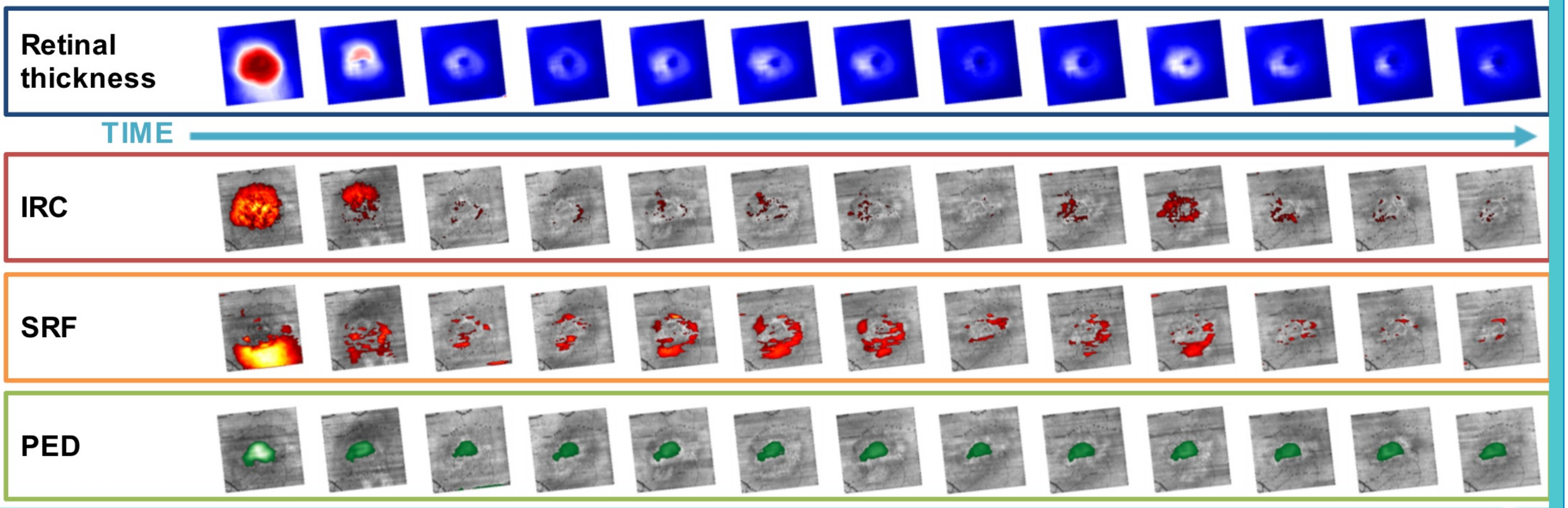
Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Detailed Study of Morphology Over Time

With SD-OCT volume information we can develop maps, which allow a detailed study of morphology changes over time.



What can be seen from these maps?

- All fluid changes resolve, given enough time/ treatment
- While most fluid changes resolve, the PED never really goes away

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Multimodal OCT: Research to Routine

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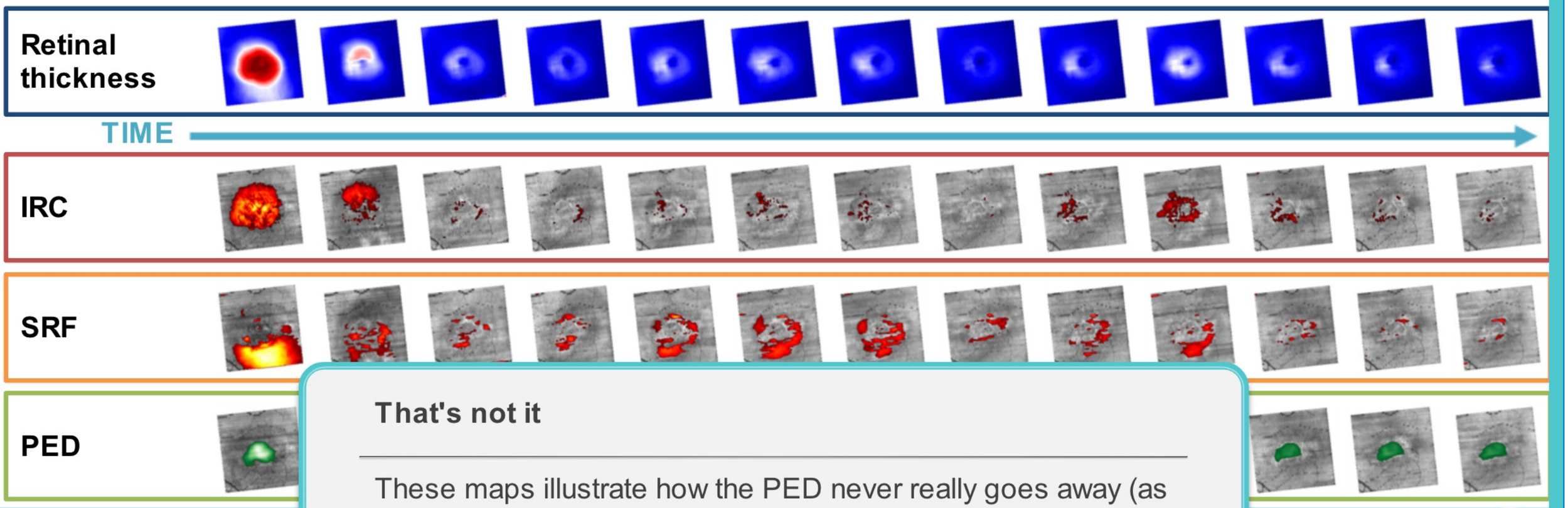

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That's not it

These maps illustrate how the PED never really goes away (as discussed in the previous topic).

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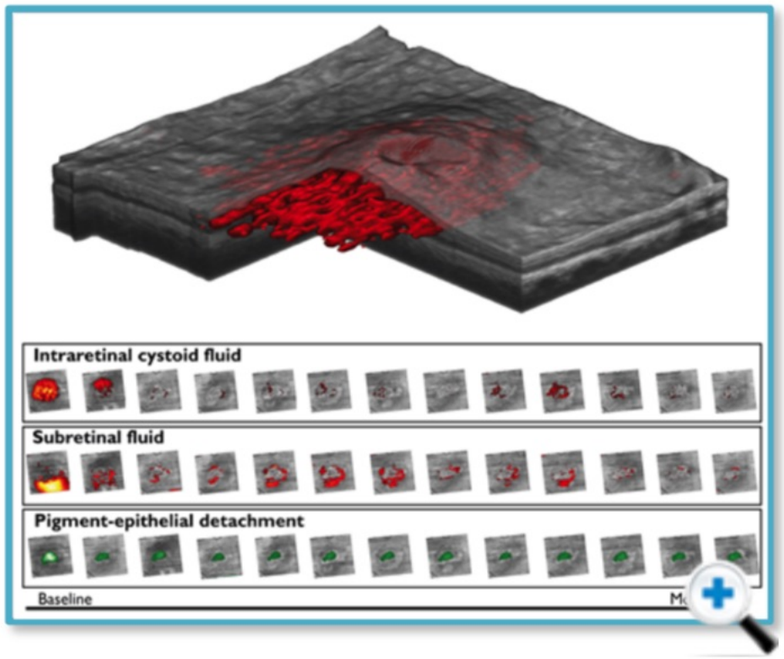
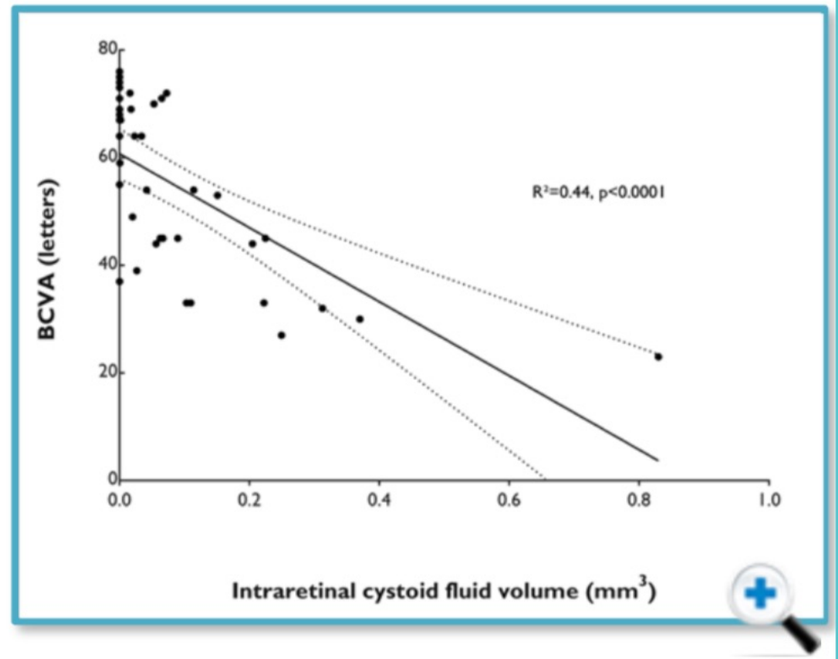
Quantification of Intraretinal Fluid

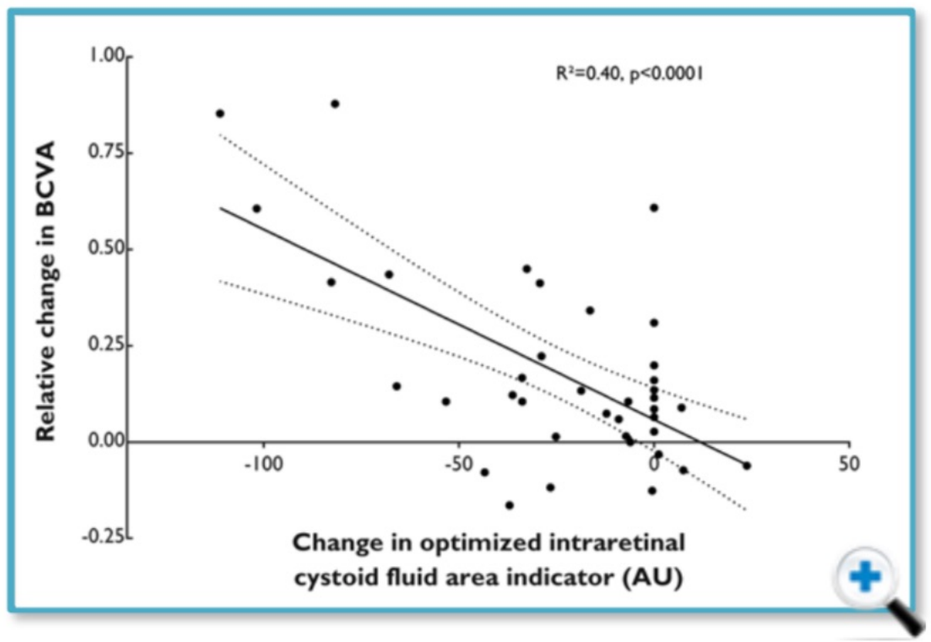
The benefit of quantifying these changes will be the ability to start correlating vision and the biomarkers in a linear fashion.

For instance, intraretinal fluid shows a fairly linear correlation: the **extent of intraretinal fluid is correlated with visual acuity at baseline**.



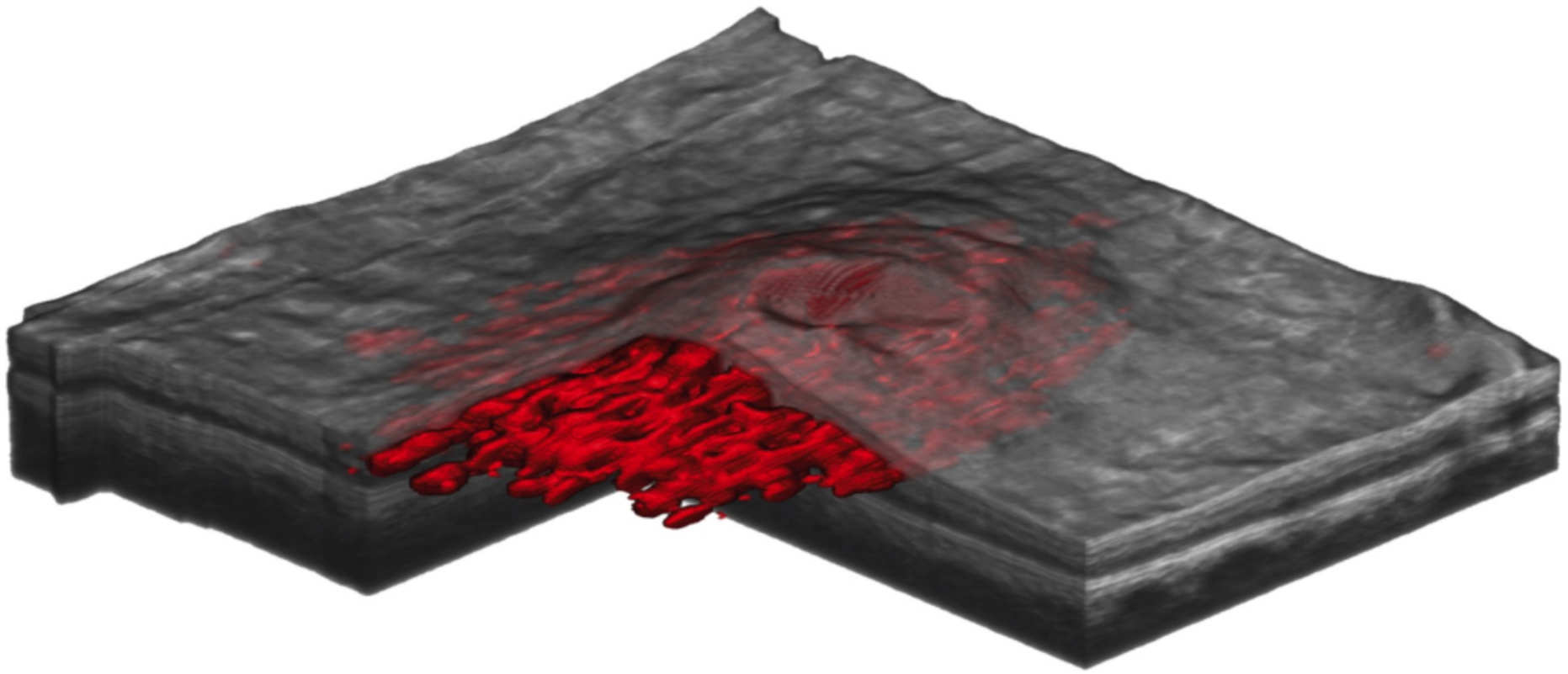


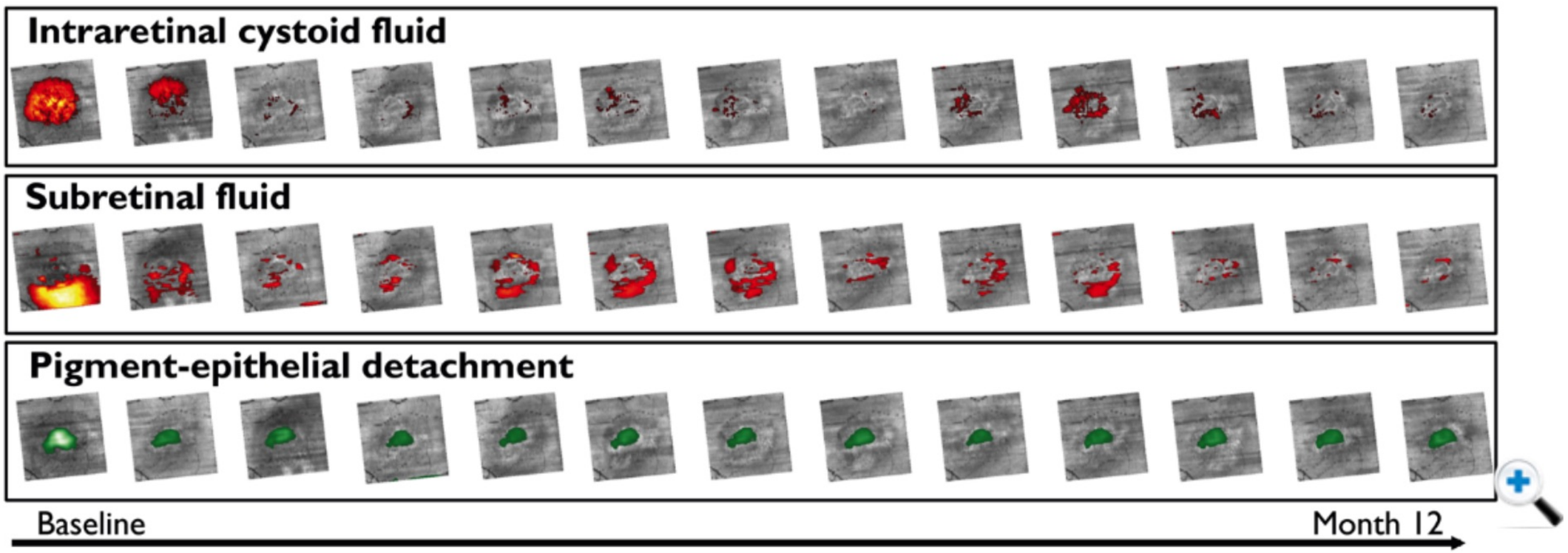
Furthermore, the **reduction of fluid** over time during treatment is **tightly linked to** gain or loss in **visual acuity**.



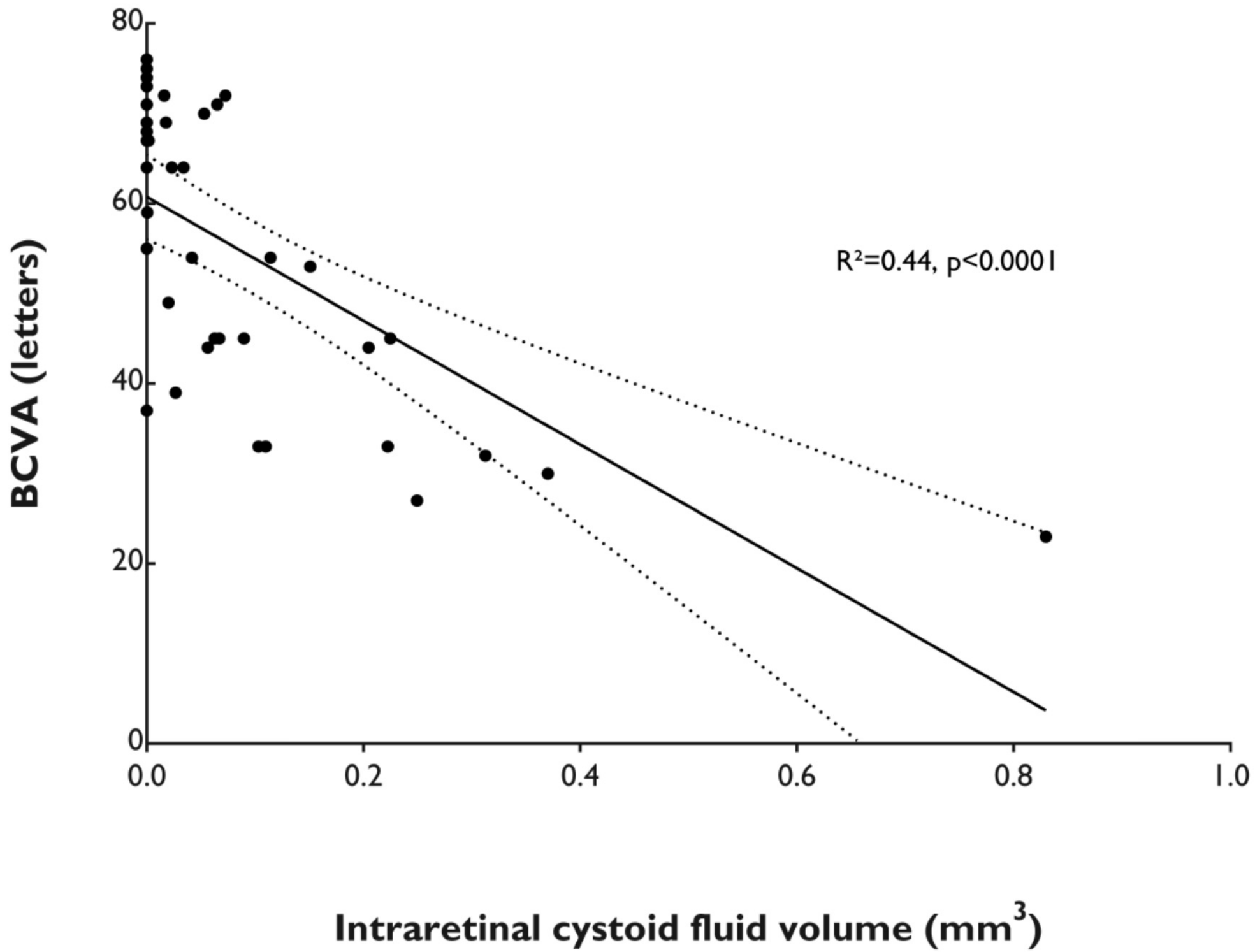
Waldstein SM, Philip AM, Leitner R, Simader C, Langs G, Gerendas BS, Schmidt-Erfurth U. Correlation of 3-Dimensionally Quantified Intraretinal and Subretinal Fluid With Visual Acuity in Neovascular Age-Related Macular Degeneration. JAMA Ophthalmol. 2015 Dec;10; 1-9. [Epub ahead of print]

Volume scan and maps illustrating reduction in fluid over time during treatment

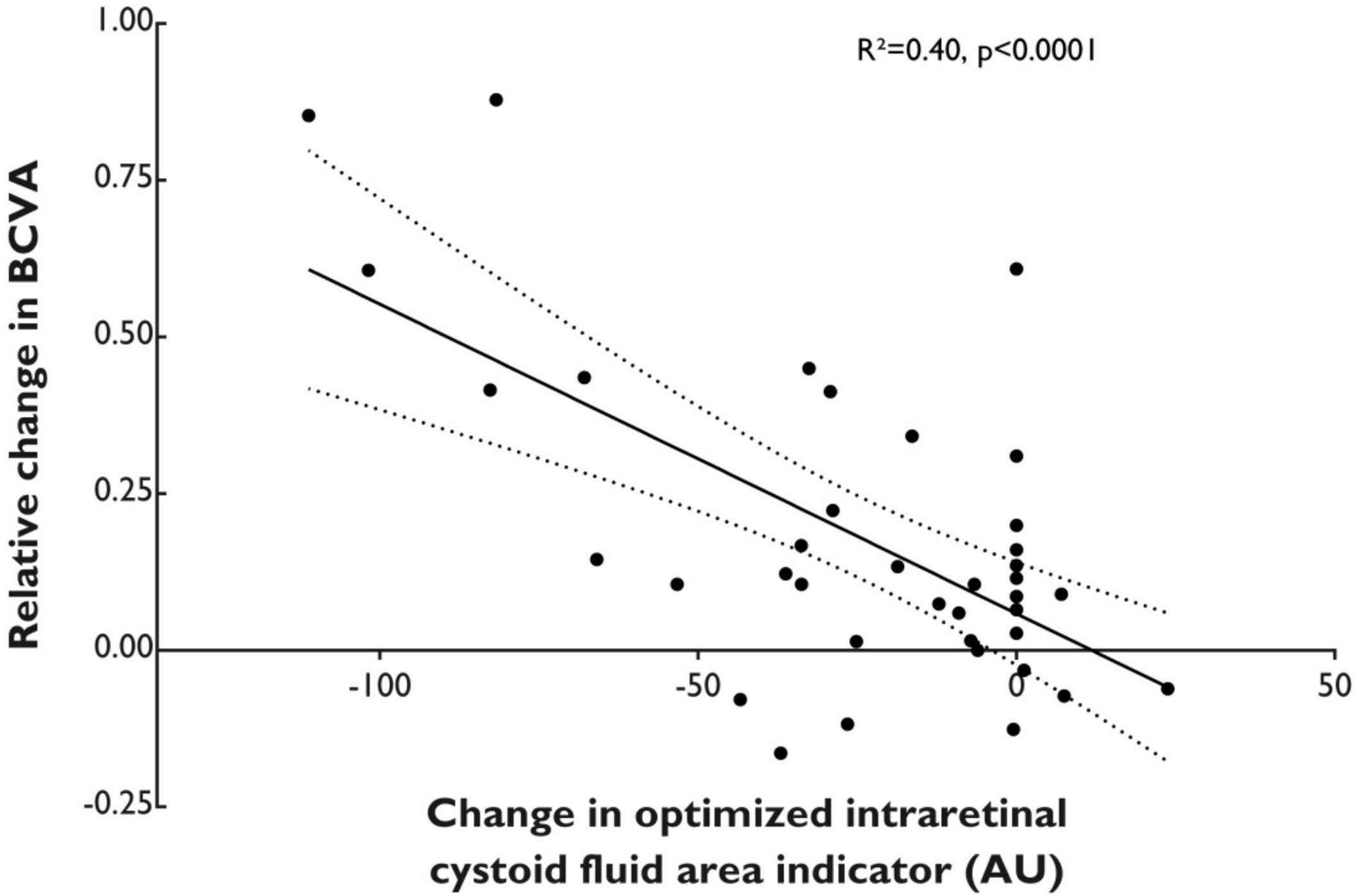




Correlation between extent of intraretinal cystoid fluid and visual acuity



Correlation between changes in intraretinal cystoid fluid and visual acuity over time during therapy



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Exudative AMD: Biomarkers of Disease & Therapy

Multimodal OCT: Research to Routine

Summary: Imaging Biomarkers of Disease & Therapy

Imaging biomarkers to predict visual function and treatment response from retinal morphology offer several benefits:

- **Prognostic value** → For patients and physicians, managing expectations
- **Efficient distribution of resources** → The right treatment for the right patient
- **Effective trial design** → More precise endpoints

Our current understanding of biomarkers for exudative AMD are:

Candidates (What we look for)	Role (What the candidate is predictive of)
Central retinal thickness	Limited value in prognosis
Fluid	
Fluid	Visual function
intraretinal	Poor BCVA (gains)
subretinal	Better VA, less GA, stable disease, less treatment
sub-RPE	Not relevant for VA, at risk during PRN treatment
Morphology	
Subretinal hyperreflective material (SRHM)	Poorer BCVA, poorer contrast sensitivity
Outer retinal tubulations (ORT)	Poorer BCVA, advanced tissue damage
Photoreceptor status	Predictive of baseline VA
Vitreous	PVD: less treatment, VMA: more treatment