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CENTRAL FLORIDA RETINA

GONZALO ORTIZ, MD

Central Florida Retina

Introduction

Gonzalo Ortiz

Central Florida Retina

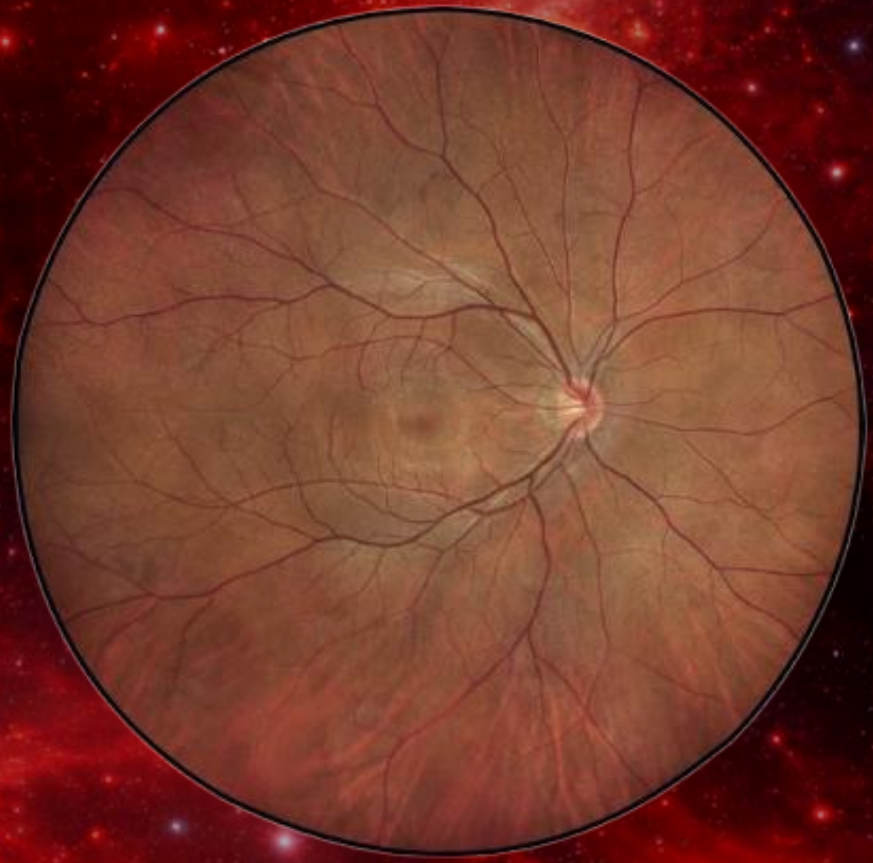
- Florida State University, BS
- University of South Florida, MD/Residency
- New Orleans, Fellowship
- Orlando, last 3 years

Why retina?

Outline

- Retinal Vascular Anatomy
- Retinal Vein Occlusion (RVO)
- Retinal Artery Occlusion (RAO)
- Diabetic Retinopathy (DR)
- Hypertensive Retinopathy & Retinal Macroaneurysms
- Rare and Secondary Vascular Retinal Diseases

Retinal Vascular Anatomy



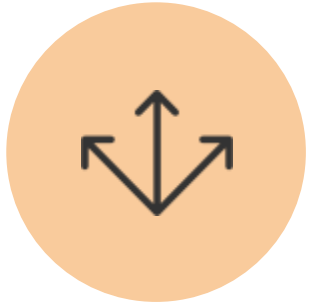
Introduction to Retinal Circulation

Central Retinal Artery

Originates from ophthalmic artery, enters eye through optic nerve, and supplies blood to the inner retinal layers

Central Retinal Vein

Drains blood from the inner retinal layers, exits the eye through the optic nerve



Branches and Areas of Perfusion

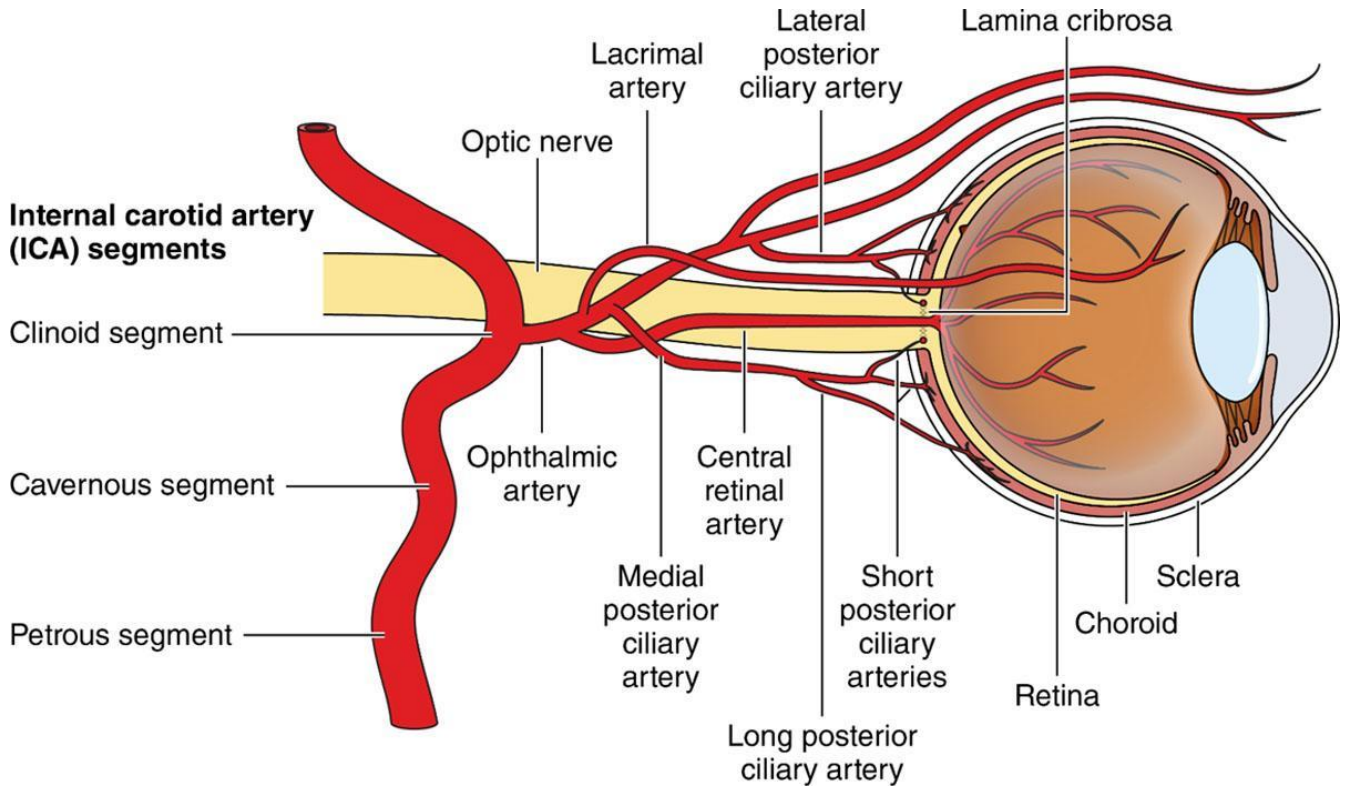
Central retinal artery and vein branch into superior and inferior divisions, each supplying blood to specific retinal quadrants

Understanding the course, branches, and areas of perfusion of the central retinal artery and vein is crucial for retina specialists in identifying and managing vascular diseases that can lead to ischemia and neovascularization.

Central Retinal Artery

- The **central retinal artery** is a branch of the **ophthalmic artery** that enters the eye within the **optic nerve** and pierces the lamina cribrosa to supply the **inner layers of the retina**.

- It divides into superior and inferior branches on the retinal surface and functions as an **end artery** with minimal collateral circulation. Because of this, occlusion of the central retinal artery causes **sudden, painless, severe vision loss**.

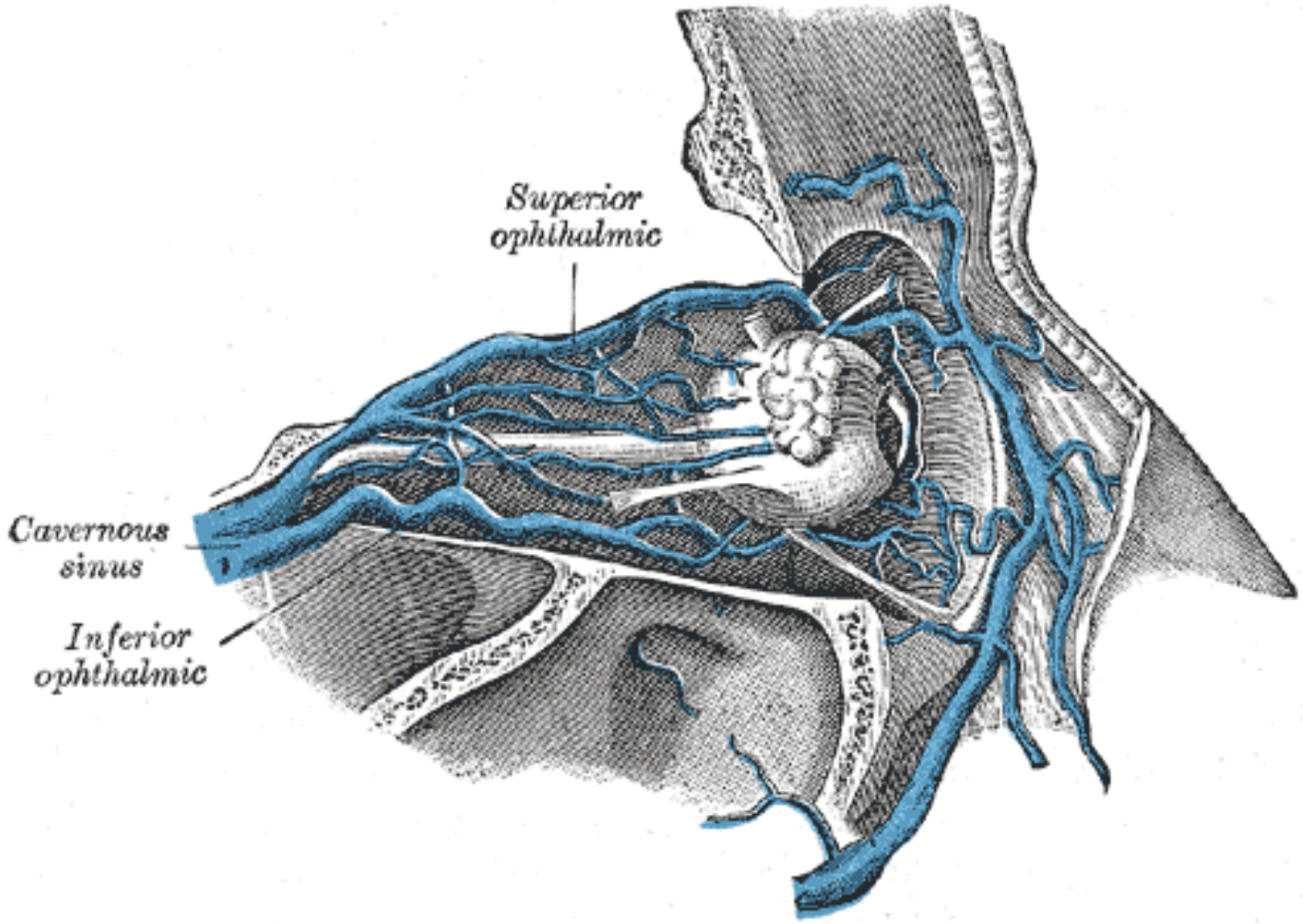


Central Retinal Vein

- The **central retinal vein** drains blood from the **inner layers of the retina**.

- It runs alongside the central retinal artery within the **optic nerve**, exits the eye through the **lamina cribrosa**, and typically drains into the **cavernous sinus** or the **superior ophthalmic vein**.

- Obstruction of this vein leads to **central retinal vein occlusion**, causing retinal hemorrhages, venous congestion, and vision impairment.



Blood-Retinal Barrier and Vascular Disease

The Blood-Retinal Barrier

The blood-retinal barrier is a specialized vascular structure that regulates the movement of substances between the blood and the retina. It consists of tight junctions between endothelial cells in the retinal vasculature.

Role in Retinal Health

The blood-retinal barrier plays a crucial role in maintaining the homeostasis of the retina,protecting it from harmful substances and ensuring the appropriate delivery of nutrients and oxygen to the retinal tissues.

Breakdown in Vascular Disease

In various vascular diseases, the integrity of the blood-retinal barrier can be compromised, leading to increased permeability. This breakdown can result in the accumulation of fluid, proteins, and other substances in the retina, contributing to the development of retinal edema and other complications.

Implications for Retinal Ischemia

The breakdown of the blood-retinal barrier is often associated with retinal ischemia, where the supply of oxygen and nutrients to the retinal tissues is disrupted. This can further exacerbate the disease process and contribute to the development of neovascularization, a hallmark of proliferative vascular diseases.

Diagnostic and Therapeutic Relevance

Understanding the role of the blood-retinal barrier and its breakdown in vascular diseases is crucial for retina specialists in diagnosing, monitoring, and managing retinal vascular disorders. This knowledge can guide the development of targeted interventions to restore the barrier's integrity and improve patient outcomes.

Perfusion and Autoregulation

Importance of Perfusion

Adequate blood flow and oxygen delivery are crucial for maintaining healthy retinal tissue. Proper perfusion ensures that the retina receives the necessary nutrients and oxygen to support its metabolic demands.

Autoregulation of Retinal Blood Flow

The retina has the ability to autoregulate its blood flow to maintain a relatively constant oxygen supply, even in the face of changes in systemic blood pressure or metabolic demands. This autoregulatory mechanism is critical for preventing ischemic injury.

Implications for Ischemia

Disruption of perfusion and autoregulation can lead to ischemia, where the retinal tissue is deprived of oxygen and nutrients. Ischemia can result in retinal cell death and the development of various vascular diseases, such as diabetic retinopathy and retinal vein occlusions.

Implications for Neovascularization

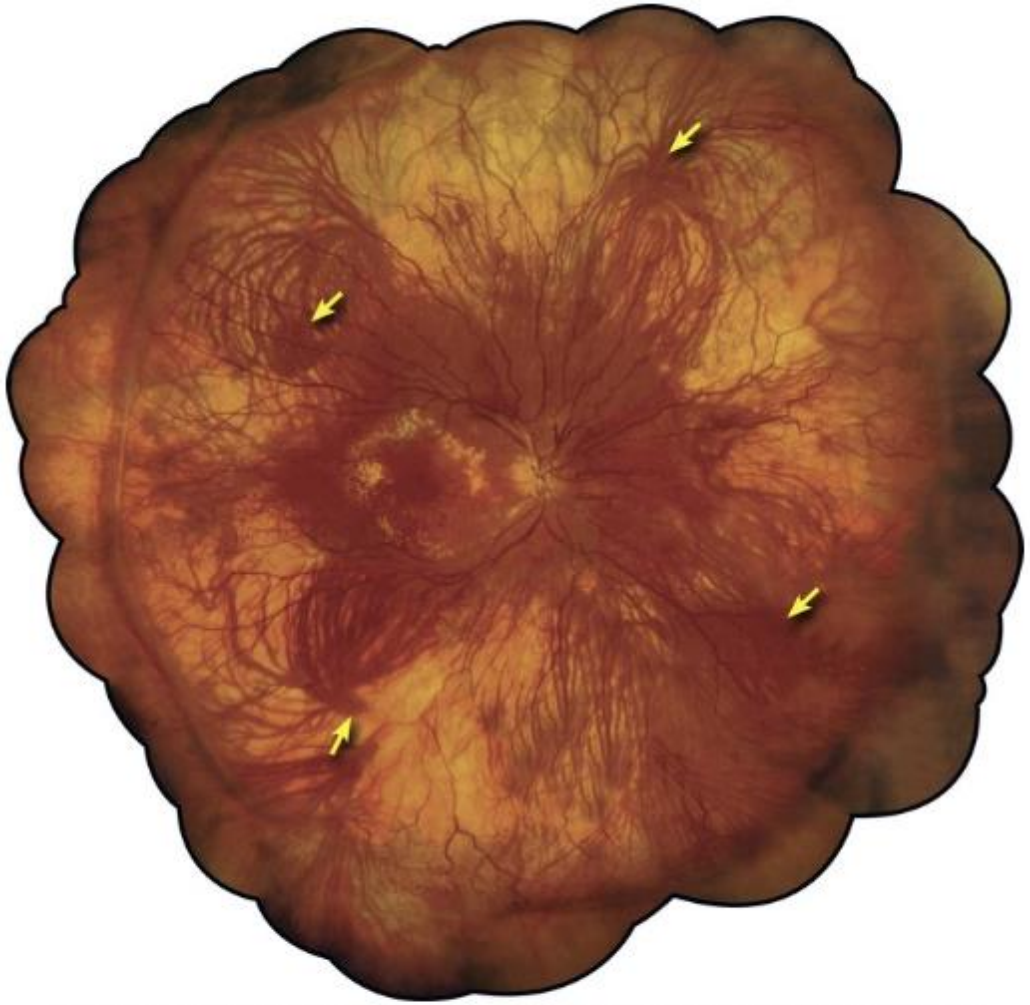
In response to ischemia, the retina can stimulate the growth of new blood vessels, a process known as neovascularization.
While this is an attempt to restore blood flow, the newly formed vessels can be fragile and prone to leakage, leading to further complications like vitreous hemorrhage and tractional retinal detachment.

Choroid

- Highly vascular system that supplies blood to the **outer retina**, particularly the **photoreceptors** and the **retinal pigment epithelium (RPE)**.

- It originates mainly from the **posterior ciliary arteries**, branches of the ophthalmic artery. These arteries form the **choriocapillaris**, a dense network of wide, fenestrated capillaries located just beneath the RPE.

- The choroidal blood flow is **one of the highest in the body**, allowing efficient delivery of oxygen and nutrients and rapid removal of metabolic waste. This is essential because photoreceptors have a very high metabolic demand.



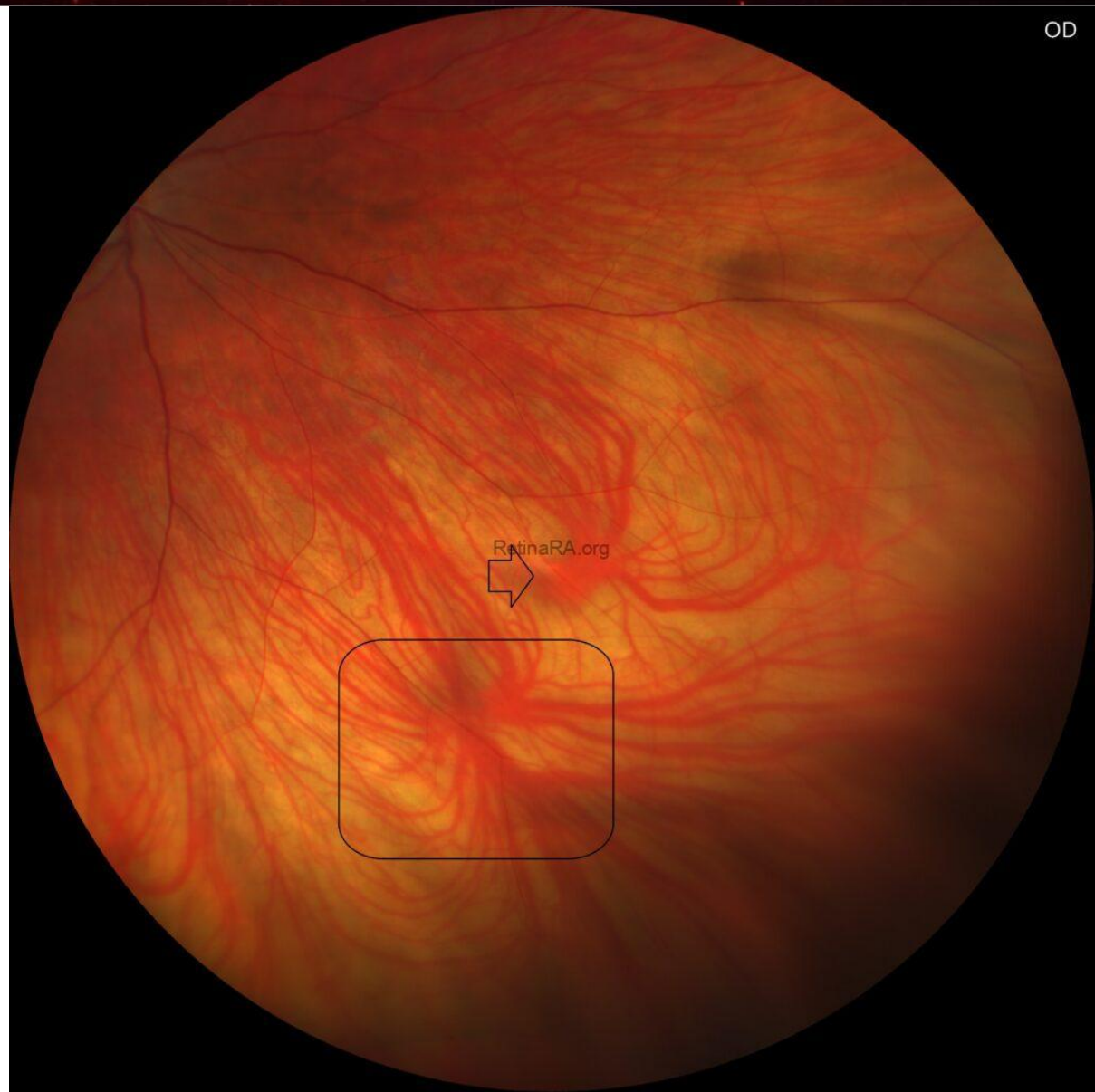
This is a color montage of a blond fundus. The choroidal circulation is visible through a mildly pigmented retinal pigment epithelium. Note the 4 vortex veins *(arrows)* in the outer choroidal circulation, which accommodate the very high flow supplied posteriorly by 10–20 short posterior ciliary branches of the ophthalmic artery. Nasal and temporal long posterior ciliary arteries supply the anterior choroid and uvea.

Choroid

- Unlike retinal circulation, the choroidal circulation has **limited autoregulation** and is primarily controlled by **autonomic innervation**, especially sympathetic input.

- Venous drainage occurs through the **vortex veins**, which drain into the ophthalmic veins.

- Helps with **thermoregulation** of the retina and contributes to maintaining normal retinal function.



Retinal Vein Occlusion

Central, Branch, and Hemiretinal Variants

Introduction to Retinal Vein Occlusion

What is Retinal Vein Occlusion (RVO)?

A condition where the blood flow in the retinal veins is blocked, leading to vision problems.

Subtypes of RVO

RVO can occur in the central retinal vein (CRVO), branch retinal vein (BRVO), or as a hemiretinal vein occlusion.

Impact on Vision

RVO can cause sudden, painless vision loss and distortion (metamorphopsia) due to the disruption of blood flow and retinal function.

Retinal Vein Occlusion is a significant ophthalmological condition that can lead to vision impairment. Understanding the different subtypes and their clinical presentation is crucial for prompt diagnosis and effective management.

Pathogenesis and Risk Factors

Virchow's Triad

The three key factors that contribute to the development of RVO: venous stasis, endothelial damage, and hypercoagulability.

Venous Stasis

Impaired venous outflow due to anatomical factors, such as compression of the vein by surrounding structures or the presence of vascular anomalies.

Endothelial Damage

Injury or dysfunction of the vascular endothelium, which can be caused by various factors, including inflammation, trauma, or atherosclerosis.

Hypercoagulability

Increased tendency for blood clot formation, which can be associated with conditions like thrombophilia, antiphospholipid syndrome, or use of certain medications.

Systemic Associations

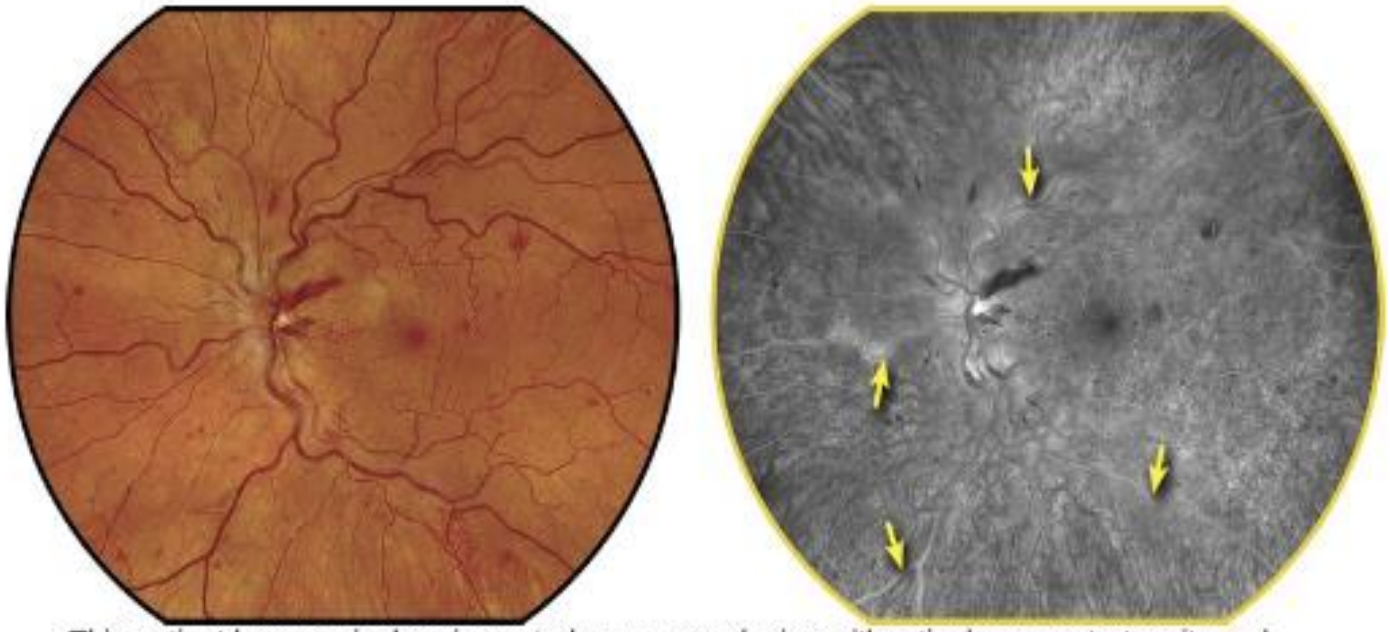
RVO is often linked to underlying systemic conditions, such as hypertension, diabetes, hyperlipidemia, and glaucoma, which can contribute to the development of the condition.

CRVO

- Patients with Central Retinal Vein Occlusion (CRVO) often experience sudden, painless vision loss and may report metamorphopsia (distorted vision).

- Retinal Vein Occlusion (RVO) can present with a range of clinical symptoms and fundus findings, depending on the specific subtype.

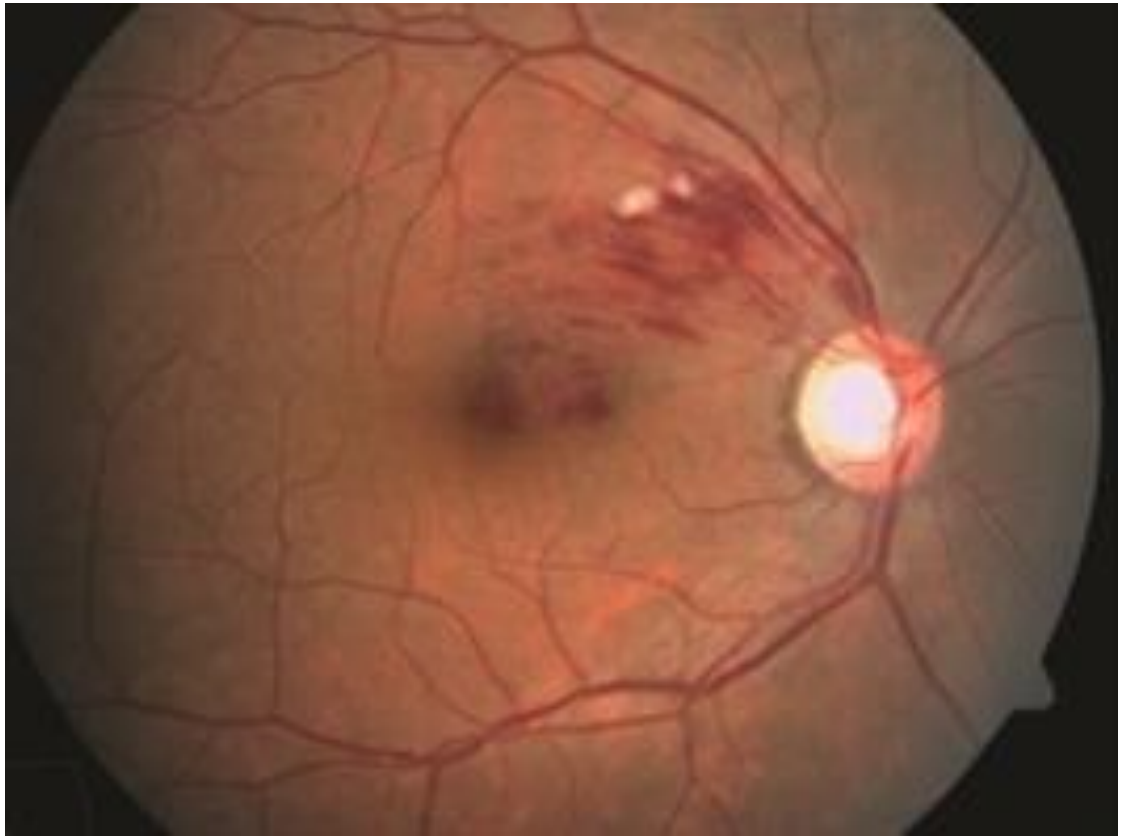
- The fundus examination typically reveals dilated and tortuous retinal veins, widespread retinal hemorrhages,

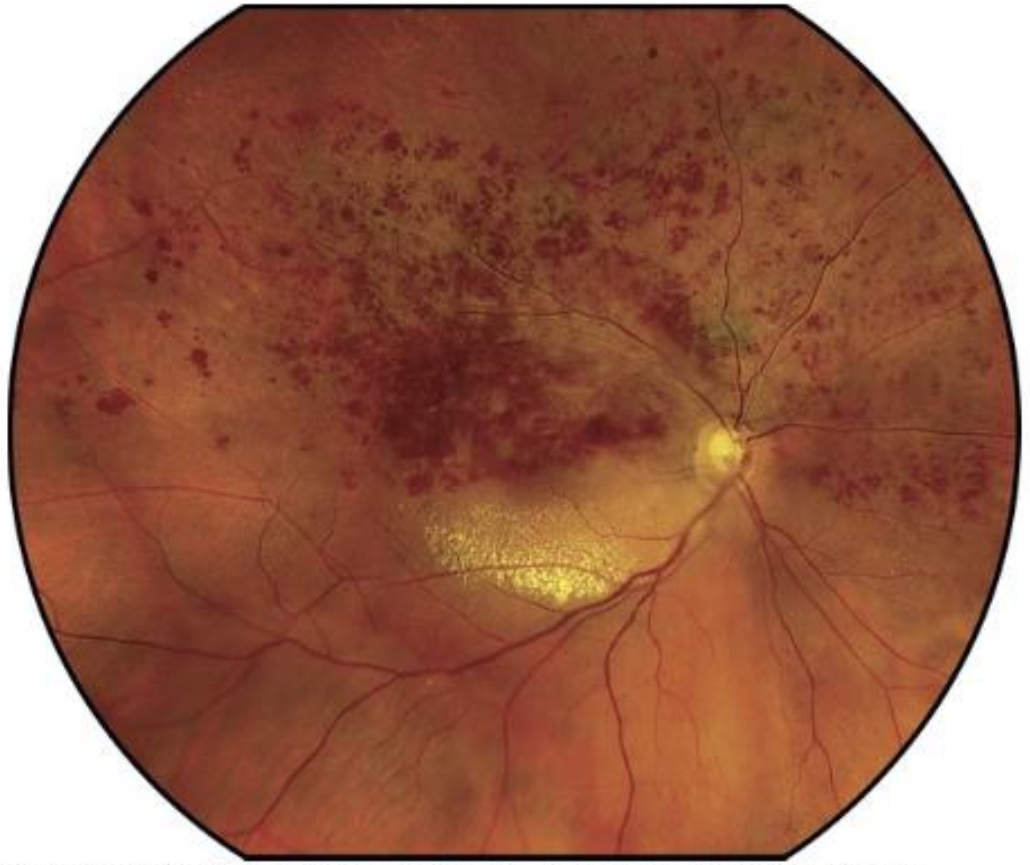


This patient has non-ischemic central venous occlusion with retinal venous tortuosity and few hemorrhages at the disc and in each quadrant of the mid periphery. The FA shows segmental staining of the venules *(arrows)* and minimal leakage at the optic nerve. There is no evidence of significant retinal capillary ischemia or non-perfusion.

BRVO/ HRVO

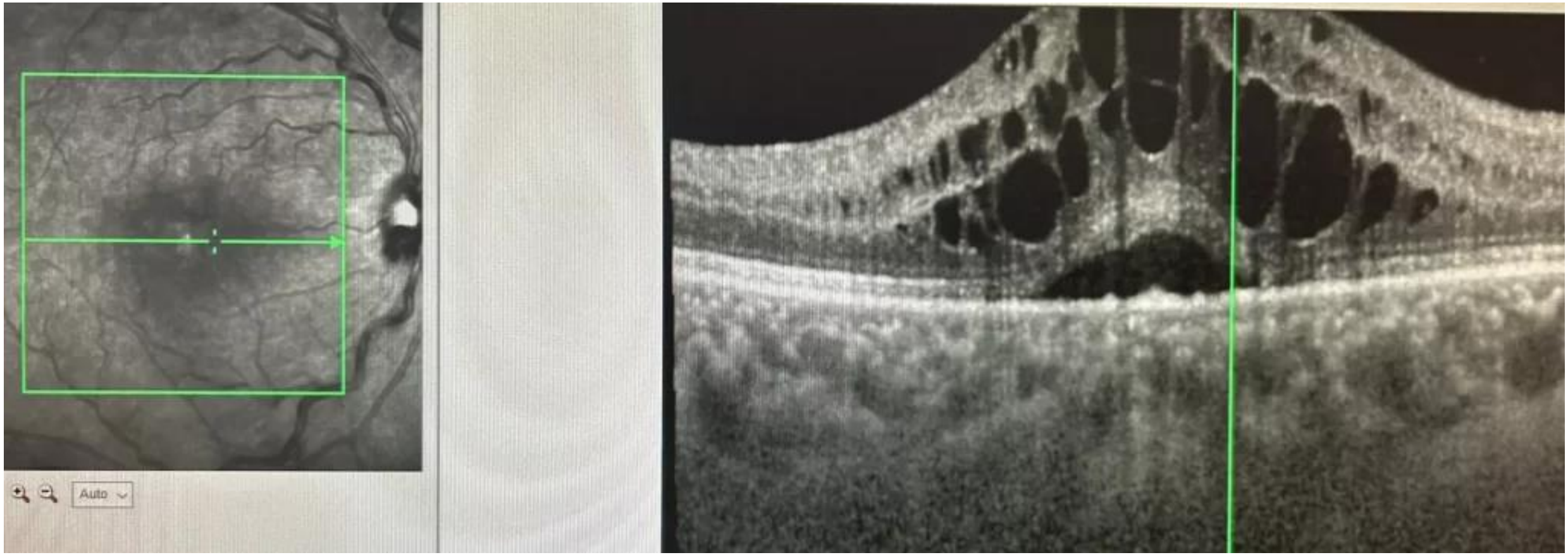
Branch Retinal Vein Occlusion (BRVO) and Hemiretinal Vein Occlusion (HRVO) share similar clinical features, with localized retinal hemorrhages, venous dilation, and macular edema corresponding to the affected vascular territory.



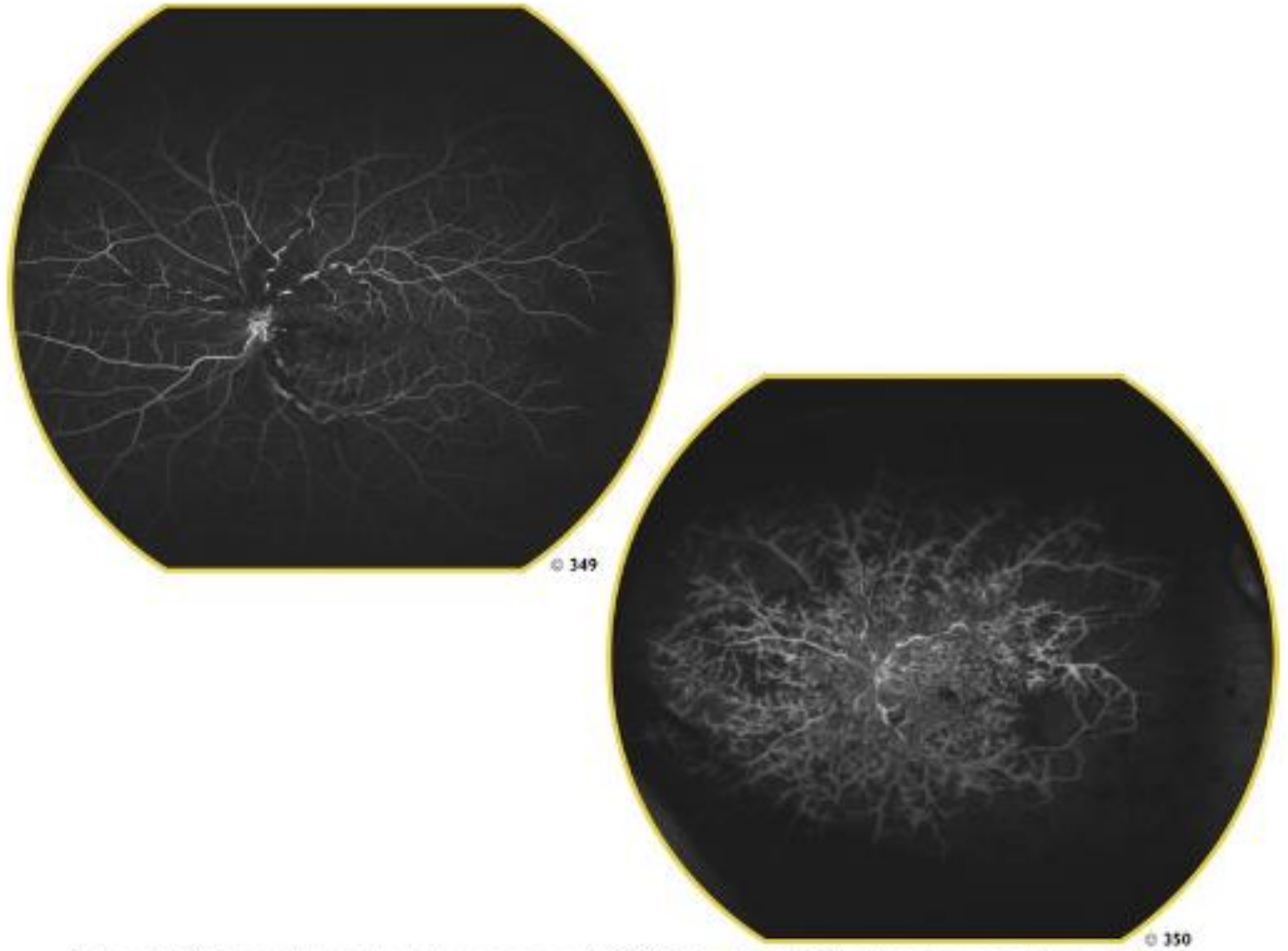


This patient has chronic exudation in the macula with lipid precipitates secondary to hemispheric retinal vein occlusion. Courtesy of Ophthalmic Imaging Systems, Inc

OCT



Fluorescein Angiography



Ultra widefield angiography of two cases of CRVO is shown. The top image shows patchy blockage from hemorrhage but intact peripheral perfusion. The lower image displays severe capillary non-perfusion.

Management Strategies

Anti-VEGF Therapy

Anti-VEGF (Vascular Endothelial Growth Factor) medications, such as ranibizumab, aflibercept, and bevacizumab, have become the mainstay of treatment for RVO. These agents target the VEGF pathway, which is known to contribute to the development of macular edema and neovascularization, helping to improve visual acuity and reduce complications.

Corticosteroid Therapy

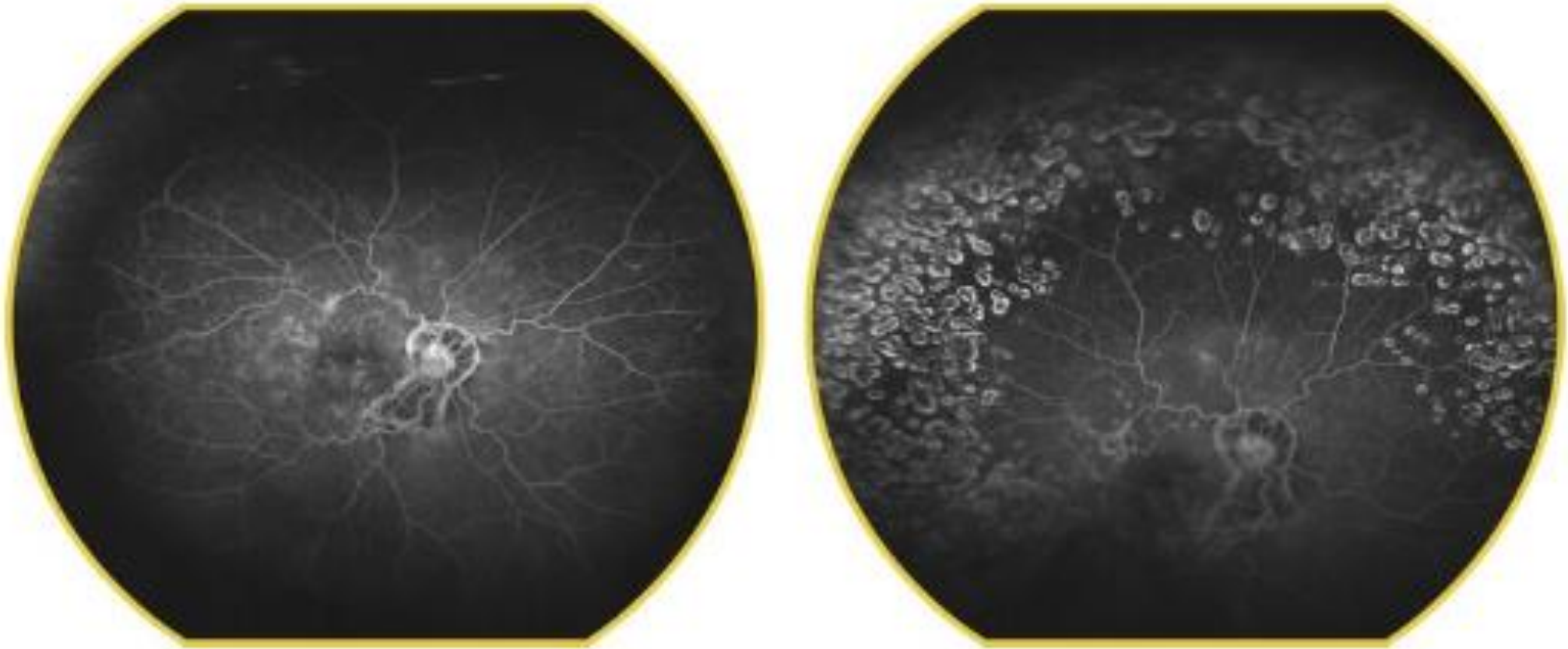
Corticosteroids, such as triamcinolone acetonide and dexamethasone implants, can also be used to treat RVO. They help reduce inflammation and macular edema, leading to improved visual outcomes. Steroid therapy is particularly beneficial in cases where anti-VEGF treatments have been ineffective or not tolerated.

Laser Therapy

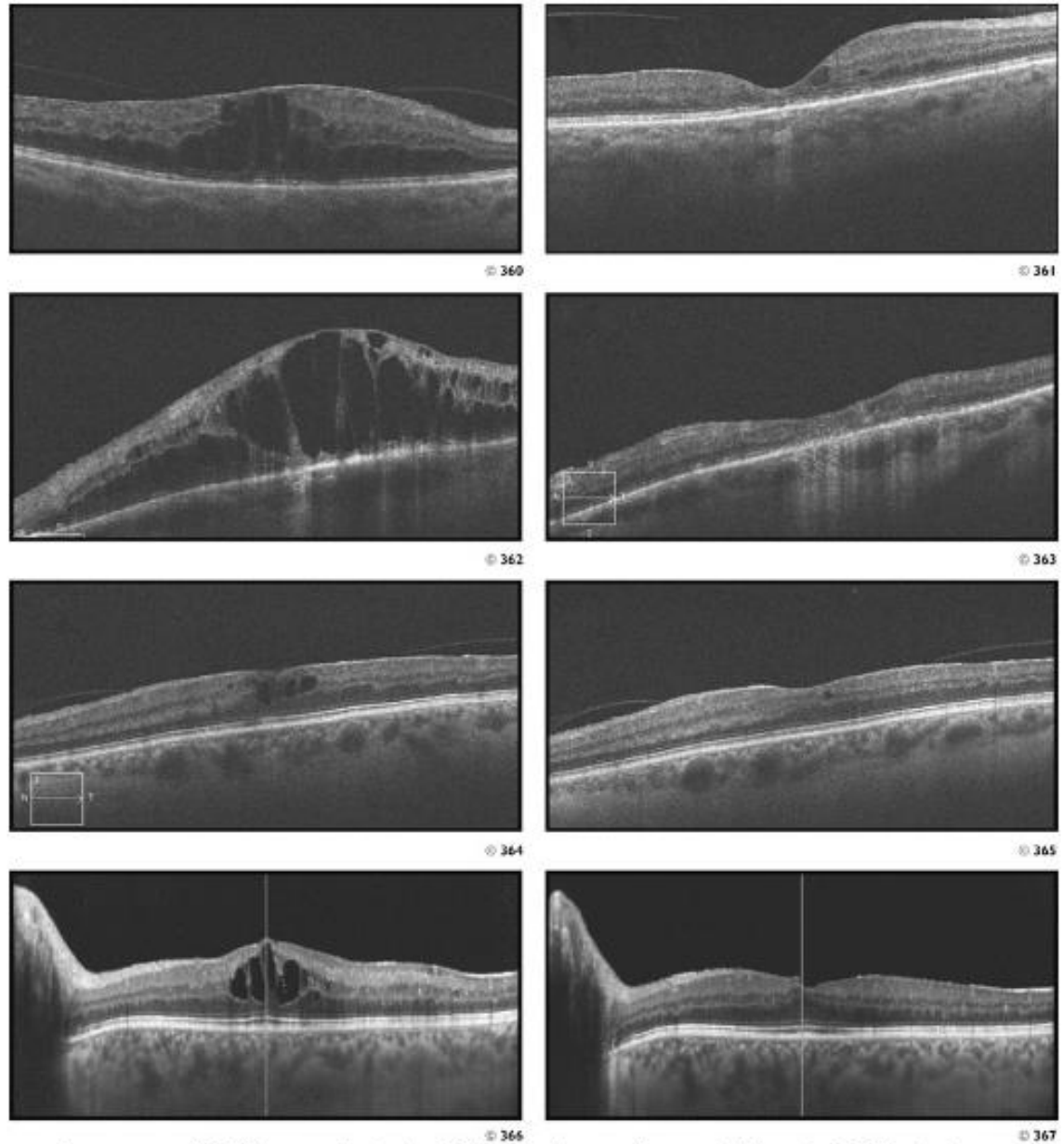
Laser treatments, such as grid laser photocoagulation and panretinal photocoagulation, can be used to address certain complications of RVO. Grid laser can help reduce macular edema, while panretinal photocoagulation can be used to prevent or treat neovascularization and its associated complications, like vitreous hemorrhage or neovascular glaucoma.

Combination Therapy

In some cases, a combination of treatments may be more effective than a single approach. For example, using anti-VEGF therapy in conjunction with corticosteroids or laser can provide synergistic benefits in terms of reducing macular edema, improving visual acuity, and preventing or managing complications.



This patient presented with a central retinal vein occlusion with widespread peripheral capillary non-perfusion illustrated with ultra-widefield fluorescein angiography *(left)*. Widefield FA six month after the placement of panretinal photocoagulation (PRP) to ablate the ischemic retina is shown on the right. Image courtesy of Richard Spaide



Four cases of CRVO complicated by CME are shown with spectral domain OCT prior to treatment *(left images)*. One month after intravitreal anti-VEGF therapy CME is significantly improved in each case *(right images)*.

Retinal Artery Occlusion (RAO)

Central, Branch, Cilioretinal

Introduction to Retinal Artery Occlusion

Definition of Retinal Artery Occlusion

Sudden interruption of blood flow in the retinal artery, leading to acute vision loss

Central Retinal Artery Occlusion (CRAO)

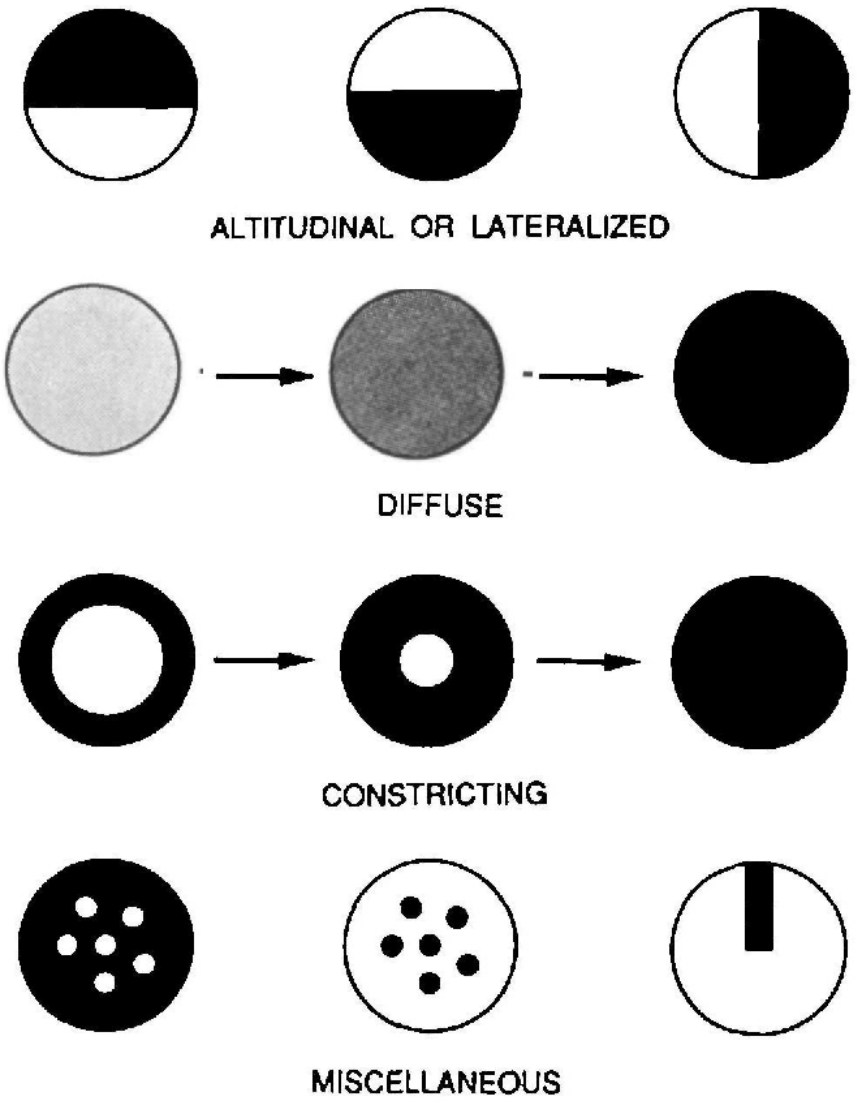
Blockage of the central retinal artery, causing widespread retinal ischemia and severe vision loss

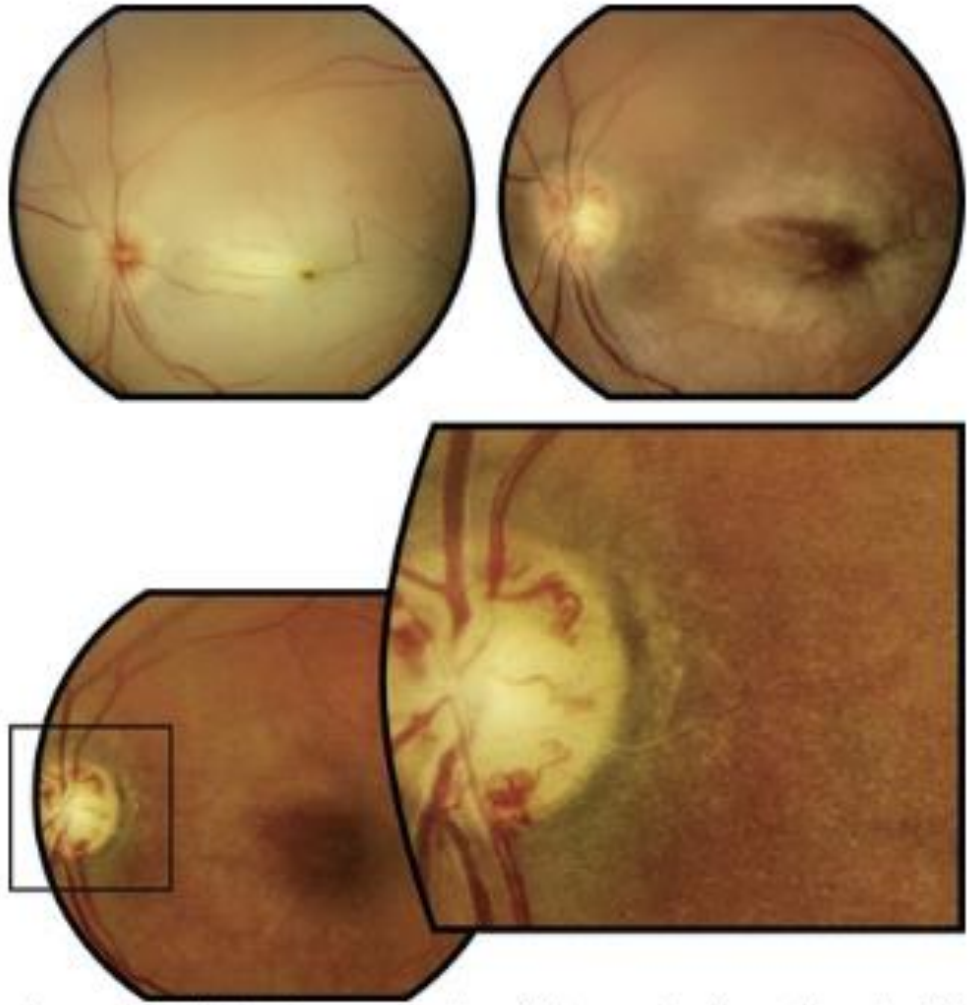
Branch Retinal Artery Occlusion (BRAO)

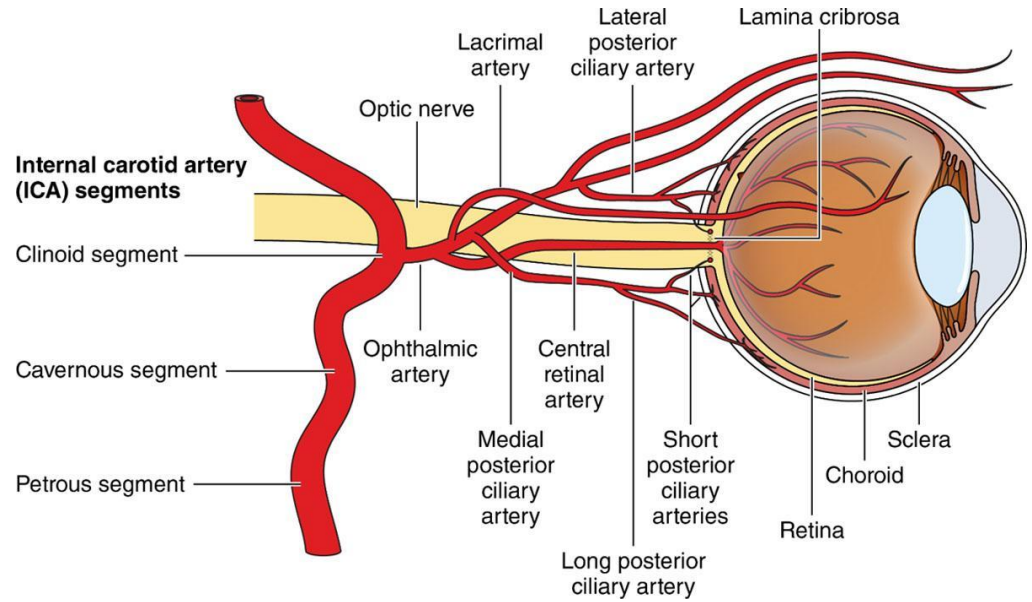
Blockage of a branch of the central retinal artery, affecting a localized area of the retina

Amaurosis Fugax

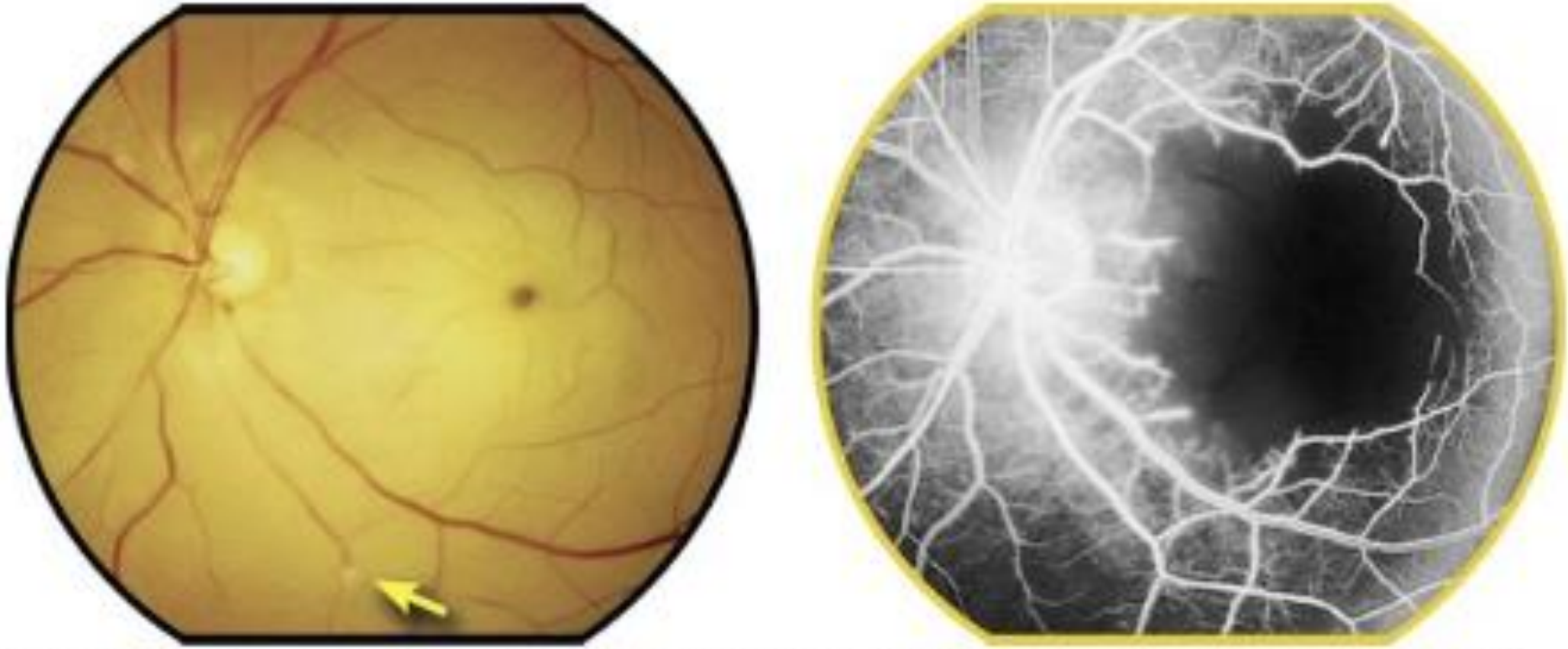
- Amaurosis fugax, a temporary and transient loss of vision, is closely linked to retinal artery occlusion.
- This sudden, painless, and temporary blindness in one eye is often an early warning sign of an underlying vascular issue, such as a blockage in the retinal artery.
- Early recognition and prompt management of amaurosis fugax can help identify and address the underlying cause, potentially preventing a more severe retinal artery occlusion event.



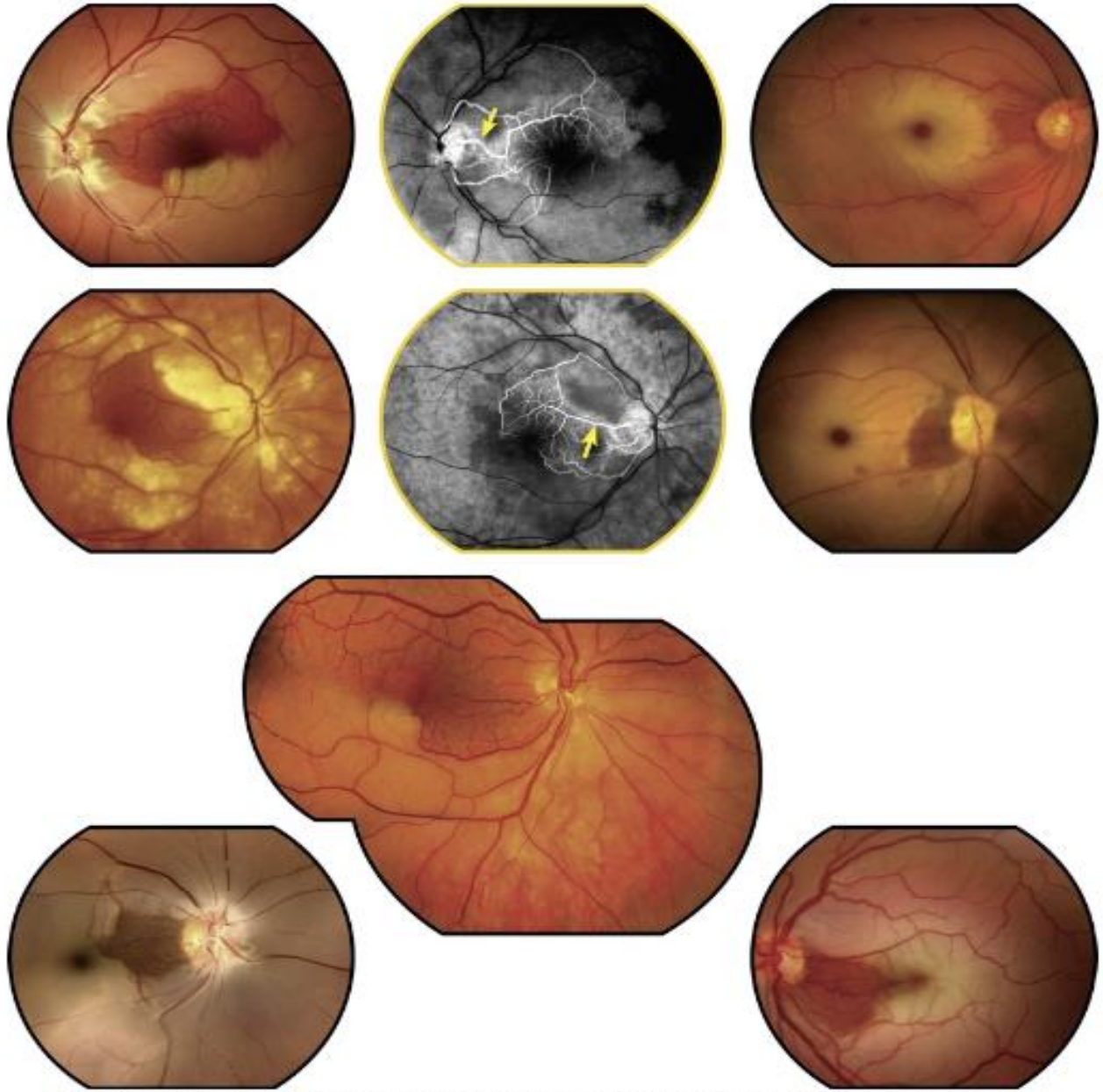




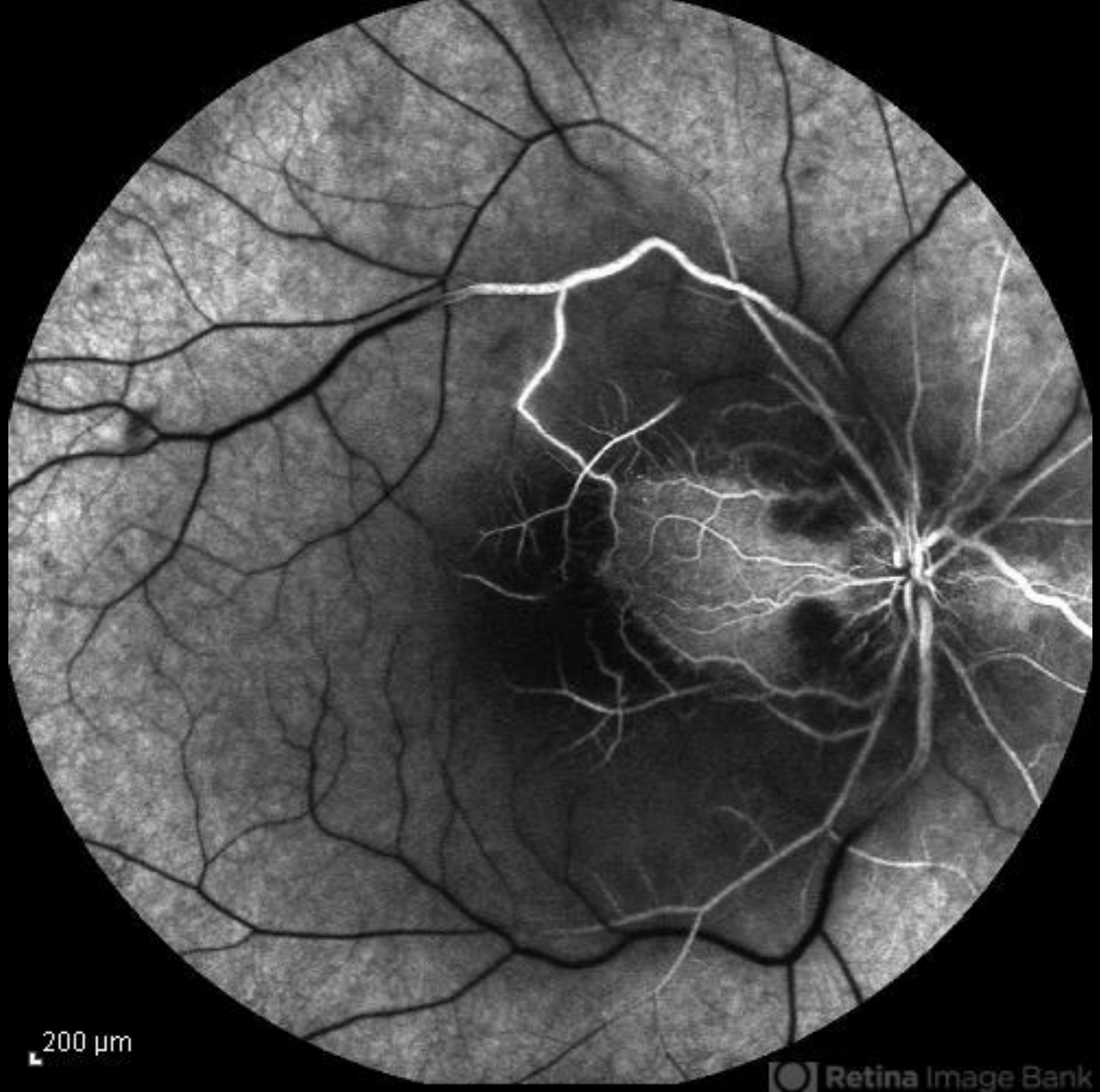
This patient had an ophthalmic artery occlusion. In the acute stage, there is diffuse whitening in the posterior fundus but no "cherry red" spot *(left upper)*. Two months later, the outer retinal ischemia has largely subsided, leaving a reddish-brown discoloration in the foveal region. There is still some perifoveal whitening of the inner retina *(right upper)*. Following resolution of the acute whitening of the retina, the fundus has diffuse RPE changes, decreased retinal vascular caliber, and sheathing irregularities *(lower left)*. Note the compensatory vessels around the circumference of the optic nerve head *(magnified inset)*, collaterals between the retinal and ciliary circulations, referred to as Nettleship collaterals.



This patient has an acute central retinal artery occlusion with a cherry red spot. Note the plaque inferiorly *(arrow)*. Fluorescein angiogram in this case reveals macular ischemia.



These patients all presented with central retinal artery occlusion with sparing of the ciliary artery. Fluorescein angiography documented persistent perfusion of the ciliary artery, partially sparing the fovea *(arrows)*. Note the presence of retinal venous filling emanating from the ciliary circulation. Images courtesy of Ophthalmic Imaging Systems, Inc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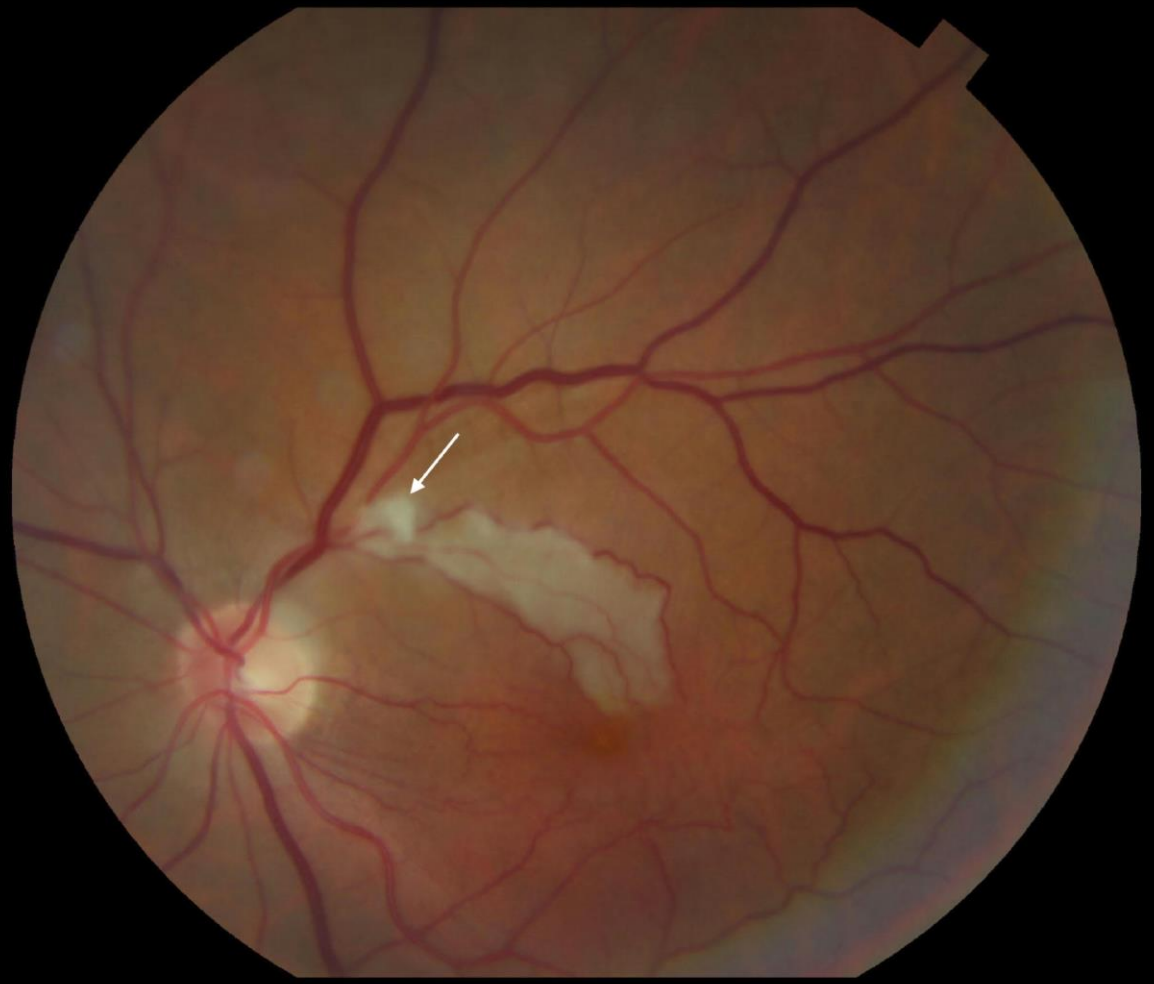
Retina Image Bank



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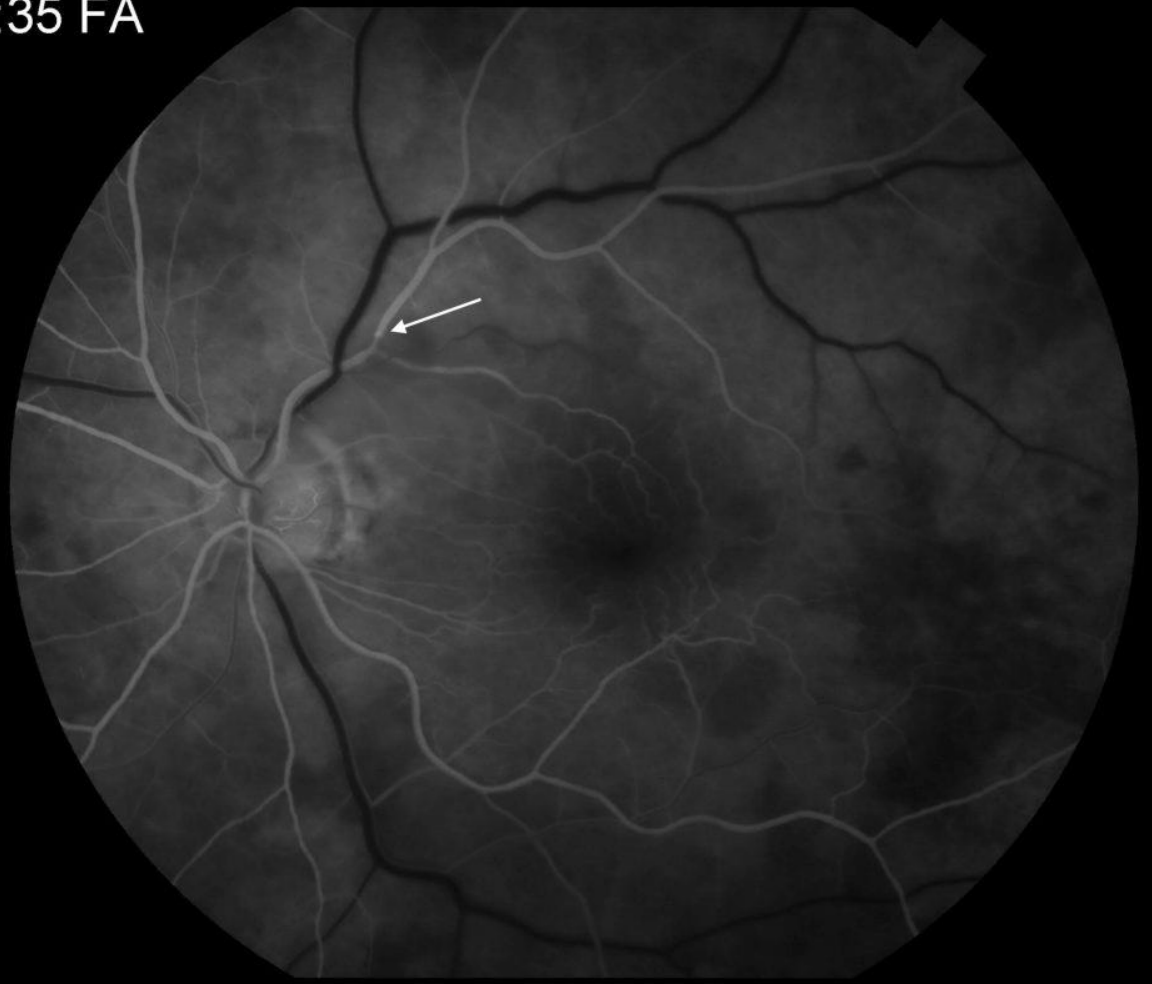
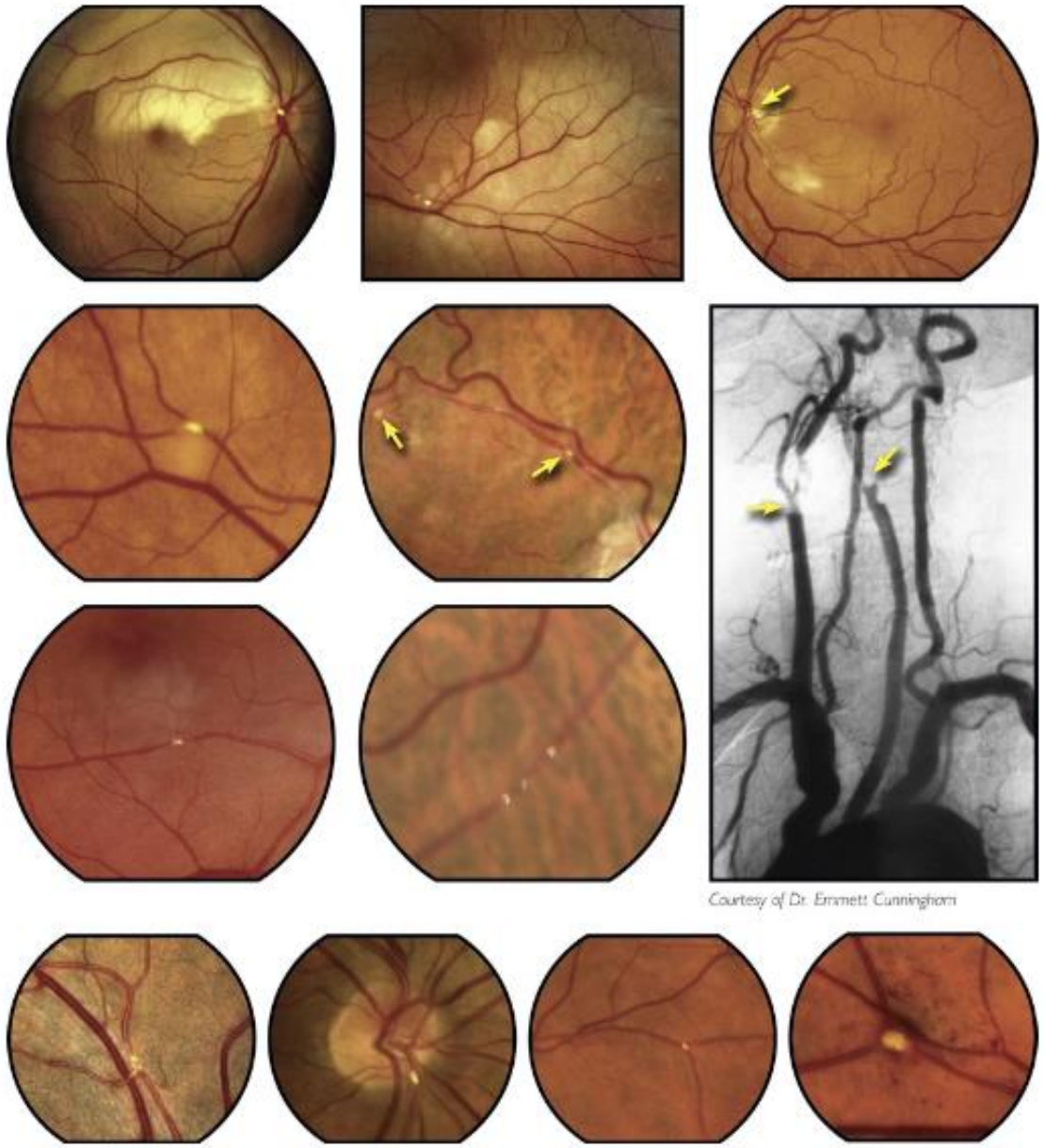
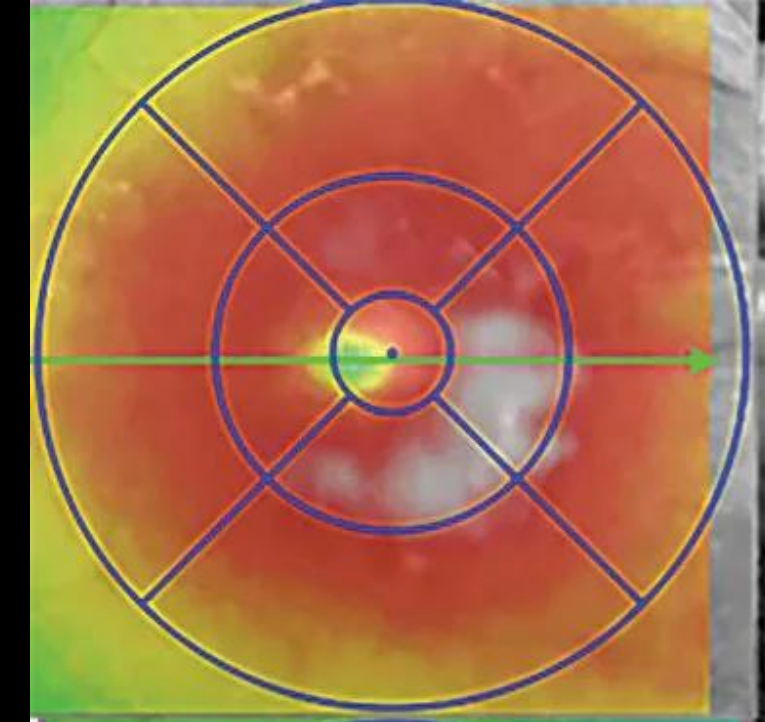


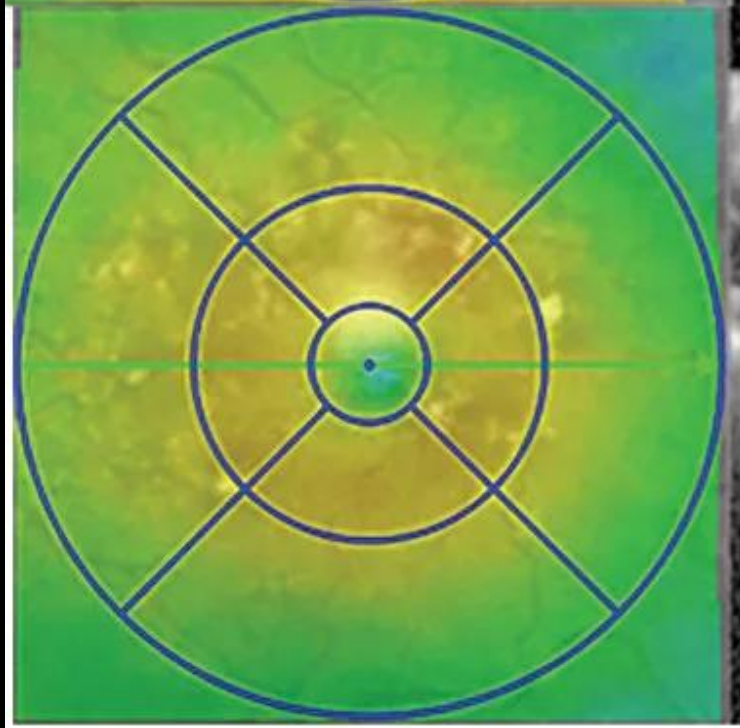
- About one-third of all retinal arteriolar occlusions are noted to be associated with plaques, some of which are glistening or mineralized.
- They are typically found at bifurcations, but not always.
- Retinal emboli originate from the carotid artery or the heart

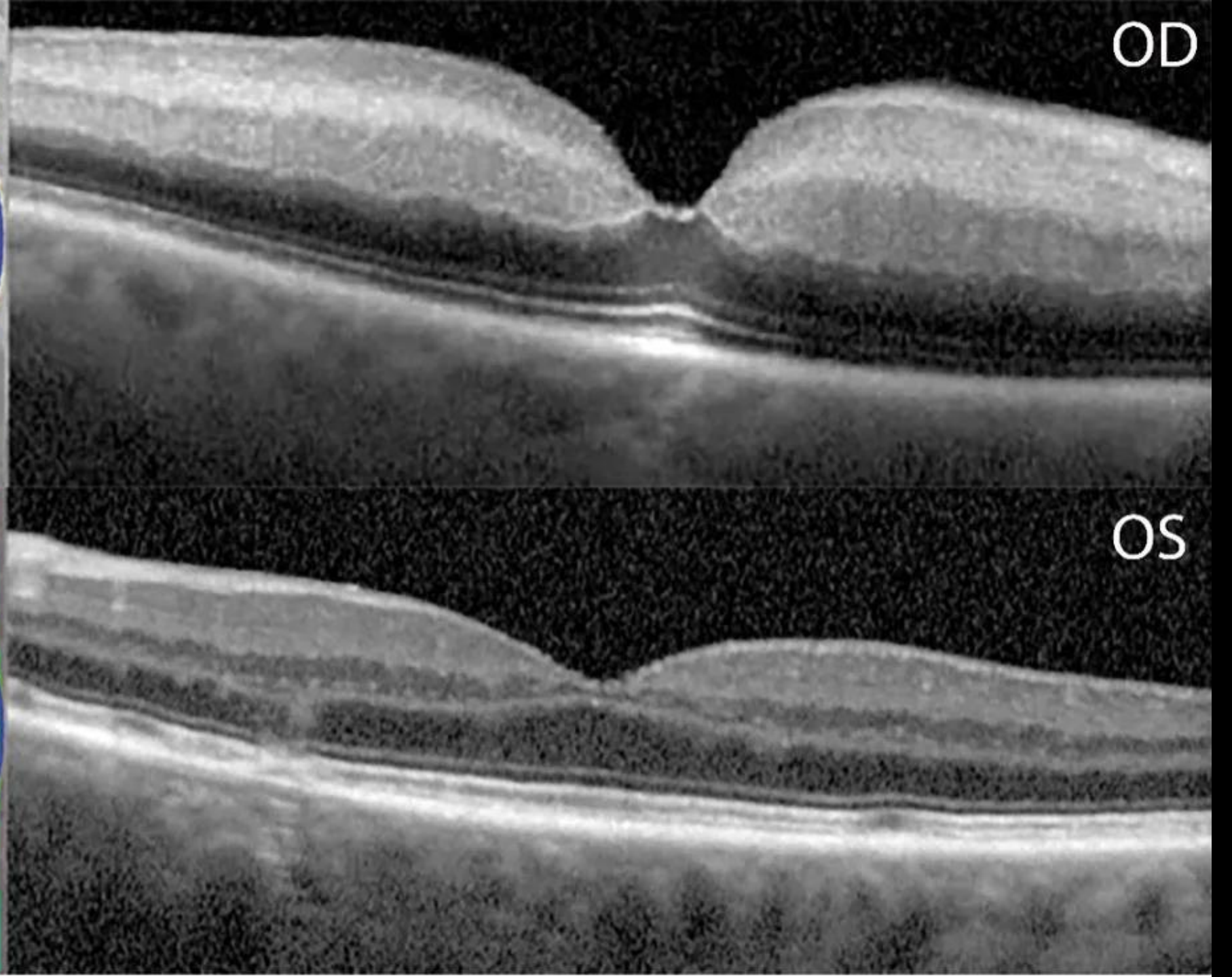


Courtesy of Dr. Emmett Cunningham

Note the multiple cases of branch retinal artery occlusion. Some are acute with ischemic whitening of the retina, whereas others have resolved. Rarely there is hemorrhage surrounding the plaque as noted in the lower right image. The carotid angiogram on the right shows multiple constrictions of the extracranial vessels perfusing the eye *(arrows)*.



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Association with Stroke and Cardiovascular Risk

- ## Shared Risk Factors

Retinal artery occlusion and stroke/cardiovascular events share common risk factors, such as hypertension, diabetes, hyperlipidemia, and atherosclerosis.

- ## Atherosclerotic Plaque Burden

Retinal artery occlusion is often a manifestation of systemic atherosclerotic disease, reflecting the overall plaque burden and increased risk of stroke and cardiovascular events.

- ## Embolic Events

Retinal artery occlusion can be caused by embolism, which can originate from the carotid arteries or the heart, indicating a higher risk of future embolic strokes.

- ## Endothelial Dysfunction

Retinal artery occlusion is associated with endothelial dysfunction, a precursor to the development of cardiovascular disease and increased stroke risk.

- ## Prognostic Indicator

The presence of retinal artery occlusion is considered a prognostic indicator for future stroke and cardiovascular events, prompting the need for comprehensive evaluation and management.

Recommended Systemic Workup

Carotid Doppler	Echocardiogram	ESR/CRP	Diagnostic Imaging
Assess the carotid arteries for atherosclerotic changes, stenosis, or occlusion that may contribute to the retinal artery occlusion.	Evaluate the heart for potential sources of emboli, such as atrial fibrillation, valvular disease, or wall motion abnormalities.	Measure the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) to identify underlying inflammatory or autoimmune conditions that may be associated with the retinal artery occlusion.	Utilize optical coherence tomography (OCT) and fluorescein angiography (FA) to assess the extent of retinal ischemia and confirm the diagnosis of retinal artery occlusion.

Management Strategies and Emergent Care

AC Paracentesis, IOP lowering drops

Urgent Stroke Team Referral

Intravenous Thrombolytic Therapy/ Hyperbaric oxygen

Emergent Endovascular Intervention

Antiplatelet/ Anticoagulant Therapy

Diabetic Retinopathy

Screening and Staging

Diabetic retinopathy is a complication of diabetes that affects the small blood vessels in the retina, the light-sensitive tissue at the back of the eye. As diabetes progresses, these blood vessels can become damaged, leading to vision problems and, in severe cases, vision loss.

Screening

- Individuals with diabetes should undergo annual comprehensive eye exams to screen for diabetic retinopathy.

Stages

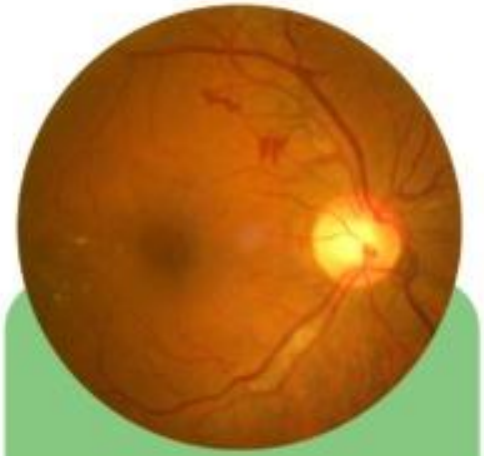
- Classified into two main stages: non-proliferative diabetic retinopathy (**NPDR**) and proliferative diabetic retinopathy (**PDR**).
- NPDR is the earlier stage, characterized by microaneurysms, hemorrhages, and exudates.
- PDR is the more advanced stage, marked by the formation of new abnormal blood vessels (neovascularization) that can lead to vision loss.

- Staging of NPDR
  - NPDR is further divided into mild, moderate, and severe stages based on the extent and severity of retinal changes. Mild NPDR involves a few microaneurysms, while moderate NPDR has more extensive changes.
  - Severe NPDR is characterized by a significant number of hemorrhages, microaneurysms, and intraretinal microvascular abnormalities.
- PDR
  - PDR is the most advanced stage of diabetic retinopathy, characterized by the growth of new, abnormal blood vessels (neovascularization) on the retina or optic nerve.
  - This can lead to vision-threatening complications, such as vitreous hemorrhage and tractional retinal detachment.

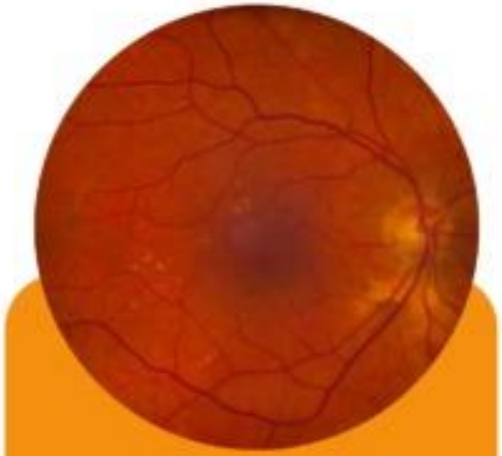
TABLE 1. Classification and stages of diabetic retinopathy[8]

Type	Stage	Fundus findings
NPDR	Mild	Few microaneurysms, retinal hemorrhages, or hard exudates
	Moderate	1-3 quadrants of retinal hemorrhages with cotton wool spots
	Severe	Having 1 criteria of the 4-2-1 rule: » Severe hemorrhages in 4 quadrants » 2 or more quadrants of venous bleeding » 1 or more quadrants of IRMA
	Very severe	Having 2 or more criteria of the 4-2-1 rule
PDR		Vitreous hemorrhage or pre–retinal hemorrhage Extraretinal neovascularisation

IRMA, intraretinal microvascular abnormalities; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy.

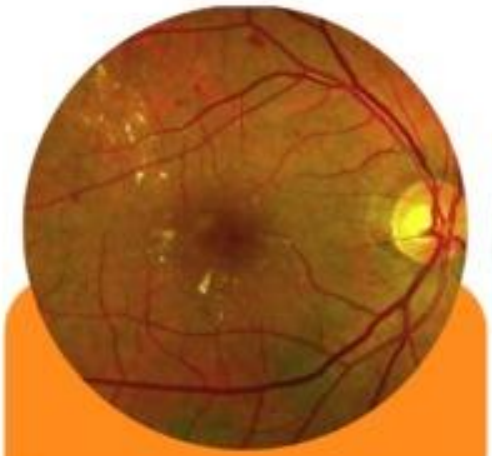


No disease visible



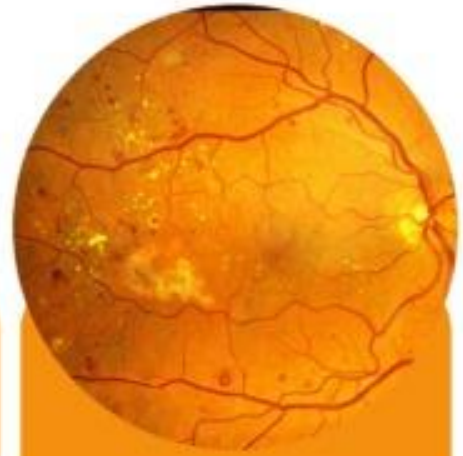
Mild nonproliferative diabetic retinopathy (NPDR)

Localized swelling of the small blood vessels in the retina (microaneurysms)



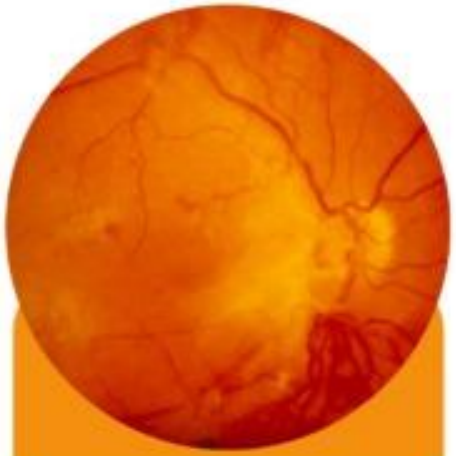
Moderate NPDR

Mild NPDR plus small bleeds (dot and blot haemorrhages), leaks (hard exudates) or closure (cotton wool spots) of small blood vessels.



Severe NPDR

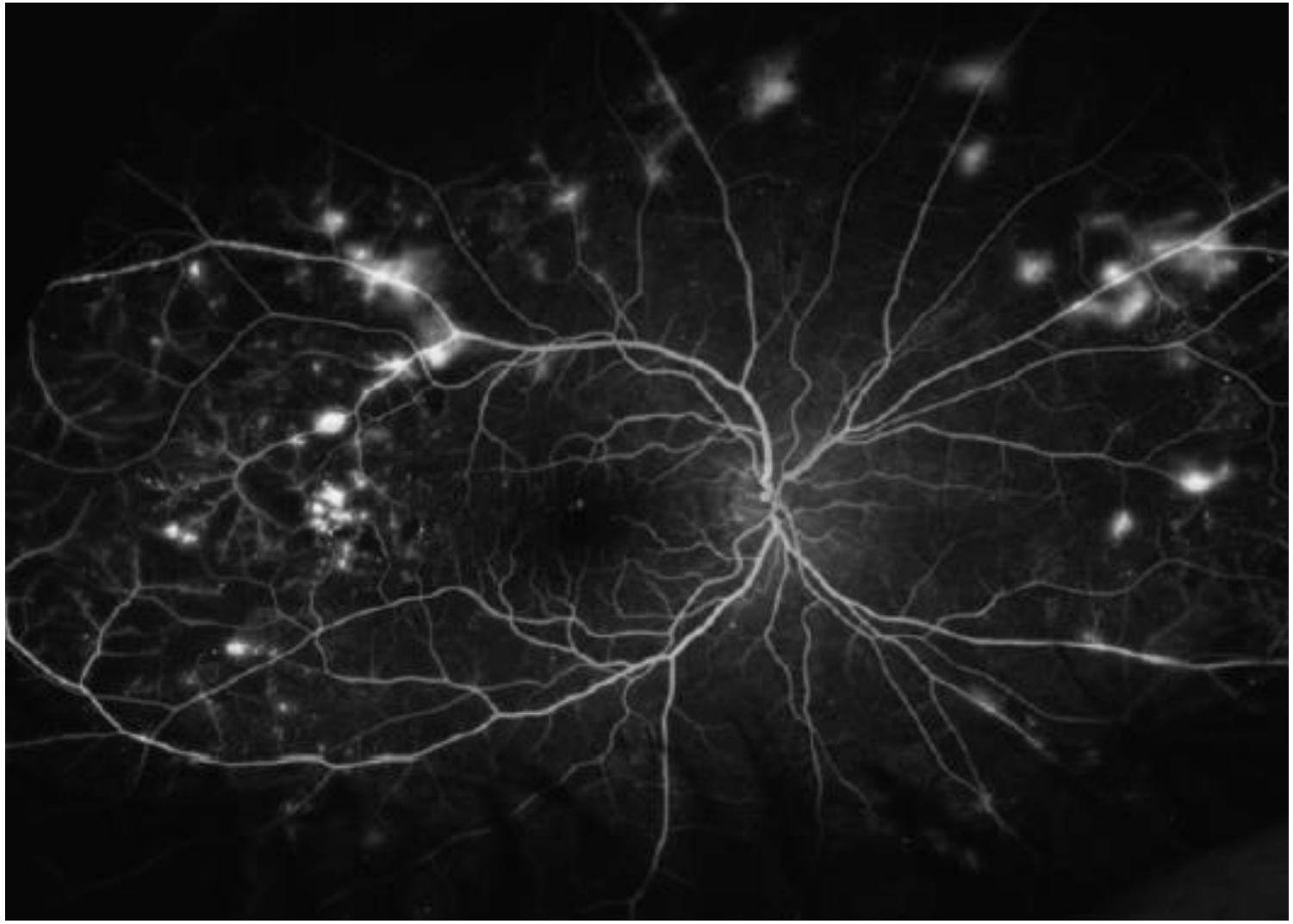
Moderate NPDR plus further damage to blood vessels (interetinal hemorrhages, venous beading, intraretinal microvascular abnormalities).

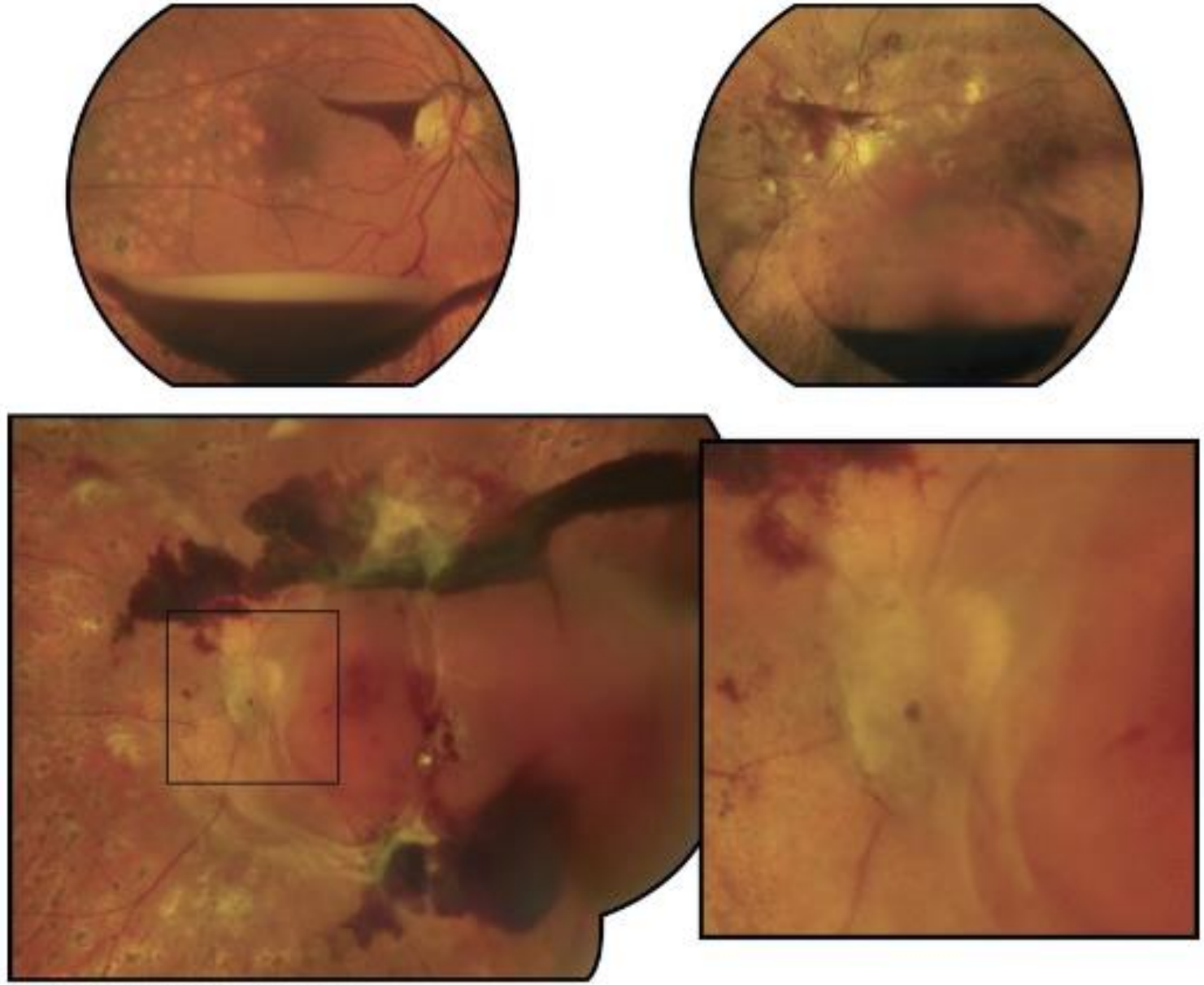


PDR

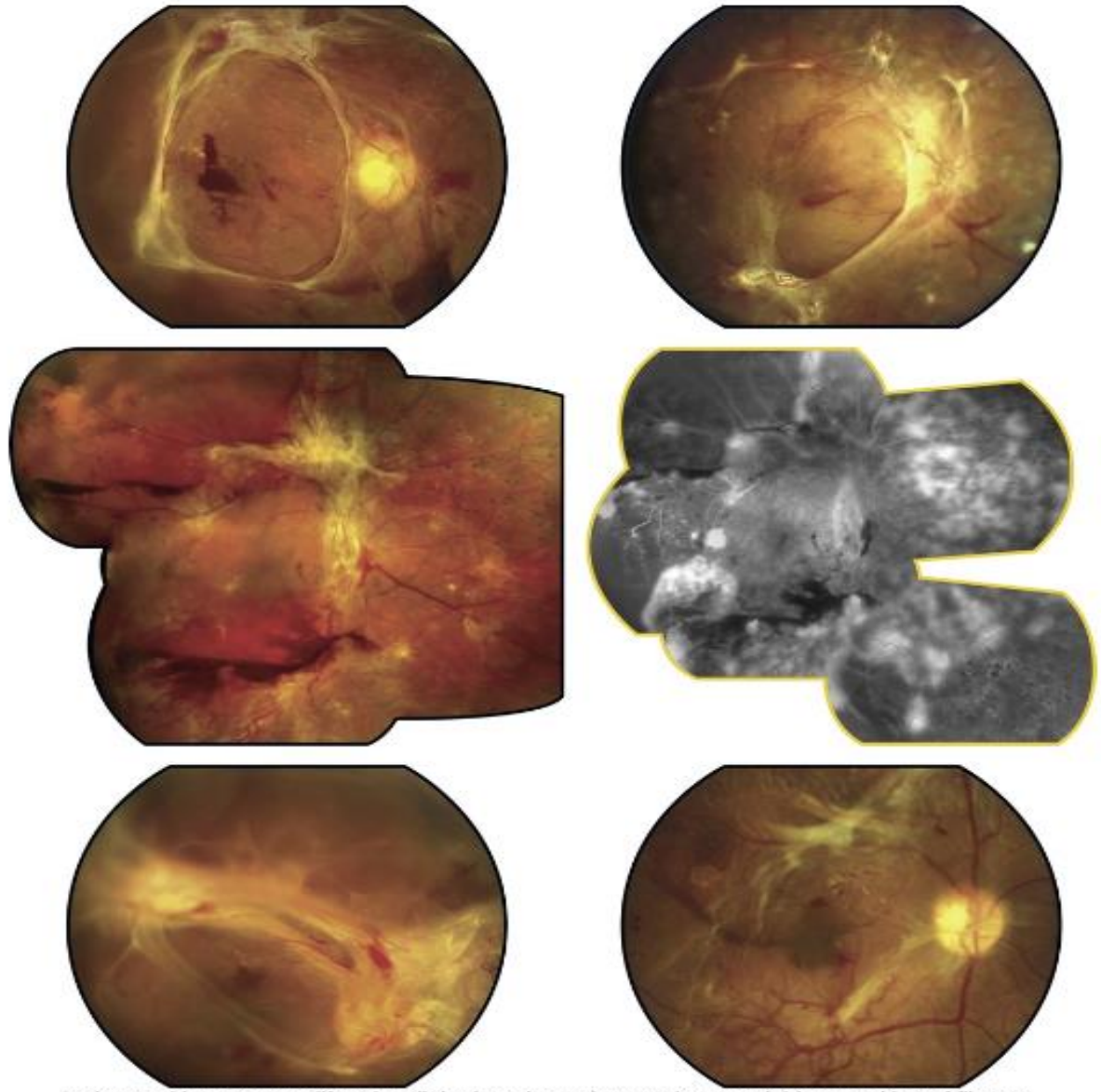
New vessel formation or vitreous/preretina l hemorrhage or tractional retinal detachment

NPDR vs PDR





Courtesy of Ophthalmic Imaging Systems, Inc



Patients with severe proliferative diabetic retinopathy may have variable severities of fibrous growth. In some instances, the fibrosis may obliterate the view of the optic nerve *(upper right, middle left, and lower left)*. There is active bleeding from the vascular component of these membranes. The FA shows widespread neovascularization and peripheral ischemia.

Diabetic Macular Edema (DME)

Definition

Diabetic macular edema (DME) is a complication of diabetic retinopathy characterized by swelling and thickening of the macula, the central part of the retina responsible for sharp, central vision.

Causes

DME is caused by the leakage of fluid and protein from damaged blood vessels in the retina, leading to the accumulation of fluid in the macula.

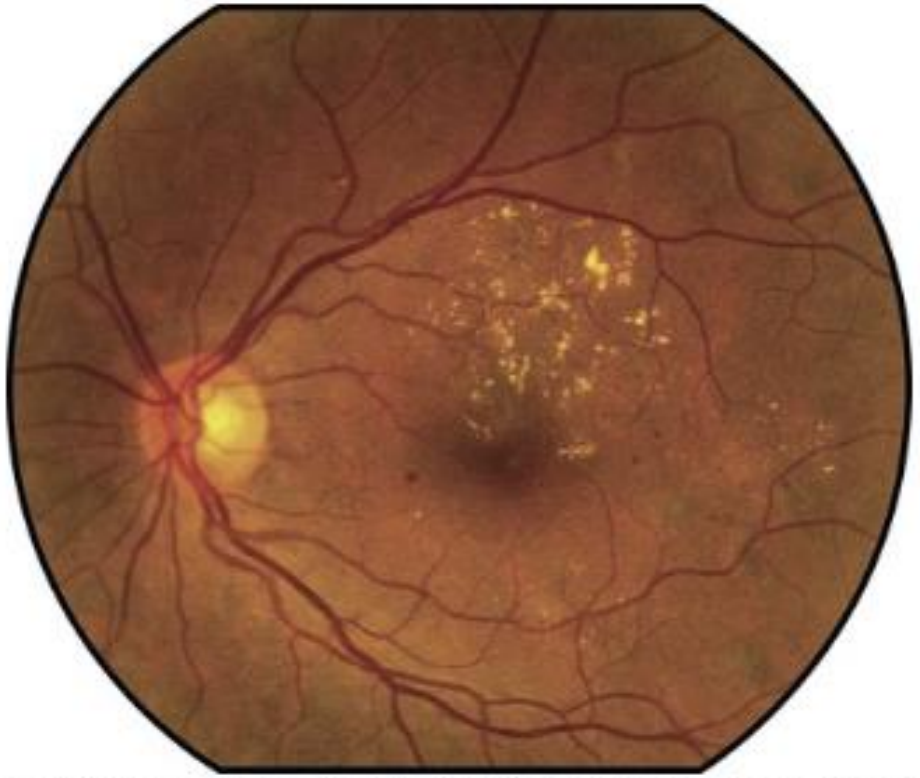
Symptoms

Symptoms of DME include blurred or distorted central vision, difficulty reading or performing tasks that require sharp vision, and in some cases, complete vision loss.

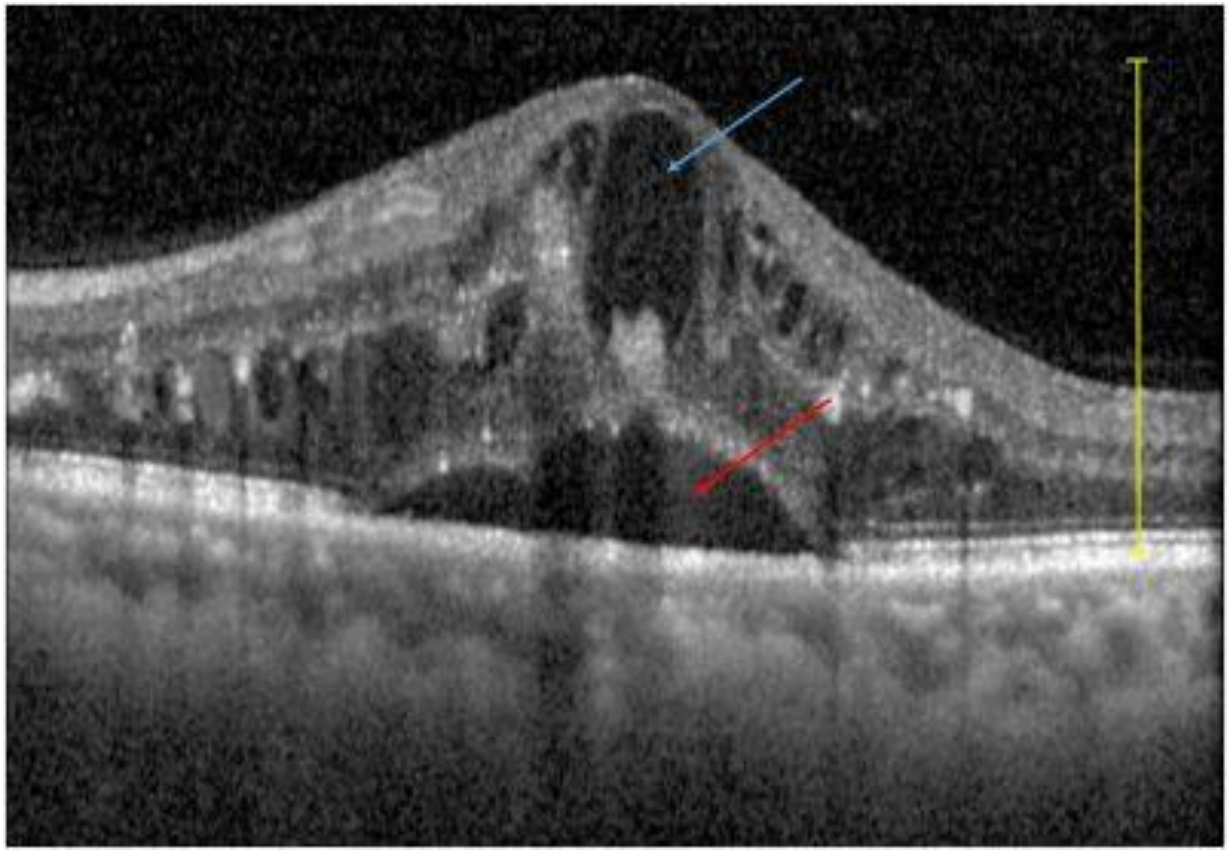
Effects

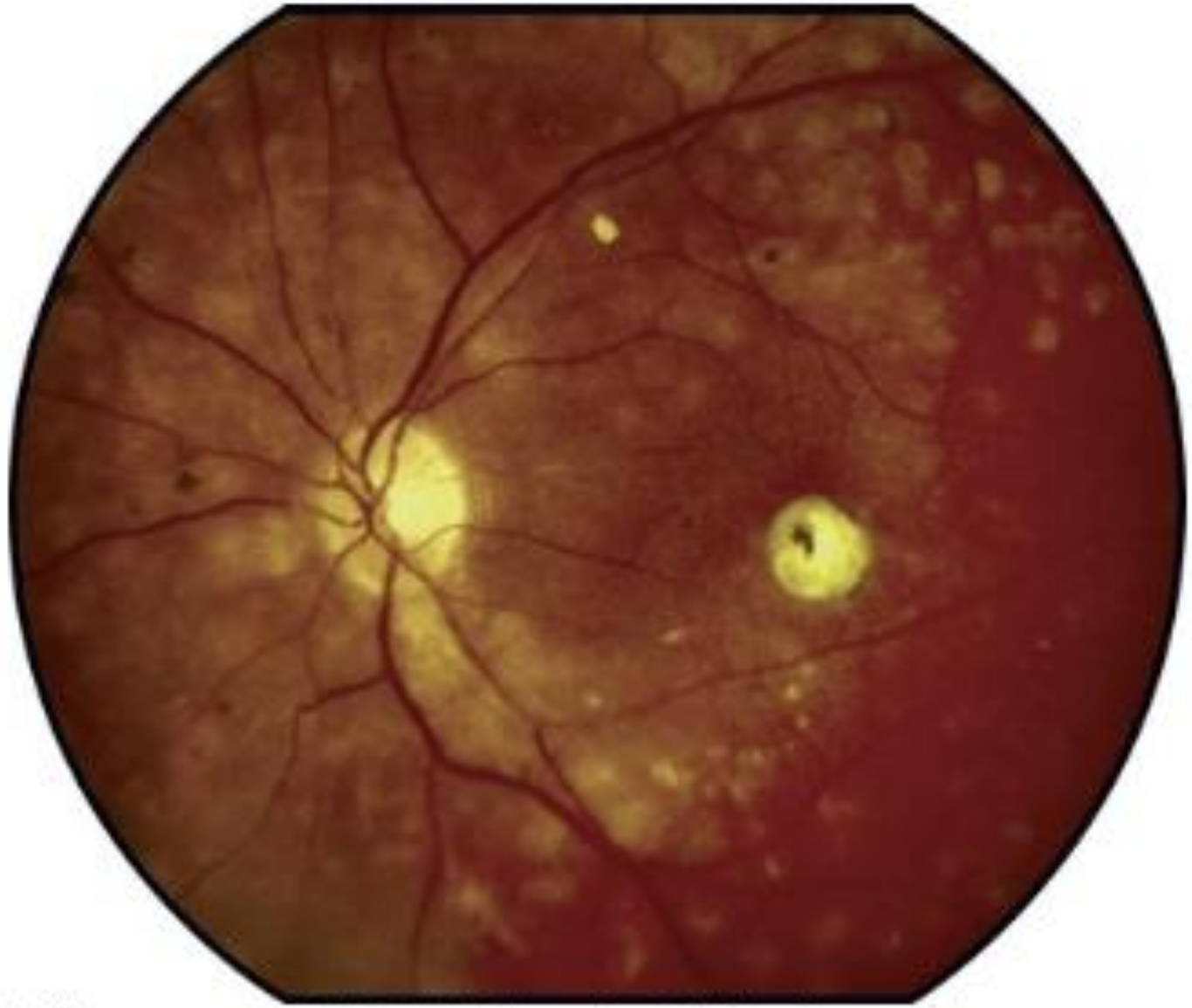
DME can significantly impact a person's visual acuity and quality of life, making it difficult to perform daily tasks, read, drive, and engage in other activities that require clear central vision.

Diabetic Macular Edema (DME)



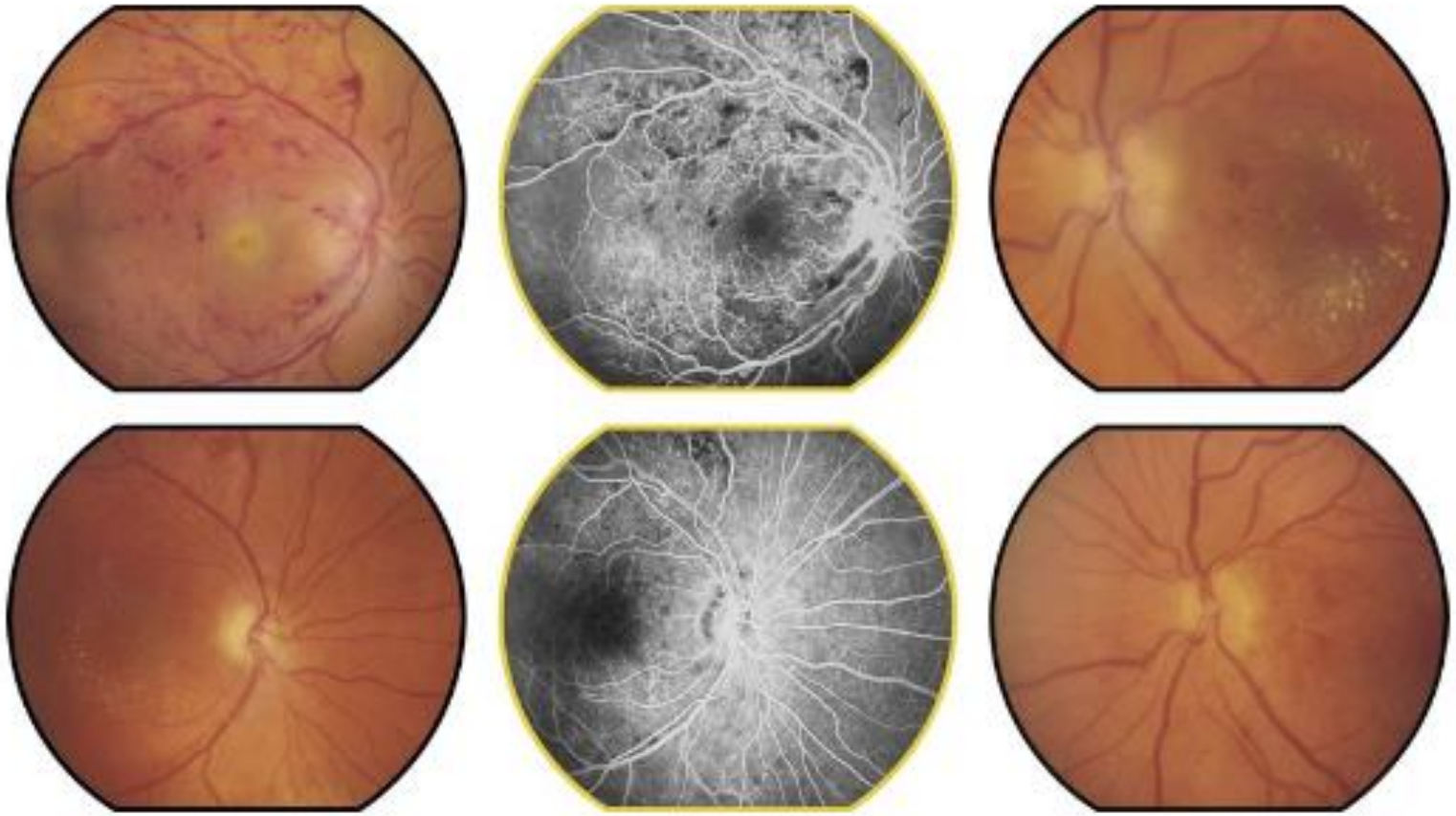
This patient has NPDR with microaneurysms and complicated by clinically significant diabetic macular edema and lipid exudation.





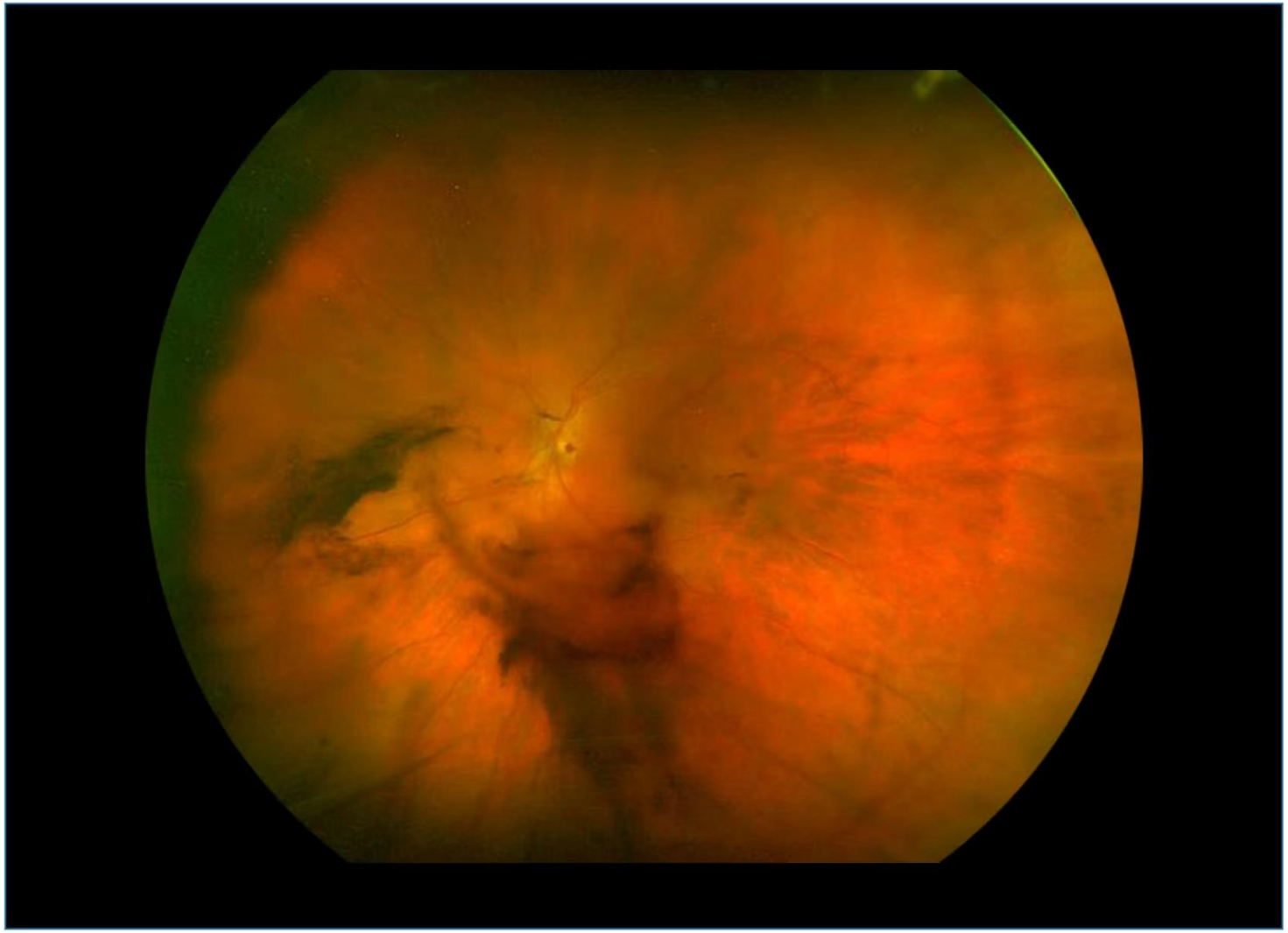
Note the central fibrous scar in this diabetic patient. Diabetic macular scars may result from chronic lipid deposition, fibrovascular proliferation, traction, or hemorrhage.

Diabetic Papillopathy

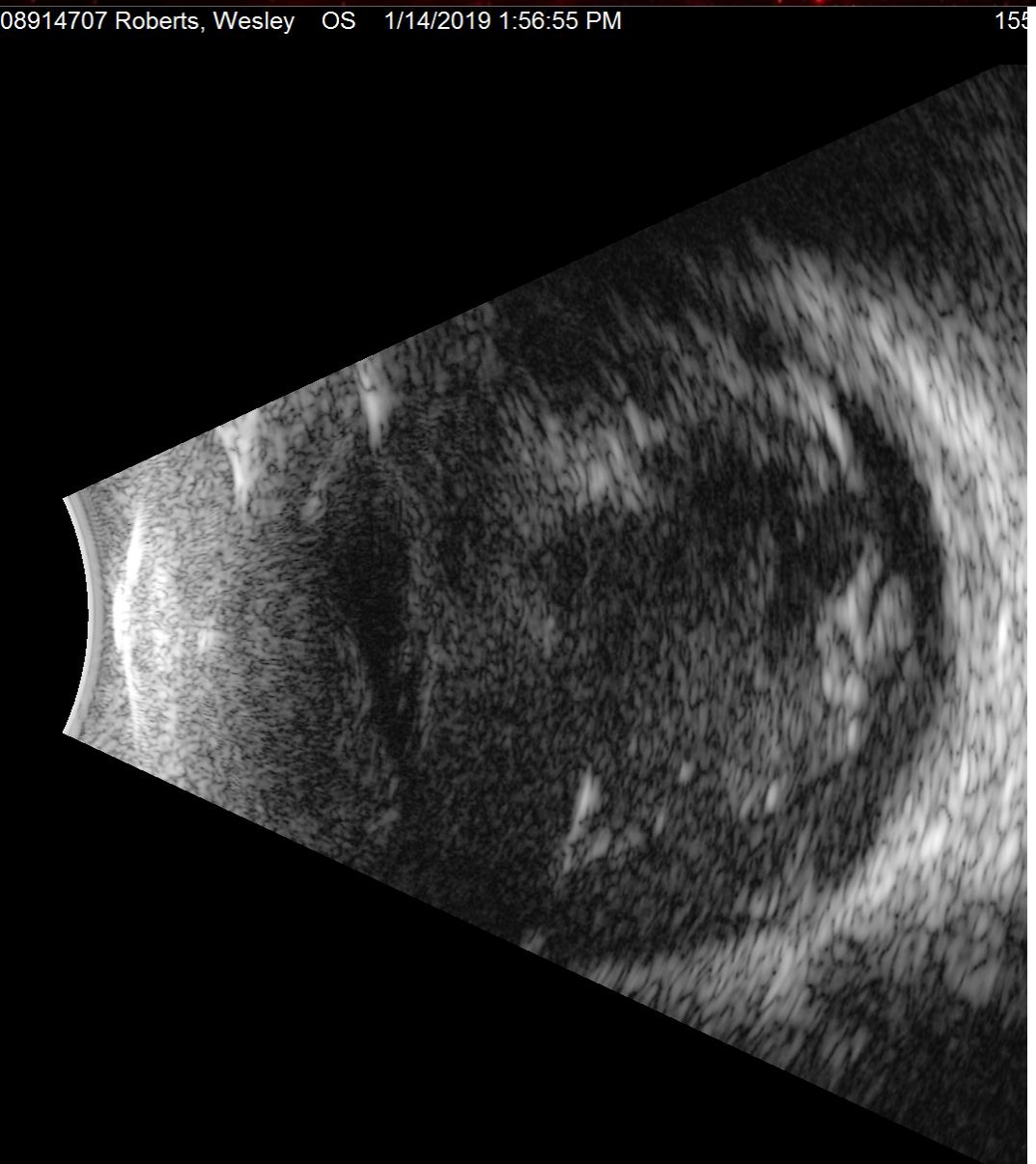


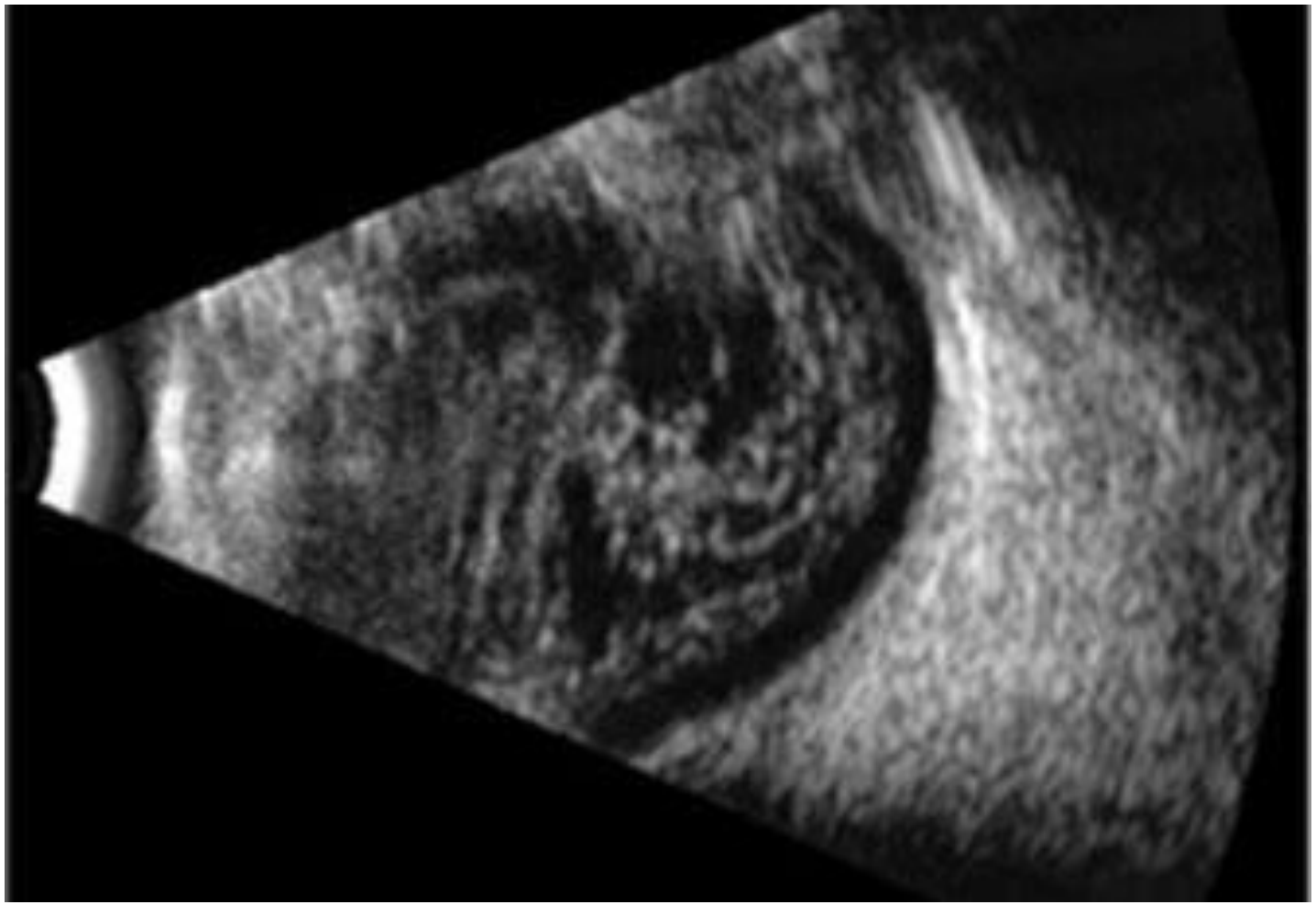
This patient presented with bilateral diabetic papillopathy. There was swelling of the nerve and associated macular edema and severe NPDR *(upper row)*. Ten weeks later, there was spontaneous resolution of the papillopathy in each eye *(lower row)* with subsequent optic atrophy and improvement of the retinopathy, as illustrated in the FA in the lower row, after panretinal laser photocoagulation therapy. Courtesy of Dr. Sohan Sing-Hayreh

Vitreous Hemorrhage



Vitreous Hemorrhage





Imaging Techniques

- ## Fundus Photography

Captures high-resolution images of the retina, allowing for detailed examination of retinal changes associated with retina disease.

- ## Fluorescein Angiography

Intravenous injection of fluorescein dye to visualize the retinal blood vessels, providing insights into vascular abnormalities and leakage associated with hypertensive retinopathy and macroaneurysms.

- ## Optical Coherence Tomography (OCT)

Non-invasive imaging technique that generates cross-sectional images of the retina, enabling assessment of retinal layer thickness and structural changes related to hypertensive retinopathy.

- ## Optical Coherence Tomography Angiography (OCTA)

Advanced OCT-based imaging modality that provides detailed visualization of the retinal vascular network, allowing for the assessment of microvascular changes in hypertensive retinopathy.

- ## Ultrasonography

Utilizes high-frequency sound waves to create images of the eye, which can be helpful in evaluating the presence and characteristics of vitreous hemorrhages.

Treatment Options

Laser Therapy

Laser photocoagulation is a common treatment for diabetic retinopathy. It can be used to treat both non-proliferative and proliferative diabetic retinopathy. Laser therapy aims to seal leaking blood vessels and prevent the growth of new abnormal blood vessels.

Intravitreal Injections

Intravitreal injections of anti-VEGF (Vascular Endothelial Growth Factor) medications, are used to treat diabetic macular edema (DME) and proliferative diabetic retinopathy. These medications help reduce fluid buildup and prevent the growth of new blood vessels.

Surgery

Surgery for patients who do not improve with anti-vegf. Tractional RDs.

Key Takeaways

Early detection is crucial

Regular eye exams and screening can help identify diabetic retinopathy in its early stages, allowing for timely intervention.

Controlling blood sugar and blood pressure

Maintaining healthy blood sugar and blood pressure levels can significantly slow the progression of diabetic retinopathy.

Prompt treatment is essential

Treatments like laser therapy, intravitreal injections, and systemic control can effectively manage diabetic retinopathy and prevent vision loss.

Diabetic macular edema requires specialized care

Diabetic macular edema, a leading cause of vision loss in diabetic retinopathy, requires prompt diagnosis and targeted treatment.

Hypertensive Retinopathy & Retinal Macroaneurysms

Acute and Chronic Hypertension

Acute Hypertension

Sudden, rapid rise in blood pressure leading to retinal vasospasm, arteriolar narrowing, and cotton wool spots

Chronic Hypertension

Sustained high blood pressure causing arterial wall thickening, arteriovenous nicking, and optic disc edema

Retinal Hemorrhages

Due to vascular fragility

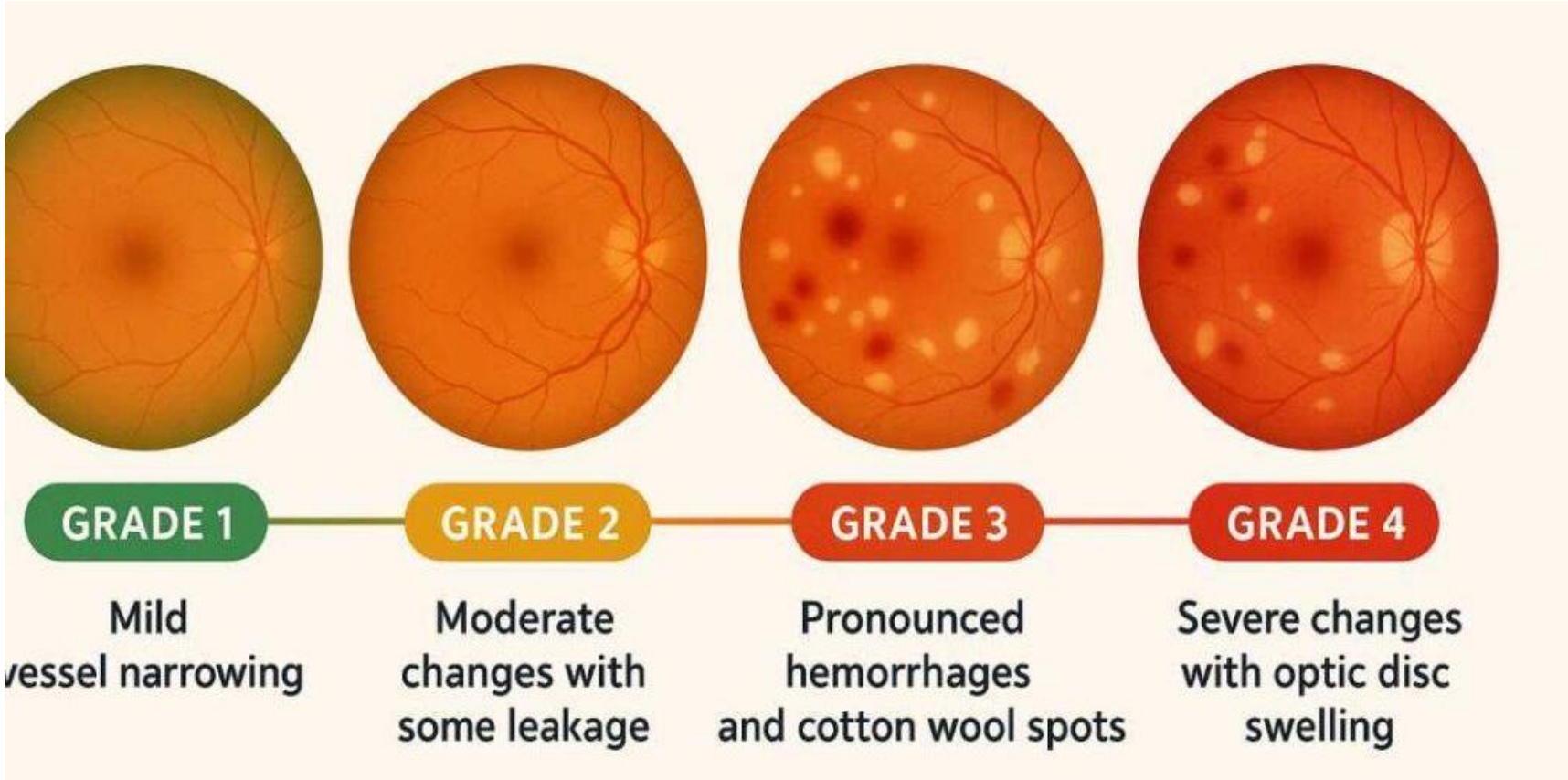
Exudates and Edema

Acute and Chronic hypertension causes retinal edema and exudates

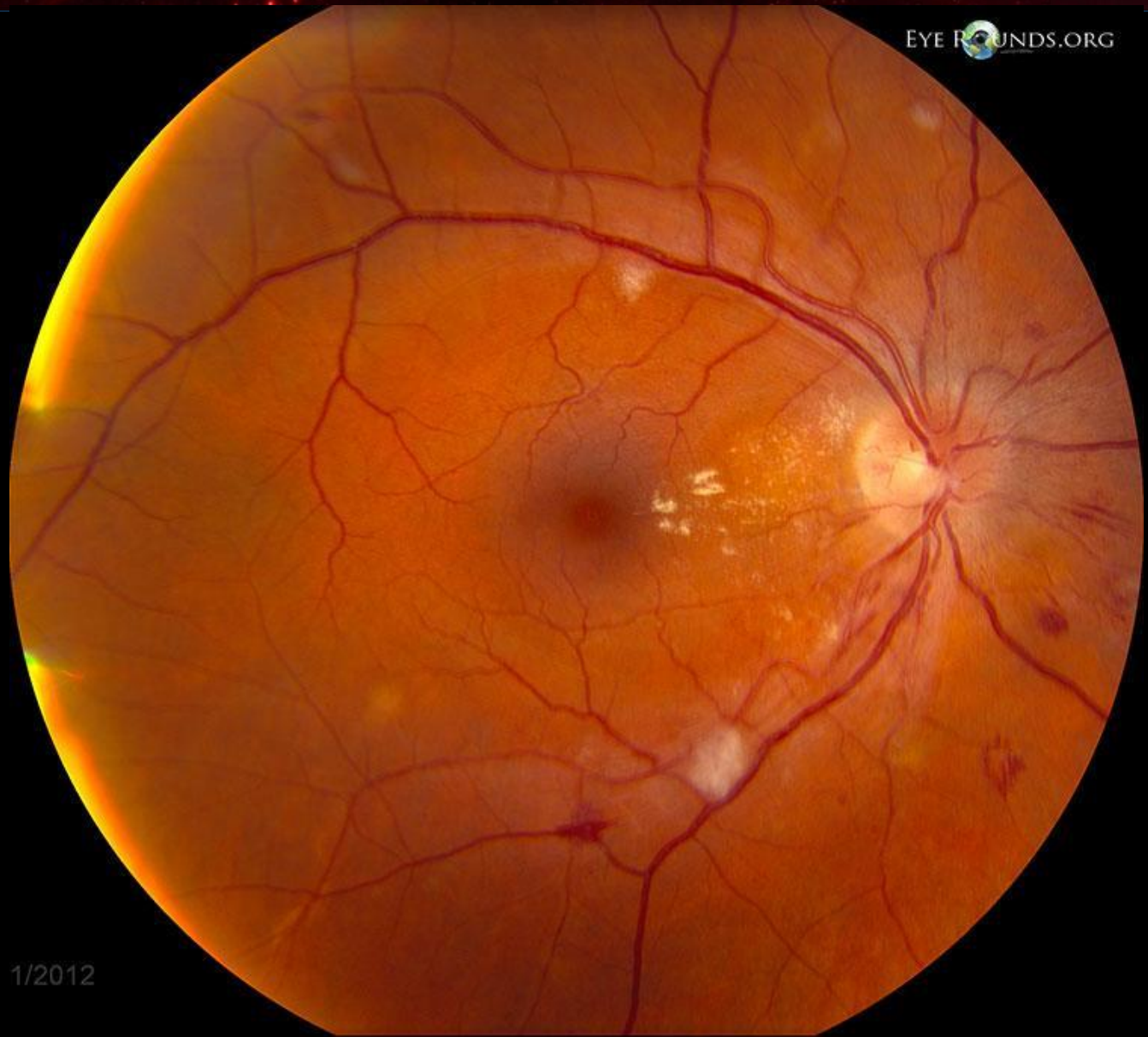
Understanding the distinct fundus changes in acute and chronic hypertension is crucial for accurate diagnosis and appropriate management of hypertensive retinopathy.

Hypertension and the Retina

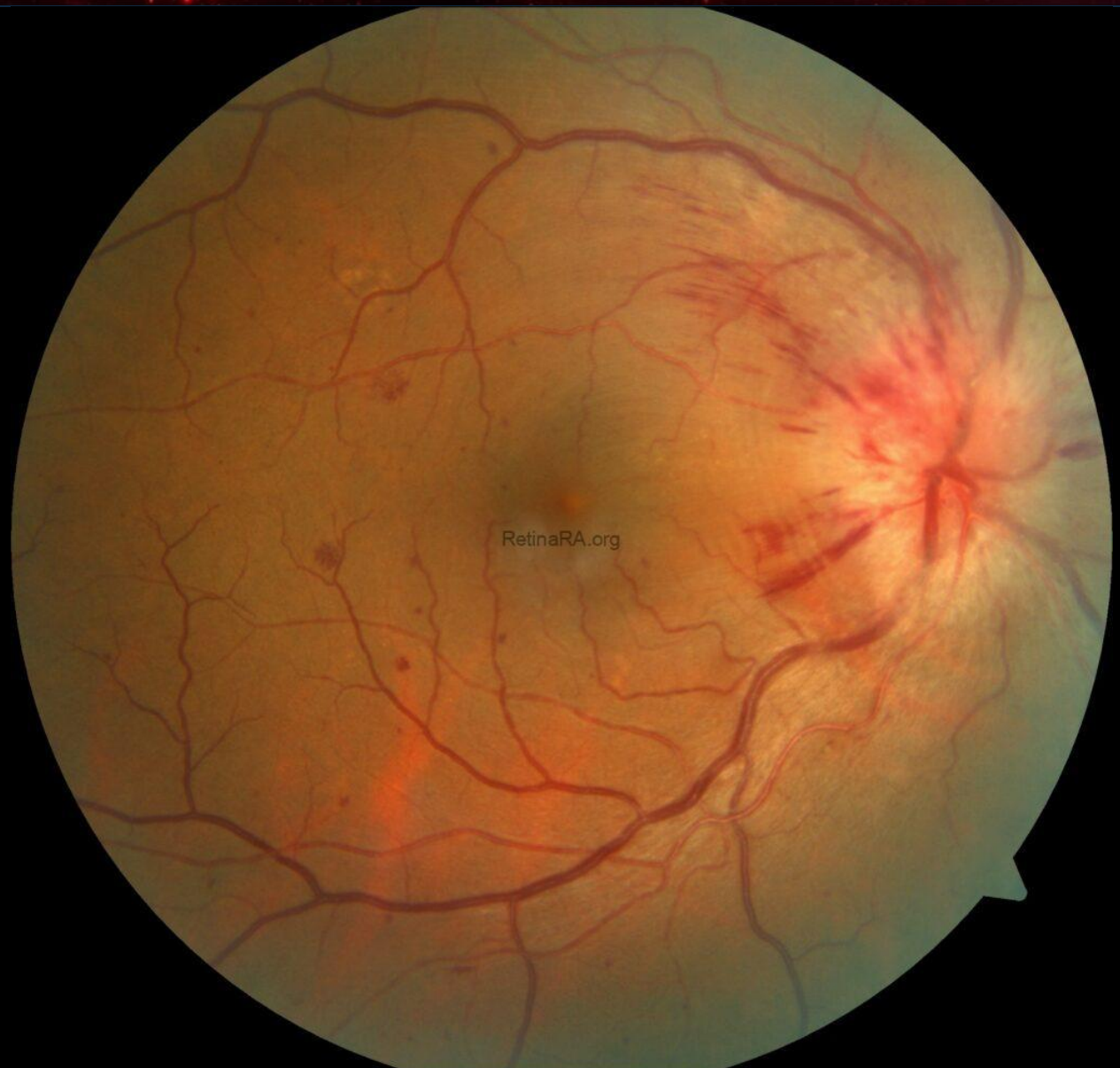
Sustained high blood pressure can damage the delicate blood vessels in the retina, leading to a range of vision-threatening complications.



Hypertensive Retinopathy



Malignant Hypertension



Retinal Arterial Macroaneurysms (RAM)

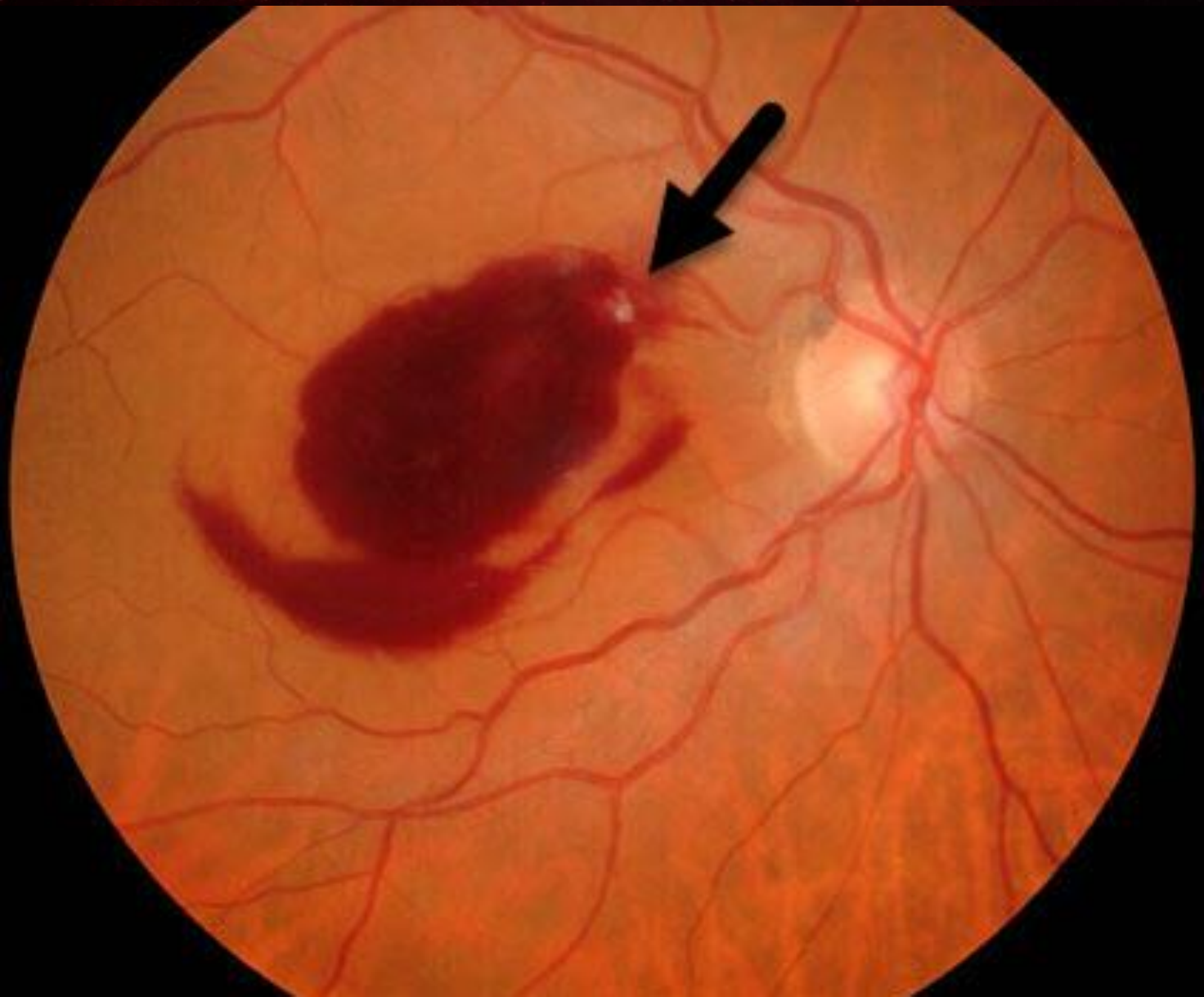
Retinal arterial macroaneurysms are localized dilatations of the retinal arteries, often occurring at arterial bifurcations or arteriovenous crossings.

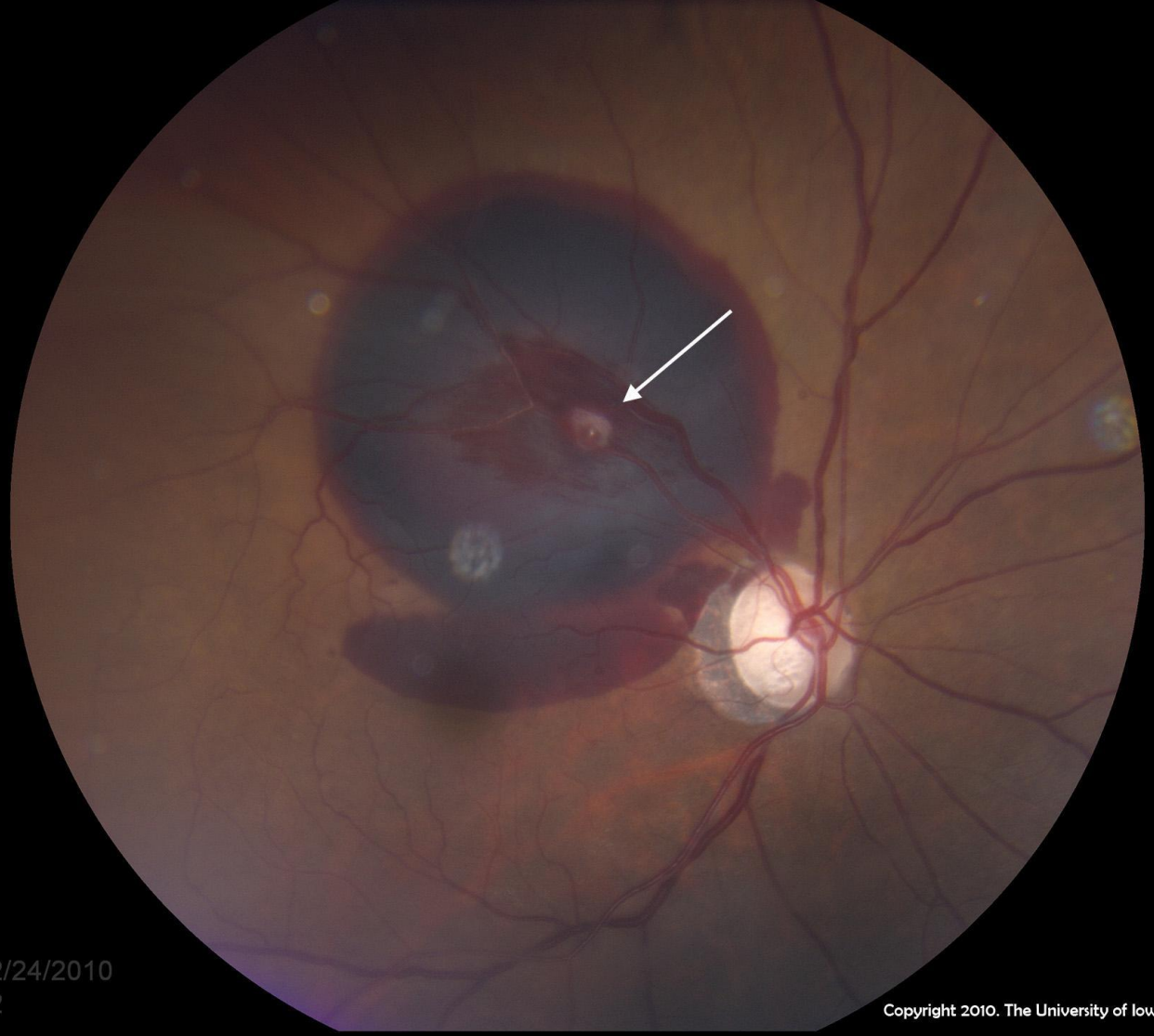
The most common causes of retinal arterial macroaneurysms are hypertension, atherosclerosis, and advanced age. They can also occur secondary to retinal vein occlusion or other vascular disorders.

Complications of retinal arterial macroaneurysms include retinal hemorrhage, exudation, and macular edema, which can lead to vision loss if left untreated.

Clinical Presentation

Patients with retinal arterial macroaneurysm may present with sudden onset of blurred vision, hemorrhage, or exudation. The macroaneurysm appears as a round, reddish-orange lesion on funduscopic examination.





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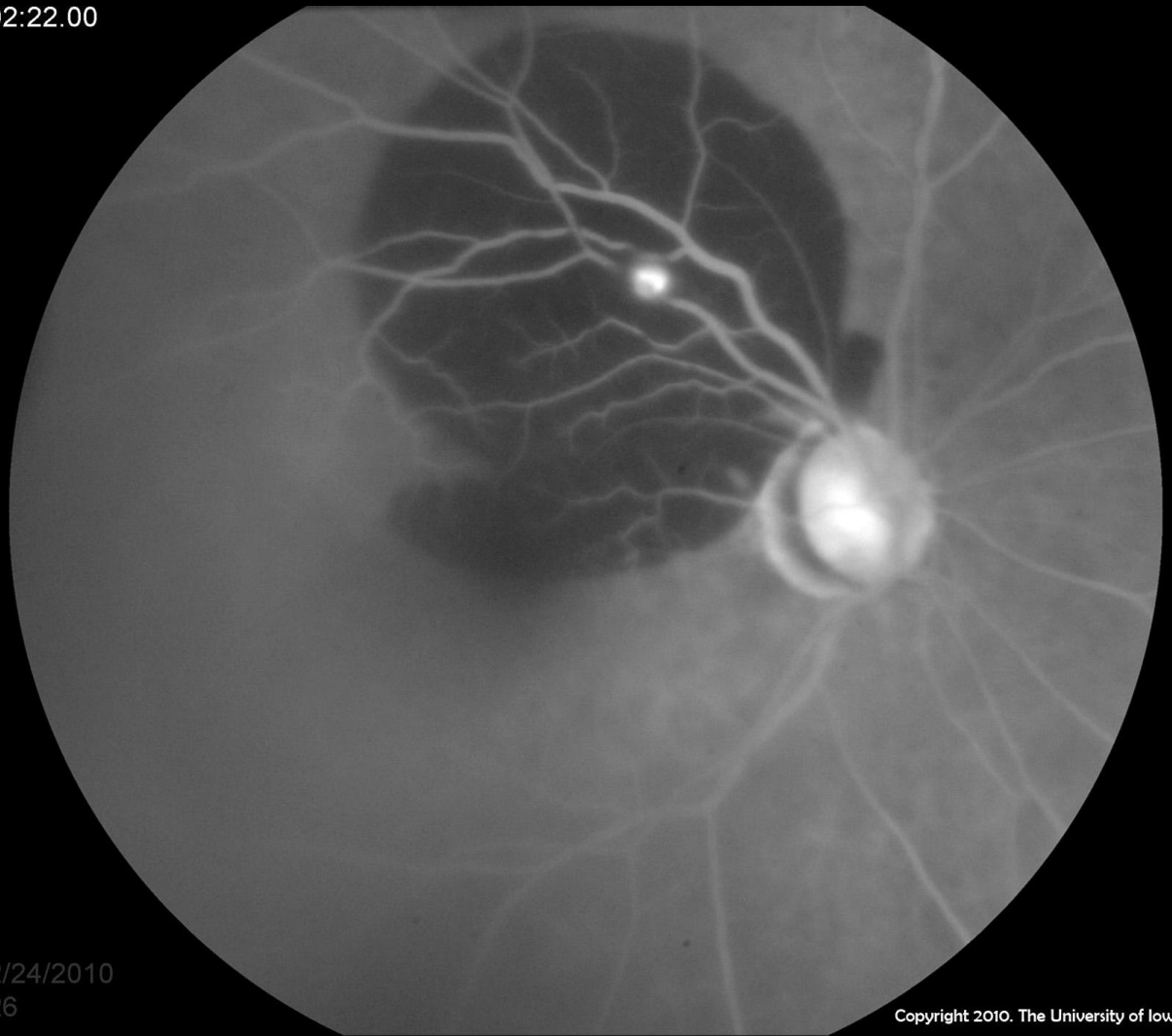

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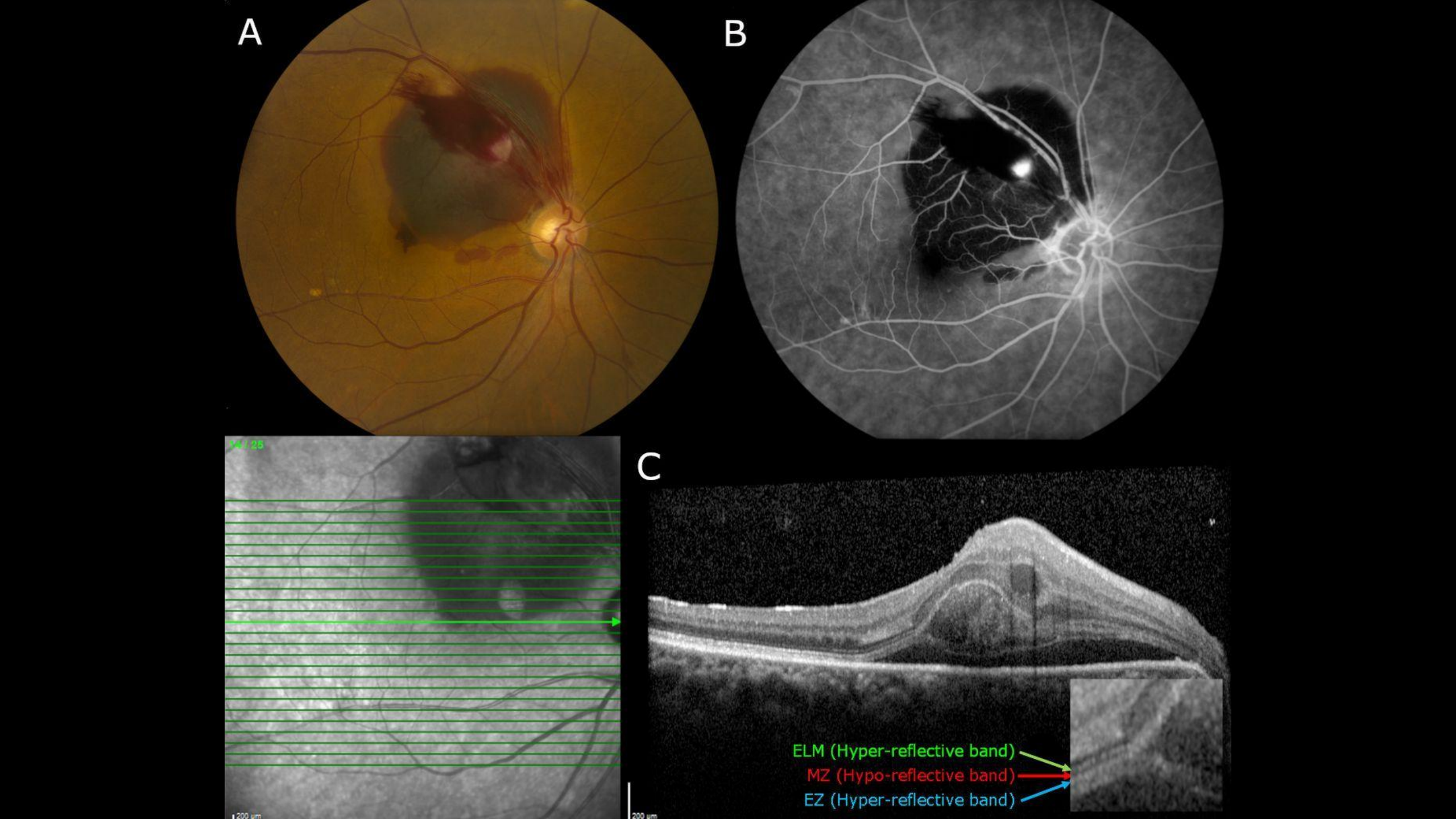

A
B
C
ELM (Hyper-reflective band)
MZ (Hypo-reflective band)
EZ (Hyper-reflective band)

Treatment Options

- Laser
- Anti-VEGF
- Surgery
- Systemic Blood pressure management

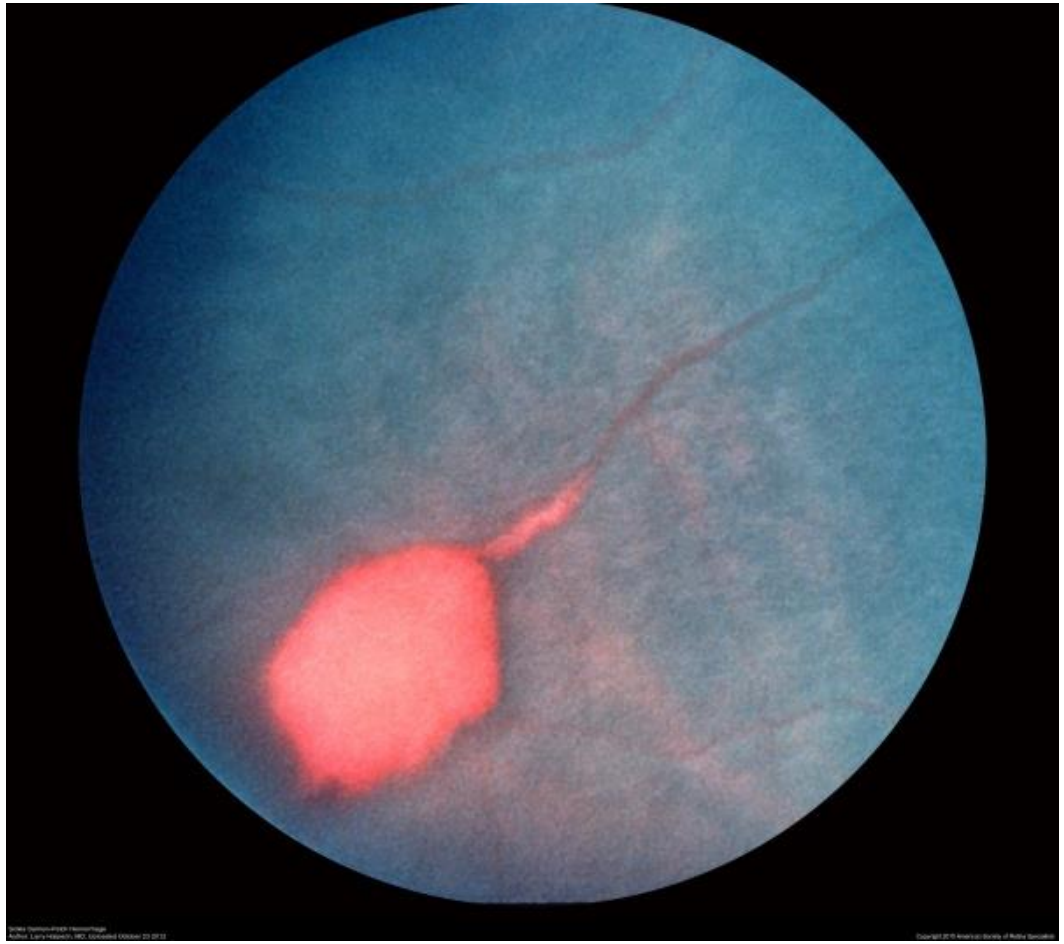
Rare and Secondary Vascular Retinal Diseases

Rare and Secondary Vascular Retinal Diseases

- Sickle cell retinopathy
- Retinopathy of prematurity (ROP)
- Radiation retinopathy
- Vasculitis (e.g., Eales disease, Behçet’s disease)
- Retinal vascular tumors (hemangiomas)

Sickle cell retinopathy

- Sickle cell retinopathy is a serious complication of sickle cell disease, a genetic disorder that affects the shape and function of red blood cells. This condition can lead to vision loss and blindness if left untreated. The abnormal sickle-shaped red blood cells can obstruct the small blood vessels in the retina, causing damage and preventing proper blood flow.



Salmon Patch

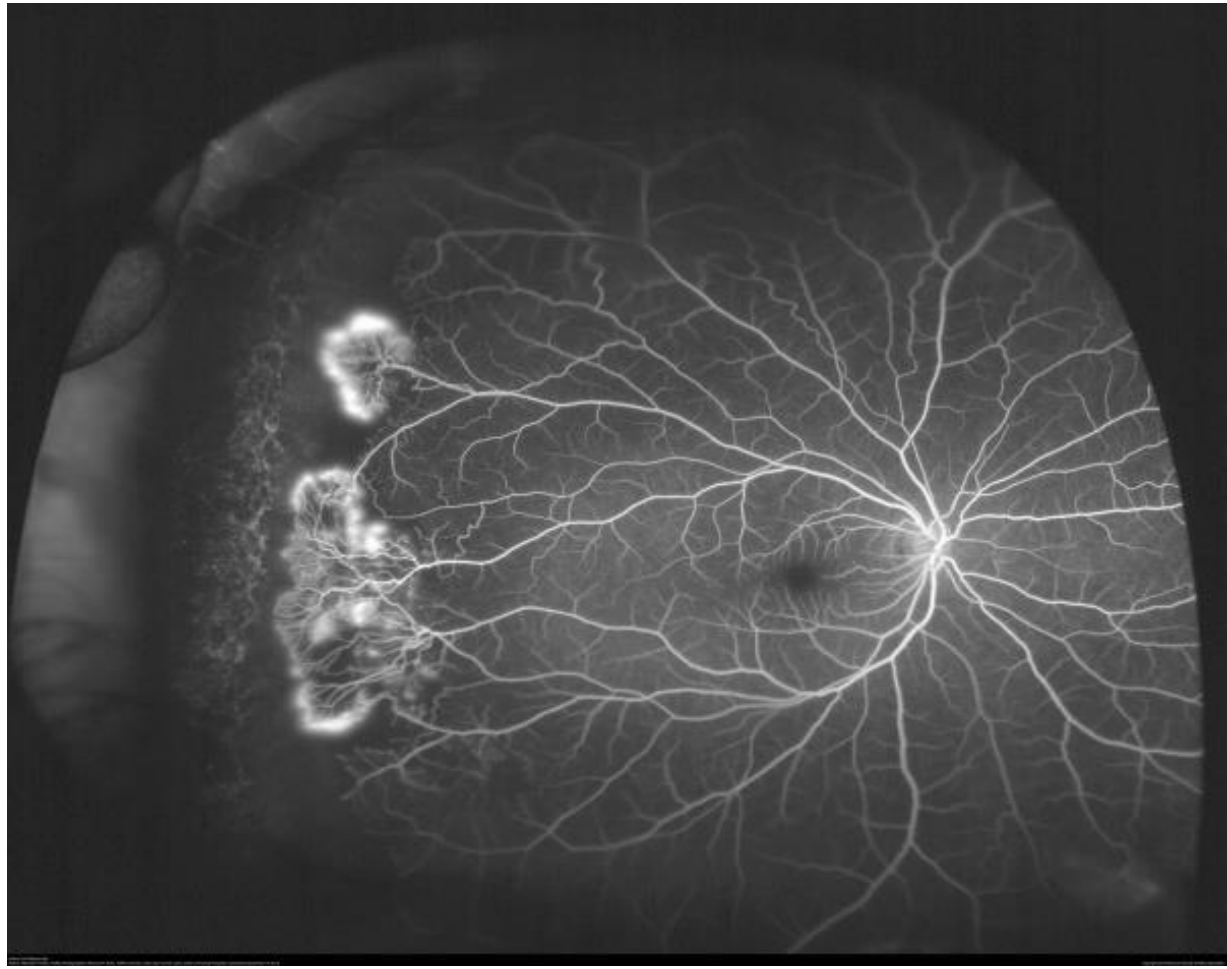
Sickle cell retinopathy

Cause / Pathophysiology

- Due to **sickling of red blood cells** → retinal **vascular occlusion**
- Leads to **retinal ischemia**, infarction, and neovascularization
- More severe in **HbSC** and **HbSβ-thalassemia** than HbSS

Types

- **Non-proliferative SCR:**
  - "Salmon patch" hemorrhages
  - "Black sunburst" lesions
  - Iridescent spots
- **Proliferative SCR:**
  - Peripheral retinal ischemia
  - **Sea-fan neovascularization**
  - Risk of **vitreous hemorrhage** and **tractional RD**

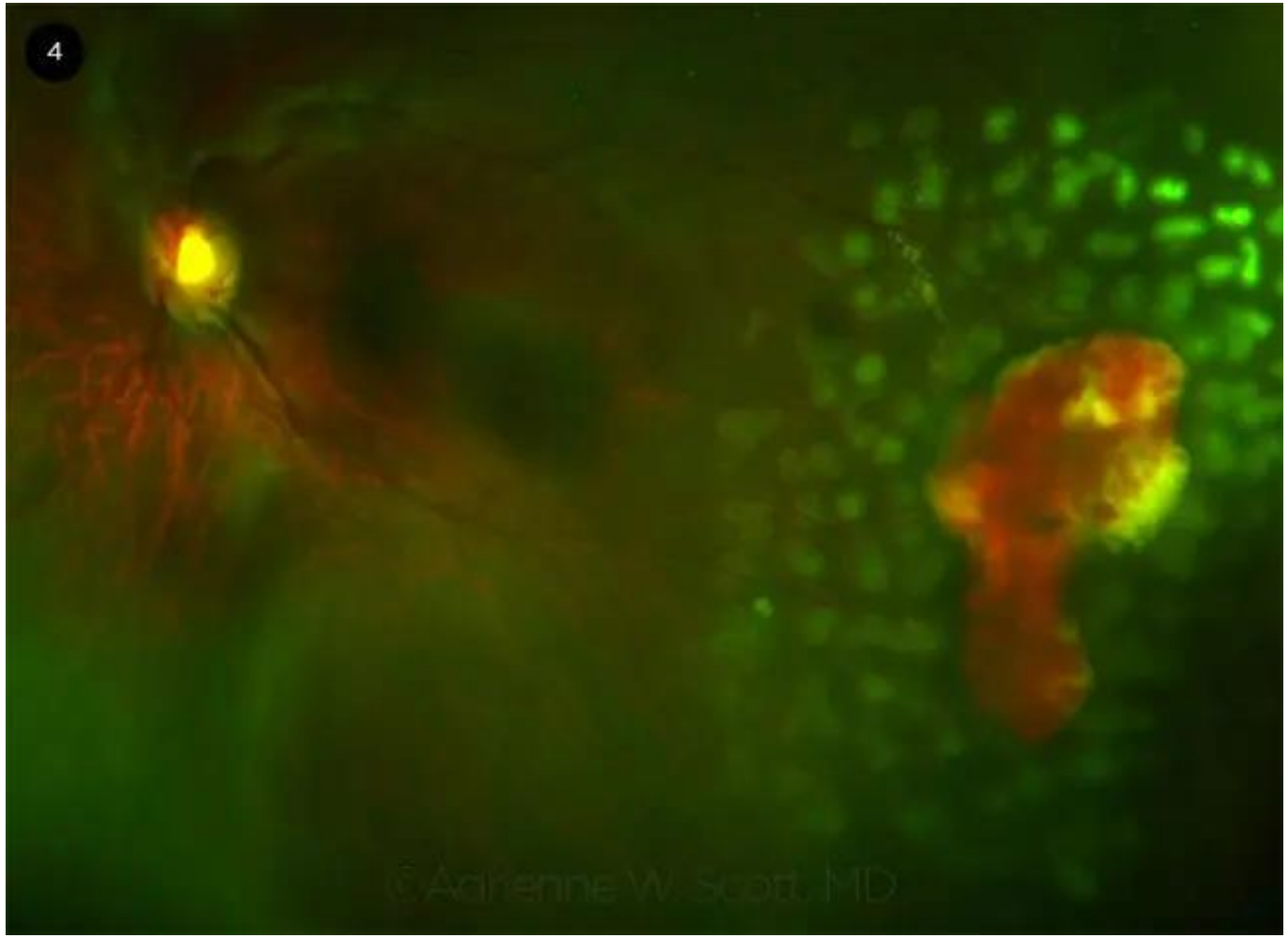


Sickle cell retinopathy

Symptoms
- Often asymptomatic early
- Floaters, blurred vision, or sudden vision loss in advanced stages

Management
- Regular dilated retinal exams
- **Laser photocoagulation** for neovascularization
- Anti-VEGF in selected cases
- Vitrectomy for complications (VH, RD)

Key Point
- Peripheral retina is primarily affected
- Early detection prevents vision-threatening complications



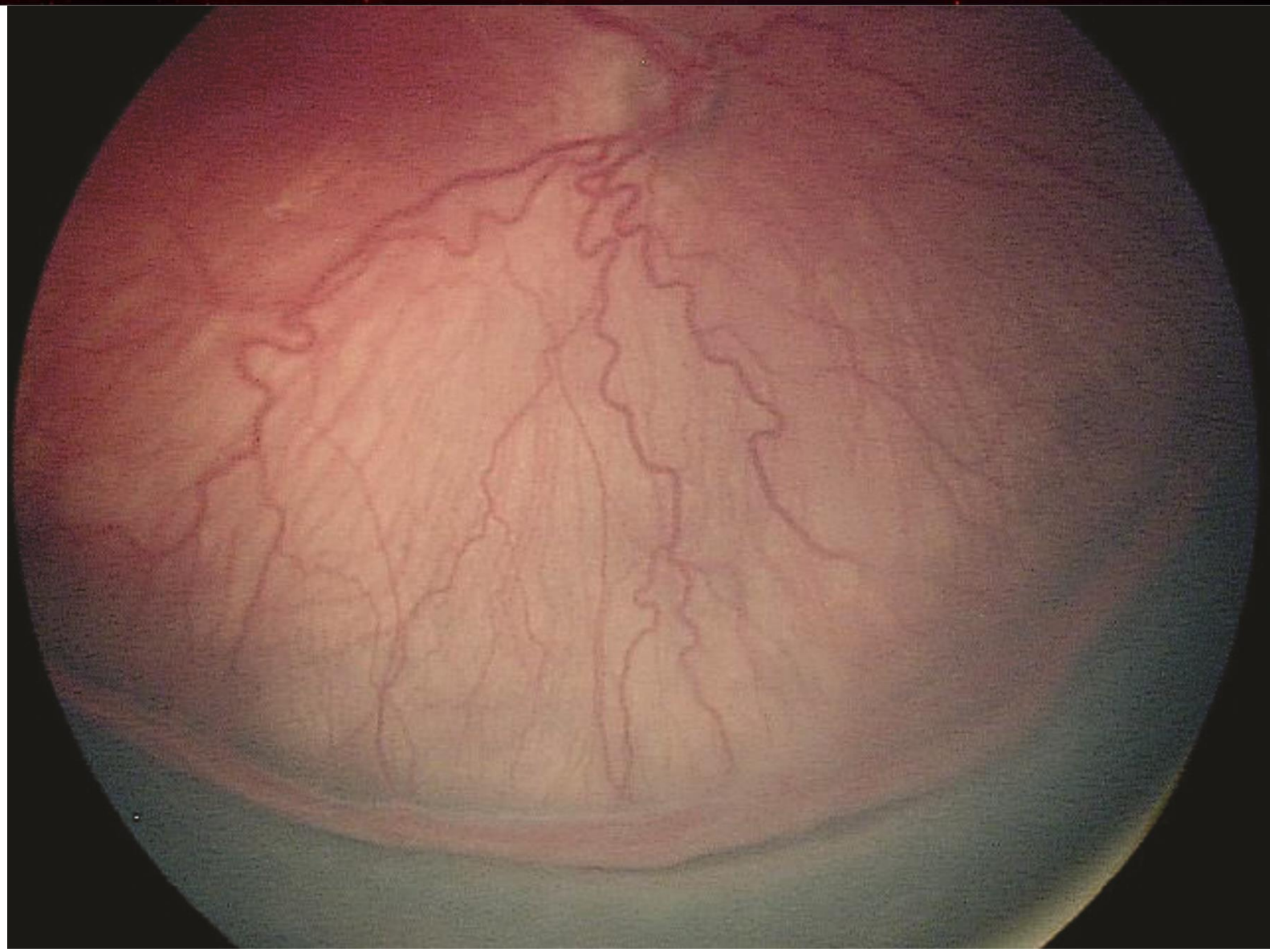
Retinopathy of Prematurity (ROP)

- A vasoproliferative retinal disease of premature/ low birth weight infants
- Abnormal development of retinal blood vessels
- Can lead to retinal detachment and blindness

- Screening
  - All at-risk premature infants, <30 weeks or <1500g
  - First exam 4–6 weeks after birth
  - Regular follow-up

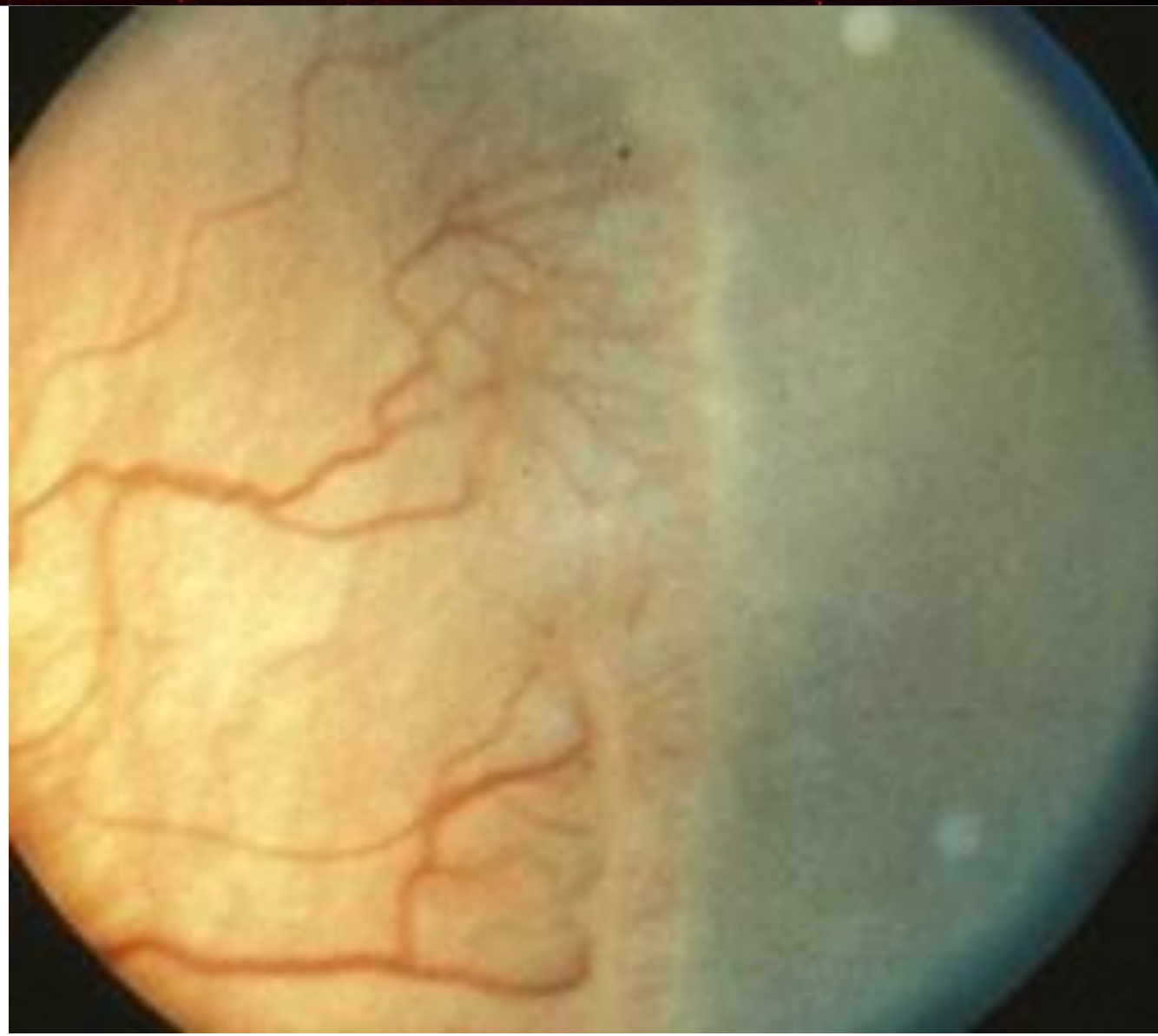
Risk Factors

- Prematurity
- Low birth weight
- Oxygen exposure
- Systemic illness



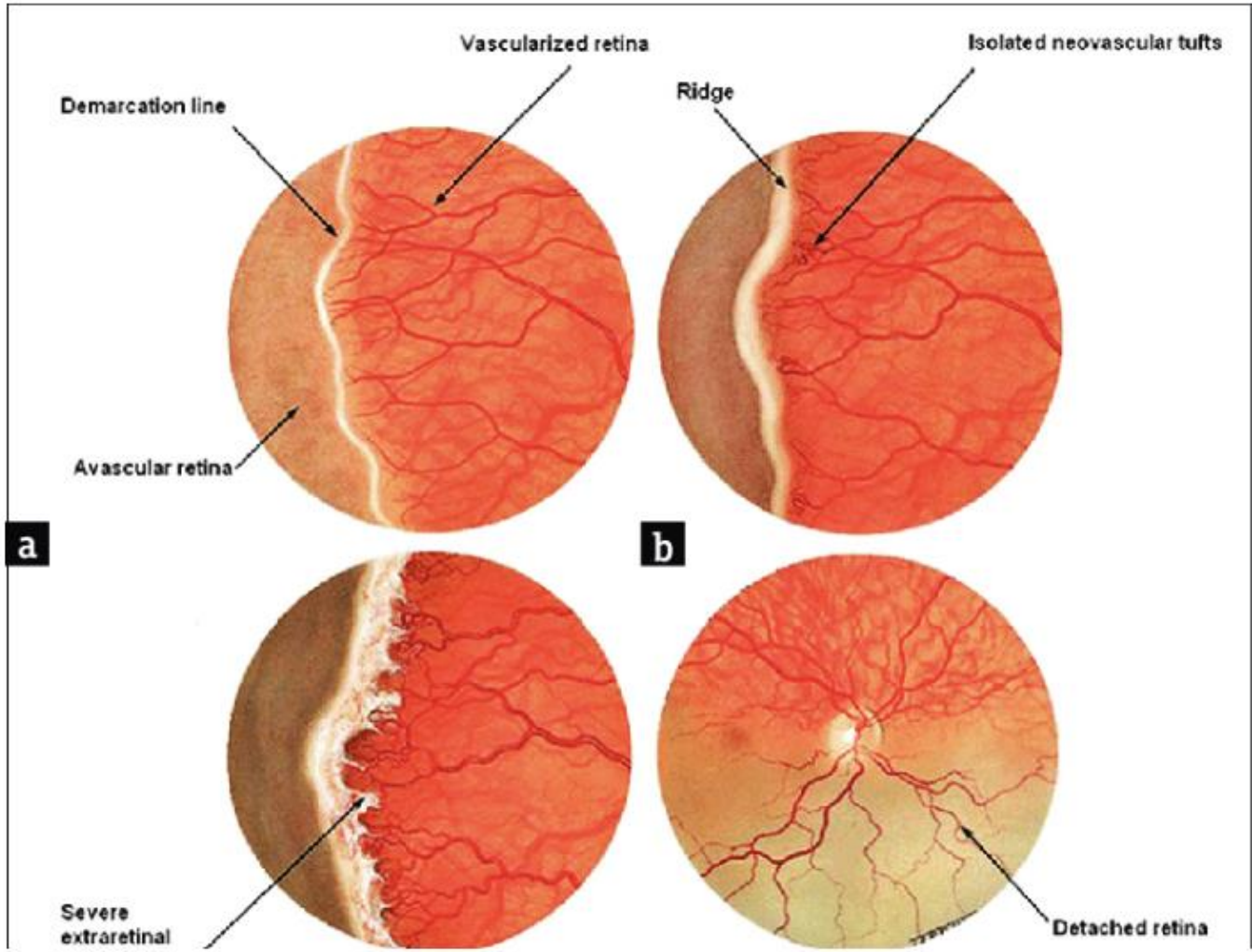
Pathophysiology

- Incomplete retinal vascularization at birth
- Oxygen fluctuations
- Abnormal vessel growth
- Neovascularization and fibrosis



Classification

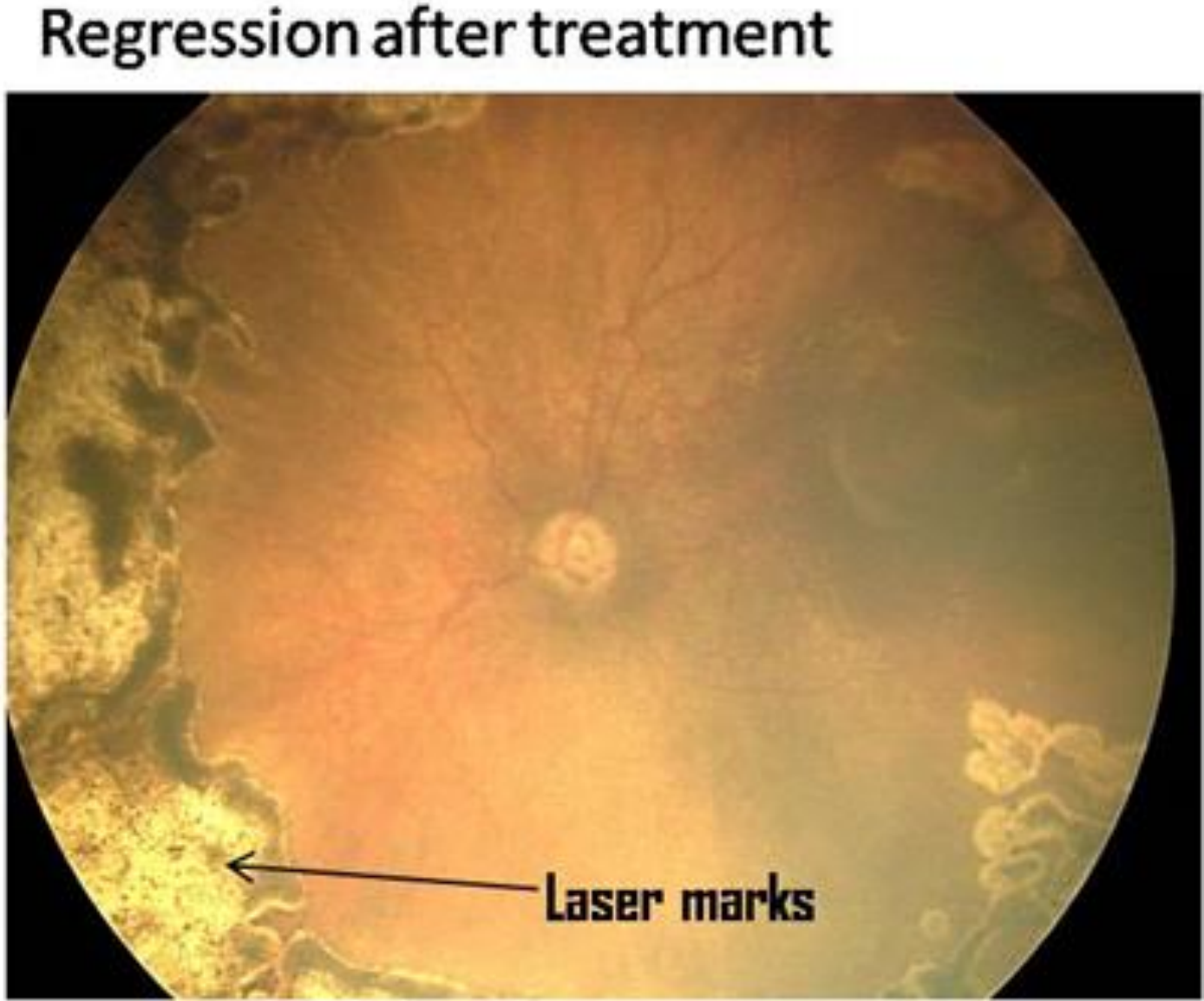
- Zones I, II, III
- Stages 1–5
- Plus disease
- Stage 5 = Total retinal detachment



Schematic representation of different stages in retinopathy of prematurity: (a) Stage 1: retinopathy of prematurity, (b) Stage 2: retinopathy of prematurity, (c) Stage 3: retinopathy of prematurity, (d) Stage 4: retinopathy of prematurity. (From: Kanski JJ. Clinical ophthalmology: A systematic approach. 6 th ed. Edinburgh: ButterworthHeinemann/Elsevier) d c

Treatment

- Laser photocoagulation
- Anti-VEGF injections
- Surgery for advanced cases



Retinopathy of Prematurity (ROP)

Leading cause of childhood blindness

Retinopathy of Prematurity (ROP) is a major cause of vision loss in children worldwide, especially in developing countries.

Affects premature infants

ROP primarily affects premature infants with underdeveloped retinal blood vessels, often those born before 30 weeks of gestation or <1500g

Abnormal blood vessel growth

In ROP, the retinal blood vessels fail to develop normally, leading to abnormal growth and leakage, which can cause scarring and retinal detachment.

Early detection and treatment

Prompt screening and early treatment, such as laser therapy or anti-VEGF injections, can help prevent vision loss in many cases of ROP.

Understanding the risk factors, early detection, and effective management of Retinopathy of Prematurity is crucial to improve visual outcomes and reduce the burden of childhood blindness.

Radiation Retinopathy

Definition

Radiation retinopathy is a condition that occurs due to damage to the retinal blood vessels caused by radiation therapy, often seen in cancer patients.

Causes

Radiation therapy, such as that used to treat cancer, can damage the delicate blood vessels in the retina, leading to a range of complications.

Symptoms

Symptoms of radiation retinopathy may include blurred vision, decreased visual acuity, floaters, and in severe cases, vision loss.

Risk Factors

Factors that increase the risk of developing radiation retinopathy include the total dose of radiation, the size of the radiation field, and the duration of the treatment.

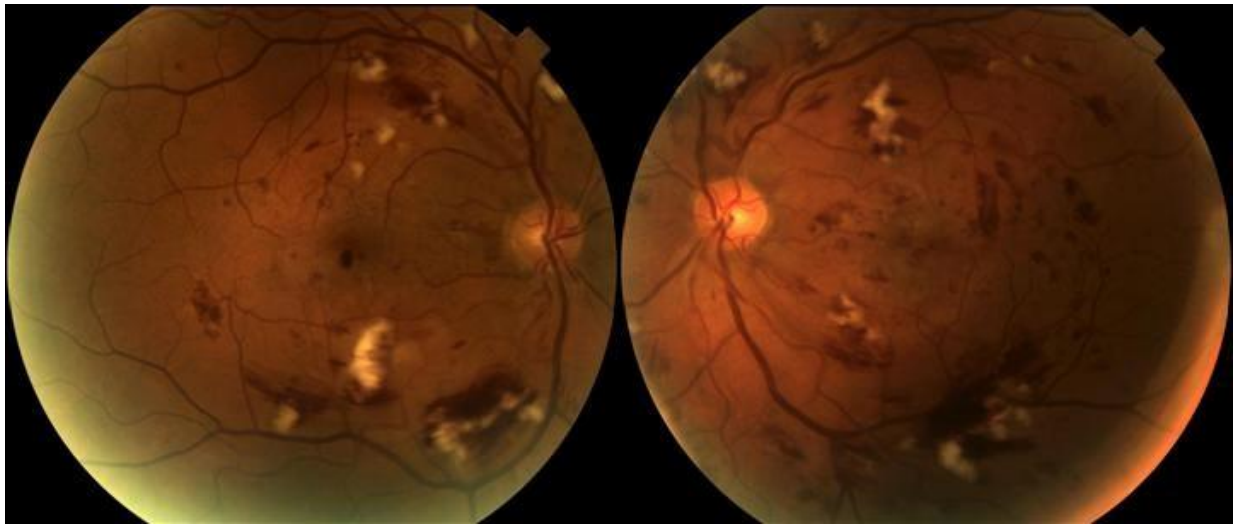
Management

Treatment options may include anti-vascular endothelial growth factor (anti-VEGF) injections, laser photocoagulation, or in some cases, surgical intervention.

- **Radiation retinopathy** is a delayed, progressive microvascular injury to the retina that occurs months to years after **ocular, orbital, or head radiation therapy**. It results from **endothelial cell damage**, leading to capillary closure, retinal ischemia, and increased vascular permeability.

- **Clinical findings** resemble diabetic retinopathy and include **microaneurysms, hemorrhages, cotton-wool spots, macular edema, and neovascularization**. Severe cases can progress to **vitreous hemorrhage** and **tractional retinal detachment**.

- **Risk factors** include high radiation dose, larger treatment fields, fractionation schedule, and comorbidities such as **diabetes or hypertension**.



Radiation Retinopathy

Management focuses on controlling complications:

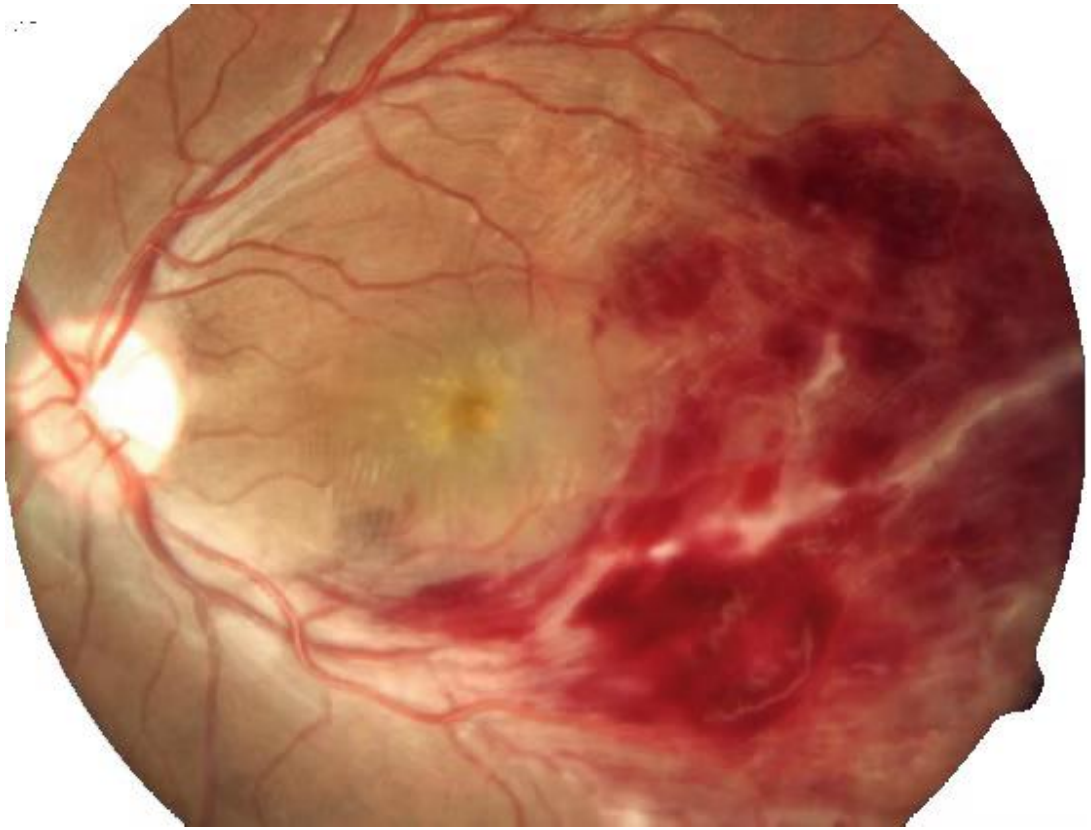
- **Anti-VEGF** for macular edema and neovascularization
- **Laser photocoagulation** for ischemia
- **Steroids** in selected cases

Early detection and treatment help preserve vision, but the condition is often **chronic and progressive**.

Vasculitis

Eales Disease

- A rare form of vasculitis that primarily affects the peripheral retinal blood vessels, leading to ischemia, neovascularization, and potentially vision-threatening complications.
- idiopathic occlusive retinal periphlebitis that typically affects young, healthy adults, especially males. It is strongly associated with hypersensitivity to Mycobacterium tuberculosis antigens, although active TB is usually absent.

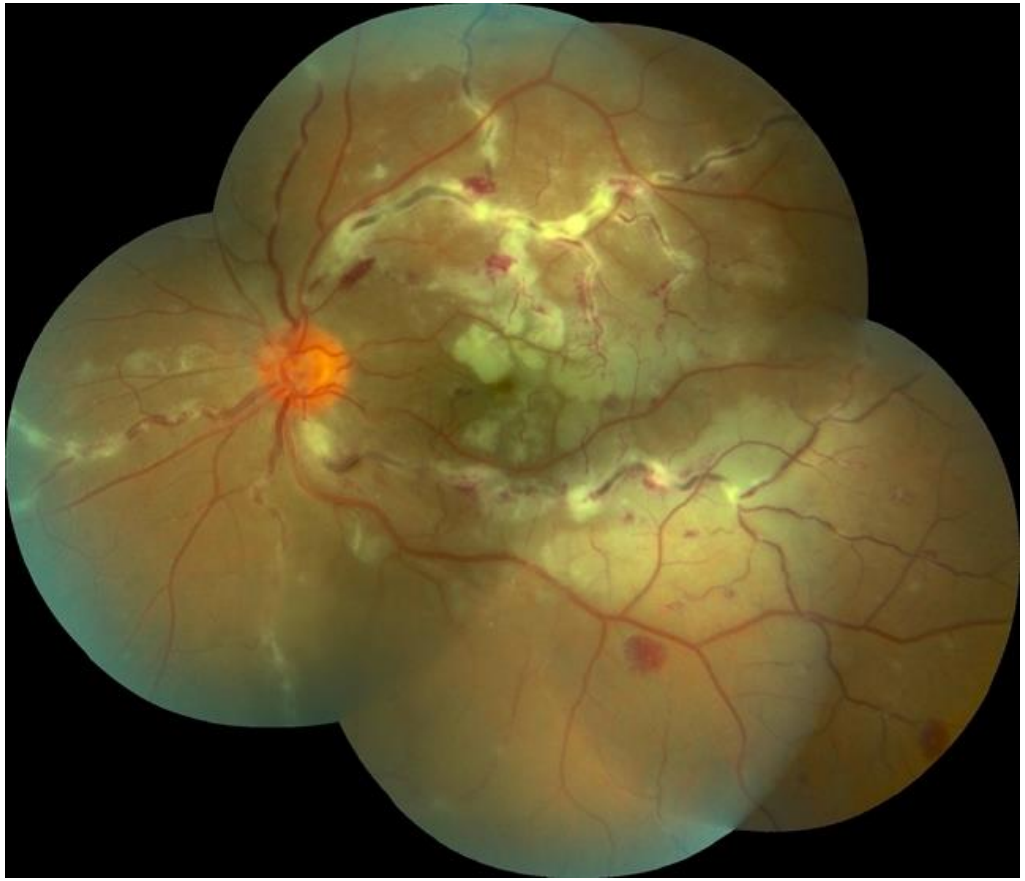


Pathophysiology

The disease progresses through **three stages**:

1.Inflammatory stage – peripheral retinal **periphlebitis** (venous vasculitis)
2.Ischemic stage – capillary nonperfusion and retinal ischemia
3.Proliferative stage – **neovascularization** leading to vitreous hemorrhage

Clinical Features:
- Recurrent **vitreous hemorrhage**
- Peripheral retinal vasculitis (sheathing of veins)
- Retinal ischemia and neovascularization
- Usually bilateral but asymmetric



https://educate.choroida.com/2022/09/28/eales-disease-case-report-and-management/

Eales

Diagnosis

- Clinical exam + **fluorescein angiography** (shows peripheral nonperfusion and leakage)
- Rule out other causes of retinal vasculitis (TB, sarcoid, Behçet, autoimmune disease)

Management:

- **Corticosteroids** for active inflammation
- **Anti-TB therapy** if TB exposure is suspected
- **Panretinal photocoagulation (PRP)** for ischemia/neovascularization
- **Vitrectomy** for non-clearing vitreous hemorrhage

Prognosis:

Vision is often good with timely treatment, but **recurrent hemorrhages** are common.

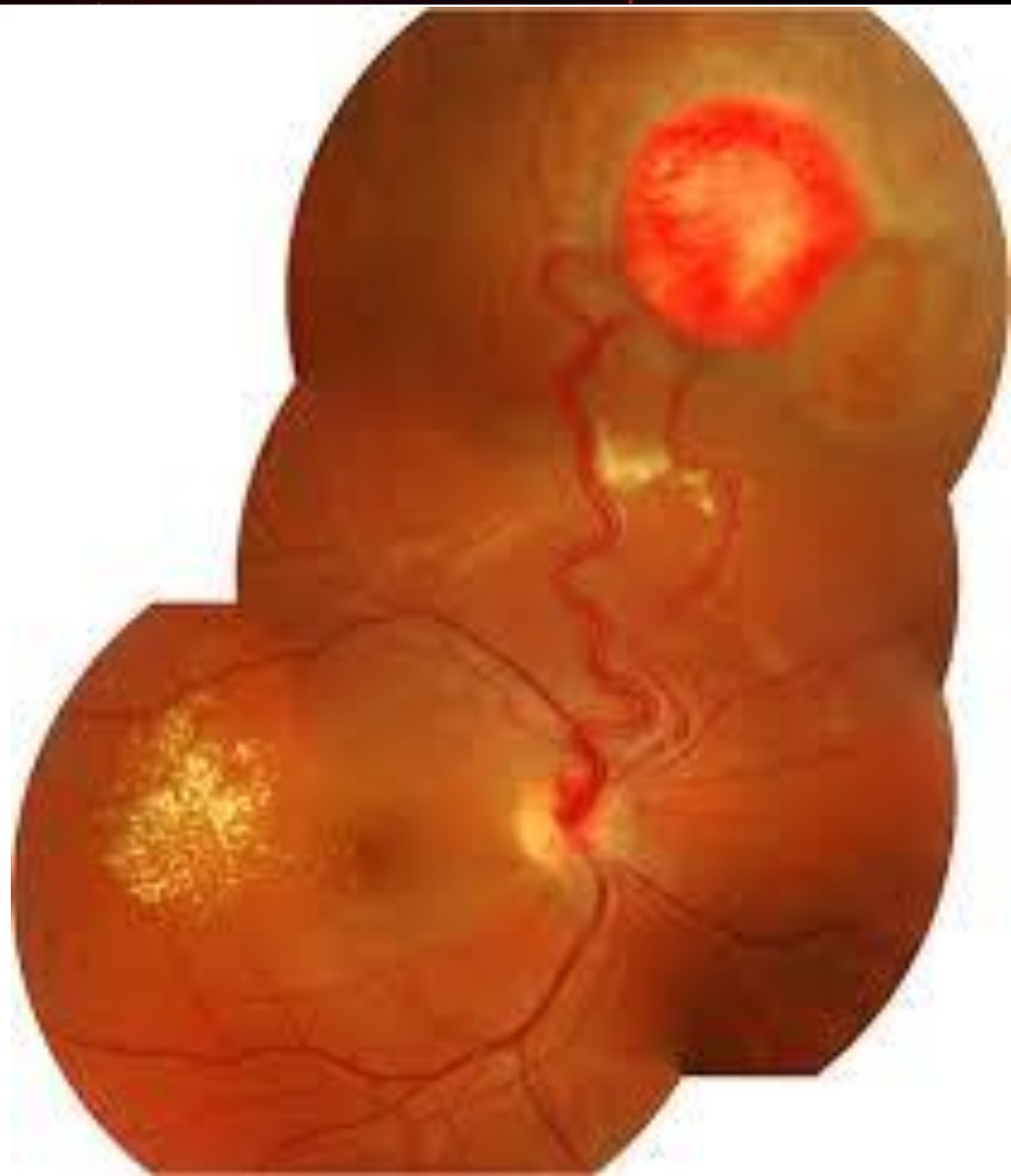
Retinal Vascular Tumors

- **Retinal vascular tumors** are rare, benign lesions arising from abnormal retinal blood vessels. The most common types are **retinal capillary hemangiomas** (often associated with **Von Hippel–Lindau disease**) and **vasoproliferative tumors**(usually idiopathic).

- These tumors can cause **exudation, macular edema, retinal detachment, vitreous hemorrhage, and vision loss** due to vascular leakage and secondary retinal changes.

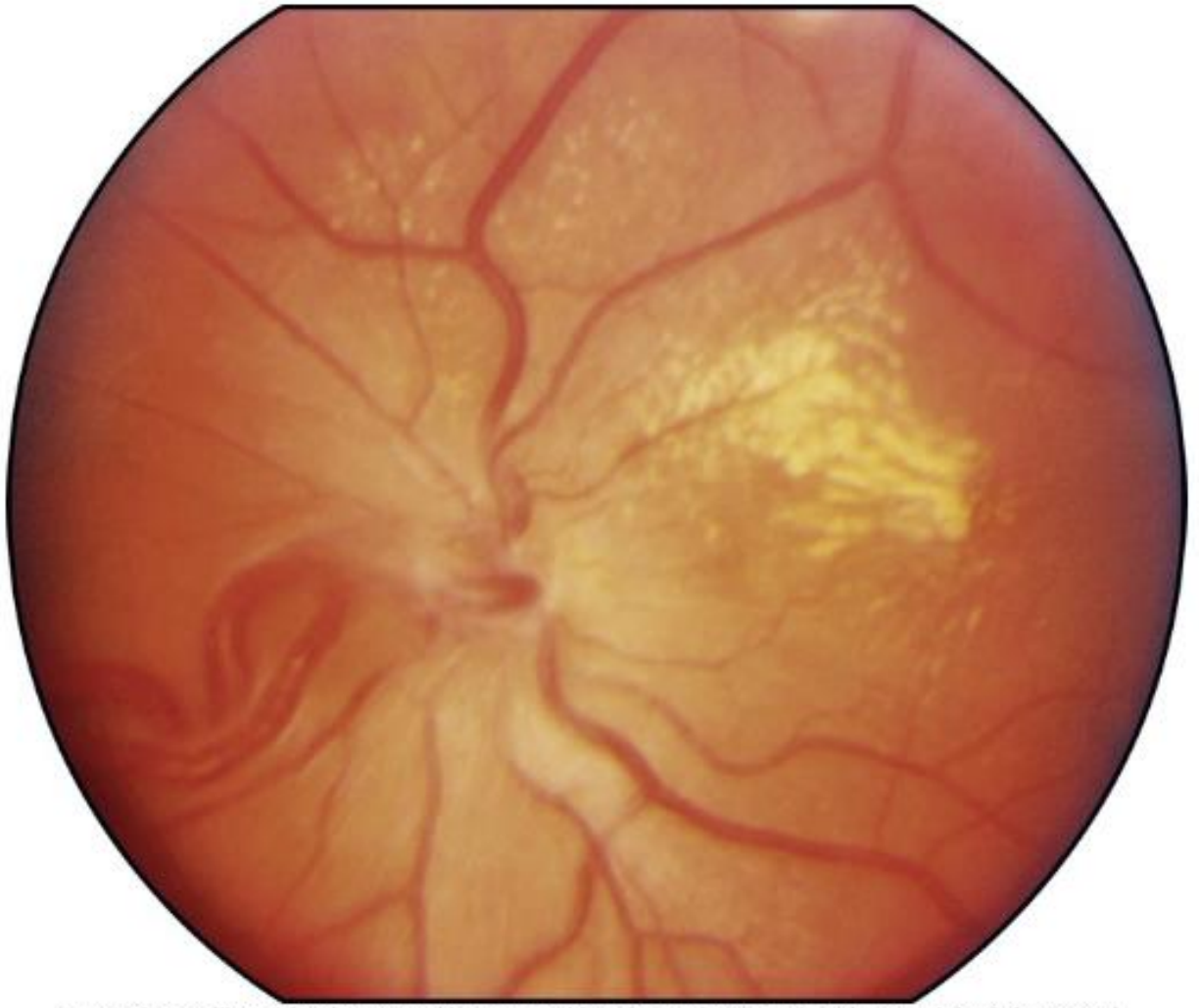
- **Diagnosis** is based on clinical exam, OCT, and fluorescein angiography, which show dilated feeding and draining vessels with leakage.

- **Management** depends on size, location, and symptoms and may include **laser photocoagulation, cryotherapy, anti-VEGF injections, photodynamic therapy, or surgery**. Early treatment helps prevent vision-threatening complications.



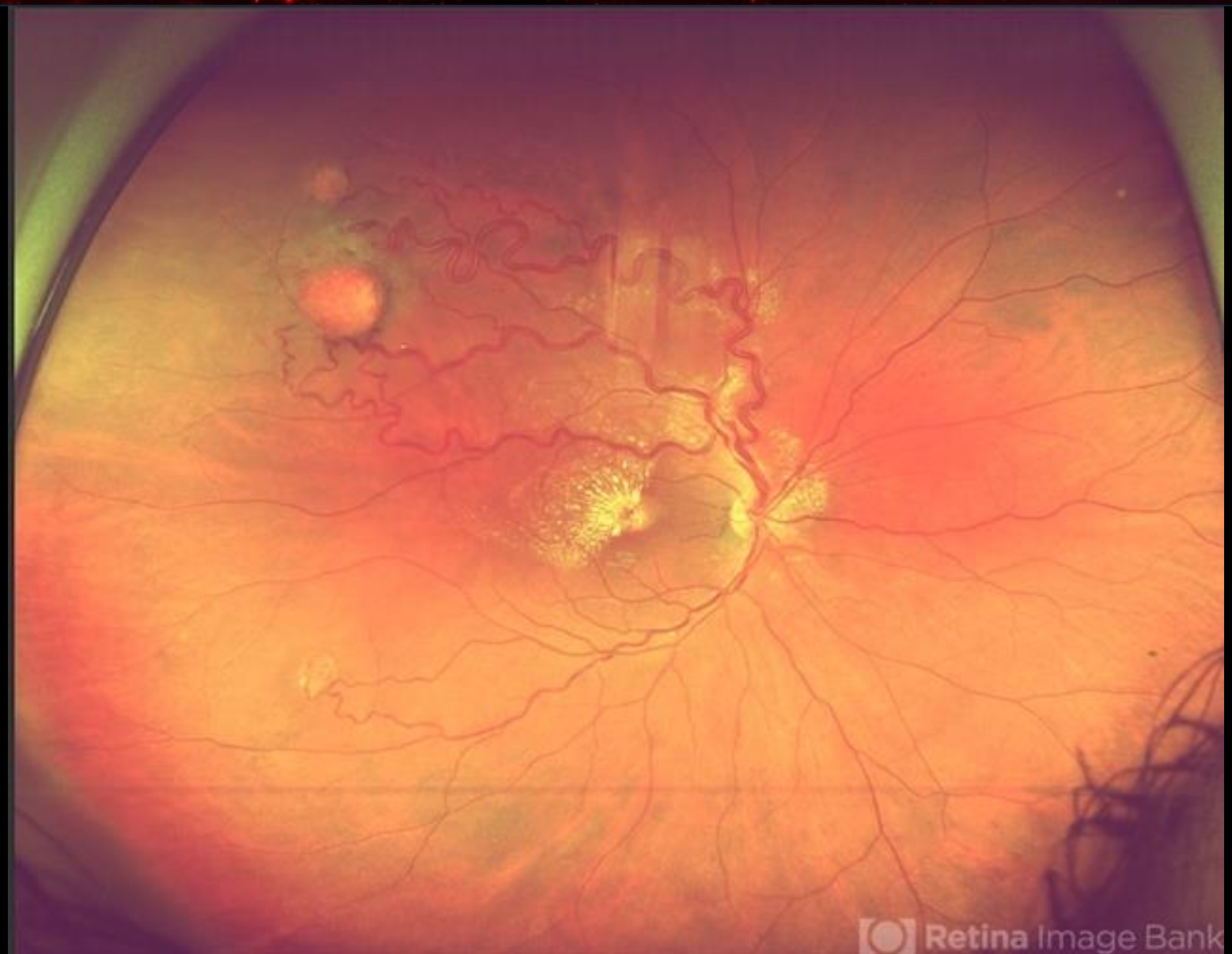
Capillary Hemangioma

Retinal capillary hemangiomas are classified as benign hamartomas. They may occur in an isolated fashion, or more commonly in association with the oculus neurocutaneous syndrome (phakomatosis) of von Hippel–Lindau. They commonly appear as a large, orange-to-red dilated retinal vessel emerging from the optic nerve. Lipid exudates and subretinal fluid surrounding the tumor are common and can affect visual function if the macula is involved.



A prominent dilated feeder vessel is seen exiting the optic nerve head toward the inferonasal periphery, where a retinal capillary hemangioma was located. There is moderate exudation in the macular region with decreased visual acuity.

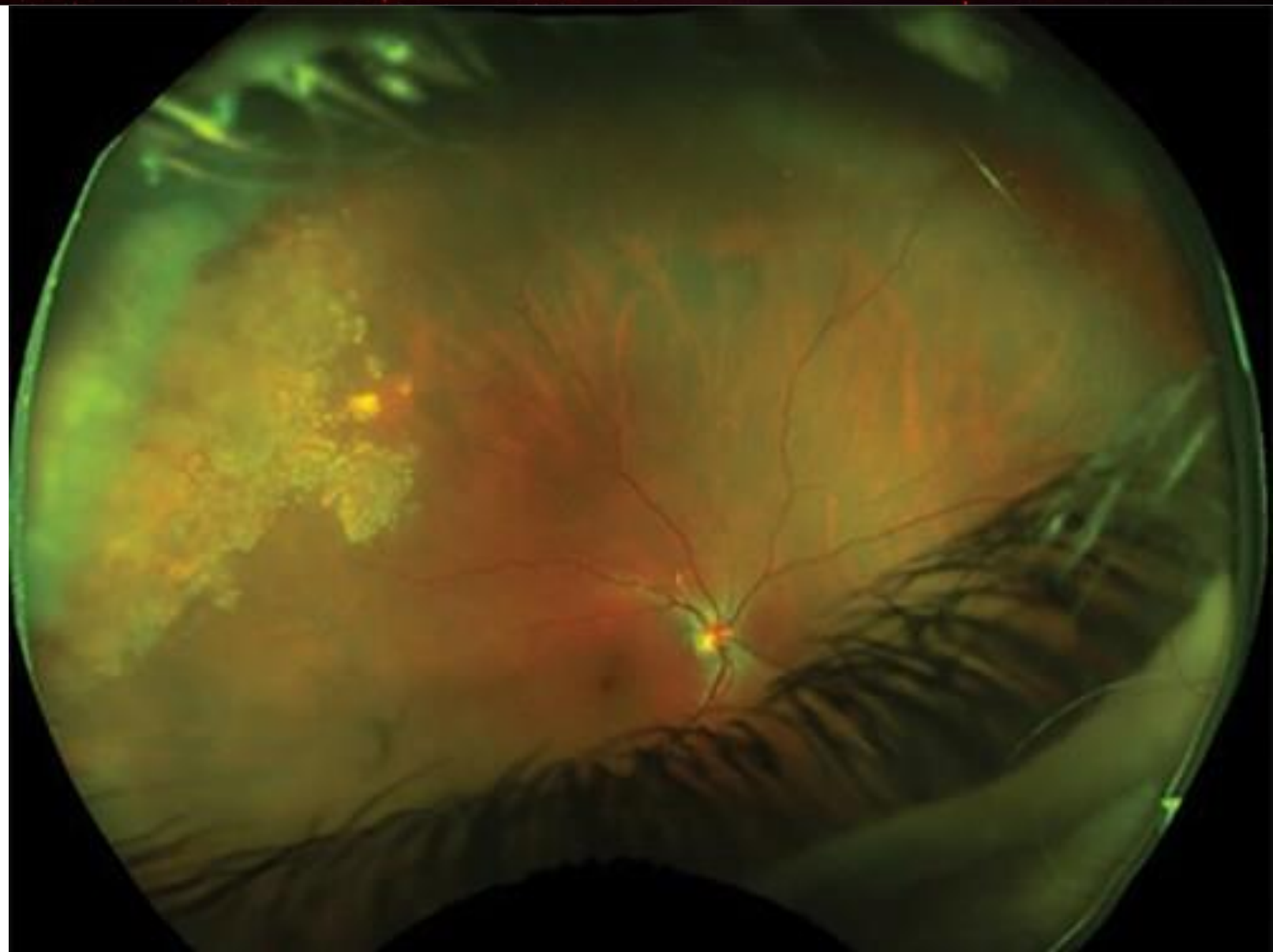
Capillary Hemangioma



Vasoproliferative tumor

Retinal vasoproliferative tumors are benign, peripheral retinal lesions characterized by abnormal proliferation of glial and vascular tissue. They are usually **idiopathic** but can be secondary to conditions such as **retinitis pigmentosa, uveitis, trauma, or retinal detachment**.

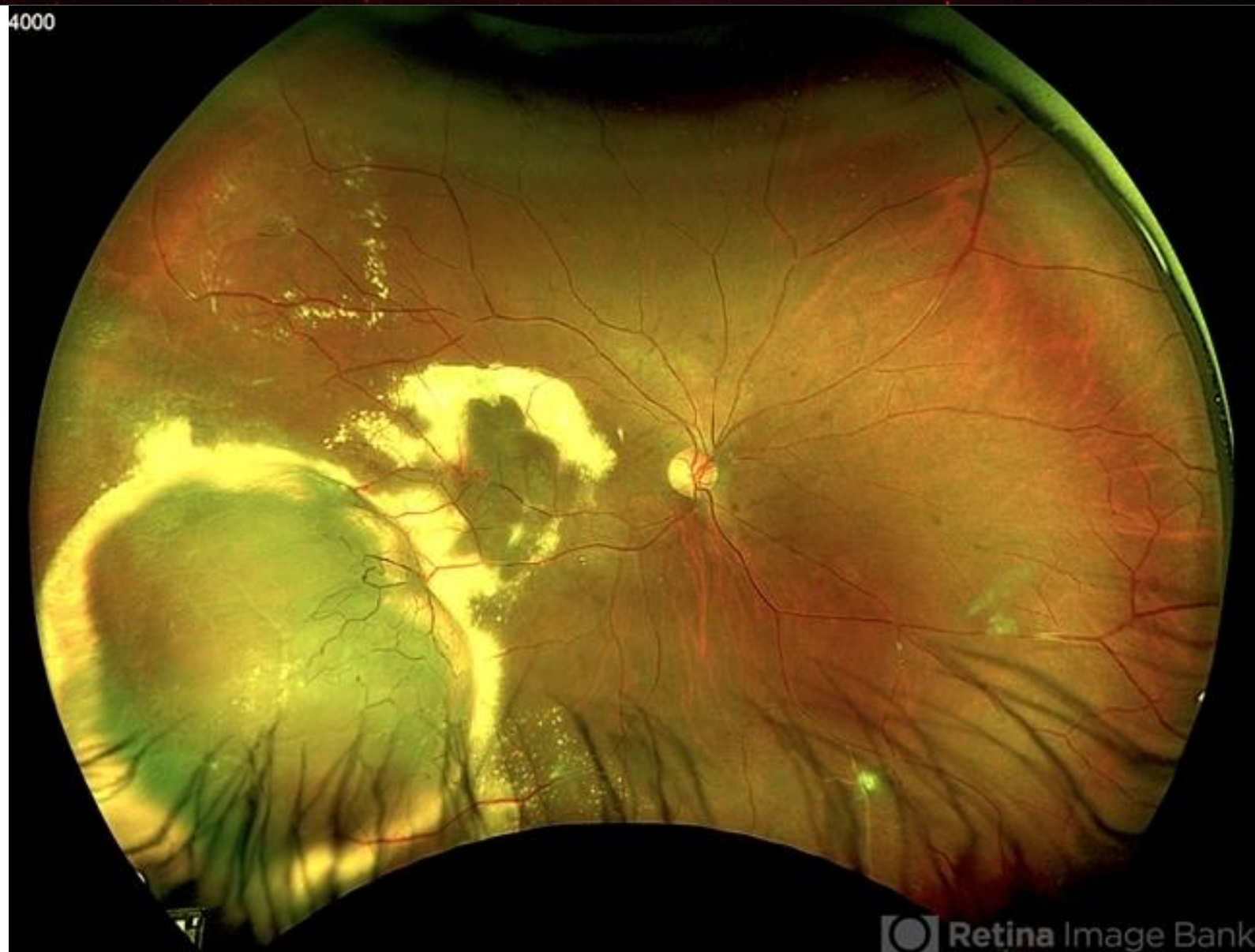
Clinically, they appear as **yellow-pink, elevated masses** in the inferotemporal periphery with surrounding **exudation, macular edema, epiretinal membrane, or exudative retinal detachment**. Unlike capillary hemangiomas, VPTs typically **lack prominent feeder vessels**.



Vasoproliferative tumor

Diagnosis is clinical, supported by **OCT, B-scan ultrasound, and fluorescein angiography** showing late leakage.

Management depends on symptoms and includes **observation**, **cryotherapy**, **laser**, **anti-VEGF**, **steroids**, **photodynamic therapy**, or **surgery** for complications. Early treatment can preserve vision.



Key Takeaways

- **Early Diagnosis is Crucial**

  Prompt recognition of vascular symptoms is vital for timely intervention and management.

- **Comprehensive Evaluation**

  Thorough assessment of risk factors, systemic associations, and underlying causes is essential for effective treatment.

- **Individualized Treatment**

  Approach Tailoring management strategies, such as anti-
  VEGF, steroids, and laser therapy, to the specific disease and patient needs.

- **Multidisciplinary Collaboration**

  Coordination between ophthalmologists, primary care providers, and specialists to manage systemic conditions

- **Importance of Patient Education**

  Educating patients on the nature of disease, the potential impact on vision, and the importance of adherence to treatment.

Summary

- By understanding the retinal vascular anatomy and its critical role in maintaining retinal health, retina specialists can better identify and manage vascular diseases that lead to ischemia and neovascularization.
- Retinal Vein Occlusion is a serious eye condition that requires prompt diagnosis and personalized treatment. By understanding the underlying pathogenesis, associated risk factors, clinical presentation, and available management strategies, healthcare professionals can provide effective care and improve outcomes for patients affected by this complex condition.
- Diabetic retinopathy is a serious and progressive eye condition that requires proactive management. By understanding the different stages, regularly screening, and pursuing timely treatment options, individuals with diabetes can take steps to preserve their vision and prevent vision loss.

Summary

- Hypertensive retinopathy and retinal macroaneurysms are serious complications of uncontrolled hypertension that can lead to vision loss. Early detection and proper management are crucial.
- Rare and secondary vascular retinal diseases require specialized care and ongoing research to improve patient outcomes.

References

- Ryans Retina
- The Retinal Atlas

EYEMED 2026

Retina Update Macular Degeneration

John Randolph, MD

Central Florida Retina

Incidence of AMD

- >11M Americans (170M worldwide) have AMD
  - Anticipated to be >22M by 2050
- Leading cause of irreversible blindness in developed countries
  - Prevalence of AMD is similar to that of all invasive cancers combined and more than double the prevalence of Alzheimer's Disease
- >400,000 Americans with severe vision loss yearly
- Annual $4.6 billion direct healthcare cost

Causes of AMD

- Age
- Genetics
- Environment
  - Sunlight exposure
  - Nutrition
  - Smoking
  - Light colored eyes
  - Cardiovascular disease

Symptoms of AMD

- AMD is a degenerative retinal disease:
  - Reduced central vision
  - Central scotoma
  - Distortion
  - Decreased contrast sensitivity
  - Decreased color vision

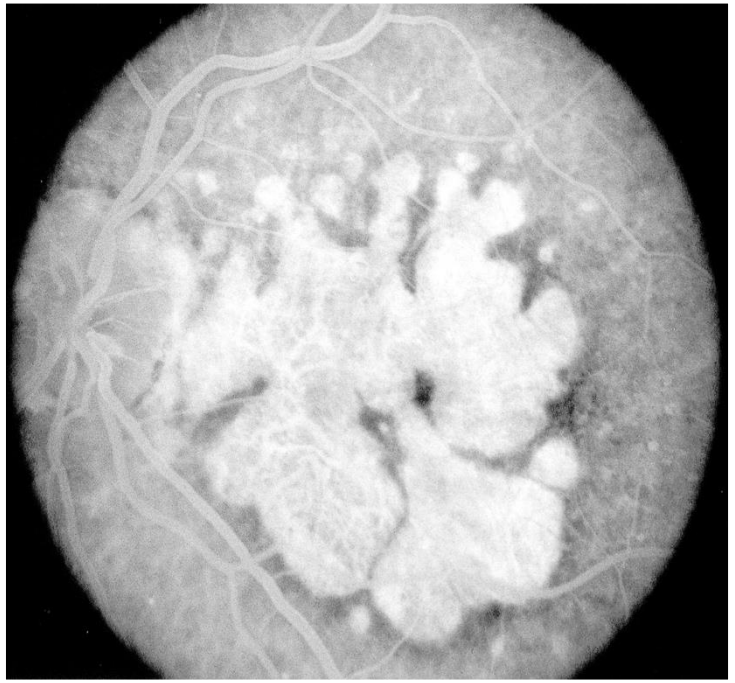
Impact of AMD on the Patient: Visual Function

Low vision optical aids help improve vision for people with macular degeneration. Many different types of magnifying devices are available. Spectacles, hand or stand magnifiers, telescopes, and closed circuit television for viewing objects are some of the available resources. Aids are either prescribed by your ophthalmologist or by referral to a low vision specialist or center. Special lamps with brighter illumination are often beneficial. Books, newspapers, and other items available in large print offer further help.

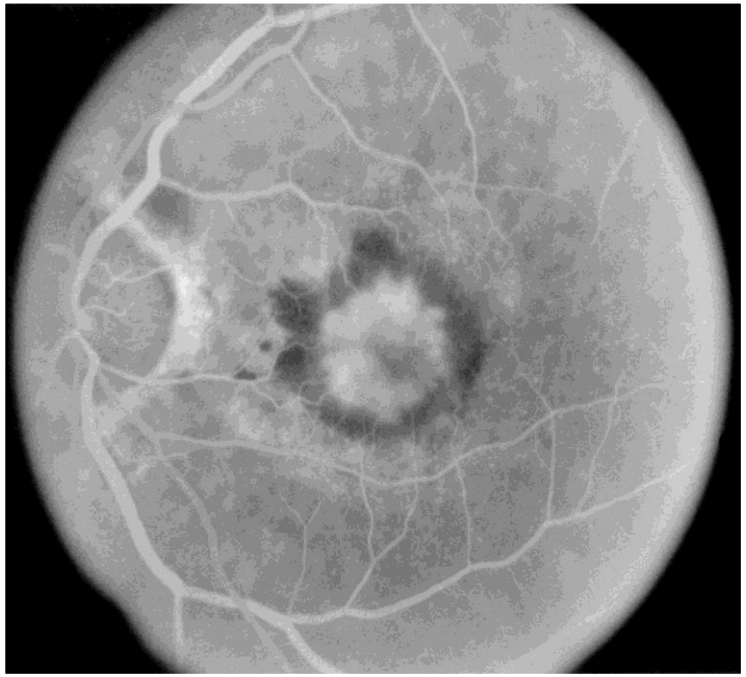
Patients with AMD may have difficulty with visual tasks:

- Reading
- Telling the time
- Recognizing faces
- Driving

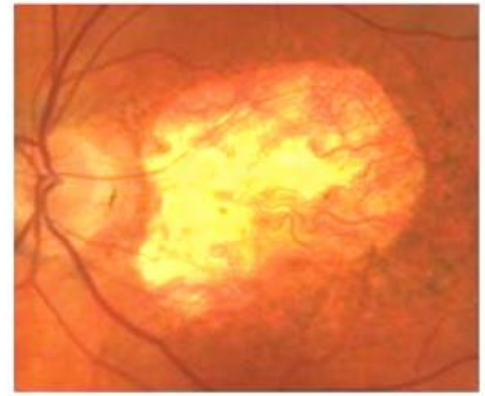
Two Forms of AMD Can Cause Severe Vision Loss



Non-neovascular
(geographic atrophy)

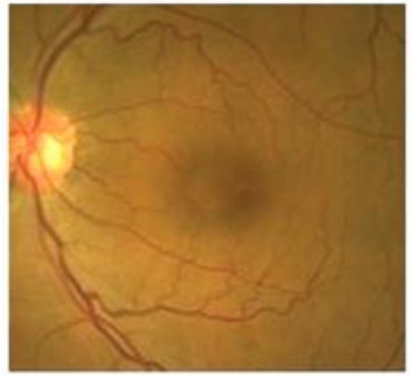


Neovascular
(choroidal
neovascularization)

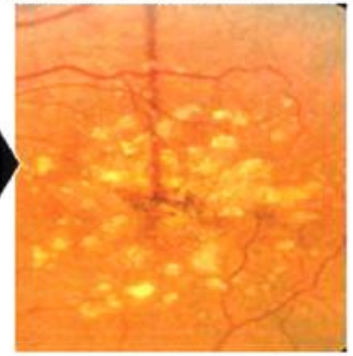


Late AMD—'Dry' form
(Geographic Atrophy)

Normal



Early AMD
(Drusen and RPE change)

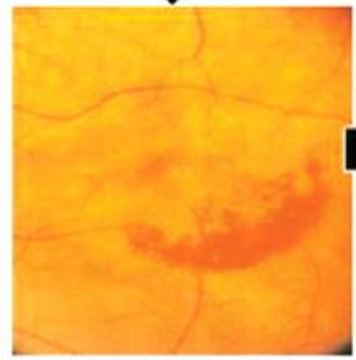


Good vision

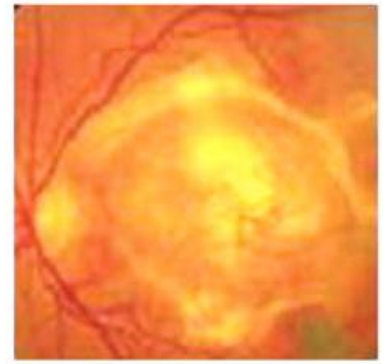
1–18% risk of progressing from early to late AMD over 5 years

Late AMD
(Poor vision)

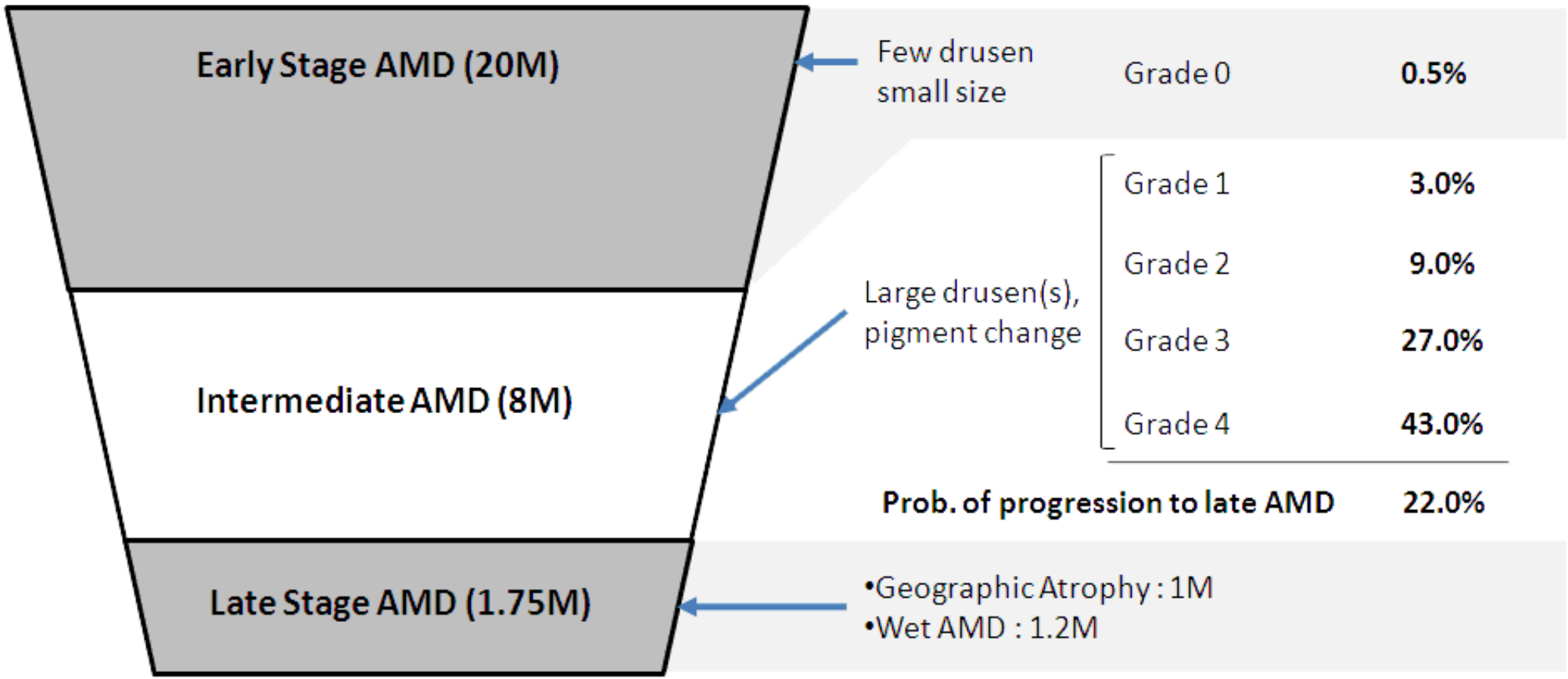
Note: many patients have early AMD with no progression to late AMD)



Late AMD—'Wet' form
(Neovascular AMD)



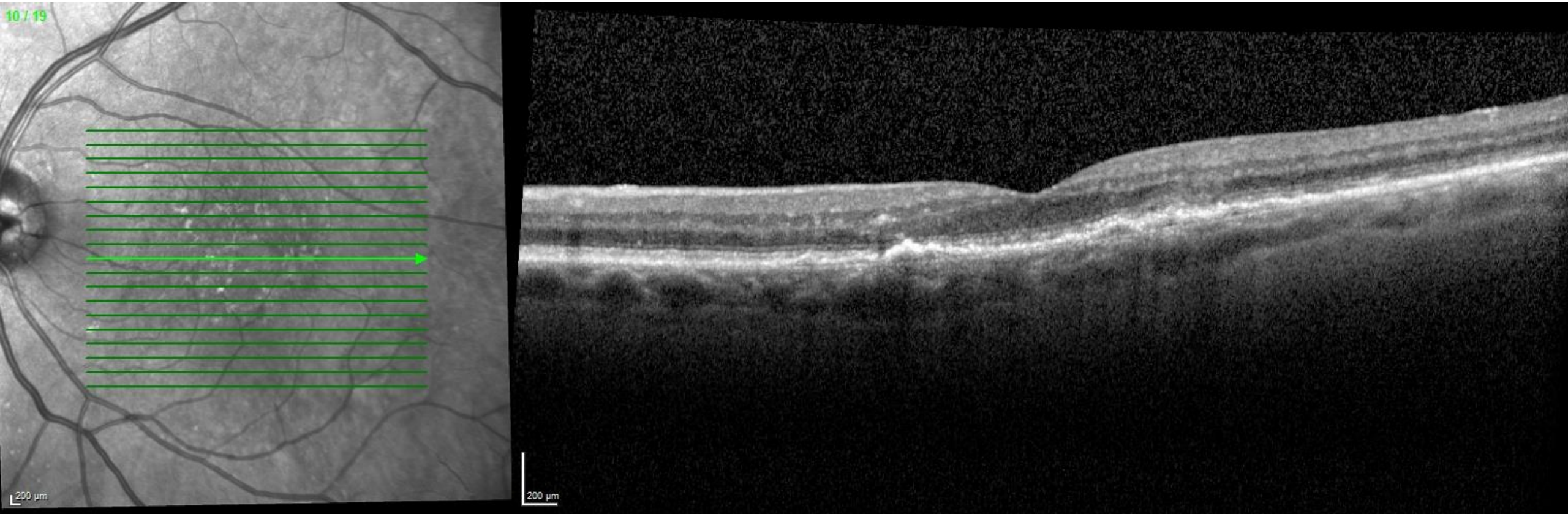
Late AMD—'Wet' form
(Macular scar)



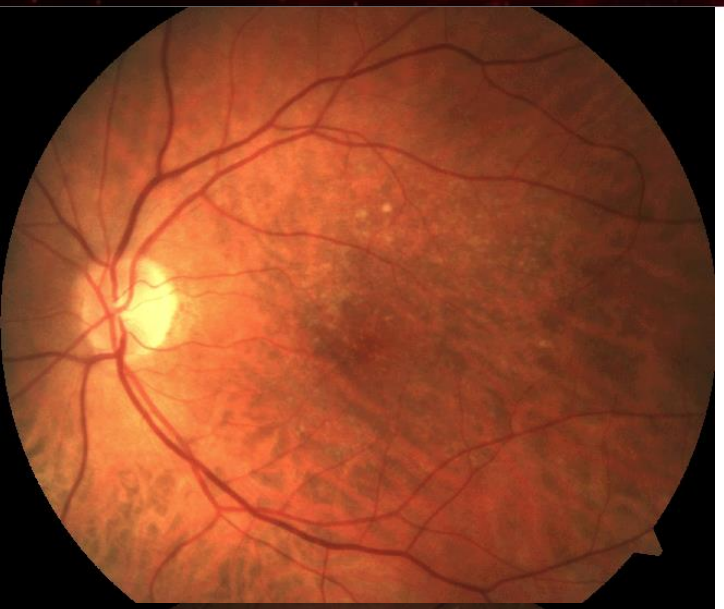
alkeus pharma

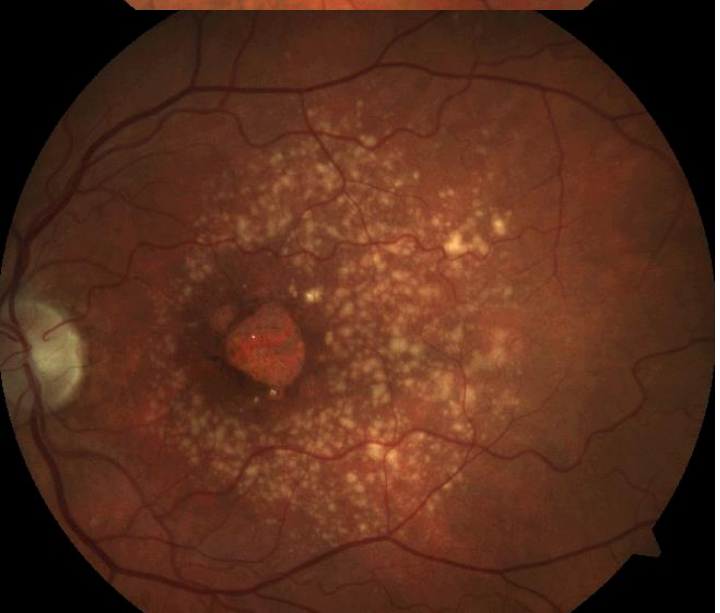
Dry AMD

- 80-90% of patients with disease
- Milder, slowly progressive
- Drusen or “aging spots” and loss of retinal cells and RPE

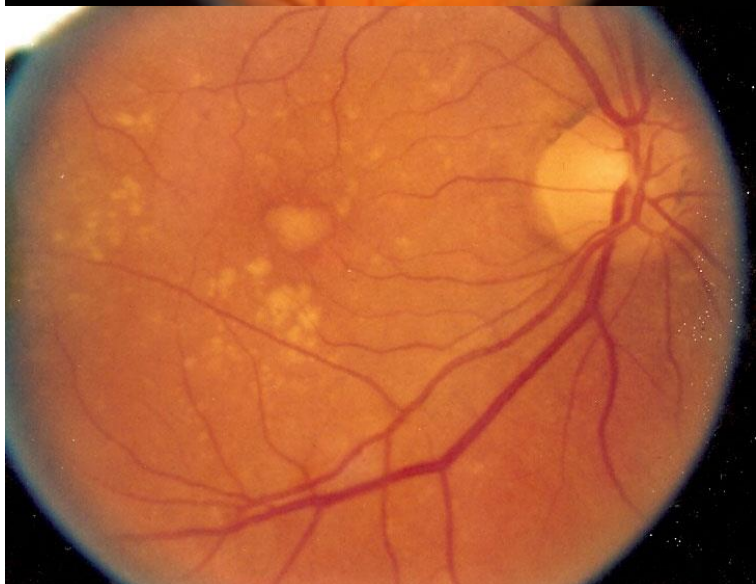


Dry macular degeneration



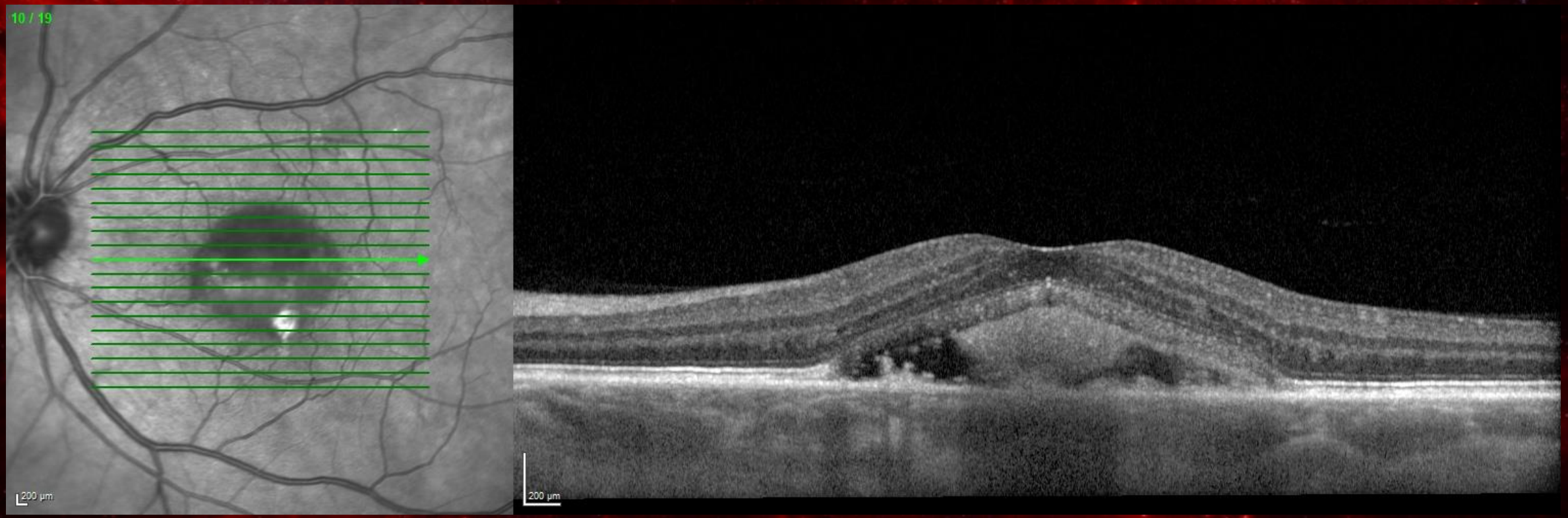


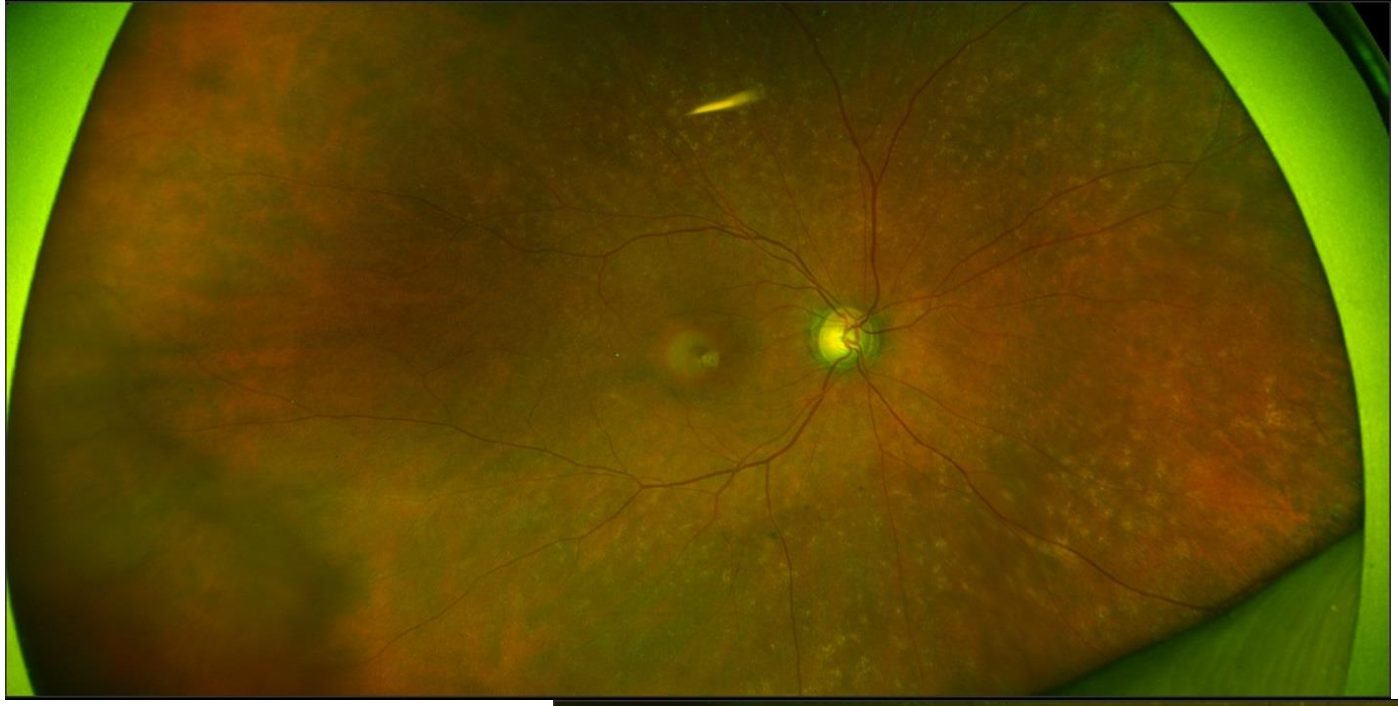
- Typical age of onset >50 yo
- Various presentations
- Small, medium and large drusen

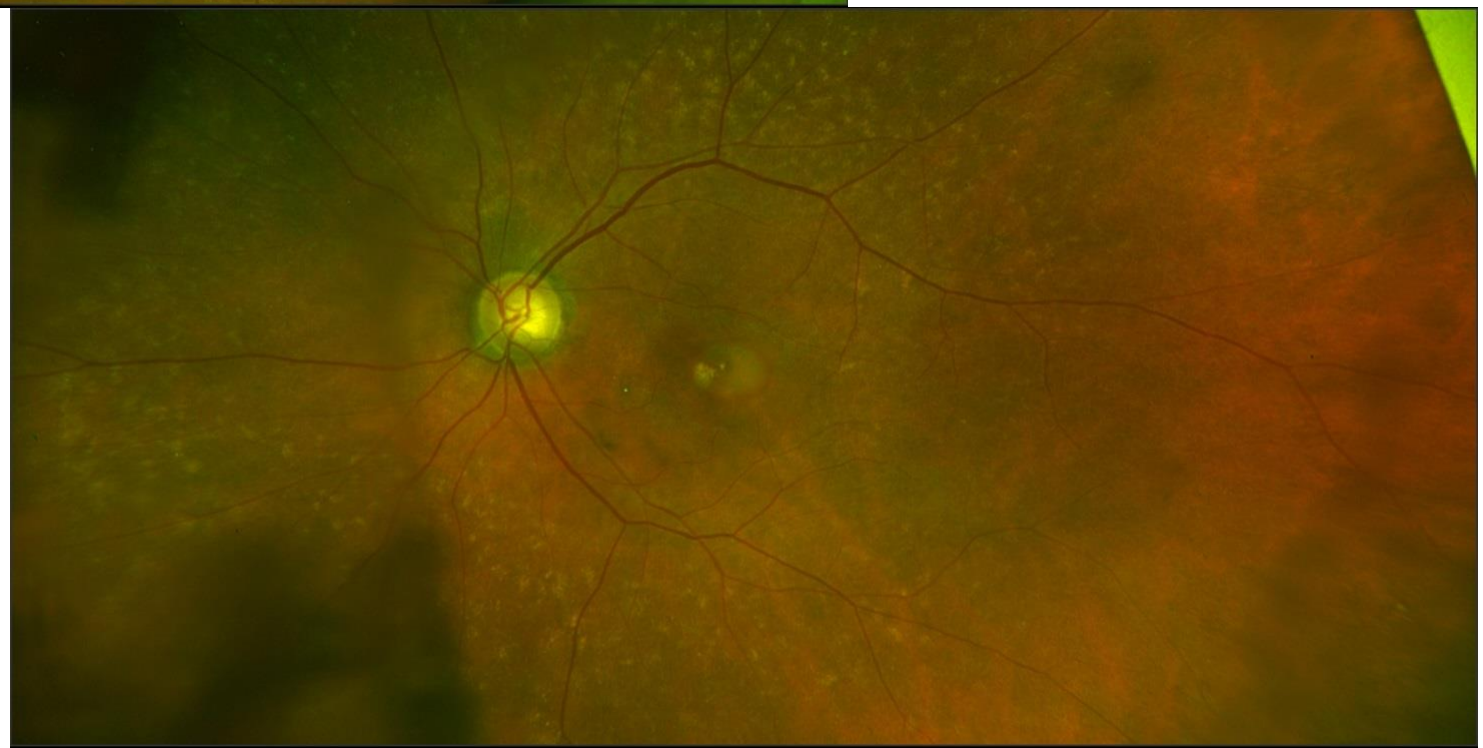


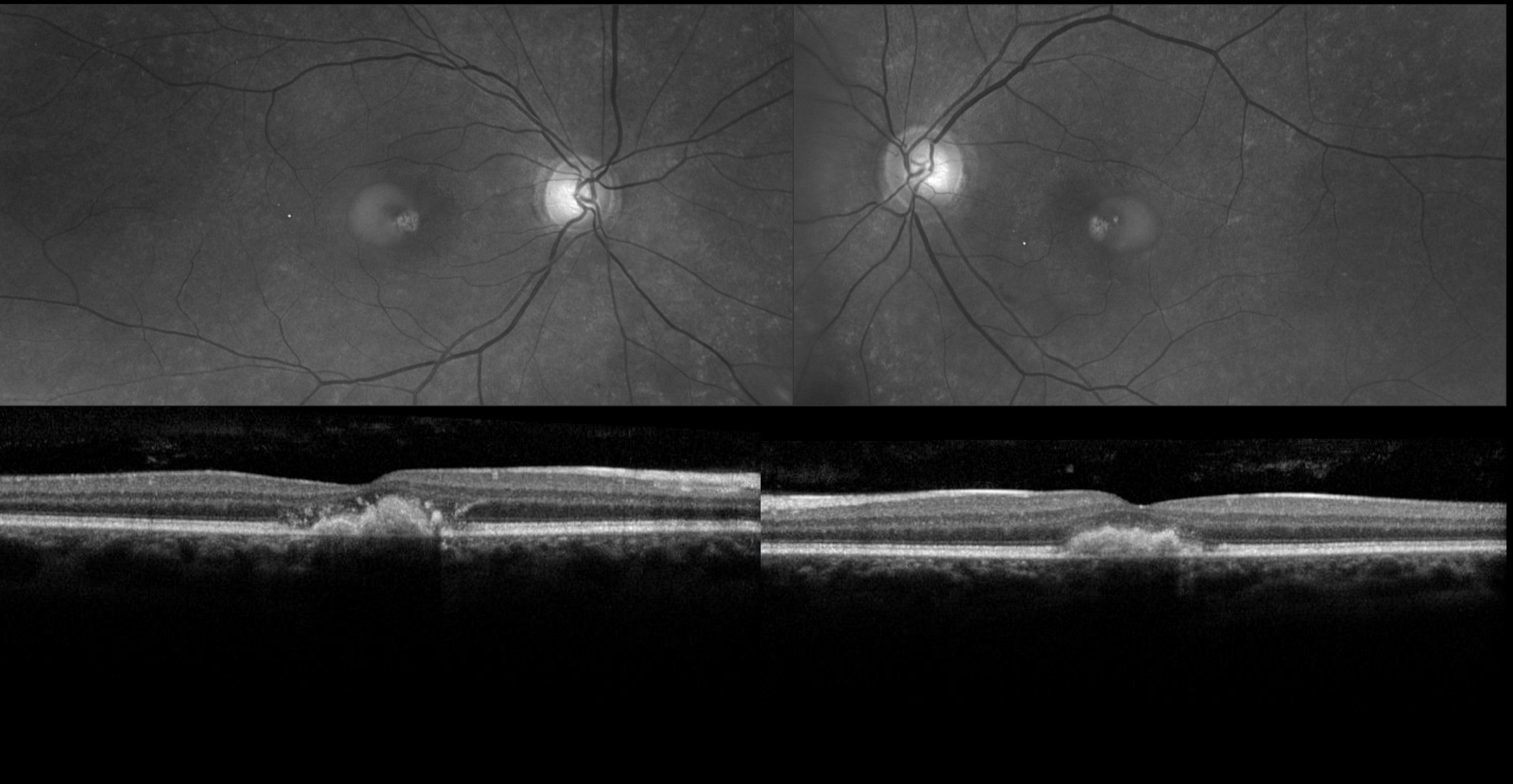
AMD CLASSIFICATION	DEFINITION (lesions assessed within two disc diameters of the fovea in either eye)
No ageing changes	No drusen and no AMD pigmentary abnormalities*
Normal ageing changes	Only drupelets (small drusen ≤63µm) and no AMD pigmentary abnormalities*
Early AMD	Medium drusen (>63µm and ≤125µm) and no AMD pigmentary abnormalities*
Intermediate AMD	Large drusen (>125 µm)^ and/or any AMD pigmentary abnormalities
Late AMD	Neovascular AMD and/or any geographic atrophy (GA)

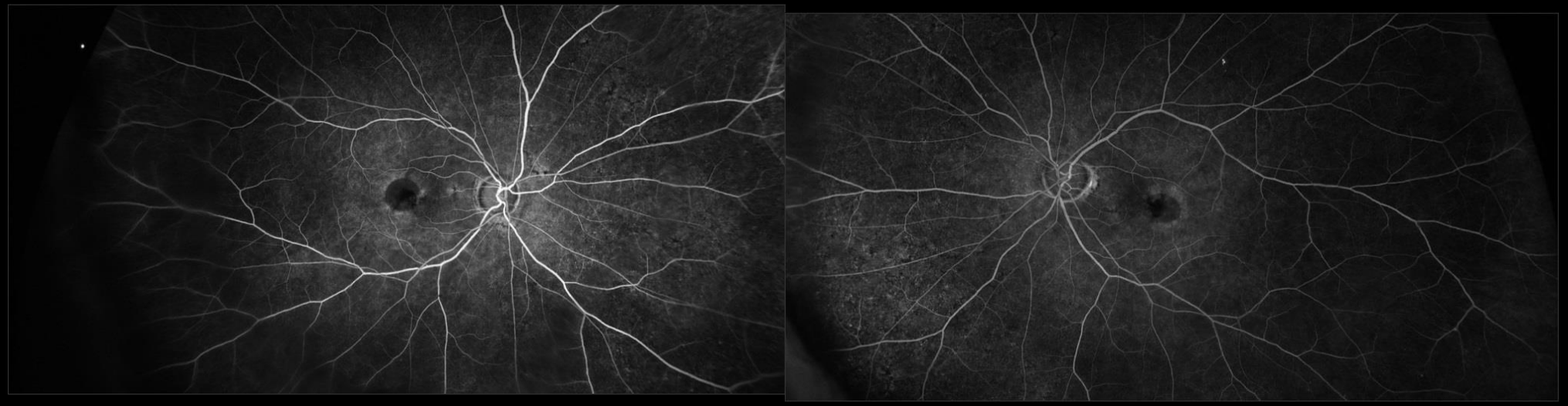
Vitelliform Macular Degeneration



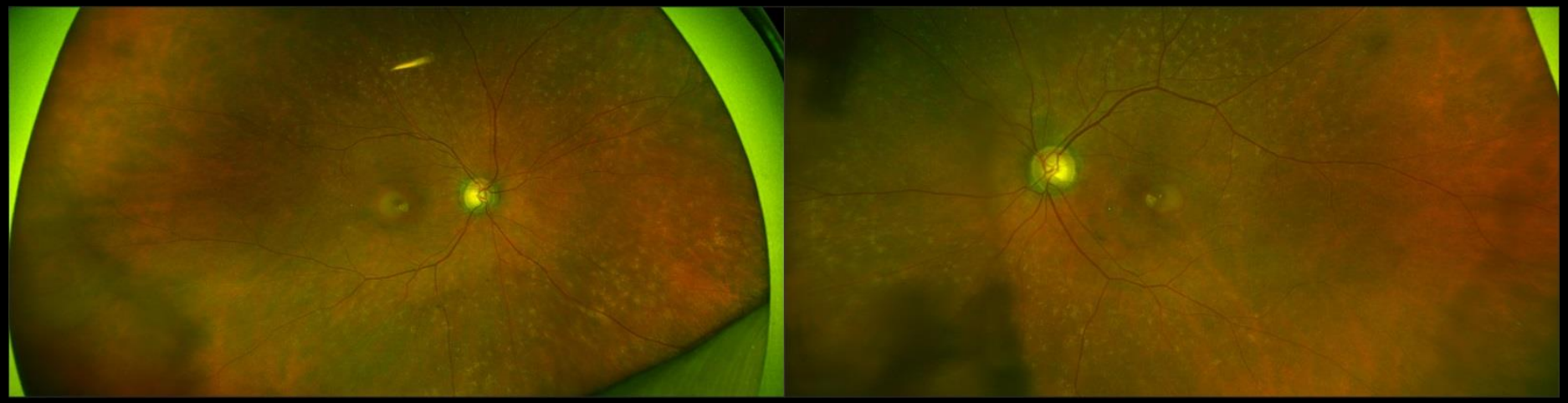




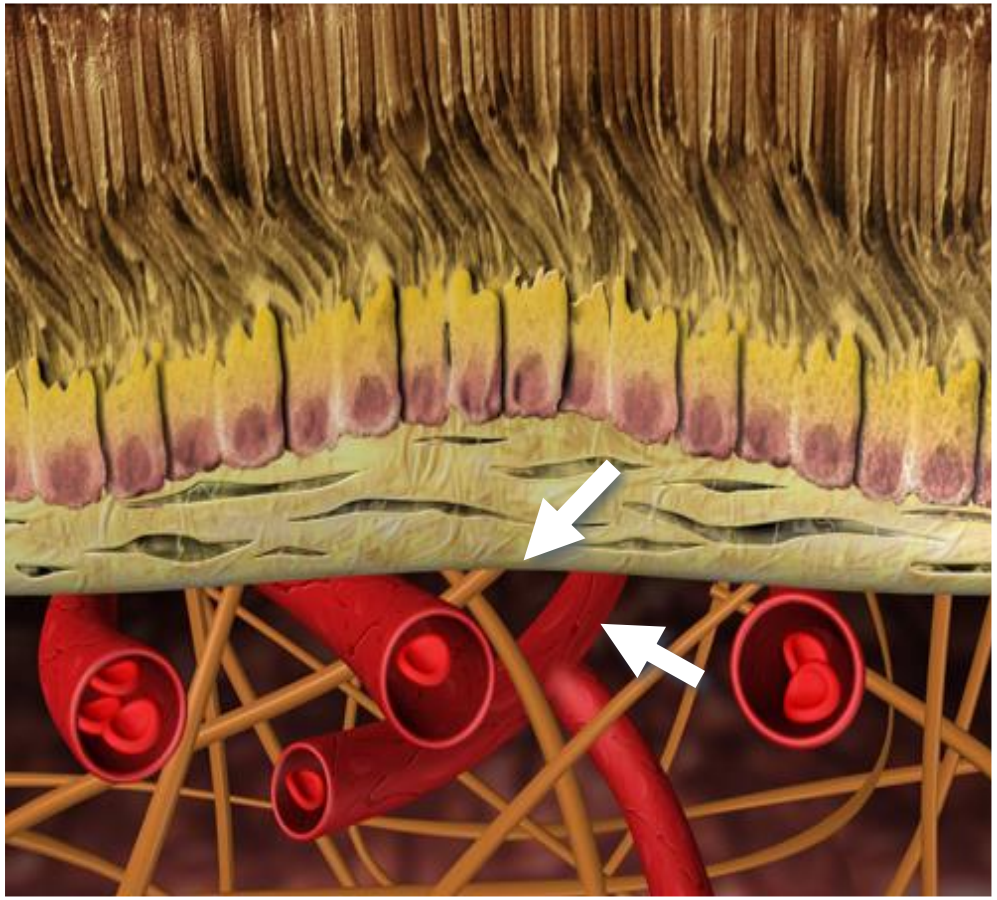


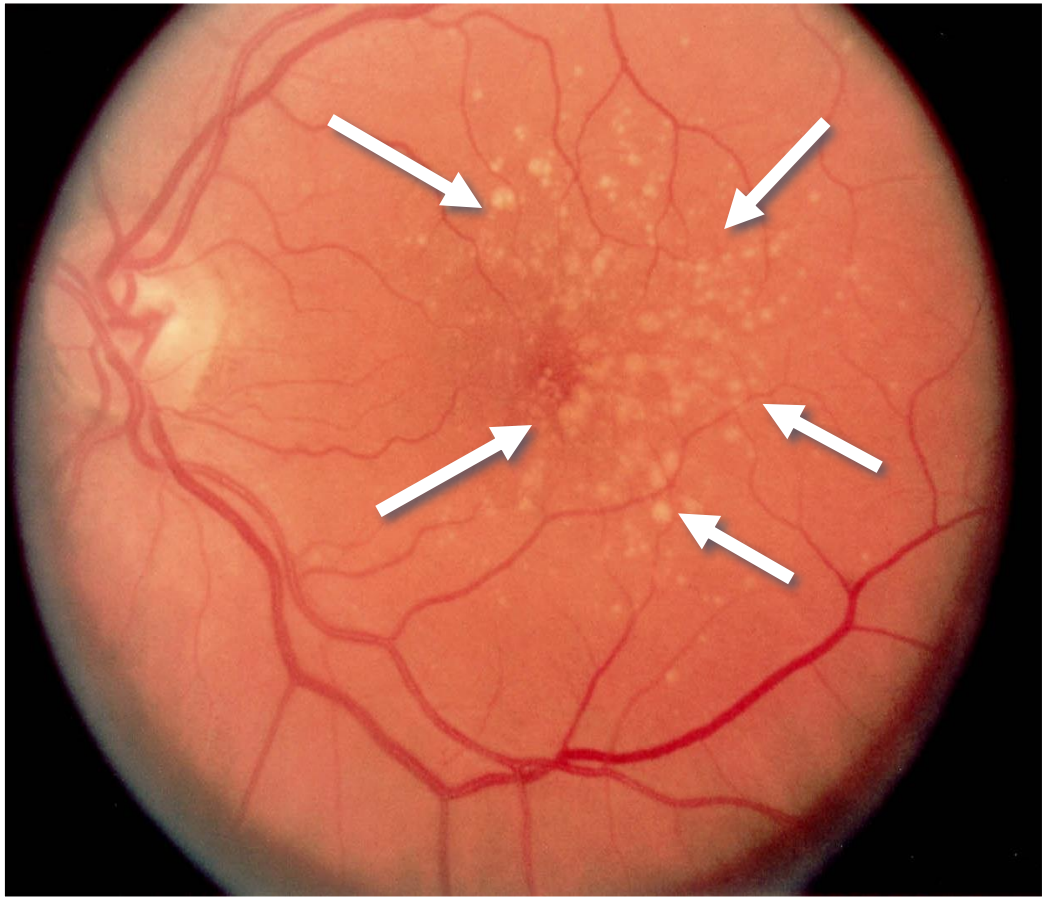


- No leakage on FA (blocked fluorescence)
- Scotoma based on size of lesion

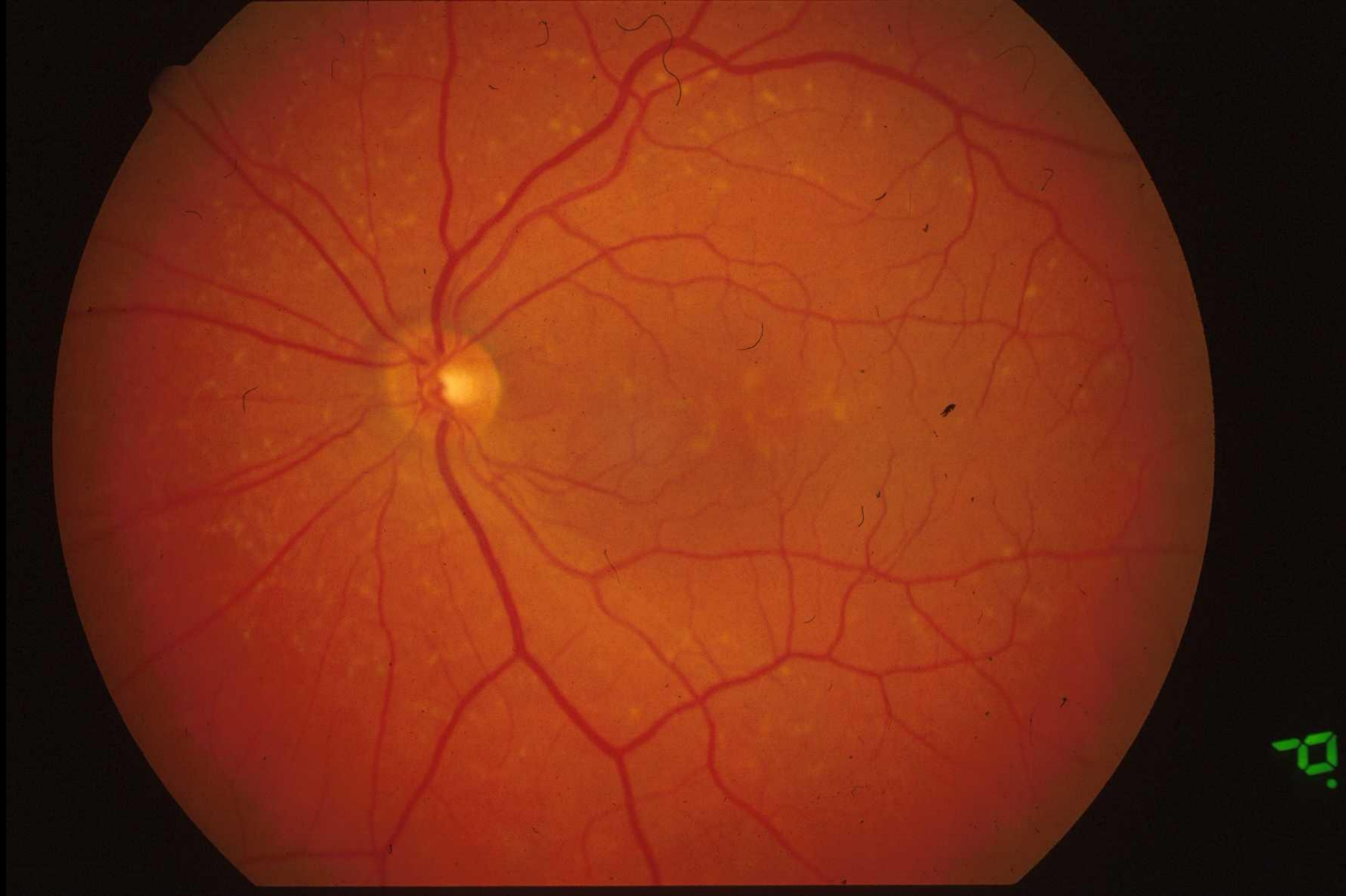


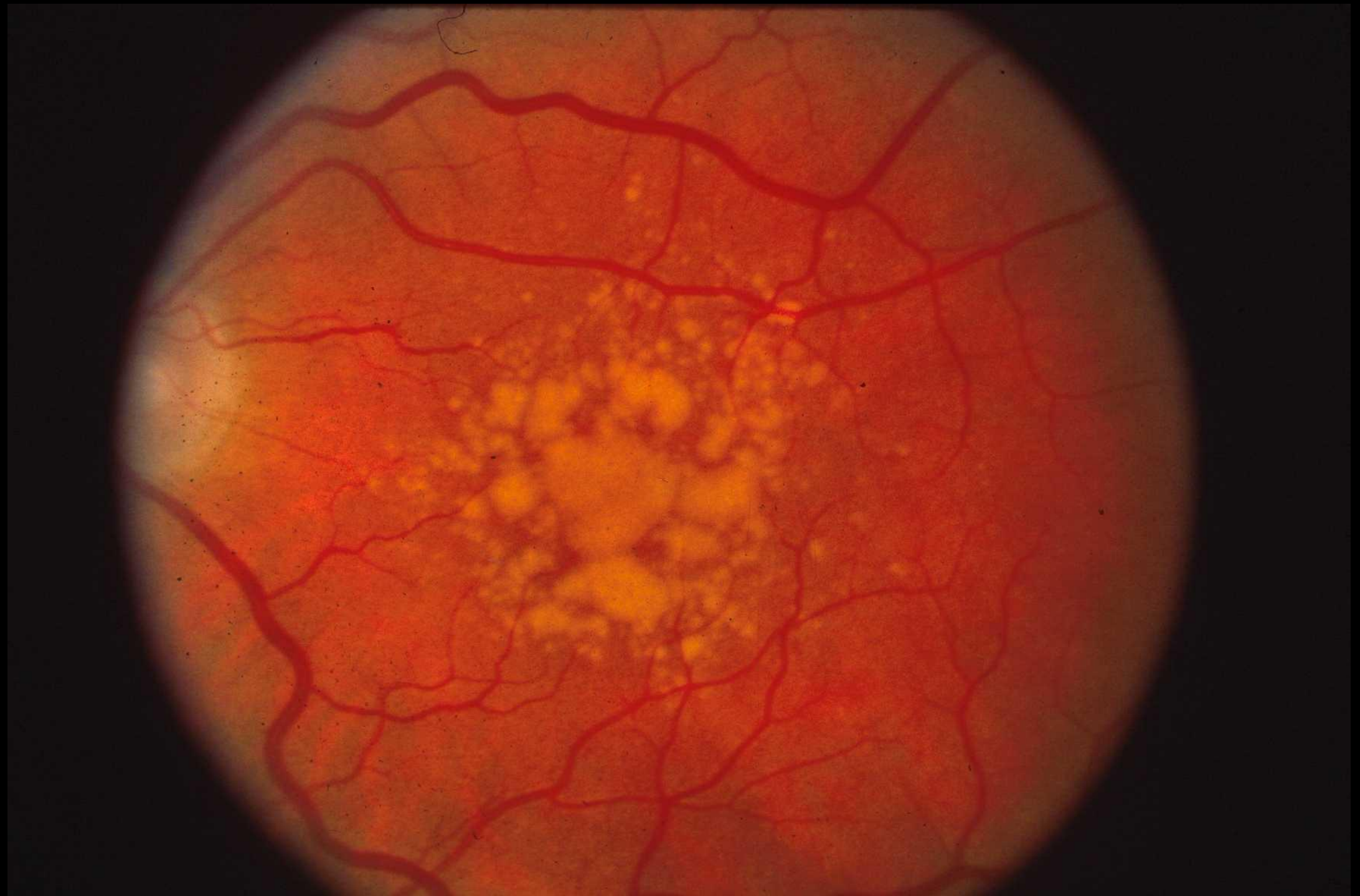
AMD: Development of Drusen

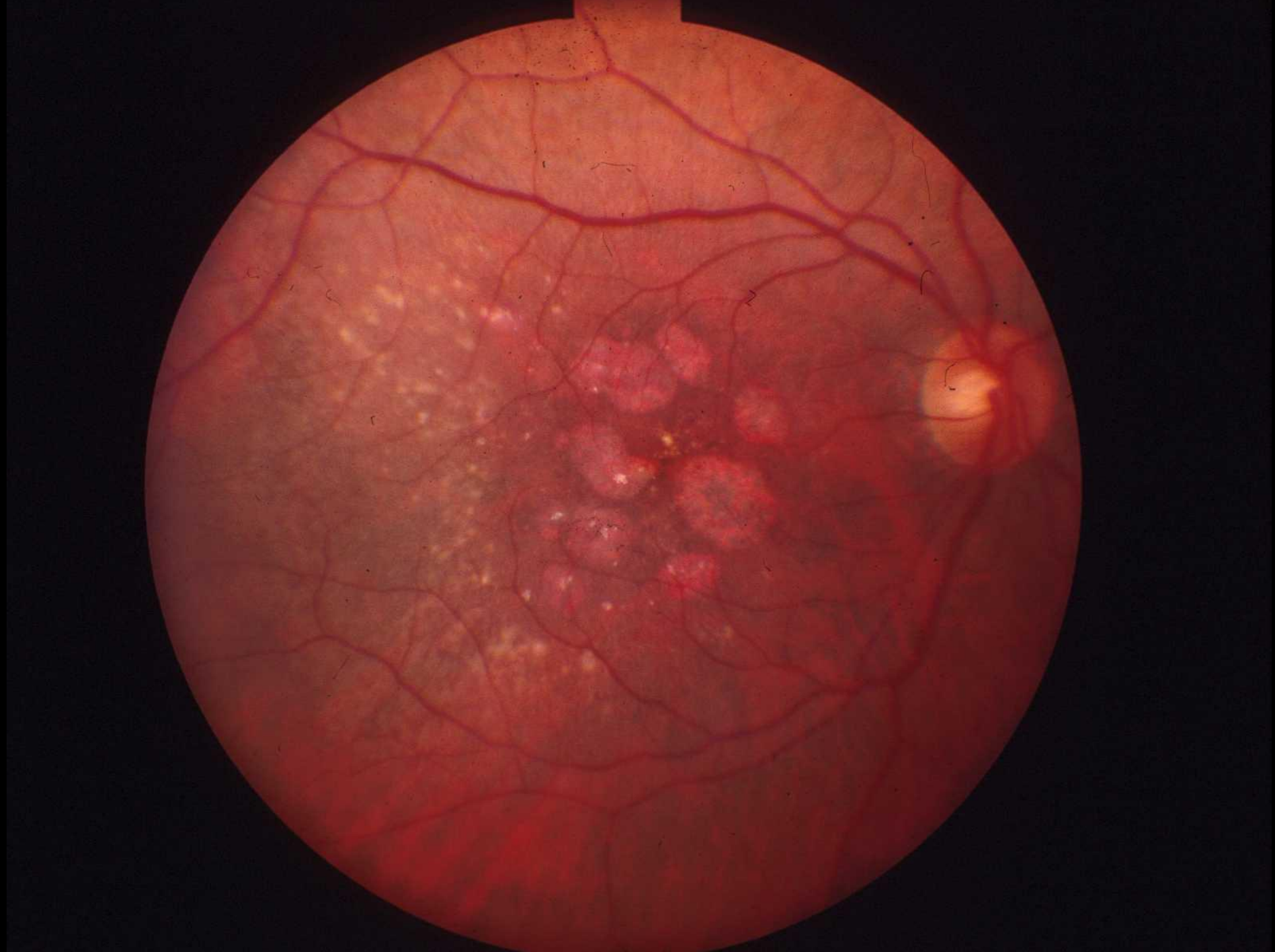


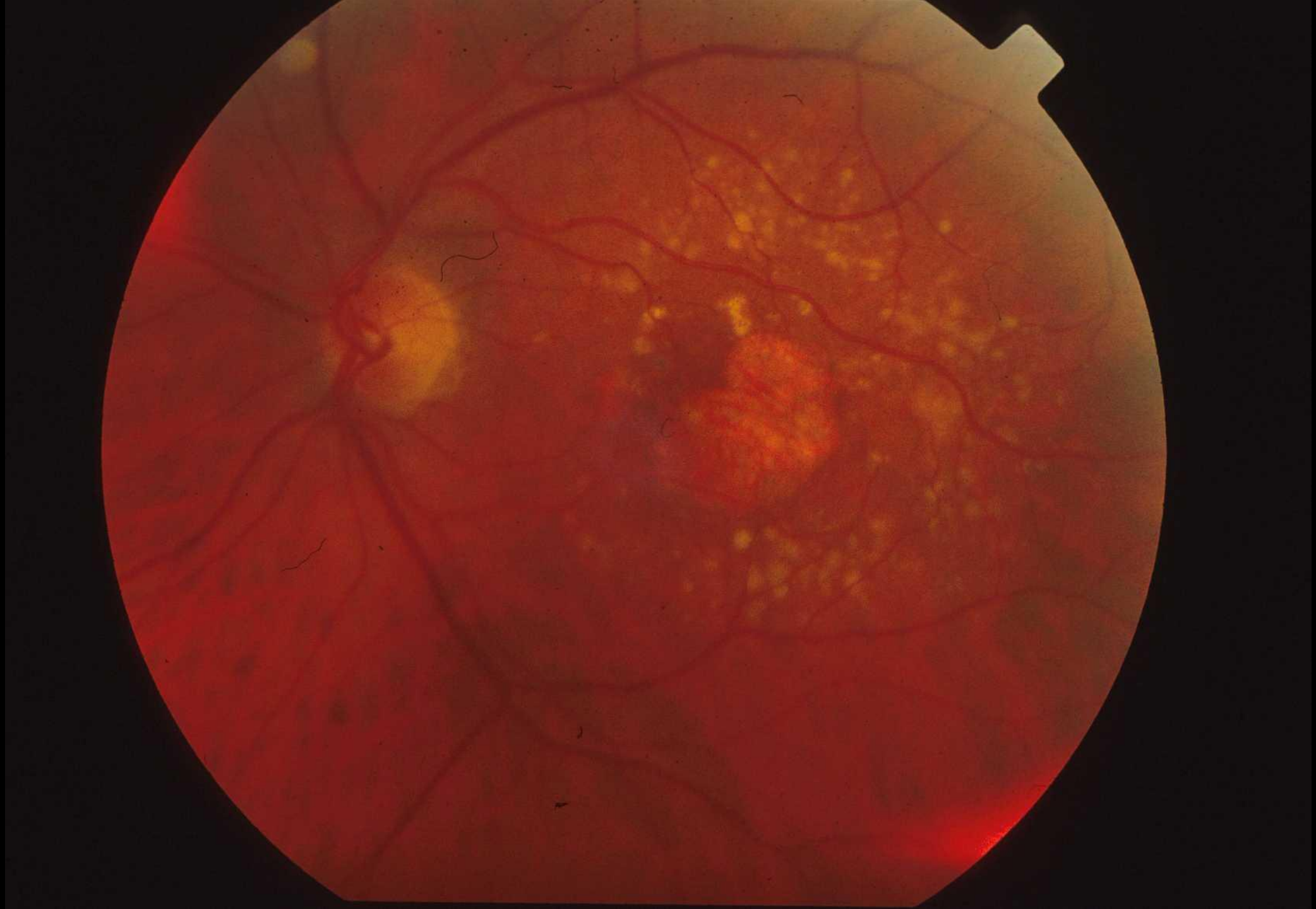


Bruch’s membrane thickens and drusen develop









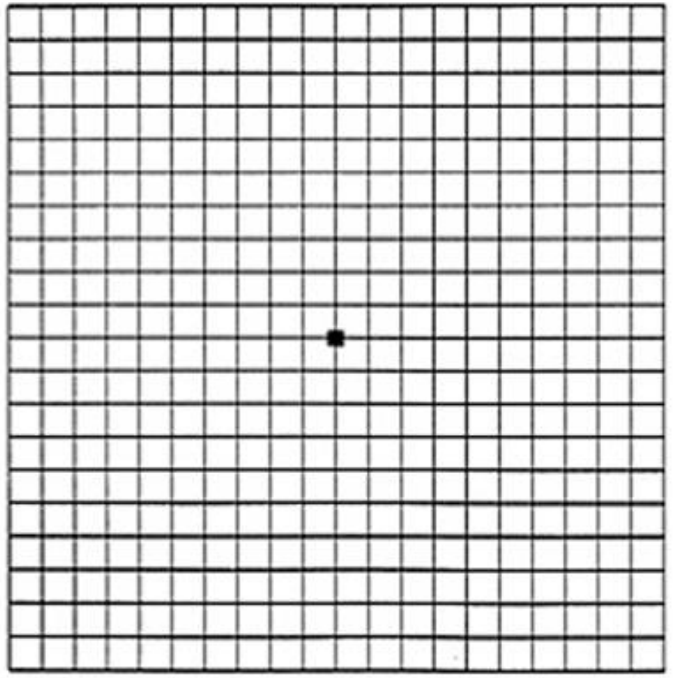
Treatment

- Dry form
  - No known treatment for early/intermediate forms
  - Benefits of micronutrients/antioxidants
    - AREDS2
      - 500 mg vitamin C
      - 400 iu vitamin E
      - 10 mg lutein
      - 2 mg zeaxanthin
      - 80 mg zinc
      - 2 mg copper
    - AREDS (*Archives of Ophthalmology,* October, 2001)
      - Lowered risk 20-25% in fellow eyes of patients with severe disease or intermediate disease in one eye
      - Emerging evidence it may aide in exudative AMD

At home screening

Amsler Grid

The Amsler Grid may appear like this for someone without AMD



The Amsler Grid may appear like this for someone with AMD

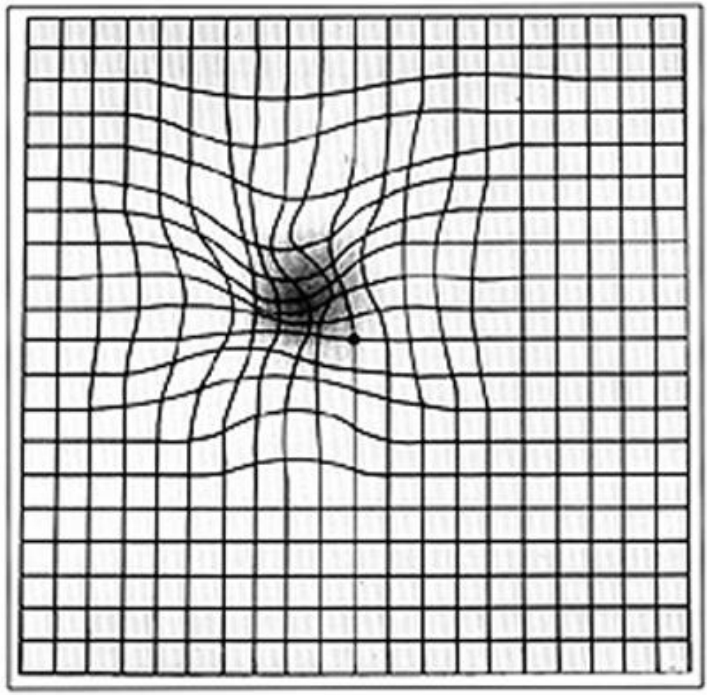


Photo Credit: National Eye Institute, National Institutes of Health Ref#: EC03 and Ref#: EC04

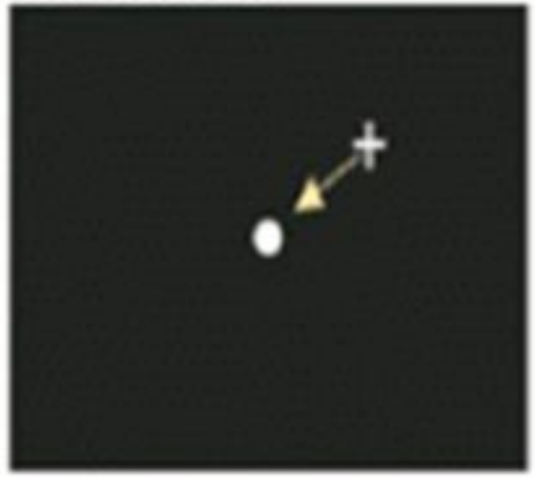
Foresee Home Device

- First FDA approved home tele-monitoring system for macular degeneration patients
- The device transmits the results of the daily test to a monitoring center via a modem or phone line
- The data center will alert the doctors office of any negative change in the patients retina and allows for much earlier intervention by the retina specialist to lessen the potential damage

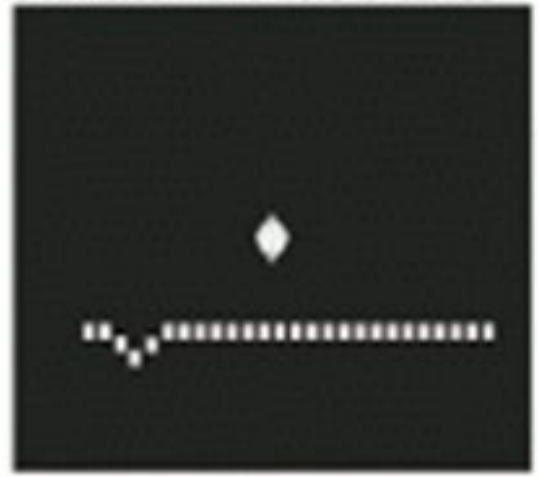

ForeverHome

The ForeseeHome test

1. The patient brings the cursor back to the center



2. When the cursor reaches the center a stimulus with a wave is flashed



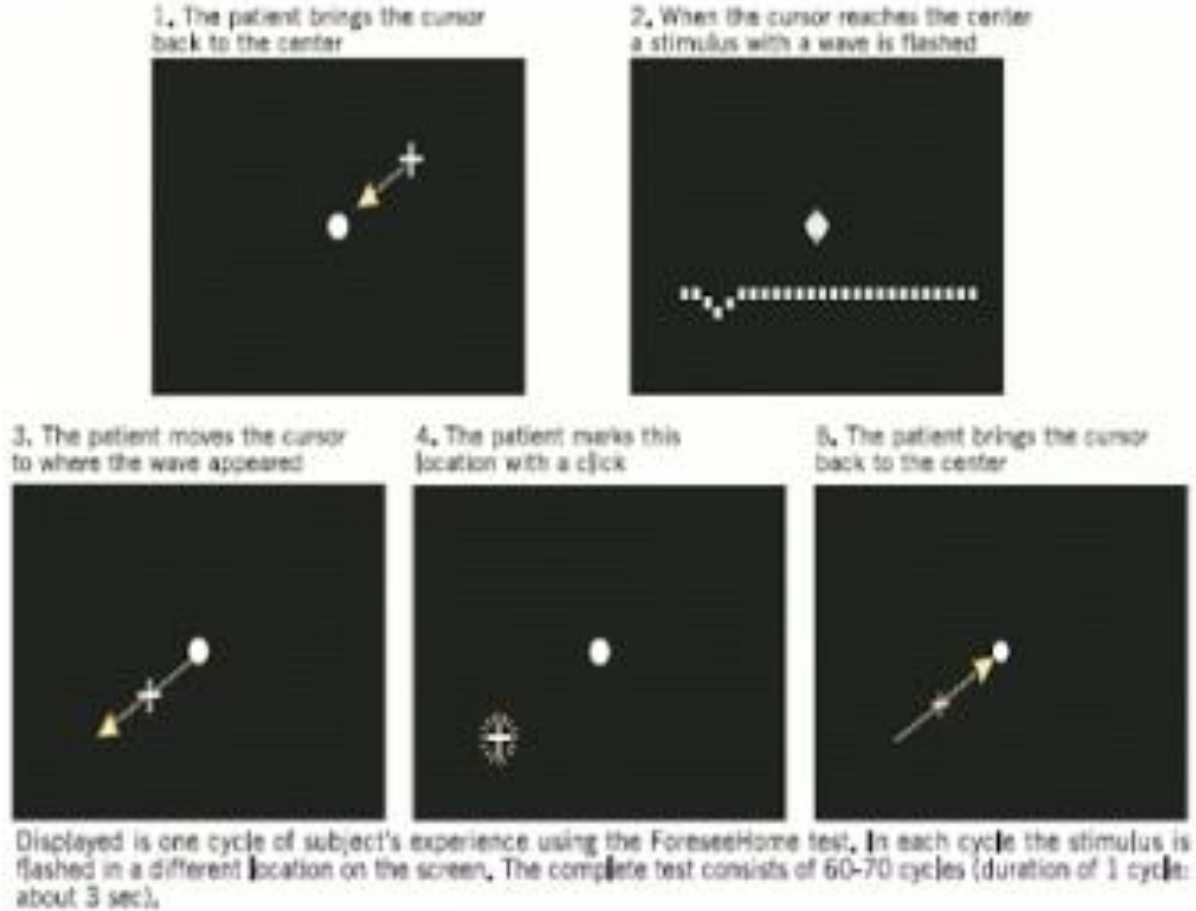
3. The patient moves the cursor to where the wave appeared

4. The patient marks this location with a click

5. The patient brings the cursor back to the center

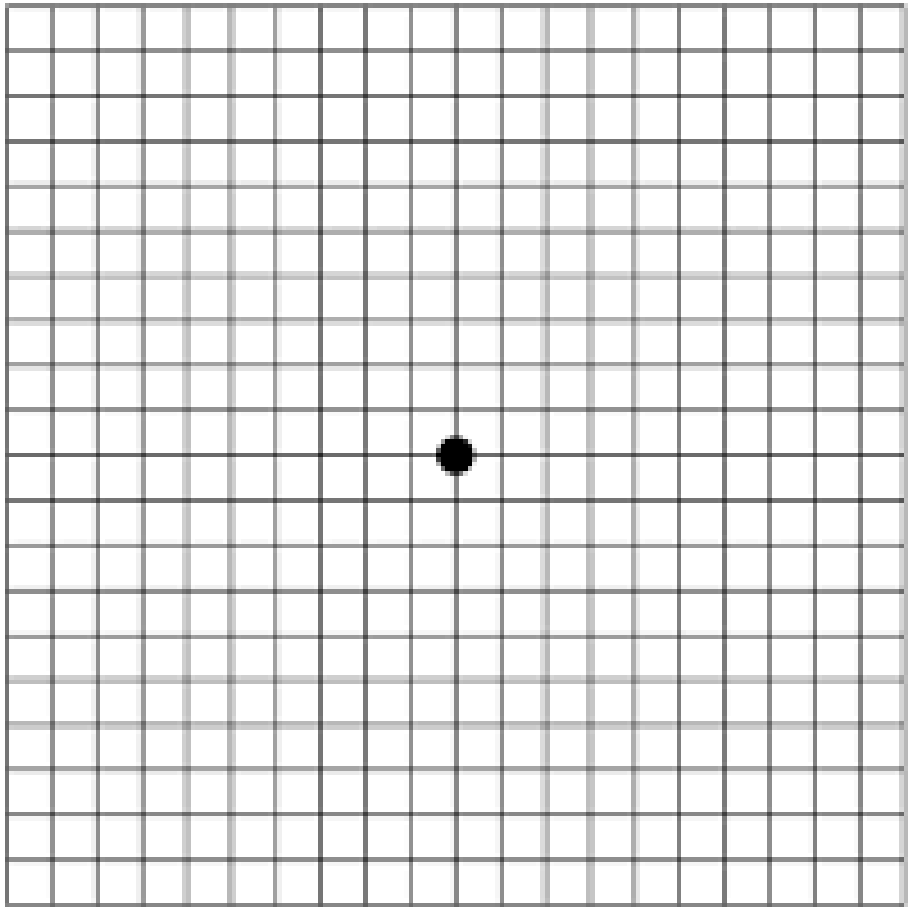
Displayed is one cycle of subject's experience using the ForeseeHome test. In each cycle the stimulus is flashed in a different location on the screen. The complete test consists of 60-70 cycles (duration of 1 cycle: about 3 sec).

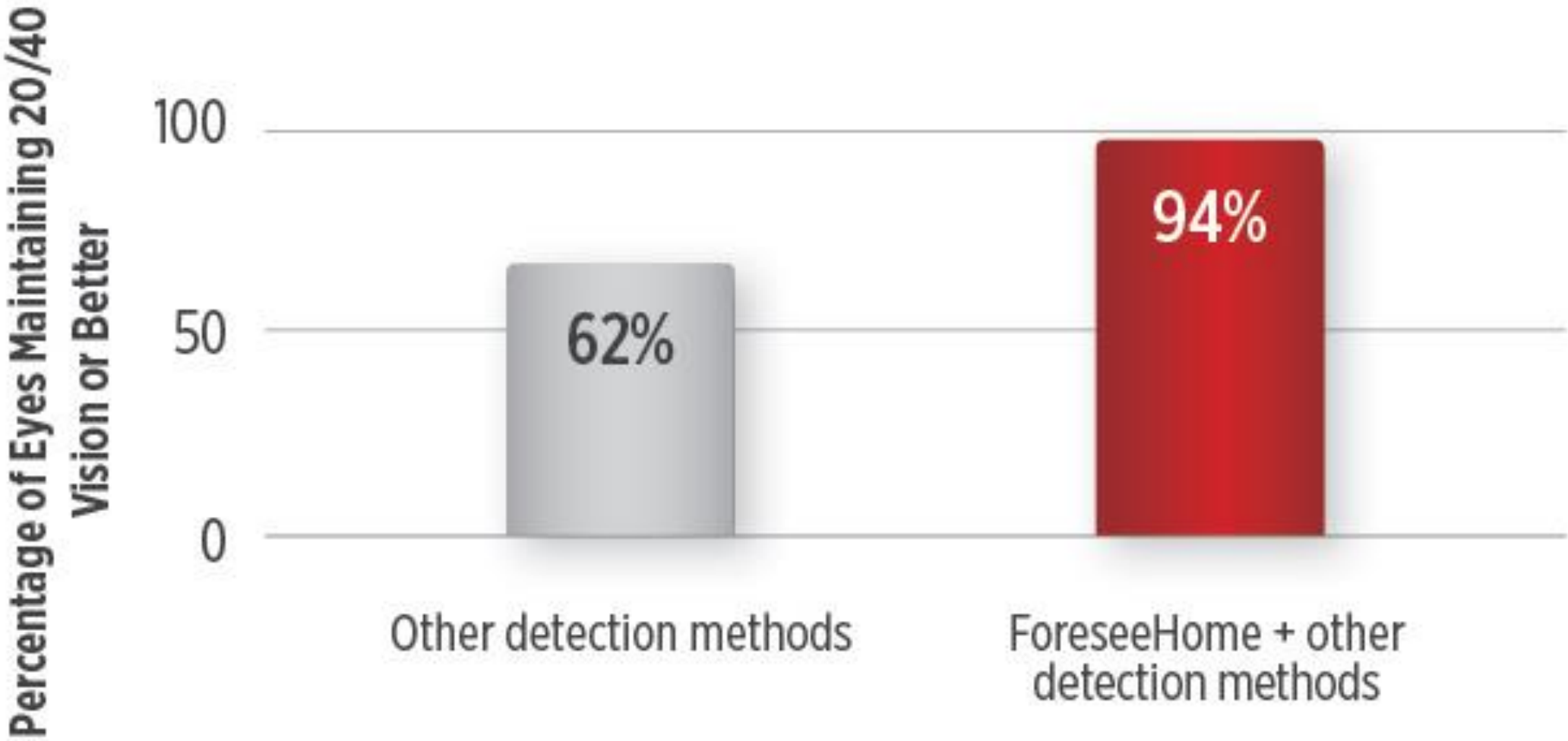
The ForeseeHome test



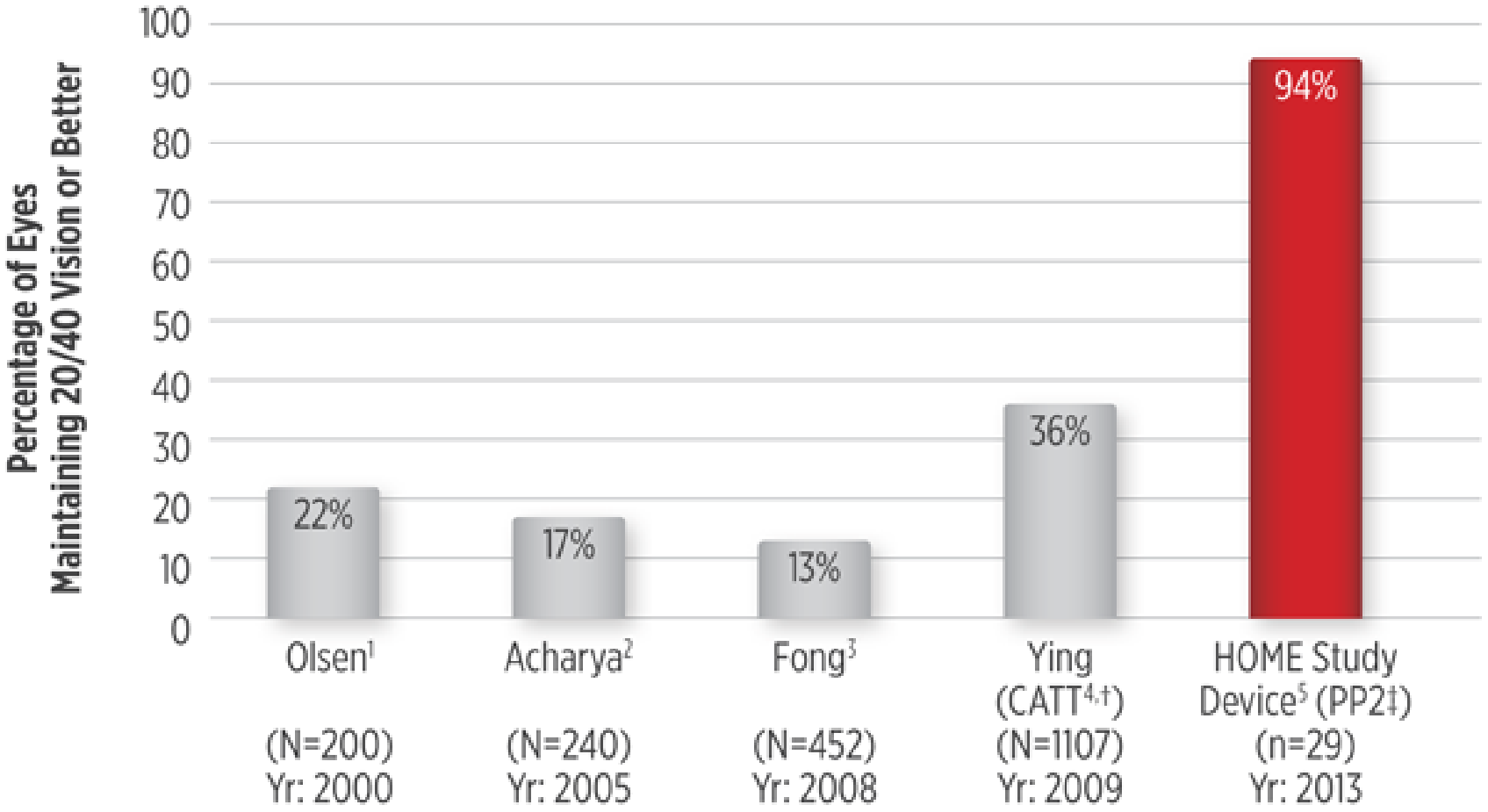
Displayed is one cycle of subject's experience using the ForeseeHome test. In each cycle the stimulus is flashed in a different location on the screen. The complete test consists of 60-70 cycles (duration of 1 cycle: about 3 sec).

Amsler Grid Test




Percentage of Eyes Maintaining 20/40 Vision or Better
100
50
0
62%
94%
Other detection methods
ForeseeHome + other detection methods

Baseline VA at CNV diagnosis in different studies
VA at detection for ForeseeHome (percentage of eyes with VA 20/40 or better[1-5])



†All but the **C**omparison of **A**ge-related Macular Degeneration **T**reatment **T**rials (CATT) included patients with VA of 20/20 or worse (CATT included ≤20/25).
‡PP2=per protocol 2 cohort.
The HOME Study used the ETDRS chart to measure the number of letters for VA; the Snellen equivalent for VA is presented here.

Valeda Laser

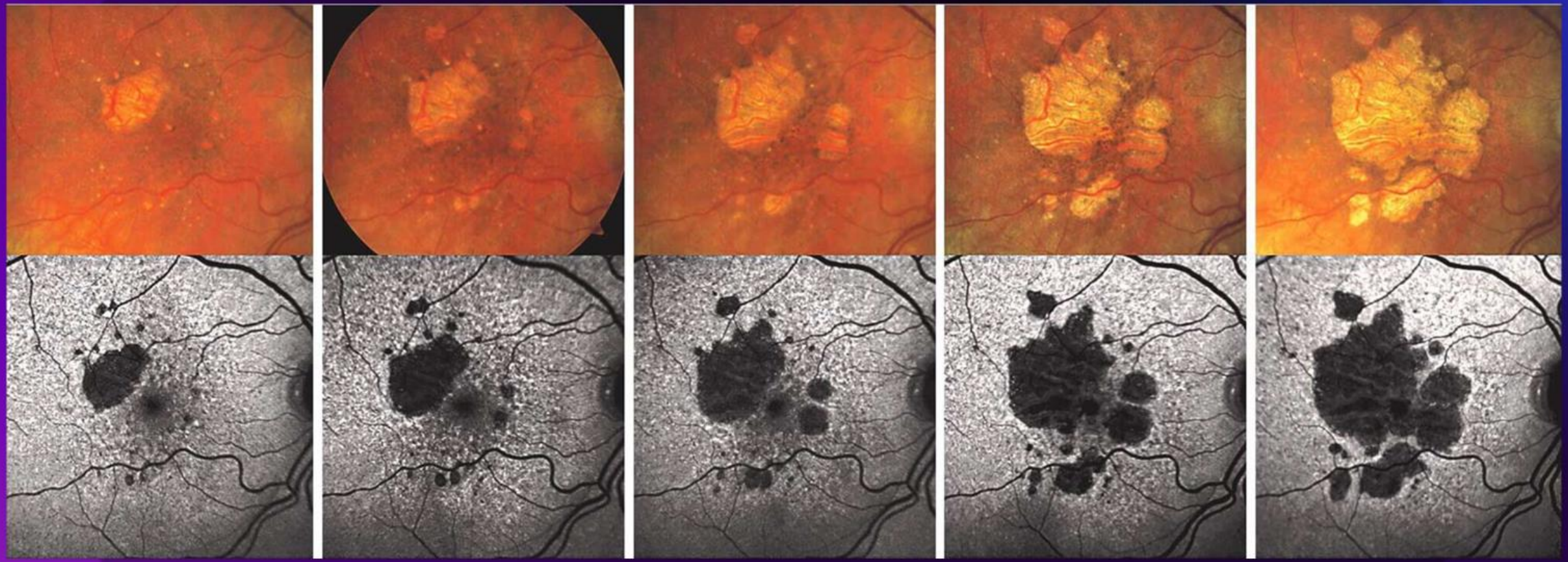
- Valeda is the first FDA-authorized, non-invasive light therapy (Photobiomodulation) for Dry Age-Related Macular Degeneration (AMD)
- Uses specific wavelengths (blue, red, near-infrared) to boost cellular energy in retinal cells, reducing oxidative stress, and slowing disease progression.
- Painless, low-intensity light treatments in a series of treatment sessions

Valeda

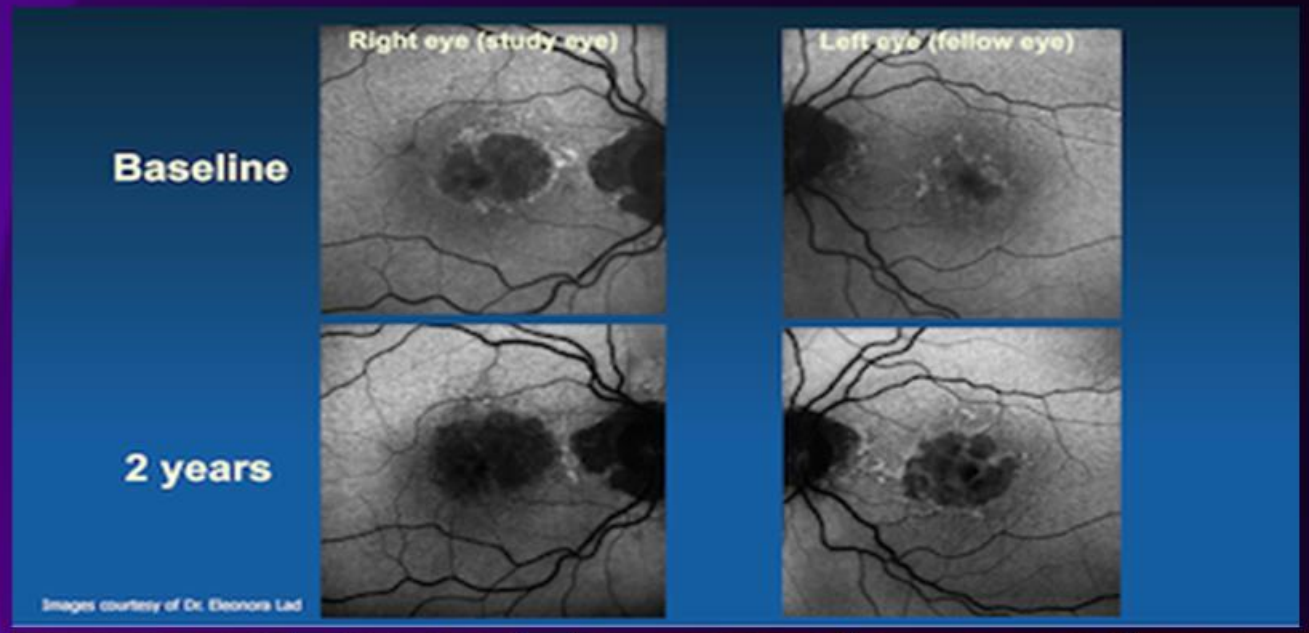
- Photobiomodulation (PBM): specific light wavelengths (amber 590nm, red 660nm, near-infrared 850nm) that directly penetrate retinal cells.
- Boost Cellular Energy : stimulates mitochondria, increasing cellular ATP production and improving cell function.
- Reduces inflammation and oxidative stress

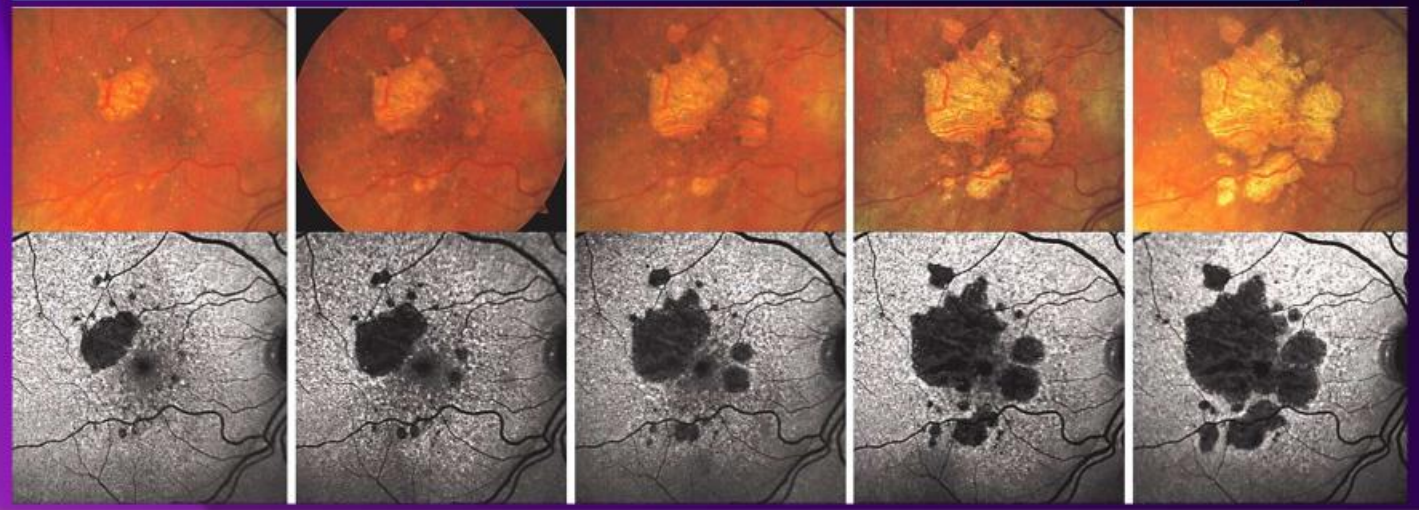

VALEDA
Select the number of eyes to be treated
1
or
2

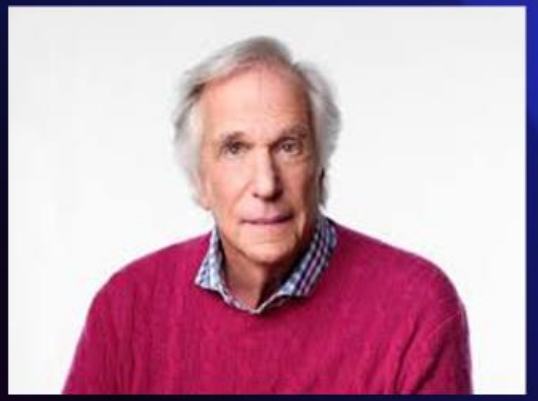
Progression of Dry AMD



DRY AMD TREATMENT

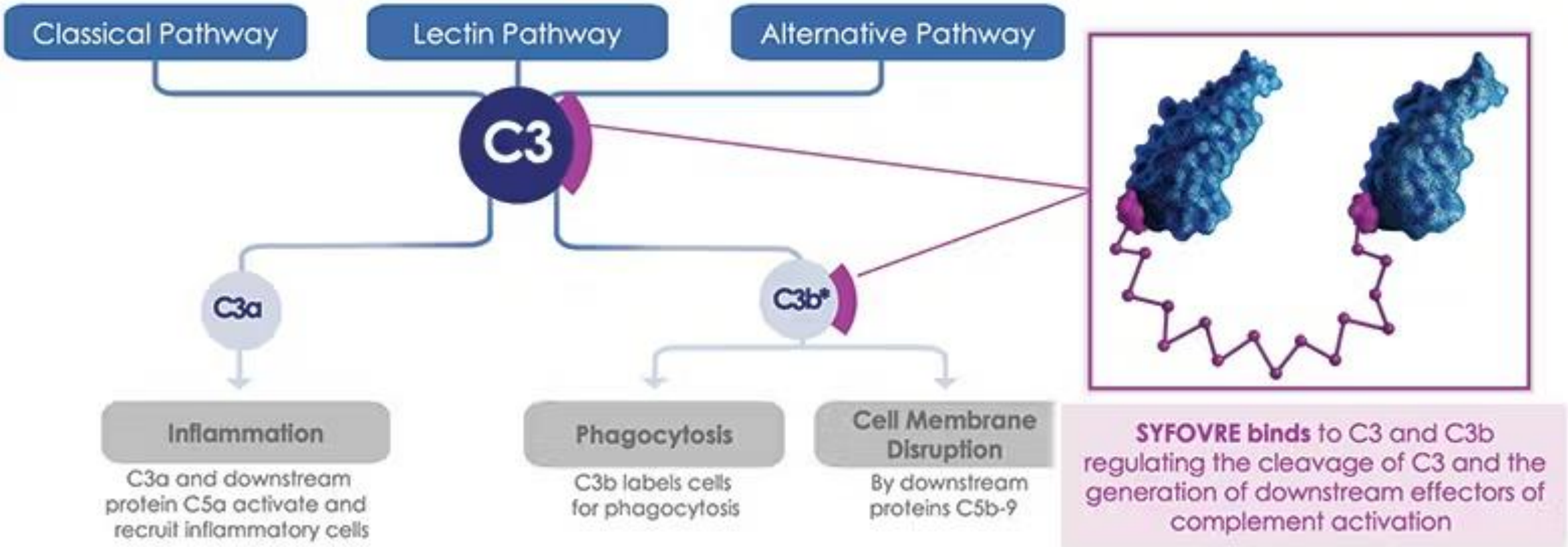






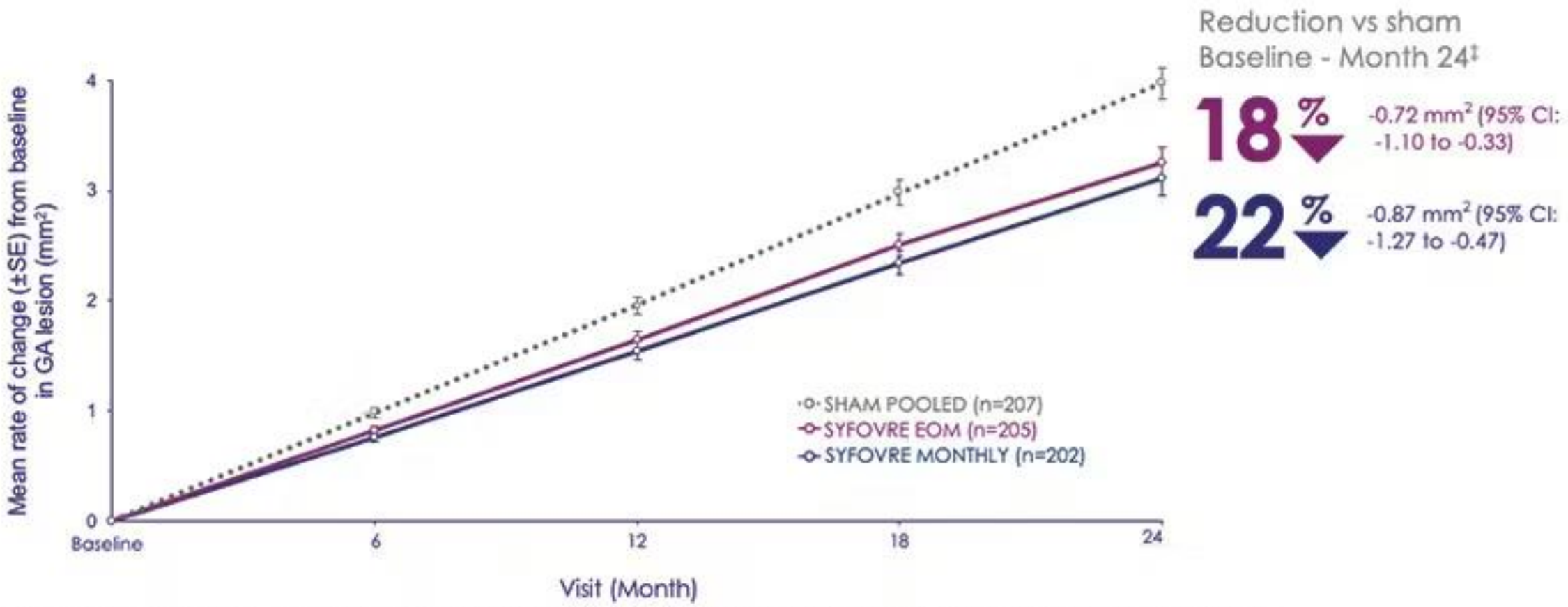
Syfovre

- Syfovre targets complement protein C3, a key component in the immune response.
- It binds to C3 and C3b, preventing them from being cleaved and stopping the production of inflammatory molecules.
- Slows Cell Death: reduces overactivation of the immune system and inflammation, which slows the progression of cell death in the macula, a hallmark of GA.



*C3b is involved in an amplification loop for complement activation.
Image does not reflect all proteins involved in the complement cascade.

REDUCTION IN LESION GROWTH RATE WITH SYFOVRE VS SHAM POOLED (OAKS and DERBY)

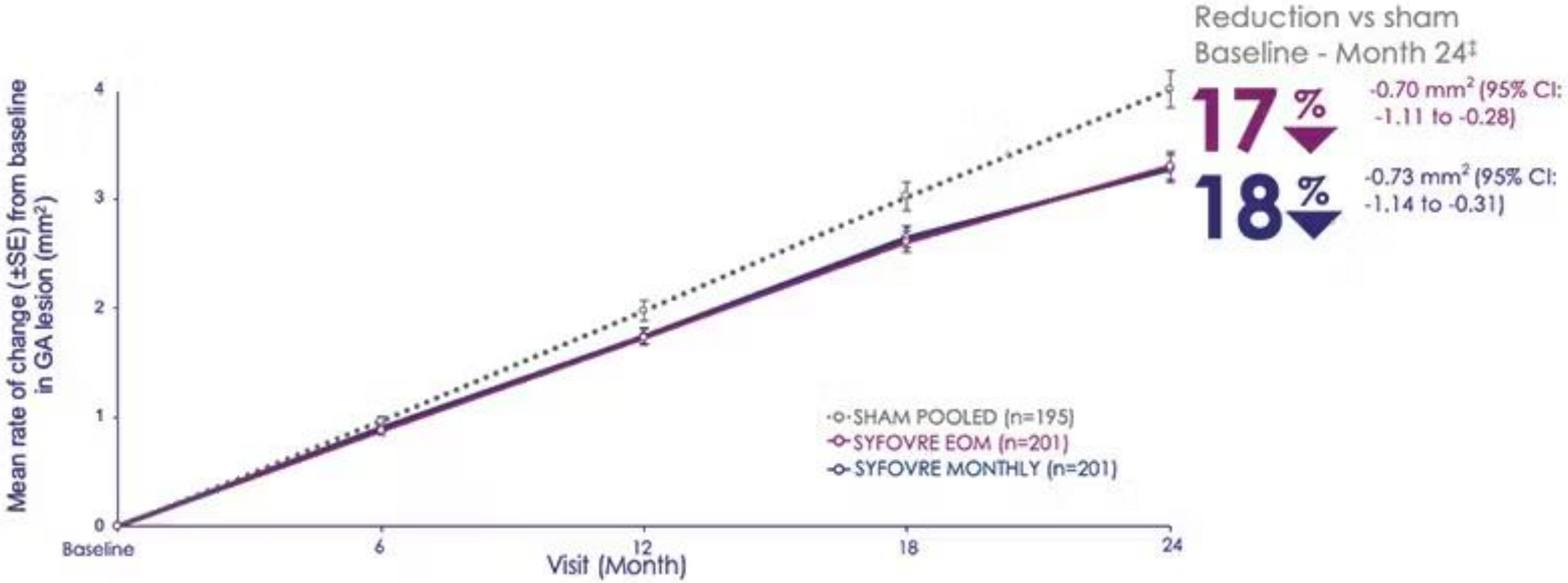


*Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

†SHAM EOM and SHAM Monthly were pooled for analysis.[2]

‡Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

SE=standard error; CI=confidence interval.



*Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

†SHAM EOM and SHAM Monthly were pooled for analysis.[2]

‡Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

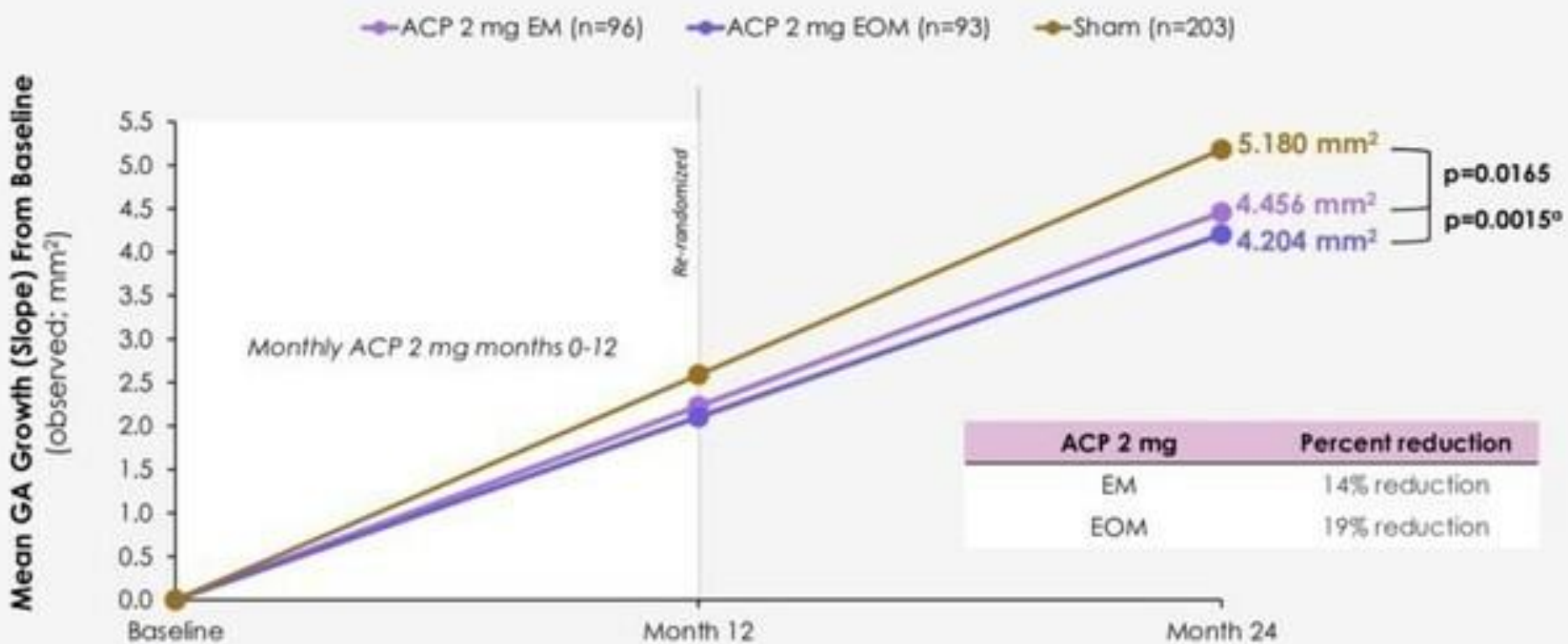
	SYFOVRE MONTHLY (n=419)	SYFOVRE EOM (n=420)	SHAM POOLED (n=417)
Ocular discomfort*	13%	10%	11%
Neovascular AMD*	12%	7%	3%
Vitreous floaters	10%	7%	1%
Conjunctival hemorrhage	8%	8%	4%
Vitreous detachment	4%	6%	3%
Retinal hemorrhage	4%	5%	3%
Punctate keratitis*	5%	3%	<1%
Posterior capsule opacification	4%	4%	3%
Intraocular inflammation*	4%	2%	<1%
Intraocular pressure increased	2%	3%	<1%

Izervay

- C5 Protein acts as a signal, telling other immune proteins to attack retinal/RPE cells, leading to cell death.
- Izervay, an RNA aptamer, binds to and blocks the C5 protein.
- By blocking C5, Izervay stops the formation of the Membrane Attack Complex (MAC), which is responsible for damaging RPE cells, reducing inflammation and protecting healthy retinal cells.

ACP reduced GA growth when dosed EM and EOM vs sham

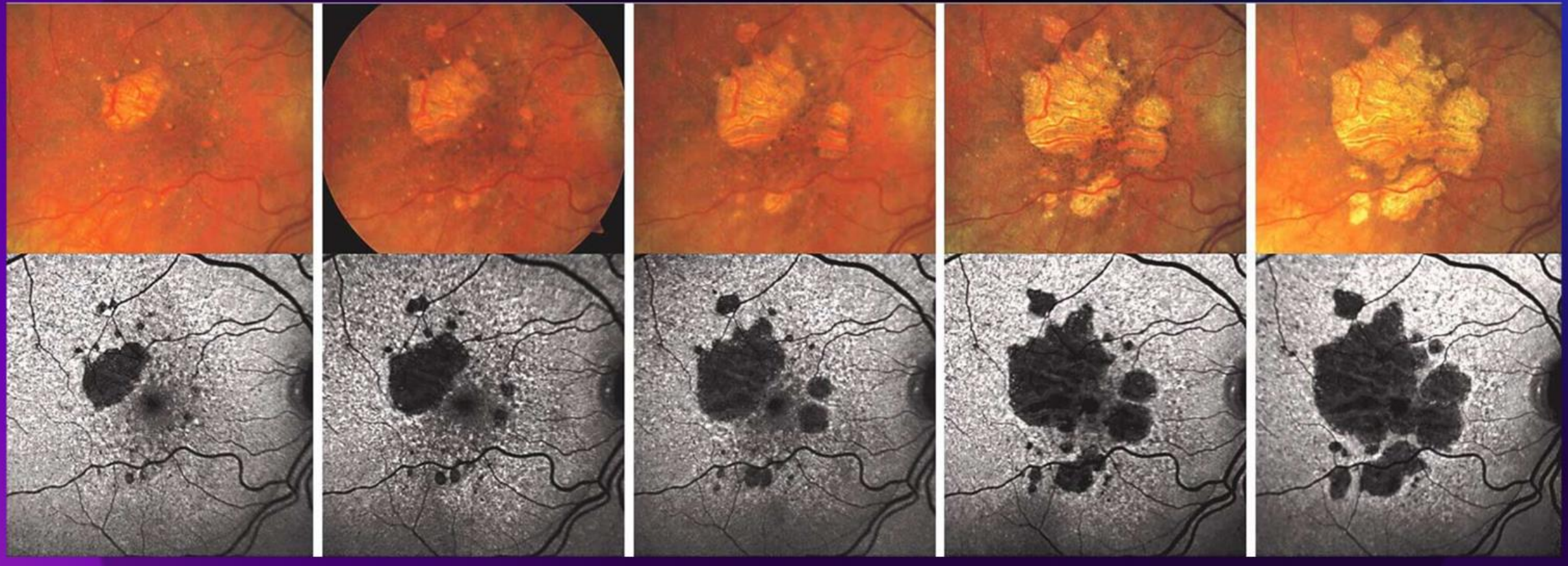
GATHER2



ACP 2 mg	Percent reduction
EM	14% reduction
EOM	19% reduction

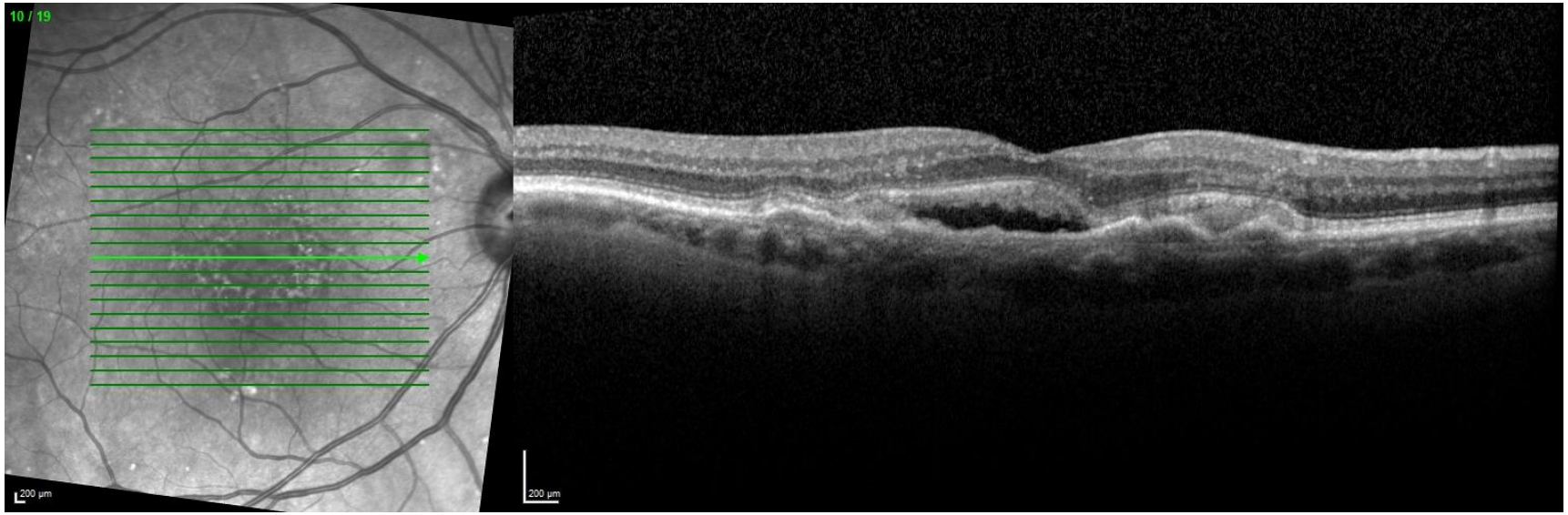
ª*P* value is nominal.
Note: This analysis is based on a mixed model assuming constant growth rate from baseline to month 24.
ACP, investigational product; CI, confidence interval; EM, every month dose; EOM, every other month; SD, standard deviation.

Progression of Dry AMD



Wet form “Exudative”

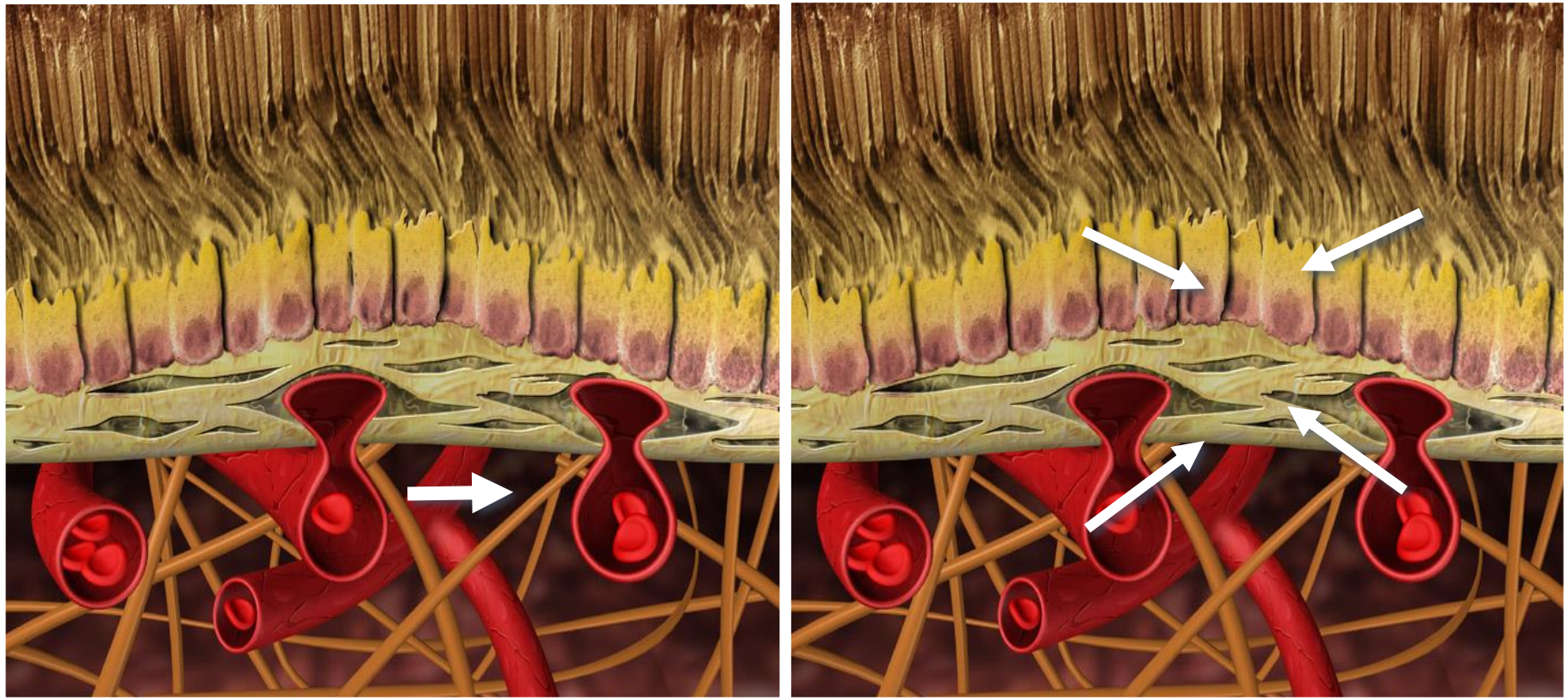
- 10-20% of patients
- Metamorphopsia or distortion by Amsler
- Abnormal choroidal neovascularization
- Bleeding and leakage
- Can have rapidly progressive severe vision loss



Pathogenesis of Wet Form Neovascularization

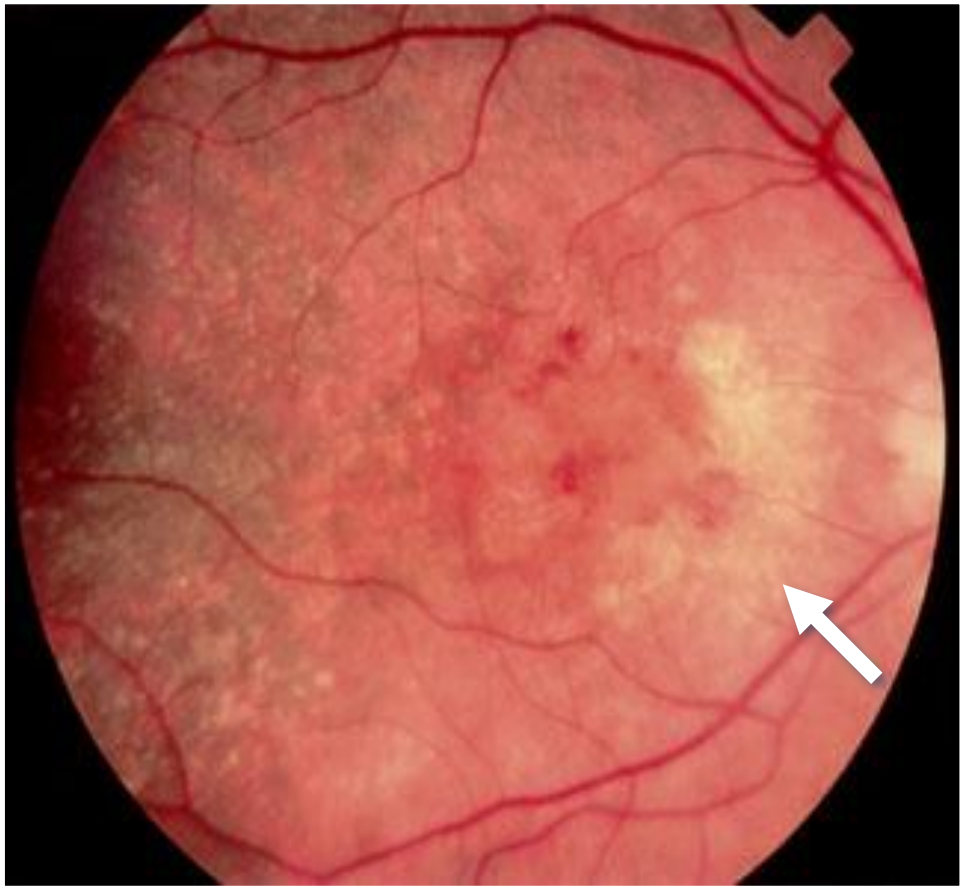
- Lipid accumulation in Bruch's membrane
- Macrophages migrate to lipid
- Inflammatory response to degenerating Bruch's
- Decreased flow from RPE to Choroid
- CNVM formation

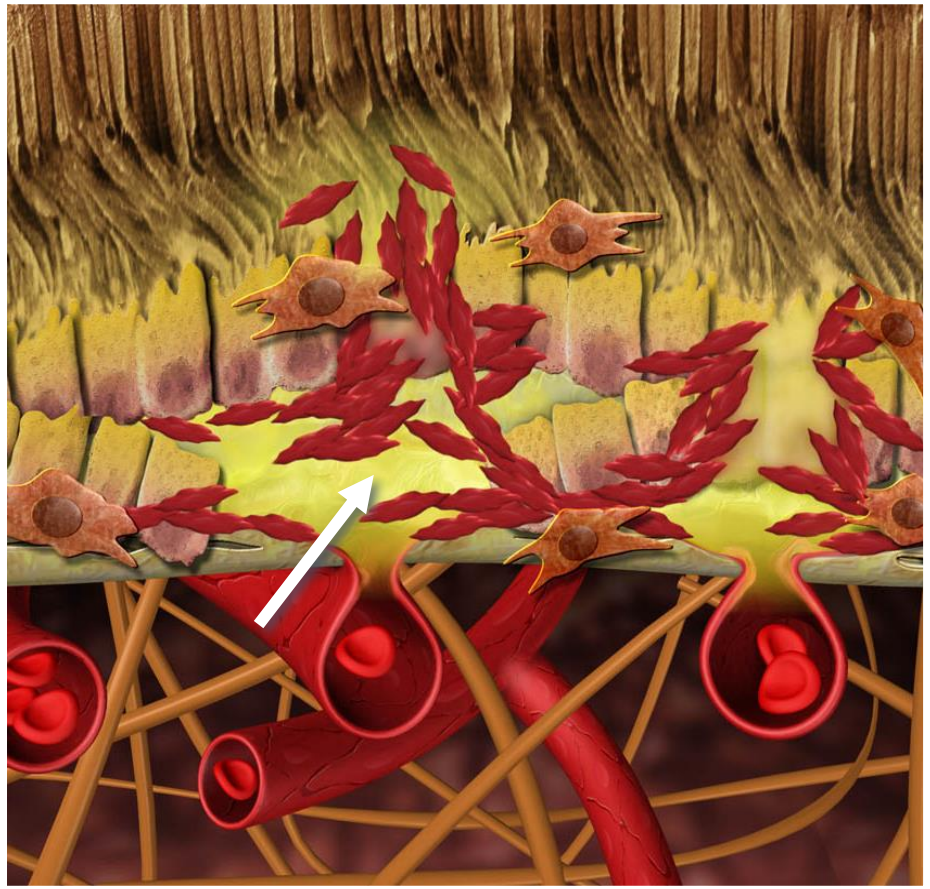
Progression of Neovascular AMD: Formation of New Vessels



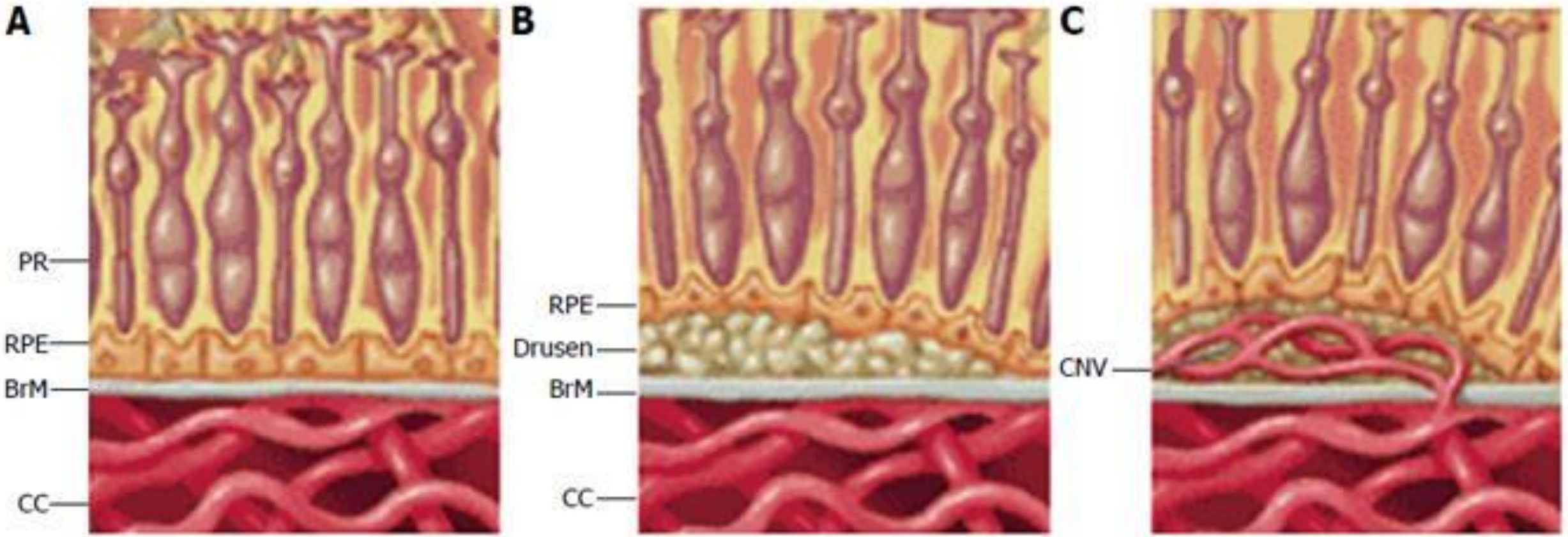
New abnormal blood vessels proliferate and penetrate Bruch's membrane

Progression of Neovascular AMD: Leakage of Fluid and Blood from CNV

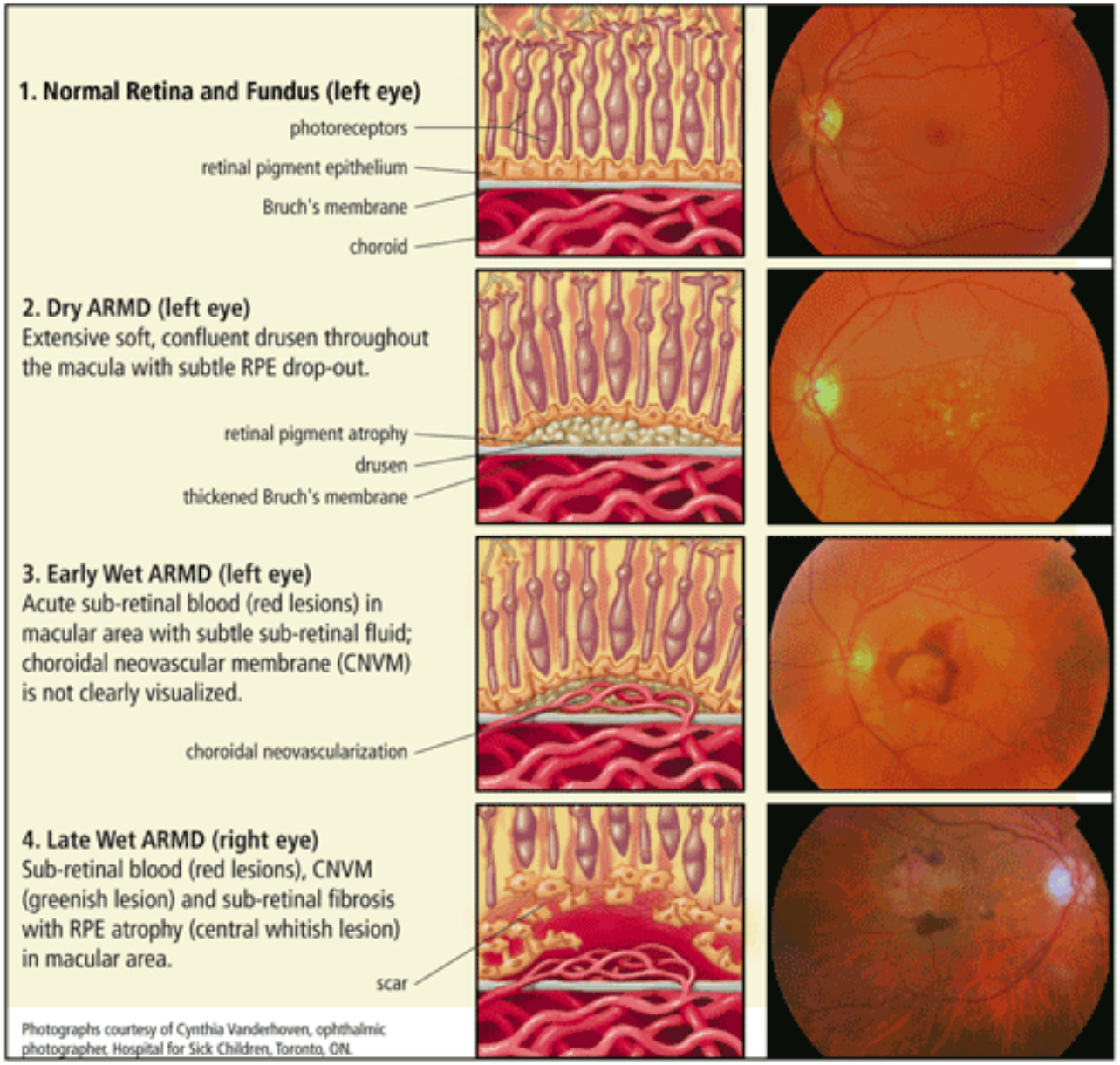




New blood vessels leak blood and fluid



World Journal of cardiology



- World J of Card

Limitations of current therapies

- Vision loss despite successful treatment for exudative disease
  - Scar formation
  - Atrophy of RPE, outer retina
- Persistent leakage despite Anti-VEGF

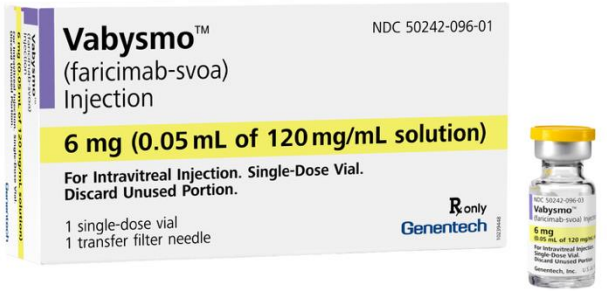
- Inability to stop or reverse (only slow) progression of geographic atrophy (Dry AMD)

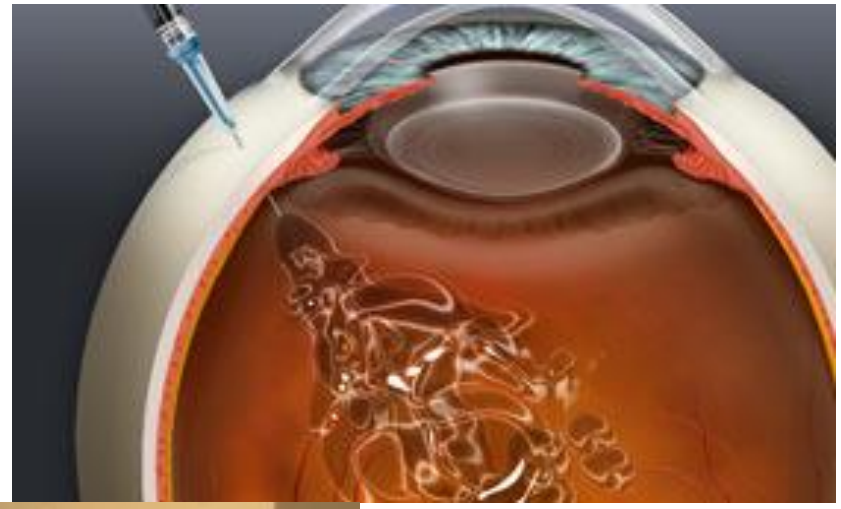
- Inability to replace lost cells

- Sustained drug delivery

Treatment

- **Wet form**
  - **Extrafoveal** (only 13%)- laser; 50% recurrence at one year
  - **Subfoveal** (majority)
    - Focal laser – poor results
    - Photodynamic therapy – FDA approved for particular fluorescein pattern only
    - Anti-VEGF treatment – Lucentis, Avastin, Eylea, Eylea HD, Beovu, Vabysmo
    - Steroids





Anti-VEGF Monotherapy

Defining the Unmet Medical Need

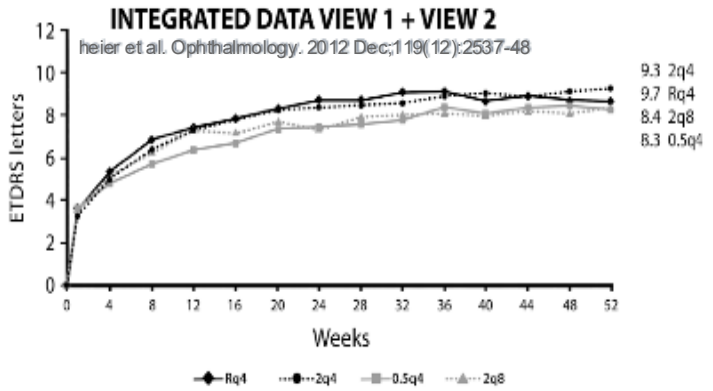
- Majority of Patients Do Not Achieve Significant Visual Gain
- Majority of Patients Do Not Achieve Final Visual Acuity of 20/40 or Better
- 18-22% Lose Vision in a controlled clinical trial setting
  (real world figures even worse)

Anti-VEGF Agents

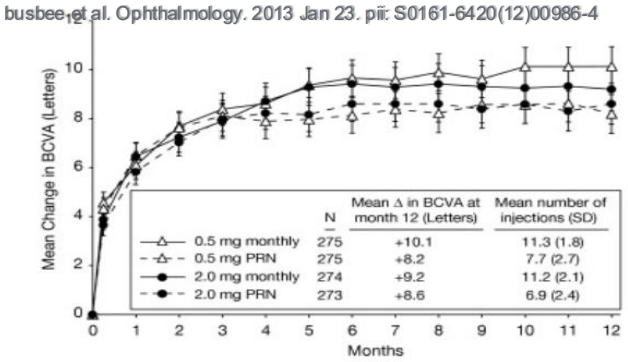
Lucentis®, Avastin®, Eylea ®

- Similar efficacy
- Ceiling of anti-VEGF efficacy
- Increasing dosage/regimen does not enhance visual outcome

VIEW Trials



HARBOR Trial



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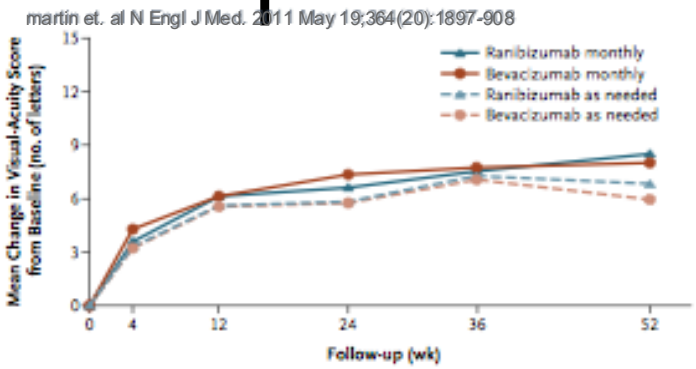
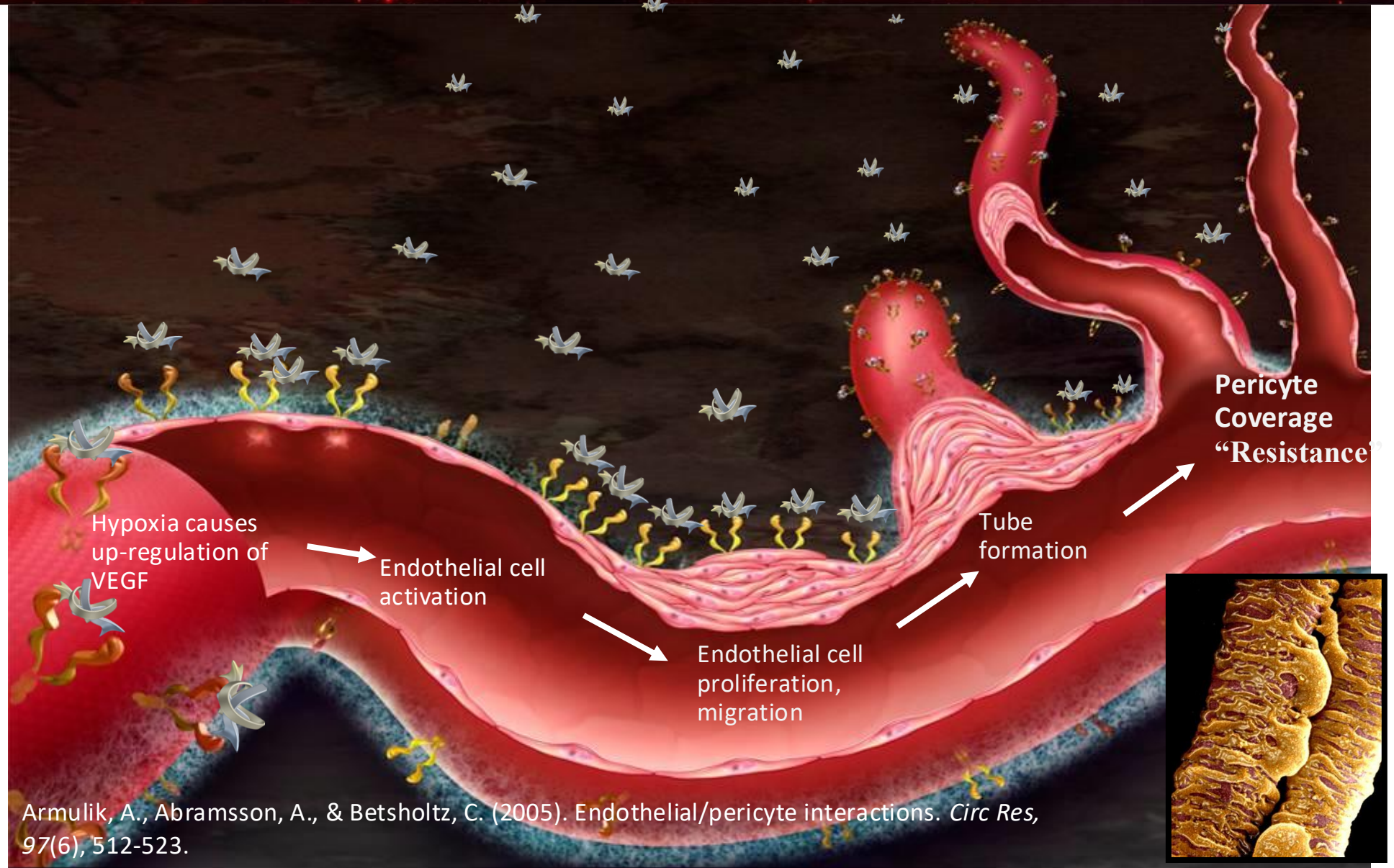
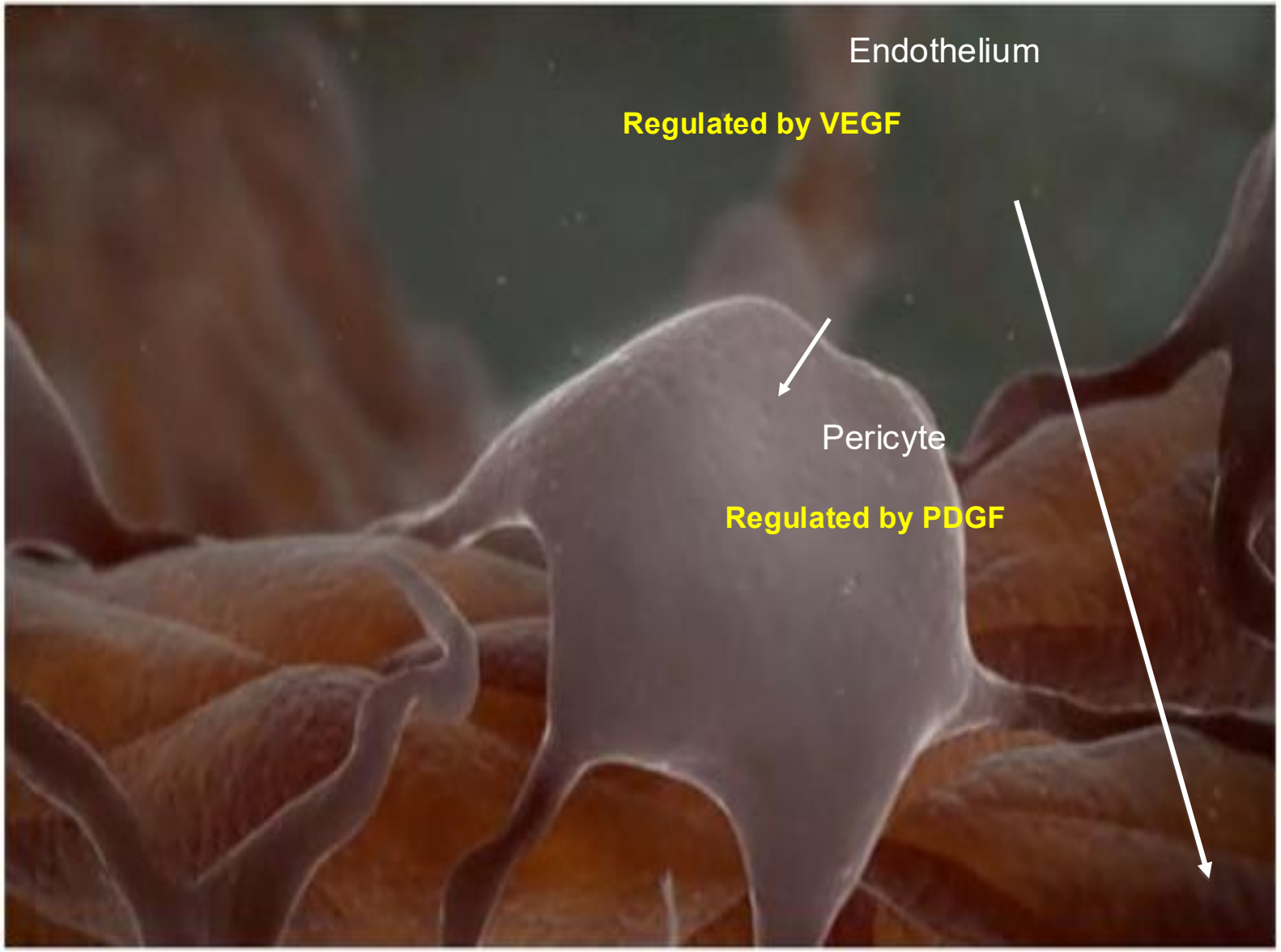


Angiogenesis and Anti-VEGF Resistance



Armulik, A., Abramsson, A., & Betsholtz, C. (2005). Endothelial/pericyte interactions. *Circ Res, 97*(6), 512-523.

Pericytes Protect The Vascular Endothelium



Pericytes

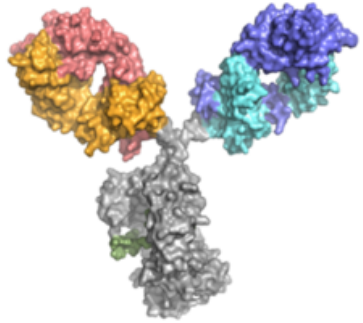
Secrete **VEGF + Other Endothelial Survival Factors**

Pericyte-Endothelial Interaction

Protect New Vessels

Vabysmo (Faricimab)

- Blocks angiopoietin-2 (Ang-2) and vascular endothelial growth factor-A (VEGF-A)
- Phase 3 Studies
  - DME--> YOSEMITE & RHINE
  - AMD--> TENAYA & LUCERNE
- ~1/2 of people receiving Faricimab could be treated q4mo in the first year
- ~3/4 of people receiving Faricimab could be treated q3mo or longer in the first year
- Rapid and consistent improvements in anatomical outcomes including central subfield thickness



anti–Ang-2

- Enhanced vessel stabilisation through Ang-2 inhibition

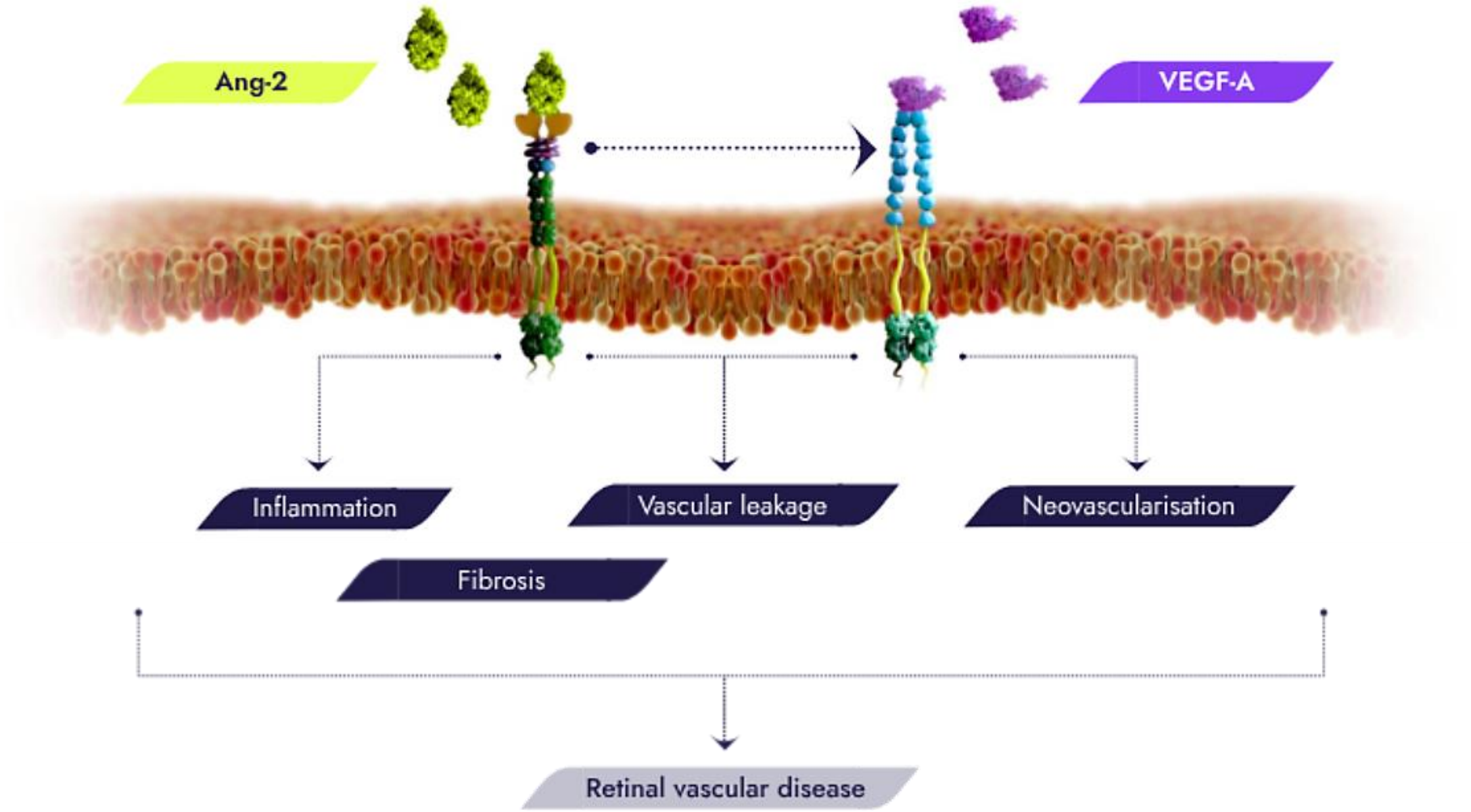
anti–VEGF-A

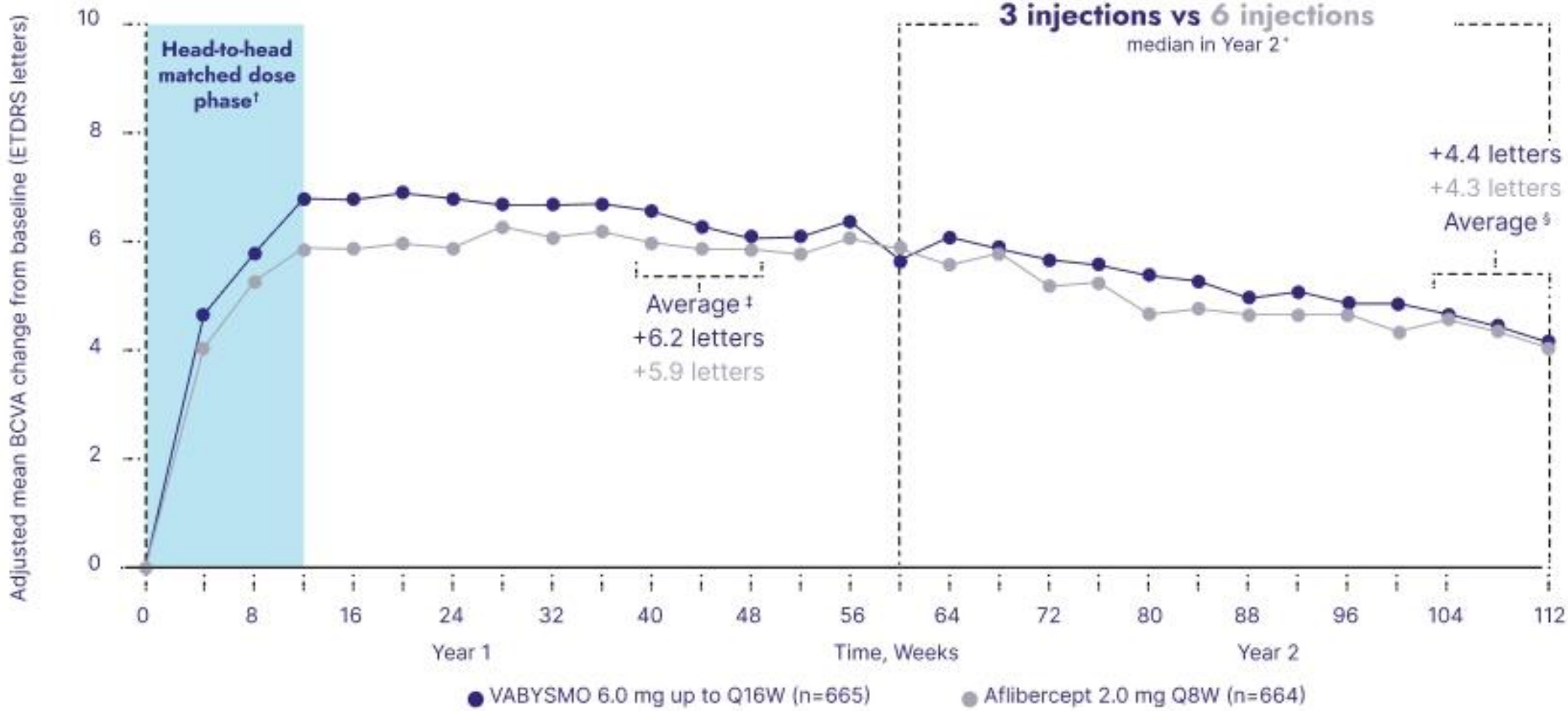
- Proven efficacy through VEGF-A inhibition

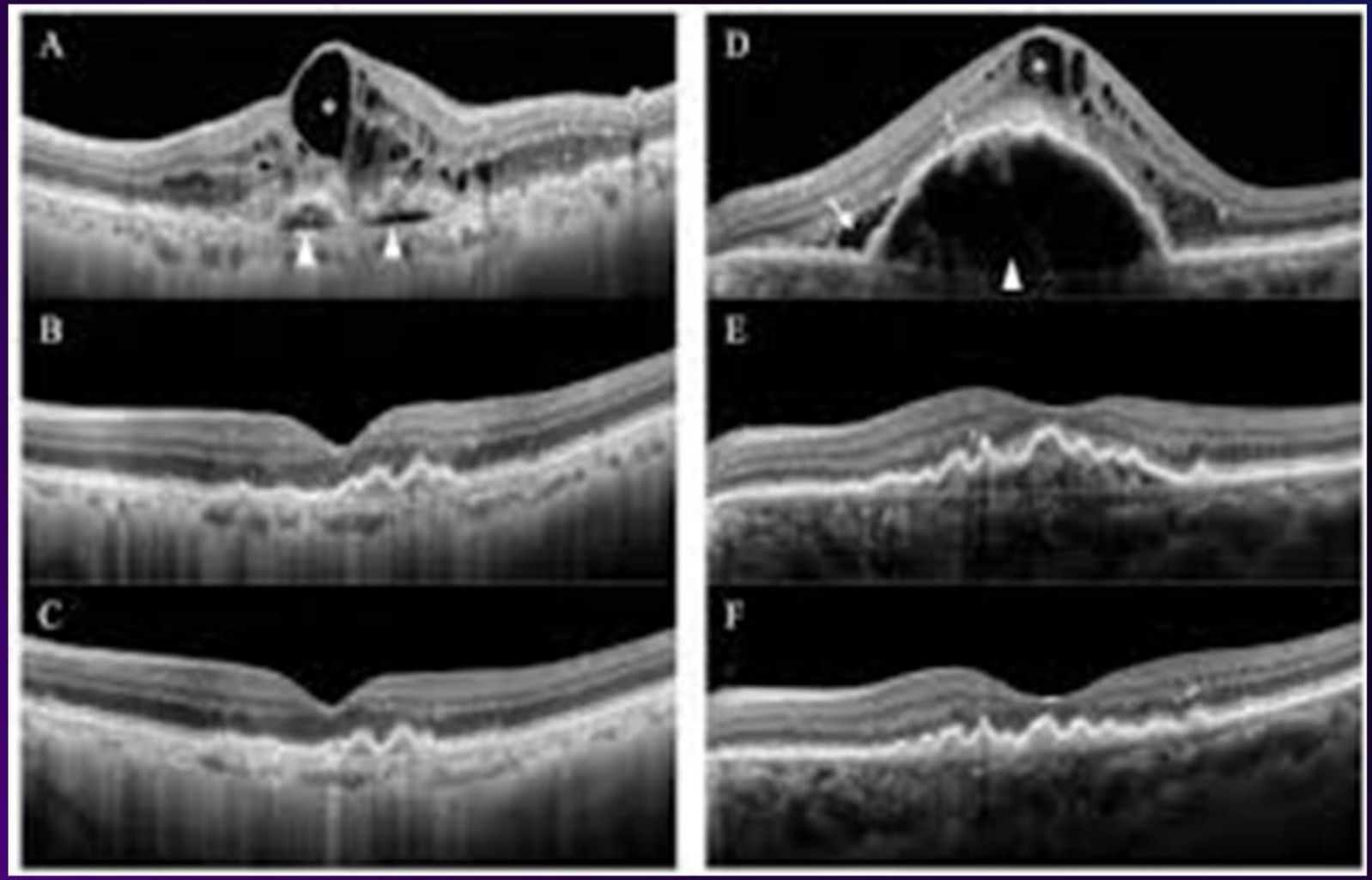
Vabysmo (faricimab)

- Blocks VEGF-A: By inhibiting VEGF-A, reduces vascular permeability (edema) and suppresses the growth of new, abnormal blood vessels (neovascularization).

- Blocks Ang-2: Ang-2 normally promotes vascular instability and works with VEGF to cause leakage; blocking it further stabilizes the blood vessels and reduces inflammation.


Ang-2
VEGF-A
Inflammation
Vascular leakage
Neovascularisation
Fibrosis
Retinal vascular disease


3 injections vs 6 injections
median in Year 2*
Head-to-head matched dose phase†
Average‡
+6.2 letters
+5.9 letters
+4.4 letters
+4.3 letters
Average§
Adjusted mean BCVA change from baseline (ETDRS letters)
10
8
6
4
2
0
0
8
16
24
32
40
48
56
64
72
80
88
96
104
112
Year 1
Time, Weeks
Year 2
VABYSMO 6.0 mg up to Q16W (n=665)
Aflibercept 2.0 mg Q8W (n=664)


A
B
C
D
E
F

RGX-314

- One-time gene therapy treatment (subretinal)
- Adeno-associated virus serotype 8 (AAV8) as its gene therapy vector
- Gene encoding a monoclonal antibody fragment to neutralizing VEGF (similar to ranibizumab)
- AAVIATE (Phase 2)- multi-center, randomized-controlled, dose-escalation trial that will evaluate the efficacy, safety and tolerability of suprachoroidal delivery of RGX-314 using the SCS Microinjector
  - Evaluating 5 distinct doses (dose dependent protein levels)
- Meaningful reduction in VEGF and treatment burden

RGX–314 PRODUCT CANDIDATE

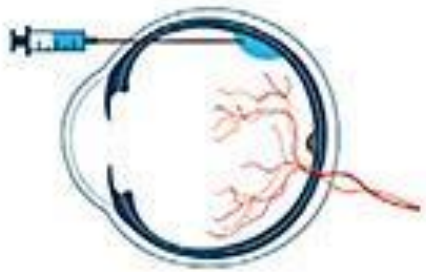
Vector: AAV8 | **Gene:** anti-VEGF fab

Mechanism of action

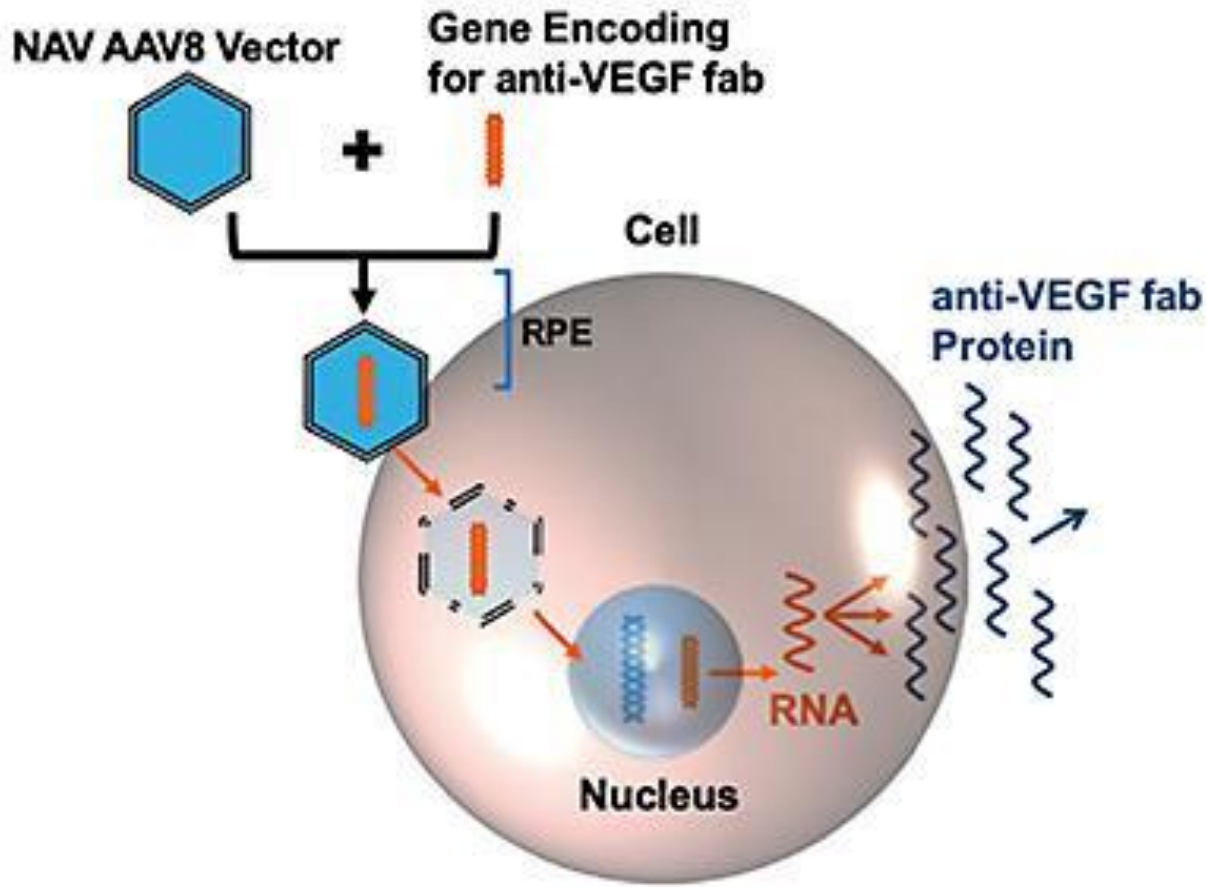
Designed to reduce leaky blood vessel formation by giving ocular cells the ability to produce an anti-VEGF fab

Route of administration

Subretinal (clinical)

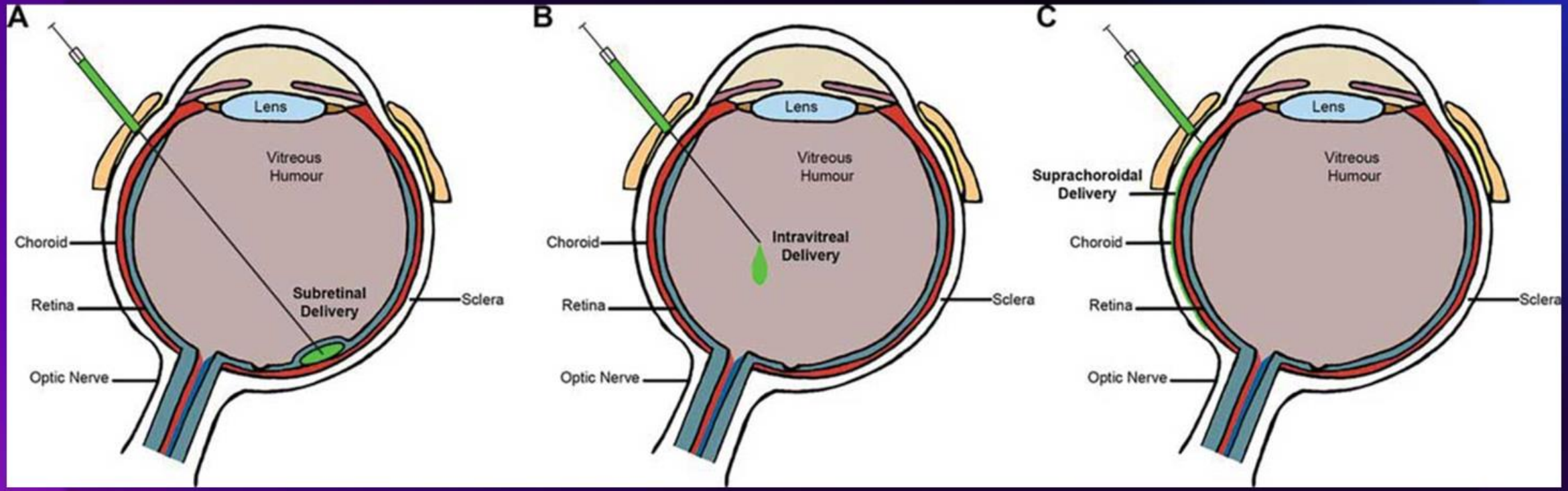


Suprachoroidal (preclinical)



RGX-314 is Designed to Deliver a Gene Encoding for an anti-VEGF fab Protein

GENE THERAPY



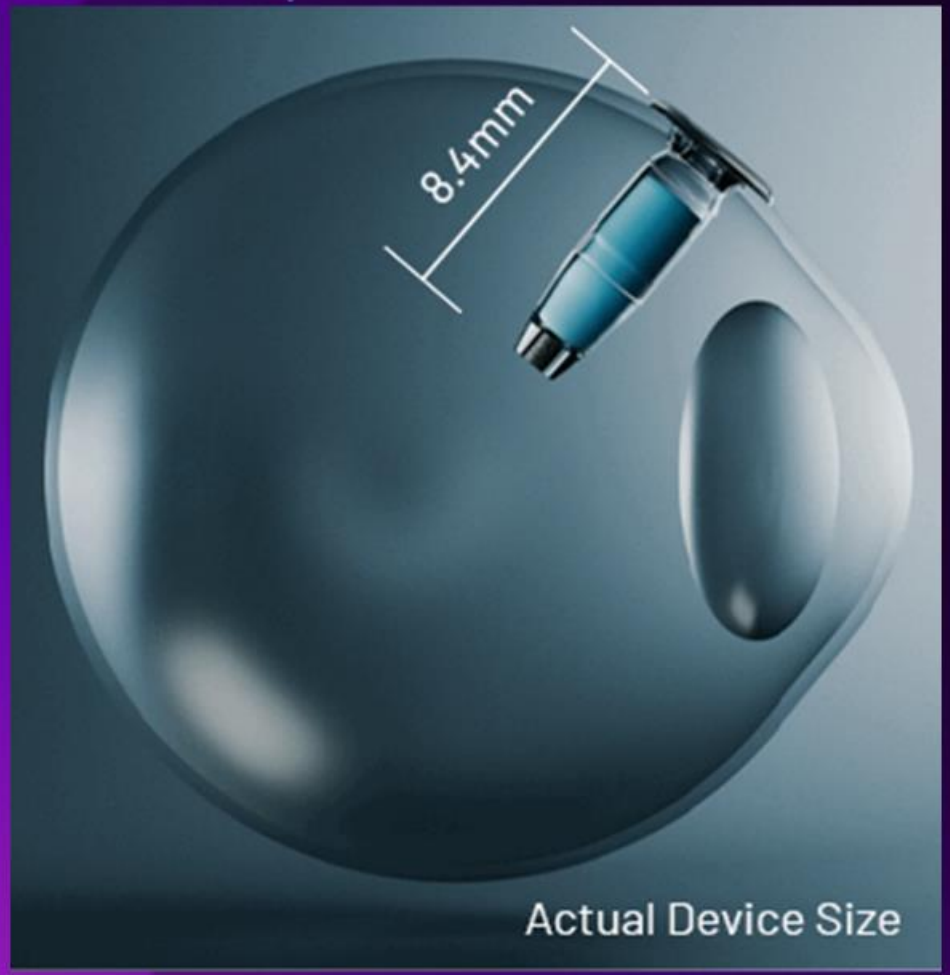
ADVM-022

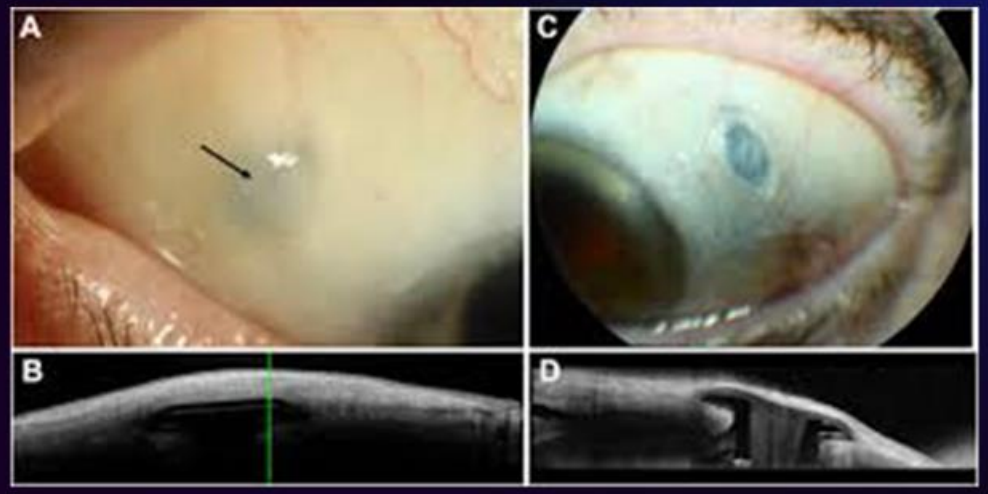
- Single in office intravitreal gene therapy
- AAV.7m8 capsid, carrying expression encoding for DNA of the Anti-VEGF aflibercept
- *OPTIC Study (Phase 1)*
  - 2 cohorts (dosing)
  - ADVM-022 was safe and well tolerated and showed consistent and sustained anatomic improvements in OCT and stable best-corrected visual acuity
  - Increased rates of intraocular inflammation
  - No vasculitis, retinitis, choroiditis, vascular occlusion, or endophthalmitis

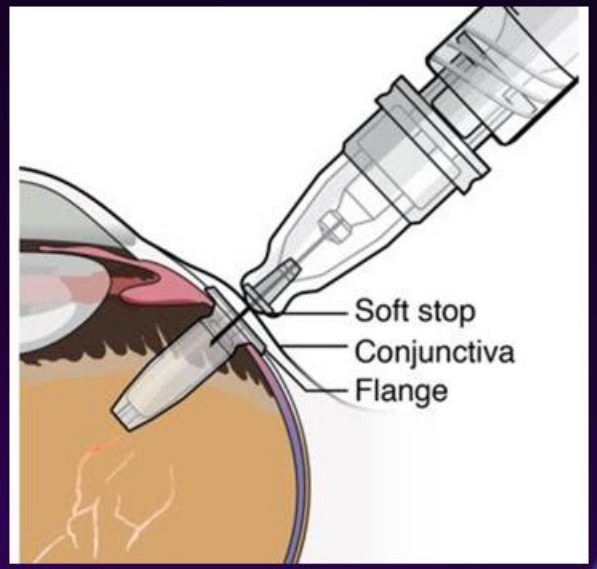
Susvimo (Port Delivery System)

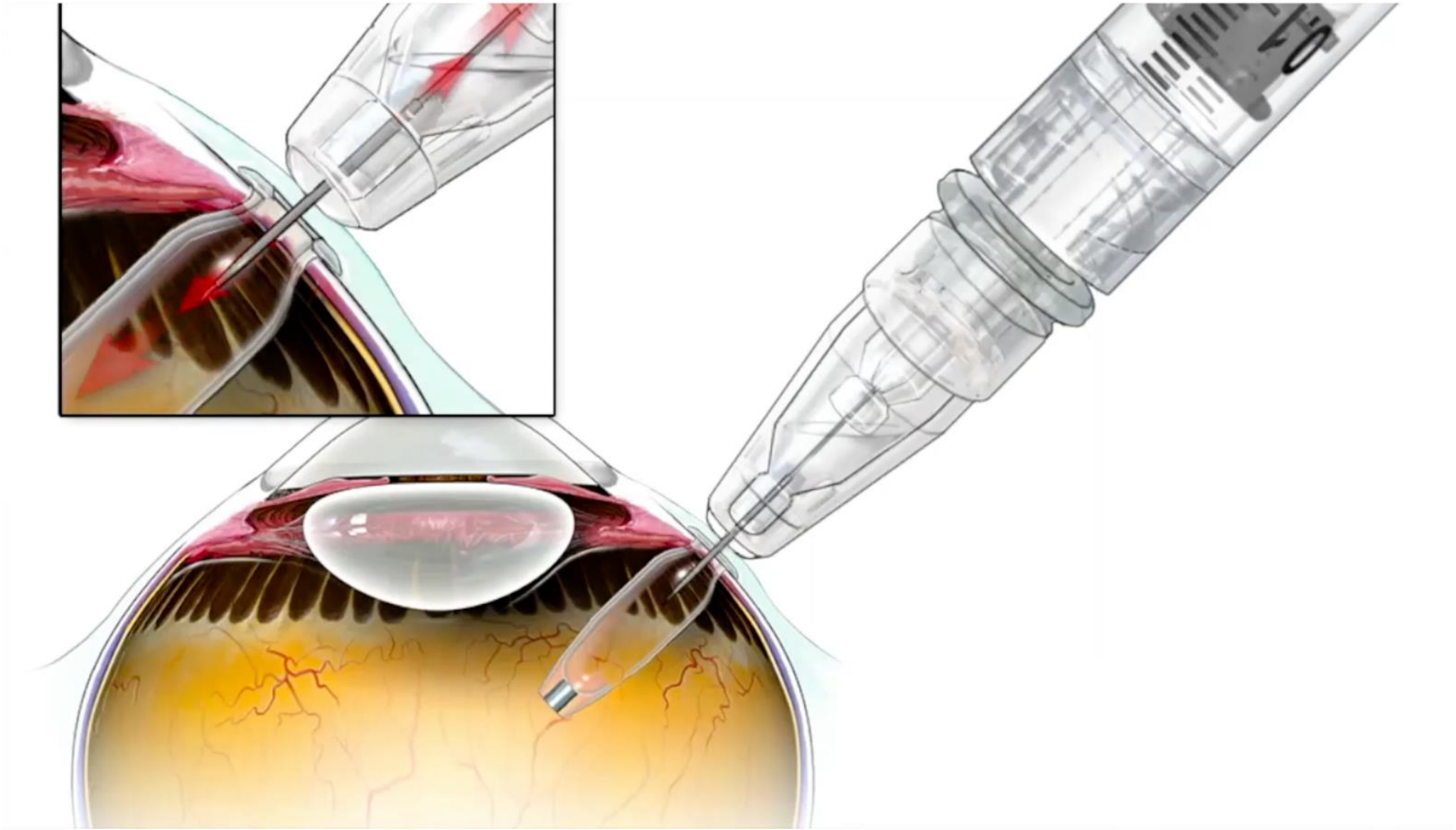
- Recent FDA approval (Surgically implanted device)
- Ranibizumab 100mg/mL- continuously delivers medicine with as few as 2 refills a year
  - Passive diffusion of Anti-VEGF
  - Self sealing septum (refillable)
- Archway phase 3 clinical trial
  - 5 cohorts (dosing)
  - PDS Q24W showed to deliver vision and anatomic outcomes comparable to Q4W intravitreal ranibizumab injections
- The SUSVIMO implant has been associated with a higher rate of endophthalmitis (2%) than monthly intravitreal injections of ranibizumab
  - Other risks: VH, RD, Conjunctival retraction/erosion
  - structures.

FUTURE TREATMENTS



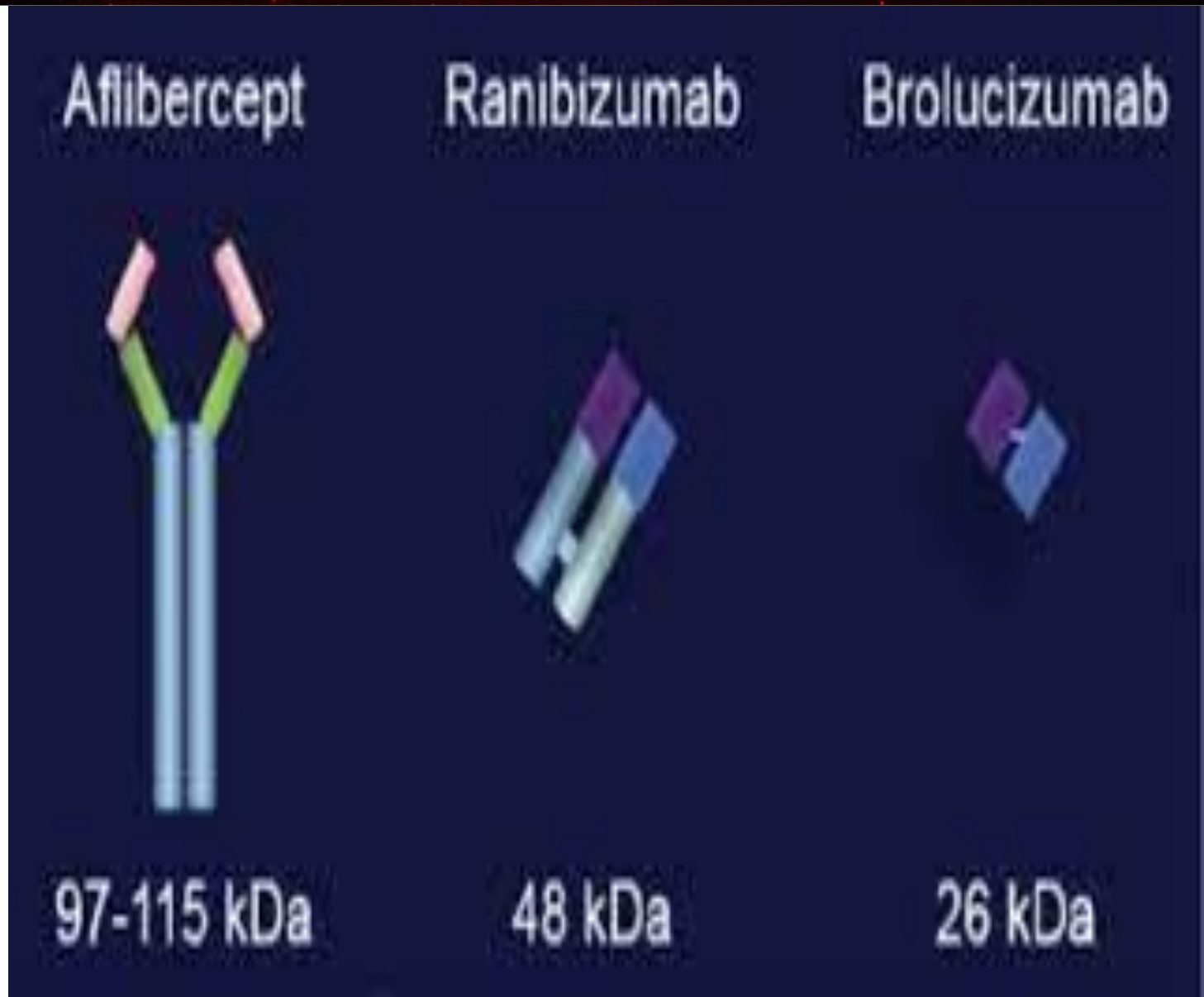






Abicipar Pegol

- DARPin molecule directed to bind all VEGF-A isoforms
  - Higher affinity and a longer intraocular half-life than ranibizumab
- Proved both durability and non-inferiority to monthly ranibizumab
- High rates of intraocular inflammation 15.4% including a 1.7% rate of severe vision loss
- Recently NOT approved by FDA

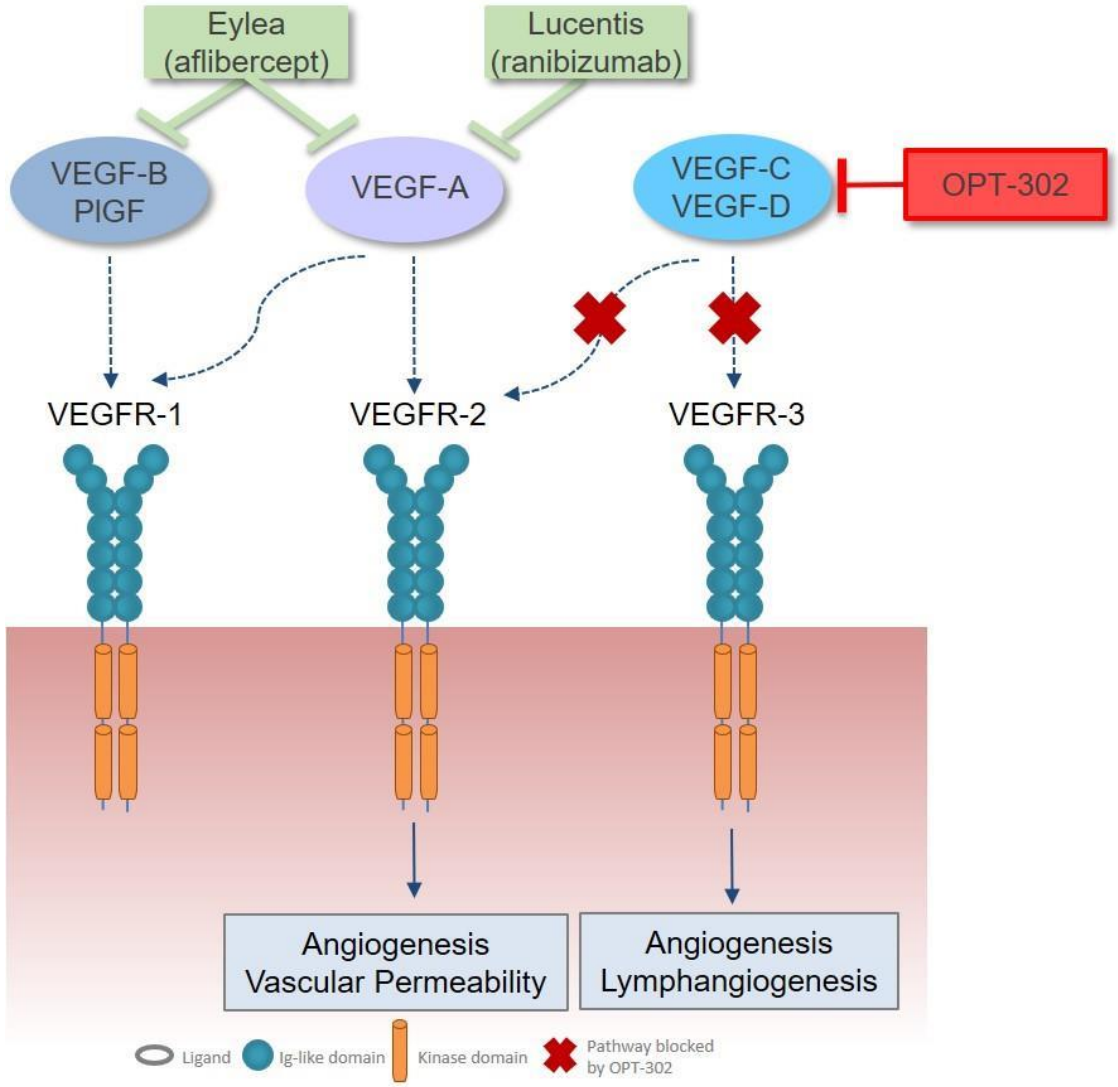


Conbercept

- Anti-VEGF- recombinant fusion protein (only available in China)
- Phase 3 of the Phoenix Study 52 week study
  - Conbercept q1mo x 3 doses -----> q3mo
    - 9.2 letter improvement, 79.2um CRT decreased
  - Delayed group- sham inj x 3 mo followed by 0.5 mg/eye q1mo x 3 mo followed by 0.5 mg/eye every 3 months
    - 8.8 letter improvement
- Preclinical evidence that Conbercept may last longer than aflibercept with similar efficacy

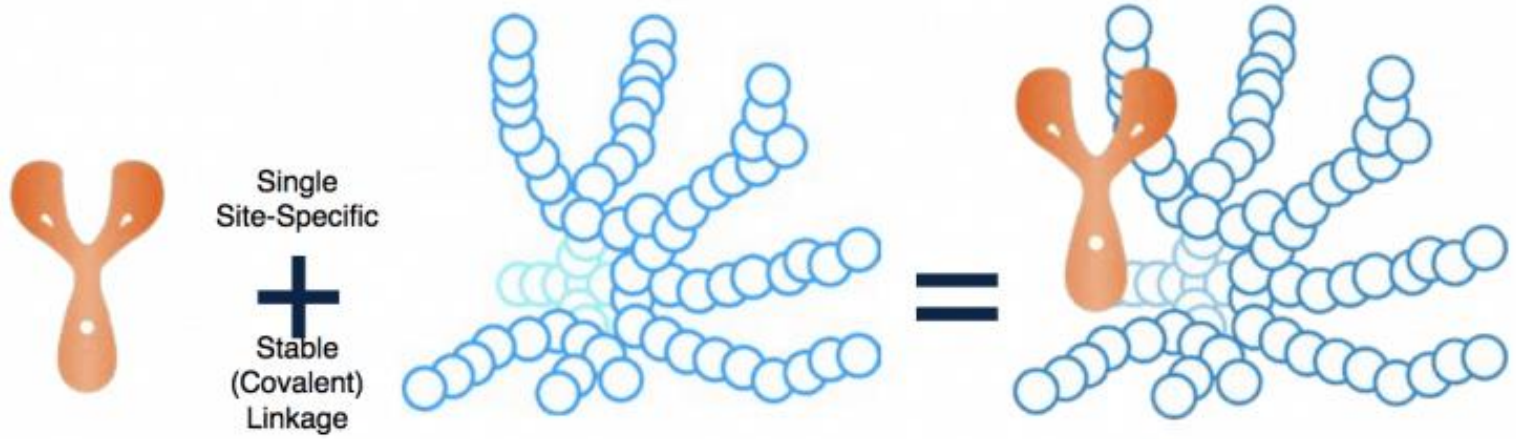
OPT-302

- VEGF C-D trap to be used in combination with anti-VEGF
- OPT-302 combination therapy achieves a more complete suppression of the VEGF/VEGFR pathway



KSI-301

- Intravitreal injection designed to provide sustained inhibition of VEGF for up to 6 months
- Phase 2b/3 DAZZLE study started June 2021
  - KSI-301 5mg q3,4,5mo after 3 monthly doses vs. Eylea q2mo after 3 monthly doses



ANTIBODY

IgG1 Antibody

Inert Immune Effector function

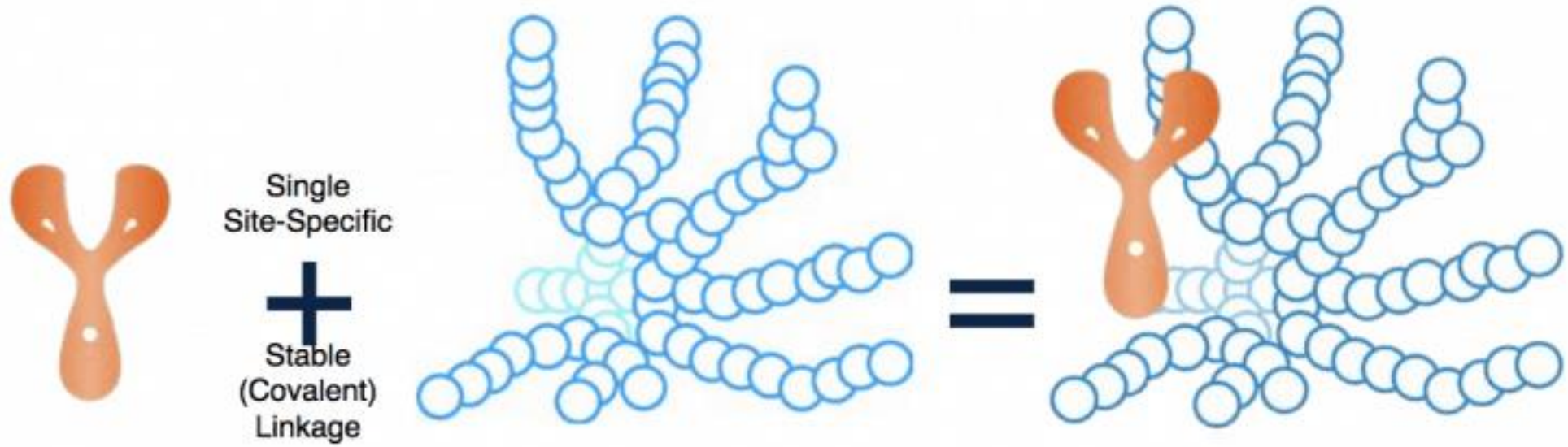
BIOPOLYMER

Branched
High Molecular Weight
Optically Clear
Phosphorylcholine Polymer

CONJUGATE

Antibody and biopolymer covalently bound via single site-specific linkage

KSI-301 is an anti-VEGF ABC designed to block all VEGF-A isoforms



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Biosimiliars

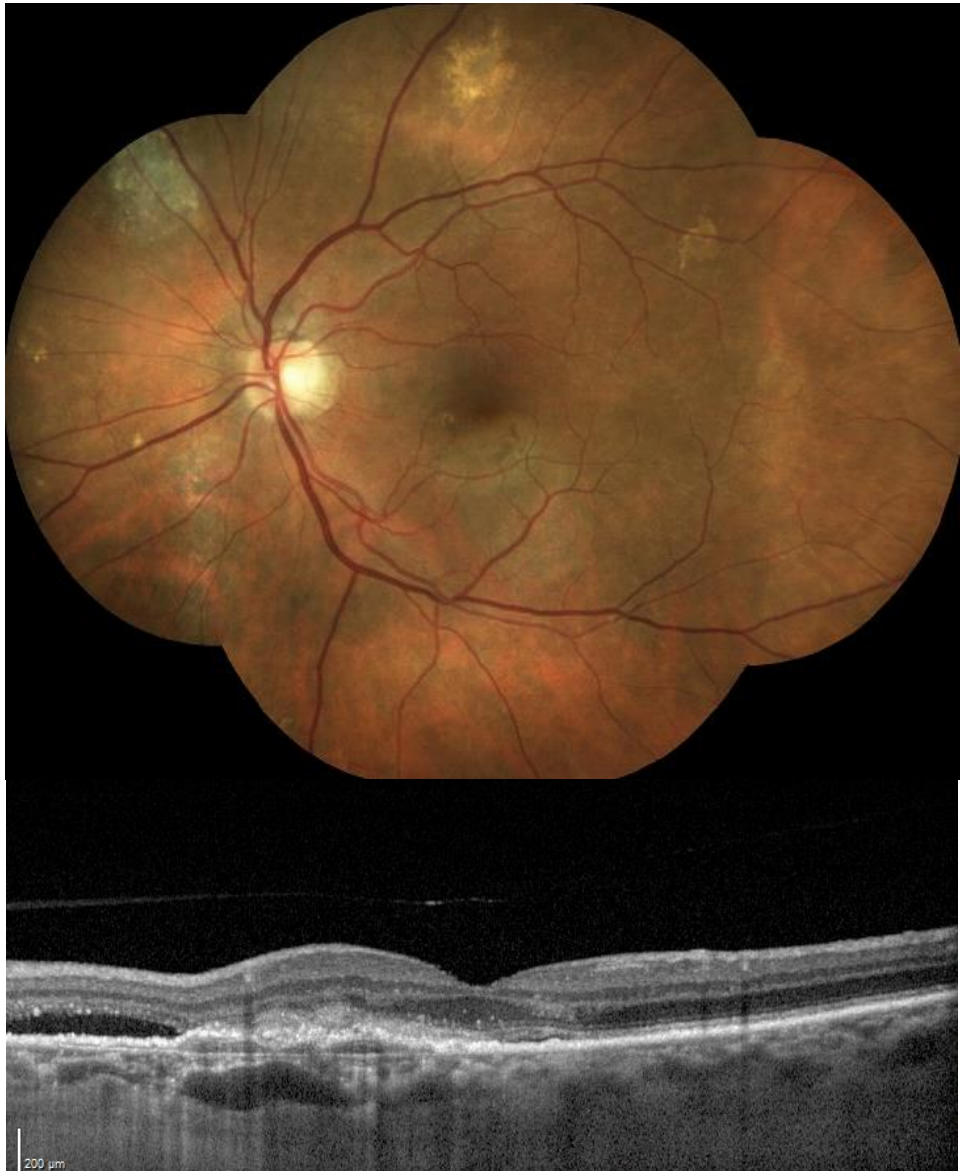
- Biosimilars are molecules with similarity to existing biologic medications
- These drugs are similar enough to proven therapies (safety and efficacy)—and they can do so more quickly and at a lower cost (barely)
- Biosimilars are not generics
- Must show that biosimilar acts the same [as the reference medication] out to q8wks (primary outcomes out to one or two years)
    - Underlying assumption for each biosimilar is that safety and efficacy were already proven for the reference product
- Reverse-engineering a biologic to a biosimilar is still costly
- Cimlerli, Byooviz, Pavblu (ranibizumab)

Polypoidal Choroidal Vasculopathy

- Multiple, recurrent serosanguinous RPE detachments
- Network of polyps with associated feeder vessel
- More common in African American or Asian ancestry
- Vitreous hemorrhage occurs more frequently than non-PCV AMD
- Pachychoroid often present on OCT
- Prognosis better than non-PCV AMD (*except in cases of severe subretinal hemorrhage*)
- OCT-A, SD-OCT and ICG Ang can be used to identify the polyps

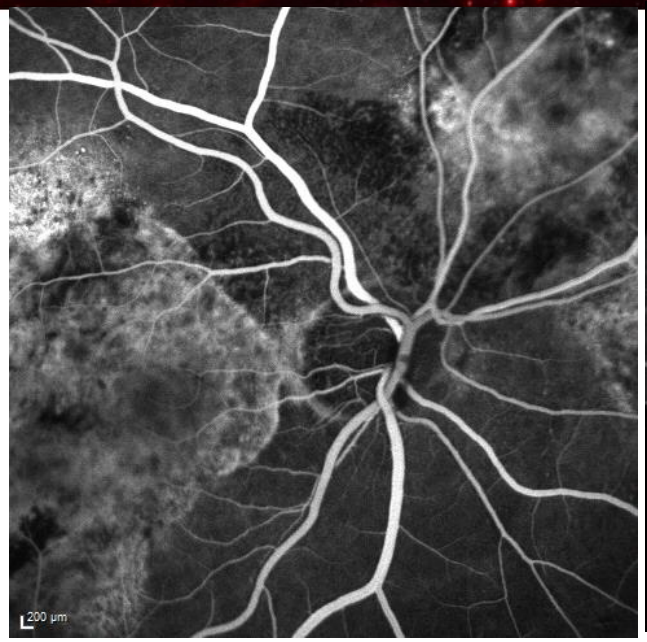
Degenerations

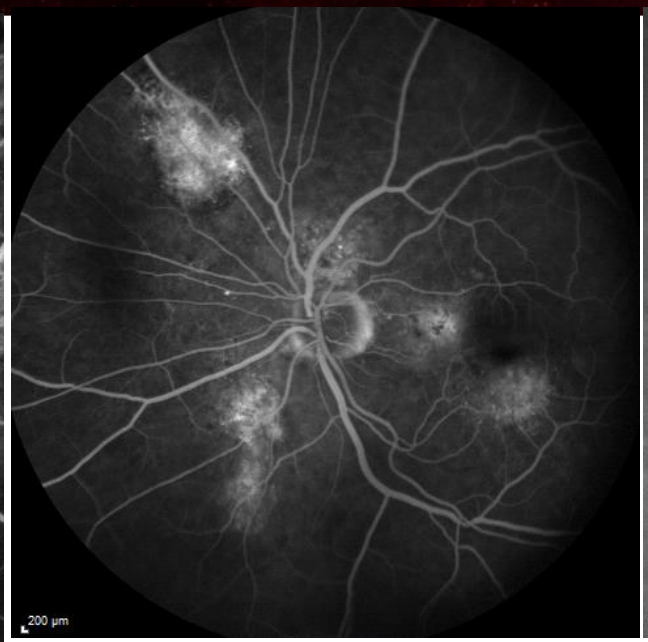
Polypoidal Choroidal Vasculopathy

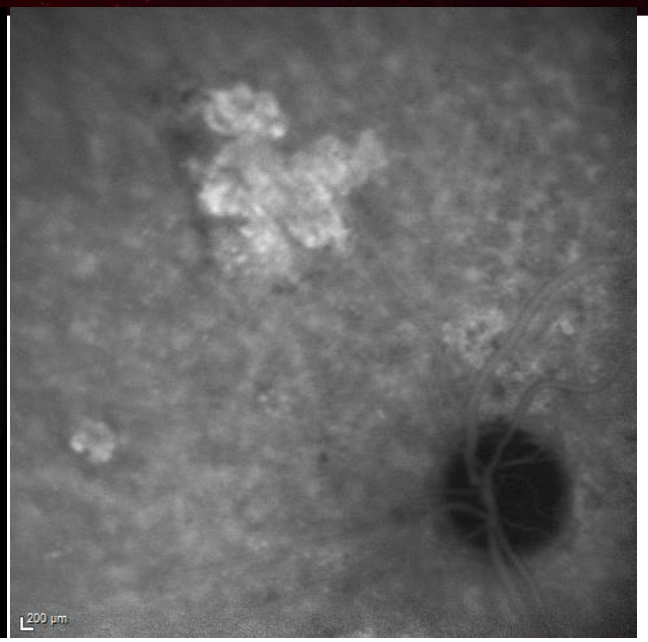


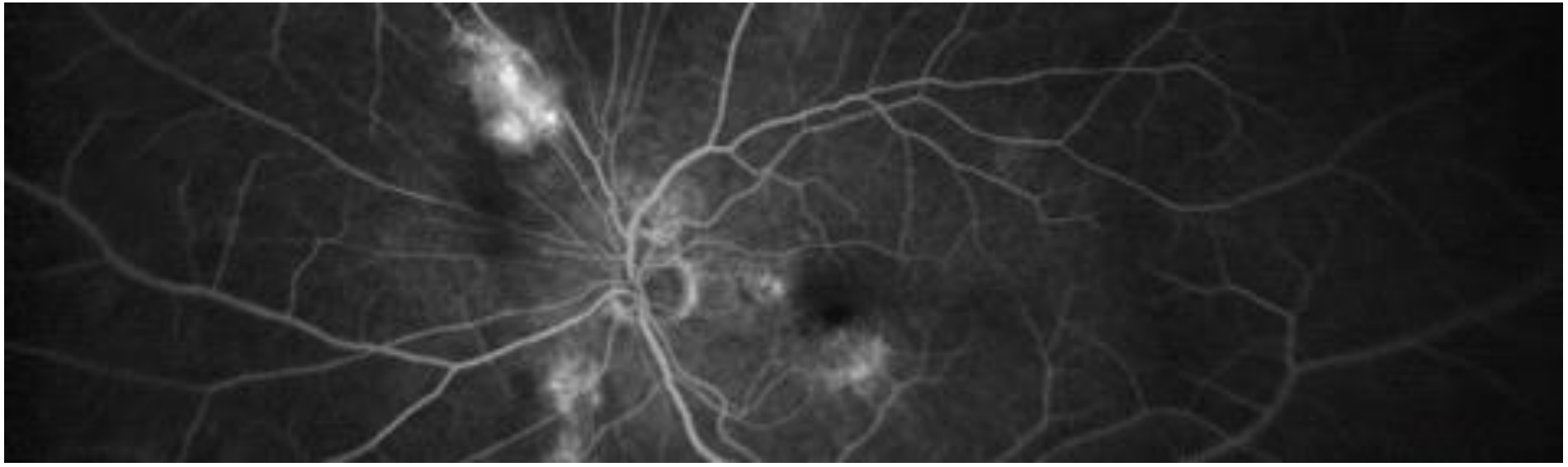
Degenerations

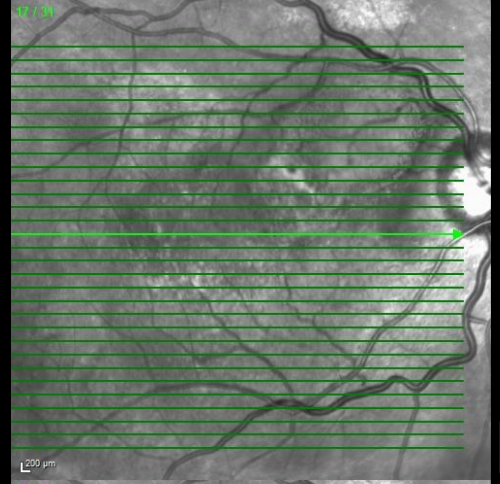
Polypoidal Choroidal Vasculopathy

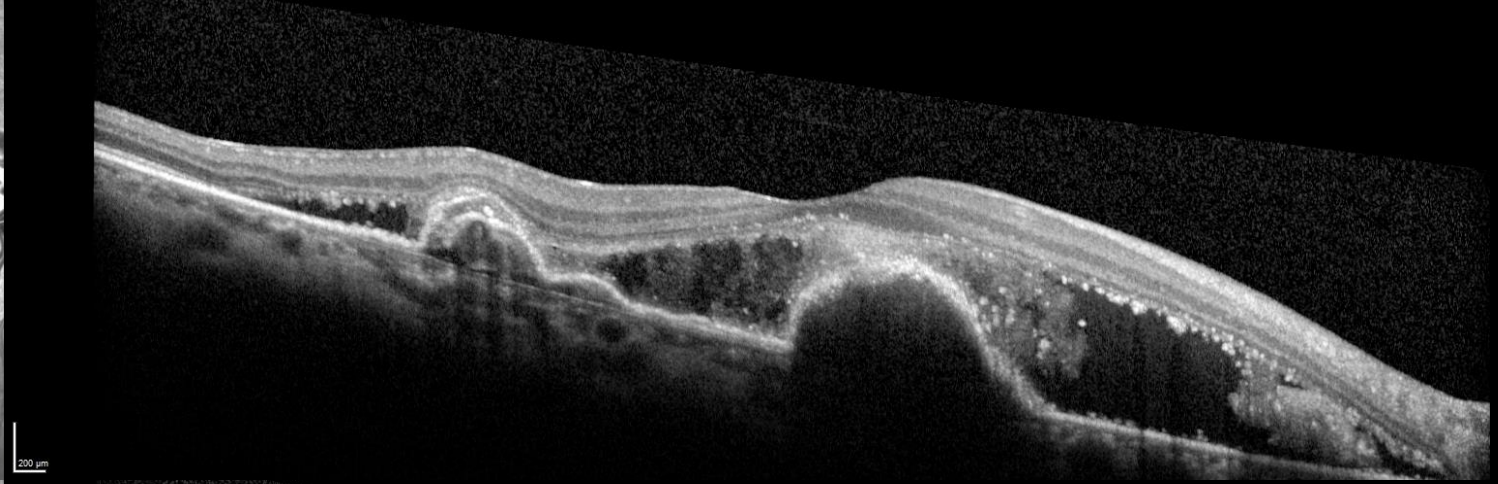









17 / 31
200 µm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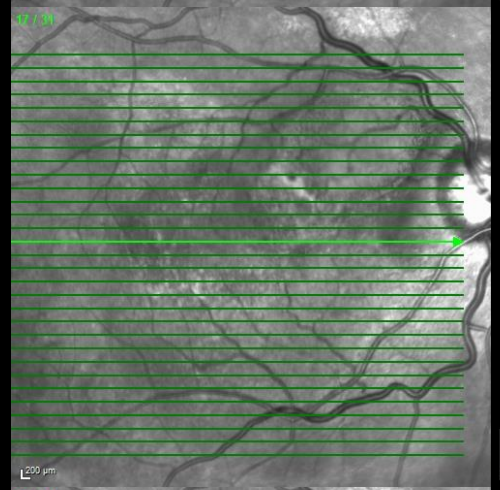
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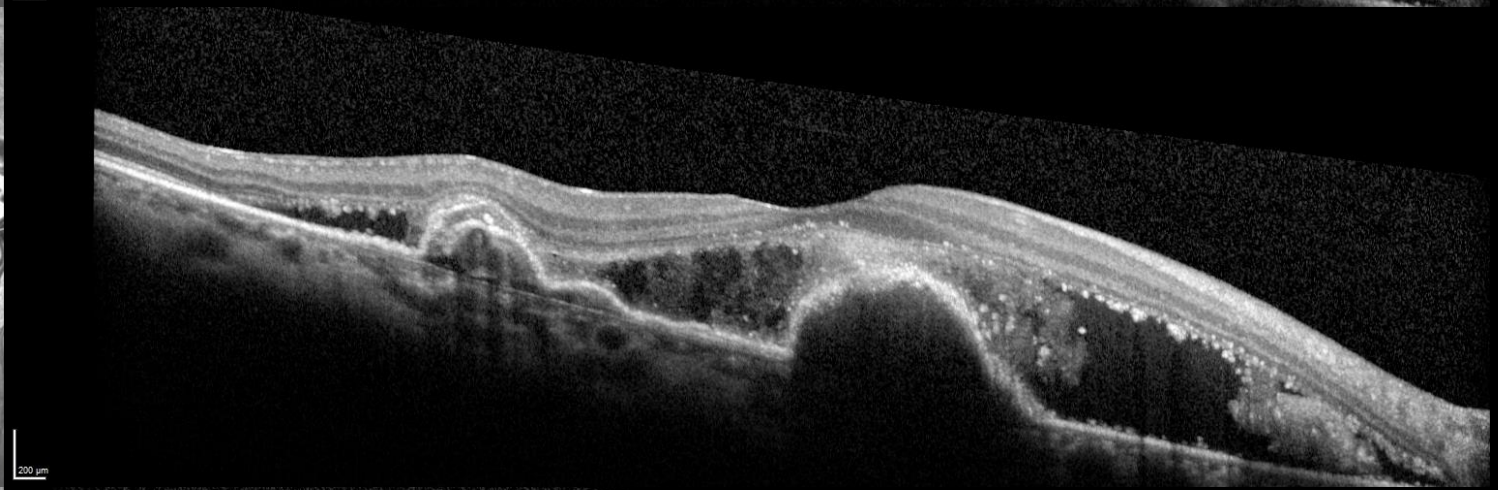
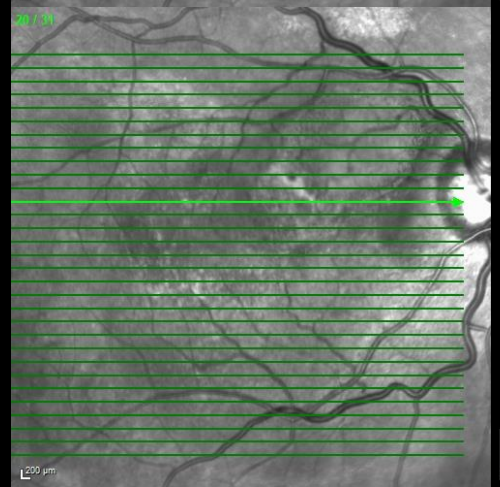
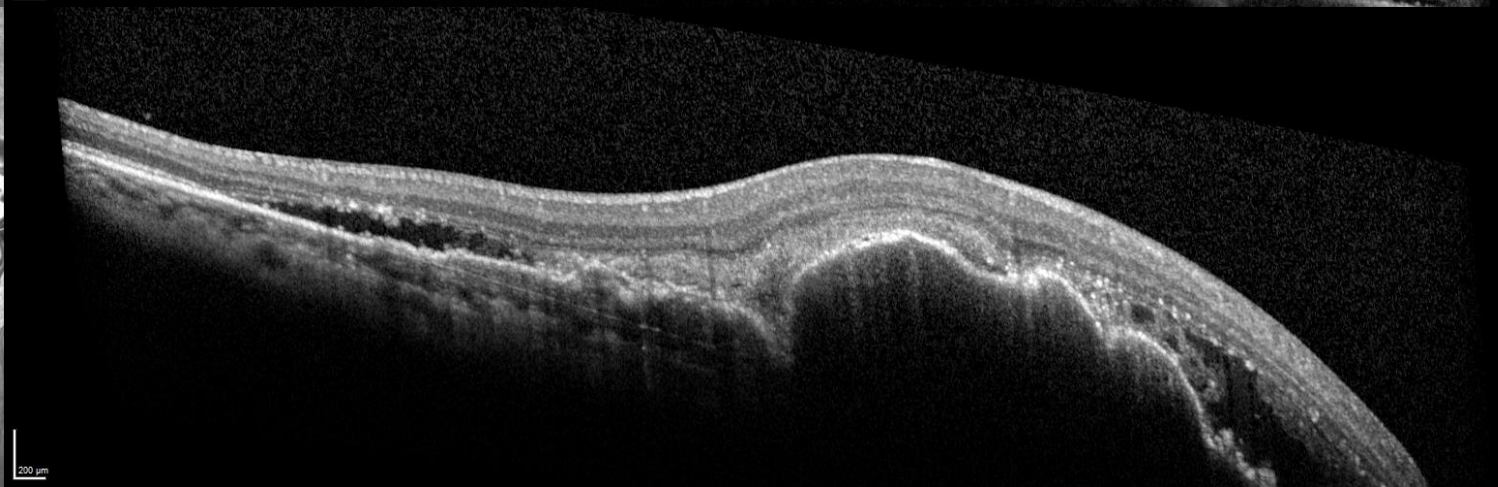

200 µm


20 / 31
200 µm


200 µm

Treatment PCV

Anti-VEGF

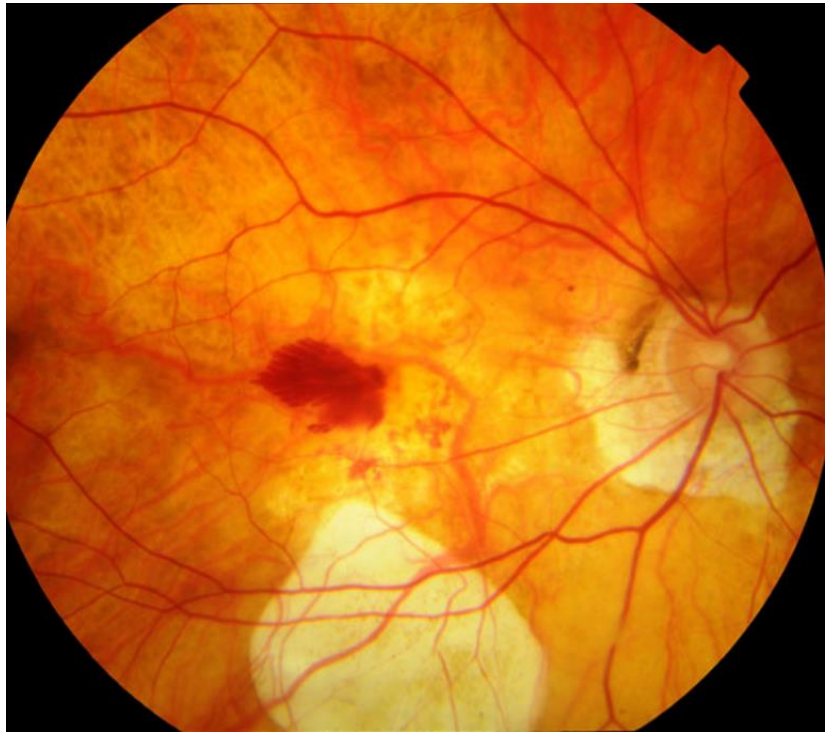
- PCV less responsive than non-PCV AMD

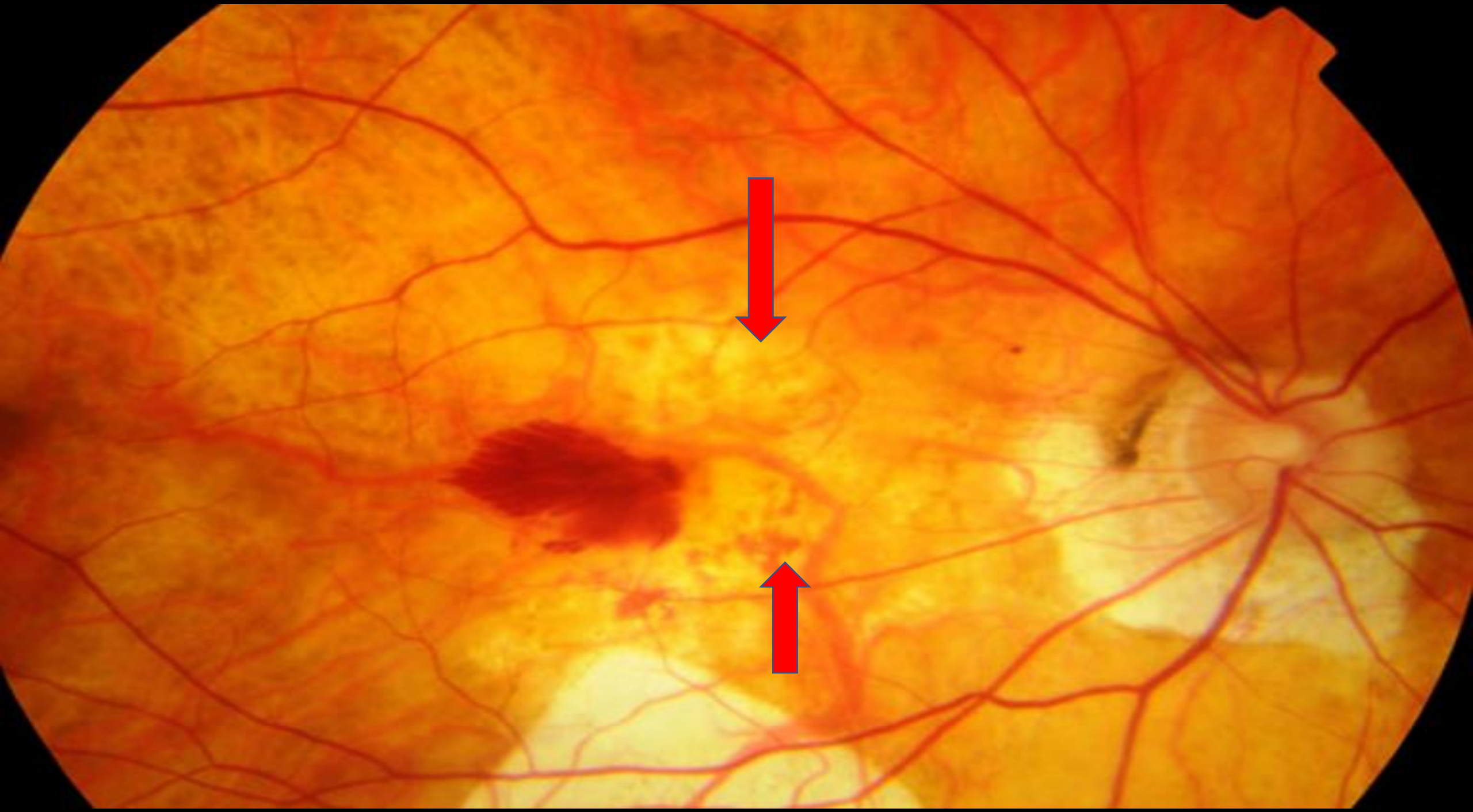
Photodynamic therapy

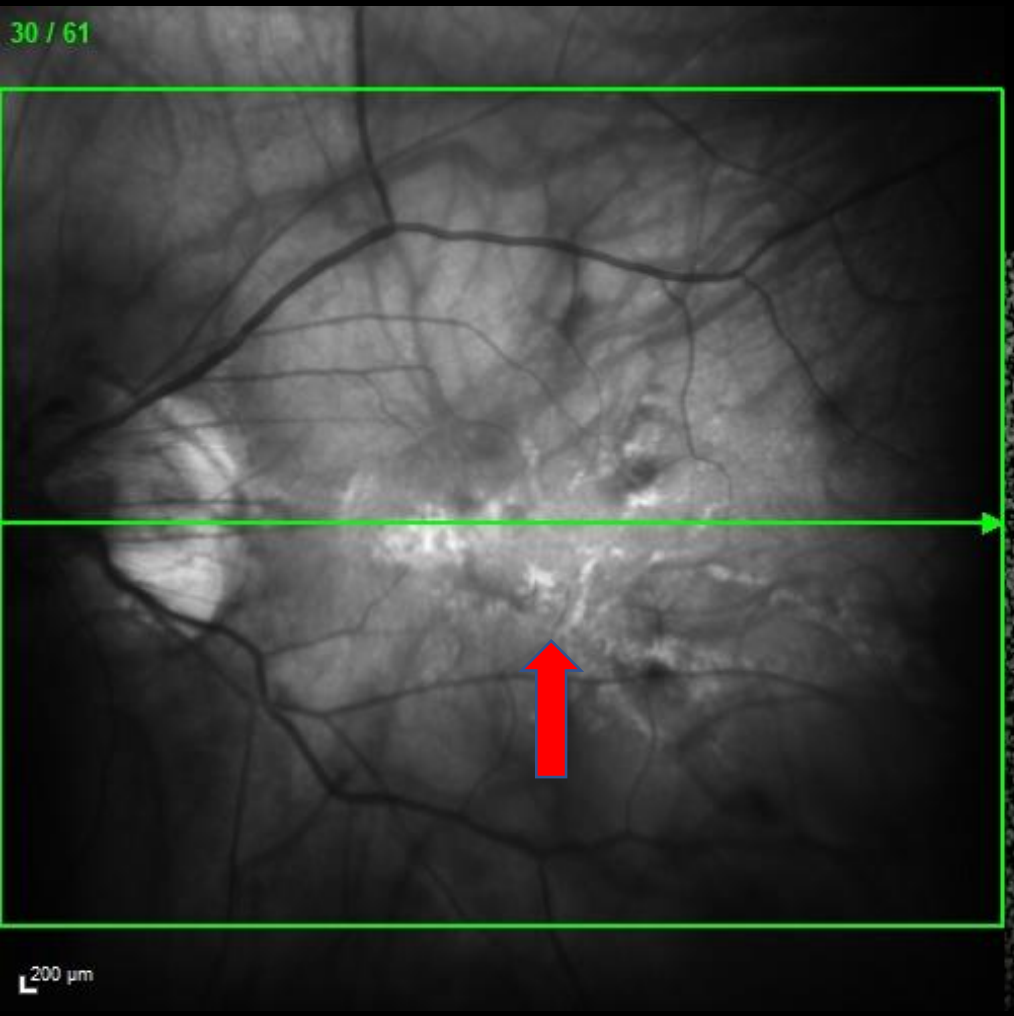
- EVEREST trial- PDT +/-Ranibizumab is better than ranibizumab alone

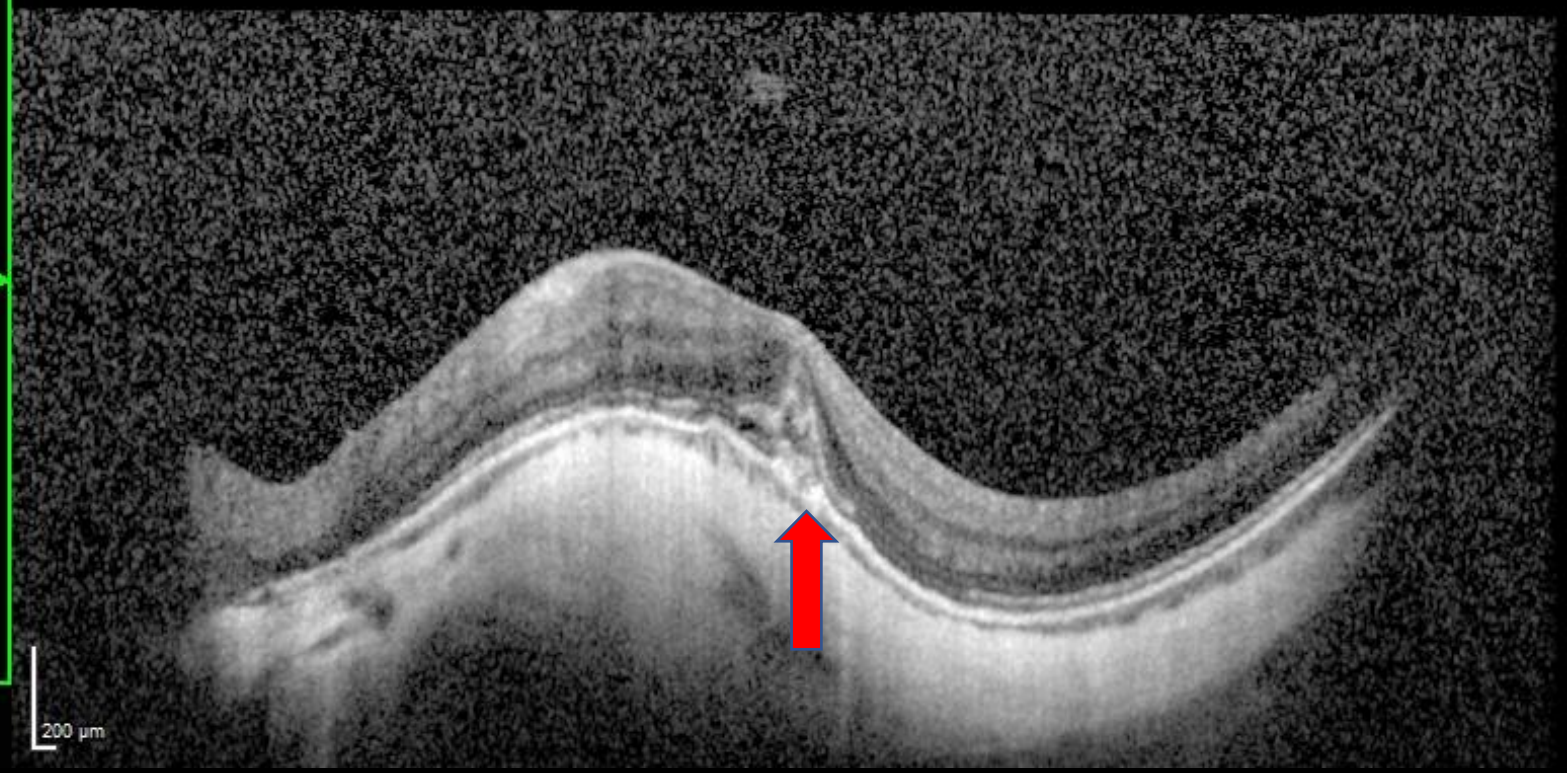
Myopic Degeneration

- **Driving force** – elongation of the axial length and posterior staphyloma.
- CNV is the most common cause of vision loss in high myopia and has been reported in 5-10%
- **RPE changes** (tessellated appearance)
- **Lacquer cracks**
  - Irregular yellow-appearing bands 2/2 breaks in Bruch's membrane may be foci of future CNVM (approx 1/3 will develop)
  - Over time these breaks can expand and stretch (can resemble GA)
- **Fuchs spots**
  - RPE hyperplasia
  - Response of the RPE to previous regressed CNV
- **Staphyloma**
  - Outpouching of scleral tissue involving the optic disc or macula
  - 35% of eyes with high myopia
  - Macular/Foveal schisis

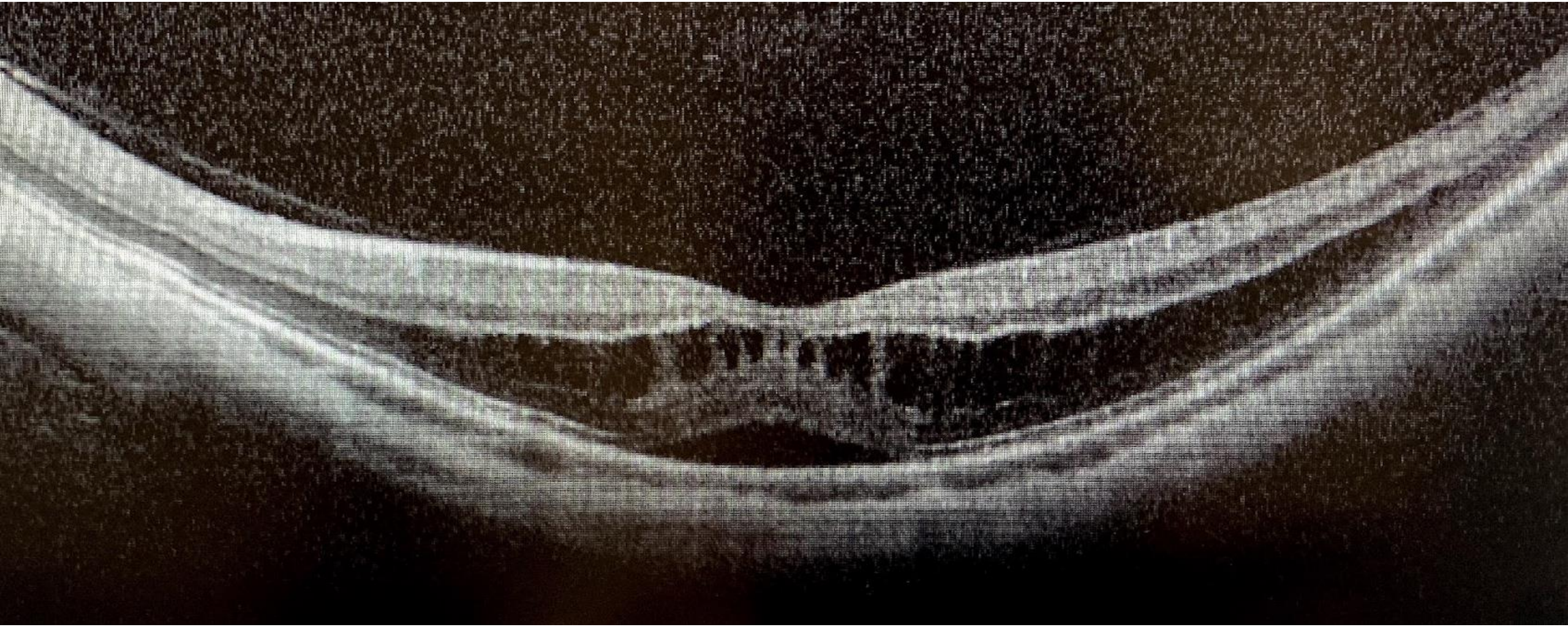





30 / 61
200 µm

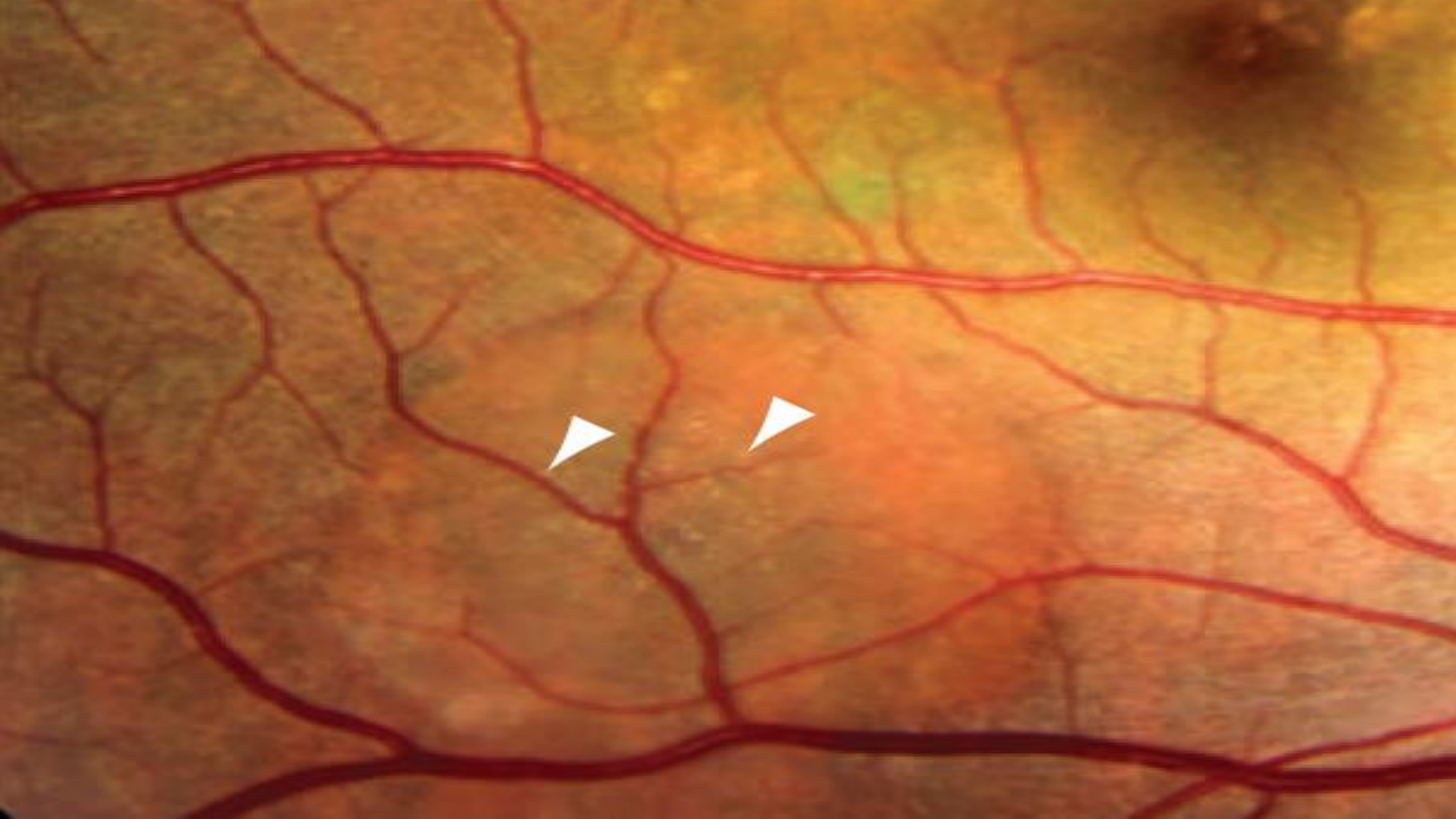

200 µm

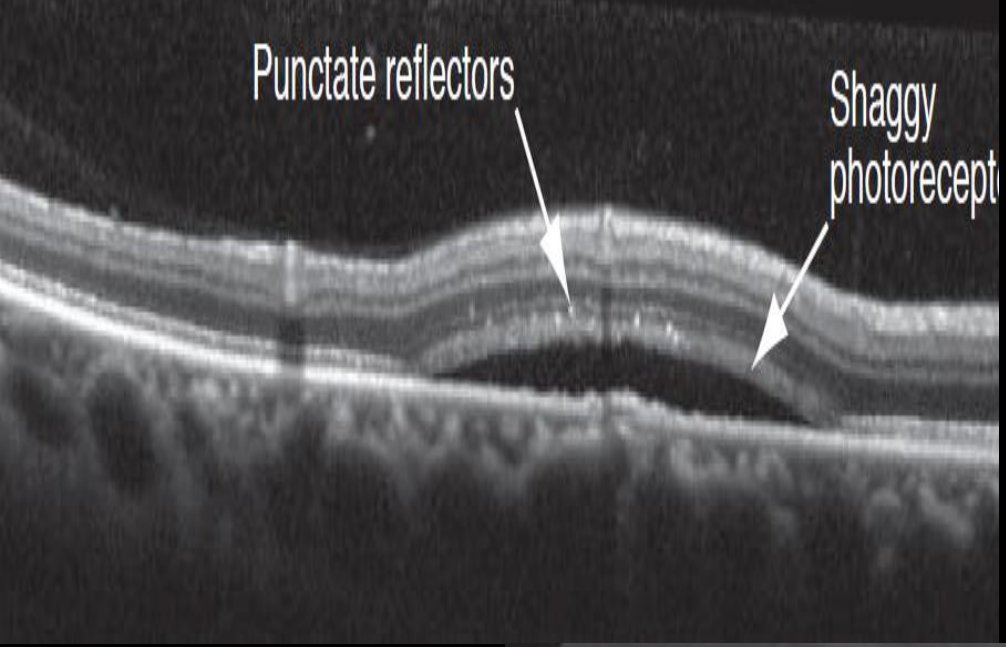
Myopic Foveal Schisis

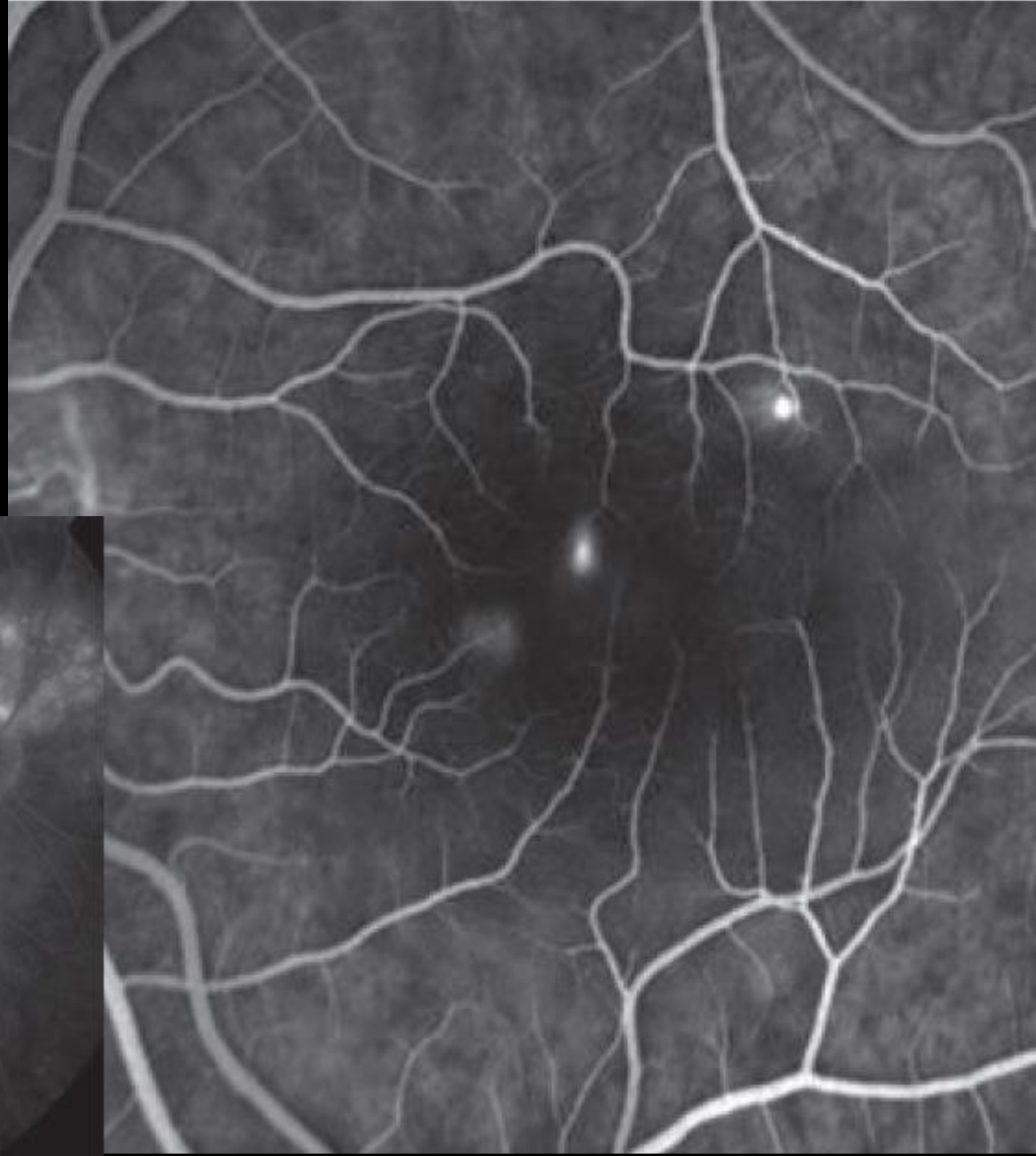


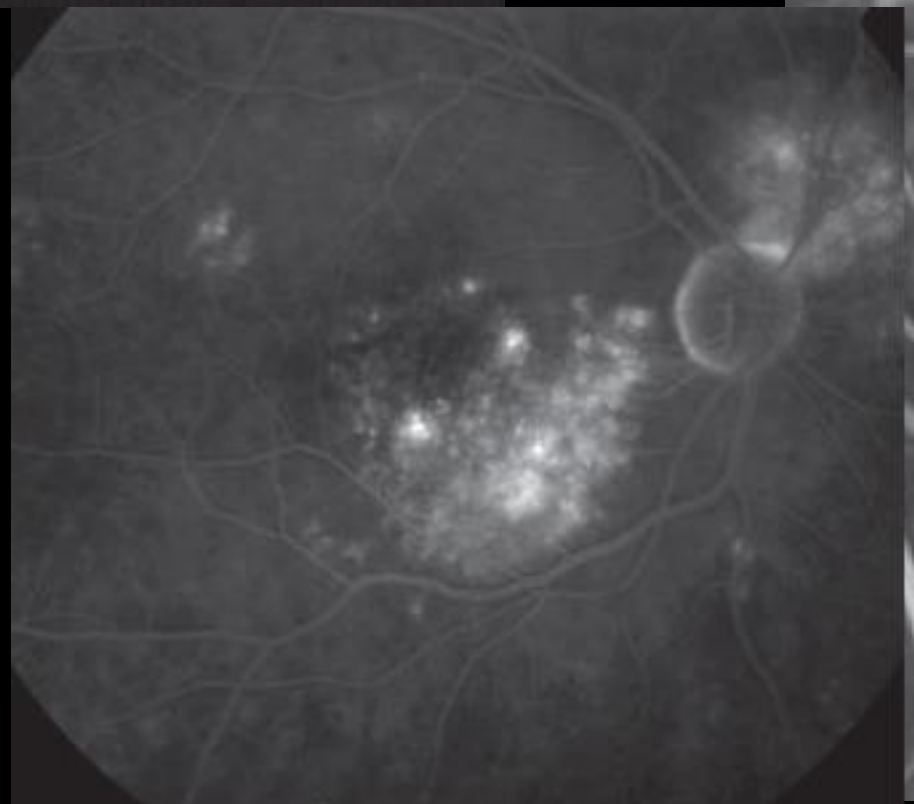
Central Serous Retinopathy

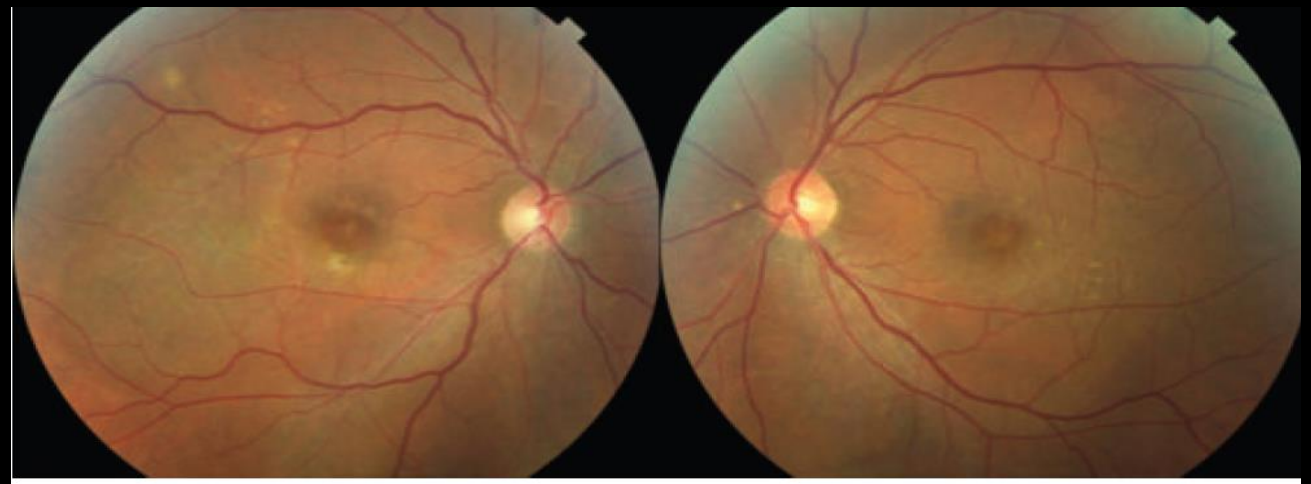
- Idiopathic serous detachment of the retina at the level of the RPE 2/2 hyperpermeability of the choriocapillaris
- M>F in 3:1 ratio
- Sx: blurred vision, dim vision, metamorphopsia, paracentral scotoma, decreased color vision, prolonged after images
- VA 20/20-20/200 (most are >20/30); can be corrected with small hyperopic correction
- Associations: stress, type A personality, steroids, Cushing's syndrome, HTN, sleep apnea, pregnancy, psychopharmacologic medications

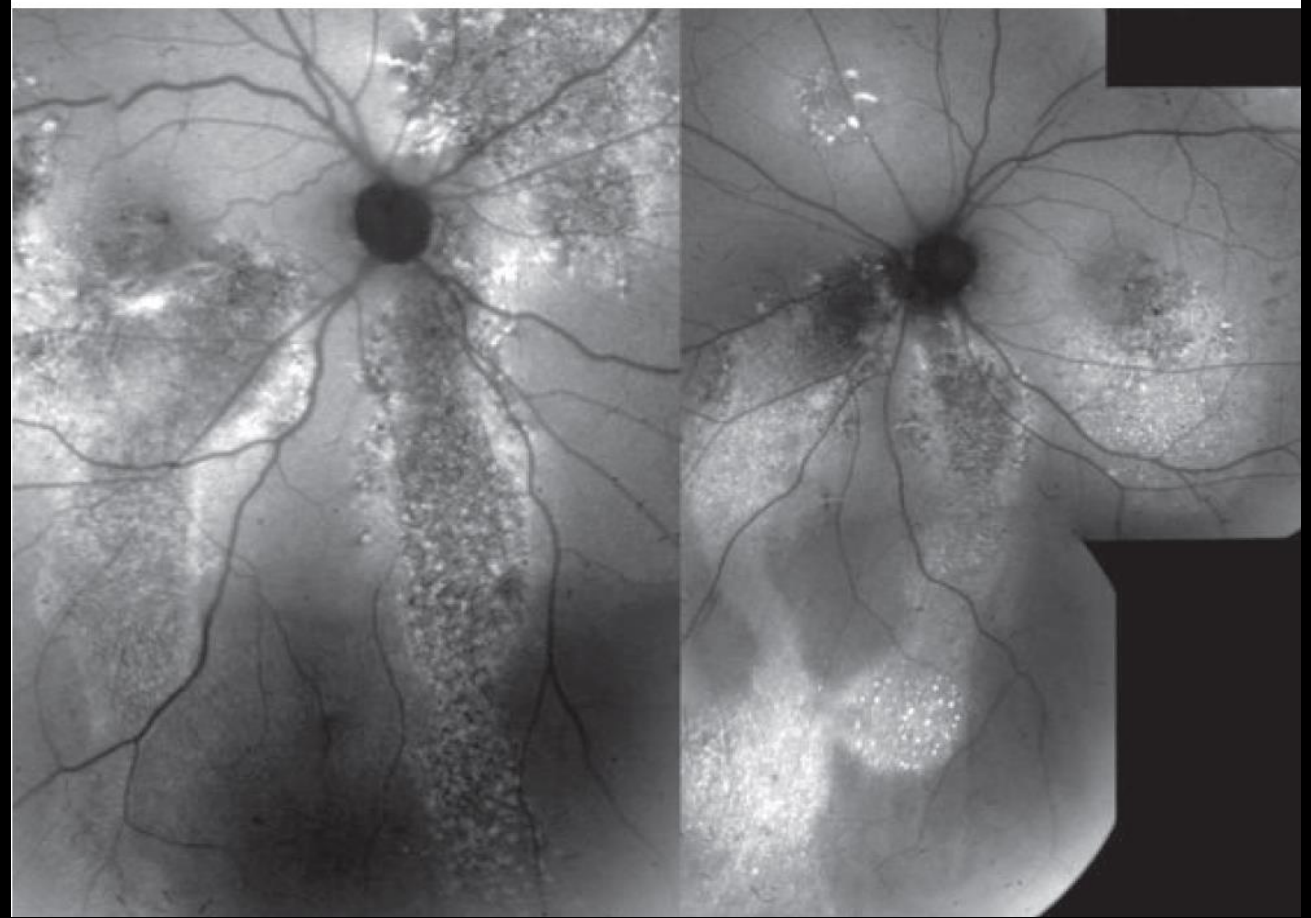


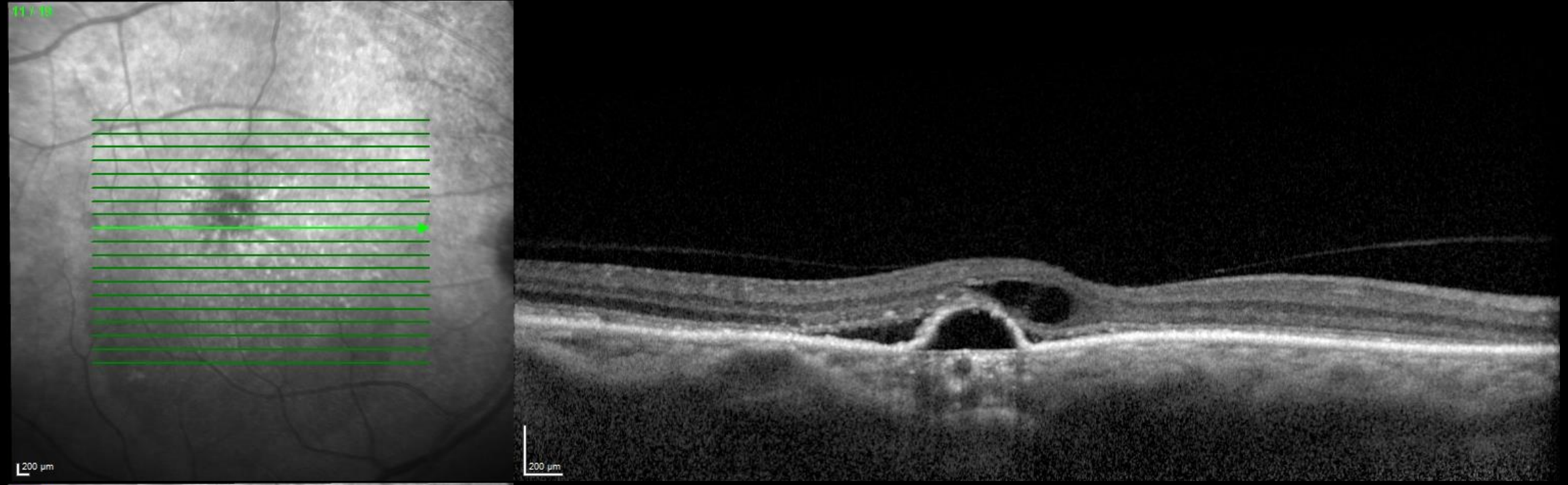

Punctate reflectors
Shaggy
photorecept

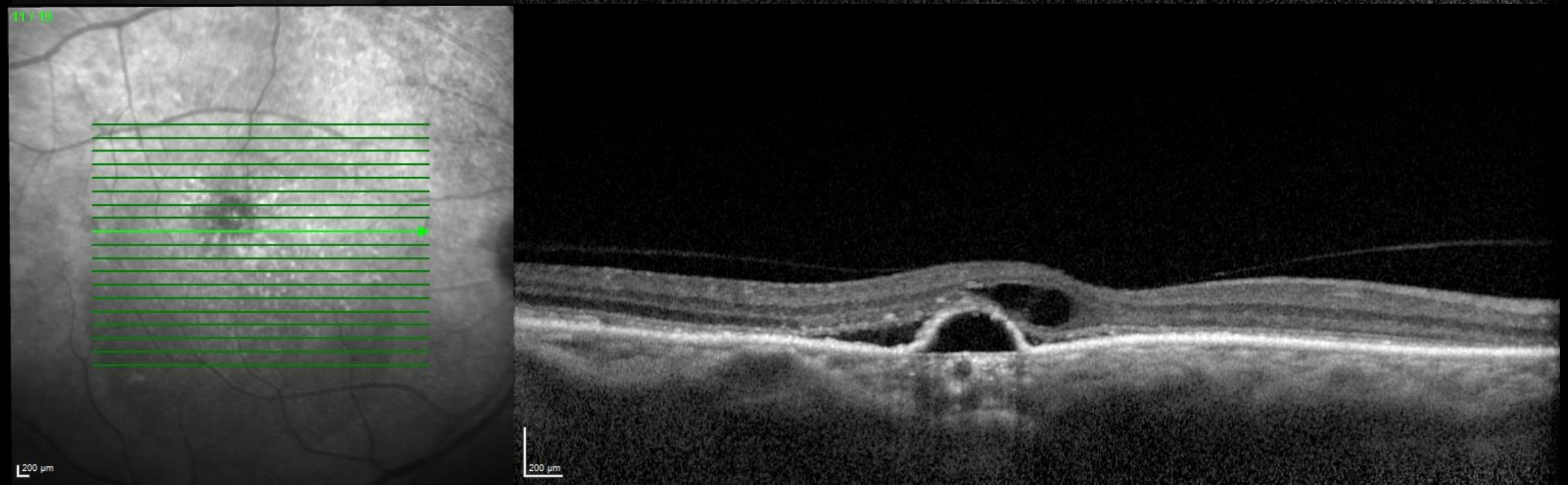


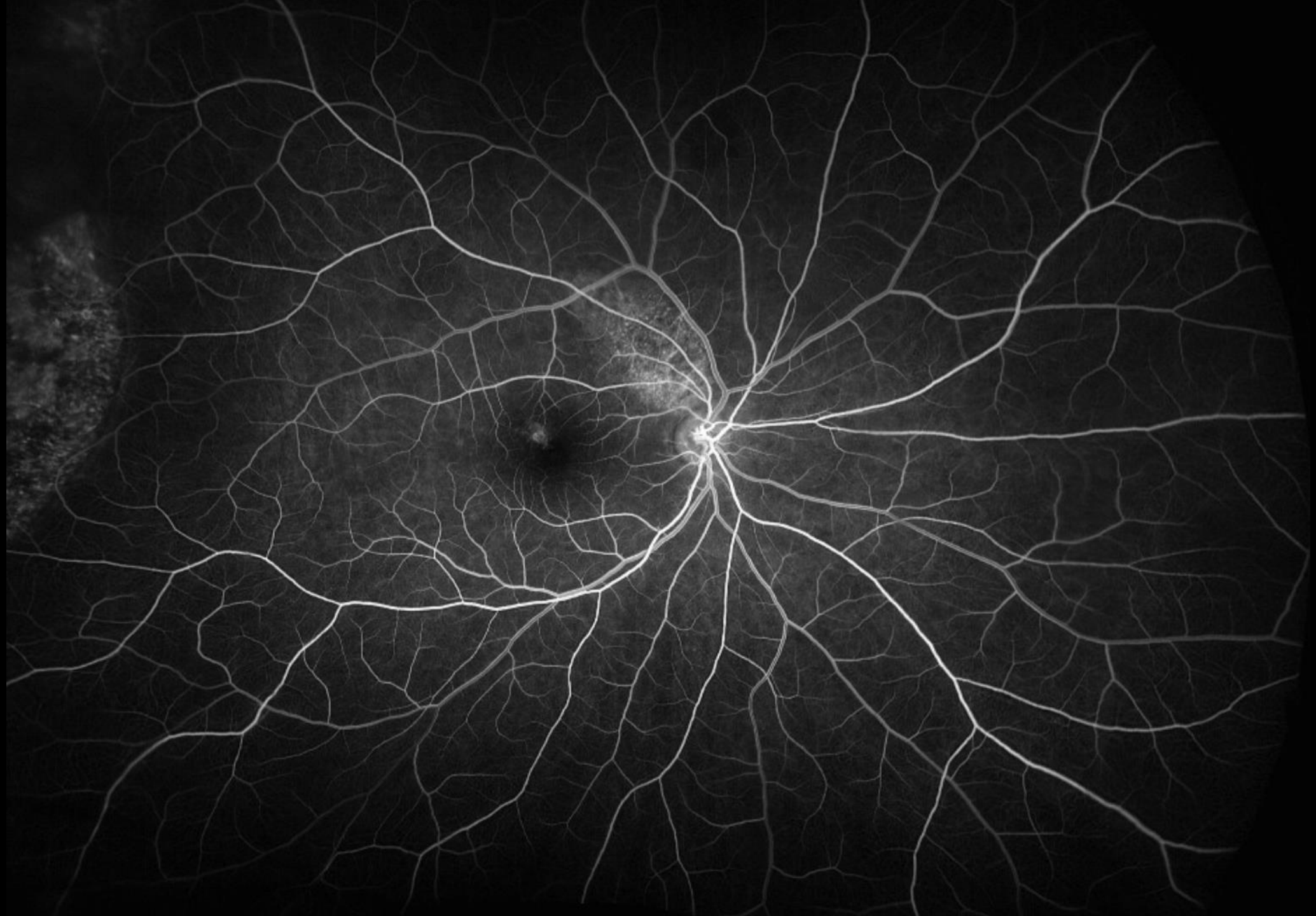


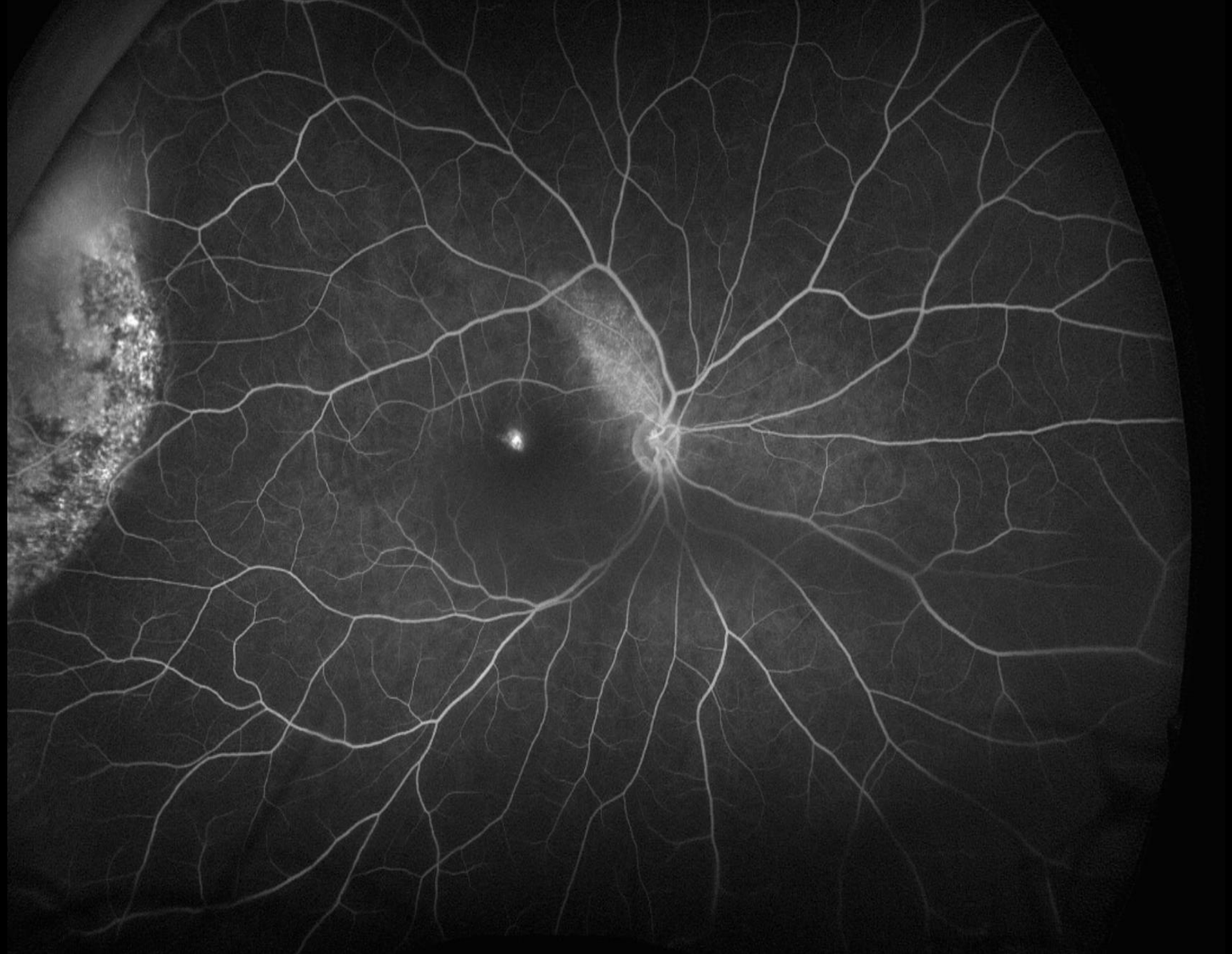





11 / 19
200 µm
200 µm


11 / 19
200 µm
200 µm





Treatment Options

- Observation
- Anti-VEGF
  - CNVM
- Focal thermal laser
  - Doesn’t reduce recurrence
- Photodynamic therapy
  - Can reduce recurrence
  - Can cause atrophy in 4%
- Mineralocorticoid receptor agonist (eplerenone, spironolactone)
  - Resolution of SRF in 25%
  - No randomized clinical trials

Solar Retinopathy

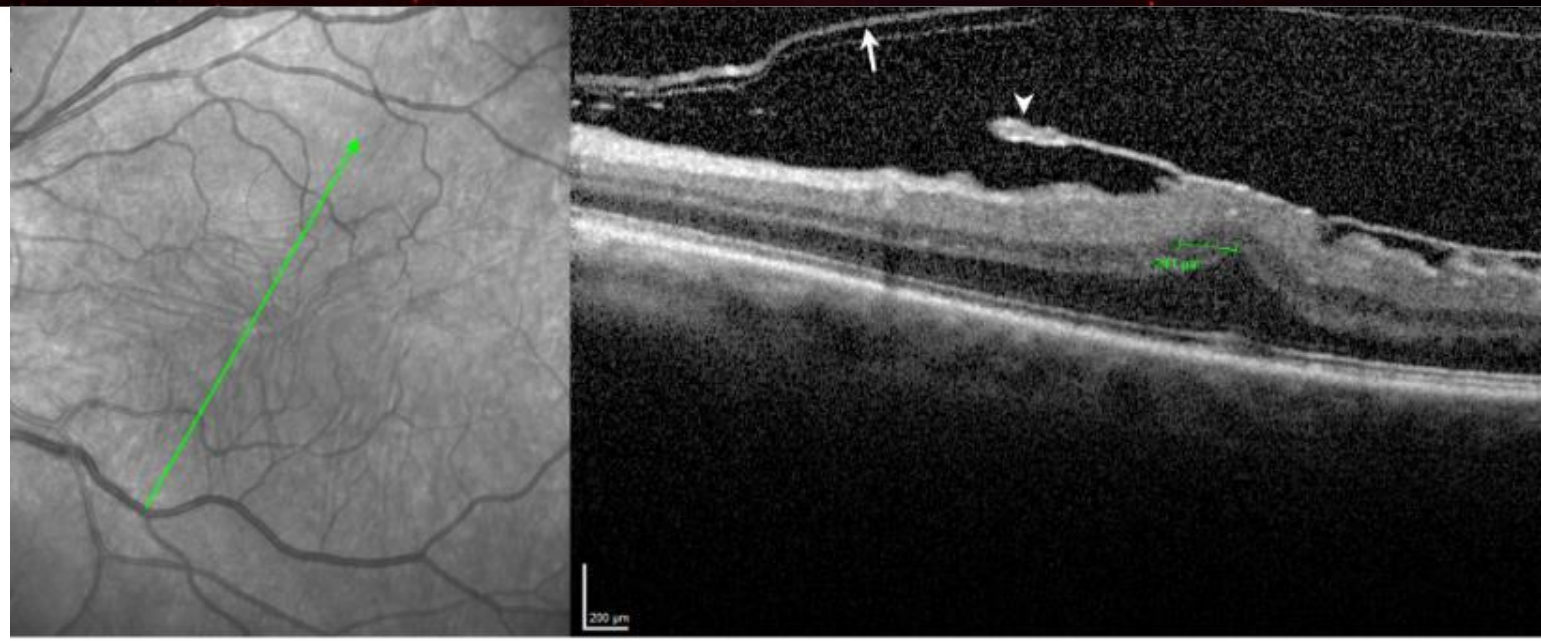
- Thermally enhance photochemical retinal injury
- Direct or indirect gazing at the sun
- Duration and Intensity of Exposure determines damage
- Younger patients with clearer lens have higher risks
- Sx: decreased vision, central scotomas, dyschromatopsia, metamorphopsia, micropsia, and frontal or temporal headache within hours of exposure.
- VA generally 20/25-20/100
- Exam: central opacified area acutely and depigmentation over time
- No treatment
- Most recover vision within 3-6 mo usually back to 20/20-20/40
- Residual metamorphopsia/scotomas may remain

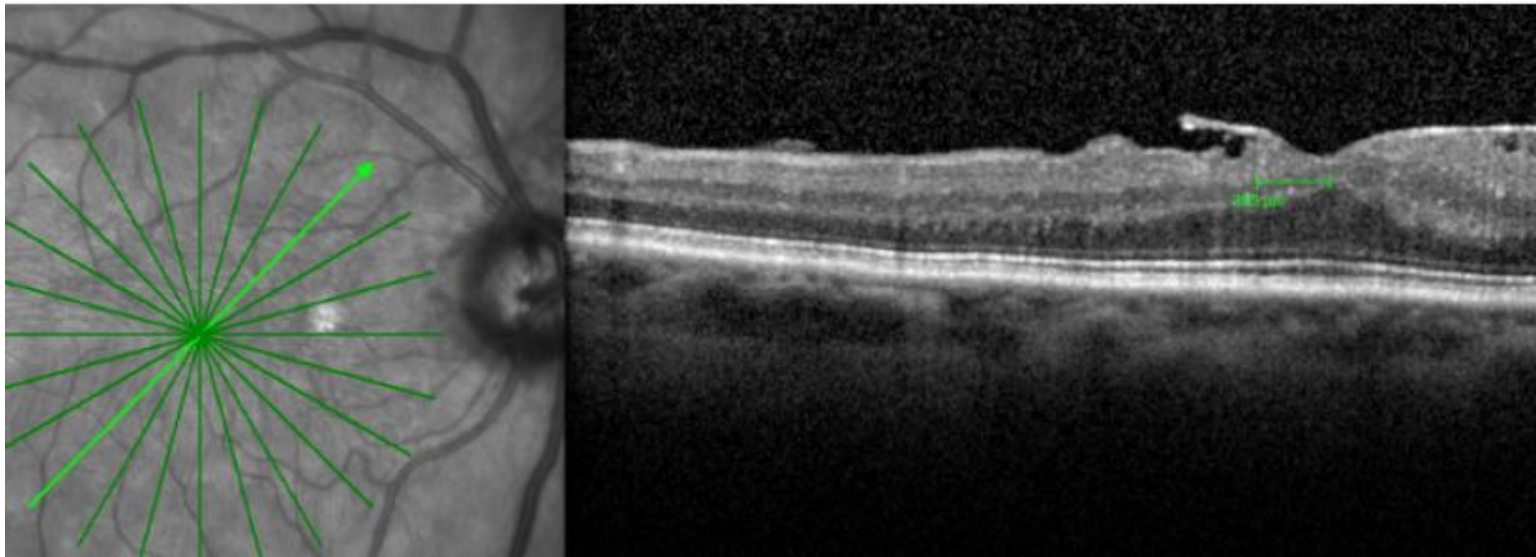
Vitreoretinal Interface

Epiretinal membrane (epimacular)

Vitreous=type II collagen
ILM=type IV collagen

Gliotic change at interface=epiretinal membrane, epimacular membrane, paramacular gliosis





EMM Spectrum

Idiopathic

- PVD creates ILM defect - gliosis
  (RPE cells, Muller cells, gliosis)
- Macular posterior hyaloid remnant after peripapillary PVD

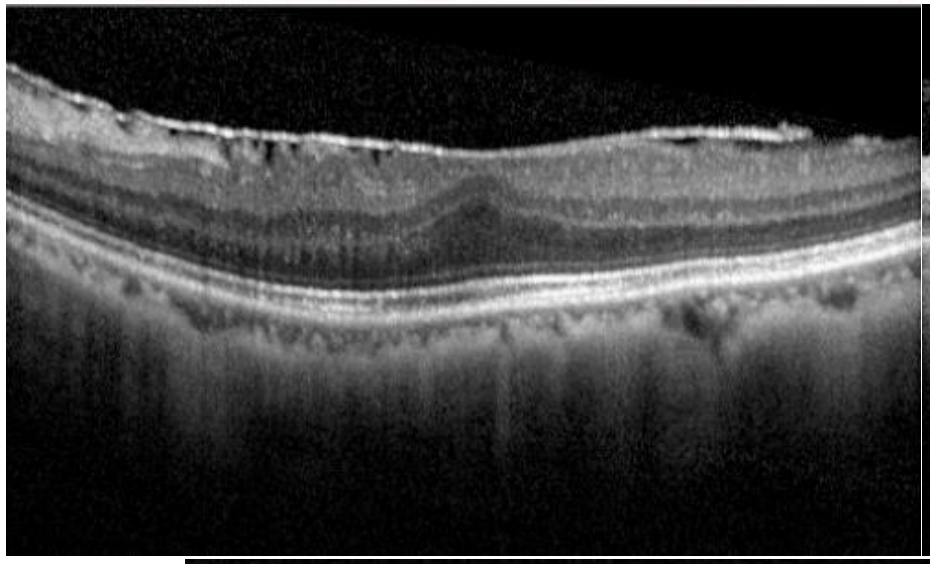
Macular PVR - after retinal break, laser , or RD

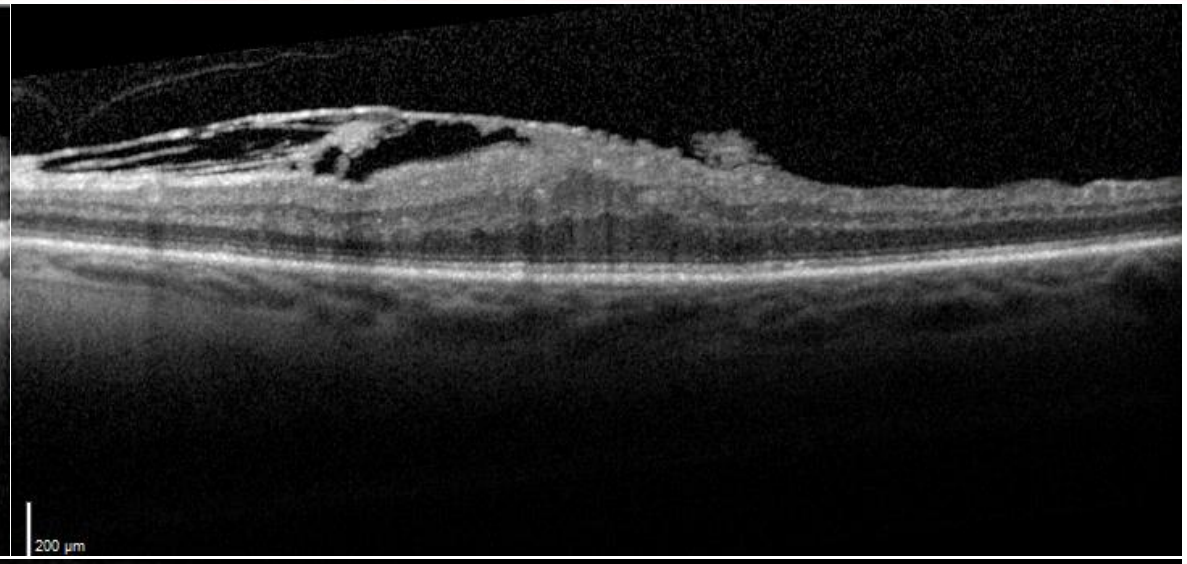
Secondary

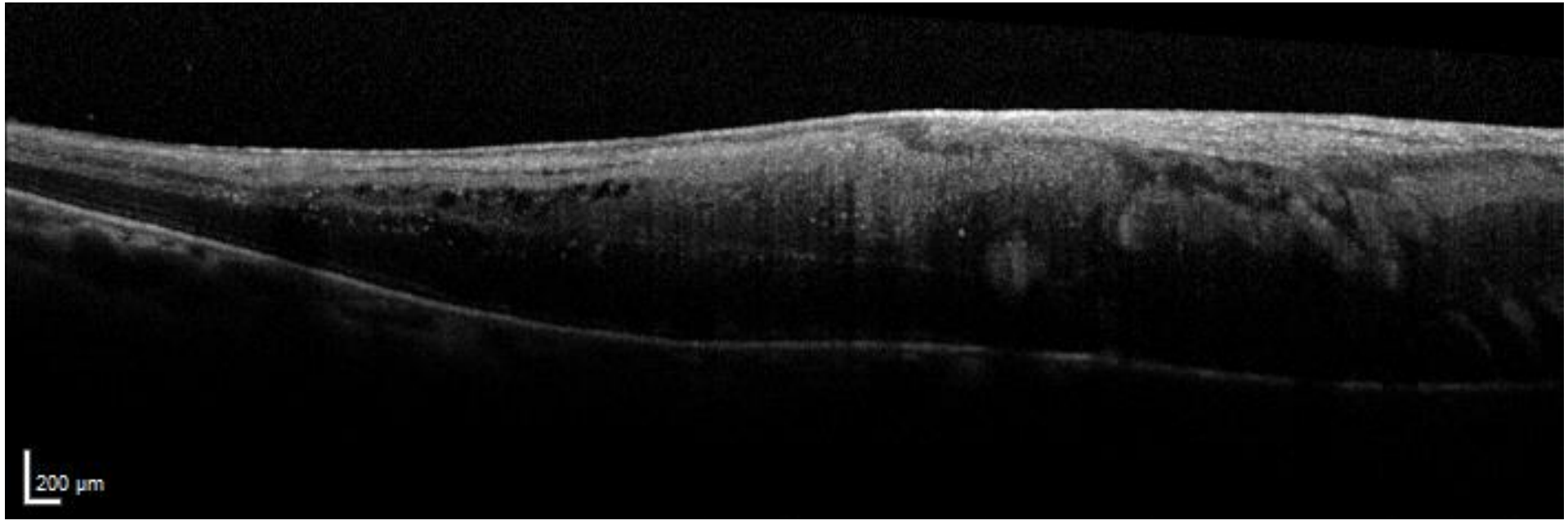
- post traumatic
- retinal vascular disease (DM) and uveitis
- vascularized membranes

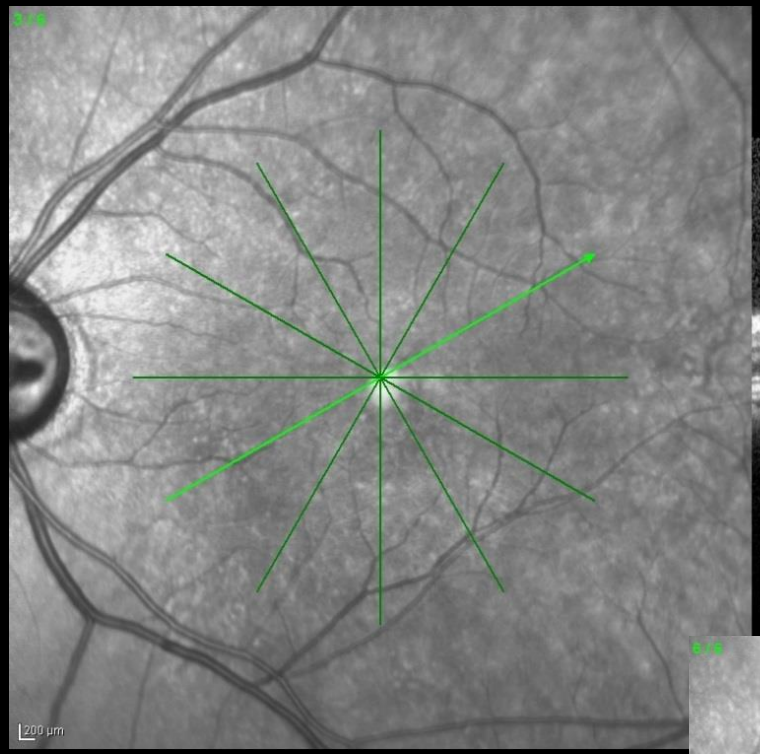
-20% over 75, 2% over 50, females>males, 2:1
-stable vision over 70%, >20/50 in 75%

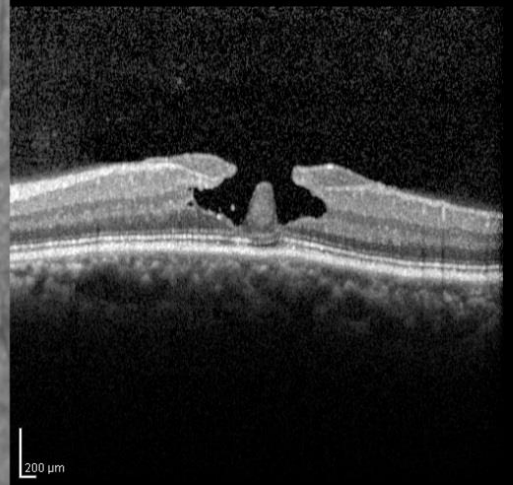
Posterior Hyaloid, Macular PVR, Vascularized

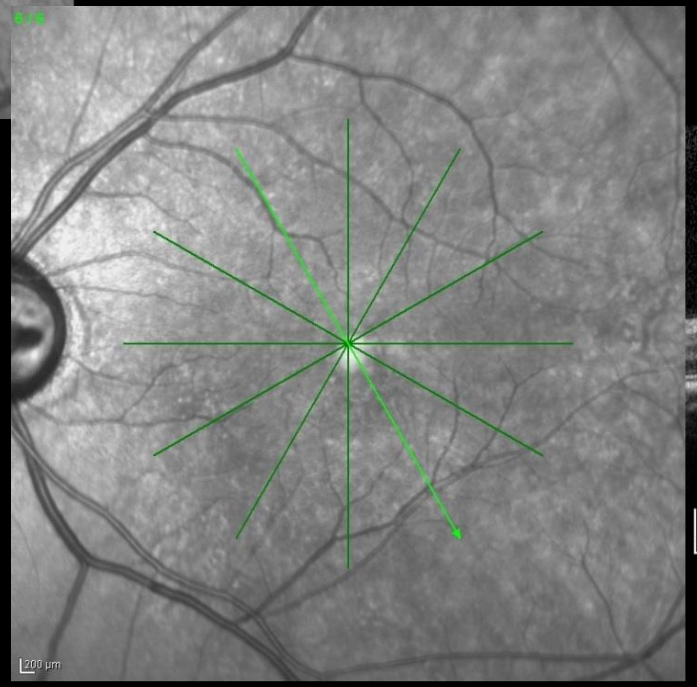


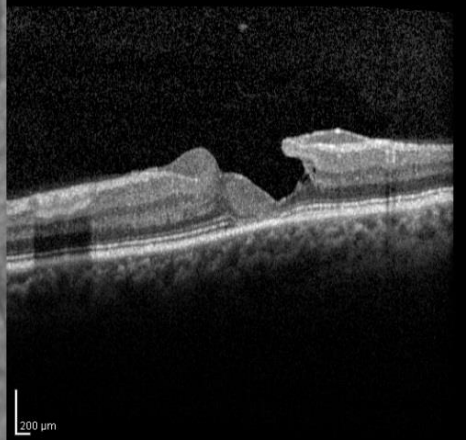





3 / 6
200 µm


200 µm

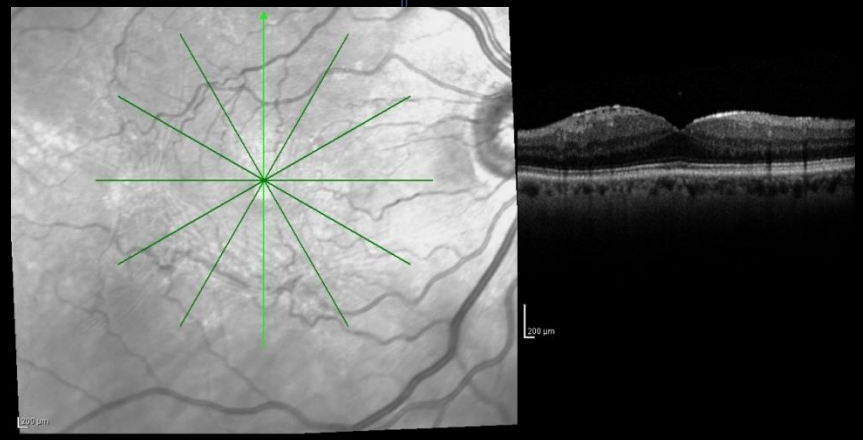

6 / 6
200 µm


200 µm

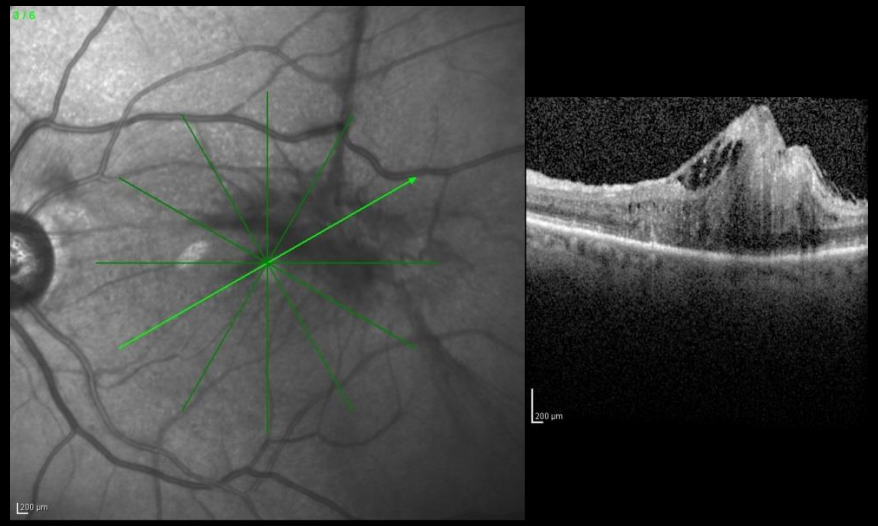
Typical Patient – Mild ERM with Stable Vision

Low risk of progression

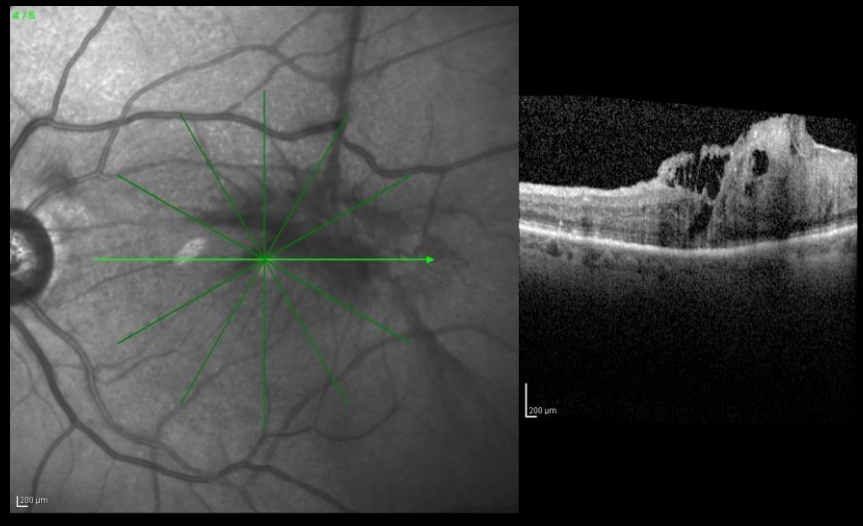
Observation every 6-12 months



ERM Pre & Post Op



6/8/2016, OS
IR&OCT 30° ART [HS] ART(7) Q: 21
HEIDELBERG ENGINEERING



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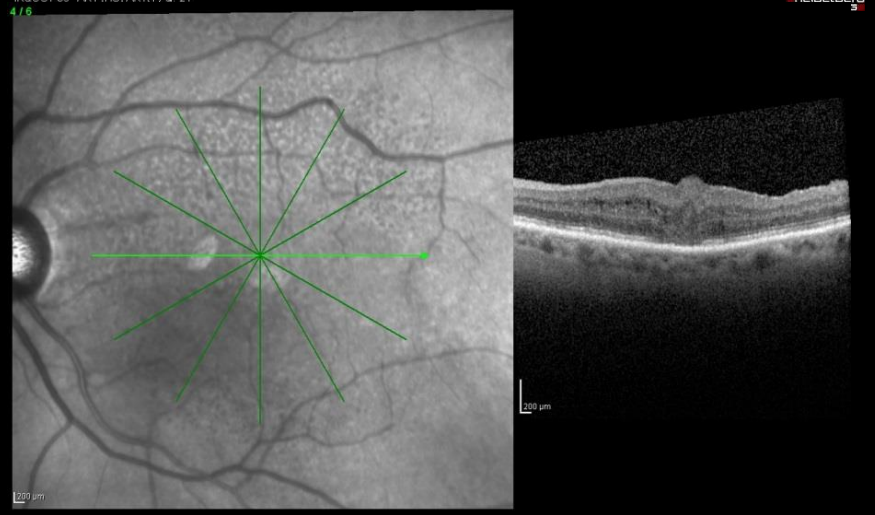

8/31/2016, OS
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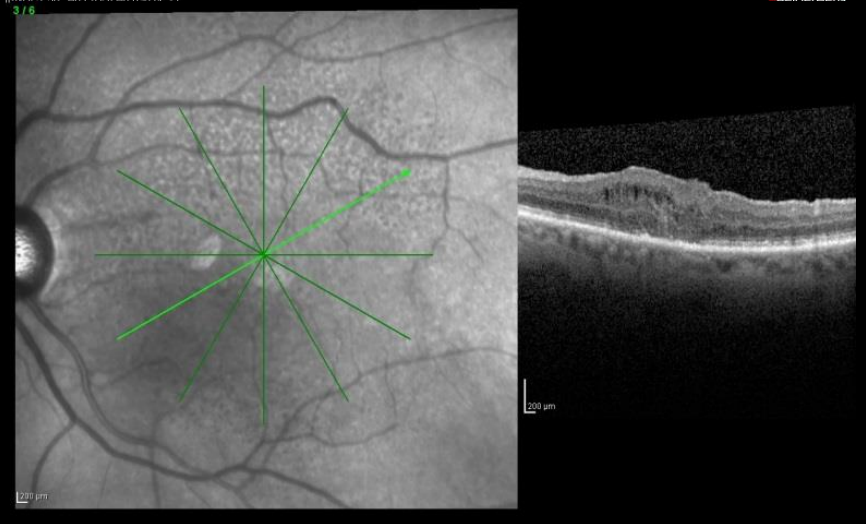
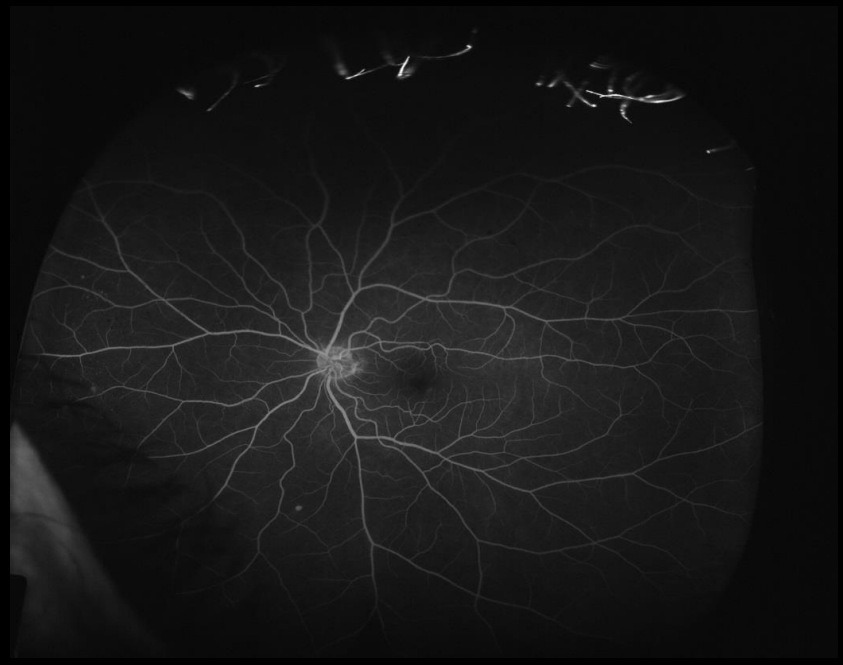


8/31/2016, OS
IR&OCT 30° ART [HS] ART(11) Q: 23
HEIDELBERG ENGINEERING

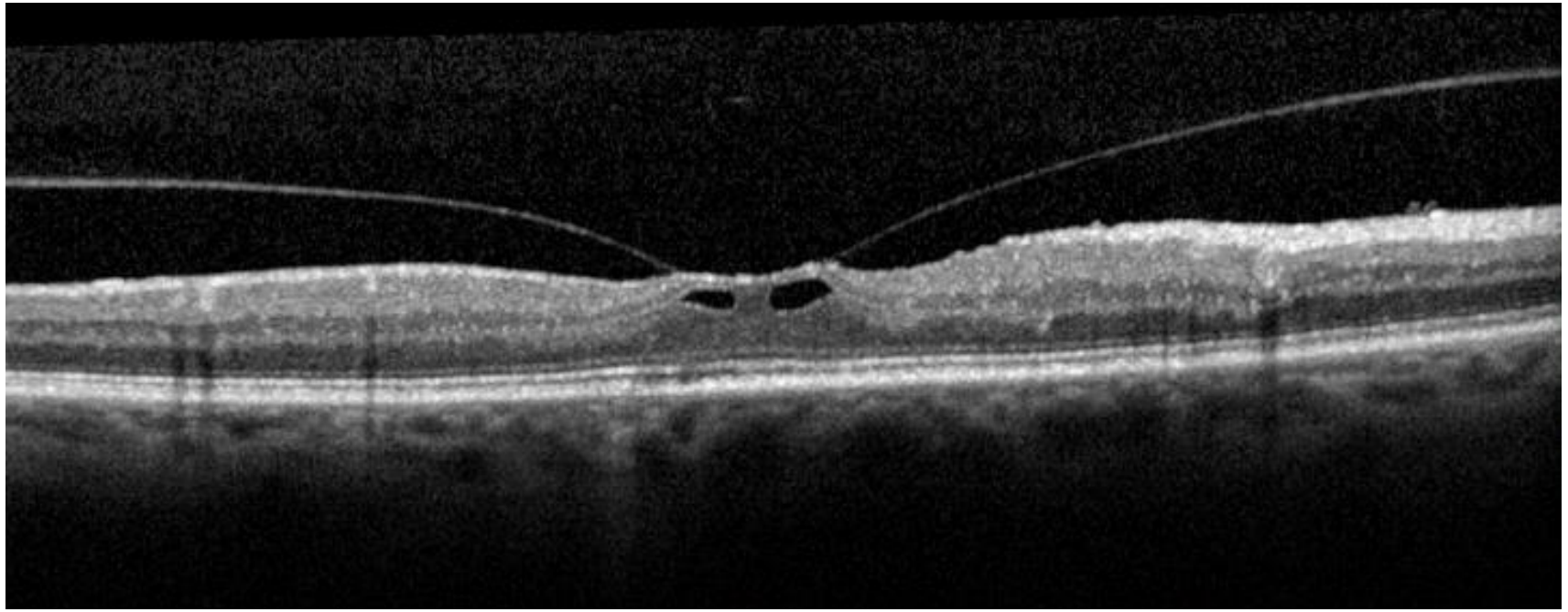
ERM Pre & Post




4/29/2016, OS
IR&OCT 30° ART [HS] ART(10) Q: 17
4/29/2016, OS
IR&OCT 30° ART [HS] ART(8) Q: 21
10/12/2016, OS
IR&OCT 30° ART [HS] ART(9) Q: 22

Vitreoretinal Interface

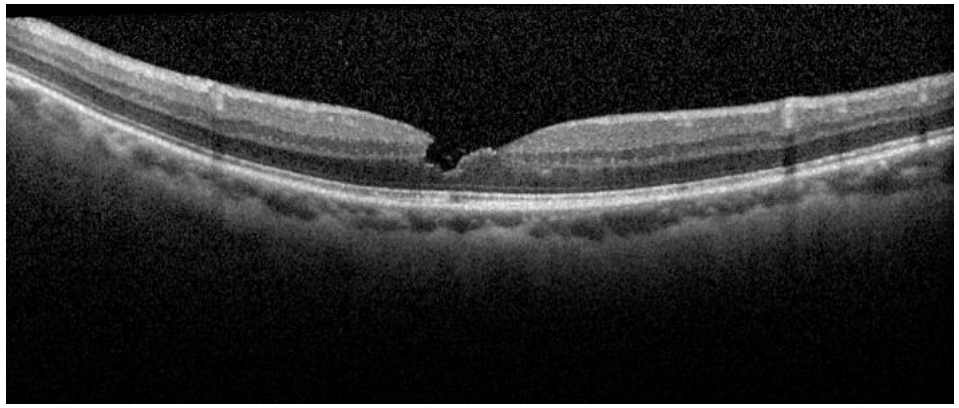
Vitreomacular a (vitreofoveal traction)

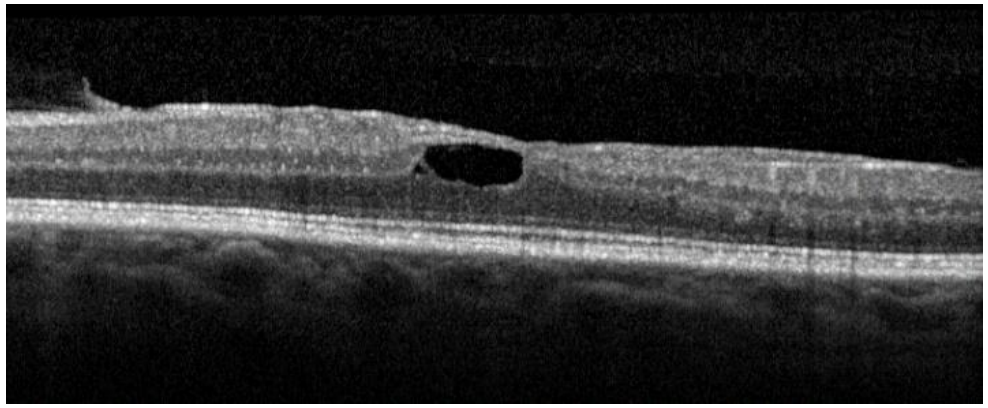


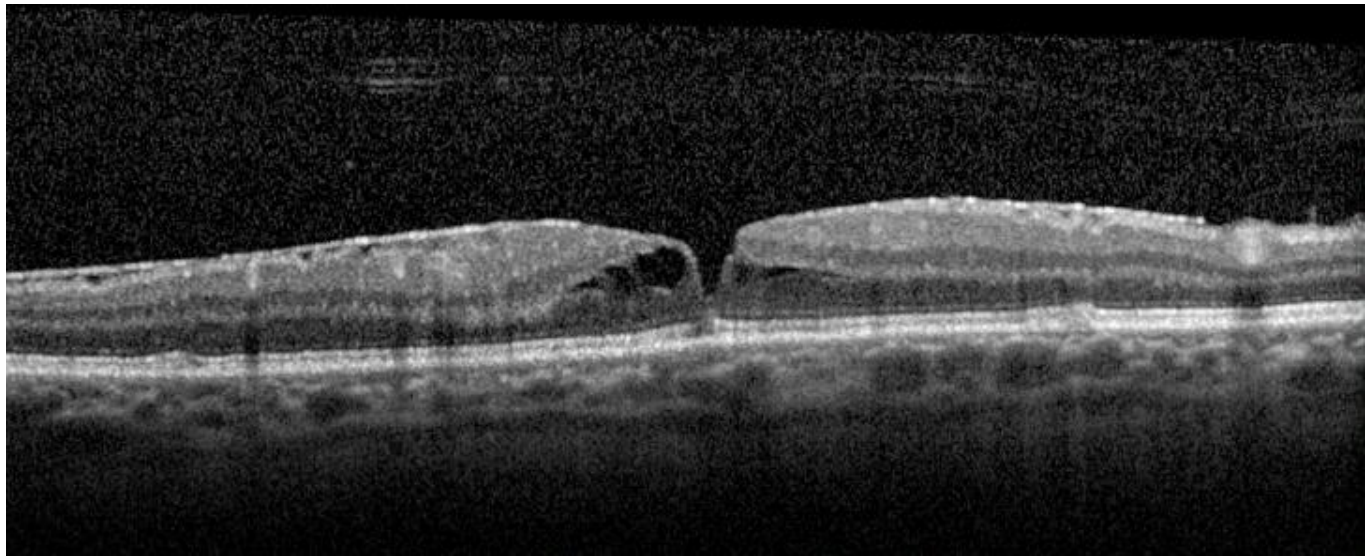
Consider surgery if symptomatic, many intravitreal enzymatic therapies attempted but failed real world efficacy.

Vitreoretinal Interface

Lamellar macular hole/acquired macular schisis





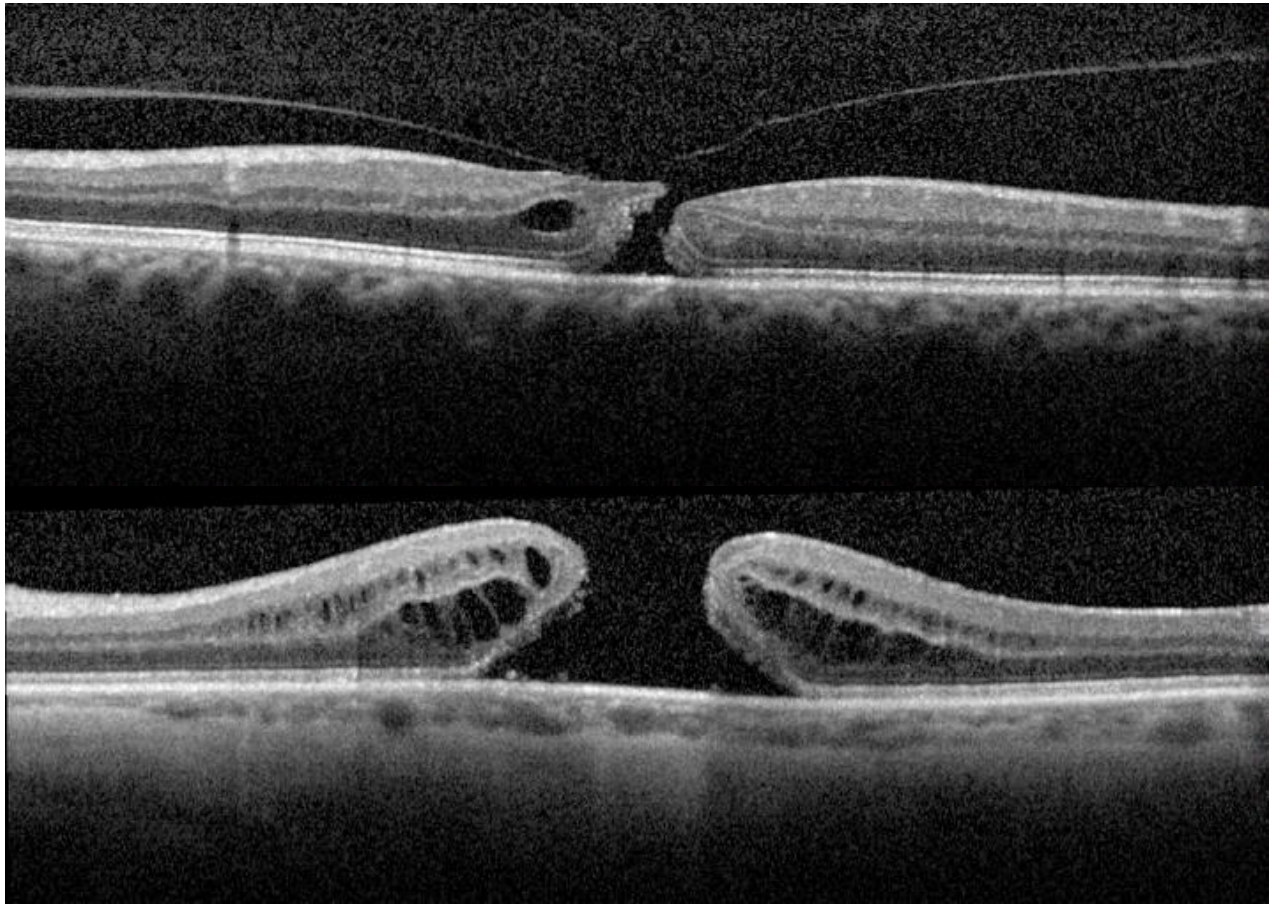


Stage 1

Vitreoretinal Interface

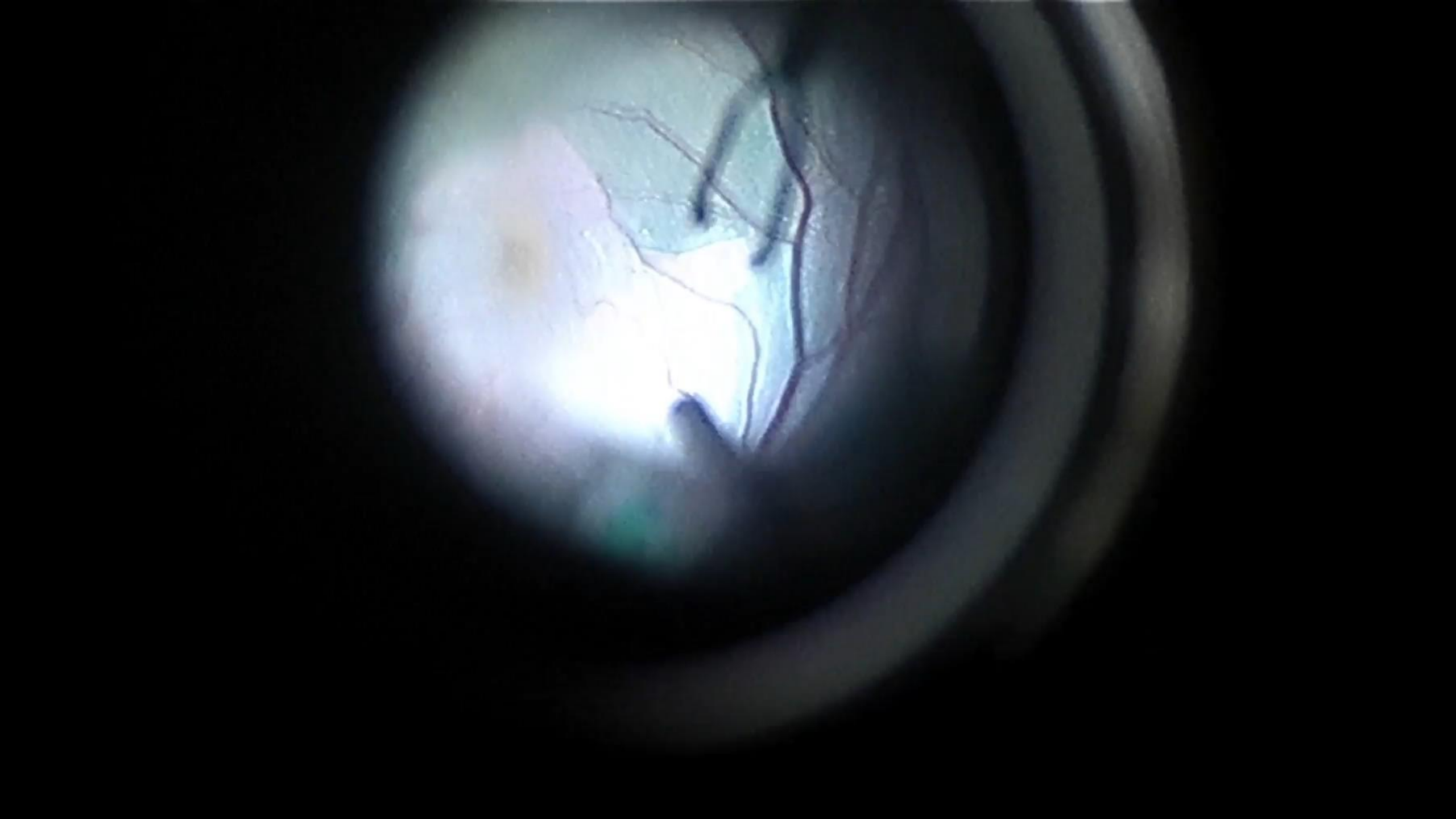
Macular Hole (full-thickness) - less than 5% close, tx: PPV+PVD creation+ILM peel up to 100% success (>90%)

>800 µm=large hole; flat, open, no RPE function on FAF are poor predictors



Stage 2
<400µm

Stage 3
>400µm
Stage 4=
+Weiss Ring



Questions

Office: (407) 425-7188

Dr. Randolph: (321) 247-2939

Dr. Ortiz: (786) 208-6340

Dr. Feinstein: (804) 241-5655

Dr. Kumar: (847) 406-0688

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- **Presenters:**
  - Dr. John Randolph
  - Dr. Gonzalo Ortiz
- **Affiliation:**
  - Central Florida Retina
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