The Dilemma of Non Neovascular AMD
Present and Future

By

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Age related macular degeneration

Age-related macular degeneration (AMD) is a chronic multifactorial, degenerative eye disease affecting macula causing progressive central vision loss above 60 years

Epidemiology

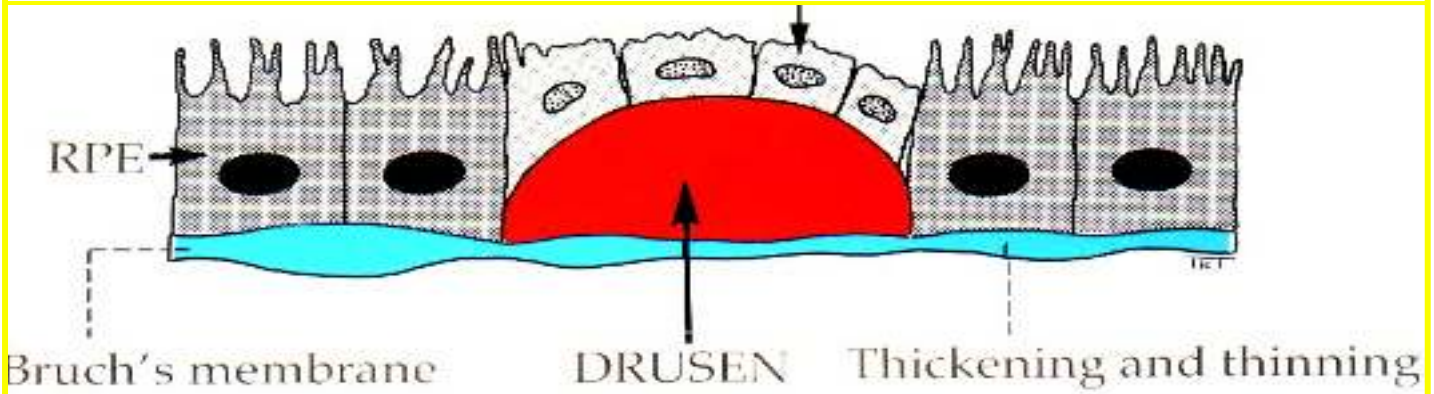
- • Affects nearly 200 million people worldwide.
- • Risk factors include age, genetics (CFH, ARMS2), smoking, and diet.
- • Incidence increases significantly after age 60.

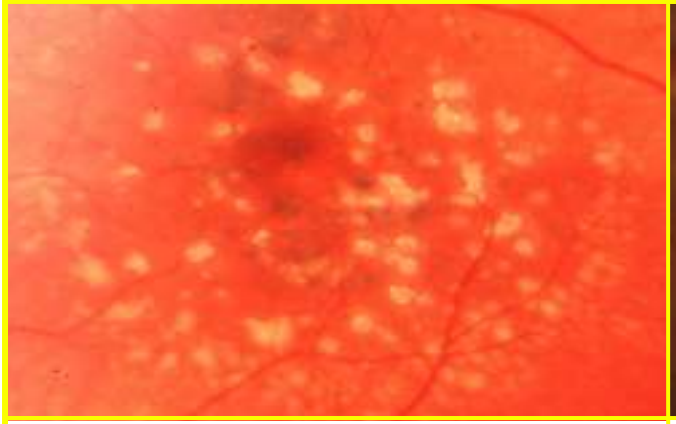
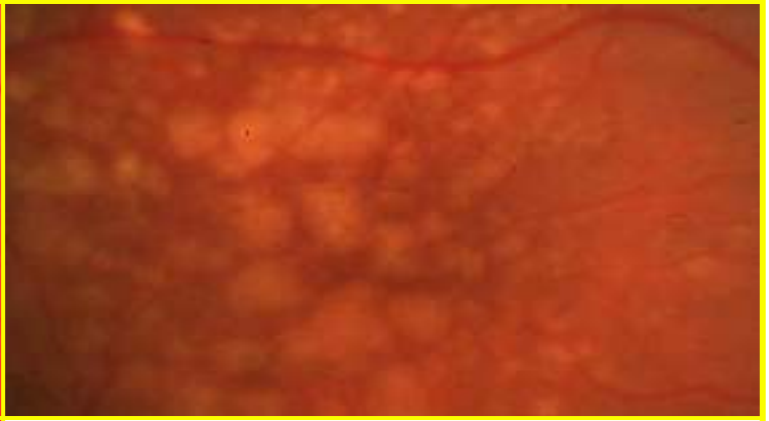
Pathophysiology

- ·Characterized by drusen accumulation and RPE atrophy.
- • Progresses to geographic atrophy (GA) in advanced stages.
- • Involves oxidative stress and chronic inflammation.

Drusen

Histopathology



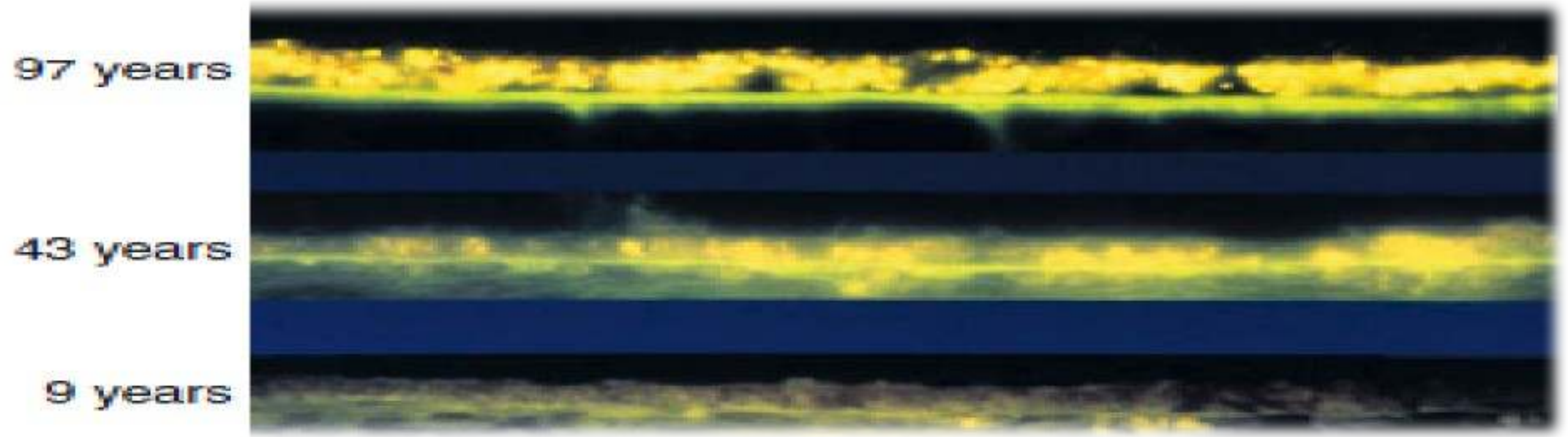
Hard	Soft
	
• Small well-defined spots • Usually innocuous	• Larger, ill-defined spots • May enlarge and coalesce • Increased risk of AMD

Pathogenesis

Lipofuscin accumulation in RPE cells

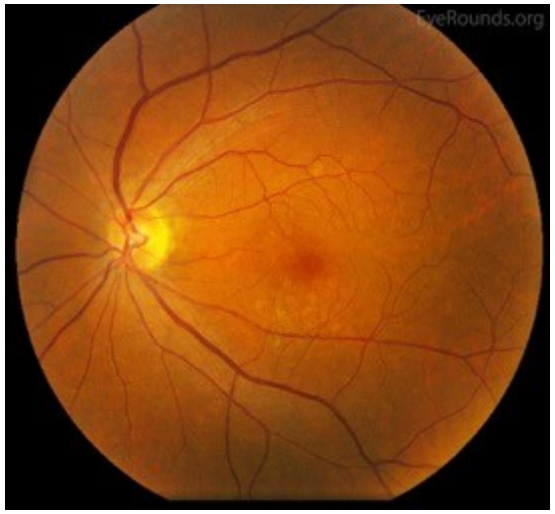
Choroidal ischemia

Oxidative damage



Ryan (Beckman)
Initiative for macular research classification

Aged retina

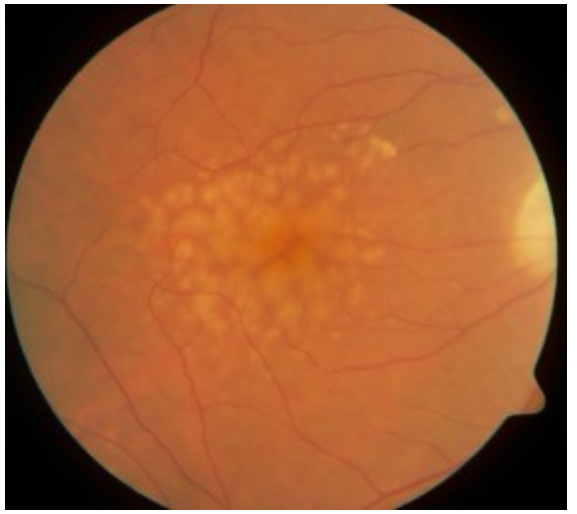


Small sized drusen < 63 um

Early AMD

Medium sized drusen 63-125 um

Intermediate AMD

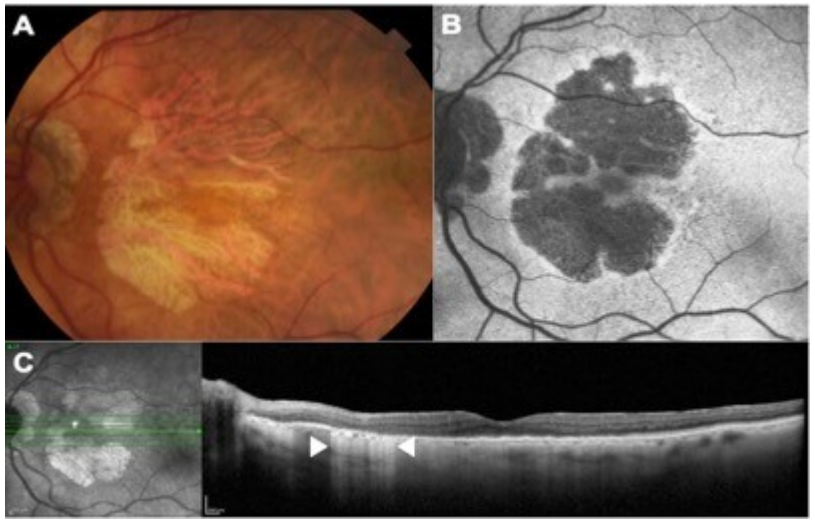


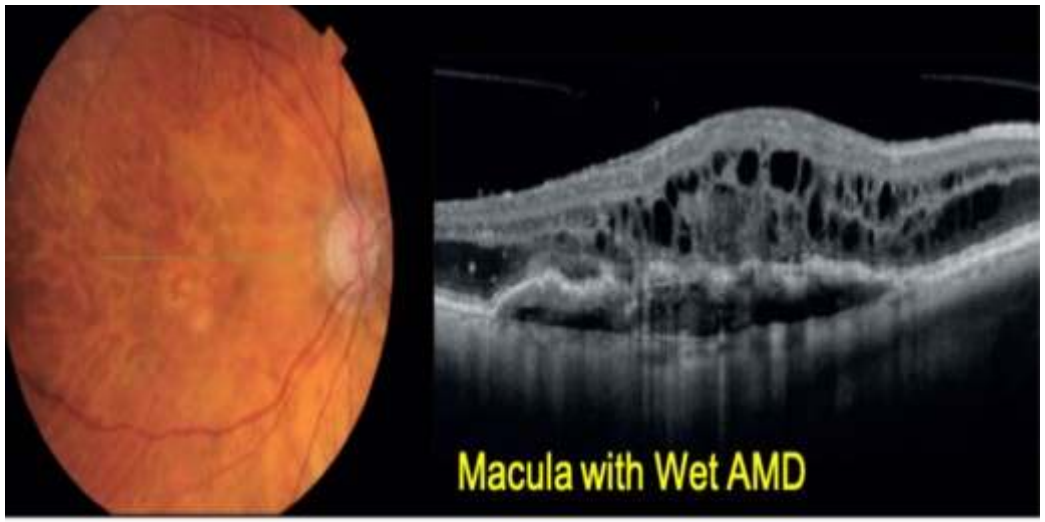
Large drusen > 125 um (emerging disc vein size)+/- pigmentary changes

Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, Sadda SR; **Beckman Initiative for Macular Research Classification Committee. Clinical classification of age-related macular degeneration. Ophthalmology. 2013 Apr;120(4):844-51**

Ryan (Beckman)
Initiative for macular research classification

Advanced (late) AMD





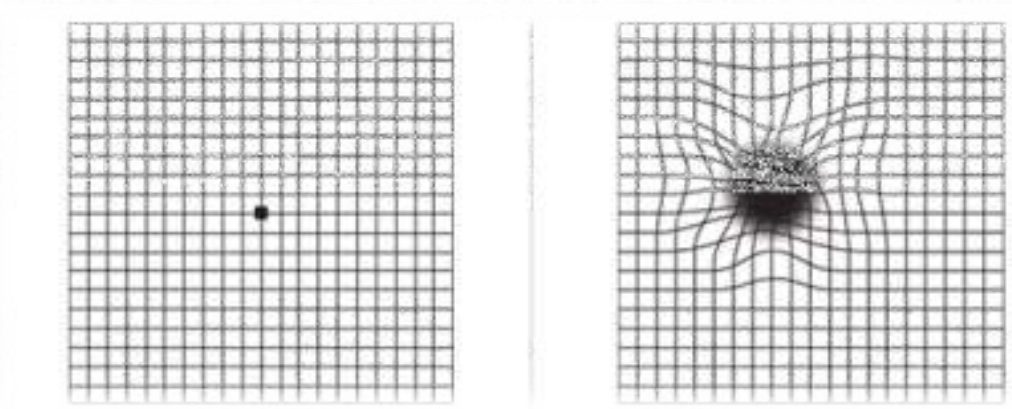
Dry AMD
(Geographic atrophy or c-RORA)
85-90 %
Slow vision loss

Wet AMD
(macular neovascularization, MNV)
10-15 %
Rapid vision loss

Ferris FL 3rd, Wilkinson CP, Bird A, Chakravarthy U, Chew E, Csaky K, Sadda SR; **Beckman Initiative for Macular Research Classification Committee. Clinical classification of age-related macular degeneration.** Ophthalmology. 2013 Apr;120(4):844-51.

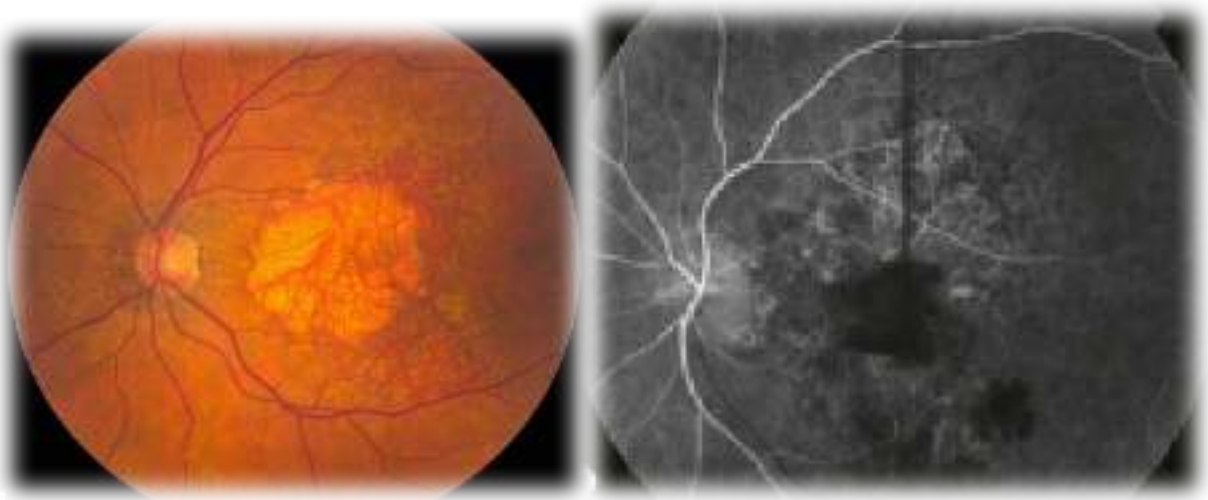
Clinical Presentation

- Gradual central vision loss.
- Difficulty reading or recognizing faces.
- Symptoms may be subtle in early stages.



Diagnostic Tools

- Fundus photography: visualizes drusen.
- OCT: detects retinal thinning and drusen.
- FAF: highlights areas of RPE dysfunction.



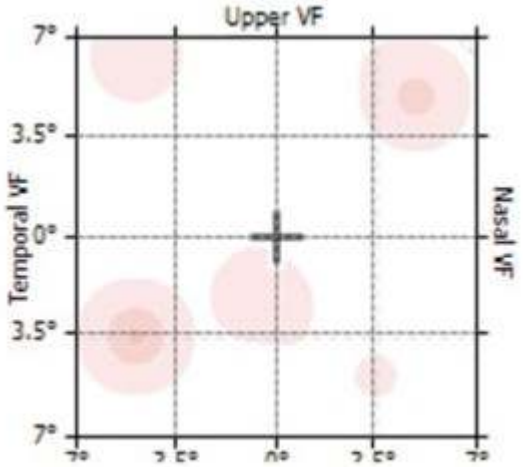
Dilemma 1: Early Detection

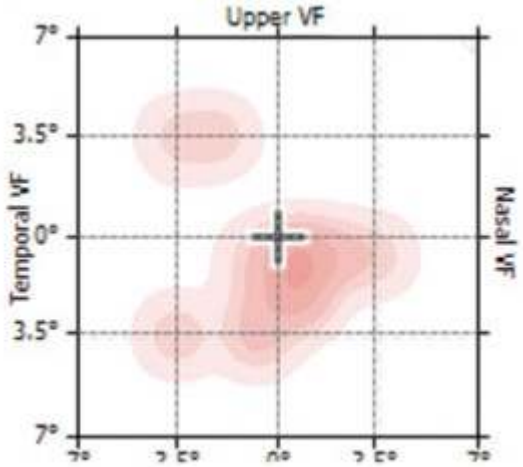
- ·· **Difficulty predicting which patients will progress.**
- •• **Need for biomarkers and advanced imaging.**
- •• **Monitoring remains clinical and imaging-based.**

Home patient monitoring & Telemedicine

Forsee Home Device

Patient daily self assessment hyperacuity testing and quantifying changes with physician electronic alert for potential progression of AMD





Yu HJ, Kiernan DF, Eichenbaum D, Sheth VS, Wykoff CC: **Home Monitoring of Age-Related Macular Degeneration: Utility of the ForeseeHome Device for Detection of Neovascularization.** Ophthalmol Retina 2021, 5:348-56

Home patient monitoring & Telemedicine (Mobile Apps)

Alleye 4+
For your eye health
OCULOCARE medical AG
Designed for iPad
★★★★★ 5.0 • 1 Rating
Free
View in Mac App Store ↗

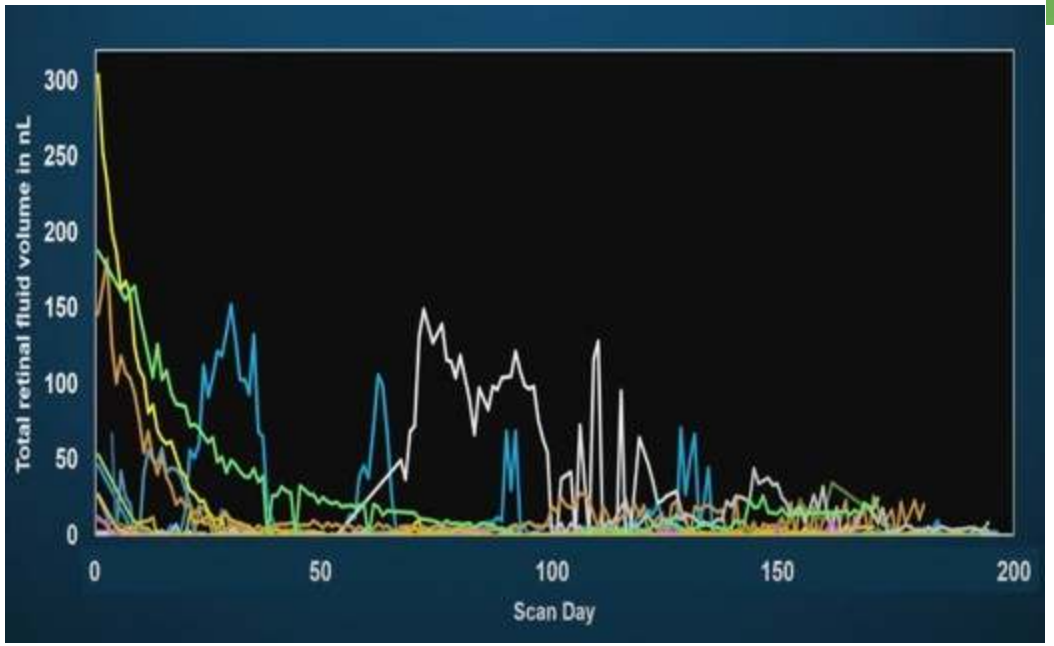
myVisionTrack 17+
F. Hoffmann-La Roche
★★★★★ 5.0 • 2 Ratings
Free

Patient daily self assessment hyperacuity testing and quantifying changes with physician electronic alert for potential progression of AMD

Hogg RE et al., **Home-Monitoring Vision Tests to Detect Active Neovascular Age-Related Macular Degeneration**. JAMA Ophthalmol 2024, 142:512-20

Home patient monitoring & Telemedicine

Home-based OCT

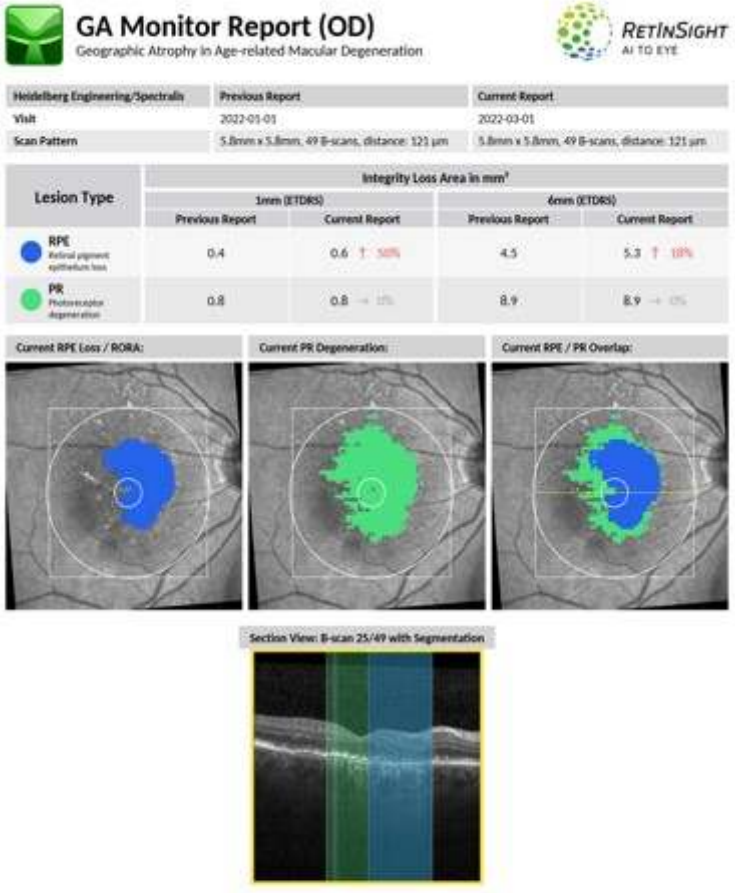


SCANLY®
HOME OCT Monitoring Program

- **Patient self OCT imaging assessment.**
- **Treatment can be tailored based on response and given before predicted activation with decrease of burden on health system.**

Oakley JD et al., **Quantitative Assessment of Automated Optical Coherence Tomography Image Analysis Using a Home-Based Device for Self-Monitoring Neovascular Age-Related Macular Degeneration**. Retina 2023, 43:433-43

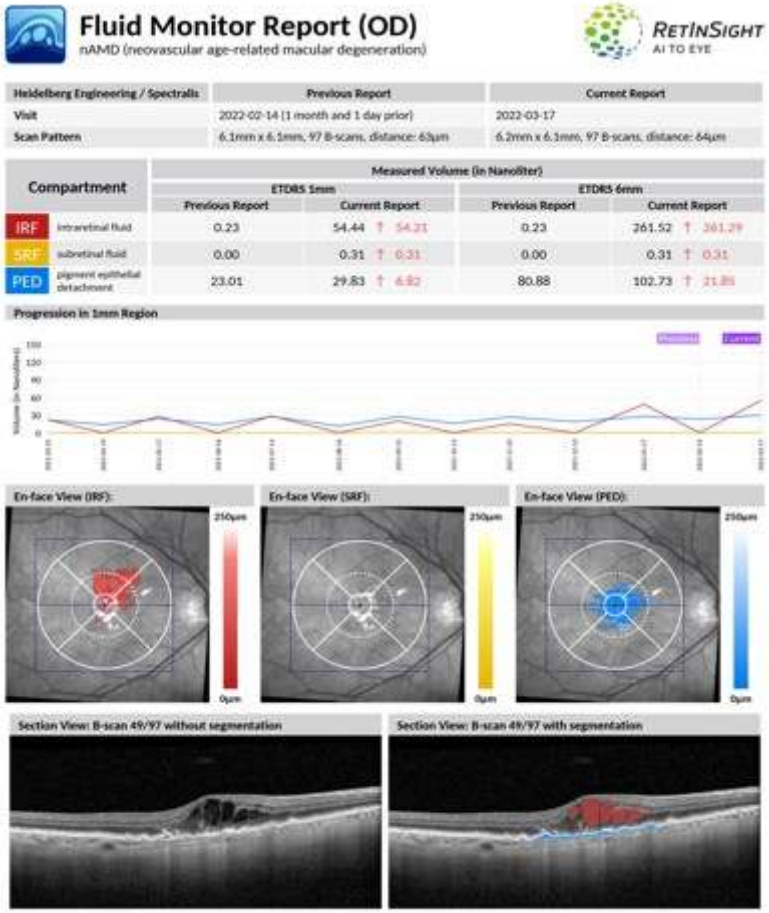
Artificial intelligence integration into Retinal Imaging



RETINSIGHT
AI TO EYE

New measurements

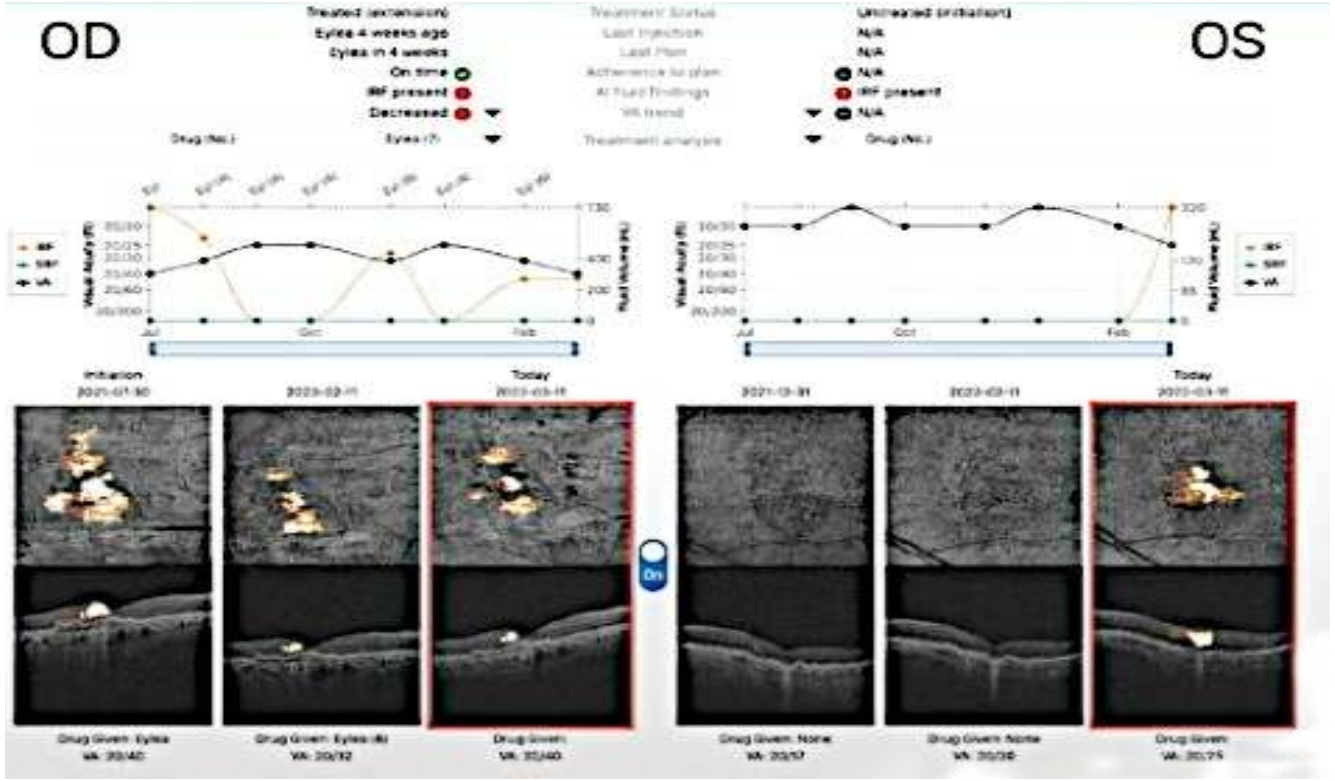
- Area of atrophy (mm2)
- Location & volume of fluid (nl)



Gerendas BS, et al., **VALIDATION OF AN AUTOMATED FLUID ALGORITHM ON REAL-WORLD DATA OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OVER FIVE YEARS**. RETINA 2022, 42:1673-82..

Artificial intelligence integration into Retinal Imaging

MACUJECT



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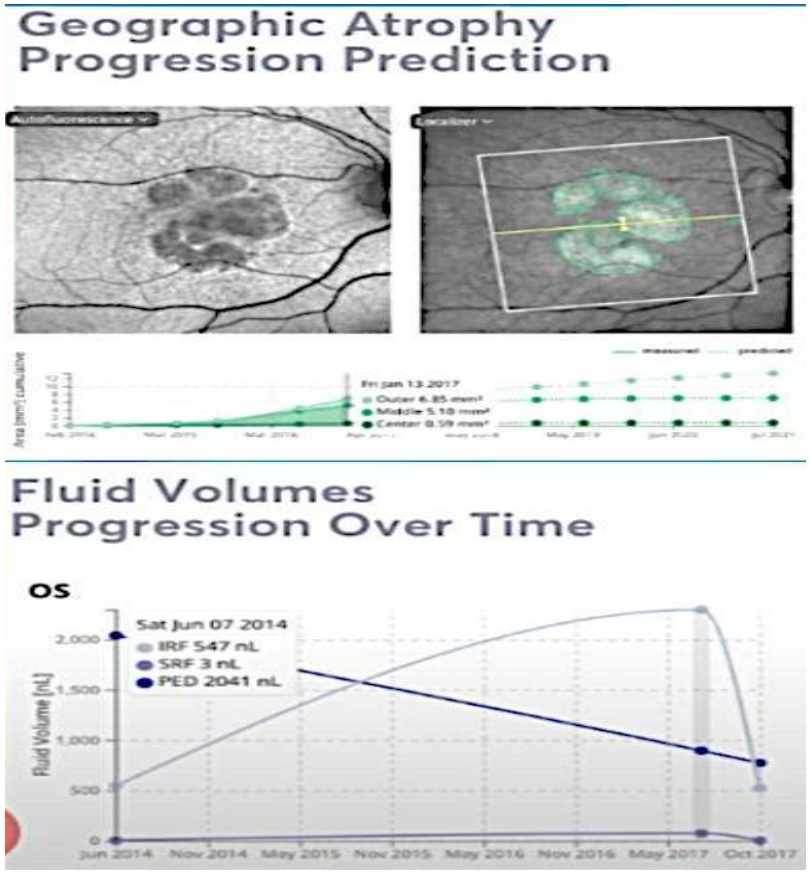


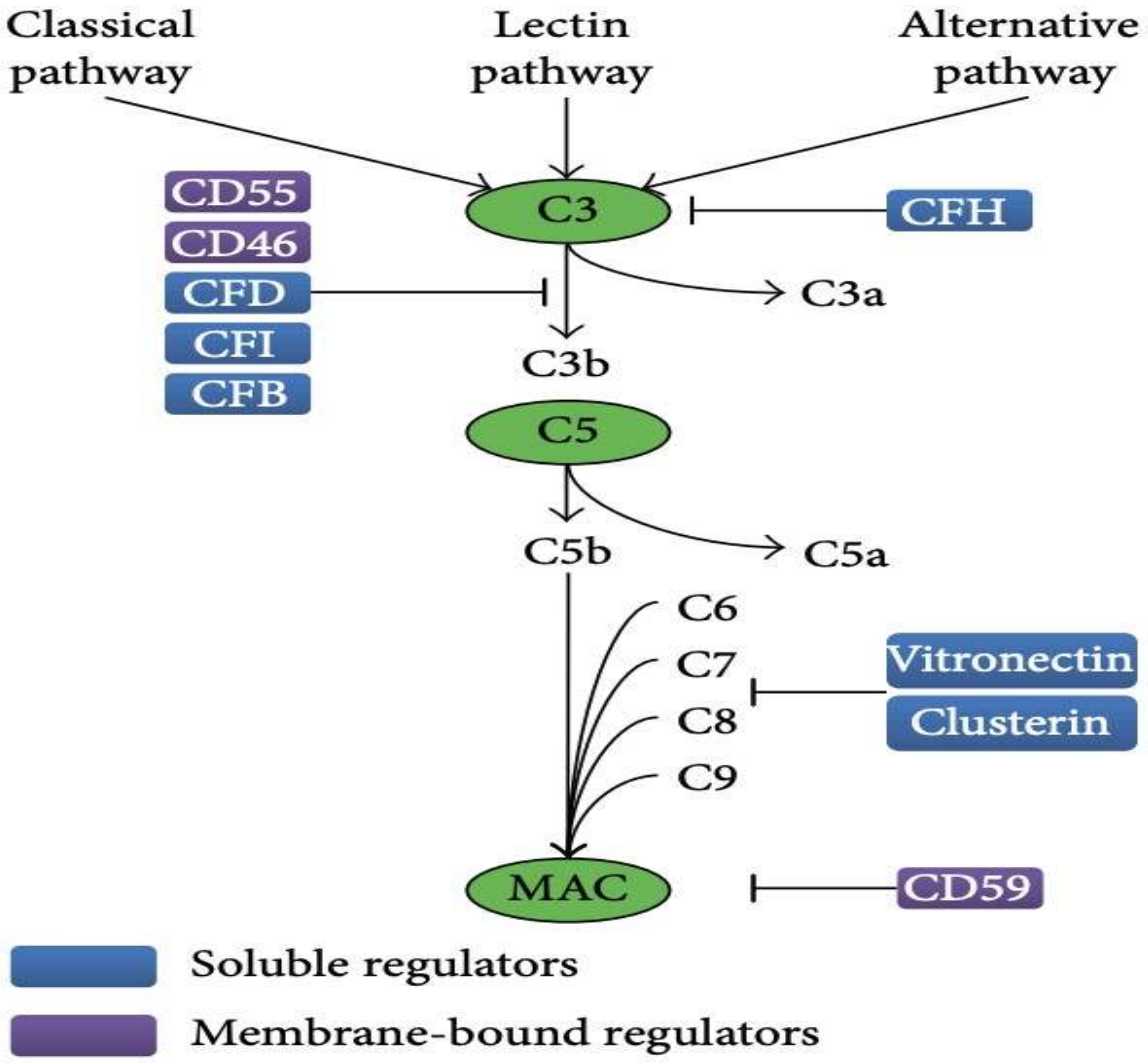
Gerendas BS, et al., **VALIDATION OF AN AUTOMATED FLUID ALGORITHM ON REAL-WORLD DATA OF NEOVASCULAR AGE-RELATED MACULAR DEGENERATION OVER FIVE YEARS**. RETINA 2022, 42:1673-82..

Dilemma 2: No Definitive Treatment

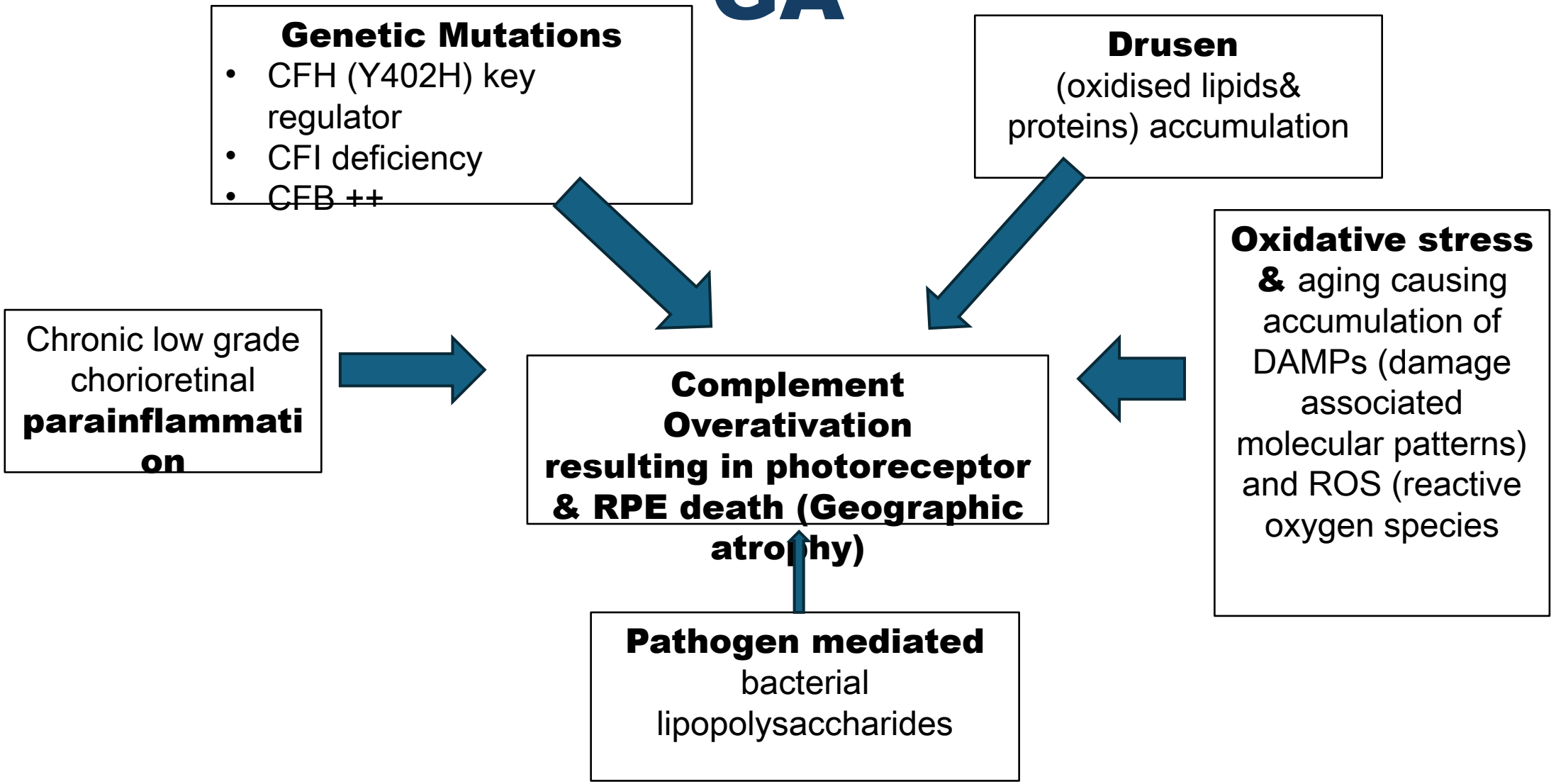
- AREDS2 supplements may slow progression.
- No approved treatment for GA.
- New therapies in development (e.g., complement inhibitors).

Role of complement system in GA

- The complement system is a group of **> 30 proteins** in the blood and tissues.
- It **helps the immune system** by marking pathogens, promoting inflammation, and clearing damaged cells.
- It is **overactive** in AMD resulting in RPE & photoreceptors phagocytosis
- Key players in activation pathway **C3 and C5**



Role of complement system in GA

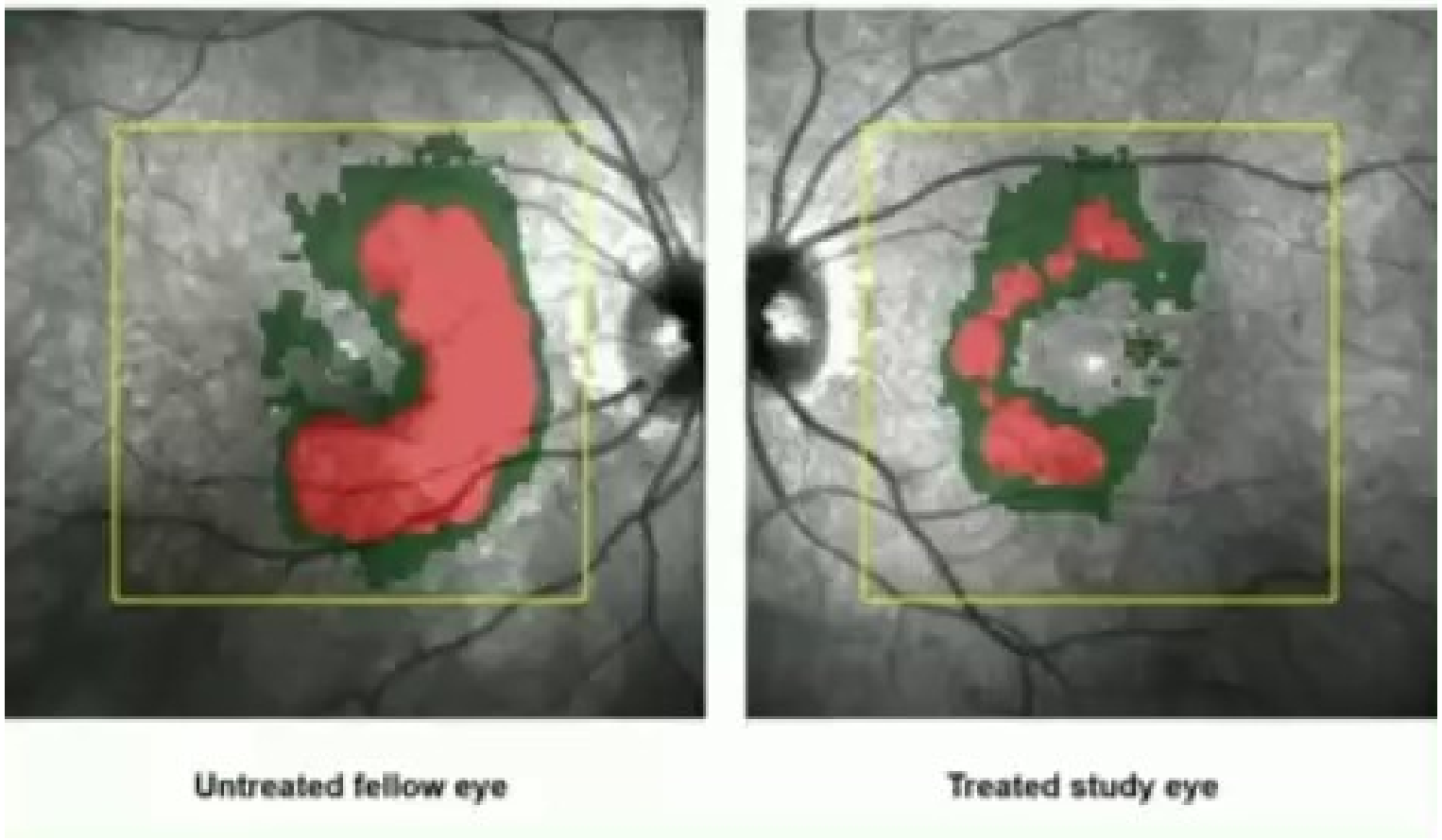


1. Pegcetacoplan (Syfovre, Apellis pharma, old name APL2)

DERBY & OAK and its extension GALE studies

- It is **C3 Inhibitor** (central key factor in three complement activation pathways)
- Resulting in **19-22% Reduction in growth of GA**
- Retrospective evaluation showed higher protection rate of phororeceptor atrophy
- FDA approved in **Feb 2023**

Progression of photoreceptor & RPE loss

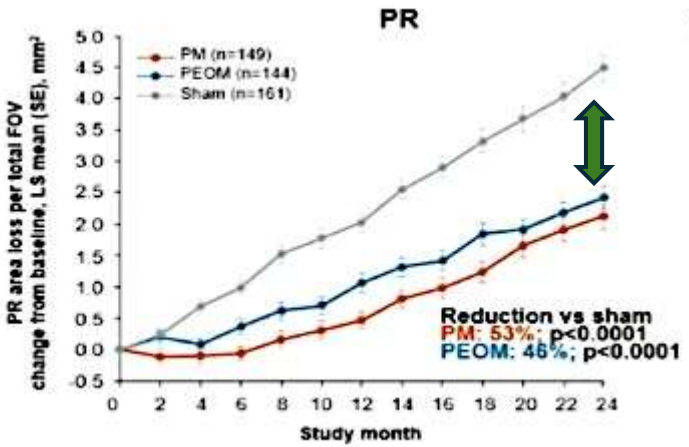


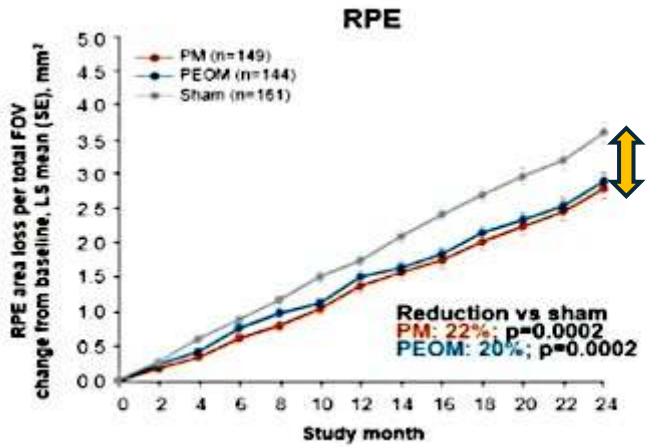
Heier JS et al., **Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials**. Lancet 2023, 402:1434-48

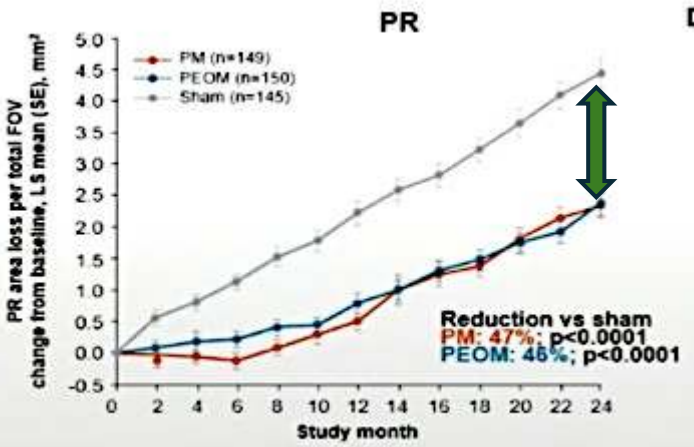
1. Pegcetacoplan (Syfovre, Apellis pharma, old name APL2)

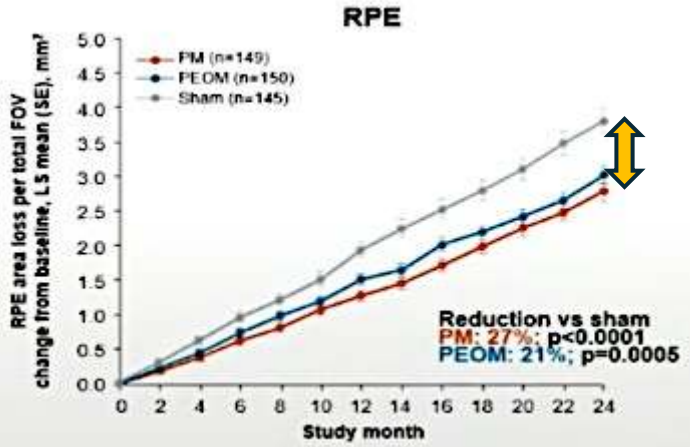
ERBY & OAK and its extension GALE studies

- Reduction in growth of GA **18-22% (DERBY study) & 16-18 % (OAKS study)**
- Retrospective evaluation showed higher protection rate of phororeceptor atrophy
- **No difference in visual function results**
- Dose **15 mg/0.1 ml**
- FDA approved in Feb 2023









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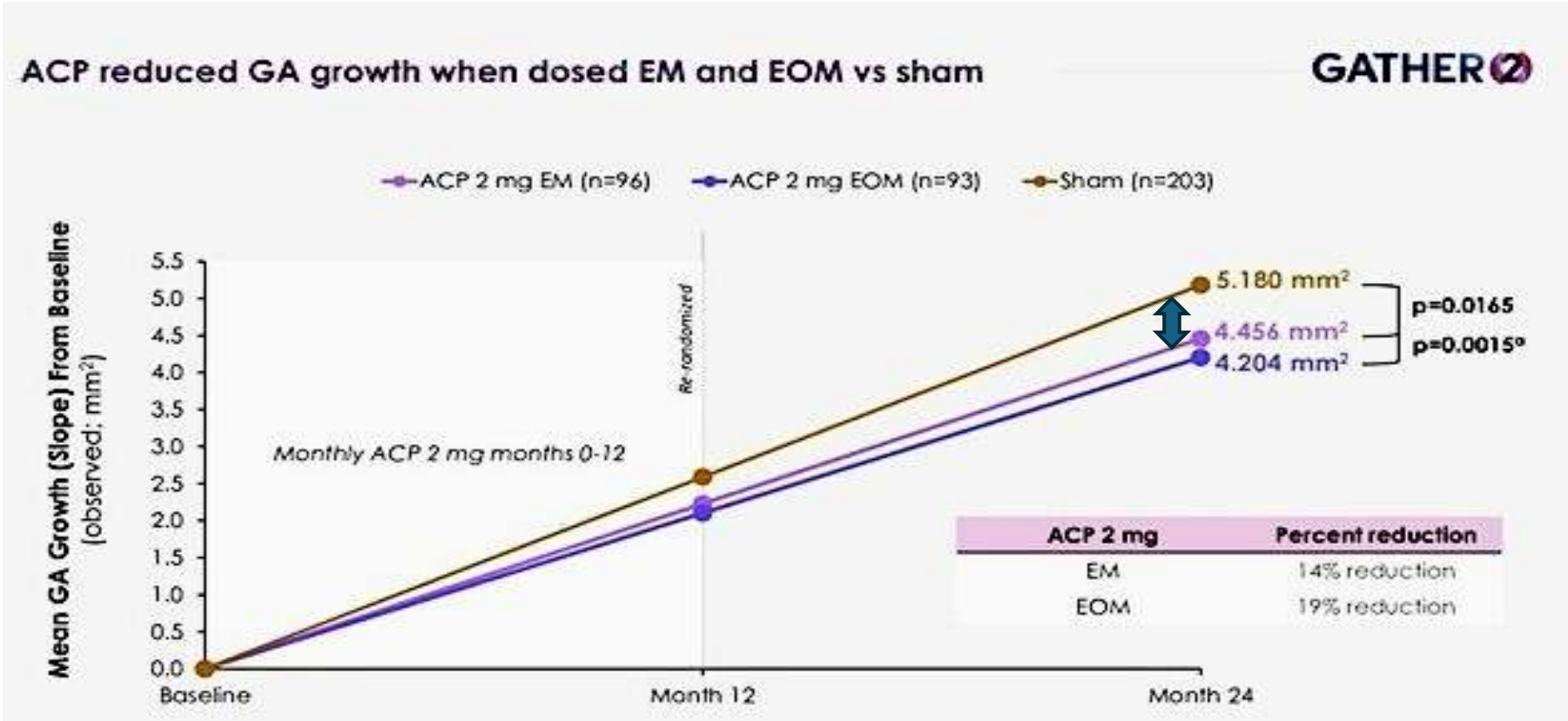
2. Avacincapted Pegol (Izervay, Astellas Pharma, old name Zimura)
GATHER 1 & 2 studies

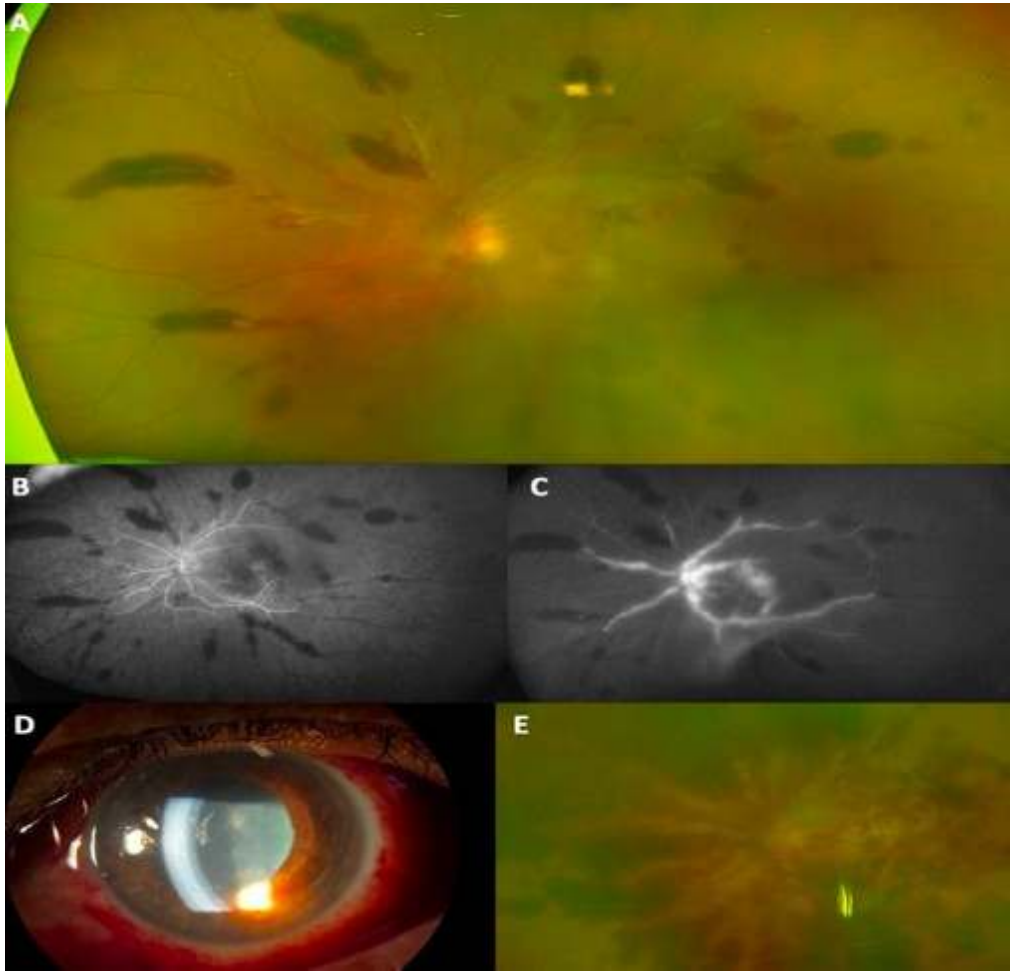
- It is a **C5 Inhibitor** (Terminal factor in MAC formation)
- Resulting in **14-19% Reduction** in growth of GA (though higher 4 mg dose showed better reduction in GATHER 1)
- **No difference in visual function results**
- Dose **2 mg/0.1 ml**
- FDA approved in Aug 2023



Khanani A et al., **Efficacy and safety of avacincaptad pegol in patients with geographic atrophy (GATHER2): 12-month results from a randomised, double-masked, phase 3 trial**. Lancet 2023, 402:1449-58.

Adverse events (Safety)
Pegcetacoplan (Syfovre) & Avcincapted pegol (Izervay)

- **Conversion to nAMD**
  - Syfovre--4-fold increase (12% PM, 7% EOM, 3% sham)
  - Izervay--2-fold increase (7% PM, 4% sham)
- **Introcular inflammation (IOI)**
  - Syfovre-- 4% PM, 2% EOM, 1% sham
  - Izervay—None
- **Ischemic optic neuropathy**
  - Syfovre-- 2% PM, 1% EOM, 0% sham
  - Izervay—None
- **Severe occlusive retinal vasculitis**
  - Only with Syfovre



Witkin AJ, Jaffe GJ, Srivastava SK, Davis JL, Kim JE: **Retinal Vasculitis After Intravitreal Pegcetacoplan: Report From the ASRS Research and Safety in Therapeutics (ReST) Committee**. J Vitreoretin Dis 2024, 8:9-20.

Dilemma 3: Emerging Therapies

- ·Pegcetacoplan and avacincaptad pegol target complement pathway.
- • Gene therapies under trial.
- • High cost and limited access remain barriers.

Genetics & AMD

Age-related macular degeneration (AMD) has a strong genetic component, with numerous genes implicated in its development

Class	Gene	Role
Complement system	**CFH* (1q32)**, C3, C2, CFB, CFI	Immune regulation, inflammation
Angiogenesis/oxidative stress	VEGFA, **ARMS2**, HTRA1*** (10q26)**	Neovascularization, oxidative damage
Lipid metabolism	APOE, LIPC, ABCA1	Lipid transport, drusen formation
Extracellular matrix	TIMP3, COL8A1, COL8A2	Structural integrity, matrix remodeling
Mitochondrial Function	SOD2, MT-ND2	Energy metabolism, oxidative stress
Immune/Inflammation	IL-8, CX3CR1	Pro-inflammatory pathways

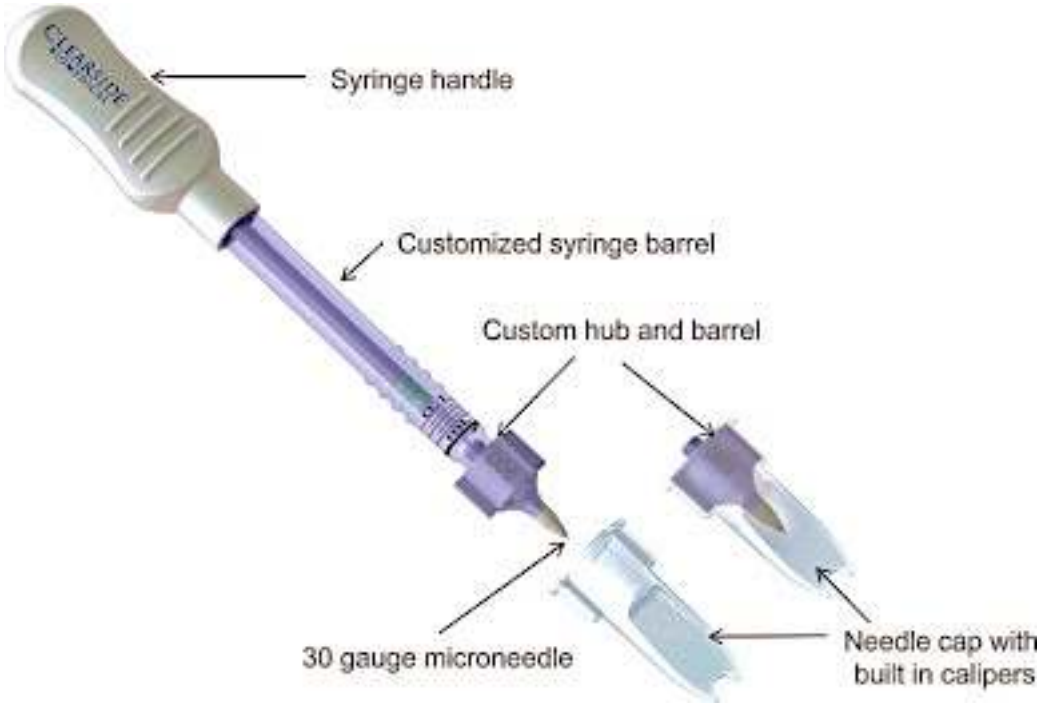
Methods of Gene therapy

- **Gene replacement** (RPE65 gene in Luxturna in RP & LHON)
- **Gene editing** (CRISPR-based therapies for sickle cell anemia)
- **Gene silencing** (small interfering RNA (siRNA) to block overexpression of harmful genes)
- **Introducing new Suicidal Gene** Killing of Diseased Cells (HSV-TK gene therapy for glioblastoma)
- **Enhancement of endogenous Protective Gene (CFI for AMD)**
- **Introducing a NEW therapeutic-protein producing gene (produces anti-VEGF)**

Gene therapy RGX-314 (REGENXBIO & AbbVie)

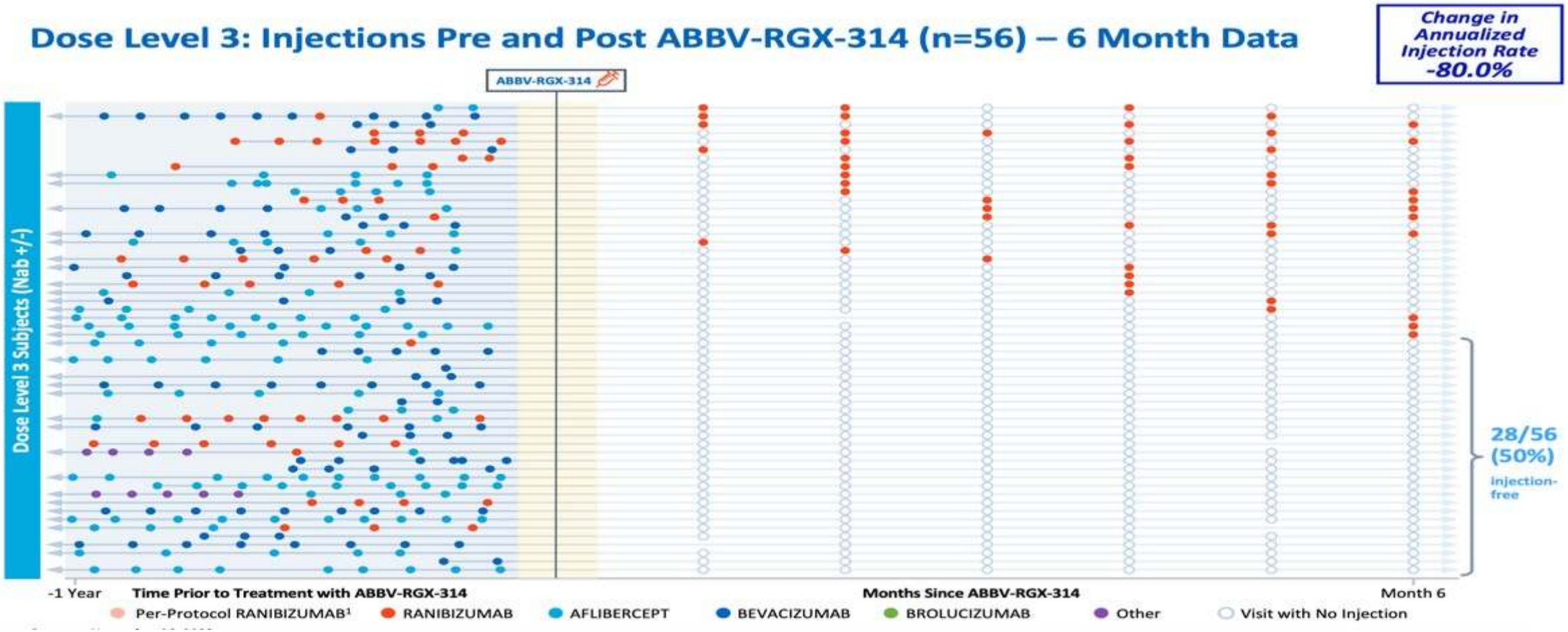
ATMOSPHERE and ASCENT trial

- **Adeno-Associated Virus** serotype 8 (AAV8) vector expressing a **ranibizumab like anti-VEGF Fab** as a one-time treatment.
- **Route:** Suprachoroidal (SCI-office based), Subretinal (SRI requires PPV surgery).
- **Phase 3 ATMOSPHERE and ASCENT trial** is ongoing for subretinal RGX-314



Suprachoroidal injector

Gene therapy RGX-314
(AAVIATE phase 1/2a study)



Campochiaro PA et al., **Gene therapy for neovascular age-related macular degeneration by subretinal delivery of RGX-314: a phase 1/2a dose-escalation study**. The Lancet 2024, 403:1563-73.

Stem cell therapy

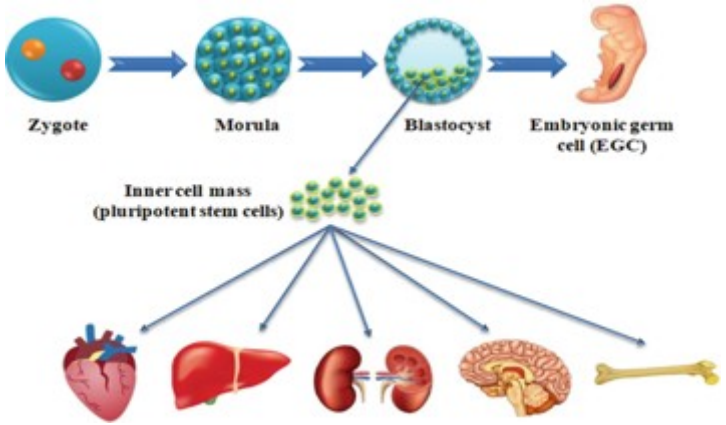
Stem cells Have the ability to differentiate & continuously divide

Used in

Drug testing (Biotechnology) and Tissue or organ replacement (Regenerative therapy)

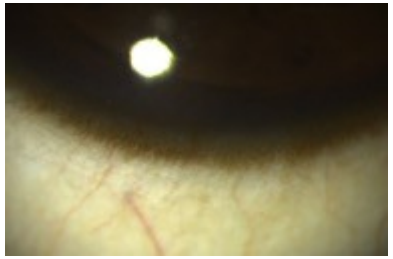
1

Embryonic Stem Cells



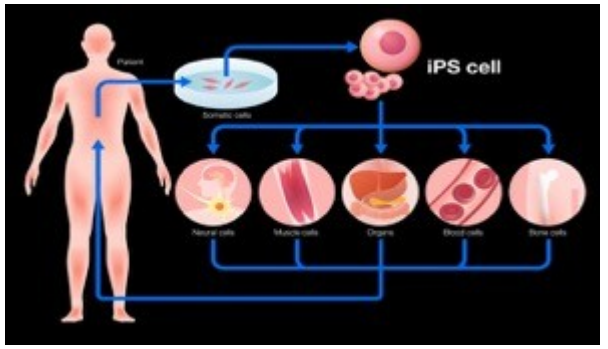
2

Adult Stem Cells (Autologous or Allogenic)



3

Induced Pluripotent Stem Cells (iPSC)



Nobel Winner 2012

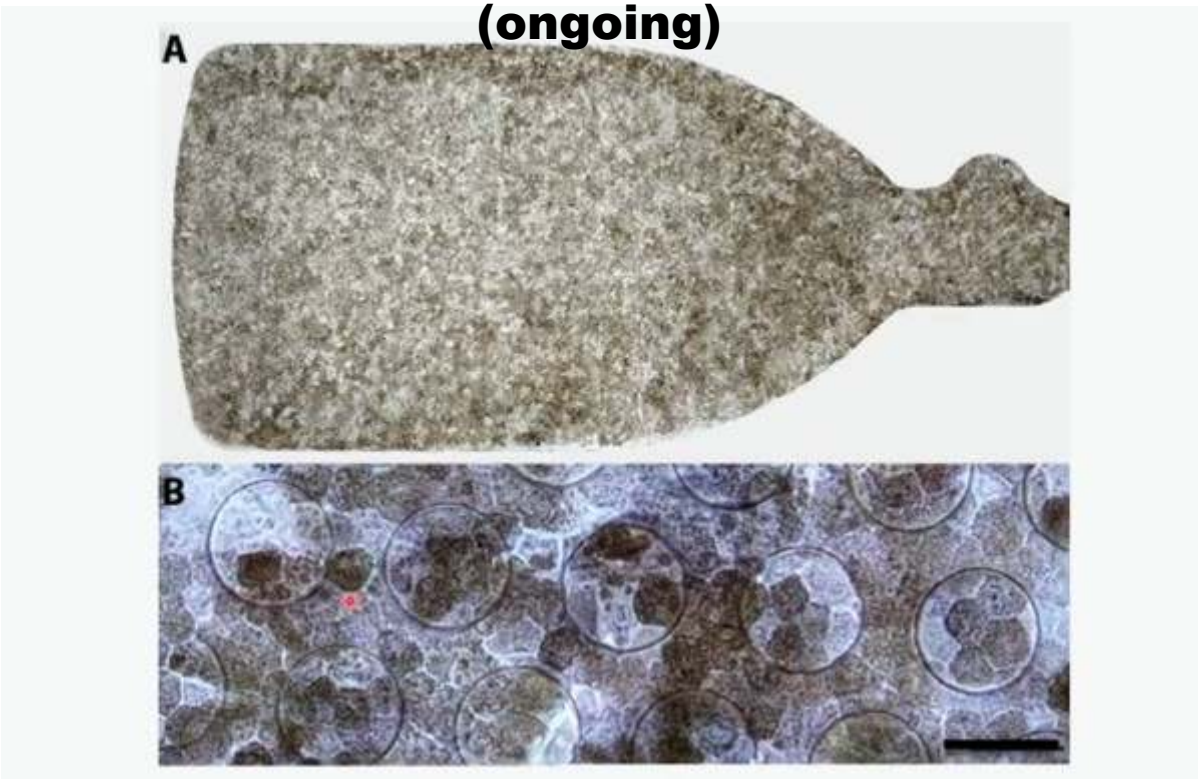
akahashi K, Tanabe K, Ohnuki M, Narita M, Ichisaka T, Tomoda K, Yamanaka S: **Induction of Pluripotent Stem Cells from Adult Human Fibroblasts by Defined Factors.** Cell 2007, 131:861-72.

Stem cell therapy

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Studies using intravitreal retinal progenitor cells in suspension (stopped)

Subretinal polarised RPE cultured cells on a biosheet implanted subretinally (ongoing)



Stem cell therapy

CIRM
CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE

Subretinal polarised RPE cultured cells on a biosheet implanted subretinally

Stem cell therapy
Success & Safety concerns

- **Several phase 1/2 trials are still underway that demonstrate visual gain**
- **<u>Concerns</u>**
  1. **Immue rejection**
     - **Many studies use immunosuppressives**
  2. **Oncogenicity brought by continuous division of cells**

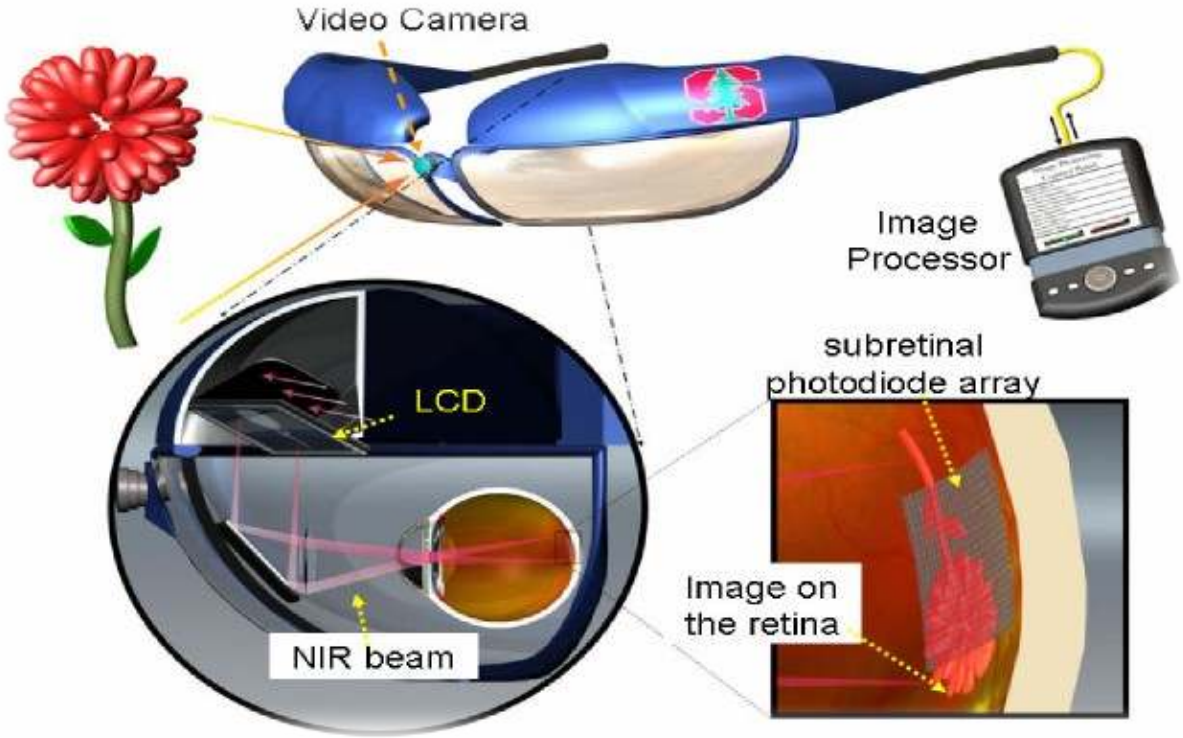
Table 1 Summary of recent completed and ongoing clinical trials involving transplantation of RPE in patients with diagnosed eye ailments

Patient population	Clinical trial ID (Status)	Sponsor	Implant details	Immunosuppression regimen	Adverse events	Outcomes
Dry AMD: 13 patients (age 70–88 years), BCVA ≤ 20/400 STGD: 13 patients (20–71 years), BCVA ≤ 20/400	NCT01345006, NCT01344993, NCT03178149, (Completed, phase 1/2, median 22-month follow-up)	Astellas Institute for Regenerative Medicine	Cell source: hESC (MA09) derived RPE, allogenic Form: cell suspension	Tacrolimus and mycophenolate started 1 week prior to surgery and 12 weeks post-surgery.	One eye developed endophthalmitis One eye developed vitreous inflammation that resolved in 6 months Three eyes developed preretinal patches, noncontractile Four eyes developed cataract One eye developed subretinal bleb	Dry AMD: median VA improved (14 letters versus 1 letter, $P = 0.0117$) STGD: trend toward improved VA in treated eye (12 letters versus 2 letter); no adverse proliferation
STGD: 12 patients (34–53 years), BCVA ≤ 20/400	NCT01469832 (Completed, phase 1/2)	Astellas Institute for Regenerative Medicine	Cell source: hESC (MA09) derived RPE, allogenic Form: cell suspension	Tacrolimus and mycophenolate	No adverse events reported	STGD: Borderline BCVA improvement
Dry AMD: 12 patients, BCVA 20/64 – 20/250	NCT05626114 (Recruiting, phase 2a)	Genentech, Inc.	Cell source: hESC (OpRegen) derived RPE, allogenic Form: cell suspension	No disclosure	No disclosure	At 1 year, improvement or maintenance in BCVA (+7.6 letters). Slower rates of RPE and ELM loss. The correlation between GA area changes and ELM loss was weaker in treated eyes.
nAMD: 2 patients (age 60 and 84 years) with VA on ETDRS chart (10 and 8)	NCT01691261 (Unknown status, phase 1, 4–12 months follow-up)	Moorfields Eye Hospital NHS Foundation Trust	Cell source: hESC (SHEF-1) derived RPE, allogenic Form: cell monolayer with PET membrane	Received, oral prednisolone and long-term intraocular steroid implants. Non-disclosed local drug	Exposure of the suture for fluocinolone implant in patient 1 Worsening of diabetes in patient 2 PVR with tractional membranes in patient 2	Patient 1 and Patient 2 had 29- and 21-letter improvements respectively RPE cell migration off the patch
Dry AMD: 16 patients (age 69–85 years) with cohort 1: BCVA ≤ 20/200, cohort 2: 20/80 to 20/400	NCT02590692 (Unknow status, phase 1/2a, 3-year median follow-up)	Regenerative Patch Technologies, LLC	Cell source: hESC (H9) derived RPE, allogenic Form: cell monolayer with parylene C substrate	Tacrolimus started 8 days before surgery, continued to day 42, and gradually reduced until day 60	One patient could not be transplanted Patients in cohort 1 had subretinal haemorrhage, retinal or macular edema, focal retinal detachment, or RPE detachment, which was mitigated in cohort 2 with an improved haemostasis during surgery	Implanted eyes improved by > 5 letters BCVA throughout median 3-year follow-up Safe and well-tolerant in all patients 3 patients had fixation detected over the transplant in cohort 1
One nAMD patient (77 years) with BCVA 20/200 right eye	UMIN000011929 (Completed, 4-year follow-up)	RIKEN	Cell source: iPSC derived RPE, autologous Form: cell sheet	No immunosuppressants	No adverse events	At the 4-year follow-up, the transplanted RPE survived under the retina with slight pigment expansion. No evidence of leakage or recurrence of hemorrhage BCVA remained stable at 20/200
RPE-impaired disease: estimated 50 patients (age > 20 years), VA < 0.3	jRCTa050210178 (Recruiting)	Kobe City Eye Hospital	Cell source: iPSC derived RPE, allogenic Form: cell strip	No disclosure	No disclosure	Reduction of window defect area (RPE abnormal lesion) by engraftment of transplanted allogeneic iPSC-derived RPE cells
RP (due to monogenic mutation): ~12 patients with VA ≤ 20/200 or 20/63–20/200. (age 18–65 years)	NCT03963154 (Active, not recruiting, Phase 1/2)	Centre d'Etude des Cellules Souches	Cell source: hESC (RC-9) derived RPE, allogenic Form: cell monolayer with hAM scaffold	No disclosure	No major adverse events disclosed	7 patients were transplanted so far where nystagmus stabilization and fixation observed in some.
Dry AMD: estimated 20 patients (age 55–95 years), BCVA: 20/100 - CF	NCT04339764 (Recruiting, phase 1/2a)	National Eye Institute (NEI)	Cell source: iPSC derived RPE, autologous Form: cell monolayer with PLGA scaffold	Will receive, no disclosure on specific drug usage	No disclosure	No disclosure

Retinal Prostheses

A system consists of a glass-mounted camera and an external image processor connected through a telemetric link to an intraocular electrode array

This implant restored the ability to detect motion and to discriminate common household objects



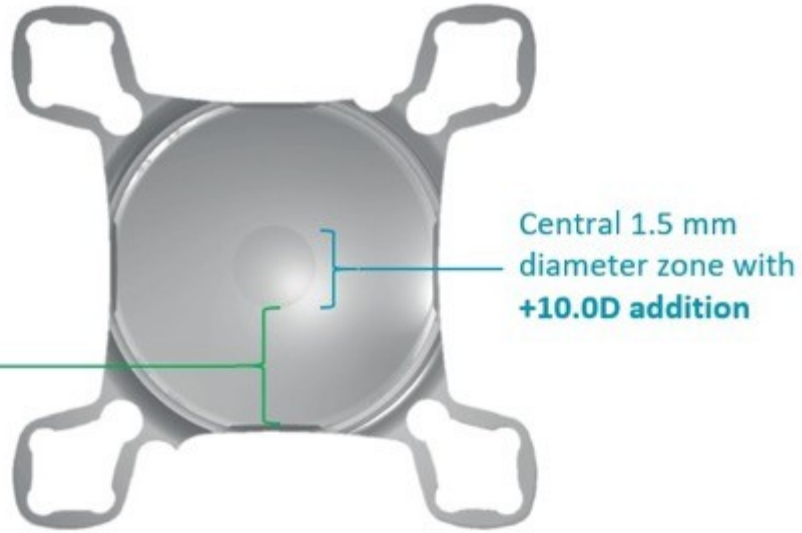
Intraocular lenses for Advanced AMD

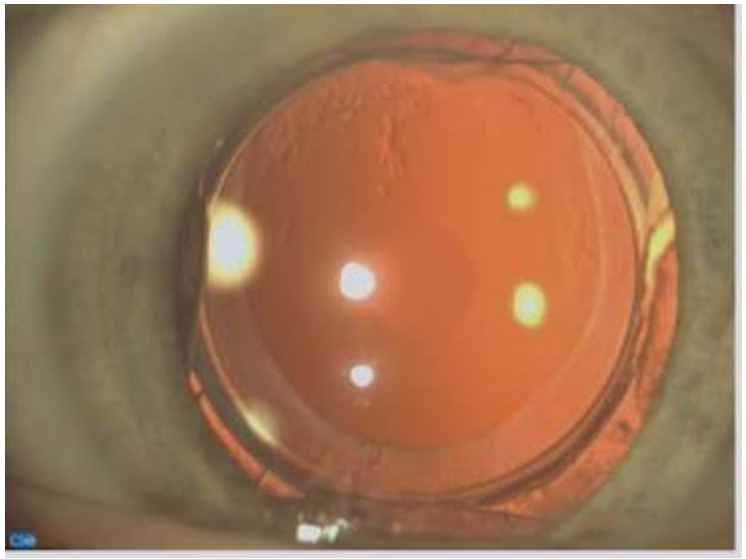
Sharioth Add on macula lens (SML)

MEDICENTUR

Piggyback ciliary sulcus lens

Bifocal design:



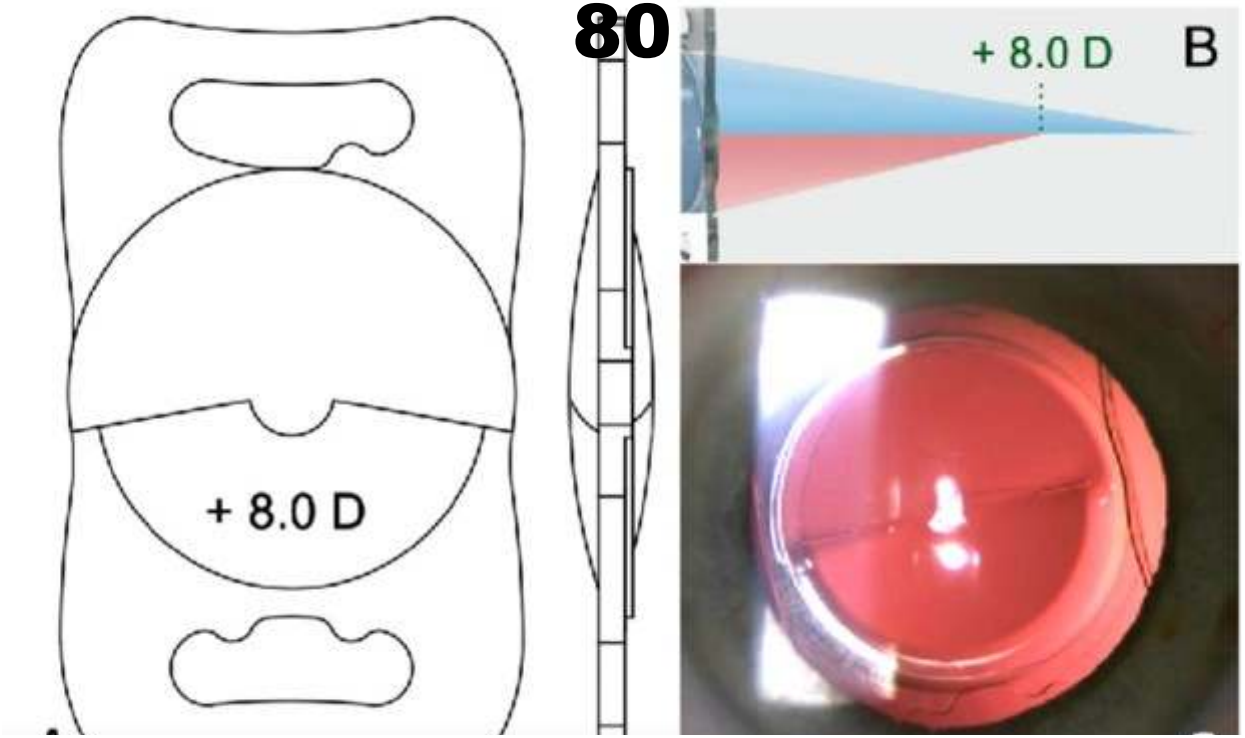


Srinivasan S, Scharioth G, Riehl A, Tanev IV, Rozsival P, Acker EV, Nagy ZZ, Balta F, Nekolova J: **Implantation of Scharioth macula lens in patients with age-related macular degeneration: results of a prospective European multicentre clinical trial**. BMJ Open Ophthalmol 2019, 4:e000322.

Intraocular lenses for Advanced AMD

Oculentis bifocal +8 D

Lentimax LS313-MF 80



Auffarth GU, Reiter J, Leitritz M, Bartz-Schmidt KU, Höhn F, Breyer D, Kaymak H, Rohrschneider K, Khoramnia R, Yildirim TM: **High-addition segmented refractive bifocal intraocular lens in inactive age-related macular degeneration: A multicenter pilot study**. PLoS One 2021, 16:e0256985.

Intraocular lenses for Advanced AMD

SING-Implantable Miniatute Telescopic lenses
Concerto study

SAMSARA VISION

11 - 12 mm incision

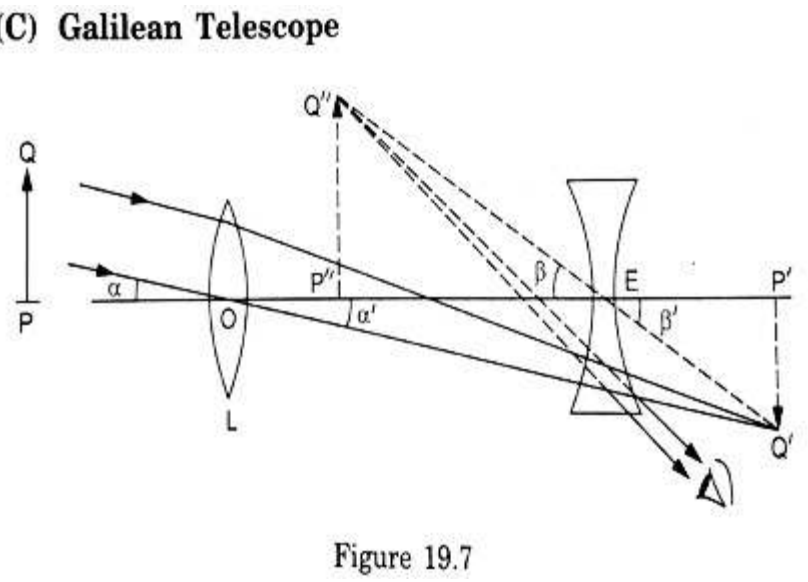


Figure 19.7

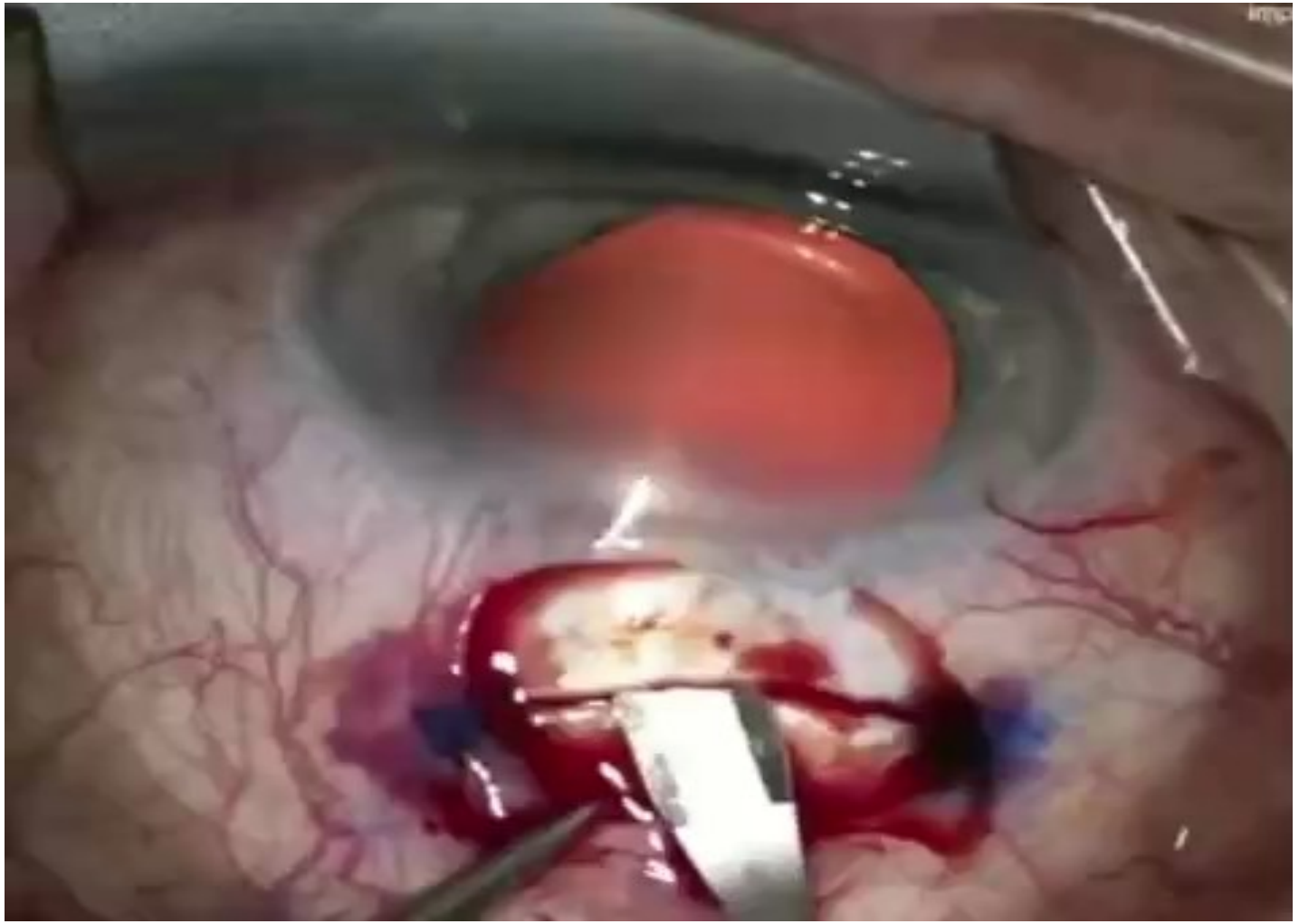
7 - 8 mm incision

Sasso P, Savastano A, Vidal-Aroca F, Minnella AM, Francione G, Sammarco L, Cima V, Ghiraldelli R, Mattei R, Rizzo S: **Enhancing the Functional Performance of Patients with Late-Stage Age-Related Macular Degeneration Implanted with a Miniature Telescope using Rehabilitation Training**. Ophthalmol Ther 2024, 13:697-707.

SING-Implantable Miniatute Telescopic lenses

Concerto study

SAMSARA VISION



Summary

- Non Neovascular AMD is a global leading cause of vision loss with high economic burden.
- With numerous advances, new management innovations are genuinely revolutionary.
- Anti-Complement drugs may carry hope for slowing or reversing vision loss.
- Genetic profiling, gene therapy and stem cell-based therapy are future pipelines for treatment.


Thank You