

Hot topics in retina!

- Steven Ferrucci OD
 - Chief, optometry Sepulveda VA
 - Professor, SCCO
- Mark Dunbar, OD, FAAO
 - Bascom palmer Eye Institute

1

Disclosures: Ferrucci

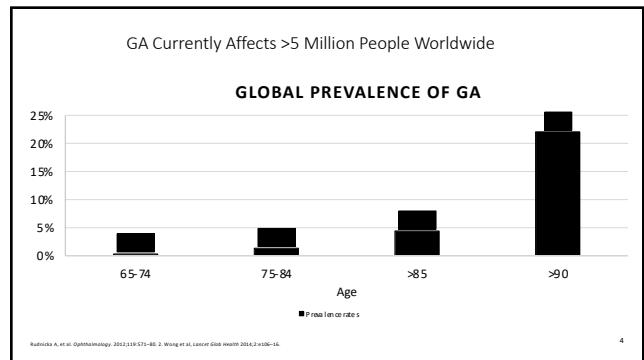
- I serve on the speaker bureau or advisory board for the following companies
 - Apellis
 - Astellas
 - B&L
 - I-care
 - LENS Therapeutics
 - LKC Technologies
 - Notal vision Science Based Health
 - Visible Genomics
- All relevant relationships have been mitigated

2

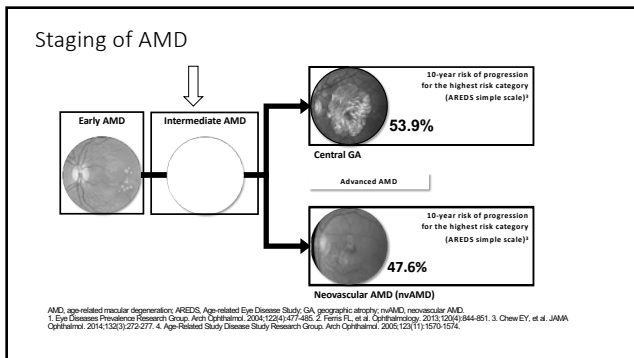
Disclosures : Dunbar

- Orasis
- Tarsus
- Astellas
- Sun pharma
- Visus
- Topcon
- apellis
- Thea
- Glaukos
- Sight sciences
- B&I
- Azura
- Sydnexis
- Cloudbreak
- tenpoint

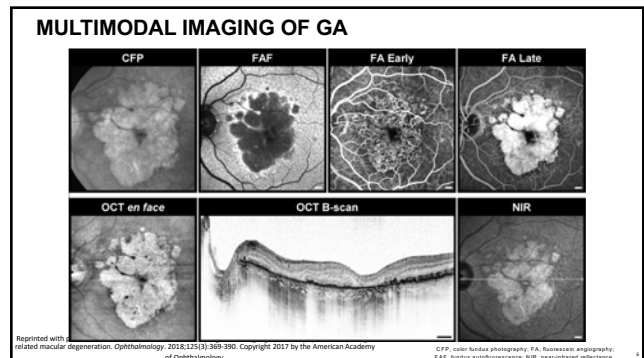
3



4



5



6

GA IMAGING- COLOR FUNDUS PHOTOGRAPHY (CFP)

- A sharply demarcated, usually circular zone of partial or complete RPE depigmentation, typically with exposure of underlying large choroidal blood vessels
- **Less sensitive in detecting early GA** and NOT an ideal way track enlargement over time

7

GA IMAGING - FUNDUS AUTOFLUORESCENCE (FAF)
ONE OF THE PRIMARY METHODS USED TO DETECT & MONITOR GA LESIONS (SUPERIOR FOR EARLY GA DETECTION COMPARED TO CFP)!!!

Fundus Autofluorescence

GA = well-demarcated hypofluorescent or dark areas

8

GA IMAGING - FUNDUS AUTOFLUORESCENCE (FAF)
ONE OF THE PRIMARY METHODS USED TO DETECT, MONITOR, AND QUANTIFY GA LESIONS!!!

9

GA IMAGING - OCT ANGIOGRAPHY (OCTA) IMAGING OF GA

Highlights loss of the choriocapillaris!!! (allows for visualization of the deep/larger choroidal vessels)

Angiography 6x8 mm

10

Geographic Atrophy Features on OCT

Zone of RPE loss/attenuation & overlying PR degeneration $\geq 250\mu\text{m}$ in diameter

hyper-transmission

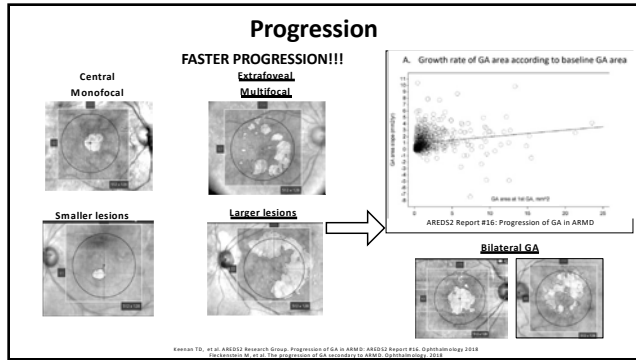
11

OCT En-Face ANALYSIS (Sub-RPE Slab) - GA

GA area enlarges over time

Distance to center of fovea

12



13

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

Review Article

OCT Biomarkers in Neovascular Age-Related Macular Degeneration: A Narrative Review

Cristian Motroșanu^{1,2}, Simone D'Amico^{1,2}, Marco Marzella^{1,2}, Ludiana Fontana^{1,2}, Walter Medina^{1,2}, Giulia D'Alonzo^{1,2}, Maria Robino^{1,2}, Paolo Radice^{1,2}, Elise Frezza^{1,2} and Claudio Amadiè^{1,2}

¹Specialized Eye Hospital of Gerardo of Fondazione IRCCS, 20127 Sesto San Giovanni, Milan, Italy; ²Department of Medicine and Surgery, University of Insubria, Varese, Italy; ³Department of Ophthalmology, University of Padua, Padua, Italy

Review

Retinal Progression Biomarkers of Early and Intermediate Age-Related Macular Degeneration

Rita Flores^{1,2,3}, Angela Casarini¹, Sandra Tassone^{1,2} and Miguel C. Saubá^{1,4}

14

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

- Drusen volume
- Increased drusen height
- Disappearance of drusen

Advanced RPE Analysis : Macular Cube 200x200

OD OS

Prior Visit

Current Visit

RPE Elevation Map

15

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

- Hyper-Reflective Foci (HRF)
- Reticular pseudo drusen
- Hyper-transmission defects

- Hyper-Reflective Foci (HRF)
- Reticular pseudo drusen
- Hyper-transmission defects

doi:10.1371/journal.pone.0201054

16

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

Hyper-Reflective Foci (HRF)

- Extracellular pigment granules and outer segment debris (outer HRF)
- May also represent displacement and clumping of degenerated RPE cells
- AREDS2 study: Patients with HRF had 5 X increased risk of progression to GA at 2 years vs. controls

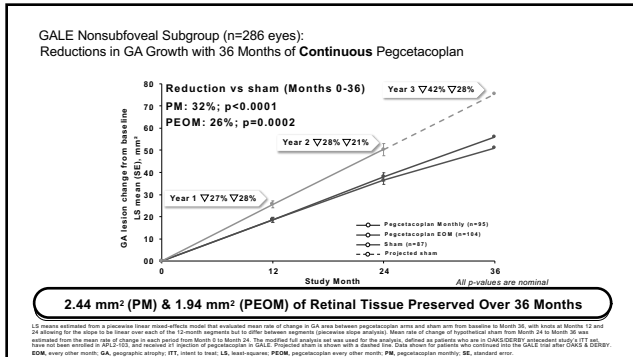
17

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

Geographic atrophy

- Lesions grow with time, at various rates
 - Larger lesions, multi-focal lesions, extrafoveal lesions grow faster
- Treatment geared at decrease in lesion growth
- Growth associated with over-activation of complement system
 - Various targets being investigated: C3, C5

18

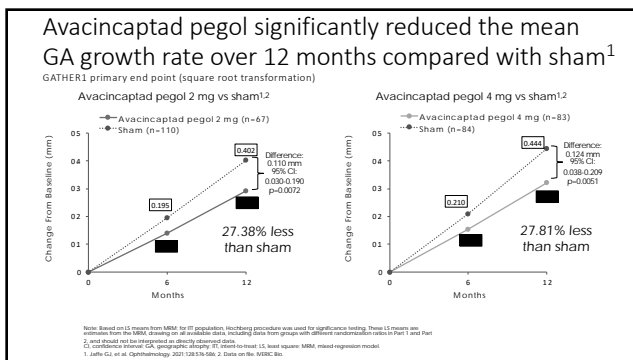


25

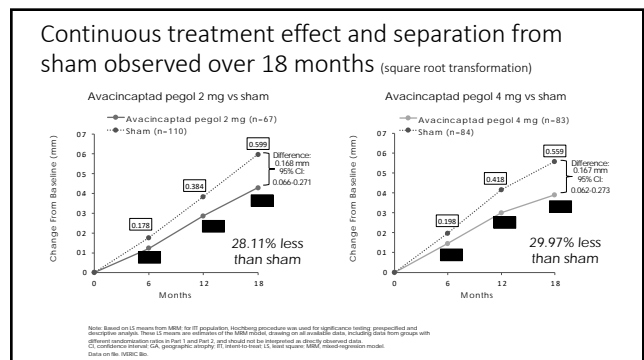
Izervay™

- Avacincaptad pegol (ACP)
- FDA approved August 5, 2023
- Approved for the treatment of GA secondary to AMD
- 2 mg monthly injections

26



27



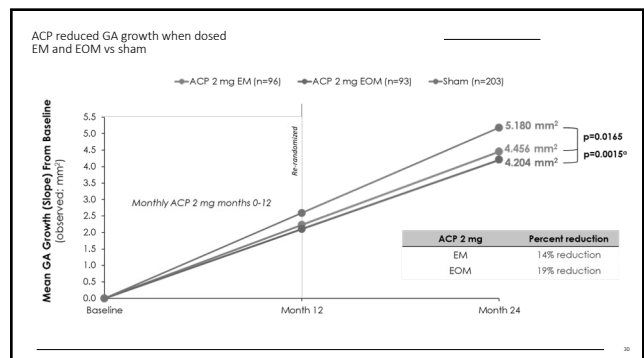
28

Ocular TEAEs ≥2% in study eye

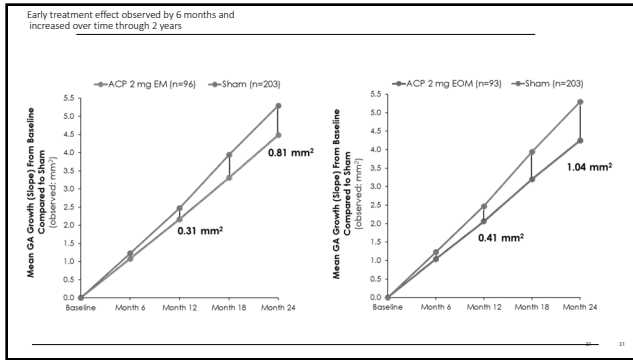
Ocular TEAEs, n (%)	12 Months ^{1,2,a}		12 Months ²	
	ACP 2 mg (n=97)	Sham (n=101)	ACP 2 mg (n=222)	Sham (n=222)
Conjunctival hemorrhage	10 (14.9)	13 (11.8)	27 (12.0)	17 (7.7)
Punctate keratitis	4 (6.0)	8 (7.3)	11 (4.9)	14 (6.3)
Conjunctival hyperemia	3 (4.5)	4 (3.6)	12 (5.3)	13 (5.9)
Chorioidal neovascularization	4 (7.0)	3 (2.7)	15 (6.7)	9 (4.1)
Dry eye	0	2 (1.8)	8 (3.6)	8 (3.6)
Eye pain	2 (3.0)	3 (2.7)	9 (4.0)	6 (2.7)
Vitreous detachment	2 (3.0)	5 (4.5)	7 (3.1)	6 (2.7)
Visual acuity reduced	2 (3.0)	4 (3.6)	3 (1.3)	5 (2.3)
Vision blurred	1 (1.5)	2 (1.8)	6 (2.7)	2 (0.9)
Visual impairment	0	0	6 (2.7)	2 (0.9)
Intraocular pressure increased	4 (6.0)	1 (0.9)	21 (9.3)	2 (0.9)
Vitreous floaters	1 (1.5)	1 (0.9)	6 (2.7)	1 (0.5)
Visual acuity reduced transiently	—	—	6 (2.7)	1 (0.5)
Blepharitis	0	1 (0.9)	6 (2.7)	0
Ocular hypertension	—	—	5 (2.2)	0

29

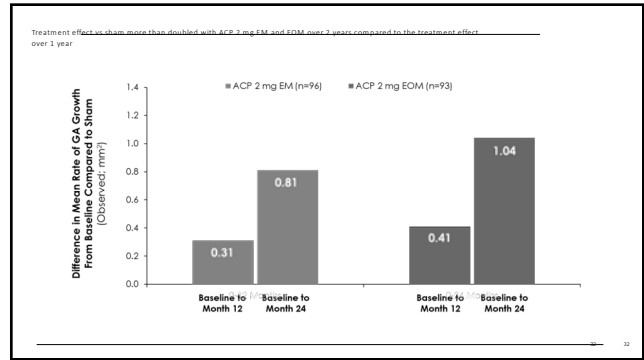
29



30



31



32

When to Refer?

- Any GA that is **threatening** central visual function
- Any GA that encroaching the fovea
- Large extrafoveal lesions
- Lesions showing progression

Progression to subfoveal involvement 18 mo

33

When NOT to Refer?

- Extrafoveal lesions that are not a threat to central Va
- Central GA lesions that have already have sig loss of visual function

34

Valeda® Light Delivery System

Valeda Overview

- Valeda treatment delivery very similar to many ophthalmology office diagnostic and treatment devices
- Implementation support available from LumiThera Customer Success Team
- Treatment is simple to learn and easy to train for operators
- No pupil dilation required
- Nine (9) flexible treatment sessions delivered over 3-4 weeks
- 2-3 treatment cycles per annum

35

Photobiomodulation (PBM) Approach

PBM uses low-level light to stimulate cells to restore energy production and improve cellular health

Valeda Wavelengths (nm)	Cellular Targets	Secondary Effects
590	Stimulates CCO activity, increases nitric oxide (NO) synthesis, inhibits VEGF expression	Vasodilation, Improves local O ₂ and nutrient delivery, VEGF reduction
660	Promotes O ₂ binding to CCO active Cus/Fe ₂ site	Upregulates Electron Transport Pathway, Increases energy (ATP), Reduces inflammation and cell death
850	Drives electron transfer at Cus site of CCO	Upregulates Electron Transport Pathway, Increases energy (ATP), Reduces inflammation and cell death

Valeda wavelengths were selected based on their cellular targets and importance in AMD

Wong-Riley MTT, et al. J Biol Chem. 2005; 280: 4761-71.
Ball SA, et al. J Photochem Photobiol B Biol. 2012; 100: 182-91.

36

FDA Authorizes Breakthrough Valeda Therapeutic for Dry AMD to Improve Vision (November 04, 2024)

Valeda Light Delivery System

- Five successful clinical studies
- US LIGHTSITE III pivotal trial data met BCVA primary endpoint
- Data from two-year LIGHTSITE III trial used to support Valeda FDA submission
- First FDA authorized therapy for Dry AMD Patients to improve vision
- CE marked: Available in Europe and other countries
- Non-invasive, safe therapy for patients

37

First FDA treatment for Dry AMD Patients to Improve Vision

Indications for Use:

The Valeda Light Delivery System is intended to provide improved visual acuity in patients with best corrected visual acuity (BCVA) of 20/32 through 20/70 and who have dry age-related macular degeneration (AMD) characterized by:

- The presence of at least 3 medium drusen (> 63 µm and 125 µm in diameter), or large drusen (> 125 µm in diameter), or non-central geographic atrophy, AND
- The absence of neovascular maculopathy or center-involving geographic atrophy

After about two years, the Valeda Light Delivery System treatment provides improved mean visual acuity of approximately one line of visual acuity (ETDRS) compared to those not receiving the treatment.

38

LIGHTSITE III: Safety Summary

- Similar frequencies of adverse events (AE) (Sham, 25.5%; PBM, 25.8%) and ocular-specific AEs (Sham, 20.0%; PBM, 22.6%) observed between treatment groups
- Three subjects had ocular-specific AEs considered related to the procedure: punctate keratitis (Sham; n = 2; 3.6%), visual perseveration (after image) (Sham; n = 1; 1.8%), and application site warmth (PBM; n = 1; 1.1%). No ocular-specific AEs led to study discontinuation.
- Seven (7.5%) ocular-specific serious adverse events (SAE) of nAMD were reported in the PBM group and three (5.5%) ocular-specific SAEs (2 nAMD, 1 cystoid macular edema) were reported in the Sham group. No SAEs were considered associated to the treatment by the primary investigator.
- Severity of AEs reported were mostly mild/moderate in both treatment groups
- No signs of phototoxicity
- No adverse effect on color vision or perimetry

39

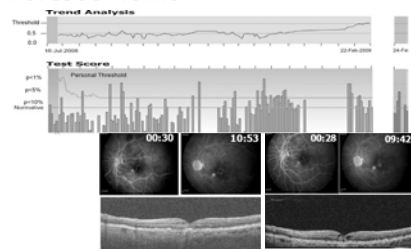
LIGHTSITE III: Study Summary

LIGHTSITE III study results show significant effect on clinical and anatomical outcomes that support vision improvement and disease modifying effects

- LIGHTSITE III met the primary efficacy endpoint with a statistically significant improvement in BCVA in the PBM versus the Sham group
- Eyes with worse BCVA at baseline showed larger magnitude gains in BCVA
- Increased rate of > 5, 10, and 15 letter BCVA gains following PBM compared to BCVA loss in the Sham group
- Cox proportional analyses showed a significant reduction in the hazard ratios for BCVA vision loss and incident GA in PBM vs Sham treatment groups
- Reduced occurrence of incident GA and other exploratory markers of disease progression
- Reduced macular drusen volume
- Improved QoL in VFQ-25 Composite score and select subscales
- A favorable safety profile was observed with no signs of phototoxicity and no deterioration in other visual outcomes, including contrast sensitivity, low luminance BCVA, Radner reading, perimetry, or color vision observed

40

Foresee Home



41

At-risk Patients May Convert to Wet AMD at Any Point Between Follow-up Visits



Reference: Raach R, et al. Retina. 2012;32(7):1040-1044

42

42

Amsler grid alone has limited ability to detect visual changes

- Accurately taking the test^{1,2}
 - Fixation
 - Testing distance
 - Test questions
 - Compliance
- Cortical completion¹
- Low sensitivity; subjectivity exam to exam, patient to patient¹

References: 1. Mitchell S, Scolding S. Ophthalmol Res. 2015;5(1):26-30. 2. Hsu H, et al. Arch Ophthalmol. 2007;125(3):373-3. 3. Lu Y, et al. JAMA Ophthalmol. 2011;129(2):255-260. 4. Wang Y, et al. Ophthalmology. 2008;115(1):116-20.

43

AREDS2-HOME Study

ForeseeHome plus standard care arm	Intent to Treat (ITT) population results	Standard care arm
763 participants	1520 participants	757 participants
51 CNV events	Mean follow up 1.4 yr ± 0.6 years Mean VA at entry 20/25	31 CNV events
<ul style="list-style-type: none"> Routine monitoring Patient symptoms ForeseeHome 		<ul style="list-style-type: none"> Routine monitoring Patient symptoms

***Primary outcome:** Change in BCVA from baseline to CNV detection

Reference: AREDS2-HOME Study Research Group. Ophthalmology. 2014;123(2):335-344.

44

ForeseeHome Arm

Intent to Treat (ITT)

Per Protocol 1 (PP1) | Per Protocol 2 (PP2)

at least 1 test throughout the study

≥ 2x per week (8x per month)

Reference: AREDS2-HOME Study Research Group. Ophthalmology. 2014;123(2):335-344.

45

More patients who used ForeseeHome maintained ≥20/40 VA

Standard care	ITT	PP1	PP2
N=18	N=40	N=32	N=29
62% ≥20/40	87% ≥20/40 (P<.014)	91% ≥20/40 (P<.005)	94% ≥20/40 (P<.003)

50% MORE patients maintained 20/40 or better when using ForeseeHome vs standard of care alone

94% of patients maintained 20/40 at time of wet AMD diagnosis; Absolute visual acuity at time of wet AMD diagnosis is critical to visual acuity outcomes at year 1

Reference: AREDS2-HOME Study Research Group. Ophthalmology. 2014;123(2):335-344.

46

Home oct

- SCANLY AI Powered home OCT approved 5/16/24
- Two us trials over 500 pts
 - Safe and efficacious way to visualize intra and sub-retinal edema
 - 5,426 scans performed, 97% successful
 - Adherence of 5.9 scans/week
 - Self-imaging took 44 seconds on average

47

Home OCT

- Monitoring of intra- and subretinal fluid based on daily patient self-imaging
 - Easy-to-use, patient-operated device
 - Takes less than one minute per eye
 - AI algorithm analyzes images on cloud
- Remote diagnostic clinic, provider of monitoring program, reports changes meeting physician-selected fluid volume thresholds to referring physician
 - 24/7 physician access to all data
- Great way for retina MDs to know when next injection truly needed

48

Is AMD in our DNA?

- AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk
- Other 30% is environmental/lifestyle
- Risk factors
 - Non-modifiable: age, race, gender
 - Modifiable: Smoking, increased BMI, poor diet/nutrition, UV exposure

49

How can we use this information?

- Increased surveillance for those at higher risk
 - Sooner/more frequent appointments
 - More diligent home monitoring
- More diligence with modifiable risk factors
- Consider earlier vitamin supplementation
- Potential treatments in the future

50

AMD Risk Testing for a Full Spectrum of Patients

AMDiGuard DNA Progression Assessment

For people ≥ 55 yo with or without AMD findings

For people < 55 yo WITH AMD findings

- Assesses a patient's risk of progression to advanced AMD within 2, 5, 10, 20 and 30 years
- Delaying progression to advanced AMD with secondary prevention including AREDS vitamins, increased surveillance (home monitoring)

AMDiGuard DNA Risk Assessment

For people < 55 yo without AMD findings

- Assesses a patient's lifetime risk of developing advanced AMD (GA or CNV) allowing preventive lifestyle changes at younger age
- Delaying onset of disease with primary prevention including lifestyle modifications, supplementation (i.e. nutrition) and nutritional intervention

PRIVATE AND CONFIDENTIAL. DO NOT SHARE.

51

AMD Gene Panel

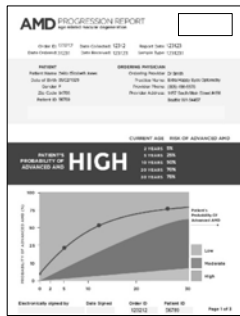
- Based on the latest in AMD Genetics research
- Clinically Proven and Clinically Actionable to be the most impactful variations on AMD progression
- Combines both genetic + non-genetic markers

23andMe SNPs

Gene	SNP No.	Allele Variants	AMD Risk	Chromosome	Pathway
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	R1108022A (A59)	GG	Lower Risk (Reference)	10q26	Immune/inflammatory
		GT	Moderate Risk		
		TT	Higher Risk		
CFH (Complement Factor H)	R13021170 (T4024)	TT	Highly Protective	1q31	Complement
		CT	Moderately Protective		
		CC	Higher Risk (Reference)		
	R123913059 (R1230C)	CT	Moderate Risk		
		TT	Higher Risk		
		AA	Highly Protective		
C3 (Complement Component 3)	R11410996 (T514)	GA	Moderately Protective	19p13	Complement
		GG	Higher Risk (Reference)		
	R12230199 (R102G)	GG	Lower Risk (Reference)		
		GC	Moderate Risk		
	CC	Higher Risk			

PRIVATE AND CONFIDENTIAL. DO NOT SHARE.

52



53

Genetic treatments

- Several companies looking at genetic treatment for AMD
- Viral vectors are used to introduce an anti-VEGF encoding transgene to allow the eye to begin to secrete anti-VEGF
 - Transforms the eye into a "biofactory"
 - Produces its own anti-VEGF supply
 - Reduces need for extrinsic injections
- RGX-314 and ADVM-022

54

Anti-Vegf AGents

- The OG
 - Macugen (Pegaptanib) 2004
 - Lucentis (ranibizumab) 2006
 - Eylea (afibercept) 2011
 - Beovu (Brolucizumab) 2019
 - Avastin (bevacizumab) ≈2005

55

High Dose Aflibercept (Eylea)

- PULSAR (AMD) and PHOTON (DME) Studies
 - Looked at 8 mg vs 2 mg of Eylea
 - Demonstrated non-inferior and clinically equivalent vision gains at 48 weeks with 8 mg at 12 and 16 week dosing after 3 initial doses compared to Eylea every 8 weeks after initial dosing
- Eylea HD FDA approved 8/18/2023 for AMD, DME and DR
 - Recommended dose 1 injection every 4 weeks for first 3 mos for all indications, then every 8-16 weeks (2-4 mos) for AMD and DME and every 8-12 weeks (2-3 mos) for DR

56

Vabysmo (faricimab)

- Roche/Genentech
 - FDA approved January 3, 2022 for AMD and DME
- First bi-phasic antibody for intraocular use
 - One arm: VegfA inhibitor
 - Other arm: Angiotensin-2 (Ang-2) inhibitor
 - growth factor that promotes vascular destabilization and inflammation
 - Dual inhibition of VEGF and Ang-2 have proven more effective than inhibiting either target alone
- Multiple studies show similar results to monthly Lucentis/Eylea but able to inject less frequently, many pts q 16 weeks
- May be FDA approved for RVO by end of year

57

Susvimo

- Previously called Genentech Port Delivery System (PDS)
 - Refillable port placed under conjunctiva to allow steady supply of Lucentis
- Studies (LADDER, ARCHWAY) demonstrated equivalent results to monthly Lucentis at 40 weeks
 - Large % of pts did not need refill prior to 6 or 12 mos
- FDA approved 10/1
- Recalled 10/22
 - Issue with implants breaking when refilled
- Reapproved July 8, 2024 with new implant and refill needle

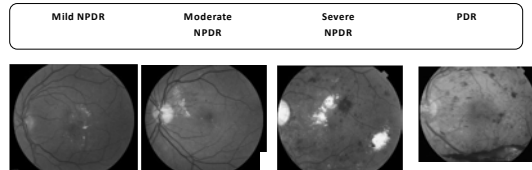
58

Anti-Vegf Biosimilars

- 3 FDA approved Lucentis (Ranibizumab) Biosimilars
 - Byovoiz (Samsung) approved Sept 2021
 - Cimertli (Cohesus) approved Oct 2022
 - Nufymco (Formycon/Bioeq) Dec 2025
- 6 FDA approved two Eylea (Aflibercept) Biosimilars
 - Yesafili (aflibercept-jbvf) Biocon Biologics; May 2024
 - Opuziv(aflibercept-yszy) Samsung Bioepis/Biogen/Mmay 2024
 - Ahzantive (aflibercept-mrb) Formycon; June 2024
 - Pavblu (aflibercept-ayrh) Amgen; August 2024
 - Enzeevu (aflibercept-abzv) Sandoz; Dec 2024
 - Eydenzelt (aflibercept-boau) Celltrion; Oct 2025
- MANY others in the works...

59

Is our DR Grading Scale Antiquated?

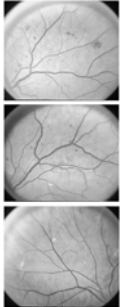


Wilkinson CP, Ferris FL, Klein RE, et al. Proposed international clinical diabetic retinopathy and diabetic macular edema severity scales. *Ophthalmology* 2003;110:1677-1682

60

Diabetic Retinopathy Grading

- Developed as a means of creating a **"prognostic standard"**
 - Risk of vision loss if not treated
- Based on ETDRS/DRS Studies that were done in the 1980's
- Utilizes fundus photography with a set of "Standard Slides"
- Photographs only captured images mainly of the posterior pole between the arcades
- Does not incorporate changes seen in the retina using newer modalities



61

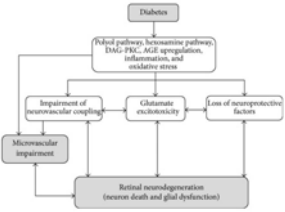
Diabetic Retinal Neurodegeneration (DRN)

- May be a **"preclinical manifestation"** of diabetic retinal disease (DRD)
 - Develops in the early stages of DRD
- Identified as **progressive retinal thinning** and **visual dysfunction** in patients with DM before the development of DR
- Early retinal neurodegeneration may precede vascular pathology - suggesting that neuronal damage may contribute to disease pathogenesis and represent an independent target for intervention
- DRN may be an initial component - another stage - of DRD

62

Neurodegenerative mechanisms

- Glutamate excitotoxicity
- Oxidative stress
- Inflammation
- Renin-angiotensin system activation



63

The Landscape of Imaging Modalities

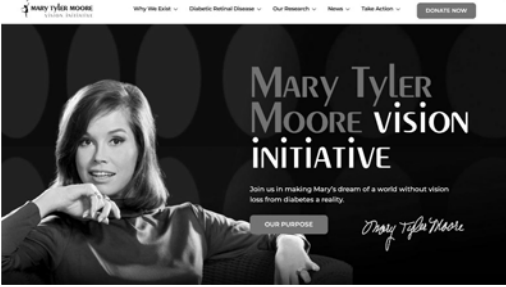
- Wide-field fundus photography
- SD OCT
- OCT angiography
- Adaptive optics
- ERG

64

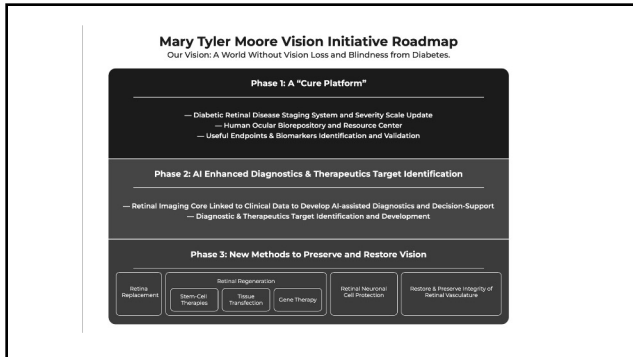
Diabetic Retinopathy Grading

- The **traditional end-point** for DR has evolved:
 - Laser PRP (or vitrectomy) once pts progressed to PDR
 - Focal/grid laser once they developed CSME
- To now anti-VEGF treatments
 - CI-DME
 - Severe NPDR and PDR
- Earlier intervention before PDR

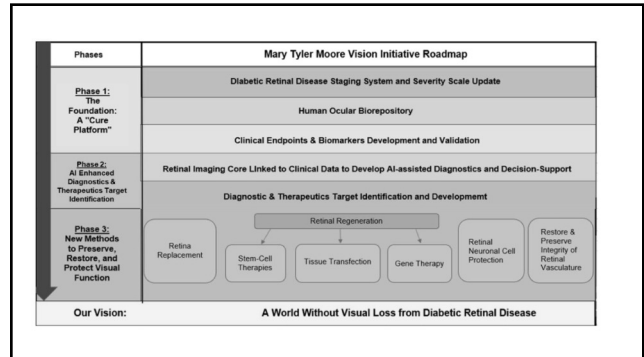
65



66



67



68

WHAT IS ERG?

Electroretinography

ERG measures the electrical responses of various cell types in the retina, including the **photoreceptors** (rods and cones), **inner retinal cells** (bipolar and amacrine cells), and the **ganglion cells** in response to a stimulus.

69

WHAT IS ERG?

The ERG waveform

A Wave Photoreceptor function, generally driven by cones.

B Wave Bipolar cell function, driven by rods from photoreceptors and transmitted to the inner plexiform layer.

PhNR Presence of the innermost retinal layer, ganglion cell function.

A delay in **implicit time** indicates cellular stress / abnormal metabolism.

Reduction in **amplitude** indicates cells are dying; number of cells is decreasing.

70

Pupillary response is also impacted by DR

DR assessment protocol combines:

- IMPLICIT TIME (ERG)** How long it takes the retina to respond
- AMPLITUDE (ERG)** How strong the signal from the retina is
- PUPIL RESPONSE** Change in pupil diameter—dim vs. bright
- PATIENT AGE**

71

A Global DR Score Predicts Who Will Need Tx

- N = 237 in US
- Primary outcome: % receiving laser, IV therapy and/or vitrectomy over 3 yrs
- Clinically observable SEVERE NPDR in tandem with ERG+pupillometry score > 23.5 best predicted Tx

DR Score	ERG+pupillometry score	% Patients Needing Treatment in 3 Years
RET mod < 23.5 & No Structural Signs	< 23.5	6%
RET mod < 23.5 & Structural Signs	< 23.5	19%
RET mod > 23.5 & No Structural Signs	> 23.5	20%
RET mod > 23.5 & Structural Signs	> 23.5	57%

8% Patients Not Requiring Treatment in 3 Years

Engell MG, Chiang B, Maa AY, Davis CD. Enhancing Risk Assessment in Patients with Diabetic Retinopathy by Combining Measures of Retinal Function and Structure. *Transl Vis Sci Tech.* 2020;9(9):40-40.

72

Function: Assess Risk

Each 1-point change in the DR Score increases the probability of ocular intervention over 3 years by 28%

Higher DR Score & change over time dramatically increases risk:

- Risk of intervention more than **doubles** with a 3-point increase in DR Score (e.g. 20 to 23)
- Risk of intervention **triples** with a 4.5-point increase in DR Score (e.g. 20 to 24.5)
- Risk of intervention **increases 5x** with a 6.5-point increase in DR Score (e.g. 20 to 26.5)
- Risk of intervention **increases 12x** with a 10-point increase in DR Score (e.g. 16 to 26)

Corresponding relative risk values from the chart: 2.1x (0.5), 3x (1), 5x (1.5), 7.5x (2), 12x (2.5), 18x (3), 27x (3.5), 40x (4), 60x (4.5), 84x (5), 126x (5.5), 180x (6), 252x (6.5), 360x (7), 504x (7.5), 700x (8), 972x (8.5), 1350x (9), 1800x (9.5), 2520x (10).

Corresponding hazard ratio analysis (CI = 1.17-1.40, p < 0.0001)
Source: Elgert AM, Chang B, Ma A, Davis CO. Evaluating Risk Assessment in Patients with Diabetic Retinopathy by Combining Measures of Retinal Structure and Structure. Trans Am Ophthalmol Soc. 2020;118:48-58.

73

DIABETIC RETINOPATHY

Newest study shows the DR Score was the strongest predictor of progression to VTC

79%

- Longitudinal prospective study published in *Ophthalmology Science*, the journal of the American Academy of Ophthalmology
- 48 weeks (~11 months)
- 74 patients with moderate to severe NPDR tested with ERG
- Evaluated 56 parameters at multiple US sites from 4 testing modalities:
 - RETeval DR Assessment (ERG + pupillometry)
 - Color fundus photography (FP)
 - OCT angiography (OCT-A)
 - Ultra-widefield fluorescein angiography (UWF-FA)

Patients with a DR Score of 26.9 or higher had a 79% chance of progressing to needing treatment in less than 1 year.

Davis, C. Quantifying the Predicting Progression to Vision-Threatening Complications in Diabetic Retinopathy. Ophthalmology Science, online June 17, 2025, 10089

74

DIABETIC RETINOPATHY

Study shows the DR Score was the strongest predictor of progression to VTC

RETeval DR Score was the strongest predictor of progression to vision-threatening complications!

Parameter	Relative Risk
RETeval DR Score > 26.9	5.6
UWF-FA total ischemic index	5.3
RETeval DR Score > 23.5	3.7
OCT-A FAZ area	3.6
FP DRSS	2.1

Davis, C. Quantifying the Predicting Progression to Vision-Threatening Complications in Diabetic Retinopathy. Ophthalmology Science online June 17, 2025, 10089

75

DIABETIC RETINOPATHY

Why the DR Score matters

- Enables risk stratification to identify patients who need close monitoring or early referral, even when structural imaging appears stable.
- Allows targeted referrals and/or resource prioritization, reducing overtreatment and missed progression.
- Creates potential to improve DR staging systems and support value-based care models.

76

DIABETIC RETINOPATHY

How to use the DR Score in practice → interpretation guide

PATIENT TEST CONDITIONS
Test is always done un-dilated. Patient is diabetic with suspected retinopathy or diabetic with existing retinopathy.

PROTOCOL
DR Assessment

RESULTS
If the Operator-selected limit is marked red with text **Outside limits**, the patient is at risk to develop vision threatening DR within the coming 18 months.

Predicting DR progression

DR SCORE <23.5:
Patient is much less likely to progress to needing treatment in the next few years.

DR SCORE ≥23.5:
High chance of requiring treatment in next 3 years

DR SCORE ≥26.9:
Patient is 79% likely to progress to needing treatment in less than 1 year

77

DME

- Old definitions being replaced with newer ones based on OCT findings
 - Center involved
 - Non-center involved
 - OCT best way to evaluate retina for DME
- DME responsible for more cases of moderate visual loss in pts with Type 2 DM than DR
- New treatments

CSME

- RT within 500 microns (1/3 DD) from FAZ
- Hard exudates with associated thickening 500 microns from FAZ
- RT > 1DD in area any part of which is within 1DD from FAZ

78

Protocol V

- 702 pts with CI-DME with VA 20/25 or better
- 3 treatment groups
 - Eylea
 - FML
 - Observation
- At end of 2 years, rate of loss of 5 letters or more similar in all 3 groups
- Avg acuity in all 3 groups was 20/20
- Bottom line: pts with CI-DME and good VA can be observed

79

Optomed Aurora Aeye

- First FDA cleared handheld AI fundus camera
- Uses AI to assess level of DR
 - Referrable DR detected
 - No referrable DR detected
 - Over 90% specific and sensitive
 - 99% imageability
 - Results in under 90 seconds

80

AI Optics Sentinel camera

- Fda approved jan 29, 2025
- Handheld digital imaging system
- Has ai capabilities but not yet approved

81

The Burdon of Floaters

Retrospective Study Bascom Palmer Eye Institute 2008-2011

- 7.2% of patients referred to a retinal specialist had floaters
- 5th most common diagnosis over that time
 - > 60 yo 3rd most common Dx
- Vitrectomy: very successful, technically simple, with low side-effect profile
 - Risk of Cataract, ERM, and retinal tears/detachments

82

Options for Treatment of Floaters

- Yag vitreolysis
- Pars plana vitrectomy

83

Important Considerations in Patients with Floaters

Are they acute or chronic?

- Acute Floaters – often from PVD
 - Usually resolve
- Chronic floaters that impact daily activities

84

Reasons for Surgery for Floaters

Symptoms that impact the quality of life

- Unable to read continuously
- Unable to safely drive a car
 - The floaters/cloud moves in front of their vision and they nearly have to pull over for fear of having an accident
- Affects ability to perform your job

85

The Ideal Candidate for Treatment of Floaters

- Symptomatic
- Pseudophakic
- PVD

The **NOT** Ideal Candidate for Treatment of Floaters

- Young
- Phakic
- Attached vitreous
- High myope

86

Laser Vitreolysis for Floaters

- Done with a Yag
- Highly variable results
- Complications:
 - Cataract (hitting the lens)
 - Posterior capsule tears
 - Retinal burns
 - Foveal burns
 - Choroidal rupture
 - Choroidal hemorrhages
 - Retinal tear

87

Long-Term Follow-Up of Efficacy and Safety of YAG Vitreolysis for Symptomatic Weiss Ring Floaters

Ching P. Shah, MD, MPH; Jeffrey S. Heier, MD

- 35 of 52 patients randomized to Yag vitreolysis or Control followed for 2.3 years
- 50% felt their symptoms were significantly or completely better at 6 months
 - ~60% overall improvement in symptoms
- 3 patients developed retinal tears after 6 months (not symptomatic)

Ophthalmic Surg Lasers Imaging Retina 2020

88

omy 2023

- Smaller-gauge instruments (25 or 27) compared with the 20-gauge needles used less than 15 years ago
- Smaller vitrectomy instruments allow for sutureless procedures
 - Smaller sclerotomy
 - Trocars allow for small, thin-wall cannula
- Less inflammation
- Fewer complications
- Much greater success rate

89

Risk Factors for Vitrectomy

- Cataract
- Retinal tear or detachment
- ERM/Macular pucker
- Macular edema
- Endophthalmitis

90

Induce a PVD....or not

- Risk of developing a retinal tear by inducing PVD
- Reduced risk/time of developing cataract with partial vitrectomy

91

Bascom Palmer Vitrectomy for Floaters Study

- Retrospective Chart Review
- PPV for symptomatic primary vitreous floaters
- **150 patients** evaluated between 1/1/2012– 1/1/2023
- Age of onset 66/67
- Gender: 65 female, 85 male
- **# of eyes: 208**
- Symptoms duration **12.3 mo ± 8 mo**
- 74% Pseudophakia

Ocular Disease
 - 4 eyes treated tears
 - 5 eyes glaucoma
 - 10 eyes refractive surgery
 - 2 asteroid hyalosis
 - 10 high myopia

92

Complications

Post Op Complications	# Eyes	Mean Time of Dx following Surgery
Cataract	18 (53%)	9.13 ± 6 months
Steroid induced Increase in IOP	10 (4.8%)	1 moth
Vit Heme	8 (3.9%)	4 ± 4 days
Retinal Detachment	7 (3.4%)	20 ± 37 months
Symptomatic CME	4 (1.9%)	16.8 ± months
ERM	3 (1.4%)	15 ± months
Endophthalmitis	1 (0.5%)	1 day
Hyphema	1 (0.5%)	1 day
Symptomatic floats	1 (0.5)	6 months

93

Rate of Complications for Vitrectomy for Vitreous Floaters is "Low"

Needs to be discussed with the patient

- RRD: 7 eyes (3.4%)
- VH: 7 eyes (3.4%): all cleared
- Other
 - Endophthalmitis 1 eye
 - Redo surgery 1 eye

94

ARVO Annual Meeting Abstract | June 2013
Long-term Safety of Vitrectomy for Patients with Floaters

Christianne Wa; Kenneth Yee; Laura Huang; Alfredo Sadun; J Sebag

- 66 eyes in 52 patients (age = 63 ± 12 years) were included
- 36/66 (54.5%) eyes were phakic
- Average duration of coping was 30 months
- Etiology of floaters was PVD in 44/66 (67%), myopia in 19/66 (28%), asteroid hyalosis in 8/66 (12%)
- Retinopexy for retinal breaks occurring at the time of PVD was performed in 16 eyes (36% of all eyes with PVD; 24% of all eyes), a **minimum of 3 months prior to vitrectomy**
- **22 eyes without PVD: PVD NOT induced and vitreous remained intact peripherally.**
- Main outcome: incidence of ret tears/detachments and cataract requiring surgery

95

ARVO Annual Meeting Abstract | June 2013
Long-term Safety of Vitrectomy for Patients with Floaters

Christianne Wa; Kenneth Yee; Laura Huang; Alfredo Sadun; J Sebag

- **Floaters symptoms resolved in 65 of 66 eyes (98.5%)**
- No patients (0/66; 0%) developed retinal breaks, hemorrhage, infection, or glaucoma (3 month – 3 years)
- **No retinal breaks/ detachments in the 22 patients without PVD pre-operatively (0/22 vs 9/30)**
- **Only 7/36 (19%) phakic eyes developed cataracts** requiring surgery, an average of 16.5 months post-vitrectomy (7/36 vs 18/36 (50%))

96

Ophthalmology Retina

Long-Term Safety and Efficacy of Limited Vitrectomy for Vision Degrading Vitreopathy Resulting from Vitreous Floaters

2018
 J. Sebag, MD, FARVD, J. Kenneth M.P. Yee, BS, Justin H. Nguyen, BA, Jeanine Nguyen-Cuu, BS
 Published: May 11, 2018 • DOI: <https://doi.org/10.1016/j.oret.2018.03.011> • [Check for updates](#)

Methods 195 Eyes

Limited vitrectomy with 25-gauge instruments was performed **without surgical PVD induction** preserving 3 to 4 mm of retrolental vitreous in **phakic eyes**. Follow-up averaged 32.6 ± 23.5 months (range, 3–115 months), with 2 years or more in 144 eyes, 3 years or more in 69 eyes, 4 years or more in 51 eyes, and 5 years or more in 24 eyes.

Conclusions

Limited vitrectomy for Vision Degrading Vitreopathy decreases vitreous echodensity, improves patient well-being, improves VA, and normalizes CSF. The long-term efficacy and safety profiles suggest this may be a safe and effective treatment for clinically significant vitreous floaters, warranting a prospective randomized trial.

97

Table 2. Postoperative Complications

Complication	No. (n = 195 Eyes)	%
Vitreous hemorrhage	2	1.0
Retinal detachment	3	1.5
Retinal tear	3	1.5
BRVO	3	1.5
CRAO	2	1.0
Endophthalmitis	0	0.0
Glaucoma	1	0.5
Cataract surgery (124 phakic eyes)	21/24	16.9
PVD (40 without PVD before surgery)	4/40	9.3
Macular pucker	2	1.0

BRVO = branch retinal vein occlusion; CRAO = central retinal artery occlusion; PVD = posterior vitreous detachment.

98

Dietary Intervention With a Targeted Micronutrient Formulation Reduces the Visual Discomfort Associated With Vitreous Degeneration

Emmanuel Askamuh, Marisa Green Gomez, Warren Roche, Eugene Ng, Ulrich Wedge, Lüben, Thomas Kaercher, and John M. Nolan.

- 61 pts followed for 60 days
- Less discomfort from floaters in treated pts from initial visit to final visit
- Less effect of floaters on daily life in treated pts from initial visit to final visit
- Decrease in vitreous opacities in 20/26 (76.9%) of treated pts vs 28.6% in placebo
- Increase in contrast sensitivity in treated pts
- Overall, 66.6% of treated pts experience an improvement in visual comfort

99

Macular hole surgery

- Vitrectomy and membrane peel
- Filled with gas which dissipates over 4-6 weeks
- Face down positioning
 - 14 days traditional
 - Newer studies evaluating less vs none
- 95% success rate if operated within 1 yr
- Risks
 - Endophthalmitis: 1:1000
 - RD: 5%
 - Cataract formation: many pts need cataract surgery within 1 year of vitrectomy

100

Macular hole medical therapy

- 49 pts with FTMH started on PF, NSAID, CAI
- 18/49 (36.7%) achieved closure with drops
 - higher % in small holes and those without VMT
- Hole size directly related to chance of closure
 - Every 10 µm decrease in size increased odds for closure by 1.2X
 - Best results less than 200µm
 - 200-300µm ≈ 25% closure
 - No FTMH over 300 µm had closure
- Avg time to closure was 107.2 days (range 20-512 days)
- If no response at all within first 1-3 mos response unlikely and surgical candidate

Wang J, et al. Full-thickness macular hole closure with topical medical therapy. Retina 44:392-399, 2024.

101

Rate of FTMH closure on medical therapy

Macular Hole Size (µm)	% Closed on Drops
<200	~70%
200-300	~25%
>300	0%

102

Take home

- My take home:
 - If < 300 um, try consider trying
 - PF qid
 - Nsaid (Voltaren, Acular) Qid
 - CAI (trusopt) bid until sees retina
 - Refer to retina 1 mos
 - Send oct to compare
 - If no improvement in 1 mos, unlikely to have change so surgical candidate
 - If improvement, try for 3 mos then decide on surgery

103

Vuity to Treat Presbyopia

- 1.25% pilocarpine
- FDA approval Oct 2021
- Positive phase 2 phase 3 results, GEMINI 1 and GEMINI 2
 - 750 patients who used Vuity daily for 30 days
 - **29% of patients experienced a ≥ 3 line increase** in distance-corrected near visual acuity at day 30, hour 3 vs 10% in controls.
 - Adverse events (AE) were all mild and included headaches (14.1%), visual impairment (4.3%), conjunctival hyperemia (2.5%), vision blur (2.5%), eye irritation (2.5%), eye pain (2.5%), increased lacrimation (2.5%), nausea (2.5%), and punctate keratitis (0.6%)
 - **no cases of retinal tears, RD, macular holes, or vitreomacular traction**

104

AMERICAN JOURNAL OF OPHTHALMOLOGY

Retinal Detachments Associated With Topical Pilocarpine Use for Presbyopia

MAY 2022

HAMENIN AL-KHERSAN, HARRY W. FEYNN JR, AND JUSTIN H. TOWNSEND

PURPOSE: To present a case series of retinal detachments associated with the use of pilocarpine for presbyopia.

DESIGN: Multicenter case series of 3 eyes from 2 patients.

RESULTS: Patient 1, a 47-year-old man, presented with flashes and floaters in both eyes. The patient had started pilocarpine 1.25% drops 1 month prior for presbyopia in both eyes. He noted the onset of flashes and floaters 3 days after he initiated the drops. A dilated examination revealed an inferior-temporal retinal detachment in the right eye with an associated retinal tear inferior-temporally. The left eye demonstrated a retinal detachment in the superior quadrant with an associated horseshoe tear at 12 o'clock. Patient 2, a 46-year-old man, presented 5 weeks after initiating topical pilocarpine 1.25% drops for presbyopia. He noted a nasal visual field defect in his left eye that progressed to include his central vision. A dilated examination revealed a superior retinal detachment from 11 to 3 o'clock with subretinal fluid extending into the macula.

CONCLUSIONS: Pilocarpine and other miotics have long been suspected to be associated with an increased risk of retinal detachment. Prior to prescribing pilocarpine for presbyopia, physicians should inform patients of this potential adverse event and consider that these patients undergo a screening dilated examination, particularly if they are myopic, to determine if they are at higher risk for retinal detachment. Before the initiation of therapy, patients should be appropriately informed regarding symptoms of retinal tears or detachment, which include flashes, floaters, and visual field loss. (Am J Ophthalmol 2022;242: 52-55. © 2022 Elsevier Inc. All rights reserved.)

105

Herein, we present cases of retinal detachment from 3 eyes of 2 patients occurring after the initiation of pilocarpine 1.25% topical ophthalmic drops for presbyopia. Although these cases of retinal detachment cannot be definitively associated with the initiation of the pilocarpine therapy, the incidence shortly after initiation of treatment is concerning. Particularly, the occurrence of a bilateral concurrent retinal detachment in the patient in case 1 who became symptomatic with flashes and floaters just 3 days after starting the pilocarpine 1.25% topical drops warrants further investigation of retinal detachments as a possible adverse effect of treatment.

106

Retinal Complications Associated with Vuity

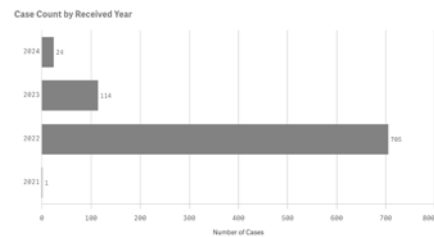
- FDA Adverse Events Reporting System (FAERS) Dashboard²⁴ (latest data)
- 550 Total Cases
- 121 viewed as Serious Cases
- 161 visual impairment
 - 42 retinal detachments
 - 25 retinal tears
 - 9 Vitreomacular traction
 - 11 Visual field defect
 - 56 Vitreous floaters

Number of Cases	
550	Total Cases
161	Visual Impairment
142	Vision Blurred
86	Eye Irritation
64	Eye Pain
61	Ocular Hypersaemia
56	Vitreous Floaters
45	Vitreous Detachment
42	Retinal Detachment
32	Photopsia
25	Retinal Tear
22	Miosis

<https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f71c25ee/sheet/45beeb74-30ab-46be-8267-5756582633b4/state/analysis>

107

Retinal Complications Associated with Vuity



108

Retinal Complications Associated with Vuity

September 2024

	24
Number of Cases	19
Visual Impairment	6
Vision Blurred	5
Retinal Detachment	4
Ocular Hyperaemia	3
Eye Pain	2
Blindness Unilateral	2
Miosis	2
Retinal Tear	2
Eye Pruritus	1
Eye Irritation	1
Mydriasis	1
Vitreous Detachment	1
Retinal Degeneration	1

109

- ### Why Retinal Complications?
- Contraction of the ciliary body
 - Rapid anterior displacement of the vitreous
 - Shifting the vitreous body forward
 - Resulting in traction on the retina
 - May predispose some patients
 - Lattice degeneration and peripheral retinal pathology
 - Abnormal vitreomacular interface

110

Rates Observed with Vuity Did not Exceed the Natural History in this age Group, And...

...THEY WERE FURTHER REDUCED FOLLOWING POST-LAUNCH EDUCATION EFFORTS

<p>Indiscriminate Use Initially >25% Rte from Non-ECPs 6 Months Post-Launch</p> <ul style="list-style-type: none"> • 122,000 New VUITY Prescriptions (January to December 2022) • FDA Adverse Events reported <ul style="list-style-type: none"> • 30 RDEs (as of December 2022 – only 1 reported 2H 2022) • 30 reports/122,000 new prescriptions = 0.025% 	<p>Following Education by ADN and Professional Societies Rates Decreased</p> <ul style="list-style-type: none"> • 19,000 New VUITY Prescriptions (January to June 2023) • FDA Adverse Events reported <ul style="list-style-type: none"> • 2 RDEs (as of June 2023) • 2 reports/19,000 new prescriptions = 0.011%
---	---

QLOS! education initiatives will help guide ECP patient selection and calibrate expectations on RD risk relative to the most common complications ECPs (OD primarily) manage with other treatments they frequently use, i.e. contact lenses / microbial keratitis

111

AMERICAN JOURNAL OF OPHTHALMOLOGY

Nov 2024

Using Real-World Data to Assess the Association of Retinal Detachment With Topical Pilocarpine Use

ABDELRAHMAN M. ELHUSSEINY*, MUHAMMAD Z. CHALUJAN†, SAYENA JARREHDAR, NAYEF ALSHAMMARI, SARAH JONG, PAUL H. PHILLIPS, AND AHMED B. SALLAM

Study Design

This was a retrospective cohort study that used data from patients included in the TriNetX database to assess the risk of retinal detachment after initiation of topical pilocarpine for presbyopia. A total of 4494 patients aged ≥40 years newly started on pilocarpine for presbyopia were compared to 4494 control patients who received artificial tears. Patients were propensity score-matched for baseline characteristics (e.g., age, gender, race/ethnicity, systemic disease) as well as known risk factors for retinal detachment (e.g., myopia, vitreous degeneration, vitreomacular adhesion/traction, lattice degeneration, retinal breaks, pseudophakia, history of IOL procedures, glaucoma). Patients were excluded if they had history of other diseases that would be treated with pilocarpine, had previous vitrectomy or ocular trauma, or had other intraocular procedures within a year of starting pilocarpine.

Outcomes

The risk of RRD was significantly higher in patients who received pilocarpine than in patients who received artificial tears at post-treatment month 3 (0.53% vs 0.25%, RR: 2.18), post-treatment month 6 (0.60% vs 0.31%, RR: 1.93), and post-treatment year 1 (0.78% vs 0.33%, RR: 2.33). Approximately half of the RRD cases occurred within 2–3 months of treatment initiation. Among patients who used pilocarpine, certain covariates further increased the risk of RRD, including lattice degeneration (aHR: 3.71), pseudophakia (aHR: 3.48), a history of myopia (aHR: 2.36), and vitreous degeneration (aHR: 2.22).

112

REVIEW Leadership in clinical care
of OPTOMETRY

Published November 8, 2024

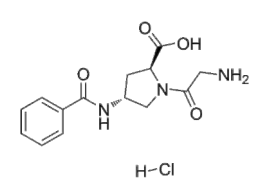
Likelihood of RRD About Threefold Greater with Topical Pilocarpine Use

Additional factors indicating increased odds included male sex, myopia, vitreous degeneration, lattice degeneration and pseudophakia.

113

Danegaptide

- Breye Therapeutics
- Gap junction modifier
- Potential oral therapy for NPDR
- Phase 1 study:
 - 24 pts with NPDR and associated edema
 - Well tolerated
 - Imaging showed reduced retinal vascular leakage and "improvements in anatomical parameters"
- Phase 2 to begin soon



114

TKI Inhibitors

- Tyrosine Kinase Inhibitors
 - Small molecules that can act intracellularly to inhibit multiple pathways involved in the pathogenesis or retinal disease
 - May be a more durable treatment approach, reducing treatment burden over avny/VEGF
 - Early studies show promise
- AIV007 (Aiviva BioPharma): Phase 1, single periocular injection for DME and nAMD,
- D-4517.2 (Ashavattha Therapeutics): Phase 2 TEJAS study, subcutaneous or oral for DME and nAMD
- EYP-1901 (EyePoint Pharmaceuticals): LUGANO andCLUCIA trials in AMD; VERONA in DME
- OTX-TKI (Ocular Therapeutix): Apaxli, bioresorbable intravitreal implant for AMD and DR
- CLS-AX (Clearside Therapeutics): suprachoroidal injection of axitinib for nAMD
- PAN-90806 (Zhaoke Ophthalmology): Topical KI eye drop for AMD

115

Duravyu

- Voralanib intravitreal insert (previously eyp-1901) by EyePoint Pharmaceuticals
- Did not meet endpoint of improvement of at least 2 DRSS levels as of week 36
 - 12 mos data still coming
- Did have some positive results
 - 86% of pts in 3 mg arm and 80% in 2 mg arm were stable or improved vs 70% control
 - 0% in 3 mg and 5% in 2 mg worsened > 2 steps vs 10% in control
 - 5% in 3 mg and 0% in 2 mg improved > 2 steps vs 5% control
 - Well tolerated with no serious adverse events of endophthalmitis

116

NEUROTECH PHARMACEUTICALS

- Encelto approved 3/6/2025 First and only approved treatment for mac tel
- ENCAPSULATED CELL THERAPY
 - A SMALL SEMI-PERMEABLE CAPSULE SURGICALLY IMPLANTED INTO THE PATIENTS VITREOUS AND SUTURED TO THE SCLERAL WHICH ALLOWS THERAPEUTIC PROTEINS AND ESSENTIAL NUTRIENTS TO ENTER THE EYE TO TREAT CHRONIC RETINAL DISEASES
- HEADQUARTERS IN CUMBERLAND, RI
- PRICE: 200-250K!!

117