Greatest Posterior Segment Disease Talk - Ever!

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Mark Dunbar: Disclosure

- Optometry Consultant
  - Carl Zeiss
  - Allergan
  - Regeneron
  - Iveric
  - Sight Sciences
  - Visus

Mark Dunbar does not own stock in any of the above companies

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Ferrucci Disclosures

- Centervue/I-Care
- Genentech
- Optovue
- Maculogix
- Notal Vision
- Regeneron
- Science based health
- Visible Genomics

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Financial Disclosures

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- Heidelberg Engineering-
- Optos
- Notal Vision
- Spark Therapeutics
- Apellis Therapeutics
- Iveric
- Clinical Investigator (Sub-I)
  - Regenxbio
  - Ophthea
  - F. Hoffmann-La Roche
  - Roche Genentech
  - Novartis
  - Neurotech Pharmaceutical
  - The Lowry Medical Research Institute
  - Outlook Therapeutics
  - Regeneron

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Hot Topics

- New Tx for GA
- Presbyopia
- Diabetic Retinopathy
  - Changing paradigm in the management of diabetic retinopathy
  - AI
- Evolution of wide-field imaging
- OCT and OCTA
  - Will the new anti-VEGF drugs any better?
- Management of flashes/floaters

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Macular Degeneration

- One of the most common causes for vision loss in the elderly population
- 85% with dry AMD; 15% with Wet AMD
- Nutritional supplements have been shown to decrease the risk of progression to wet AMD
- Newer Anti-VEGF treatments have greatly improved the visual outcome
  - Earlier detection of CNV results in even better visual come
- We now understand there is a strong genetic link to AMD
  - There is a genetic test commercially available – ArticDx

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Release Details

FDA Approves SYFOVRE™ (pegcetacoplan injection) as the First and Only Treatment for Geographic Atrophy (GA), a Leading Cause of Blindness

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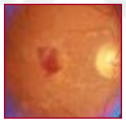
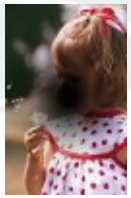
Age-related Macular Degeneration (AMD)

- Degenerative disorder that affects the macula
- Leading cause of legal blindness in people > 65 yo
- 90% of vision loss is 2º to CNV





- Patients Affected
  - 90% dry or nonexudative
  - 10 % wet or exudative
- VA < 20/200
  - 80-90% exudative
  - 10-20% dry

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What We Now Know

- Genetic background
- Environmental/lifestyle risk factors
- The interaction between these variables, predispose to AMD
- Treatments for wet AMD target VEGF
  - Hugely successful
- The future of AMD will target dry AMD

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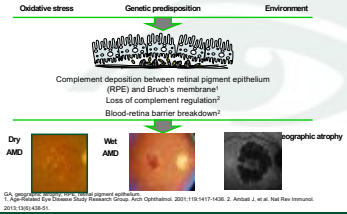
Current Hypothesis for AMD Pathophysiology



GA, geographic atrophy; RPE, retinal pigment epithelium.
1. Age-Related Eye Disease Study Research Group. Arch Ophthalmol. 2001;119:1417-1436. 2. Ambati J, et al. Nat Rev Immunol. 2013;13(6):438-51.

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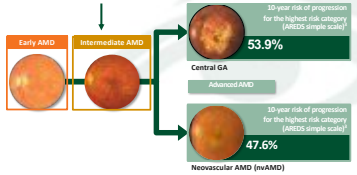
Staging of AMD



AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; GA, geographic atrophy; nvAMD, neovascular AMD.
1. Eye Diseases Prevalence Research Group. Arch Ophthalmol. 2004;122(4):477-485. 2. Ferris FL, et al. Ophthalmology. 2013;120(4):844-851. 3. Chew EY, et al. JAMA Ophthalmol. 2014;132(3):272-277. 4. Age-Related Study Disease Study Research Group. Arch Ophthalmol. 2005;123(11):1570-1574.

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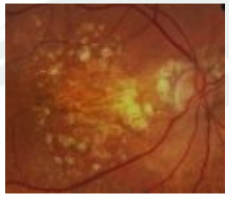
Geographic Atrophy

- Advanced/late form of dry AMD
- Atrophy of the RPE and photoreceptors



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Imaging Modalities in Diagnosing and Monitoring AMD

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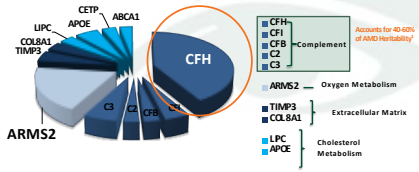
Key Genes Involved in the Development of AMD



CFH
CFI
CFB
C2
C3
Complement
Accounts for 40-60% of AMD Heritability[1]

ARMS2 — Oxygen Metabolism

TIMP3
COL8A1
Extracellular Matrix

LPC
APOE
Cholesterol Metabolism

1. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: Genetics and biology coming together. Annu Rev Genomics Hum Genet. 2014;15:151-171.

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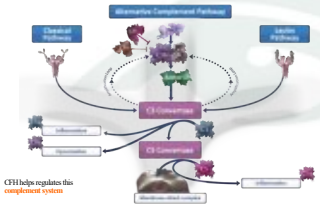
Pathways for Complement Activation

Required for the initiation and amplification of the alternative complement pathway



CFH helps regulates this complement system

Figure based on the scientific information from the following sources: Owen J., Punt J. and Stanford S. (2013) Kuby Immunology 7th edition, New York: W.H. Freeman and Co Ltd; Weiport M. N Engl J Med 2001;344:1058-66.

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Complement System and Potential GA Therapies

- The complement cascade is a strategic target for GA therapy
- The COMPLEMENT SYSTEM is first line of defense of the immune system
- It protects us from microorganisms
- It constitutes our innate immunity, which is not adaptable and does not change as we age
- Activated by the adaptive immune system (through antigen antibody interaction)

Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The Pathophysiology Of Geographic Atrophy Secondary to Age-related Macular Degeneration and the Complement Pathway as a Therapeutic Target. Retina. 2017;37(5):819-835.

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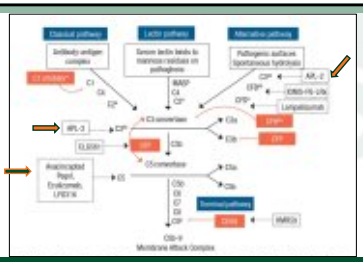

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Potential Treatments for Geographic Atrophy

- **Pegcetacoplan (Syfovre) :** C3 inhibitor by Apellis
- Blocks all the pathways of complement activation

MAC = membrane attack complex

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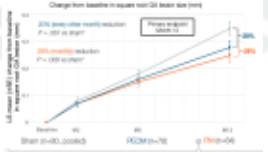
Pegcetacoplan (Syfovre)

Phase 3 DERBY & OAKS Objective:
Assess the efficacy and safety of multiple intravitreal injections of pegcetacoplan in patients with GA secondary to AMD

Phase 2 FILLY Results



*P <0.1 was the predefined threshold for statistical significance in FILLY. LS=least squares; M=Month; PEOM=pegcetacoplan every other month; PM=pegcetacoplan monthly; SE=standard error.

Liao DS, et al. Ophthalmology. 2020;127:186-95.

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Global Phase 3 Program: OAKS & DERBY Study Design

Primary Analysis: MMRM Methodology

Fixed Effects:
- Treatment*, time, treatment x time interaction
- baseline GA lesion and fellow eye CNV +area strata
- baseline GA lesion strata × time interaction

*Sham Monthly and ECM were pooled for analysis

Double-Masked, Randomized 2:2:1:1

- Pegcetacoplan 15 mg/0.1 mL monthly
- Pegcetacoplan 15 mg/0.1 mL EOM
- Sham monthly
- Sham EOM

Primary Endpoint at 12 Months
Change in total area of GA lesions based on fundus autofluorescence

End of study at 24 months
- BCVA, LL-BCVA, low-luminance deficit
- Reading speed
- FRI Index composite score
- Microperimetry (OAKS only) – Macular Integrity Assessment (MAIA) device

GALE Extension Study (3 years)

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OAKS and DERBY

Monthly and every-other-month pegcetacoplan continued to reduce GA lesion growth at 18 months

Pegcetacoplan showed continued and clinically meaningful reductions in GA lesion growth from baseline to month 18.

Apellis. Apellis announces pegcetacoplan showed continuous and clinically meaningful effects at month 18 in phase 3 DERBY and OAKS studies for geographic atrophy (GA). https://investors.apellis.com/news-releases/news-release-details/apellis-announces-pegcetacoplan-showed-continuous-and-clinically. Updated March 16, 2022. Accessed March 16, 2022.

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Pegcetacoplan: Take-Away Points

- Pegcetacoplan monthly and every other month met the primary endpoint in OAKS
- Pegcetacoplan monthly and every other month **did not meet the primary endpoint** in DERBY
- Data at 18 months from the combined studies show the potential for improving treatment effects with pegcetacoplan over time.
- **Pegcetacoplan treatment effect accelerated between months 18-24,** demonstrating a robust reduction of GA lesion growth compared to sham

1. https://investors.apellis.com/news-releases/news-release-details/apellis-announces-plans-submit-24-month-phase-3-data-fda

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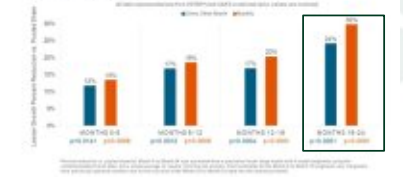
OAKS and DERBY

Pegcetacoplan treatment effect accelerated between months 18-24, demonstrating a robust reduction of GA lesion growth compared to sham



https://investors.apellis.com/news-releases/news-release-details/apellis-announces-24-month-results-showing-increased-effects

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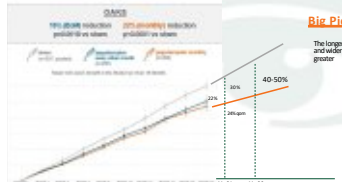
OAKS and DERBY



Big Picture

The longer you go the delta gets wider and wider and the treatment effect is greater

40-50%

30%

22%

24% gain

Mo 24

Mo 36

Apellis. Apellis announces pegcetacoplan showed continuous and clinically meaningful effects at month 18 in phase 3 DERBY and OAKS studies for geographic atrophy (GA). https://investors.apellis.com/news-releases/news-release-details/apellis-announces-pegcetacoplan-showed-continuous-and-clinically. Updated March 16, 2022. Accessed March 16, 2022.

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Apellis: Pegcetacoplan

Is that a significant treatment effect for GA?

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Pegcetacoplan: Take-Away Points

- Pegcetacoplan **treatment effect accelerated between months 18-24, demonstrating a robust reduction of GA lesion growth compared to sham**
- Pegcetacoplan demonstrated greater efficacy in patients with extrafoveal lesions at baseline
- In a post-hoc analysis, after correcting for disparities in baseline characteristics, OAKS and DERBY results are more convergent
- OAKS and DERBY show consistent efficacy of pegcetacoplan in treated study eyes versus untreated fellow eyes
- Overall, pegcetacoplan administered monthly or every other month was well tolerated in patients with GA
  - Majority of IOI cases were mild, and most patients resumed IP administration
  - **6.0%, 4.1%, and 2.4% of patients in the combined PM, PEOM, and sham groups experienced new-onset investigator-determined exudative AMD**

1. https://investors.apellis.com/news-releases/news-release-details/apellis-announces-plans-submit-24-month-phase-3-data-fda

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Avacincaptad Pegol (Zimuria): Iveric

- Complement C5 inhibitor
- Reduction in GA growth for patients receiving Zimura in the U.S. was **25.5 - 32.0%**
- **Expected to receive FDA approval August 2023**

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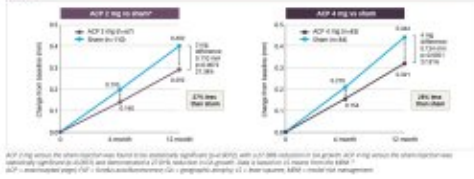

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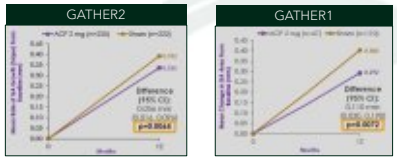
Avacincaptad Pegol:

First Investigational GA Therapy to Achieve the 12-month Prespecified, Primary Endpoint in 2 Pivotal Phase 3 Studies



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Cross-trial comparison of Zimura and intravitreal pegcetacoplan in geographic atrophy

Project (company)	Zimura (Iveric Bio)		Intravitreal pegcetacoplan (Apellis)			
Trial	Gather2	Gather1	Derby		Oaks	
			Monthly	Every other month	Monthly	Every other month
Change in GA area vs sham at 12mo	14%*	27%*	12%	11%	22%	16%
p value	0.0064	0.0072**	0.0528 (NS)	0.0750 (NS)	0.0003	0.0052
Choroidal neovascularisations	7%***	9%***	7%*	3%*	5%*	5%*

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Where we are today with GA?

- An FDA approved treatment
  - By August we will likely have a 2nd Treatment
- Monthly intravitreal injection
- Takes at least ~ 12 months to show any significant therapeutic benefit
- By 18-24 months the treatment affect accelerates
- Keep in mind many patients will have good acuity

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Anti-VEGF Standard of Care for Wet AMD

- Require frequent injections
- 1/3 of eyes develop geographic atrophy
- Significant vision loss after 5–7 years of therapy

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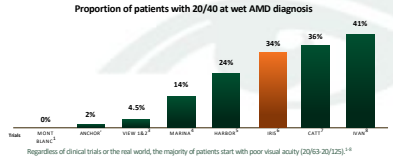
Too few patients have ≥20/40 at wet AMD diagnosis



Regardless of clinical trials or the real world, the majority of patients start with poor visual acuity (20/63-20/125).[1-3]

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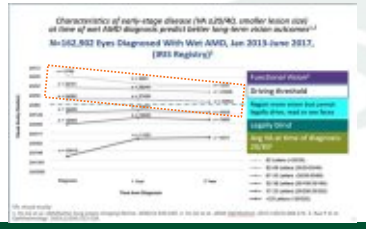
Importance of Early Detection of "Wet" AMD



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Home Monitoring of AMD

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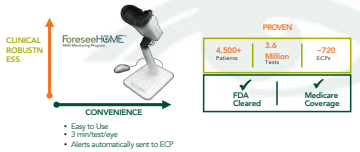
ForeseeHome®



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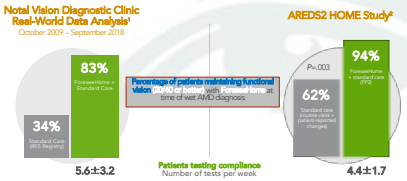
ForeseeHome helps physicians detect wet AMD earlier: Real-world performance resembles pivotal trial results



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Remote Monitoring of AMD Vs. Standard of Care Monitoring

- 2,123 dry AMD patients from 5 retina practices over 10 years followed
- Results: VA at conversion to wet AMD was **20/39 for ALOFT patients**, vs. **20/83 using current standard of care** of office visits and patient self-reported symptoms alone
- Patients whose conversion to wet AMD detected by ForeseeHome had an average VA of **20/32 at 2.7 years of treatment** vs. **20/80 after 2 years with current standard of care** monitoring.

Ophthalmology Retina April 25, 2022

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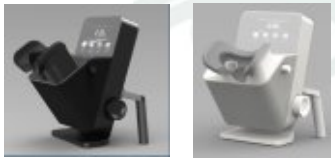
What's Next in OCT?

Notal Home-OCT



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AMD Treatment Durability

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Next Generation of Treatments for Wet AMD

- Beovu (Brolucizumab - Novartis)
  - Small size of the molecule allows higher dosing per volume results in a longer-lasting effect
- Vabysmo: Farcimab (Genentech)
- Port Delivery System (Genentech): Susvimo
  - Surgically implanted, refillable reservoir
  - Median time to first refill was 18 months
    - But large range: 7-8 months - 2 years

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Recent FDA Approvals for AMD and DME

- Port Delivery System (PDS): Susvimo
- Vabysmo: Farcimab: Vabysmo

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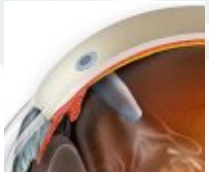
Port Delivery System (Genentech)

- Surgically implanted, refillable reservoir
- Median time to first refill was 18 months
  - But large range: 7-8 months - 2 years



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Port Delivery System

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Voluntary Recall of the PDS Ocular Implant

October 2022

- The manufacturer initiated a voluntary recall of the Port Delivery System with ranibizumab (PDS) ocular implant and insertion tool assembly, including the drug vial and initial fill needle.
- The recall does not include the ranibizumab 100 mg/ml drug vial for refill exchange procedures or the refill needle so that patients who have already received the PDS can continue refill exchange procedures.
  The recall also does not include the PDS explant tool.
- The US Food and Drug Administration (FDA) was informed and is aligned with the approach.

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Reason For Recall

- An investigation into septum dislodgement cases in the PDS phase 3 clinical trial program identified a need for additional testing of the commercial implant supply.
- The additional testing involved repeatedly puncturing the PDS implants with a needle, to evaluate performance of the septum of the implant over the long-term via multiple refills. The results showed that some implants did not perform up to standards.
- As of August 31st, 2022, there have been 33 reported cases of septum dislodgement in approximately 1,419 patients with implants (2.3%, includes re-implantations) and 5,236 refill-exchange procedures (0.63%) across PDS clinical trials.

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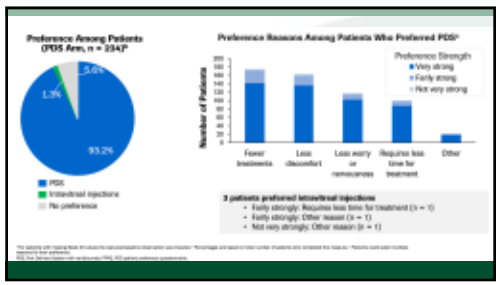

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January 31, 2022

FDA approves Roche's Vabysmo, the first bispecific antibody for the eye, to treat two leading causes of vision loss

- Vabysmo (faricimab-svoa) targets and inhibits two disease pathways that drive neovascular or "wet" age-related macular degeneration (nAMD) and diabetic macular edema (DME)
- Vabysmo is the only injectable eye medicine approved simultaneously in the US for nAMD and DME, with flexible dosing regimens based on patient need

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Angiopoietin/Tie-2 Signaling Pathway Faricimab: Vabysmo

A key player in the pathogenesis of AMD and DME

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The Angiopoietin/Tie2 signaling pathway maintains vascular homeostasis

- Responsible for blood vessel growth during embryonic development
- Controls vascular stability, vascular permeability, and inflammation

Key Players

Ligands/growth factors		Receptor
Angiopoietin-1 Constitutively expressed to maintain healthy vasculature	**Angiopoietin-2** Only upregulated under pathological conditions	**Tie2** Expressed in the endothelium

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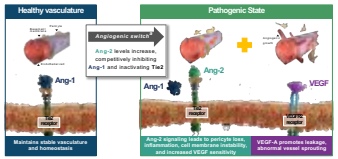
Ang-2 and VEGF-A are key drivers of angiogenesis, leakage, and microvascular inflammation



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Faricimab

Bispecific antibody targeting both Ang-2 and VEGF

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Faricimab phase 2 program: 578 patients, 3 studies in DME and neovascular AMD

DME	Neovascular AMD	
BOULEVARD	AVENUE	STAIRWAY
N = 229 Primary endpoint: 24 weeks	N = 273 Primary endpoint: 36 weeks	N = 76 Primary endpoint: 40 weeks
NCT02699450	NCT02484690	NCT03038880

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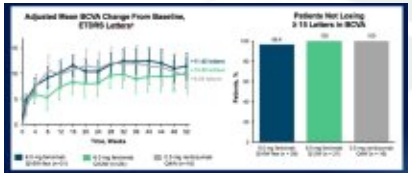
BCVA Outcomes with q 16 W and q 12 W Farcimab were Comparable to q4 Ranibizumab at 52 Weeks



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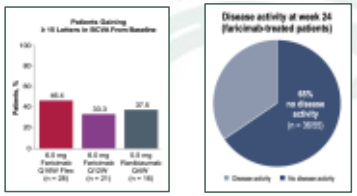
BCVA Outcomes with q 16 W and q 12 W Farcimab were Comparable to q4 Ranibizumab at 52 weeks



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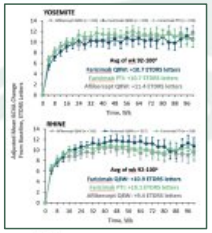
Faricimab for DME

At 100 wk, noninferior vision gains with faricimab up to Q16W vs aflibercept Q8W

- ~80% able to maintain Q12W-Q16W dosing

No new safety signals



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HOME SERVICES NEWS EDUCATION ABOUT US
OcuTerra Therapeutics Announces First Patient Dosed in OTT166 Phase 2 DR:EAM Clinical Trial for Diabetic Retinopathy

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OcuTerra Therapeutics Announces First Patient Dosed in OTT166 Phase 2 DR:EAM Clinical Trial for Diabetic Retinopathy

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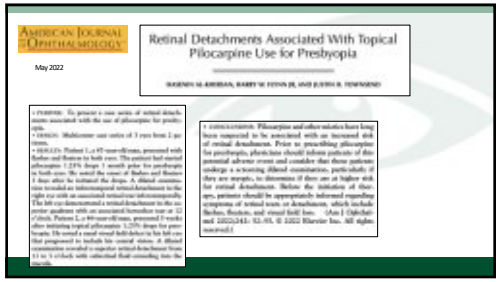
Vuity to Treat Presbyopia

- 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**

60



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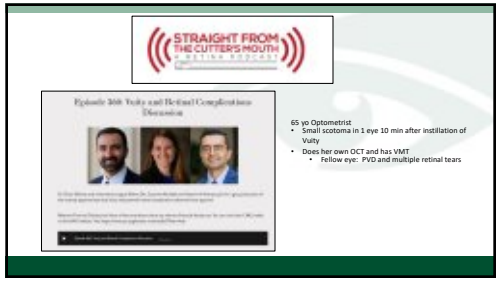

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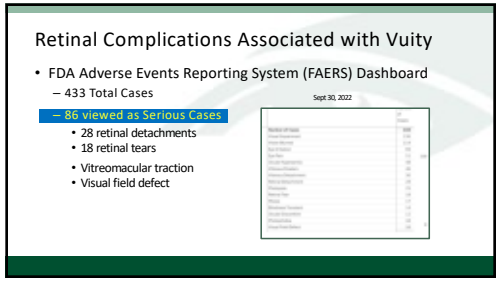

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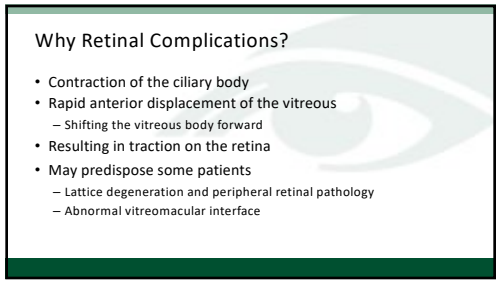

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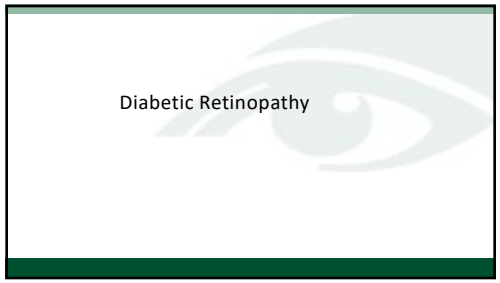


66

2022 National Diabetes Statistics Report

Diabetes is Occurring in Epidemic Proportions

- Affects over 11% of the US population (37.3 million people)[1]
  - 14% of all US adults ≥ 18 years old
- By 2050 between 1 in 5 and 1 in 3 US adults (estimated) will have diabetes

67

Diabetes by the Numbers

- Diabetes is increasing at epic proportions
- Optometrists are are on the front line as primary eye care providers
  - We play an important role as part of the healthcare team
- Effective treatment is now available that can improve vision, not just slow disease progression
- If we can detect early and treat early, we can preserve and improve vision in many patients

68

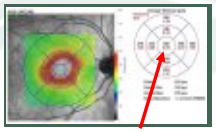
Diabetic Retinopathy 2022

- Anti-VEGF is the standard for treating DME
- The diagnosis of DME has changed
- The treatment of PDR is evolving
  - PRP vs. anti-VEGF vs. Combination
- We may need to refer before PDR
  - Earlier treatment may be beneficial (severe NPDR)

69

2017 DME Classification: Center Involved or Not?

- ETDRS definition of "clinically significant macular edema" modified in era of OCT
- Randomized clinical trials of anti-VEGF agents used presence of DME in OCT central subfield

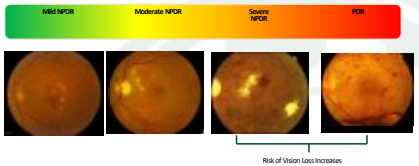


Brown DM, et al. *Ophthalmology*. 2015;122(10):2044-52.
Nguyen QD, et al. *Ophthalmology*. 2012;119(4):789-801.

70

Diabetic Retinopathy Severity Scale

International Scale



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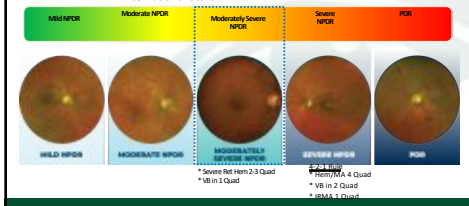
Diabetic Retinopathy Severity Scale

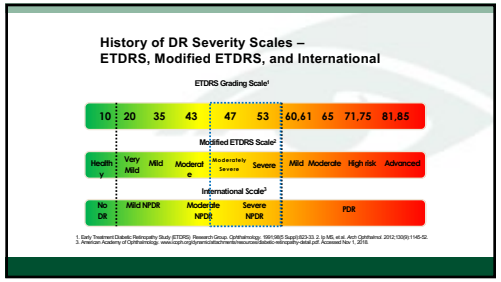
International Scale



* Severe Ret Hem 2-3 Quad
* VB in 1 Quad

* Hem/MA 4 Quad
* VB in 2 Quad
* IRMA 1 Quad

72



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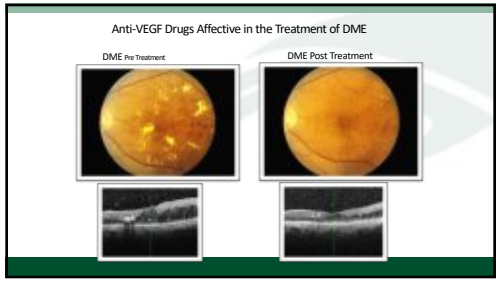

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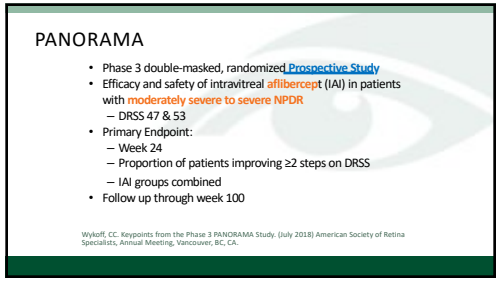

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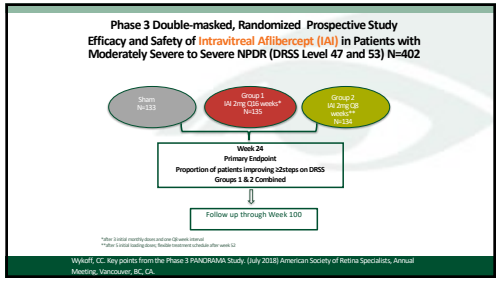

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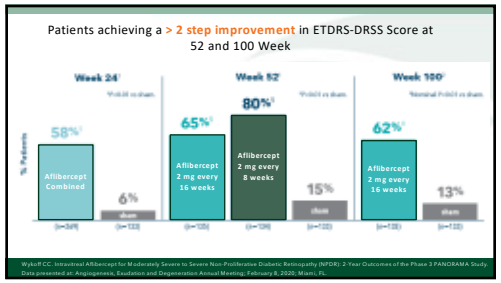

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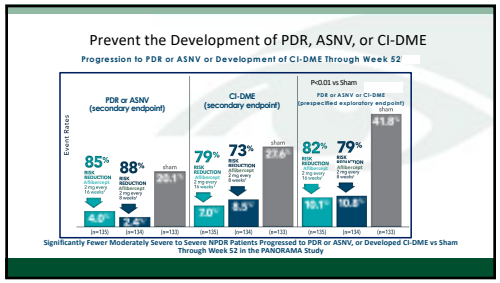
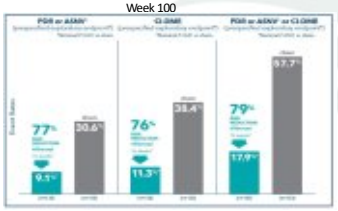


78

Prevent the Development of PDR, ASNV, or CI-DME

Week 100



Wykoff CC. Intravitreal Aflibercept for Moderately Severe to Severe Non-Proliferative Diabetic Retinopathy (NPDR): 2-Year Outcomes of the Phase 3 PANORAMA Study. Data presented at: Angiogenesis, Exudation and Degeneration Annual Meeting; February 8, 2020; Miami, FL.

79

Diabetic Retinopathy Severity Score (DRSS)

Level*	ETDRS Older Severity	Description
1	10 and 12	DR absent
2	14, 15, 20	DR questionable, microaneurysms only
3	35	Mild NPDR
4	43	Moderate NPDR
5	47	Moderately severe NPDR
6	53	Severe NPDR
7	60, 61	Mild PDR
8	65	Moderate PDR
9	71	High-risk PDR
10	75	High-risk PDR

2-Step Improvement in DRSS
From DRSS level 53, Severe NPDR (level6)
To DRSS level 43, Moderate NPDR (level 4)

The Diabetes Control and Complications Trial. *Arch Ophthalmol*. 1995;113:36-51; Aiello LM. *Am J Ophthalmol*. 2003;136:122-135

80

PANORAMA
Week 52 Results

- Vision threatening complications were reduced by 82% to 85% compared with sham injection
- Development of CI-DME was reduced by 68% to 74% compared with sham

81

Ophthalmology Retina October 2018

Ranibizumab Induces Regression of Diabetic Retinopathy in Most Patients at High Risk of Progression to Proliferative Diabetic Retinopathy

- The main objective of this exploratory post hoc analysis of the RIDE and RISE clinical trials was to examine DR outcomes in patients who were at highest risk for progressing to PDR (baseline DRSS levels 47/53).

82

RISE AND RIDE POST HOC ANALYSIS
PATIENTS WHO HAD NPDR AND PDR WITH DME

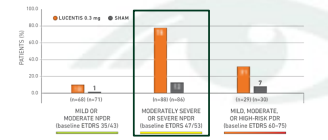
Post hoc analysis:

- Included 746 patients (LUCENTIS 0.3 mg, n=245; LUCENTIS 0.5 mg, n=247; sham, n=254) who had DR with DME and were randomized for treatment in RISE & RIDE
- DR outcomes with LUCENTIS were evaluated in patients along the spectrum of the severity scale (baseline ETDRS levels 10–75)
- Patients with prior panretinal photocoagulation (PRP) were not included in this analysis

Wykoff et al. *Ophthalmology Retina*. 2018.

83

RISE AND RIDE POST HOC ANALYSIS
≥2-STEP REGRESSION IN DR AT 2 YEARS



Limitations of this analysis include that it is post hoc (ie, not prespecified in protocols). The statistical significance of these results cannot be determined, and the clinical significance of these results is unknown. Results between groups should not be compared.

Wykoff et al. *Ophthalmology Retina*. 2018.

84

Ranibizumab induces Regression of Diabetic Retinopathy

Wycoff et al, Ophthalmology Retina October 2018

- At month 24, DR levels 47/53 **80% of eyes had a 2-step** improvement in ranibizumab treated eyes **vs 12% in the sham treated eyes**
- The regression of DR was not seen in earlier in less severe DR or in more severe DR
- **Study Conclusion**: In patients with baseline DR levels 47/53, ranibizumab treatment reduced the probability of patients experiencing a new proliferative event at month 36 by **3 X vs. sham Tx**

85

JAMA Ophthalmology | Original Investigation

Effect of Intravitreous Anti-Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy

The Protocol W Randomized Clinical Trial

Raj K. Maturi, MD; Adam R. Glassman, MS; Kristin Josic, PhD; Andrew N. Antoszyk, MD; Barbara A. Blodi, MD; Lee M. Jampol, MD; Bonnie M. Marcus, MD; Daniel F. Martin, MD; Michele Melia, ScM; Yoni Saikin-Hazi, MD; Cynthia R. Stockdale, MSPH; Omar S. Punjabi, MD; Jennifer K. Sun, MD, MPH; for the DRCR Retina Network

CONCLUSIONS AND RELEVANCE In this randomized clinical trial, among eyes with moderate to severe NPDR, the proportion of eyes that developed PDR or vision-reducing CI-DME was lower with periodic aflibercept compared with sham treatment. However, through 2 years, preventive treatment did not confer visual acuity benefit compared with observation plus treatment with aflibercept only after development of PDR or vision-reducing CI-DME. The 4-year results will be important to assess longer-term visual acuity outcomes.

Jama Ophthalmology, March 30, 2021

86

JAMA Ophthalmology | Original Investigation

Effect of Intravitreous Anti-Vascular Endothelial Growth Factor vs Sham Treatment for Prevention of Vision-Threatening Complications of Diabetic Retinopathy

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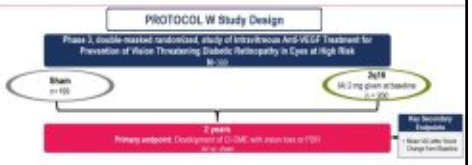
through 2 years,

preventive treatment did not confer visual acuity benefit compared with observation plus treatment with aflibercept only after development of PDR or vision-reducing CI-DME.

Jama Ophthalmology, March 30, 2021

87

PROTOCOL W: EYLEA VS. SHAM IN MODERATE TO SEVERE NPDR (DRSS OF 43 – 53)



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Protocol W: 2 Year Conclusions

- The 2-year data did not confer visual acuity benefit compared to sham group
  - Note: sham group received aflibercept once they developed DME or PDR

Jama Ophthalmology, March 30, 2021

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Is there a benefit from early Tx of Severe NPDR?

- So, what is the benefit of early treatment if it doesn't result in any visual acuity improvement?
- Does it matter that there is a regression in DR if when all and said and done the patient ends up with the same visual outcome?

90

Discussion

- Does the data suggest patients with severe NPDR should be treated?
- How early should we refer patients with DR?
- It becomes important to be able to accurately recognize severe NPDR
- Will the burden of early treatment be too overwhelming for ophthalmology?

91

AI device for detecting diabetic retinopathy earns swift FDA approval

- Images captured by Topcon NW400 non-mydriatic retinal camera
- Images sent to a cloud-based server that utilizes the IDx-DR software and a **'deep learning'** algorithm
- The technology was **87% sensitive and 90% specific** for detecting **more than mild** diabetic retinopathy
- The algorithm correctly identified **100% of with ETDRS level 43 or higher (moderate NPDR)**

92

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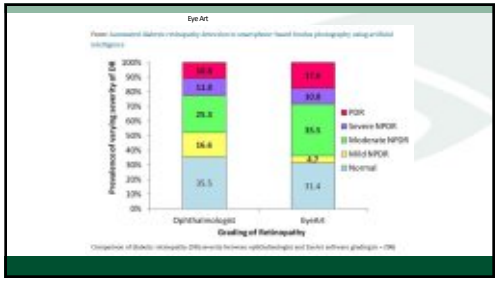

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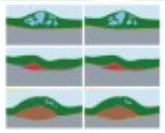
Google's AI product detects retinal diseases with unprecedented accuracy



95

May/June 2022 | Features

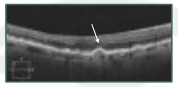
Artificial Intelligence in AMD Imaging

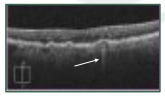
Here is a look at what to expect as this tool becomes more ubiquitous in research and the clinic.

96

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

- Drusen Volume
- Hyper-Reflective Foci (HRF)
- Retucular pseudo drusen
- Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy (iRORA)
  - Without RPE loss
  - Replaces "Nasacent cGA"
- Hyper-transmission defects
- OCT-Reflective Drusen Substructures





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OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

98

In a primary eye care setting do we need to dilate every patient?

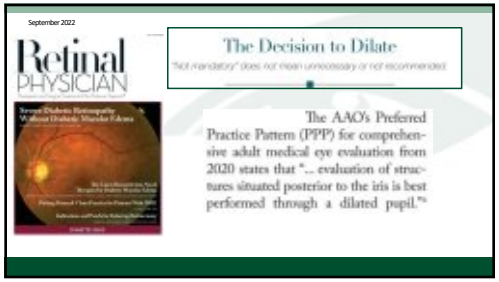
The reality:

- In a young patient population, the incidence of peripheral retinal pathology is exceedingly rare
  - You have to dilate a lot of patients to see any meaningful retinal pathology
- With changes in health care – there are greater demands to see more patient
- Is it an unreasonable medical expense?

99

Can it substitute for a dilated fundus exam?

100



101

Is UWF Imaging a Substitute for a DFE?

- While UWF imaging can show most of the retina, it will not reveal lesion anterior to the equator

It Should be Used as a Complement to DFE

- One study showed 30% increase in retinal lesion discovery comparted to traditional DFE alone

102

The Decision to Dilate…

Insistence on a DFE may also be motivated by potential malpractice litigation against ophthalmologists that is frequently based on missed retinal pathologies due to failure to dilate.

The medicolegal issue may outweigh any other consideration. Anything you would tell a judge about the reason you chose DFE pales beside what the patient might lose.

103

The Decision to Dilate…

Significantly, the definition of an eye exam does not, in any instance, include fundus photography; rather, it mentions ophthalmoscopy — which is dynamic and personally performed by the physician. Going further, extended ophthalmoscopy (92201, 92202) is not imaging.[3] We conclude therefore that UWF imaging should not be offered solely as a substitute for dilation. RP

Binocular indirect ophthalmoscopy (BIO) remains the gold standard.[3] Therefore, we conclude that UWF imaging should be used only as an adjunct to a DFE that includes careful peripheral retinal examination.

104

The Evolution of OCT Imaging

- OCT has changed how clinicians look at the retina
- The assessment of retinal abnormalities based on OCT imaging has advanced eye care
- OCT in Optometry practices ~ 70% +
- As the technology has evolved -> prices continue to come down

105

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD


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

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

106

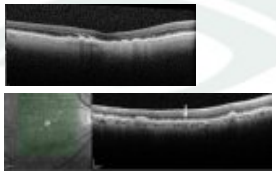
OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

- Drusen volume
- Increased drusen height
- Abnormal thinning of the RPE layer

107

OCT Biomarkers May Help Predict Conversion to GA or Wet AMD

- Hyper-Reflective Foci (HRF)
- Retucular pseudo drusen
- Incomplete Retinal Pigment Epithelial and Outer Retinal Atrophy (iRORA)
  - Without RPE loss
  - Replaces "Nasacent GA"
- Hyper-transmission defects
- OCT-Reflective Drusen Substructures



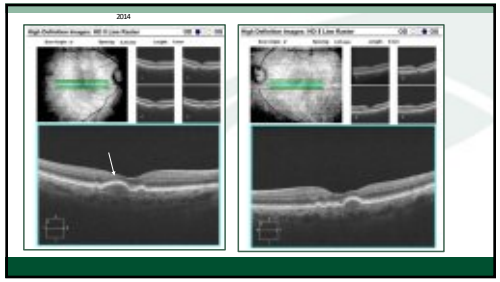
108

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

109



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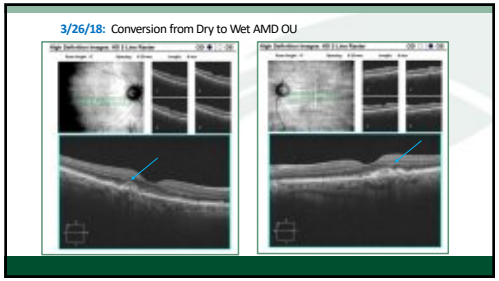

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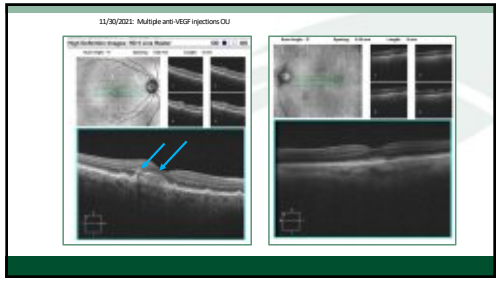

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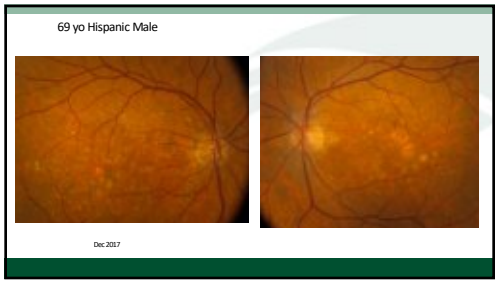

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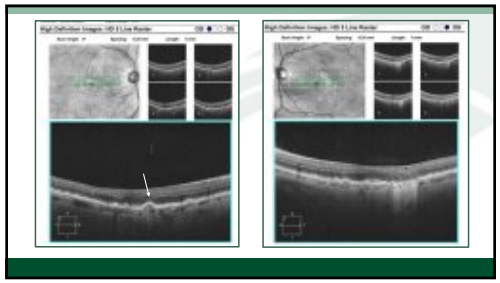

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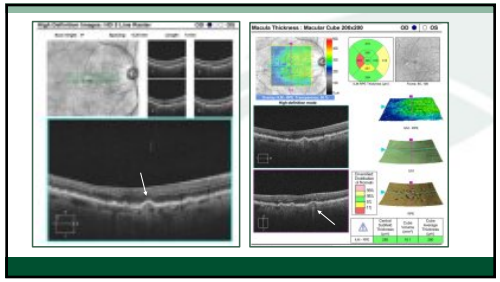

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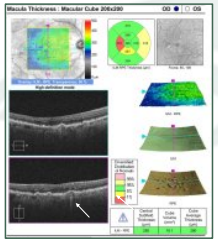
Hyper-reflective Columns

- Narrow strips of light transmission
- Overlying RPE appears intact
  - May represent micro-cracks
- Increased risk of progression to GA
  - Present in 27% of eyes that progressed to GA nAMD



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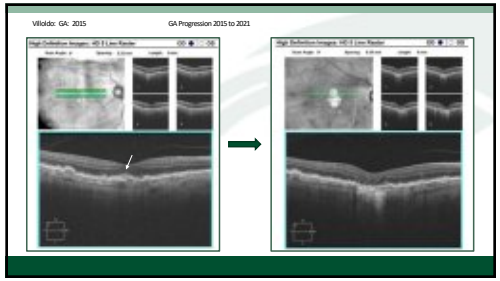

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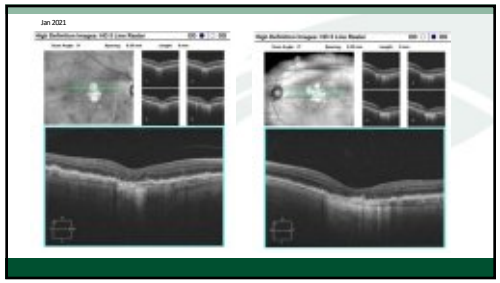


120

55 yo Caucasian Male

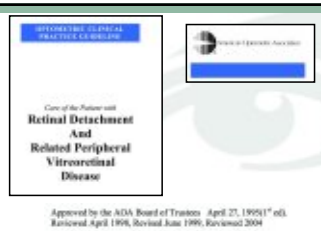
- **Presents with sudden onset of floaters RE**
  - "Feels like I am looking through an oil slick or water"
- BCVA: 20/20 each eye
- CVF: FTFC OU
- Dilated patient with 1% Tropicamide, 2½% Neo
- Examines with 90 D and peripheral retina with BIO and 20 D lens
- Notes Weiss Ring and attached retina

121

55 yo Caucasian Male

- Diagnosis: PVD
- Educated regarding signs and symptoms of retinal detachment
- Explains need to **return immediately** if he should see these symptoms
- RTC 1 yr

122



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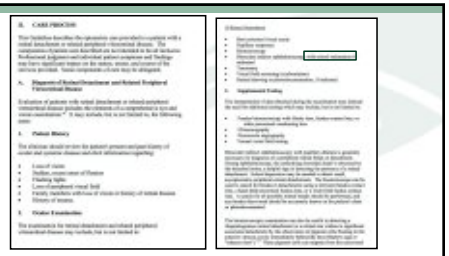

124

the detached retina, a helpful sign in detecting the presence of a retinal detachment. Scleral depression may be needed to detect small, asymptomatic peripheral retinal detachments. The biomicroscope can be used to search for breaks in detachments using a mirrored fundus contact lens, a hand-held precorneal fundus lens, or a wide-field fundus contact lens. A search for all possible retinal breaks should be performed, and

125

Crossfire Topics

- Do you feel comfortable managing patients with symptomatic PVD's?
- Do you perform scleral depression on your patients with symptomatic flashes and floaters?
- The standard of care for evaluating a patient with flashes and floaters is **scleral depression**

126

PVD

- Retinal tears occur 8-15% of eyes with symptomatic PVD
  - 90% are superior
- VH occurs in 13-19% of symptomatic PVD's
- VH + PVD -> 70% will have a retinal break
- PVD No VH -> 2-4% will have retinal break

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Lattice Degeneration

- Present 5-20% of the general population
- Localized area of retinal thinning associated with a fluid pocket in the overlying cortical vitreous

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Lattice Degeneration and Risk of RD

- RD develop in 0.7% of eyes with lattice degeneration followed for 10.8 yrs
- Eyes with lattice that developed tractional retinal tears
  - 40% occurred in areas not associated with lattice…normal-appearing retina

Byer NE. Ophthalmology. 1989; 96:1401-1402

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