Hot Topics in Retina

TRENDING NOW

Mark T. Dunbar, OD, FAAO
Bascom Palmer Eye Institute
University of Miami
Miami, FL 33136
mdunbar@miami.edu

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Mark Dunbar: Disclosure

- Optometry Consultant/Advisory Board
  - Carl Zeiss
  - Allergan
  - Regeneron
  - Genentech
  - Tarsus
  - Orasis
  - Iveric

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Hot Topics in Retina

- Vuity
- Treatments for GA
- Better Treatments for Wet AMD
- The paradigm shift in the diagnosis and management of diabetes

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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**

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AMERICAN JOURNAL OF OPHTHALMOLOGY
May 2022

Retinal Detachments Associated With Topical Pilocarpine Use for Presbyopia

HASENIN AL-KHERSAN, HARRY W. FLYNN 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 inferotemporal retinal detachment in the right eye with an associated retinal tear inferotemporally. The left eye demonstrated a retinal detachment in the superior quadrant with an associated horseshoe tear at 12 o'clock. Patient 2, a 66-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.)

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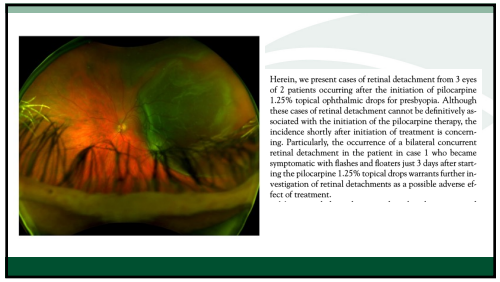

Herein, we present cases of retinal detachment from 3 eyes of 2 patients occurring after the initiation of pilocarpine 1.25% topical ophthalmic drops for presbyopia. Although these cases of retinal detachment cannot be definitively associated with the initiation of the pilocarpine therapy, the incidence 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.

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JULY/AUGUST 2022
www.retinalphysician.com
Retinal PHYSICIAN

Vitreoretinal Views on Vuity

Choose and monitor patients carefully.

SUZANNE MICHALAK, MD • PRITHVI MRUTHYUNJAYA, MD, MHS • EHSAN RAHIMY, MD

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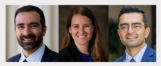
STRAIGHT FROM THE CUTTER'S MOUTH
A RETINA PODCAST

Episode 360: Vuity and Retinal Complications Discussion



65 yo Optometrist

- Small scotoma in 1 eye 10 min after instillation of Vuity
- Does her own OCT and has VMT
  - Fellow eye: PVD and multiple retinal tears

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Retinal Complications Associated with Vuity

- FDA Adverse Events Reporting System (FAERS) Dashboard
  - 425 Total Cases
  - 71 viewed as Serious Cases
    - 19 retinal detachments
    - 6 retinal tears
    - Vitreomacular traction
    - Visual field defect

Case Count by Received Year Sept 22

Category	Number of Cases	Percentage
2022	424	99.765
2021	1	0.24%
Totals	425	100.00%

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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

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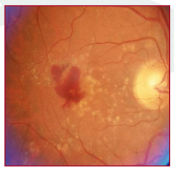
Age-related Macular Degeneration (AMD)

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



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ARMD

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

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AMD "Factoids"

- 1 in 3 people older then 75 will be affected by AMD
  - The number of people > 75 is steadily increasing
  - 10,000 people turn 65 in the US every day
- By 2025, there will be 44% more people in the US in this "high-risk" age group than there are today

Special Issue

The Prevalence of Age-Related Eye Diseases and Visual Impairment in Aging: Current Estimates

Ronald Klein and Barbara E. K. Klein

Invest Ophthalmol Vis Sci. Dec 2013; 54(14): ORSF14-ORSF17.
Published online Dec 13, 2013. doi: 10.1167/iovs.13-13782

Eye Disease	2000 /# in Millions (%)	2020 /# in Millions
Cataract*	20.5 (17.2)	30.1
Pseudophakia†	6.1 (5.1)	9.5
Diabetic retinopathy	4.1 (3.4)	6.1
Vision-threatening diabetic retinopathy	0.9 (0.8)	1.4
Open-angle glaucoma	2.2 (1.9)	3.4
Late age-related macular degeneration	1.8 (1.5)	3.0
Large drusen	7.3 (6.1)	13.7
Blindness	0.9 (0.8)	1.6
Low vision	2.4 (2.0)	3.9

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Neovascular AMD: Risk Factors

- Emerging risk factors
  - Age[1]
  - Race[1]
  - Smoking[2]
  - Family history[3]
  - Variation in the complement factor H gene[4-6] and other genes[7]

1. Friedman et al. *Arch Ophthalmol*. 2004;122:564; 2. Kohn et al. *Br J Ophthalmol*. 2006;90:75; 3. Buch et al. *Acta Ophthalmol Scand*. 2005;83:409; 4. Klein et al. *Science*. 2005;308:385; 5. Haines et al. *Science*. 2005;308:419; 6. Sepp et al. *Invest Ophthalmol Vis Sci*. 2006;47:536; 7. Haines et al. *Invest Ophthalmol Vis Sci*. 2006;47:329.

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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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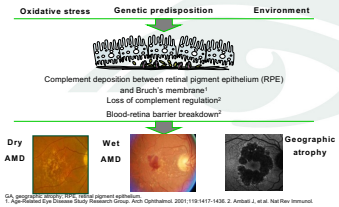
Current Hypothesis for AMD Pathophysiology



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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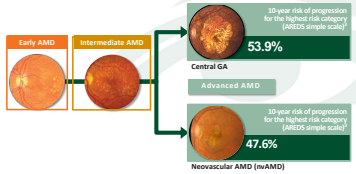
AMD Is the Leading Cause of Blindness for Caucasians in the US[1]



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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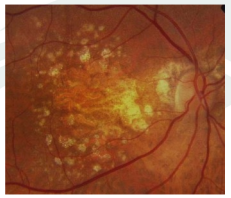
Geographic Atrophy

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



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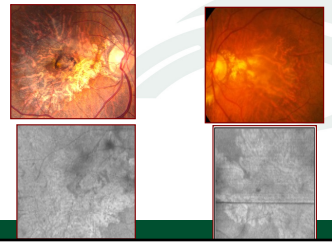
Esther: Geographic Atrophy



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Geographic Atrophy Impact on Quality of Life

- **Global Geographic Atrophy Insights Survey (GAINS)**
  - Sponsored by Apellis Pharmaceuticals and conducted by The Harris Poll last year
    - Included 203 adult participants with GA, in 9 countries
  - **7 in 10** believe the impact on their independence and quality of life due to visual decline is worse than they expected
  - **Majority felt** the disease negatively affects their ability to read, drive, and travel;
  - **1 in 3 recently withdrawn from social activities** due to their disease

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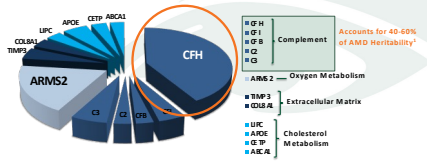
Key Genes Involved in the Development of AMD



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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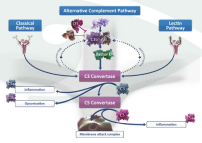
The Compliment System

- **Complement Pathway** is one of the body's primitive defense immune systems
  - Made up of a group of proteins that:
    - Mounts inflammation
    - Destroys foreign invaders
    - Removes debris resulting from that destruction
- Complement Factor H is a gene that gives instructions for making Factor H
  - Factor H is an important ***inhibitory regulator*** of this system
- Drusen contain most all of the proteins that make up the complement system



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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)

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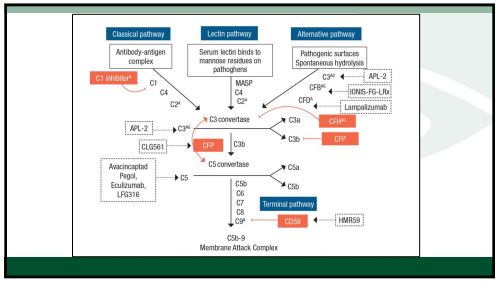

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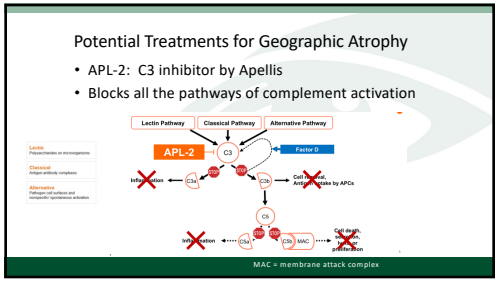

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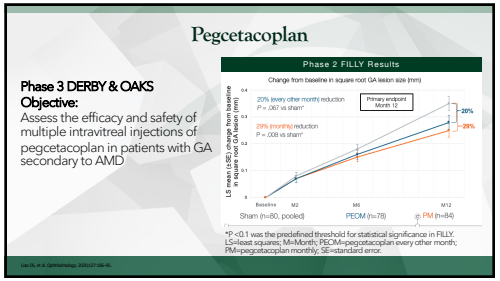

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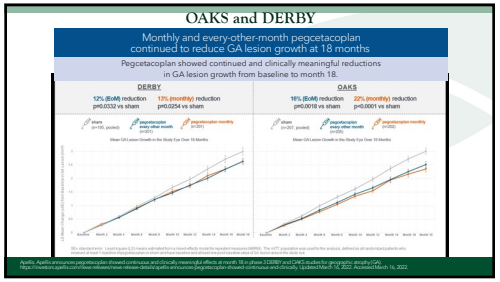

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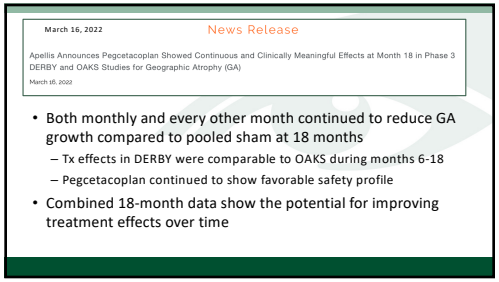

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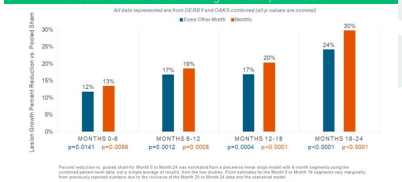
OAKS and DERBY

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



Percent reduction vs. pooled sham for Month 0 to Month 24 was estimated from a piecewise linear slope model with 6-month segments using the combined patient-level data, not a simple average of results from the two studies. Point estimates for the Month 0 to Month 18 segments vary marginally from previously reported numbers due to the inclusion of the Month 20 to Month 24 data into the statistical model.

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

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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
- 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 ICI 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
- The company plans to submit the 24-month efficacy data from the Phase 3 DERBY and OAKS studies as part of its NDA
- ✓ PDUFA target action date is February 2023[1]

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 (Zimura): Iveric

- Complement C5 inhibitor
- Reduction in GA growth for patients receiving Zimura in the U.S. was **25.5 - 32.0%**

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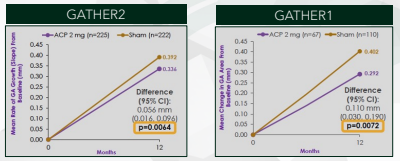
Avacincaptad Pegol:

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 mnth	Monthly	Every other mnth
Change in GA area vs sham at 12mo	14%*	27%*	12%	11%	22%	16%
p value	0.0064	0.0072**	0.0528 (N/S)	0.0750 (N/S)	0.0003	0.0052
Choroidal neovascularisations	7%***	9%***	7%^	3%^	5%^	5%^

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Anti-VEGF Standard of Care for Wet AMD

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

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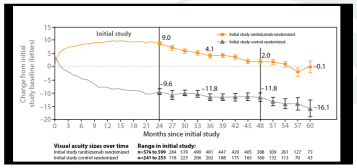
HORIZON: Extension Study



Visual acuity sizes over time

Range in initial study:

Extension study evaluating the ≥2-year frequency, safety, tolerability, and efficacy of multiple intravitreal ranibizumab injections in Wet AMD patients who completed 1 of 3 initial studies: MARINA, ANCHOR, or FOCUS

Ranibizumab 0.5 mg was administered at the investigator's discretion

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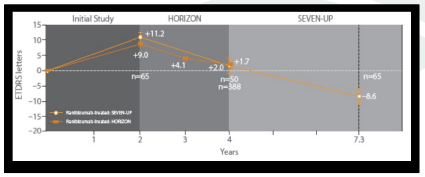
SEVEN-UP Study: 7-Year Outcomes in Treated Patients in MARINA, ANCHOR, and HORIZON



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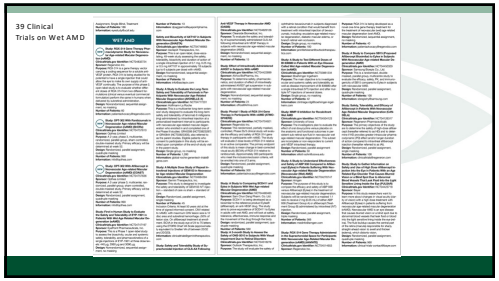
39 Clinical Trials on Wet AMD



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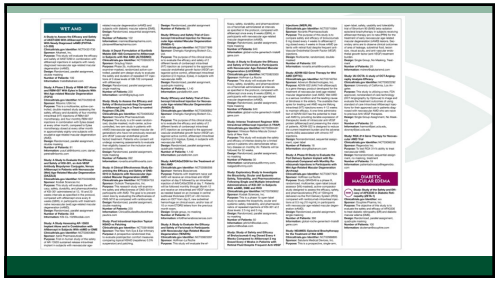

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15 Studies Dry AMD

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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
- 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)
- Vabysmo: Farcimab

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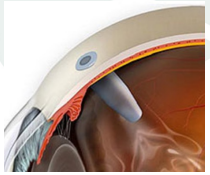
Port Delivery System (Genentech)

- 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 (PDS)

- A permanent refillable eye implant that continuously delivers ranibizumab over a period of months
- Refilled every **6 months**, PDS demonstrated non-inferior and equivalent efficacy compared to the standard of care – monthly ranibizumab eye injections
- Archway Study: Phase 3 results presented July 2020
  - Port delivery equivalent to monthly Ranibizumab injections
  - 248 pts PDS vs. 167 monthly injections
  - **98% did not need supplement injection**

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Wet AMD Patients Prefer PDS Implant Over Injections

Patients underwent only 2 procedures in 40 weeks.

- Patients in Genentech's phase 3 ARCHWAY trial **strongly preferred the PDS** sustained-release implant over regular injections of ranibizumab
- > 93% of the 228 patients who received the implant cited such reasons as **fewer injections**, **reduced discomfort**, and **less nervousness** and apprehension
- Patients in injection arm averaged ~ 10 injections over 40 weeks
  - Implant had only the initial implantation in the operating room and a mandated in-office refill at 24 weeks
  - **Only 4 of 228 patients required a PDS refill prior to 24 weeks.**
- PDS with a custom formulation of ranibizumab **provided** essentially **the same efficacy as monthly injections of regular ranibizumab**

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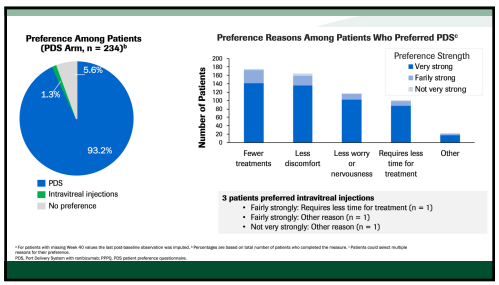

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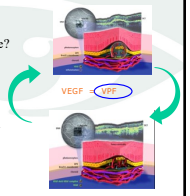
Anti – VEGF Monotherapy

- AMD is a complicated disease
- Is it really initiated/driven by only one cytokine?
- The existing does not disappear
- Once the Anti-VEGF molecule is not present edema may come back
- This may explain the need for retreatment until existing CNV becomes inactive



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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

A key player in the pathogenesis of AMD and DME

VABYSMO
faricimab-svoa injection 6 mg

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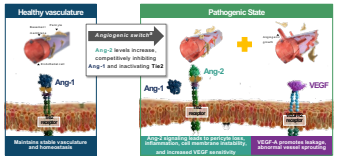
Ang-2 and VEGF-A are key drivers of angiogenesis, leakage, and microvascular inflammation



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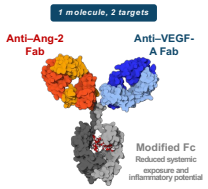
Faricimab: first bispecific antibody designed for intraocular use

- Engineered for efficacy, duration within the eye, and fast systemic clearance



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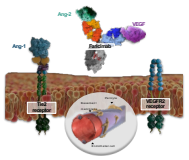
Neutralizing both Ang-2 and VEGF with faricimab



Targeting both:

- Promotes pericyte and vessel stabilization
- Reduces fluid leakage
- Reduces growth of new vessels
- Reduces inflammation

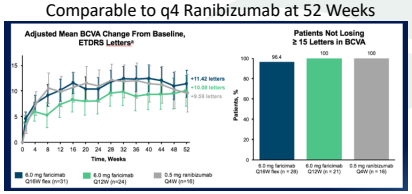
55

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 NCT02699450	N = 273 Primary endpoint: 36 weeks NCT02484690	N = 76 Primary endpoint: 40 weeks NCT03038880

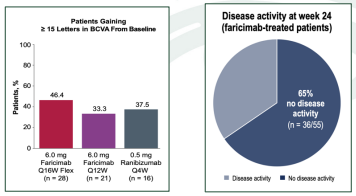
56

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



57

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



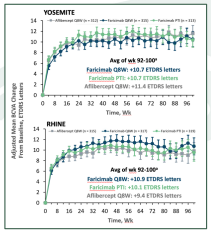
58

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



59

The Optometrist's Role in Diagnosing and Managing Patients with Diabetes

- Optometrists play a critical role as a part of the healthcare team managing patients with diabetes
- It is paramount to recognize the presence of diabetic retinopathy
- Recognizing when it's more than moderate nonproliferative diabetic retinopathy
- Accurate DR staging is critical for timely referral and treatment
  - Clinical exam vs. wide-field imaging

60

2022 National Diabetes Statistics Report

Diabetes is Occurring in Epidemic Proportions

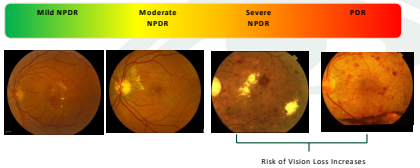
- Affects over 11% of the US population (37.3 million people)[1]
  - 14% of all US adults ≥ 18 years old
- By 2050 between 1 in 5 and 1 in 3 US adults (estimated) will have diabetes

Data sources: US Diabetes Surveillance System; Behavioral Risk Factor Surveillance System.

61

Diabetic Retinopathy Severity Scale

International Scale



62

ETDRS vs. International Classification of DR

Diabetic Retinopathy	ETDRS	International Scale
Mild NPDR	At least one Ma	Ma only
Moderate NPDR	H/Ma > Standard Slide 2A or soft exudates, VB, IRMA	More than just Ma, but less than Severe NPDR
Severe NPDR	One of the following: • H/Ma ≥ standard photo 2A in all 4 quadrants • VB present in at least 2 quadrants • IRMA > standard photo 8A in at least 1 quadrant	No signs of PDR with any of the following: • > 20 intraretinal hemorrhages in each of 4 quadrants; • Definite VB in ≥2 quadrants; • Prominent IRMA in ≥1 quadrant
PDR/High Risk PDR		Severe NPDR and one or both of the following: • Neovascularization; • Vitreous/preretinal hemorrhage

Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology. ISBN 1817421

63

Severe Nonproliferative Diabetic Retinopathy (NPDR)

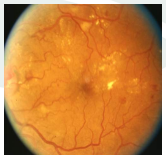
4-2-1 Rule

- 20 Hemorrhages & Ma in each 4 quadrants
- Significant venous beading in 2 quadrants
- Prominent IRMA in 1 quadrant

64

Risk for Progression to PDR

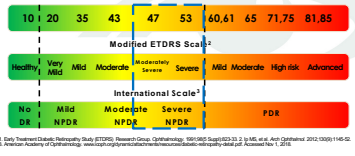
	1 year	5 year High-Risk PDR
Mild NPDR	5%	15%
Moderate NPDR	12%	33%
Severe NPDR	52%	60-75%
Very Severe NPDR	72%	75%



https://aao.uberflip.com/i/1183814-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition/59?m4=

65

History of DR Severity Scales – ETDRS, Modified ETDRS, and International

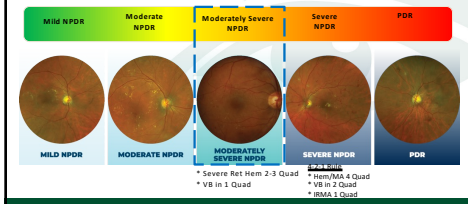


1. Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group. Ophthalmology. 1991;98(5 Suppl):823-33. 2. Ip MS, et al. Arch Ophthalmol. 2012;130(9):1145-52.
3. American Academy of Ophthalmology. www.aopht.org/preferredpracticepatterns/resources/diabetic-retinopathy-latest.pdf. Accessed Nov 1, 2018.

66

Diabetic Retinopathy Severity Scale

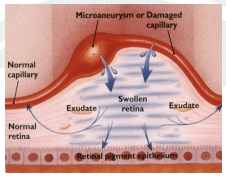
International Scale



67

Macular Edema

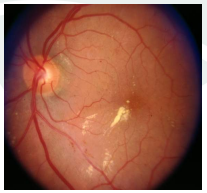
- Thickening of the retina
- Secondary to leaky microaneurysms
- **90% of visual loss in diabetes**



68

CSME

- Retinal thickening within 500 microns from the center of the FAZ
- Hard exudates associated with retinal thickening 500 microns from center of FAZ
- Zones of retinal thickening > 1 DD in area, any part of which is 1 DD from the center of the fovea



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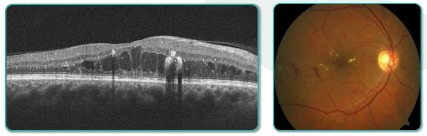
Diabetic Macular Edema (DME)



SD-OCT of a retina with DME

Color Fundus photo with DME

70

How we diagnose diabetic macular edema is changing

ETDRS definition has been modified in the era of OCT and anti-VEGF therapy

71

Diabetic Macular Edema (DME)

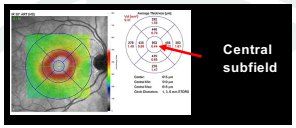
- CSME
- Center involved vs. Not center involved

72

2017 DME Classification:

Center Involved of 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



Wang: Quin Dong, et al. "Ranibizumab for diabetic macular edema: results from 2 phase III randomized trials: RISE and RIDE." Ophthalmology 119.4 (2012): 789-801.
Brown, David M., et al. "Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies." Ophthalmology 122.10 (2015): 2044-2052.

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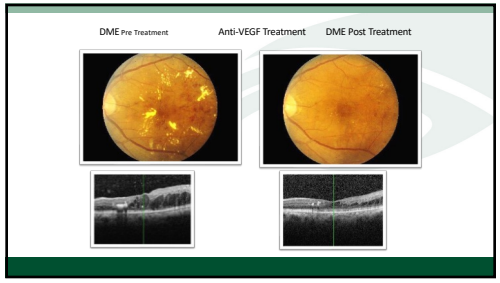

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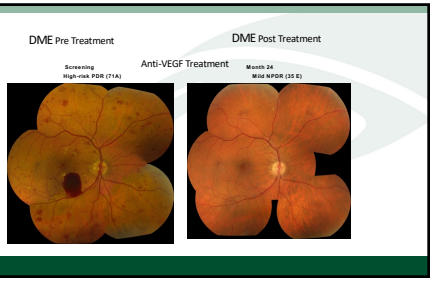

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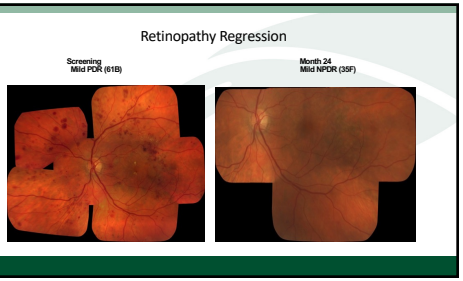


76

"The Fate of 47…"

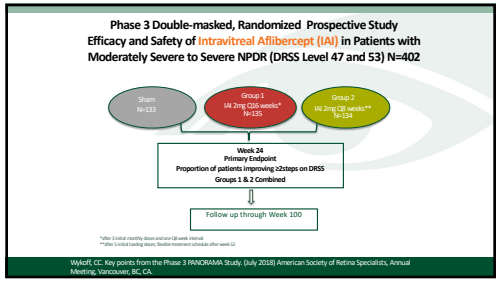
77

PANORAMA

- Phase 3 double-masked, randomized Prospective Study
- Efficacy and safety of intravitreal aflibercept (IAI) in patients with moderately severe to severe NPDR
  - DRSS 47 & 53
- Primary Endpoint:
  - Week 24
  - Proportion of patients improving ≥2 steps on DRSS
  - IAI groups combined
- Follow up through week 100

Wykoff, CC. Keypoints from the Phase 3 PANORAMA Study. (July 2018) American Society of Retina Specialists, Annual Meeting, Vancouver, BC, CA.

78



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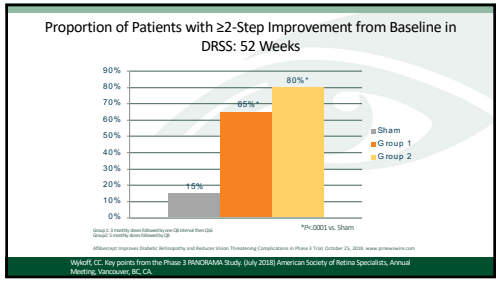

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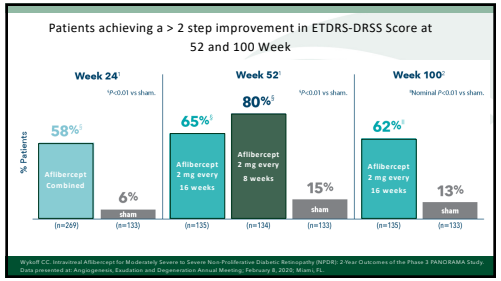

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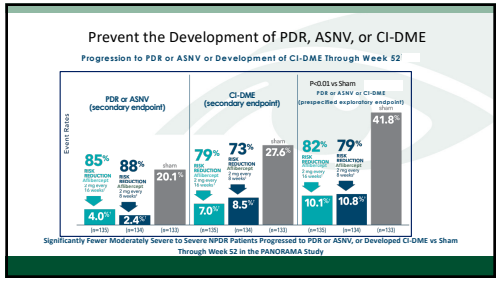

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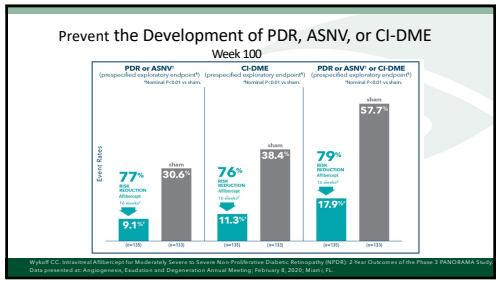

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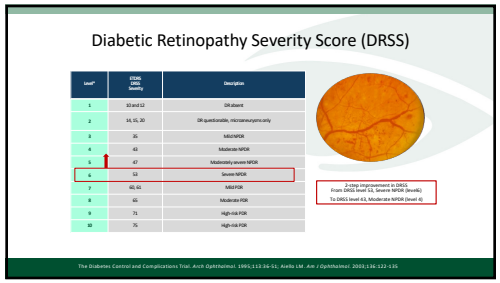


84

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

85

AMERICAN ACADEMY OF OPHTHALMOLOGY

Ophthalmology Retina October 2018

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

Charles C. Wykoff, MD, PhD,[1] David A. Eichenbaum, MD,[2] Daniel B. Roth, MD,[3] Lauren Hill, MS,[4] Anne E. Fung, MD,[5] Zdenka Haskova, MD, PhD[6]

- 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).

86

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

CENTIS DIABETIC MACULOPATHY

Post hoc analysis:

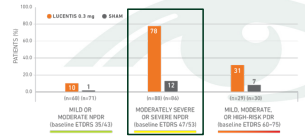
- Included 746 patients (LUCENTIS 0.3 mg, n=245; LUCENTIS 0.5 mg, n=247; sham, n=254) who had DR with DME and were randomized for treatment in RISE & RIDE
- DR outcomes with LUCENTIS were evaluated in patients along the spectrum of the severity scale (baseline ETDRS levels 10–75)
- Patients with prior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

Wykoff et al. *Ophthalmology Retina*. 2018.

87

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

CENTIS DIABETIC MACULOPATHY



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.

88

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 times vs. sham treatment**

89

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; Dennis M. Marcus, MD; Daniel F. Martin, MD; Michele Melia, ScM; Hani Salehi-Had, 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

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

PROTOCOL W Study Design

Phase 3, double-masked randomized, study of Intravitreous Anti-VEGF Treatment for Prevention of Vision Threatening Diabetic Retinopathy in Eyes at High Risk
N=399

Sham
n=199

2q16
IAI 2 mg given at baseline
n = 200

2 years
Primary endpoint: Development of CI-DME with vision loss or PDR
IAI vs. sham

Key Secondary Endpoints
- Mean VA Letter Score Change from Baseline

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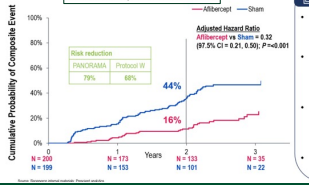
Protocol W: 2 Year Conclusions

Time to Development of DME or PDR



VTC Prevention and long-term VA benefit

- **Protocol W confirmed findings of PANORAMA** with similar magnitude of the treatment effect
- **Protocol W showed benefit of aflibercept treatment in patients with moderate disease** (DRSS 43) for the first time
- Preventative treatment with **aflibercept did not confer VA benefit compared with anti-VEGF** initiated after PDR or DME development
- 4-year results will provide **long-term VA outcomes**

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?

93

Artificial Intelligence

AI is poised to revolutionize medicine.

94

npj | Digital Medicine Nov 2019

ARTICLE OPEN

Deep learning algorithm predicts diabetic retinopathy progression in individual patients

In-person expert examinations are impractical and unsustainable given the pandemic size of the diabetic population. As such, AI may offer a solution to this conundrum. DL, and specifically, deep convolutional neural networks (DCNNs), can be used for an end-to-end assessment of raw medical images to produce a target outcome prediction, the authors wrote.

95

APR 12, 2018

AI device for detecting diabetic retinopathy earns swift FDA approval

By Keng Jin Lee
FDA

- 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)**

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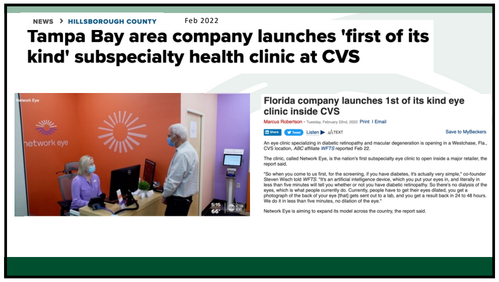

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August 6, 2020 FDA Clears EyeArt: AI System for Diabetic Retinopathy Detection

EyeArt is the first FDA cleared AI technology for autonomous detection of both more than mild and vision-threatening diabetic retinopathy. It is the most extensively validated autonomous AI technology, tested in the real-world on more than half million patients and nearly two million retinal images globally..

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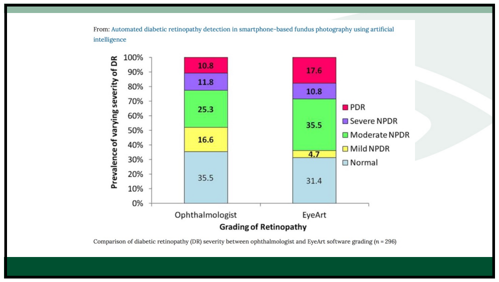

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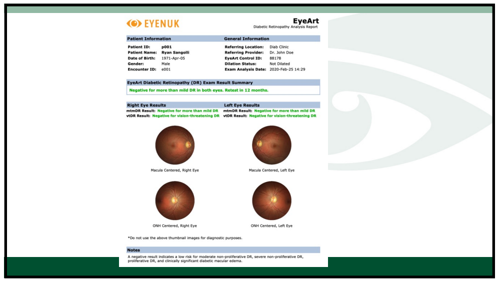

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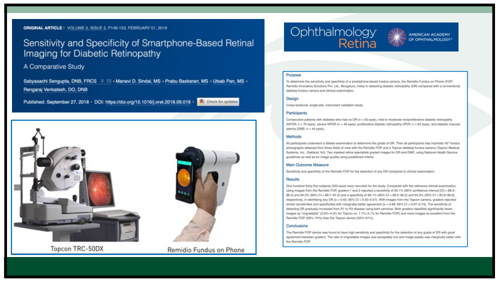

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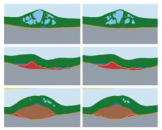
AUG 20, 2018

Google's AI product detects retinal diseases with unprecedented accuracy

By Anni Griswold
DeepMind
Comprehensive Ophthalmology, Retina/Vitreous



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ARTIFICIAL INTELLIGENCE

Google's medical AI was super accurate in a lab. Real life was a different story.

If AI is really going to make a difference to patients we need to know how it works when real humans get their hands on it, in real situations.

MIT Technology Review

April 27, 2020
Will Douglas Heaven

Thailand Study

- Many of the images rejected (20%)
  - Poor lighting
- Images uploaded to the cloud but issues with internet speed
- Time wasted re-taking images
- **When it did work – it worked well**
  - **One nurse was able to see > 1000 pts**
- Patients didn't really care that it was an AI rather than a human reading their images – just wanted good experience

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HOME› SMART HOME

Google Health wants to speed up healthcare with machine learning and smartphones

Accurate results in a flash

BY JULES WANG
PUBLISHED MAR 24, 2022

2

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May/June 2022 | Features

RT | Retina Today

Artificial Intelligence in AMD Imaging

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

AT A GLANCE

- Advances in retinal imaging have led to the identification of biomarkers for AMD progression that may one day shape how we diagnose, treat, and follow patients with AMD.
- Artificial intelligence (AI) algorithms may be able to provide analyses to assist physicians in diagnosing conditions based on specific features extrapolated from large volumes of imaging data.
- Researchers have demonstrated AI's ability to objectively identify, localize, and quantify subretinal fluid and high-risk structural biomarkers on OCT using a fully automated tool.
- AI-based imaging may be particularly useful in the era of personalized medicine, where we may be able to accurately predict outcomes and choose the optimal therapeutic strategies.

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