Greatest Posterior Segment Disease Talk - Ever!

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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: 2022-2023

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- Iveric
- Notal
- National Vision
- Reliance
- Novartis
- OcuTerra

3

Mark Dunbar: Disclosure

- Optometry Consultant/Advisory Board
  - Carl Zeiss
  - Allergan
  - Regeneron
  - Genentech
  - Tarsus
  - Orasis
  - B&L
  - Visus
  - Apellis
  - Iveric
  - Avellino

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Hot Topics

- AMD – will we have a Tx for dry
  - Will the new anti-VEGF drugs any better?
- Changing paradigm in the management of diabetic retinopathy
- AI
- OCT and OCTA
- Management of flashes/floaters
- Pigmented lesion of the fundus

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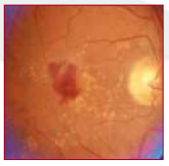
Age-related Macular Degeneration (AMD)

- 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

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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. Kahn 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. Segg 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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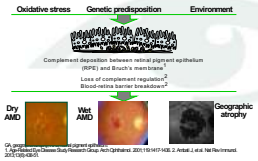
Current Hypothesis for AMD Pathophysiology



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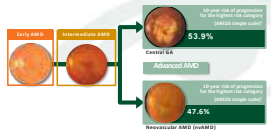
AMD Is the Leading Cause of Blindness for Caucasians in the US[1]



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Geographic Atrophy

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

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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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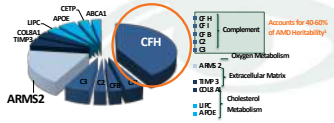
Key Genes Involved in the Development of AMD



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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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August 4, 2023

Iveric Bio Receives U.S. FDA Approval for IZERVAY™ (avacincaptad pegol intravitreal solution), a New Treatment for Geographic Atrophy

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2/17/2023

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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Current FDA Approved Complement Inhibitors – 2nd Generation

NOVEL THERAPIES FOR GA THAT TARGET THE COMPLEMENT PATHWAY

Study drug (Company)	Complement Target	Delivery Method	Current Trial Phase	Most Recent Trials	Study Status
Avacincaptad pegol (Iveric Bio)	C5	IVI	3	GATHER2 GATHER1	Complete
Pegcetacoplan (Apellis)	C3	IVI	3	OAKS, DERBY	Complete

GA, geographic atrophy; IVI, intravitreal injection

Liu Y, Nesar JS. Geographic Atrophy: Targeting the Complement Pathway. Retina Today. November/December 2021. https://retinatoday.com/articles/2021-nov-dec/geographic-atrophy-targeting-the-complement-pathway?view=visual-feed. Updated Dec 15, 2021. Accessed March 1, 2022.

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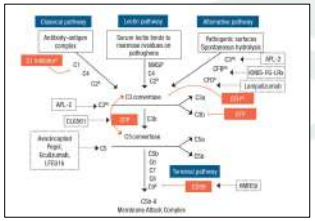

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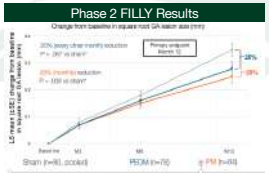
Pegcetacoplan (Syfovre)

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.

22

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 x time interaction

*Sham Monthly and EOM 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
- NEI VFQ-25
- FBI 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 14, 2022. Accessed March 14, 2022.

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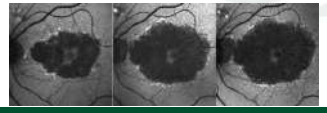
Pegcetacoplan: Take-Away Points

- 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

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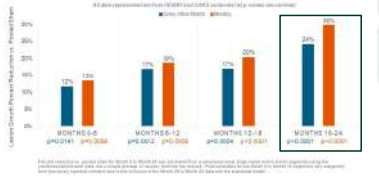

https://investors.apellis.com/news-releases/news-release-details/apellis-announces-24-month-results-showing-increased-effects

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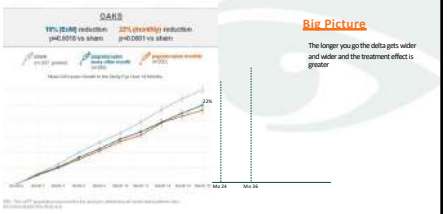
OAKS and DERBY



Big Picture

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

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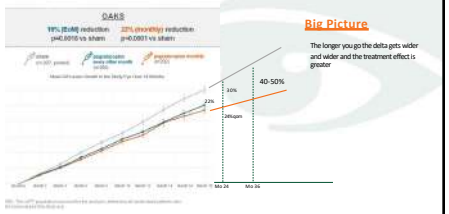
OAKS and DERBY



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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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Apellis: Pegcetacoplan

Is that a significant treatment effect for GA?

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July 19, 2023

ASRS American Society of Retina Specialists

ASRS reports six cases of occlusive retinal vasculitis linked to pegcetacoplan injection

Jul 19, 2023

David Hutton

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Syfovre – Serious Adverse Events (SAE's)

Here is what we know

- July 15 initial email from ASRS describing 6 cases of occlusive retinal vasculitis
- Developed between 7-13 days after initial injection
- To date: 83,000 total injections
  - 1 in 10,000 risk
    - Lower than endophthalmitis
    - Is that an acceptable risk?
- Retinal specialists are "spooked"

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Avacincaptad Pegol (Izervay): Iveric

- Complement C5 inhibitor
- Reduction in GA growth for patients receiving Izervay in the U.S. was **25.5 - 35.0%**

August 4

Iveric Bio Receives U.S. FDA Approval for IZERVAY™ (avacincaptad pegol intravitreal solution), a New Treatment for Geographic Atrophy

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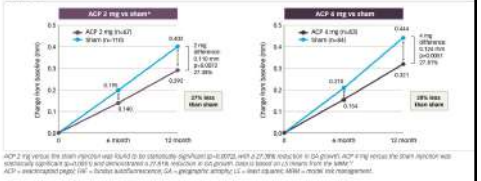
Both 2 mg and 4 mg were effective

Figure 1: Mean rate of change in square-root GA from baseline to month 12 measured at three timepoints via FAF in GATHER1



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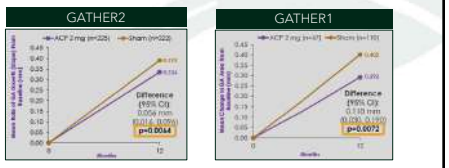
Avacincaptad Pegol:

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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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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Where we are today with GA?

- 2 FDA approved treatment
- Monthly intravitreal injection
- Syfovre: takes at least ~ 12 months to show any significant therapeutic benefit
  - By 18-24 months the treatment affect accelerates
  - Increased risk of occlusive vasculitis
- Izervay shows up to 35% reduction in growth rate at 12 mo
  - May be too early to know about SAE or IOI
- Keep in mind many patients will have good acuity

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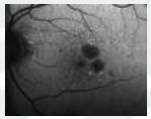
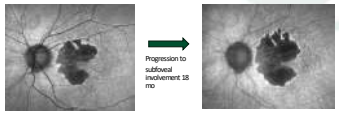
When to Refer?



- Any GA that is **threatening** central visual function
- Any GA that is beginning to involve the fovea
  - likely already having reduced Va
- Large extrafoveal lesions



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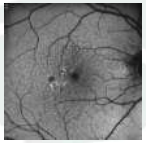
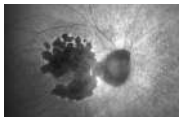
When to Refer?



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



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What do we tell our patients who have genetic link to AMD?

53 yo white male

- Father lost central vision from AMD by age 70
- RE macular is normal; LE has a few small drusen

- What do you tell this patient?
  - Genetic testing
  - Nutritional supplement

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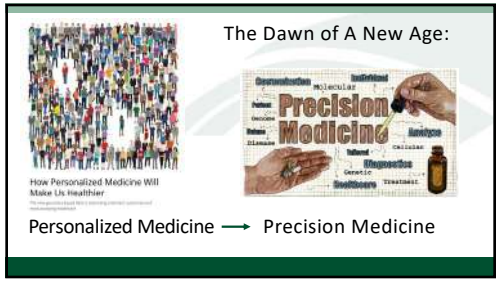

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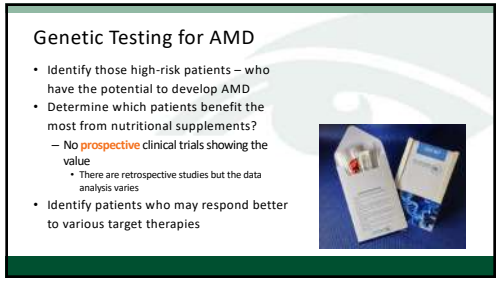

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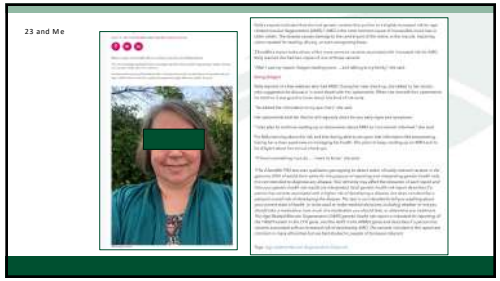

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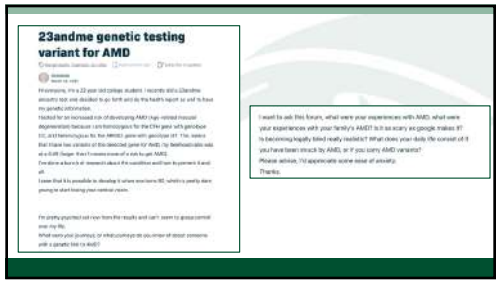

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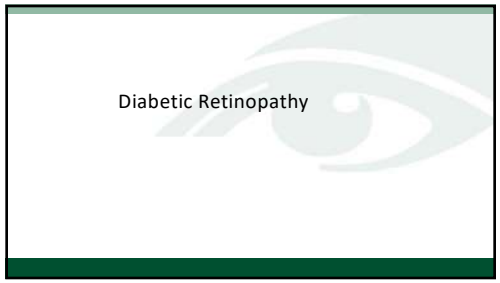

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The Optometrist's Role in Diagnosing and Managing Patients with Diabetes

- 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

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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

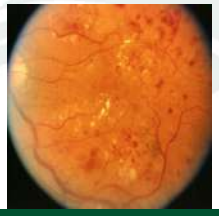
Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology 1991;98:741.

50

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



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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://ksa.uberflip.com/i/1163026-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition/59?m4=

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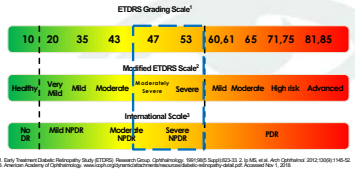
History of DR Severity Scales – ETDRS, Modified ETDRS, and International



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.aao.org/preferred-practice-pattern/diabetic-retinopathy-ideal-pdf. Accessed Nov 1, 2016.

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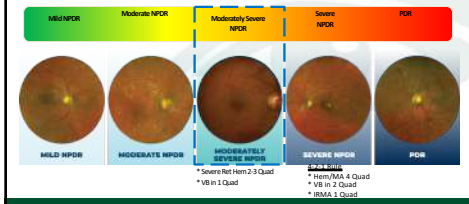
Diabetic Retinopathy Severity Scale

International Scale



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

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

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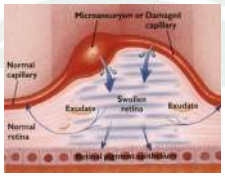
Macular Edema

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



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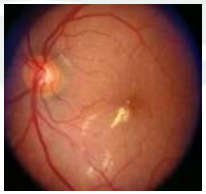
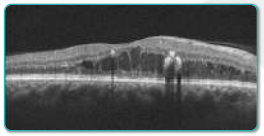
CSME

- 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



56

Diabetic Macular Edema (DME)



SD-OCT of a retina with DME

Color Fundus photo with DME

57

How we diagnose diabetic macular edema is changing

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

58

Diabetic Macular Edema (DME)

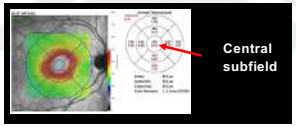
- CSME
- Center involved vs. Not center involved

59

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**



60

The Debate…

- Is it better to treating early – before they develop PDR?
  - Would earlier treatment result in better visual outcomes?
  - Would it result in less # of injections?
  - Does the cost/burden of treatment warrant early treatment?

61

"The Fate of 47…"

62

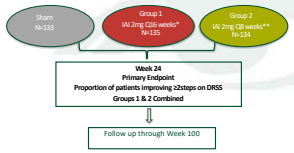
PANORAMA

- 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.

63

Phase 3 Double-masked, Randomized Prospective Study Efficacy and Safety of Intravitreal Aflibercept (IAI) in Patients with Moderately Severe to Severe NPDR (DRSS Level 47 and 53) N=402

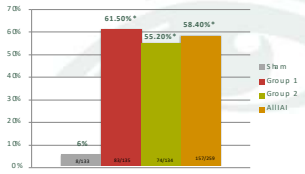


*after 3 initial monthly doses and one Q8 week interval
**after 5 initial loading doses, flexible treatment schedule after week 52

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

64

Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS 24 weeks



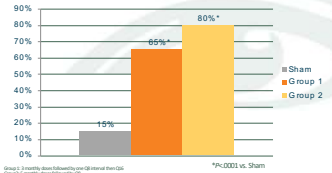
Group 1: 3monthly doses followed by one Q8 interval then Q16
Group2: 3monthly doses followed by Q8

*Pc.0001 vs. Sham

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

65

Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS: 52 Weeks



*Pc.0001 vs. Sham

Group 1: 3 monthly doses followed by one Q8 interval then Q16
Group2: 5 monthly doses followed by Q8

Aflibercept Improves Diabetic Retinopathy and Reduces Vision Threatening Complications in Phase 3 Trial| October 25, 2018. www.prnewswire.com

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

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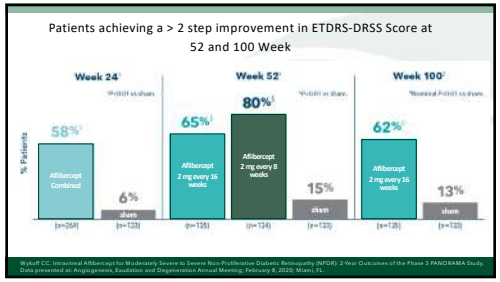

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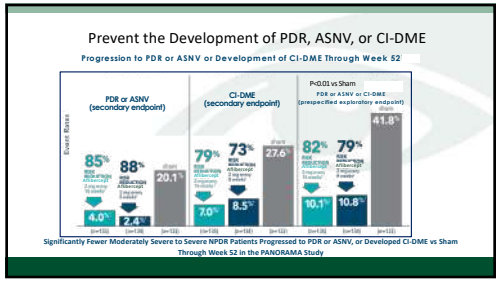

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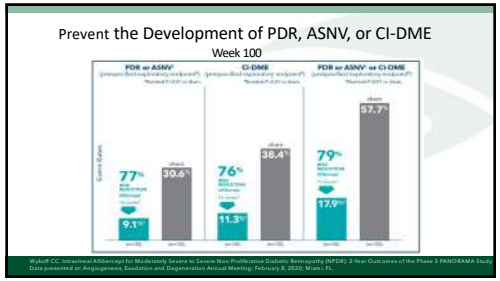

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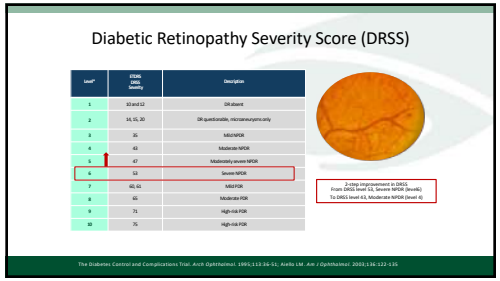
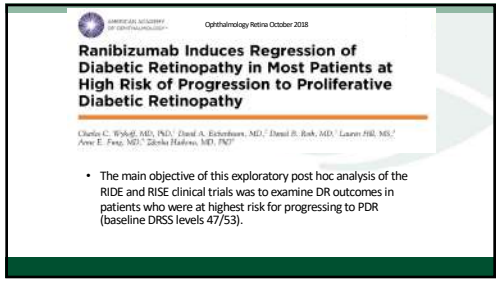


70

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

71



72

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

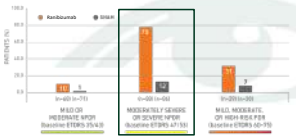
Post hoc analysis:

- 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.

73

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.

74

Ranibizumab induces Regression of Diabetic Retinopathy
Wykoff 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**

75

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; Husni Saleh Nasr, 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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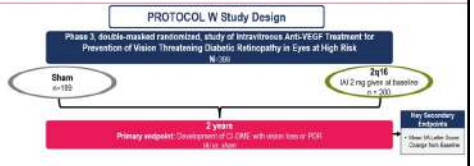
PROTOCOL W: EYLEA VS. SHAM IN MODERATE TO SEVERE NPDR (DRSS OF 43 – 53)



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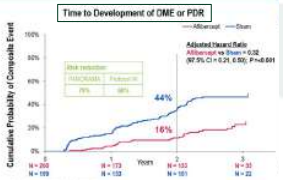
Protocol W: 2 Year Conclusions



- 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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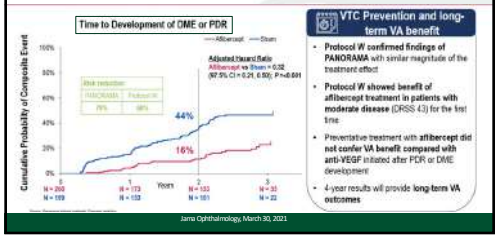
Protocol W: 2 Year Conclusions



79

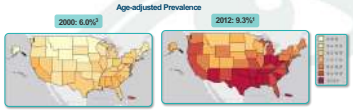
Is there a benefit from early Tx of Severe NPDR?

- 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?

80

Prevalence of Diabetes Mellitus

- Affects 9.3% of the US population (29.1 million people)[1]
- Seventh cause of death in the US[1]
- By 2050 between 1 in 5 and 1 in 3 US adults (estimated) will be diabetic



	2000	2012
Diabetes Incidence (cases/1000)	6.0[2]	7.8[1]
Obesity Prevalence (%)	20.1[2]	27.8[1]

81

Discussion

- Does the data suggest patients with severe NPDR should be treated?
- How early should we refer patients with DR?
- Will the burden of early treatment be too overwhelming for ophthalmology?

82

Retinal Imaging:

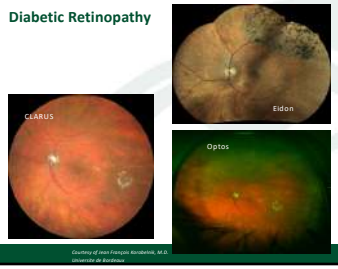
A Camera is a Camera…

Does it matter which one you have?

83

84

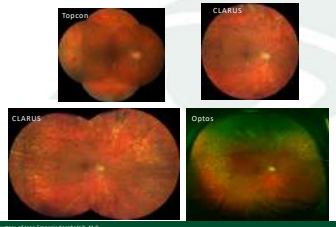
Diabetic Retinopathy



Courtesy of Jean François Korobelnik, M.D. Université de Bordeaux

85

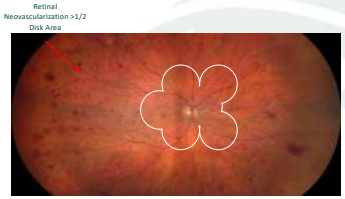
Diabetic Retinopathy



Courtesy of Jean François Korobelnik, M.D. Université de Bordeaux

86

Identification of Additional Retinal Pathology



87

Why does Wide-Field Fundus Imaging Matter?

- When do you do wide field imaging?
- Can it substitute for a dilated fundus exam?
- How do you see this technology evolving?

88

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?

89

AMERICAN ACADEMY OF OPHTHALMOLOGY | EyeNet® Magazine

November 2017

Artificial Intelligence

AI is poised to revolutionize medicine.

90

IOVS Dec 2016

Retina

Improved Automated Detection of Diabetic Retinopathy on a Publicly Available Dataset Through Integration of Deep Learning

Michael David Abràmoff,[1-3] Yiyue Lou,[4] Ali Erginay,[5] Warren Clarida,[3] Ryan Amelon,[3] James C. Folk,[1-3] and Meindert Niemeijer[3]

[1]Department of Ophthalmology and Visual Sciences, University of Iowa Hospitals and Clinics, Iowa City, Iowa, United States
[2]Iowa City Veterans Affairs Medical Center, Iowa City, Iowa, United States
[3]IDx, LLC, Iowa City, Iowa, United States
[4]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City, Iowa, United States
[5]Service d' Ophtalmologie, Hopital Lariboisiere, AHHP, Paris, France

Conclusions. A deep-learning enhanced algorithm for the automated detection of DR, achieves significantly better performance than a previously reported, otherwise essentially identical, algorithm that does not employ deep learning. Deep learning enhanced algorithms have the potential to improve the efficiency of DR screening, and thereby to prevent visual loss and blindness from this devastating disease.

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)**

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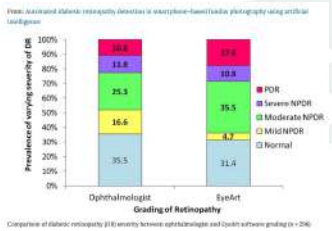


93

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 ~ 20-40%
- As the technology has evolved -> prices continue to come down

94

ARVO The Association for Research in Vision and Ophthalmology

November 2016

New Videos, Resources Launch Outreach Campaign On Vision-Preserving Technology

Impact of optical coherence tomography on patients, general public revealed

OCT has become the predominant means of detecting and monitoring diseases like macular degeneration, diabetic retinopathy and glaucoma. Everyone over the age of 60 is recommended to get an OCT scan once a year.

"Everyone over the age of 60 is recommended to get an OCT scan once a year"

95

Crossfire on OCT…

- Has OCT become "Standard of Care" in Optometry?
- Should OCT be done on "every" patient as a screening tool?
- Should OCT be done only when there is an indication?
  - Diabetes, macular degeneration

96

The Challenge…

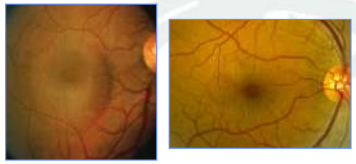
- Being able to correlate what you are seeing clinically with **what is happening anatomically**
  - **and then making the correct diagnosis**
  - Is there fluid or retinal thickening?
  - Where is the fluid?
- Being able to diagnose conditions that may not be seen with traditional ophthalmoscopy

97

Advances in Diagnostic Technology can Help Establish a Diagnosis

98

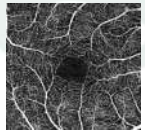
Where is the Fluid?



99

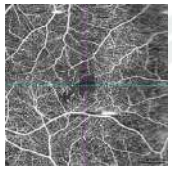
OCT Angiography: A New Way of Visualizing Vessels

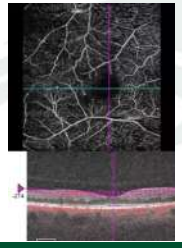
- Identify retinal circulation using the intrinsic motion of blood cells in the vessel
- Functional and structural, information with en face projections
- No contrast medium, and the data are 3-dimensional and depth resolved



100

Ischemia near the FAZ





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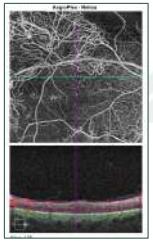
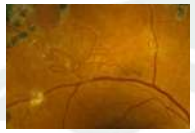
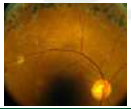






102

Crossfire on OCT…

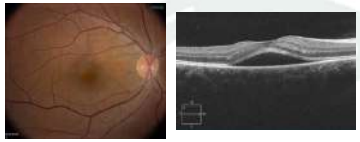
- Should every optometry practice have access to OCT?
- Has OCT become "Standard of Care" in Optometry?
- Should OCT be done on "every" patient as a screening tool?
- Should OCT be done on every patient with diabetes or macular degeneration?

103

32 yo Hispanic Male

Blurry vision in the RE X 1 week

104



High Stress

105

Management of CSR

- Reduce stress
- Observation
  - Often resolves without treatment
- Focal laser if isolated "hot" spot
- PDT recalcitrant or recurrent CSR
- Oral therapy: spironolactone
  - Diuretic to treat HTN

106

British Journal of Ophthalmology

Spironolactone versus observation in the treatment of acute central serous chorioretinopathy

Xinghong Sun,[1] Yuanfa Shao,[1] Wangyi Tong,[1] Jia Li,[1] Weizhong Ge,[2] Songtao Yuan,[3] Qinghuai Liu[1]

2018

Complete resolution of SRF was achieved in 55.6% (10/18) and 8.3% (1/12) of the eyes in the treatment group and the control group, respectively, at 2 months

Conclusions Oral spironolactone is more effective with a faster absorption of SRF than observations. It is a promising treatment for acute CSC.

107

SPIRONOLACTONE FOR NONRESOLVING CENTRAL SEROUS CHORIORETINOPATHY

A Randomized Controlled Crossover Study

Journal of Ophthalmology

Mineralocorticoid Receptor Antagonist Treatment for Steroid-Induced Central Serous Chorioretinopathy Patients with Continuous Systemic Steroid Treatment

108

Why it might work

- Strong relationship between exogenous cortisol and CSR
- Mineralocorticoid receptor (MR) pathway may play a role in the disease pathogenesis
- Aldosterone controls retinal fluid homeostasis through upregulating the ion and water channel, which is expressed in the apical region of RMGs

109

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

110

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

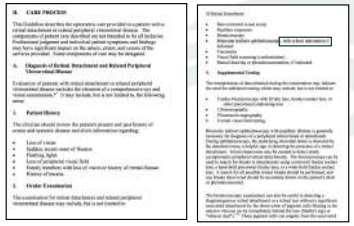
111

Crossfire…

- Did the OD manage this patient correctly?
- Was there anything else they **should have** done?
- Was he obligated to do scleral depression?
- Should he have referred this patient to a retinal specialist?

112

113



114

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

115

65 yo Caucasian Male PVD

The rest of the story…

- Patient return about 5 weeks later complaining he can't see out of his right eye for th past 4 days
- Has a macula-off RD
- RD repaired but VA 20/200

116

Crossfire Topics

- Should optometrists should refer all patients with flashes and floaters because the risk of having a retinal tear is too great?
- The standard of care for evaluating a patient with flashes and floaters is **scleral depression**

117

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

118

Lattice Degeneration as a Routine Finding?

Is this any cause for concern?

How do you manage it?

What is the Risk for developing a retinal tear or RD

119

Lattice Degeneration

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

120

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

121

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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The evolution of Anti-VEGF

- Lucentis
- Avastin
- Eylea

New drugs in the pipeline (phase III)

- Brolucizumab – Novartis: quarterly treatment
- Abicipar – Allergan: quarterly treatment

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Recent FDA Approvals for AMD and DME

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

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Port Delivery System (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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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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Angiopoietin/Tie-2 Signaling Pathway

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

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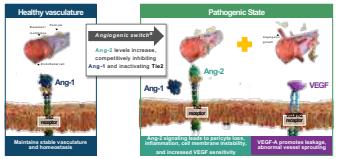
Ang-2 and VEGF-A are key drivers of angiogenesis, leakage, and microvascular inflammation



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Faricimab

Bispecific antibody targeting both Ang-2 and VEGF

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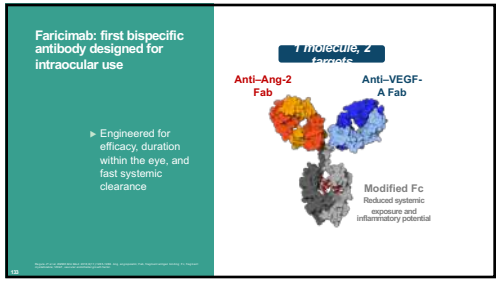

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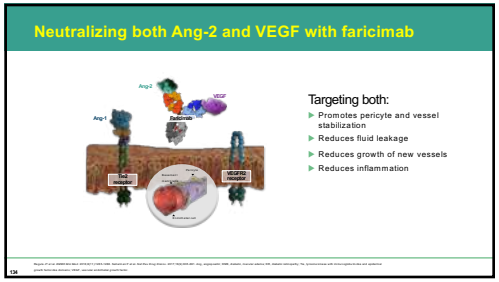

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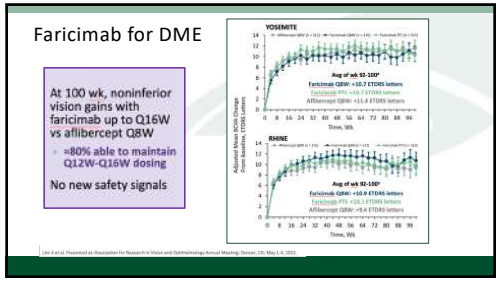

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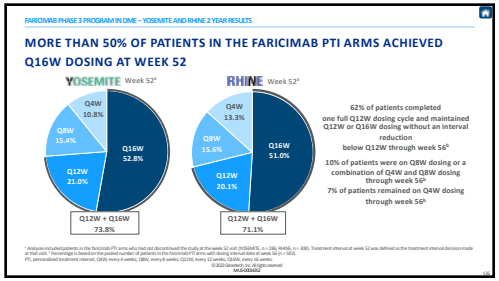

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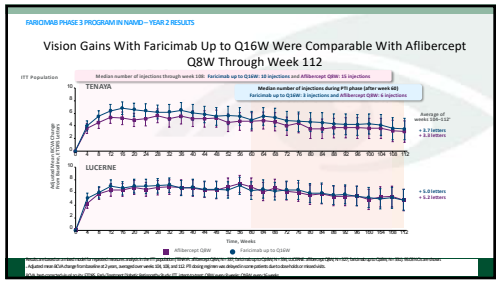

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