Hot Topics in Retina

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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

- The paradigm shift in the diagnosis and management of diabetes
- Better Treatments for Wet AMD
- The search for a treatment for dry AMD
  - Are we getting closer?
- The emergence of OCT/OCTA Imaging in retinal disease
- Targeted therapy for hereditary retinal disease
- Is vitrectomy a reasonable option for floaters?

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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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Diabetes is Occurring in Epidemic Proportions

- Affects over 10% of the US population (29.1 million people)[1]
- By 2050 between 1 in 5 and 1 in 3 US adults (estimated) will be diabetic

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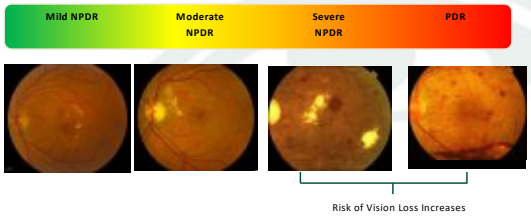
Diabetic Retinopathy Severity Scale

International Scale



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

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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

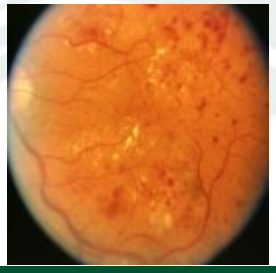
Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS report number 7. Ophthalmology 1991;98:742.

7

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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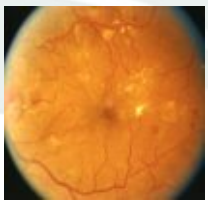
Risk for Progression to PDR

	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://aoa.uberflip.com/i/1183026-evidence-based-clinical-practice-guideline-eye-care-of-the-patient-with-diabetes-mellitus-second-edition/597m4=

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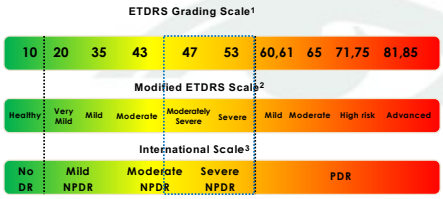
History of DR Severity Scales – ETDRS, Modified ETDRS, and International



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.icoph.org/dynamic/attachments/resources/diabetic-retinopathy-detail.pdf. Accessed Nov 1, 2018.

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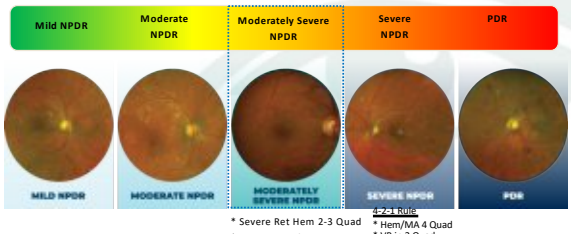
Diabetic Retinopathy Severity Scale

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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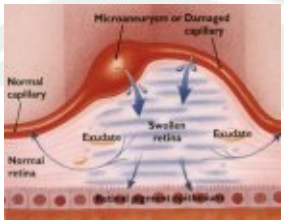
Macular Edema

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



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How we diagnose diabetic macular edema is changing

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

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Diabetic Macular Edema (DME)

- CSME
- Center involved vs. Not center involved

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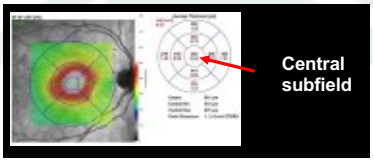
2017 DME Classification:

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**



Nguyen, Quan 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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The ABC's of DME

- RISE
- RIDE
- READ

} Genentech

- VISTA
- VIVID

} Regeneron

- Bolt

- DRCR.net
  - Protocol S
  - Protocol T
  - Protocol V
  - Protocol W

Essentially establishing the effectiveness of all the anti-VEGF drugs for the treatment of DME

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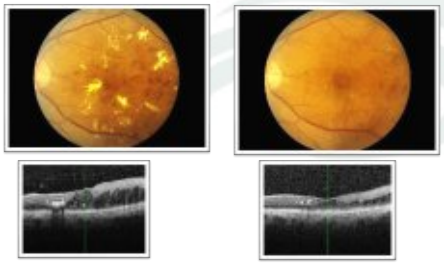
DME Pre Treatment | Anti-VEGF Treatment | DME Post Treatment



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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?

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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.

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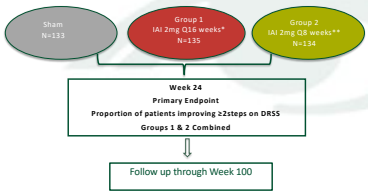
Phase 3 Double-masked, Randomized Prospective Study
Efficacy and Safety of Intravitreal Aflibercept (IAI) in Patients with Moderately Severe to Severe NPDR (DRSS Level 47 and 53) N=402



*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.

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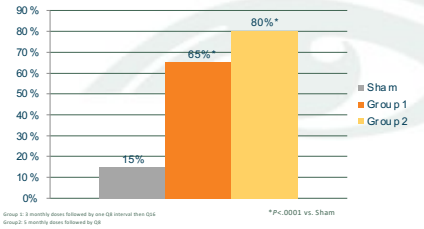
Proportion of Patients with ≥2-Step Improvement from Baseline in DRSS: 52 Weeks



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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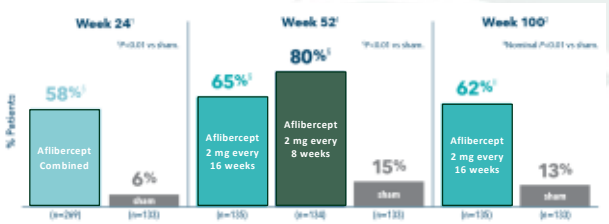
Patients achieving a > 2 step improvement in ETDRS-DRSS Score at 52 and 100 Week



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

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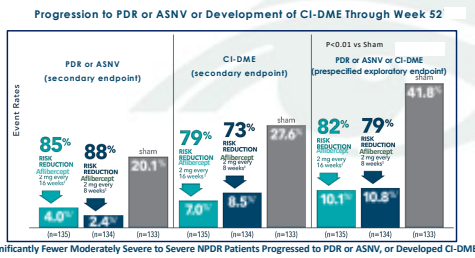
Prevent the Development of PDR, ASNV, or CI-DME



Significantly Fewer Moderately Severe to Severe NPDR Patients Progressed to PDR or ASNV, or Developed CI-DME vs Sham Through Week 52 in the PANORAMA Study

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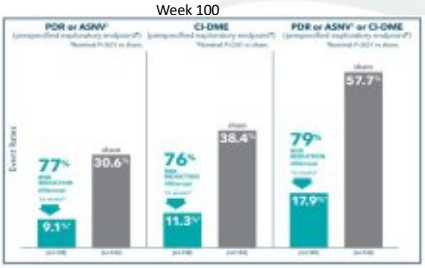
Prevent the Development of PDR, ASNV, or CI-DME

Week 100



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

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Diabetic Retinopathy Severity Score (DRSS)

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

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

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

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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

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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] David B. Roth, MD,[1] Lauren Hill, MS,[3] Anne E. Fung, MD,[1] Zdenka Haskova, MD, PhD[3]

- 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).

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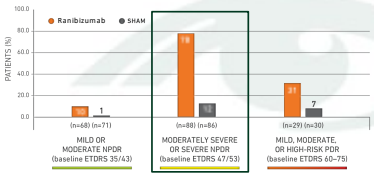
RISE AND RIDE POST HOC ANALYSIS
≥2-STEP REGRESSION IN DR AT 2 YEARS



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.

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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**

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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 Saleh-Hadi, MD; Cynthia R. Stockdale, MSPH; Omur 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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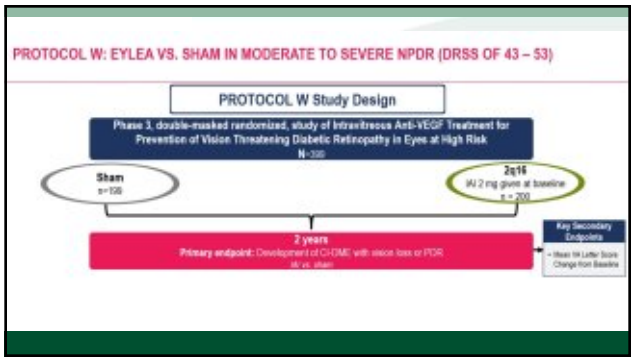

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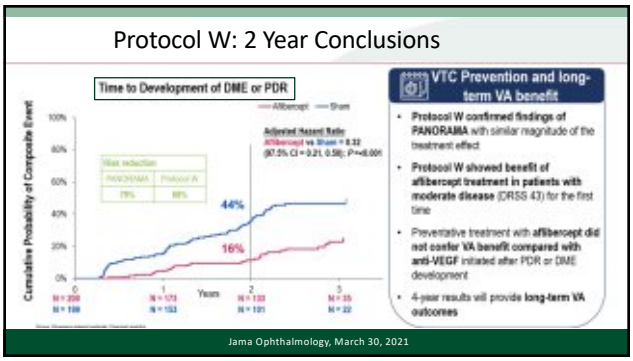

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Is there a benefit from early Tx of Severe NPDR?

- 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?

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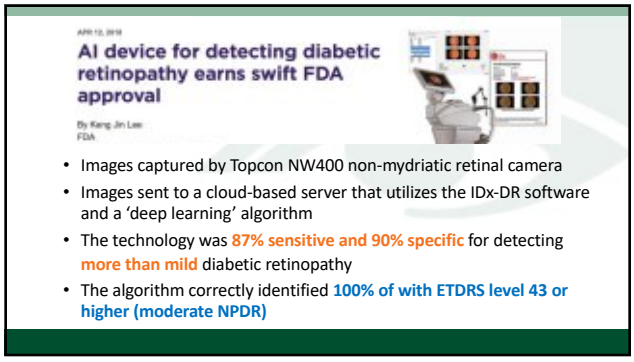

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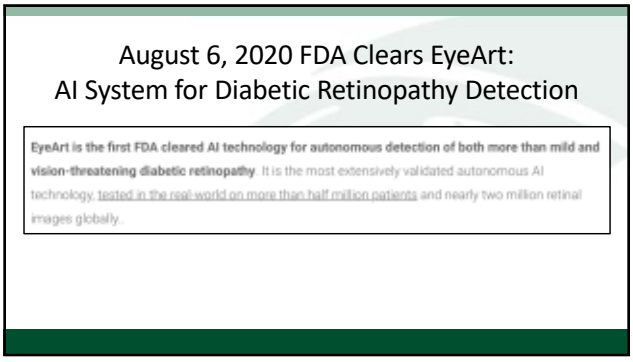

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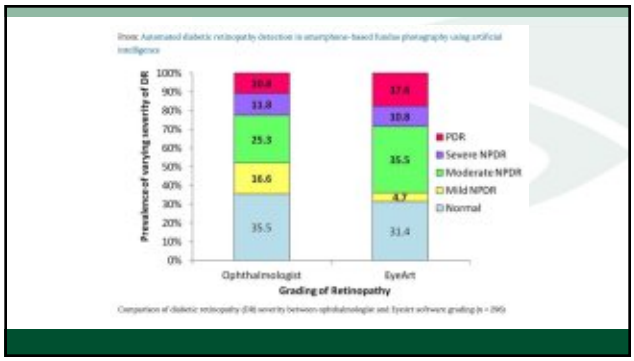

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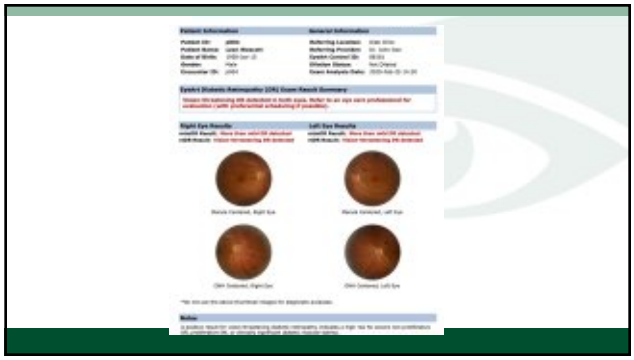

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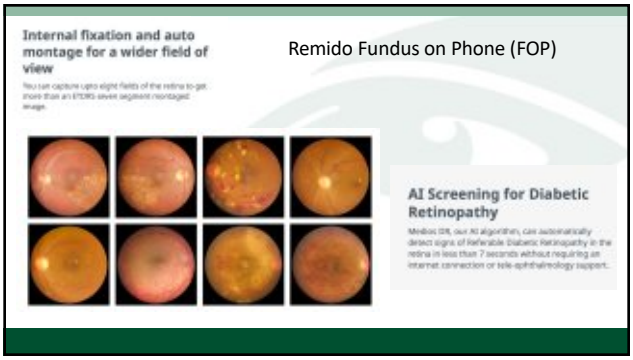

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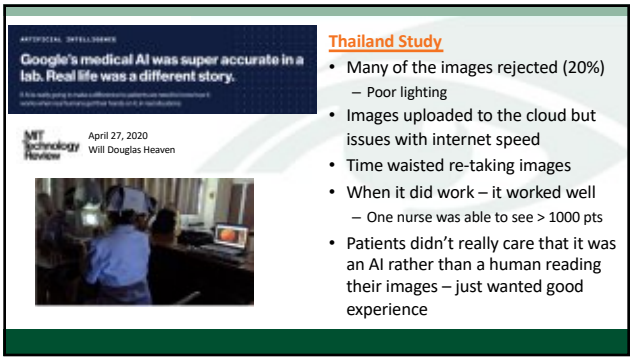

Thailand Study

- Many of the images rejected (20%)
  - Poor lighting
- Images uploaded to the cloud but issues with internet speed
- Time waisted 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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THE LANCET
Digital Health

ARTICLES | VOLUME 4, ISSUE 4, E235-E244, APRIL 01, 2022

Real-time diabetic retinopathy screening by deep learning in a multisite national screening programme: a prospective interventional cohort study

Prof Paisan Ruamviboonsuk, MD · Richa Tiwari, PhD · Rory Sayres, PhD · Variya Nganthavee, MD
Kornwipa Hemarat, MD · Apinpat Kongprayoon, MD · et al. Show all authors · Show footnotes

Open Access · Published: March 07, 2022 · DOI: https://doi.org/10.1016/S2589-7500(22)00017-6

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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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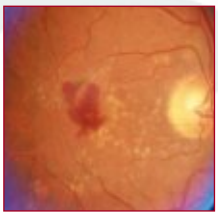
Age-related Macular Degeneration (AMD)

- 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): DSP14-DSP17.
Published online Dec 11, 2013. doi: 10.1167/iovs.13-12782

Eye Disease	2000	2020
	#in Millions (%)	#in Millions
Cataract[a]	20.9 (17.2)	30.1
Pseudophakia[b]	6.1 (5.1)	9.3
Diabetic retinopathy	4.1 (3.4)	6.1
Vision-threatening diabetic retinopathy	0.9 (0.8)	1.4
Open-angle glaucoma	2.2 (1.8)	3.4
Late age-related macular degeneration	1.8 (1.5)	3.0
Large drusen	7.3 (6.1)	11.7
Blindness	0.9 (0.8)	1.6
Low vision	2.6 (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. 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;208:419; 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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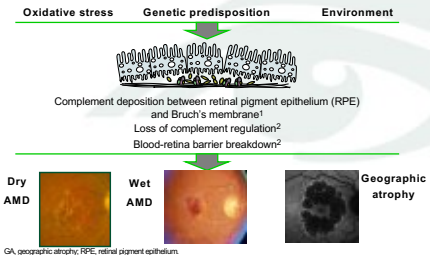
Current Hypothesis for AMD Pathophysiology



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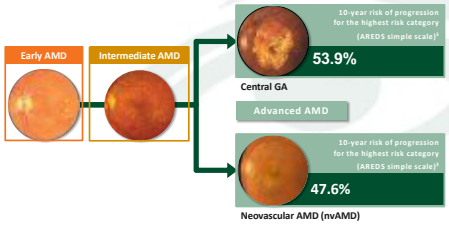
AMD Is the Leading Cause of Blindness for Caucasians in the US[1]



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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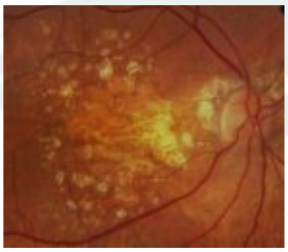
Geographic Atrophy

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



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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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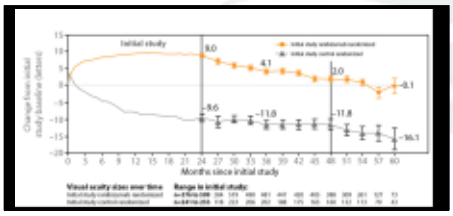
HORIZON: Extension Study

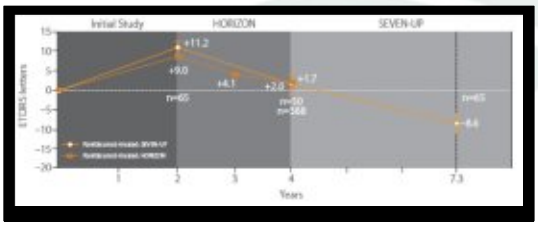


Extension study evaluating the ≥2-year frequency, safety, tolerability, and efficacy of multiple intravitreal ranibizumab injections in Wet AMD patients who completed 1 of 3 initial studies: MARINA, ANCHOR, or FOCUS

Ranibizumab 0.5 mg was administered at the investigator's discretion

54

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



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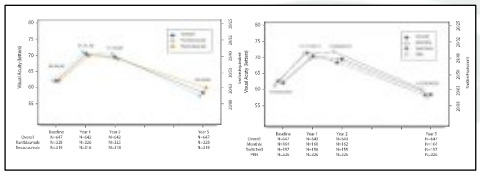
CATT 5-Year Outcomes

- Overall and by Drug Assigned



Over 3 years of clinical follow-up, mean number of injections was 15.4

At year 5 –

- 83% of patients had retinal fluid
- 61% had intraretinal fluid
- 38% had subretinal fluid
- 36% had sub-RPE fluid

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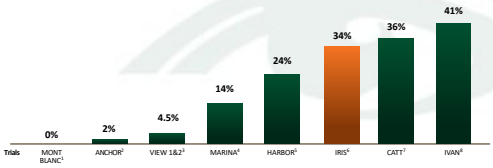
Too few patients have ≥20/40 at wet AMD diagnosis

Proportion of patients with 20/40 at wet AMD diagnosis



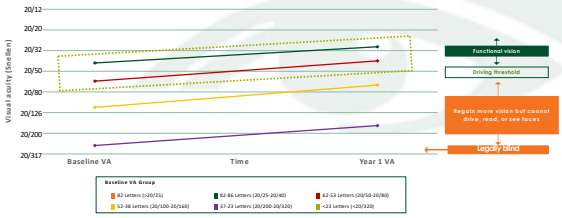
Regardless of clinical trials or the real world, the majority of patients start with poor visual acuity (20/63-20/125).[1-8]

References. 1. Larsen M, et al. *Ophthalmology*. 2012;119(5):992-1000. 2. Brown DM, et al. *Ophthalmology*. 2009;116(1):57-65. 3. Heier JS, et al. *Ophthalmology*. 2012;119(12):2537-2548. 4. Rosenfeld PJ, et al. *N Engl J Med*. 2006;355(14):1419-1431. 5. Busbee BG, et al. *Ophthalmology*. 2013;120(3):1046-1056. 6. Rao P, et al. *Ophthalmology*. 2018;125(3):522-528. 7. Ying GS, et al. *Ophthalmology*. 2015;122(12):2523-2531. 8. Chakravarthy U, et al, IVAN Study Investigators. *Ophthalmology*. 2012;119(7):1389-1411.

57

Baseline VA will predict visual outcomes at year 1

Mean change in visual acuity: Comparison of AMD Treatment Trial (CATT)[1,2]



References: 1. Ying GS, et al. *Ophthalmology*. 2013;120(1):122-129. 2. Ying GS, et al. *Ophthalmology*. 2015;122(12):2523-2531.

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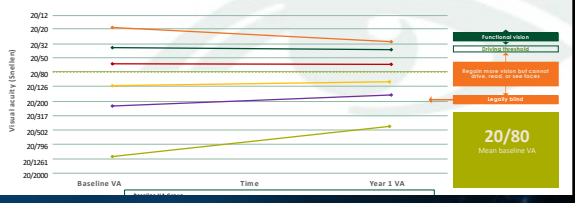
IRIS Registry confirms baseline VA will predict visual outcomes at year 1

Mean change in visual acuity: IRIS Registry



Even though patients with worse baseline VA experience the greatest relative vision gain, they do not catch up to patients who START with better VA.

59

Home Monitoring of AMD

Foresee Home Device

The First FDA Cleared Vision Monitor App

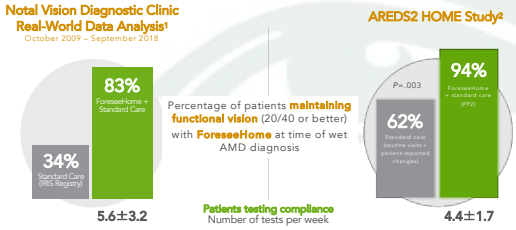
60

Preferential Hyperacuity Perimetry

When the elevation caused by CNV is larger than the artificial distortion, the patient will preferentially pick this spot of true distortion

61

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



References: 1. Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, ASRS Meeting 2020
2. Chew EY, et al. Ophthalmology. 2014;121(5):535-544.

62

Remote Monitoring of AMD Vs. Standard of Care Monitoring

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

Ophthalmology Retina April 25, 2022

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What's Next in OCT?

Notal Home-OCT

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Notal Vision's home-based OCT system granted breakthrough device designation

The FDA has granted breakthrough device designation to Notal Vision's home-based OCT system, according to a press release.

The artificial intelligence-based Home OCT System is designed to identify intraretinal and/or subretinal fluid in the central 10° of eyes diagnosed with exudative age-related macular degeneration, the release said. It allows patients to complete the test at home while the machine-learning algorithm Notal OCT Analyzer performs an automated analysis, generates a report and transmits the information to a physician.

SEE ALSO

"The FDA's Breakthrough Devices Program is designed to help expedite patient access to novel technologies through intensive interaction and guidance," Notal Vision CEO **Quinton Oswald** said in the release. "This designation validates and reaffirms our belief that home-based OCT addresses a high unmet need for clinicians and their patients."

The company expects to bring the system to the market in 2020.

65

Notal Home-OCT

US Clinical trial: 94% of elderly AMD patients with VA > 20/400 can self-operate and capture readable images following a 2-minute tutorial

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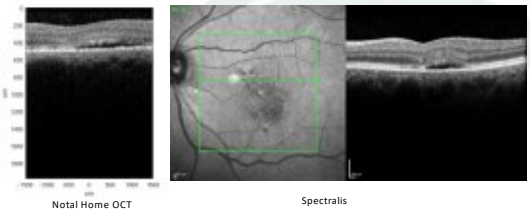
Notal Home-OCT vs. Heidelberg Spectralis

(No Averaging) With Averaging



Notal Home OCT Spectralis

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New Treatment for Wet AMD

- Beovu (Brolucizumab - Novartis)
  - Small size of the molecule allows higher dosing per volume results in a longer-lasting effect
- ~~Abicipar (Allergan)~~
- 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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Tx with Broluizumab

- 50% of patients were maintained on q12 week dosing without requiring rescue treatments.
  - Eyes that could not be maintained on a regimen of q12 weeks tended to show a need for early re-treatment
- ~ 1/3 fewer patients (vs Lucentis) had fluid (IRF and/or SRF)
- At week 48, 31% fewer patients had IRF and/or SRF in HAWK, and 41% fewer in HARRIER ($P < .0001$ for both).
- Patients receiving brolucizumab 6 mg demonstrated superior reductions in central subfield thickness.

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Beovu (Brolucizumab)

- Received FDA approval October 7, 2019 for treatment of neovascular AMD
- Shortly after approval the American Society of Retina Specialists (ASRS) began receiving reports of inflammation following intravitreal brolucizumab administration for NVAMD
- Several reported cases included **retinal vasculitis** that frequently resulted in vascular occlusion and **significant vision loss**

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2020

- On February 23, the American Society of Retinal Specialists (ASRS) shared a note with its membership stating that since approval on October 7, 2019, ASRS has received reports of 14 cases of vasculitis, of which 11 were designated as occlusive retinal vasculitis

Novartis Responds to ASRS Note Raising Safety Concerns of Beovu

- Novartis is launching an internal and external review regarding safety concerns over Beovu (brolucizumab)
- On February 23, the American Society of Retinal Specialists (ASRS) shared a note with its membership stating that since approval on October 7, 2019, ASRS has received reports of 14 cases of vasculitis, of which 11 were designated as occlusive retinal vasculitis
- Novartis estimates that 48,000 injections of Beovu have been administered in the US as of February 21
- Novartis: is aware of recently reported adverse events and is currently evaluating the cases

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Recent FDA Approvals for AMD and DME

- Port Delivery System (PDS)
- Vabysmo: Farcimab

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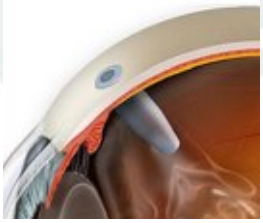
Port Delivery System (Genentech)

- 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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Port Delivery System

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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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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

78

Angiopoietin/Tie-2 Signaling Pathway

A key player in the pathogenesis of AMD and DME

79

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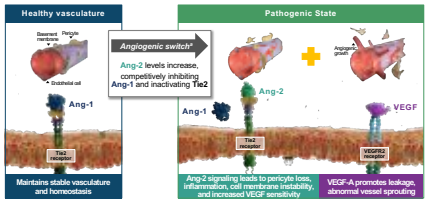
Ang-2 and VEGF-A are key drivers of angiogenesis, leakage, and microvascular inflammation



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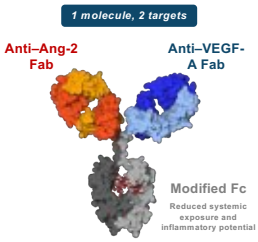
Faricimab

Bispecific antibody targeting both Ang-2 and VEGF

82

Faricimab: first bispecific antibody designed for intraocular use

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



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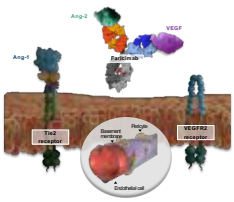
Neutralizing both Ang-2 and VEGF with faricimab

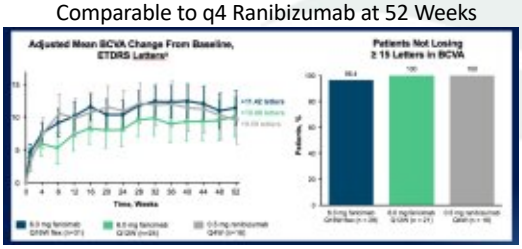


Targeting both:

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

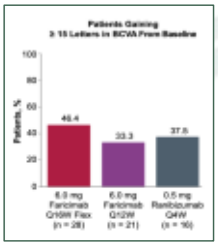
84

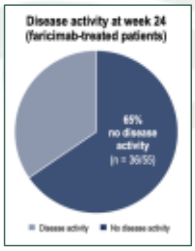
BCVA Outcomes with q 16 W and q 12 W Farcimab were Comparable to q4 Ranibizumab at 52 Weeks



85

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





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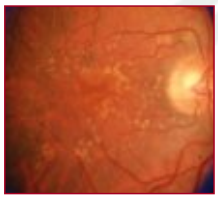
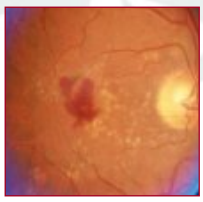
Holy Grail

- Treating Dry AMD before it develops CNV
- and Geographic Atrophy (GA)





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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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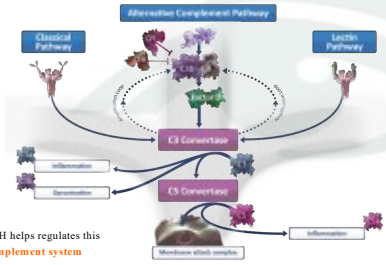
Pathways for Complement Activation

Required for the initiation and amplification of the alternative complement pathway



CFH helps regulates this **complement system**

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

89

Potential Treatments for Geographic Atrophy

- APL-2: C3 inhibitor by Apellis
- Blocks all the pathways of complement activation

MAC = membrane attack complex

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Filly Key Takeaways

- APL-2 reduced the progression of GA in the largest Phase 2 GA trial (n=246)
- Results correlated treatment frequency with increasing effect size over time
- Upon discontinuation of APL-2 treatment effect declines

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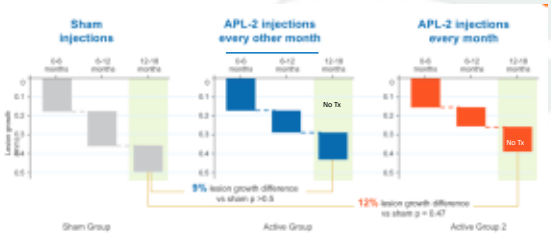
Lesion growth by 6 month periods (square root) – 18 months



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APL-2 Shows GA growth at 12 months (square root)

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March 16, 2022

News Release

Apellis Announces Pegcetacoplan Showed Continuous and Clinically Meaningful Effects at Month 18 in Phase 3 DERBY and OAKS Studies for Geographic Atrophy (GA)

March 16, 2022

- Both monthly and every other month continued to reduce GA growth compared to pooled sham at 18 months
  - Tx effects in DERBY were comparable to OAKS during months 6-18
  - Pegcetacoplan continued to show favorable safety profile
- Combined 18-month data show the potential for improving treatment effects overe time

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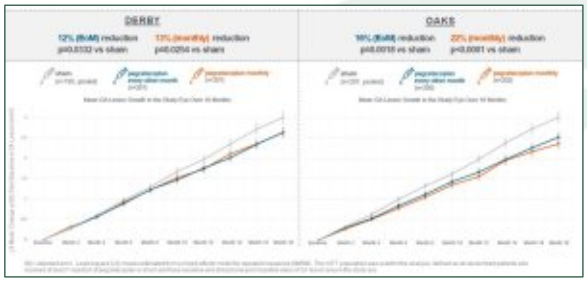
Apellis Pegcetacoplan



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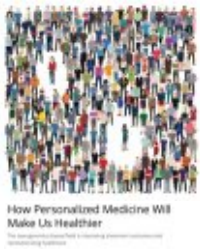

The Dawn of A New Age:

Personalized Medicine → Precision Medicine

96

Genetic Testing for AMD

- Identify those high-risk patients – who have the potential to develop AMD
- Determine which patients benefit the most from nutritional supplements?
  - No prospective clinical trials showing the value
    - There are retrospective studies but the data analysis varies
- Identify patients who may respond better to various target therapies

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Genetic Testing for AMD

- Can genetic testing be used to determine high risk patients?
- Can genetic testing identity which patients benefit the most from nutritional supplements?
- No prospective clinical trials showing the value
  - There are retrospective studies but the data analysis varies

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ASRS American Society of Retina Specialists

Interaction of Genotypes and AREDS Formulation Use in the Development of Neovascular AMD

Conclusion Patients in Genotype Group 2, i.e., high CFH and lows ARMS2 risk alleles, are more likely to develop nwAMD following exposure to routine AREDS formulation. These data support a genuine interaction between GTG2, AREDS use, and progression to nwAMD. Additional patients will be added to this analysis by the time of the 2019 ASRS Annual Meeting.

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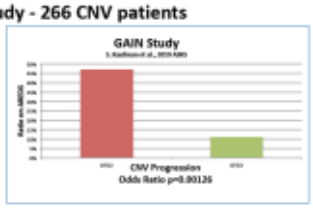
Independent Multicenter (OH, PA, CA) Study - 266 CNV patients



Patients in GTG2 should not take the AREDS Formulation

100

Special Correspondence 2017 ASRS

Journal of Vitreoretinal Diseases
2017, Vol. 1(1) 75-78

DOI: 10.1177/2474126416688671
jvrd.sagepub.com
SAGE

The Use of Genetic Testing in the Management of Patients With Age-Related Macular Degeneration: American Society of Retina Specialists Genetics Task Force Special Report

Karl G. Csaky, MD, PhD[1], Andrew P. Schachat, MD[2], Peter K. Kaiser, MD[3], Kent W. Small, MD[3], and Jeffrey S. Heier, MD[4]

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1. Age-related macular degeneration genetic testing may provide information on the progression rates from intermediate to advanced AMD. However, before ordering this testing, retina specialists should be aware of the following:
   a. Testing should be performed only at Clinical Laboratory Improvement Amendments-certified laboratories with expertise in genetic sequencing. Because of the high variability in the results, direct-to-consumer (DTC) AMD genetic testing that does not meet this standard is not recommended.
   b. Interpretation of the results of AMD genetic testing is complex.
   c. At present, there is no clinical evidence that altering the management of genetically higher risk progression patients, for example, with more frequent office visits and/or improved lifestyle changes, results in better visual outcomes for these patients compared with individuals of lower genetic susceptibility. As such, prospective studies are needed before patient care is modified.

2. Age-related macular degeneration genetic testing at present in patients with neovascular AMD does not provide clinically relevant information regarding response to anti-vascular endothelial growth factor (VEGF) treatment and is not recommended for this purpose.

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Special Correspondence

The Use of Genetic Testing in the Management of Patients With Age-Related Macular Degeneration: American Society of Retina Specialists Genetics Task Force Special Report

3. Although genetic testing to determine the optimal nutritional supplementation may in the future prove useful, at present there is insufficient data to support the use of genetic testing in patients with AMD prior to recommendation of current Age-Related Eye Disease Study (AREDS) nutritional supplement use.

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Gene Therapy: Are We On the Verge of A Gene Therapy Explosion?

104

The Eye is the Ideal Environment Gene Therapy

- Monogenic nature of most Inherited Retinal Diseases (IRD)
- Retina is a favorable favorable target for administering genetic vectors
- Immunoprivileged environment
- Direct visibility
- Multiple ways to assess sensitivity and function

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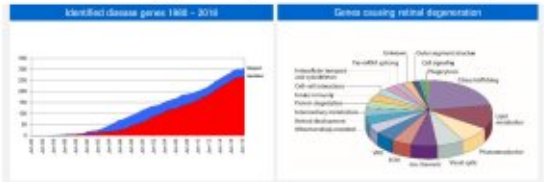
Potential for gene therapy in ophthalmology

To date more than 270 genes causing retinal disease have been identified



- To date, there over 270 identified genes that cause retinal disease
- Over 95% of the identified gene mutations initially result in death of rod photoreceptors

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Inherited/Hereditary Retinal Disease (IRD)

- A group of genetically heterogeneous disorders that result in a myriad of clinical presentations and can cause varying levels of vision loss including total blindness
- Over **100 IRD disease entities** and are caused by various **defects in over 300 genes**
- They are generally untreatable
- **Retinal dystrophies can broadly be divided into two forms:**
  - Monogenic (single-gene): Leber's (LCA), Stargardt's, Choroideremia
  - Complex (multifactorial) diseases: RP

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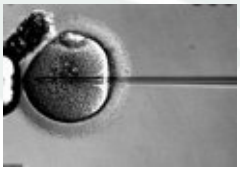
Gene Therapy for Inherited Retinal Disease

- Gene therapy refers to the use of genetic material (DNA or RNA) **"implanted"** to modify gene expression, in order to treat disease
- Delivering a working copy to a damaged gene that causes the disease
  - The goal is **restoration of gene function** in the case where a mutation has inactivated it
- **Inactivate a mutated gene** that is not functioning correctly
  - Autosomal dominant RP (adRP) caused by mutations in the rhodopsin (*RHO*) gene



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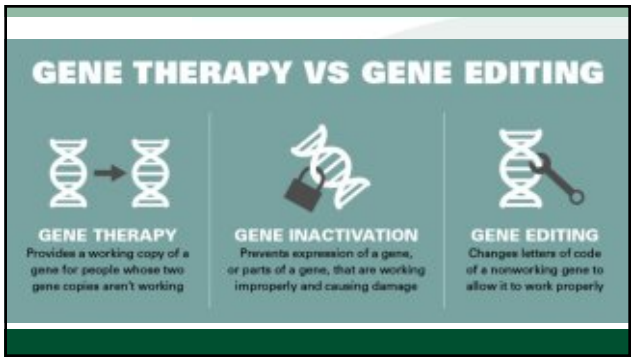

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CRISPR and CRISPR-CAS Proteins

- CRISPR is a sequence information
- Cut and manipulate our genomic material
- Replace DNA in the area of interest

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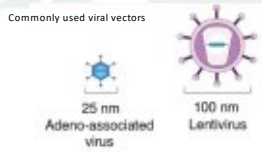
Gene Therapy for Treating Retinal Disease

- Retinal gene therapy involves a subretinal or intravitreal injection of a viral vector,
- Viral vector infects target cells to deliver a therapeutic gene, or transgene



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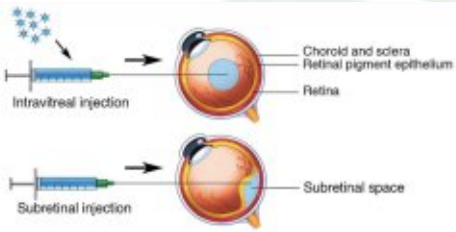
Delivery of the Vector



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Genome Editing and Gene Therapy to Treat Angiogenesis
New developments have the potential to change the way retina specialists treat disease.

- **Luxturna** (voretigene neparvorec-rzyl; Spark Therapeutics) became the 1st in vivo gene therapy approved by the US Food and Drug Administration, in 2017
- This historic landmark demonstrated that gene therapy is not only safe and effective, but also that it is potentially the answer to a number of medical conditions
- This new frontier of **precision medicine** aims to target disease more directly
- May result in a one-time treatment delivering genes that express therapeutic factors for months or years

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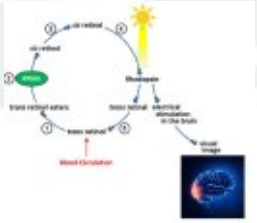
Leber's Congenital Amaurosis (LCA)

- **Monogenetic inherited retinal disease** (IRDs) that develops as a result of a mutation in the RPE65 gene (Biallelic mutation)
- **RPE65 gene** provides instructions for **making an enzyme** that is essential for normal vision
- Mutations in the RPE65 gene lead to **reduced or absent levels of RPE65 activity**, blocking the visual cycle and resulting in impaired vision
- Results in progressive deterioration of vision over time
  - Begins in childhood or adolescence
  - Ultimately progresses to complete blindness



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Gene Therapy for LCA

- Luxturna works by delivering a normal copy of the RPE65 gene directly to retinal cells
- These retinal cells then produce the normal protein that converts light to an electrical signal in the retina to restore patient's vision loss
- Luxturna uses a naturally occurring adeno-associated virus, which has been modified using recombinant DNA techniques, as the vehicle to deliver the normal human RPE65 gene to the retinal cells to restore vision

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Biallelic RPE 65 Mutation

- 41 patients between the ages of 4 and 44 years enrolled
- All participants had confirmed biallelic RPE65 mutations
- The primary endpoint: Ability to navigate an obstacle course at various light levels
  - The group of patients that received Luxturna demonstrated significant improvements in their ability to complete the obstacle course at low light levels as compared to the control group
- Cost: ~ $425,000 per eye

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How Effective is Luxturna?

- Effectiveness was measured by people's improvement in navigating an obstacle course at different light levels
- Treatment affect as early as 30 days
- **At 1 year, 65% of people who received Luxturna passed the obstacle course at the lowest light levels**
  - **No pts prior to treatment were able to navigate the obstacle course**

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Gene Therapy for Other Hereditary Retinal Diseases

Applied Genetic Technologies Corporation (AGTC)

- Biotechnology company developing gene therapies for retinal degenerative diseases and other conditions
- Positive results in gene therapy for **X-linked RP** (RPGR mutation) and **achromatopsia** (CNGB3 and CNGA3 mutations)
- **Stargardt disease:** dual-vector AAV technology, which delivers the ABCA4 gene in two halves
  - When the halves are delivered to the recipient's photoreceptors, they recombine to produce a whole, fully functional ABCA4 gene

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Gene Therapy for Other Hereditary Retinal Diseases

Allergan

- Using viral vectors to deliver CRISPR-Cas9 to genetically treat **Leber congenital amaurosis**.
  - The is a very precise gene editing technique
- BRILLIANCE study (Allergan; Editas Medicine) Phase 1/2, a CRISPR-Cas-based genome editing treatment for the treatment of Leber congenital amaurosis type 10
  - 18 participants will be enrolled in up to 5 cohorts to evaluate up to 3 dose levels of AGN-151587 in this study
  - This is the first time this technology has been used for gene therapy in the eye.
  - The medication is administered via a subretinal injection

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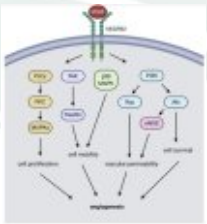
CRISPR and Cas protein gene editing

- This technology directly targets angiogenesis at a genetic level and permanently disrupt or reduce the production of pathologic factors
- **CRISPR-Cas treatment can potentially be delivered by directly manipulating the genetic code**



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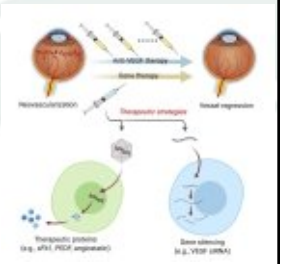
Gene therapy for AMD

- Complex multifactorial disease
- Both Environmental and genetic factors contribute
  - Smoking
  - Oxidative stress
- The immune system plays an important role in AMD
  - CFH is a key driver as well as other complement genes
- Other genes involved in Oxidative metabolism and Lipid Metabolism



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Gene Therapy in Eye Care

- 2 companies are using **adenoviral vectors (AAV)** to deliver genes that makes cells produce either a **ranibizumab-like protein** or an **aflibercept-like protein**
  - Reduce/Stop the need to anti-VEGF injections
- Numerous companies are using this same technique to target monogenetic inherited retinal degenerations

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Gene Editing for AMD: RGX-314: (Regenxbio)

- **RGX-314:** (Regenxbio) is a gene therapy that is delivered by **subretinal injection and induces the eye to produce an anti-VEGF A fab**
  - This product is a monoclonal antibody fragment, which is similar to ranibizumab, that binds to and neutralizes VEGF
- Currently in phase 1/2a, multicenter, dose-escalation study
- Given by a **one-time subretinal delivery of the AAV8 viral vector** that delivers the encoded gene
- A single treatment that has the potential to produce **constitutive anti-VEGF A** and eliminate or drastically decrease the need for additional intravitreal injections.
- Early results have demonstrated that the effects appear to be dose dependent with high viral loads leading to more efficacious treatment
- The higher-dose cohorts, 4 and 5, have shown the most significant results
  - At 1 year, there was a 61% and 85% reduction of anti-VEGF injections in cohorts 4 and 5, respectively, while 73% of patients (8 of 11) in cohort 5 remained anti-VEGF injection free.
  - The phase 2 trial (AAVIATE; NCT04514653) will consist of a new suprachoroidal delivery system that will bypass the need for intravitreal surgery and delivery..

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Gene Editing for AMD: ADVM-022

- **ADVM-022** (Adverum Biotechnologies) is a gene therapy that was designed to **produce anti-VEGF A fusion aflibercept protein** via the AAV.7m8 viral vector
- **Delivered by intravitreal injection**,
- Currently in phase 1 clinical trial (OPTIC; NCT03748784) assessing 30 participants and 2 different dose groups with a single intravitreal injection.
- The multicenter, dose-ranging trial was designed to assess the safety and tolerability of a single intravitreal ADVM-022 in patients with nAMD who are responsive to anti-VEGF treatment
- Recent updates revealed that patients in this highest dose cohort did not require rescue injections as far as 15 months out from initial treatment
  - All 6 patients in the high-dose group and 10 of 15 in the low-dose group were rescue-injection-free at the 18-month time point.

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Gene Therapy for AMD: AAVCAGsCD59

- **AAVCAGsCD59** (Hemera Biosciences) is an AAV2 gene therapy delivered as an **intravitreal injection that directly blocks membrane attack complex** (MAC) for the treatment of nAMD
- Currently Phase 1 multicenter, open-label study to assess the efficacy and safety of 2 doses of the AAV serotype 2 (AAVCAGsCD59) expressing sCD59 administered via intravitreal injection 7 days after a single intravitreal injection of anti-VEGF (NCT03585556)
- 25 total participants enrolled
  - Interim results have shown that of 22 patients with at least 6 months of therapy, 4 of 22 (18%) have not required retreatment
  - Of 11 subjects with at least 12 months of therapy, 2 (18%) have not required retreatment

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Gene Therapy or Gene Modification for Retinal Disease

- It's the dawn of a new age in treating eye disease
- Its still in its infancy
- In the coming years we will see many genetically driven targeted therapies for treating a host of varying eye disease

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I was told there was nothing to do about my floaters?

"I am a 45 yo Male and am very bothered by floaters in my vision. They are constantly in my vision and interfere with may daily activities. Is there any thing that I can do?"

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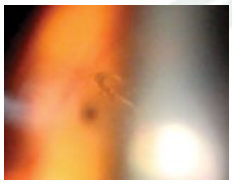
Floaterectomy?

- Is it too dangerous or a reasonable option?



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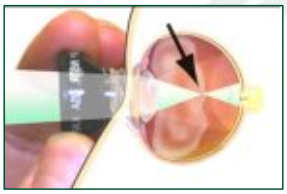
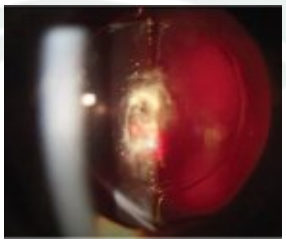
Options for Treatment of Floaters

- Yag vitreoloysis
- Pars plana vitrectomy





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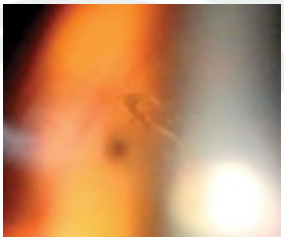
Important Considerations in Patients with Floaters

Are they acute or chronic?

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



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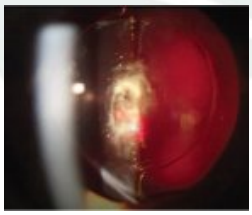
Reasons for Surgery for Floaters

Symptoms that impact the quality of life

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



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The Ideal Candidate for Treatment of Floaters

- Symptomatic
- Pseudophakic
- PVD

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

- Young
- Phakic
- Attached vitreous
- High myope

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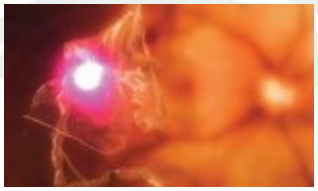
Laser Vitreolysis for Floaters

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



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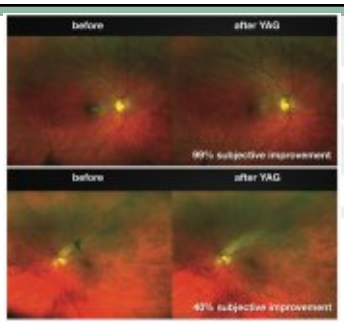

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Long-Term Follow-Up of Efficacy and Safety of YAG Vitreolysis for Symptomatic Weiss Ring Floaters

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

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

Ophthalmic Surg Lasers Imaging Retina 2020

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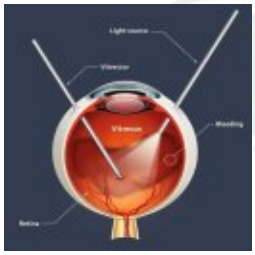
Is Vitrectomy a Better Option?



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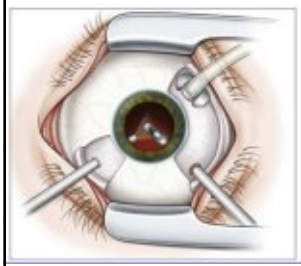

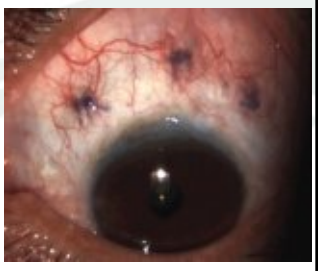

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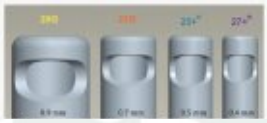
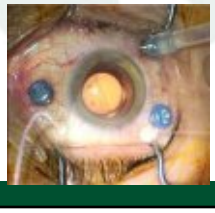
Vitrectomy 2021

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





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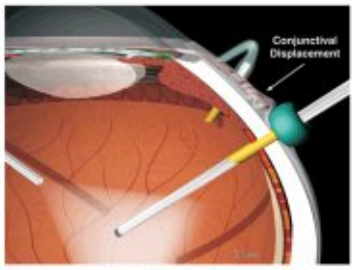

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Risk Factors for Vitrectomy

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

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Induce a PVD….or not

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

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ARVO Annual Meeting Abstract | June 2013

Long-term Safety of Vitrectomy for Patients with Floaters

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

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

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ARVO Annual Meeting Abstract | June 2013

Long-term Safety of Vitrectomy for Patients with Floaters

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

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

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Ophthalmology Retina

2018

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

J. Sebag, MD, FARVO · Kenneth M.P. Yee, BS · Justin H. Nguyen, BA · Jeannie Nguyen-Cuu, BS

Published: May 11, 2018 · DOI: https://doi.org/10.1016/j.ajo.2018.03.011

Methods 195 Eyes

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

Conclusions

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

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Would you Recommend Surgical Intervention for patients with intractable Symptoms of floaters?

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Hot Topics in Retina: Summary

- Exciting time for innovative treatments for retinal disease
- Paradigm shift in the management of diabetic retinopathy
  - Earlier treatments
  - Earlier referrals
- New Treatments for Wet AMD that may reduce the burdon to treatments for patients
  - Emerging treatments in the pipeline for dry AMD
- We are witnessing the dawn of a new age in using genetics to treat eye disease
- Imaging continues to get better and better and important part of clinical practice

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