



WHAT'S HOT IN RETINA

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FINANCIAL DISCLOSURES

- Heidelberg Engineering, Optos
- Regeneron, Notal Vision
- Apellis Pharmaceuticals, Iveric Bio, Novartis
- Clinical Investigator for
 - Regenxbio, Ophthea, F. Hoffmann-La Roche, Roche Genentech, Novartis, Neurotech Pharmaceutical
 - The Lowry Medical Research Institute
 - Outlook Therapeutics, Regeneron



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WHAT'S HOT? RESEARCH-CLINICAL TRIALS





1999

4100 Jan 2023



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"This drug's experimental status will treatment blind patients. Years later, the treatment is still trying to stop it"

4100 Jan 2023

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NOT FAKE NEWS



What?

Worldwide, the number of people with diabetes is estimated to increase from 415 million in 2020 to 642 million by 2040.


Age-related macular degeneration is already the leading cause of vision loss in the US, and the worldwide prevalence is estimated to rise from 196 million in 2020 to 288 million by 2040.

- AMD
 - Atrophic AMD
 - GA
 - nAMD
- Diabetic Retinopathy
 - DME

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WHAT ARE THE IMPLICATIONS

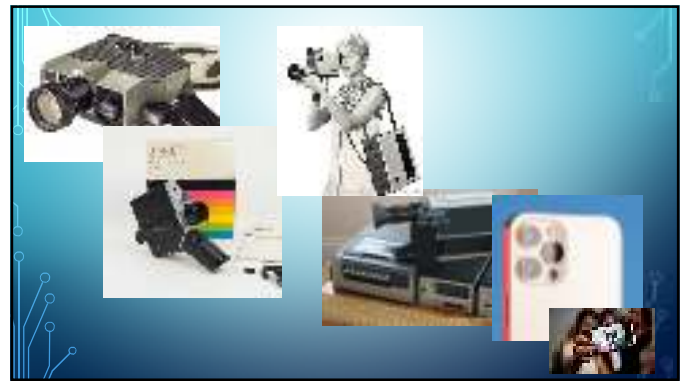
- Easier Access to Diagnosis
- Better Diagnostic Tools
- Better Treatment Options



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ADVANCES IN MANAGEMENT

- Gene Editing, Gene Splicing
- Viral Vector Gene Delivery
- On the horizon
 - Novel Therapies
 - Oral and Topicals for AMD, NPDR, DME

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AMD-Challenges and Unmet Needs

- AMD is a common, often progressive disease with the potential of poor visual outcome, negatively affecting patients and their caregivers in many aspects of life.
- Dry (Atrophic and other names) vs Wet (nAMD and other names)
- Atrophic AMD progression to GA
- Atrophic to nAMD Conversion
- nAMD to End Stage Disease

Often visual acuity remains stable as visual function diminishes

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GEOGRAPHIC ATROPHY

An Advanced form of AMD

- #Common
- #Progressive
- #Irreversible
- #No approved therapy??

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GEOGRAPHIC ATROPHY

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GA-IMPACT (PATIENT, RELATIVES, SOCIETY)

- 20% of AMD-related legal blindness is due to atrophic AMD.^{1, 2}

63-Year-old white female returns after 10 years now 73 with visual complaints and seeking help!

GA is a progressive, irreversible cause of vision loss with no current therapy!

1) Siemsen JS. The natural history of geographic atrophy, the advanced atrophic form of age-related macular degeneration. Mol Vis. 1999 Nov 3;5.
2) Gehrs KM, et al. Age-related macular degeneration-emerging pathogenetic and therapeutic concepts. Ann Med. 2006;38(7)

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DIAGNOSIS-UTILIZATION OF IMAGING TECHNOLOGIES

Mainstream Techniques

Color Fundus Photography (CFP)	Fundus Autofluorescence (FAF)	Enface Infrared (IR) or Near (NIR)	OCT (SD and SS)
(+) Most Commonly Available	(+) Diagnostic Value	(+) Early detection of drusen and reticular pseudodrusen (RPD)	(+) Pre-GA
(+) Documentation	(-) Availability	(+) Early GA detection	(+) CNV
(-) Image Manipulation (Red-Free)	(-) Familiarity	And serial follow-up	(+)(+)(+)
(-) Early Lesions Difficult to Detect	(-) Device Dependent		(-) Interpretation skill
(-) No prognostic Value			

Requires Multi-scan Lines

Jaffe GJ, et al. Imaging Features Associated with Progression to Geographic Atrophy in Age-Related Macular Degeneration: Classification of Atrophy Meeting Report 5. Ophthalmol Retina. 2021 Sep;6(9)

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UTILIZATION OF IMAGING TECHNOLOGIES

Angiography and OCT-A crucial role in the detection of CNV (nAMD)

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EXTENDED UTILIZATION OF CURRENT TECHNOLOGY

- Optical Coherence Tomography

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DISEASE BIOMARKERS

Recognition and Prediction of GA Development and Progression

The Visual Cycle

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EXTENDED UTILIZATION OF CURRENT TECHNOLOGY

GA risk Predictor

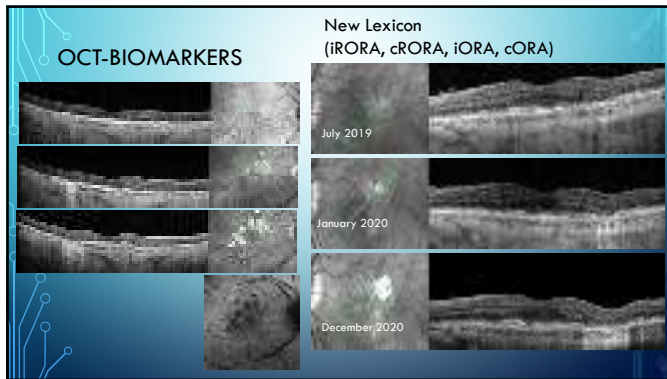
Subsidence of INL and OPL

Double-Layer Sign (DLS)
GA to CNV risk predictor

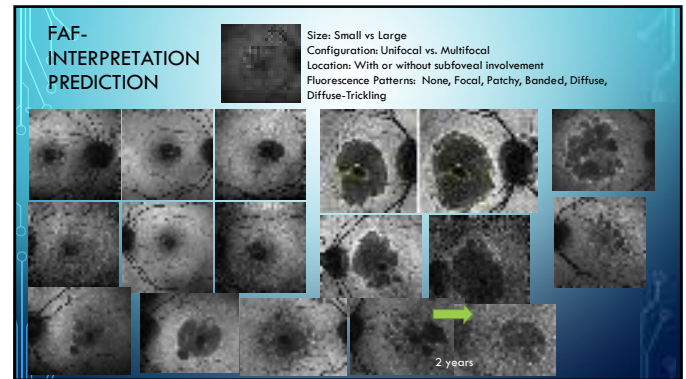
RPD visualized on NIR Reflectance, and OCT
Presents a Risk Factor for GA

Retinal Microstructure Characteristics and Associations in the Carotenoids in Age-Related Eye Disease Study 2 (CAREDS2), an Ancillary Study of the Carotenoids in Age-Related Eye Disease Study (CAREDS). Ophthalmol Retina. 2021 Aug;6(8)

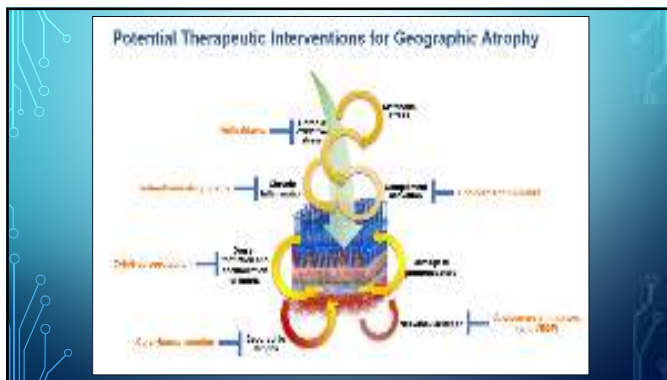
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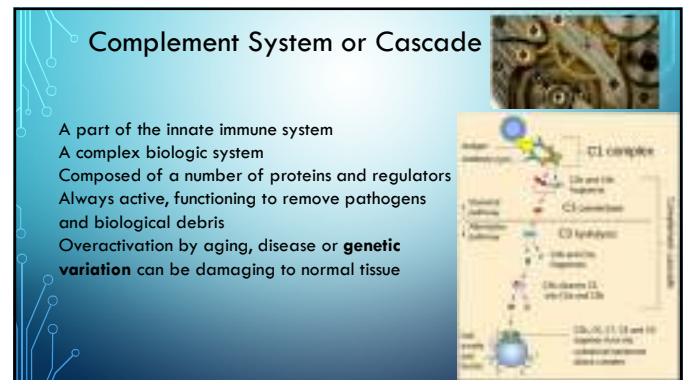
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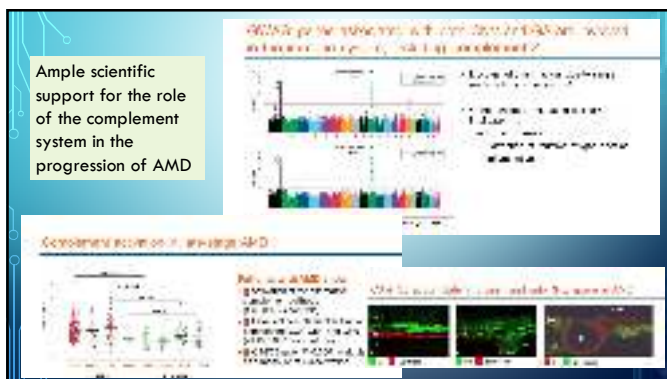
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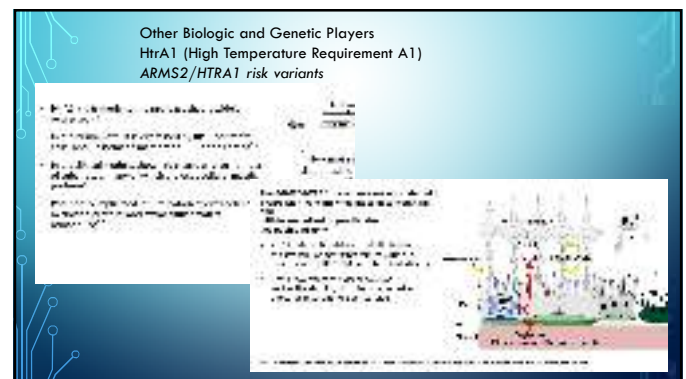
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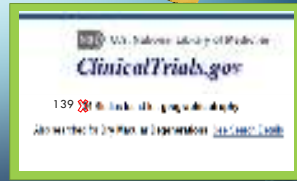
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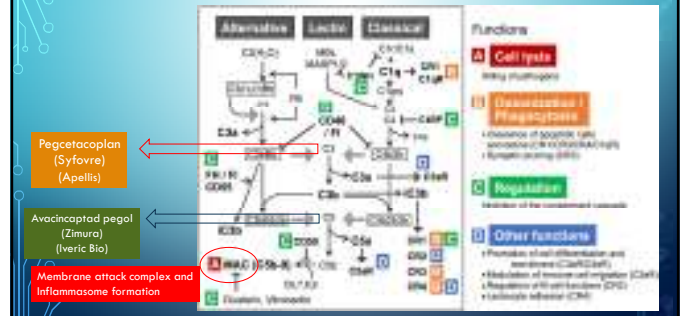
RACE TO FIND A TREATMENT

- Novel Therapies
 - Complement Inhibition
 - Antioxidants (mitochondrial dysfunction)
 - Anti-Inflammatory Agents
 - Visual Cycle Modulators
 - Gene Therapy
 - Cell-Based Therapy



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COMPLEMENT INHIBITION

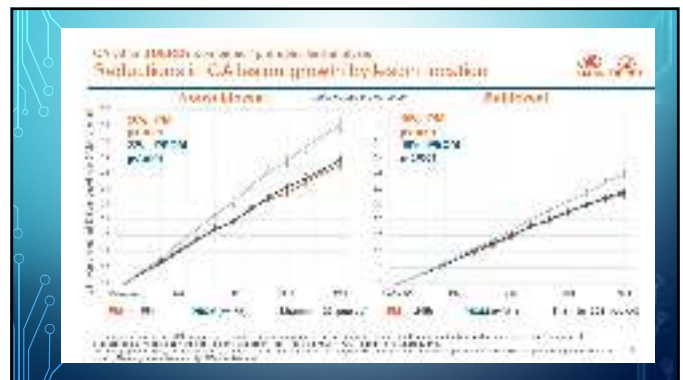


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Pegcetacoplan (Apellis)



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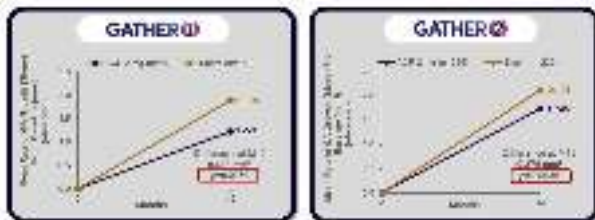


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Avacicaptad pegol (Iveric Bio)



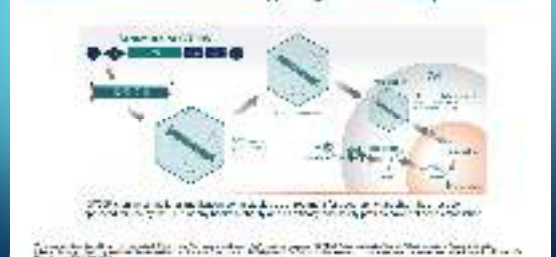
GATHER-1: GATHER-2



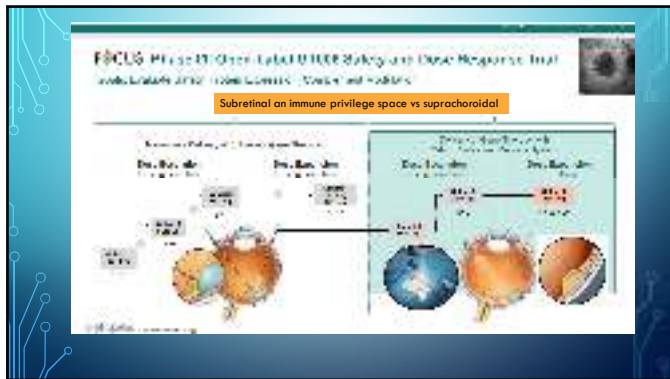
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Gyroscope Therapeutics/Novartis

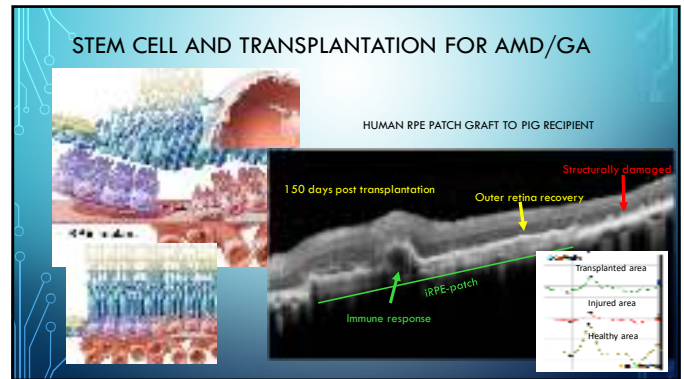
GTN001 is an AAV2-based Gene Therapy Designed to Induce Expression of CTRP9



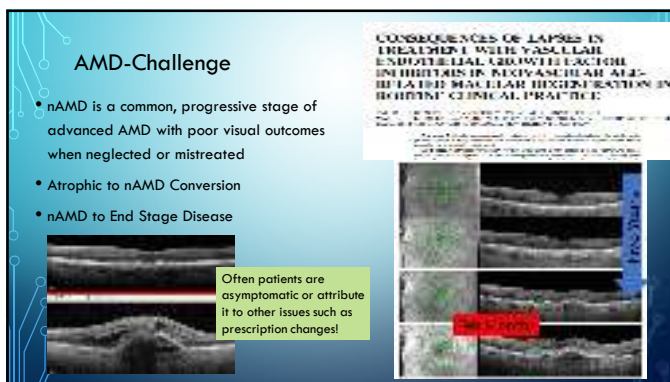
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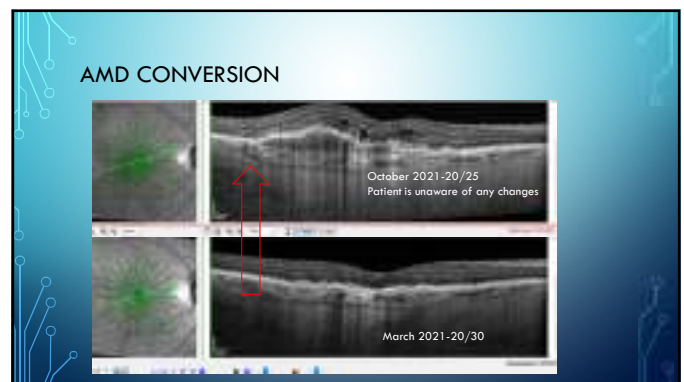
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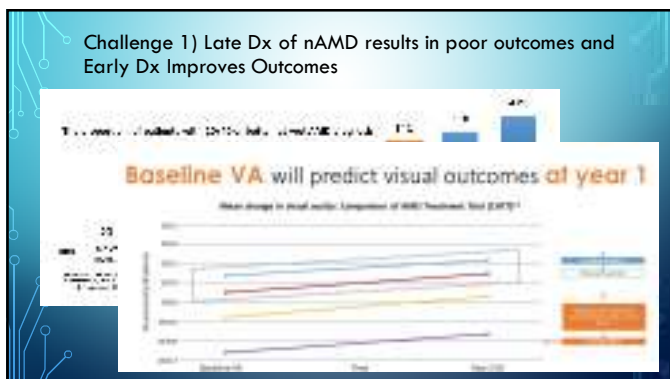
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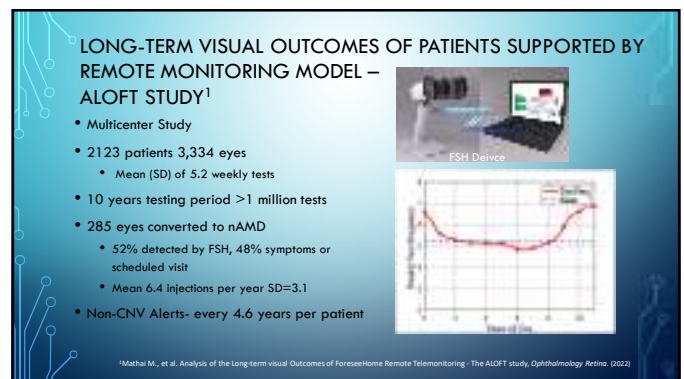
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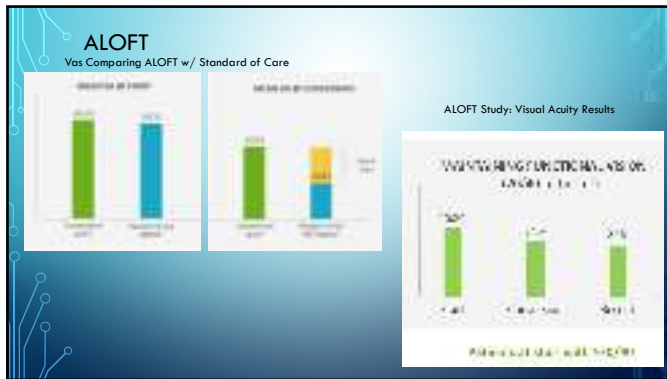
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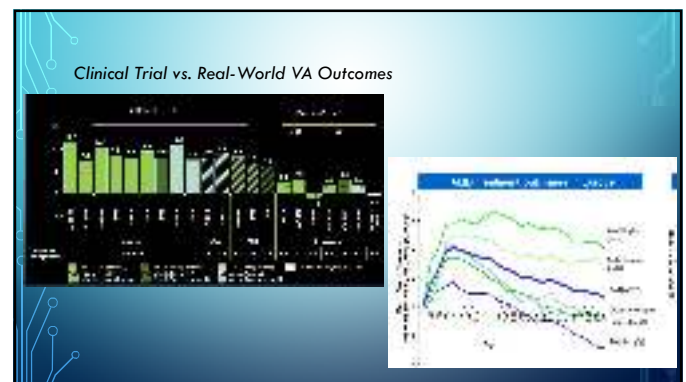


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nAMD Challenges

- Burdens and Barriers
 - Frequent injections
 - Care provider issues
 - Patients Issues

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NEW CLASS OF VEGF BLOCKERS

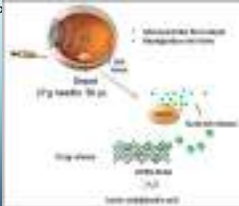
FARICIMAB VABYSMO®

- First bispecific Ab blocks VEGF-A and angiotensin-2
- Modified to reduced systemic absorption and potential ID inflammation
- New Applications of Existing Anti-VEGF
 - High Dose aflibercept

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STRATEGIES TO REDUCE INJECTIONS GB-102 (SLOW RELEASE)

- Depot formulation of sunitinib malate, tyrosine kinase inhibitor that targets both VEGF-A and PDGF
- Forms a depot in inf vit cavity and gradually biodegrades
- Phase 1/2 a was paused due to AC migration.
 - AE self-limiting, reversible no sequelae in M6
- Optimized to eliminate the particle migration
- Phase 2b ALTISSIMO study



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ADVM-022: Intravitreal Gene Therapy for nAMD

- AAV2/retb variant of AAV2 IVI delivering gene encoding for aflibercept
- Cohorts 1-4 of phase 1 OPTIC study
 - Mean BCVA maintained and CRT maintenance improved
 - Long term durability beyond 15 months from single IVI with no need for retreat
 - Well tolerated and no significant AE

Potential Issues
AAV suppression by patient Abs
Immune Privilege Sites
Lifetime Anti-VEGF

RGX-314: Subretinal Gene Therapy nAMD

- Subretinal delivery of gene encoding for anti-VEGF
- Elimination need for IVI over one year
- No significant AE
- Suprachoroidal injection in-office procedure



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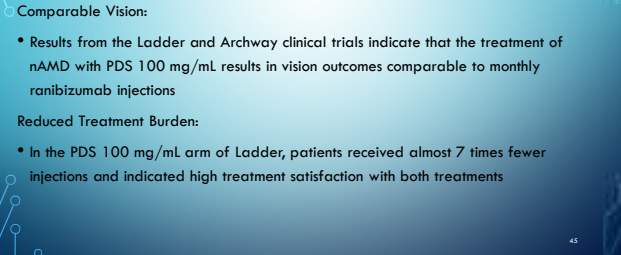
ADDRESSING INJECTION BURDEN LADDER AND ARCHWAY CLINICAL TRIALS FOR THE PDS (GENENTECH)

Comparable Vision:

- Results from the Ladder and Archway clinical trials indicate that the treatment of nAMD with PDS 100 mg/mL results in vision outcomes comparable to monthly ranibizumab injections

Reduced Treatment Burden:


- In the PDS 100 mg/mL arm of Ladder, patients received almost 7 times fewer injections and indicated high treatment satisfaction with both treatments



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Ladder and Archway clinical trials for the PDS (Genentech)

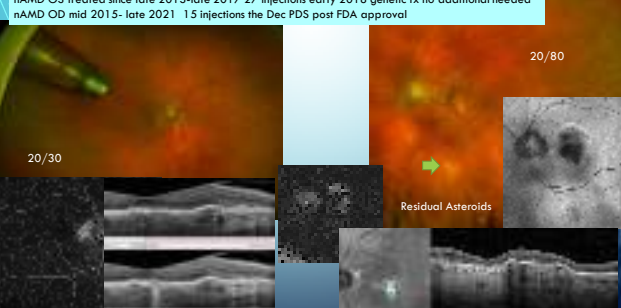
SUSVIMO™ Continuously Delivers A Customized Formulation Of Ranibizumab With As Few As 2 Refills A Year
FDA Approved Oct 2021



Genentech Voluntarily Recalls Susvimo Ocular Implant, Implantations Suspended

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78 Y/O
nAMD OS treated since late 2013-late 2017 27 injections early 2018 genetic tx no additional needed
nAMD OD mid 2015- late 2021 15 injections the Dec PDS post FDA approval



20/30

20/80

Residual Asteroids

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Prevalence of Diabetes and Diabetic Retinopathy




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Technological Advances in Management of Diabetes and Diabetic Retinopathy




Burdens and Barriers Do Exist

<https://www.healthline.com/health/diabetes/medications-list>

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AI RETINA/DR

- Benefits
 - Detection algorithm
 - Home monitoring and remote testing devices
 - Office Assistive
 - Automated Grading
 - More Sensitive than Human Grader (*JAMA*. 2017;318(22):2211-2223)
 - AI will serve to augment human intelligence and optimize the efficacy of the eyecare team in treating patients
 - Emerging AI systems will also enhance and be enhanced by telemedicine
- Limitations and disadvantages



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AI INSTRUMENTS FOR DETECTION OF DR

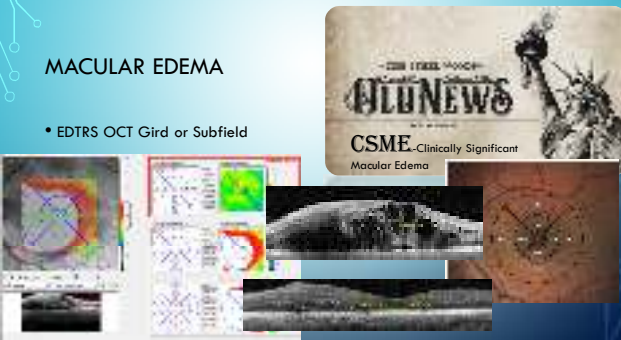
	SENSITIVITY (%)	SPECIFICITY (%)	IMAGEABILITY (%)
Aurora AEYE handheld (pending FDA clearance)	92	94	>99
AEYE & Topcon NW400	93	91	>99
EyeArt & Canon CR-2 AF/Plus AF	96	86	96
Idx-DR & Topcon NW400	87	90	88

Investigational device. Limited by United States law to investigational use only.

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MACULAR EDEMA


- EDTRS OCT Grid or Subfield



CSME...Clinically Significant Macular Edema

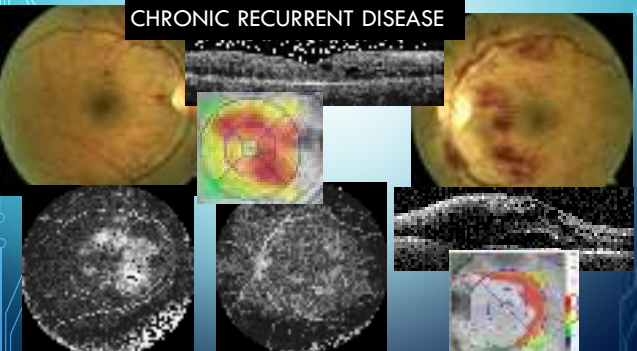
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DME-

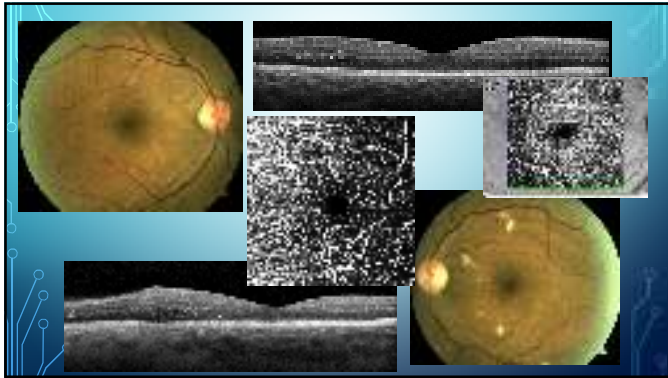


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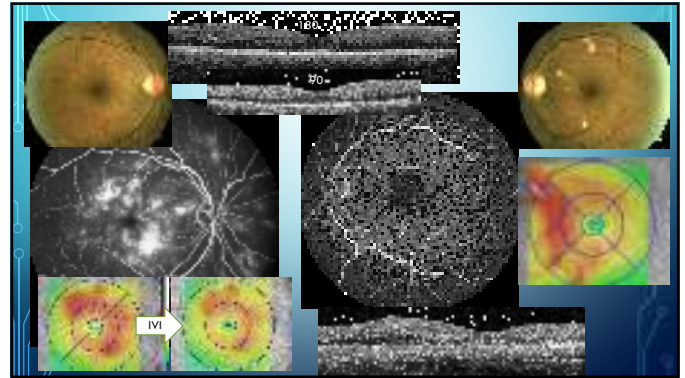
CHRONIC RECURRENT DISEASE



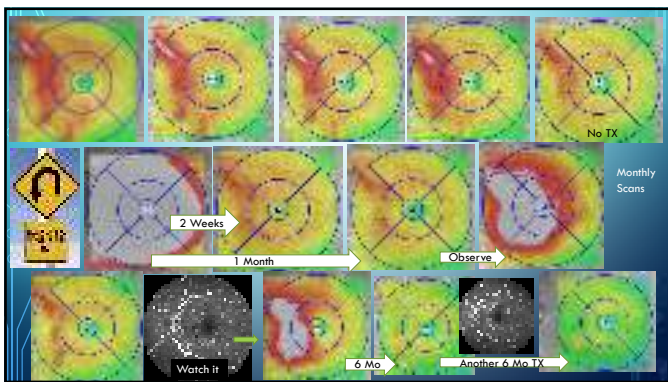
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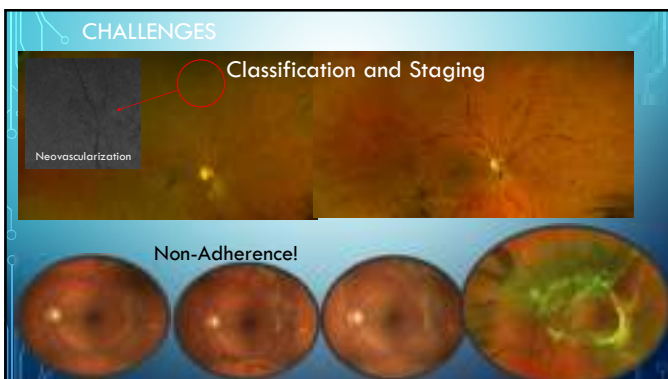
DEALING WITH PDR PANORAMA

DRCR Network Protocol S
Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

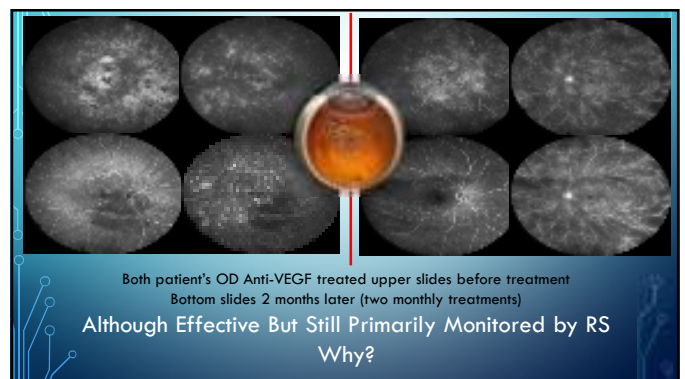
Conclusion
Our meta-analysis indicates that anti-VEGF pharmacotherapy is associated with superior visual acuity outcomes and less PDR-related complications. However, there is insufficient evidence to suggest anti-VEGF therapy as an alternative to PRP.

Protocol W
Conclusion: ranibizumab is at least as effective as PRP in treating PDR (though in both groups 40-45% of eyes had active NV at two years). There's significant data that ranibizumab is a better treatment, with superior two-year visual acuity gains, particularly in eyes with baseline DME, and dramatically less visual field loss compared to PRP. Additionally, ranibizumab treated eyes were less likely to develop DME and less likely to require vitrectomy.

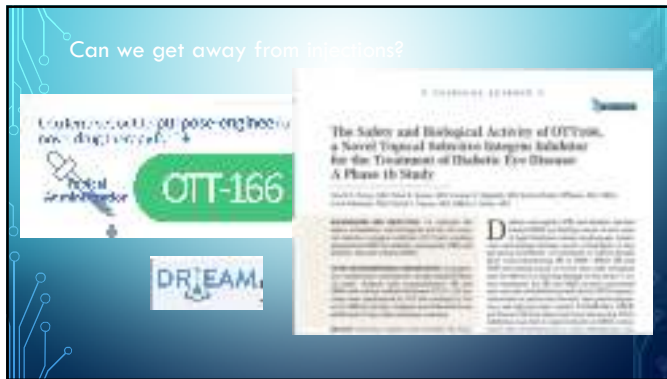
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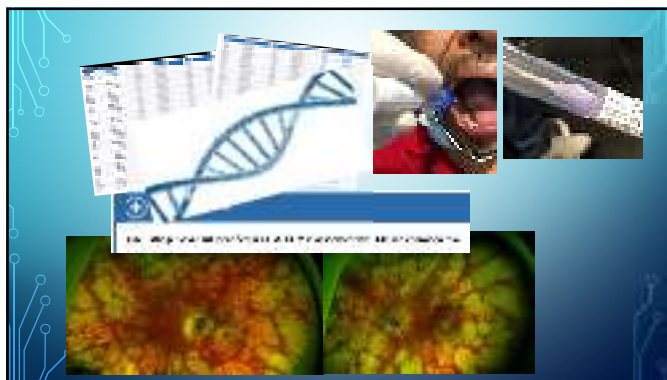
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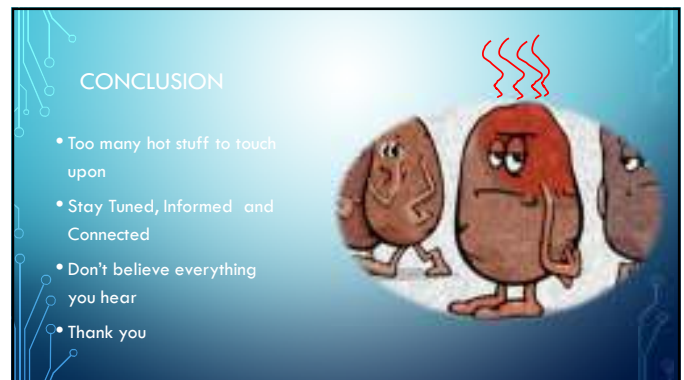
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