

WHAT'S HOT IN RETINA

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FINANCIAL DISCLOSURES

MOHAMMAD RAFIEETARY, OD, FAAO, FORS, DIP ABO AND ABCMO
CHARLES RETINA INSTITUTE, GERMANTOWN TN (MRAFIEETARY@CHARLESRETINA.COM)

- Heidelberg Engineering- Ad Board, Speaker
- Optos- Ad Board , Speaker
- Regeneron- Ad Board , Speaker
- Notal Vision- Ad Board , Speaker
- Apellis Therapeutics –Ad Board
- Iveric Bio-Ad Board
- Novartis-Ad Board

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WHAT'S HOT? RESEARCH-CLINICAL TRIALS

U.S. National Library of Medicine
ClinicalTrials.gov

Home > Search Results
Modify Search Start Over

3960 Studies found for: retina
Also searched for Retinal. See Search Details

1999 VITREORETINAL DISEASE

MAJOR CLINICAL TRIALS OF VITREORETINAL DISEASES
by Emily Y. Chen, MD

- ETRDS and DRS (1970-1980s)
- PRP for PDR
- Focal for "CSME"
- BRVO and CRVO studies (1980-1990s)
- PRP for Proliferative Stage
- Focal for Selected cases
- MPS for CNV (1980s)

ANCHOR
 MARINA
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 CAPTURE
 CONFERENCE
 OMAHART
 RAVEN
 GALLEGOS
 PANORAMA
 STAIRWAY
 PATULLAN
 SPECTRO
 ONE
 TENATA

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This clinic's experimental stem cell treatment blinded patients. Years later, the government is still trying to stop it.

Health & Science

MIAMI — In the summer of 2005, ophthalmologist Thomas Altshuler examined a patient who had suddenly lost vision in both eyes. The woman, 78, had macular degeneration and had visited a Miami clinic offering a new treatment: injections of stem cells made from fat in her body.

Instead of getting better, the woman's vision deteriorated significantly. Peering into her eyes, Altshuler said, he saw clumps of blood floating inside.

The next day, a second patient appeared in Altshuler's emergency room at the University of Miami complaining of blindness and seeing pain after receiving eye injections from the same company, U.S. Stem Cell. Altshuler reported the cases to the U.S. Food and Drug Administration, urging an investigation.

Now, the FDA is using to stop the company's treatments in federal court in Fort Lauderdale, Fla., in one of the government's most aggressive actions against the burgeoning stem cell business. With the judge expected to rule any day on the unprecedented times-call for nationwide access.

But the FDA's slow response has permitted U.S. Stem Cell to continue operating four years after those first reports of blindness. Although the company stopped injecting its fat-derived treatments into eyes after the patients sued, it continues to sell the therapy to people with spinal injuries, Parkinson's disease, multiple sclerosis and other serious chronic conditions.

Last spring, just three weeks after the government filed suit, another patient had a catastrophic reaction after visiting a South Miami clinic affiliated with U.S. Stem Cell. The 59-year-old woman felt faint and started vomiting two hours after receiving injections for arthritis pain.

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NOT FAKE NEWS

The Old News Paper

OLD WORLD NEWS

The Prevalence of age-related and comorbid ocular conditions is rising

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

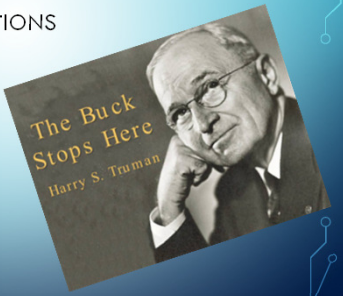
- AMD
 - Atrophic AMD
 - GA
 - nAMD
- Diabetic Retinopathy
- DME

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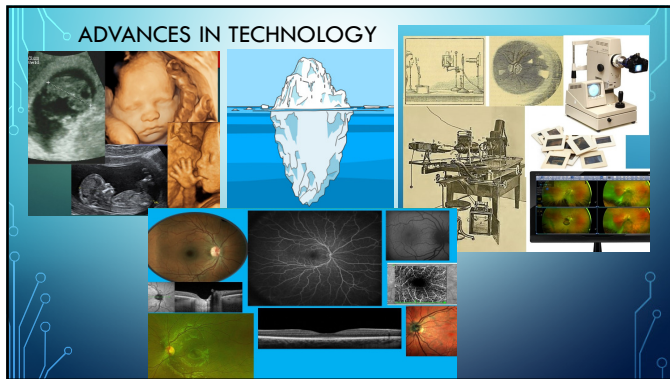
WHAT ARE THE IMPLICATIONS

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

The Buck Stops Here
Harry S. Truman



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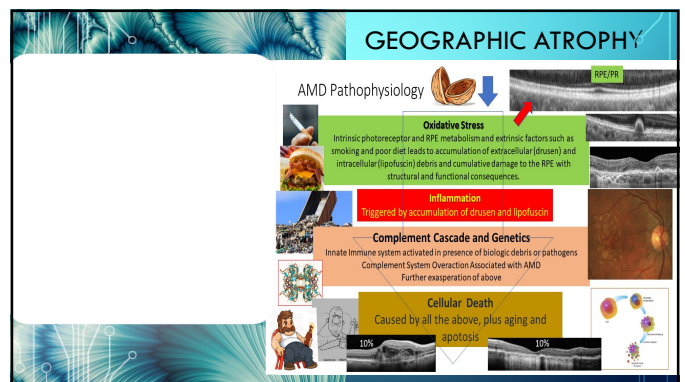
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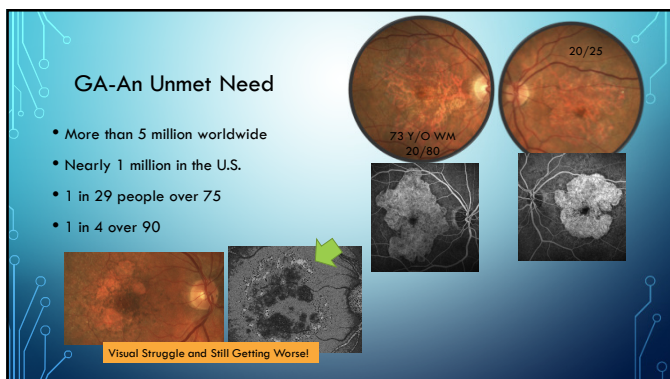
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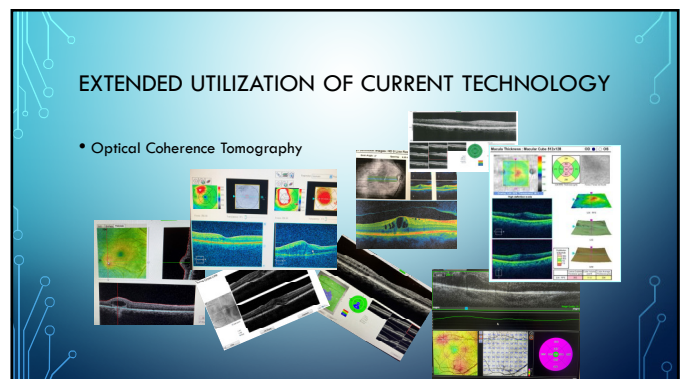
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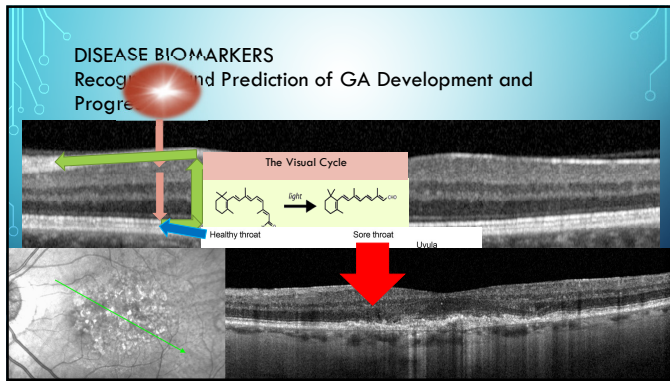
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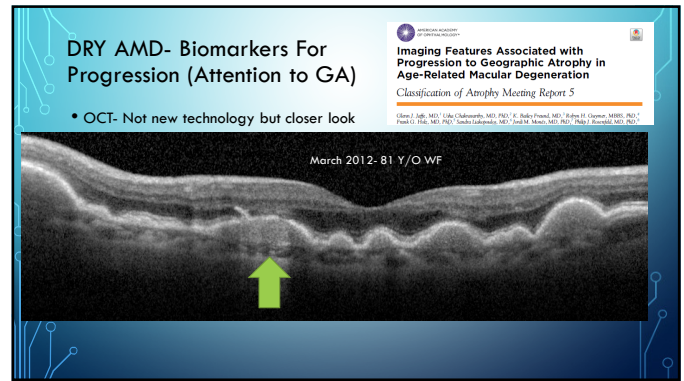
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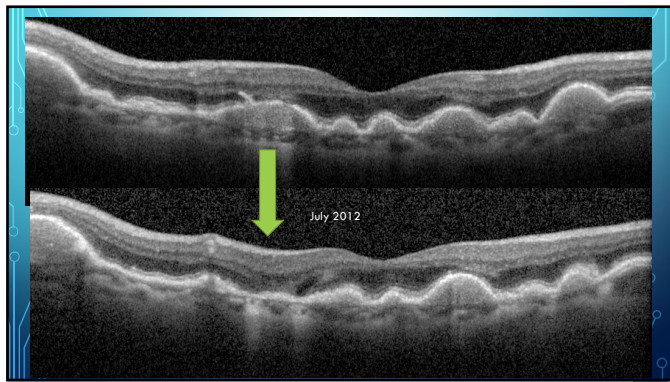
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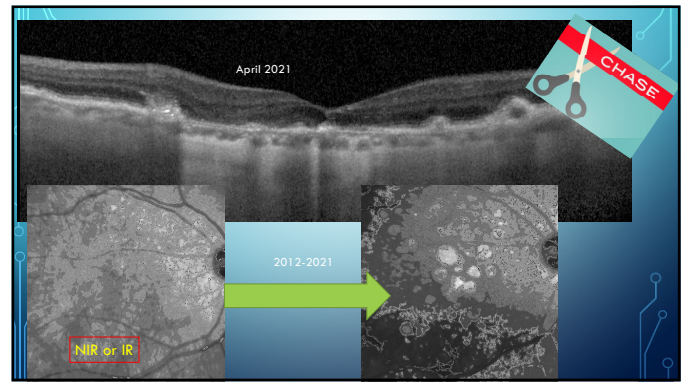
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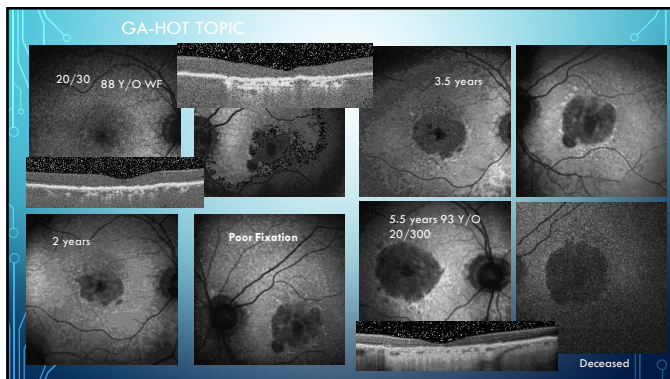
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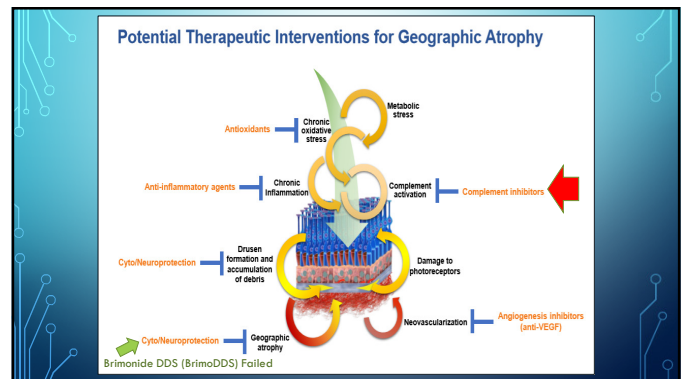
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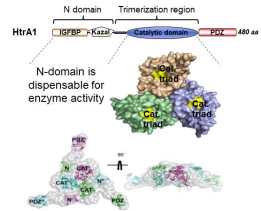
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HtrA1 (High Temperature Requirement A1)

- HtrA1 is a trimeric serine protease that is widely expressed^{1,2}
- In the human eye, it is expressed by RPE, horizontal cells, and Descemet's membrane in the cornea^{3,4}
- In preclinical models, shown to cleave a large number of substrates, many of which are extracellular matrix proteins⁵
- Potentially implicated in elimination of extracellular misfolded proteins and extracellular matrix remodeling^{1,6}



1. Kuperstein G et al. *Biochem J*. 2012;385:1545-1552. 2. Jones A et al. *Proc Natl Acad Sci*. 2011;108(20):14378-83. 3. Yang Z et al. *Science*. 2006;314(5801):882-3. 4. Deyoung T et al. *J Proteome Res*. 2012;11(5):4231-5. 5. Ouyang S et al. *J Biol Chem*. 2005;280(11):11514-9. 6. Pridgen ET et al. *J Biol Chem*. 2010;285(21):11517-11520.

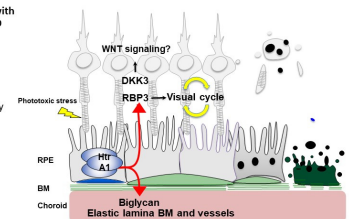
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Therapeutic Hypothesis for Targeting HtrA1

The *ARMS2/HTRA1* risk variants are associated with progression from intermediate to advanced AMD and with increased lesion growth rates in geographic atrophy.

- HtrA1 induces breakdown and elimination of extracellular matrix protein, resulting in photoreceptor, RPE, BM, and choroidal atrophy
- HtrA1 may affect the visual cycle, as well as the stability of proteins required for photoreceptor and RPE cell survival



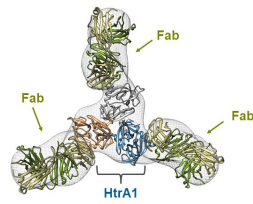
AMD, age-related macular degeneration; BM, Bruch's membrane; DKK3, Dickkopf-related protein 3; GA, geographic atrophy; HtrA1, high temperature requirement A1; RPE, retinal pigment epithelium.

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Anti-HtrA1: Fab of a Humanized Monoclonal Antibody Designed to Inhibit HtrA1 Activity

- HtrA1 is a trimer: 1 mole HtrA1 binds 3 Fab molecules
- In preclinical models, anti-HtrA1:
 - binds to recombinant human HtrA1 with high affinity
 - blocks proteolytic activity of HtrA1 with physiologically relevant substrates



1. Ouyang S et al. *Biochem J*. 2012;385:1545-1552.

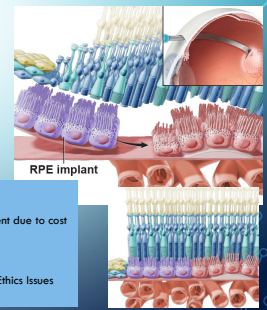
Fab, fragment antigen binding; HtrA1, high temperature requirement A1.

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STEM CELL AND TRANSPLANTATION FOR AMD/GA

- Photoreceptor Progenitor Cell (PRP) Monolayer on Biodegradable Scaffold
 - Roughly 50/50 Cone/Rod Mix or Mostly Cones
- Authentic RPE Cell in Monolayer on Biodegradable Scaffold
- Combined Photoreceptor Progenitor Cell and RPE on Biodegradable Scaffold



Cell Source

Induced Pluripotent Stem Cells Best Option

CD34+ Cells Obtained via Venipuncture from Volunteers, not patient due to cost

Tissue Typed Like Organ Transplantation

Not Skin Fibroblasts Because iPSC Quality Not Good

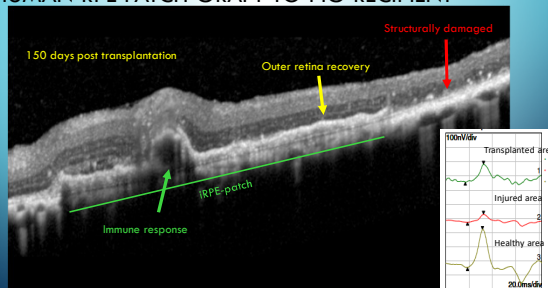
Not Embryonic Stem Cells

Recipient Must Be Immune Suppressed, Logistics Issues, Cost Issues, Ethics Issues

Not Mesenchymal Stem Cells Obtained Via Liposuction

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HUMAN RPE PATCH GRAFT TO PIG RECIPIENT



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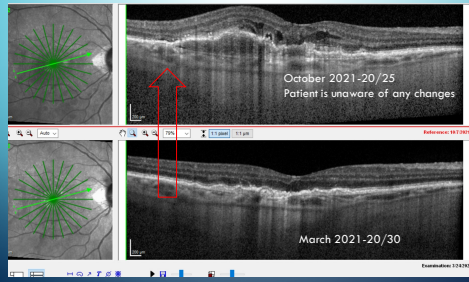
Neovascular AMD (nAMD)

- Approximately 15 million people have AMD in the US
- More than 1.7 million have advanced AMD and reaching to nearly 3 million soon
- Approximately 200,000 new cases of wet AMD are diagnosed each early in North America
- nAMD is Defined by Growth or Presence of a Choroidal Neovascular Membrane (CNVM).
 - There are different subsets of CNVM



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AMD CONVERSION



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EXISTING AND EMERGING TECHNOLOGIES FOR DETECTION

- Startups for smaller, less expensive OCT and other imaging devices
- Home Monitoring
- AI Assisted Diagnosis



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Once You Detect nAMD Patient Is Subject To The Injection Black Hole

Why?

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THAT IS WHY!

CONSEQUENCES OF LAPSES IN TREATMENT WITH VASCULAR ENDOTHELIAL GROWTH FACTOR INHIBITORS IN NEOVASCULAR AGE-RELATED MACULAR DEGENERATION IN ROUTINE CLINICAL PRACTICE

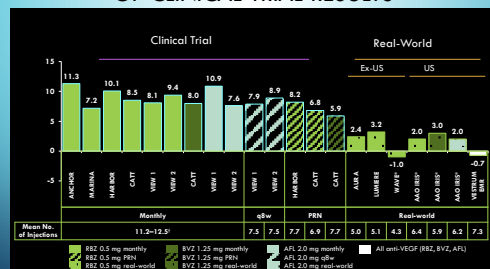
TYLER E. GREENLEE, DO,* VICTORIA Y. WANG, MS,† HANNAH KANG,‡ MARC E. OHLHAUSEN, BA,‡ ANDREW X. CHEN, BSE,*† GRANT L. HOM, BA,† THAIS F. CONTI, MD,* ISAAC BRISKIN, MA,‡ AMY S. BABICH, MD,* RISHI P. SINGH, MD*†

Purpose: Evaluating outcomes in patients receiving intravitreal anti-vascular endothelial growth factor (VEGF) inhibitors for neovascular age-related macular degeneration whom experience a lapse in treatment.

Methods: A retrospective chart review evaluating 3,304 patients in 18 years who experienced treatment lapses ≥3 months compared with control counterparts. Demographic information, macular thickness as measured by central subfield thickness, and visual acuity

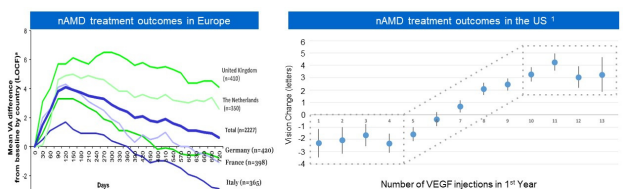
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REAL-WORLD VISUAL ACUITY OUTCOMES FALL SHORT OF CLINICAL TRIAL RESULTS



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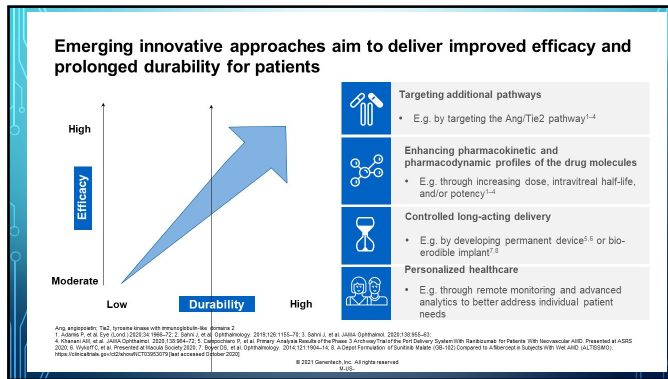
Real world outcomes with anti-VEGF intravitreal injections have significant room for improvement



*Patients received a mean of 5.0 and 2.2 injections in the 1st and 2nd year, respectively. More frequent visits and injections were associated with greater improvements in visual acuity. J.G. Holt, Br J Ophthalmol, 2015

¹ Courtesy of T. Bogan/Vision Health, presented by Dr. D. Williams at ASRS 2018. Ophthalmology Retina, nAMD=neovascular age-related macular degeneration

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NEW CLASS OF VEGF BLOCKERS

FARICIMAB VABYSMO®

- First bispecific Ab blocks VEGF-A and angiopoietin-2
- Modified to reduced systemic absorption and potential IO inflammation

- New Applications of Existing Anti-VEGF
- High Dose aflibercept

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Ranibizumab Biosimilar

	FYB201	SB11*	Xlucane
Manufacturer	Coherus	Biogen/Samsung Bioeics	Xbrane-Stada/B&L
Trial Status	Phase 3 done	Phase 3 done	Phase3 ongoing
Estimated Approval	2021/2022	2021/2022	2020

SB11 = Byoviz FDA Approved Sep 2021 (nAMD, myopic CNV, DME and RVO ME)

FDA Approves Samsung Bioeics and Biogen's BYOOVIZ™ (SB11), LUCENTIS® Biosimilar (ranibizumab-nuna)

Aflibercept Biosimilar

	SB15	ABP93B	FYB203	CHS2020	MZ10
Manufacturer	Biogen/Samsung	Amgen	Formycon	Coherus	Momenta/Mylan
Status	P3 ongoing	P3 ongoing	P3 ongoing	P3 start 2021	P3

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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

Potential Issues

- AAV7m8 variant of AAV2 IVI delivering gene encoding for aflibercept
- Cohorts 1-4 of phase 1 OPTIC study
 - Mean BCVA maintained and CRT maintained or improved
 - Long-term durability beyond 15 months from single IVI with no need for rescue
 - Well tolerated and no significant AE

RGX-314: Subretinal Gene Therapy nAMD

- Subretinal delivery of gene encoding for anti-VEGF fab protein
- Eliminates 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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SUSVIMO™ Continuously Delivers A Customized Formulation Of Ranibizumab
With As Few As 2 Refills A Year
FDA Approved Oct 2021

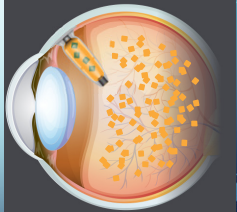


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PDS MECHANISM OF CONTINUOUS DELIVERY: PASSIVE DIFFUSION

Higher concentration in implant
Passive diffusion
Lower concentration in vitreous

- Continuous delivery mediated by passive diffusion
- Rate of diffusion is concentration dependent and decreases over time
- Follows Fick's Law

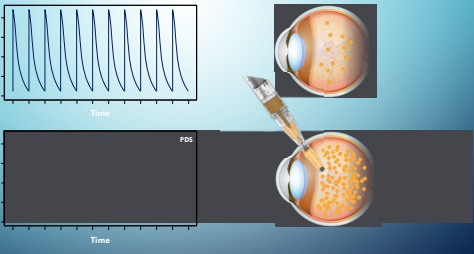


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PDS VS MONTHLY INTRAVITREAL RANIBIZUMAB THERAPY

Monthly intravitreal treatment

PDS with fixed-interval implant refill



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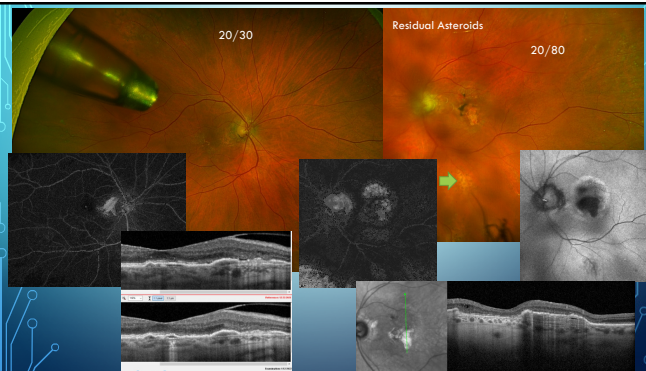
Advances in nAMD Treatment

- 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

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20/30

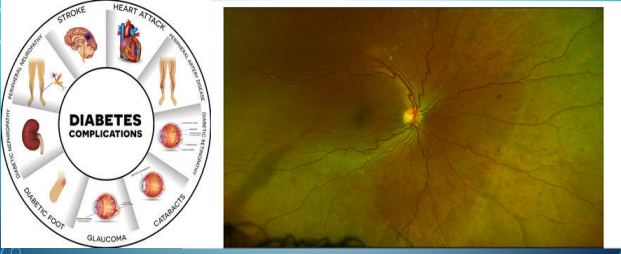
Residual Asteroids 20/80



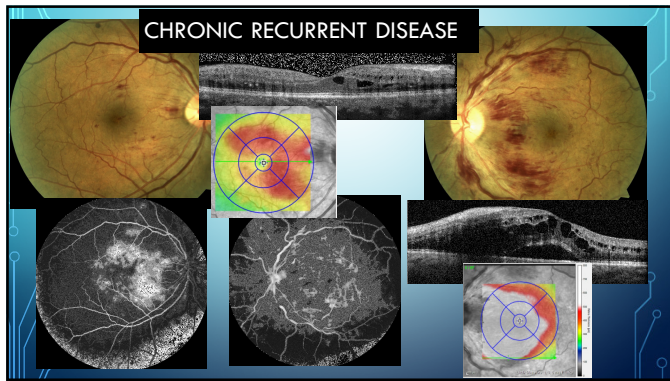
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DIABETES COMPLICATIONS

STROKE, HEART ATTACK, NEPHROPATHY, RETINOPATHY, DIABETIC FOOT, GLAUCOMA, CATARACTS



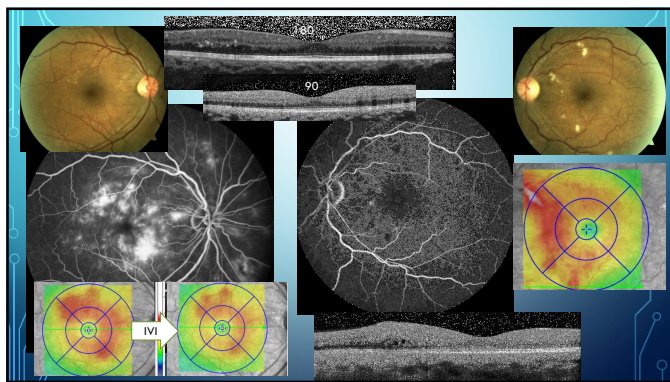
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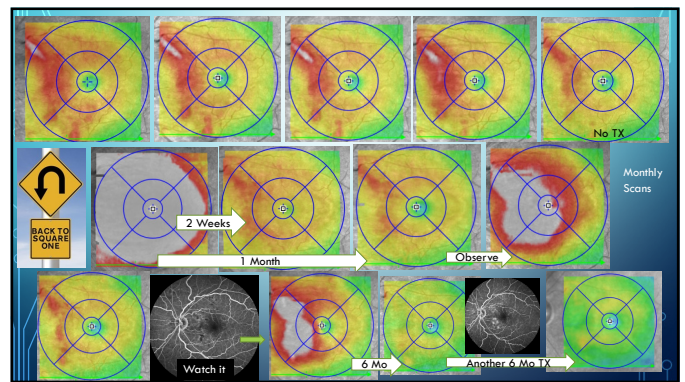
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DEALING WITH PDR

Frontiers in Pharmacology

PMCID: PMC7289996
PUBID: 3289395

Anti-Vascular Endothelial Growth Factor Therapy as an Alternative or Adjunct to Pan-Retinal Photocoagulation in Treating Proliferative Diabetic Retinopathy: Meta-Analysis of Randomized Trials

Shaojun Chen, Zhenjun Chen, Wei Li, Shaojun Chen

Author information, Article notes, Copyright and License information, Disclaimer

This article has been cited by:

Associated Data

Data Availability Statement

Abstract

Aim

To compare anti-vascular growth factor (anti-VEGF) pharmacotherapy with pan-retinal photocoagulation (PRP) for proliferative diabetic retinopathy (PDR).

Conclusion

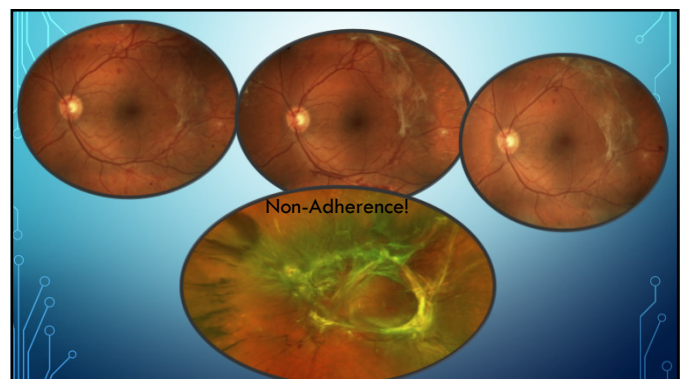
Our meta-analysis indicates that anti-VEGF pharmacotherapy is associated with superior visual acuity outcomes and less PDR-related complications. However, there is insufficient evidence to suggest anti-VEGF therapy as an alternative to PRP.

DRCR Network Protocol S

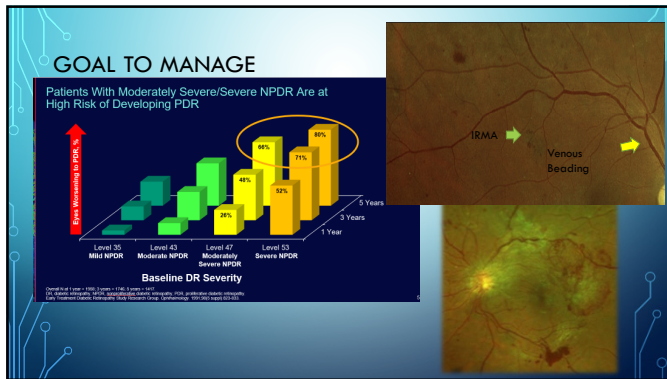
Prompt Panretinal Photocoagulation versus Intravitreal Ranibizumab with Deferred Panretinal Photocoagulation for Proliferative Diabetic Retinopathy

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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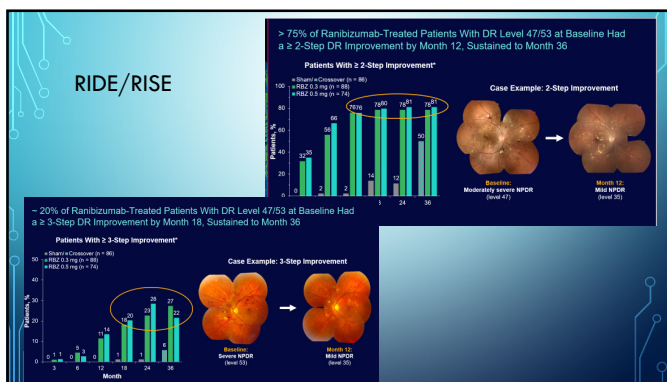


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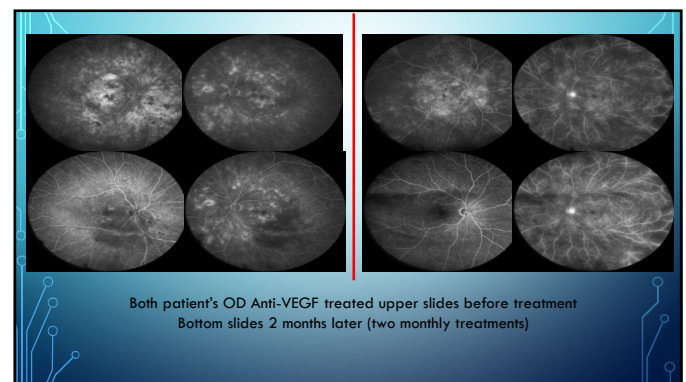
EARLY PREVENTION

- RIDE and RISE
- PANORAMA
- DRCR Network protocol W
 - Intravitreal Anti-VEGF Treatment for Prevention of Vision Threatening Diabetic Retinopathy in Eyes at High Risk

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Inherited Retinal Disease (IRD)

Spark

We don't follow footprints.

Gene Replacement

Developing Groundbreaking GENE THERAPIES FOR PATIENTS WITH RARE DISEASES

U.S. National Library of Medicine ClinicalTrials.gov

183 IRD Studies

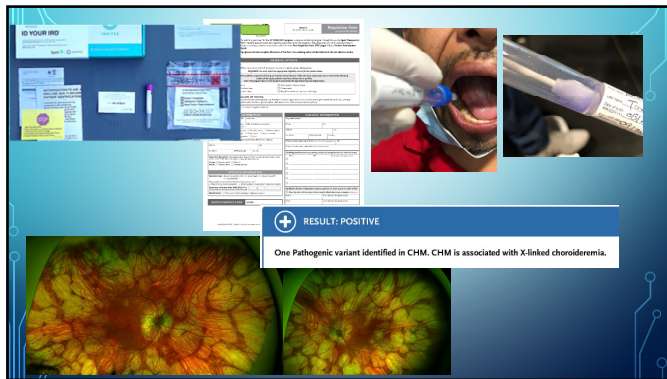
Also searched for Hereditary Retinopathy Disorders and more. See Search Details

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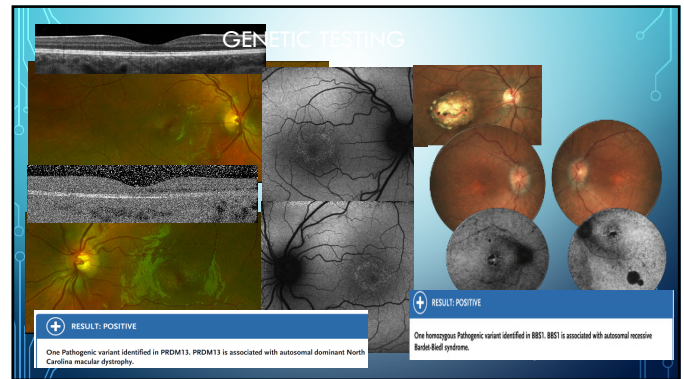
GENETICS OF IRD

- Late 1980s first retina disease gene (RHO) identified
- Today more than 300 genes identified
- ~65% gene detection by genetic testing (not a panacea)

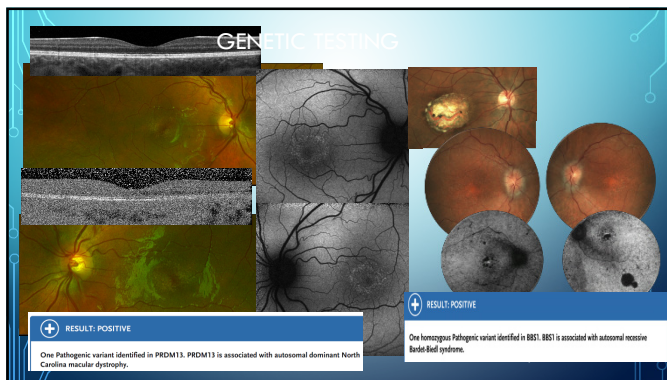
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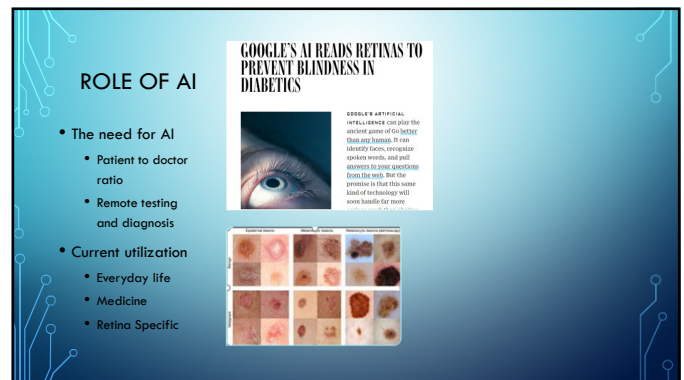
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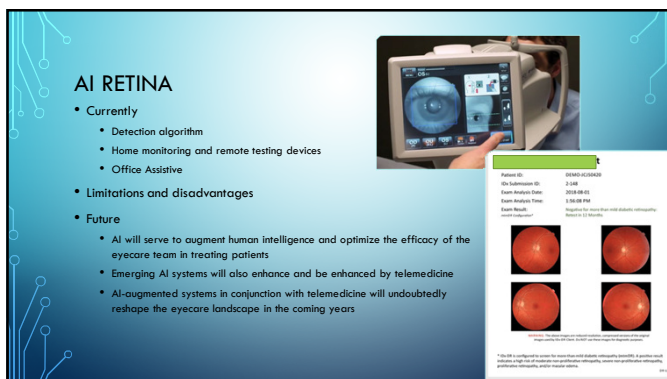
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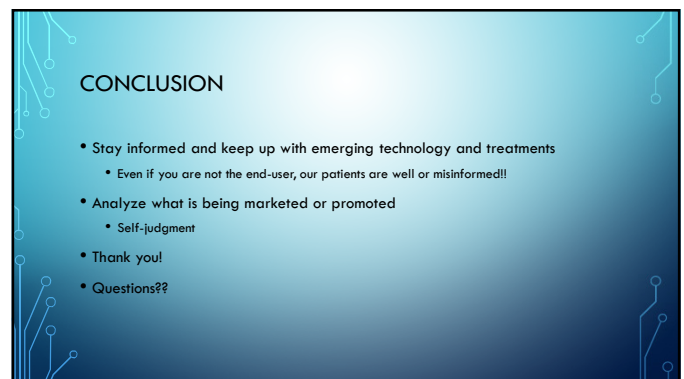
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