

AMD from Dry to Wet: Diagnosis and Management

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Speakers Disclosures



Charles Retina Institute
Apellis
Astellas
Optos
Heidelberg
Orasis
Visible Genomics
B&L
Notal
LKC

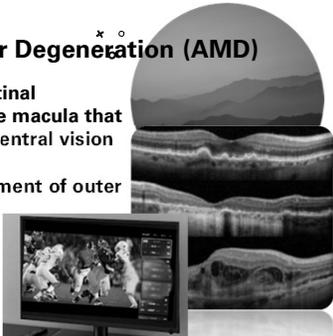
All relevant relationships have been mitigated

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Age-Related Macular Degeneration (AMD)

A specific and acquired retinal degeneration involving the macula that can cause mild to severe central vision loss by:

- Non-neovascular derangement of outer retinal tissue or
- Neovascular destruction



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Perceptions

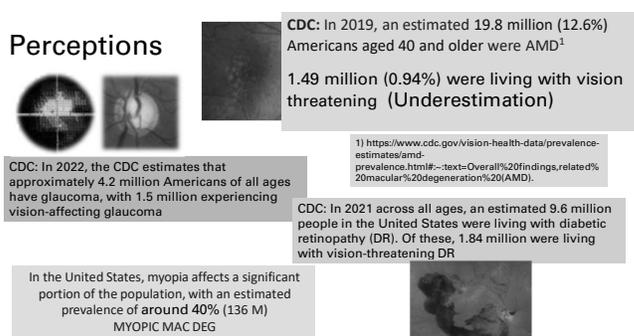
CDC: In 2019, an estimated 19.8 million (12.6%) Americans aged 40 and older were AMD¹

1.49 million (0.94%) were living with vision threatening (Underestimation)

CDC: In 2022, the CDC estimates that approximately 4.2 million Americans of all ages have glaucoma, with 1.5 million experiencing vision-affecting glaucoma

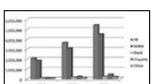
CDC: In 2021 across all ages, an estimated 9.6 million people in the United States were living with diabetic retinopathy (DR). Of these, 1.84 million were living with vision-threatening DR

In the United States, myopia affects a significant portion of the population, with an estimated prevalence of around 40% (136 M)
MYOPIA MAC DEG



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AGING AS A RISK



U.S. Census Bureau Estimated Starting 2010, *Everyday* 10,000 Americans are Turning 65 for the next 10 Years Now we are in 2020s!

Prevalence of AMD increased with age from 2% people aged 40 to 44 to 46.6% among people aged ≥85

AGING POPULATION



In the United States, there are approximately 123.2 million people aged 50 and older.

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OTHER RISK FACTORS

AMD is a Multi-Etiologic Disease

Non-modifiable

- Ethnicity
- Anatomic and Physiologic
 - Low macular Pigment, Color or the Iris

Modifiable

- Smoking** 
- Dietary Habits
- Cardiovascular Disease
- Increased BMI
- Sleep Apnea
- Medications
 - Aspirin Debate



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GENETICS FACTORS AND OF AMD

- Non-Mendelian
- More than 30 genes
- Complement Pathway
 - CFH, CFHR1, CFHR3, C3, C2, CFB, C9, CFI
- Other Pathways
 - ARMS2, TIMP3, ABCA1, APOE, VEGF, FBLN5
- Others
 - HTRA1, CX3CR1, RECC6, FGF2, Y402H

Lung Cancer 8%-15% inherited genetic mutation¹
 Coronary Artery Disease 40%-60%²
 Type 2 Diabetes 10%-15%³ (Varies per source)
 Colorectal Cancer 5%-10%⁴
AMD 70%⁵ (46-71%)

Phenotype probability differs amongst various genotype variations

1) https://ccr.cancer.gov/news/articles/genetics-not-just-smoking-influence-small-cell-lung-cancer-risk
 2) https://www.ahajournals.org/doi/10.1161/circresaha.115.306666...text=Coronary%20artery%20disease%20(CAD)%20as.4
 3) Florez Jost et al. Genetics of Type 2 Diabetes. PMID: 23691566
 4) https://www.cancer.gov/types/colorectal/histopathologic/genetics-pdq#...text=About%2075%25%20of%20patients%20with%20overall%5B%2C4%5D
 5) Warwick A. Genetics and genetic testing for age-related macular degeneration. Eye (Lond). 2018. PMID: 29125146; PMCID: PMC6944647.

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AMD Classification

Classification	Clinical Findings
No AMD	No drusen and no RPE abnormalities
Normal aging changes	Drusen ≤ 63 μm and no RPE abnormalities
Early AMD	Drusen > 63 μm and ≤ 125 μm and no RPE abnormalities
Intermediate AMD	Drusen > 125 μm and/or RPE abnormalities
Late AMD	GA and/or nAMD

Drusen Size
 Small: < 63 μm
 Medium: 64 – 124 μm
 Large: > 125 μm

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PATHOGENESIS OF PROGRESSION

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HOW DO WE DIAGNOSE AMD

- Consideration
 - Pre-Clinically Evident
 - Early.....to.....late
- Based on
 - Presenting HX, Symptoms
 - Risk Assessment

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AMD DX

• Based on Examination Findings

- Functional Testing

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Diagnosis-Utilization of Imaging Technologies

Color Fundus Photography (CFP)
 (+)Most Commonly Available
 (+)Documentation
 (-)Image Manipulation (Red-Free)
 (-)Early Lesions Difficult to Detect
 (-)No prognostic Value

Fundus Autofluorescence (FAF)
 (+) Diagnostic Value
 (+) Prognostic Value
 (-)Availability
 (-)Familiarity

Enface Infrared (IR) or Near (NIR)
 (+)Early detection of drusen and reticular pseudodrusen (RPD)
 (+) Early GA detection
 And serial follow-up
 (-)Device Dependent

OCT
 (+)Pre-GA
 (+)GA
 (+)CNV
 (+)(+)(+)
 (-)Interpretation skill

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OCT-THE WORK HORSE

Literature Search Points to OCT, as being the most used technology for diagnosis of AMD

RESEARCH ARTICLE
 Optical coherence tomography and color fundus photography in the screening of age-related macular degeneration: A comparative, population-based study

Edoardo Midena^{1,2*}, Lucia Frisconi¹, Tommaso Formisano¹, Paolo Boscolo Toledano¹, Giuseppe Migliorini¹, Elisabetta Pirelli¹

¹ Department of Ophthalmology, University of Padova, Padova, Italy, ² IRCCS-Fondazione Scler, Rome, Italy

* edoardo.midena@unipd.it

Midena E, et al. Optical coherence tomography and color fundus photography in the screening of age-related macular degeneration: A comparative, population-based study. PLoS One. 2020 Aug PMID: 32797085; PMCID: PMC7428158.

Conclusion: OCT provided gradable images in almost all examined eyes, compared to limited CFP efficiency. Moreover, OCT images allowed to detect more AMD eyes compared to gradable photos. OCT imaging appears to significantly improve the power of AMD screening in a general, unselected population, compared to CFP alone.

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Regardless, AMD is often undiagnosed

- Neely et al. Evaluated the prevalence of undiagnosed AMD in primary eye care setting
- 1288 eyes from 644 patients

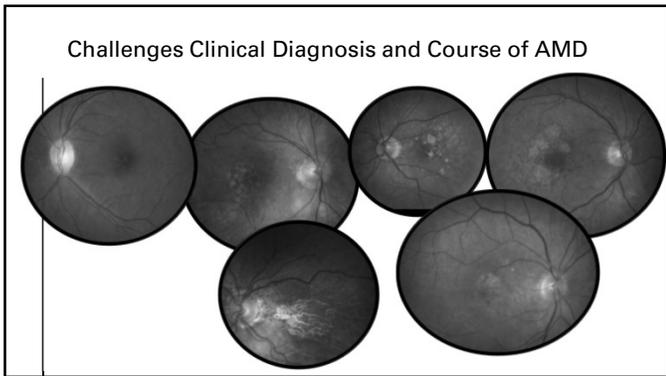
75% No AMD per medical record (n=968)

24.8% AMD despite no diagnosis in medical record (n=320)

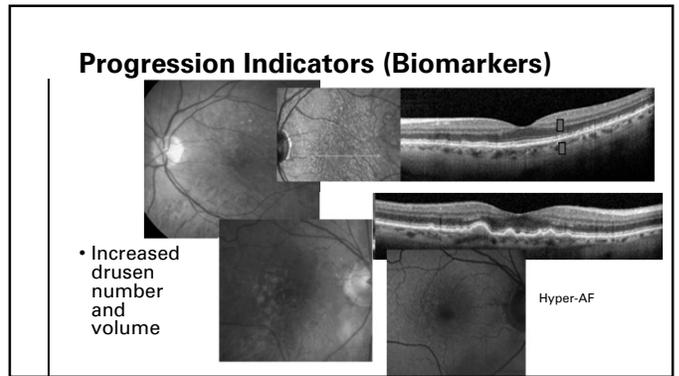
- 30% large drusen
- 10% hyperpigmentation
- 13.4% hypopigmentation
- 77.8% small drusen
- 78.1% intermediate drusen

Reference: Neely DC, et al. *JAMA Ophthalmol.* 2017;135(6):570-575.

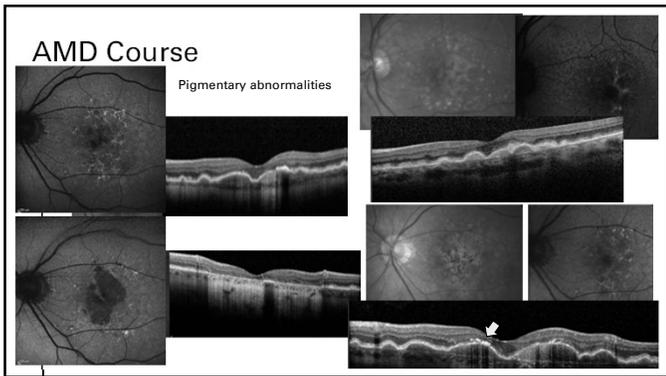
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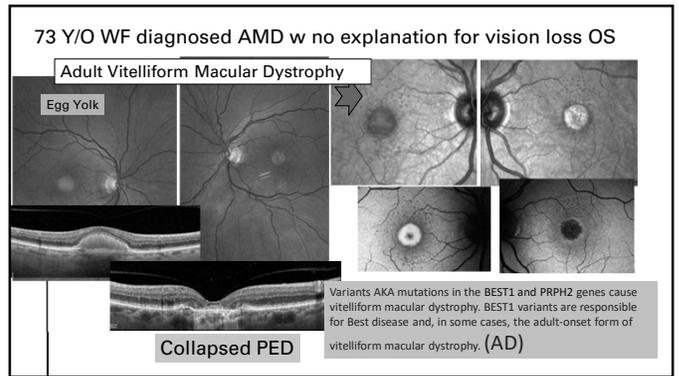
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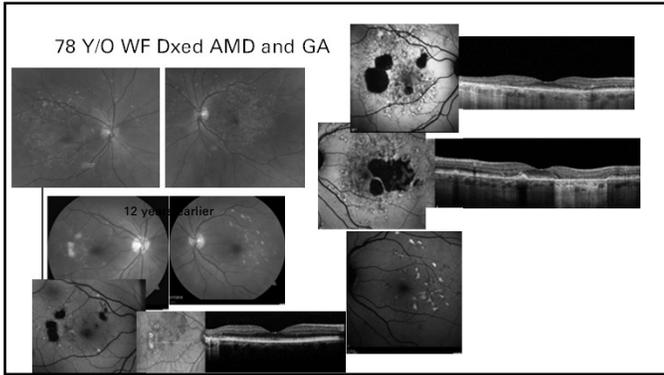
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Assessment of AMD

Classification	Clinical Manifestation
No AMD	No drusen and no RPE abnormalities
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Early AMD	Drusen > 63 μm and ≤ 125 μm and no RPE abnormalities
Intermediate AMD	Drusen > 125 μm and/or RPE abnormalities
Late AMD	GA and/or neovascular AMD

Abbreviations: AMD: age-related macular degeneration; GA: geographic atrophy; RPE: retinal pigment epithelium.

Small Drusen = < 63
Medium = 64- 124
Large > 125

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Assessment of AMD

66-Year-Old WF

Has noticed mild distortion OD recently
History of cataract surgery 5 years ago
Systemic hypertension for several years, controlled with medications.
Past smoker.

VA 20/20 IOP 16

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Classification	Clinical Manifestation
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The "conversion" patient pool risk of progression by AREDS simplified risk score

Example: risk factor scoring for patient with large drusen and pigment abnormalities in both eyes

Right eye	Large drusen	Yes = 1	Patient severity score = 4 risk factors
	Pigment changes	Yes = 1	
Left eye	Large drusen	Yes = 1	
	Pigment changes	Yes = 1	

Reference: Ferris FL, et al. Arch Ophthalmol. 2005;123(11):1570-1574.

Approximate 5-year rates of progression to advanced AMD based on AREDS (Report 8) Simplified Risk Scale

No. of risk factors	Approximate 5-year rate
0	0.5%
1	3%
2	12%
3	29%
4	50%

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Updated Risk Assessment

Rate of Progression to Late AMD at Five Years

# of Risk Factors	RPD Absent	RPD Present
0	0.3%	2.8%
1	4.3%	8.0%
2	11.6%	29.0%
3	26.7%	58.7%
4	50.0%	72.2%

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AMD MANAGEMENT

- Atrophic or Dry AMD
 - Smoking Cessation
 - Management of Comorbidities
 - Nutrition and Supplements
 - **Low Vision Rehabilitation******
 - Patient Education and Proper Follow-up Care
- GA an Advanced form of dry AMD- TX
- Wet or nAMD
 - Intravitreal Anti-VEGF
 - Various Agents
 - PDS
 - In the pipeline (including gene therapy)



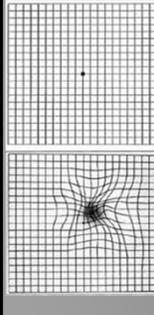
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February 16, 2023

Diagnostic Accuracy of the Amsler Grid Test for Detecting Neovascular Age-Related Macular Degeneration

A Systematic Review and Meta-analysis

Jakob Eijerog, MD¹, Miklos Schneider, MD, PhD^{2,3}, Ivan Potapenko, MD, PhD³, et al.
3 Author Affiliations
 JAMA Ophthalmol. Published online February 16, 2023. doi:10.1001/jamaophthalmol.2022.6396



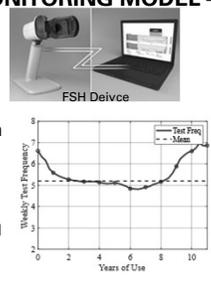
Results Of 523 records screened, 30 studies were included with a total of 1930 eyes (mean participant age ranging from 62 to 83 years). Sensitivity and specificity to diagnose neovascular AMD were 67% (95% CI, 51%-79%) and 99% (95% CI, 85%-100%), respectively, when comparators were healthy control participants and 71% (95% CI, 60%-80%) and 63% (95% CI, 49%-51%), respectively, when control participants were patients with non-neovascular AMD. Overall, potential sources of bias were low across studies.

Conclusions and Relevance Although the Amsler grid is easy and inexpensive to use for detection of metamorphopsia, its sensitivity may be at levels typically not recommended for monitoring. Coupling this lower sensitivity with only moderate specificity to identify neovascular AMD in a population at risk, these findings suggest that such patients typically should be encouraged to undergo ophthalmologic examination regularly, regardless of any results of Amsler grid self-assessment.

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LONG-TERM VISUAL OUTCOMES OF PATIENTS SUPPORTED BY REMOTE MONITORING MODEL – ALOFT STUDY¹

- Multicenter Study
- 2123 patients 3,334 eyes
 - Mean (SD) of 5.2 weekly tests
- 10 years testing period >1 million tests
- 285 eyes converted to nAMD
 - 52% detected by FSH, 48% symptoms or scheduled visit
 - Mean 6.4 injections per year SD=3.1
- Non-CNV Alerts- every 4.6 years per patient



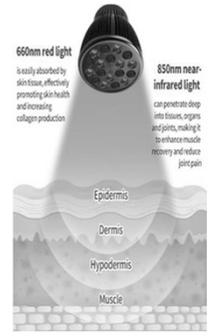
¹Mathai M, et al. Analysis of the Long-term Visual Outcomes of ForeseeHome Remote Telemonitoring: The ALOFT Study. Ophthalmology Retina. (2022)

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PHOTOBIO-MODULATION (PBM)

Photobiomodulation, also known as low-level light therapy, is the medical application of LL light to beneficial clinical effects.

- **590nm (Orange)**
 - Thought to inhibit vascular endothelial growth factor (VEGF) expression and promote nitric oxide generation.
- **660nm (Deep Red)**
 - Promotes oxygen binding and stimulates metabolic activity, potentially reducing inflammation.
- **850nm (Near IR)**
 - Stimulates metabolic activity and drives electron transfer within cells, also potentially inhibiting inflammation

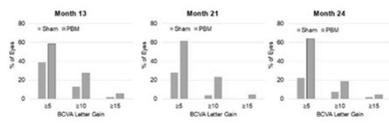


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PBM

- The Valeda treatment for dry (iAMD)
- A series of nine 15-minute sessions over 3-5 weeks
- Follow-up cycles every 4 months
- This device was FDA approved in October of 2024 (LumiThera) and acquired by Alcon in July 2025
- BE AWARE OF NONAPPROVED DEVICES

LIGHTSITE III: BCVA Letter Gain Distribution



The PBM group showed a higher frequency of ≥ 5 letter, ≥ 10 letter, and ≥ 15 BCVA letter gains compared to the Sham group at Months 13, 21, and 24.

(Used by permission of LumiThera)

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Geographic Atrophy (GA)

An advanced form of dry AMD

- **#Common and Underdiagnosed**
 - 1-2 million Americans
 - 75% undiagnosed
- **#Progressive**
 - 2.5 years from diagnosis to foveal involvement
- **#Irreversible vision loss**
 - 50% lose 2 lines VA in 2 years
 - 66% Severely impaired or legally blind

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RISK FACTORS

- Aging
 - 4X incidence/10 years after 50 Y/O
- Smoking, poor diet
- Comorbidities: Obesity HTN, Lipid disorders, Sleep Apnea
- Genetics

The *ABMA2*/*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 proteins, 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

Phenotypic effect: **Disrupts Visual cycle**

Target: **Extracellular matrix (ECM) and vessels**

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Complement Factor

Complement Cascade (System)

- A part of the innate immune system
- A complex biological system
- Composed of several proteins and regulators
- Always active, functioning to remove pathogens and biological debris
- Overactivation by aging, disease or **genetic variation** can be damaging to normal tissue biological

Classical pathway: Antigen Antibody (IgG) → C1 complex → C2 and C4b fragments → C3 convertase → C3b and C3a fragments

Alternative pathway: C3 hydrolysis → C3b and C3a fragments

C3b cleaves C5 into C5a and C5b

C5b, C6, C7, C8 and C9 together form the cylindrical membrane attack complex

Cell lysis and bursts

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Current FDA approved agents are complement inhibitors

Functions

A Cell lysis
Killing of pathogens

B Opsonization / Phagocytosis
• Clearance of apoptotic cells and debris (CR1/CR3/CR4/C1qR)
• Synaptic pruning (CR3)

C Regulation
Inhibition of the complement cascade

D Other functions
• Promotion of cell differentiation and recruitment (C3aR/C5aR)
• Modulation of immune cell migration (C3aR)
• Regulation of B-cell functions (CR2)
• Leukocyte adhesion (CR4)

Pegcetacoplan (SYFOVRE) (Apellis) → C3a

Avacincaptad pegol (IZERVAY) (Astellas) → C5a

Membrane attack complex and Inflammasome formation → C5b-9

Clusterin, Vitronectin → C3b

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CFP vs Optical Coherence Tomography (OCT)

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OCT- GA PREDICTORS AND BIOMARKERS

- Multiple predictive factors for the development of GA
 - Drusen and pigment epithelial detachment (PED) to Incomplete- (iRORA) and Completed retinal pigment epithelial and outer retinal atrophy (cRORA)

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OCT- GA PREDICTORS AND BIOMARKERS

- Reticular Pseudodrusen (RPD)
- Hyperreflective Foci and Columns
- Hyperreflective and Hypertransmission Columns

Images: Mohammad Rafieetary, C

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OCT- GA PREDICTORS AND BIOMARKERS

- Nascent GA-detected by Subsidence of Inner Retinal Layers

Jia, G.J. 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;5(9):855-867. doi: 10.1016/j.oret.2020.12.009. Epub 2020 Dec 22. PMID: 33348085.
Fleckenstein M, et al. The Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration. Ophthalmology. 2018 May; 125(5):309-306. Images: Mohammad Rafieetary, OD

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CFP vs. Fundus Autofluorescence (FAF)

Images : Mohammad Rafieetary, OD

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FAF: Predictors and Biomarkers

Size: small vs large
 Configuration: unifocal vs multifocal
 Location: with or without subfoveal involvement
 Fluorescence patterns: none, focal, patchy, banded, diffuse, diffuse-trickling

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CFP vs FAF

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CFP/OCT/FAF Comparison- Multimodal imaging

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- 60-Year-old white female C/O night vision, reading etc.
- No Remarkable MHX, Daily Smoker
- She is coming back not satisfied with the current spectacle RX she got!!
- SLE OU: 2+ NS & 1 to 2+ Cortical
- OD: 20/25, OS: 20/40

Please Look at the pictures and answer the follow up questions

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AFTER THE POLL

- My decision was "right on"

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#Common
#Progressive
#Irreversible

3 years

20/100-20/300

20/30-20/80

Goal

Careful Examination
#Multimodal Imaging
#Patient Education
#Appropriate Referral

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- nAMD is a common, progressive stage of advanced AMD with poor visual outcomes when neglected or misdiagnosed
- nAMD-Challenge**
- Atrophic to nAMD Conversion
 - Conversion rate depends on the stage but generally 10-15% of patients with AMD
 - 2.0% early AMD, 6.1% for iAMD, and 6.7% for advanced dry AMD.
- nAMD to End Stage Disease

Often patients are asymptomatic or attribute it to other issues such as prescription changes!

Five Years

Ten Months

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

TYLER E. GREENLEE, MD, VICTORIA Y. WANG, MD, HANNAH KANG, MD, MARY E. TORRES-ROSA, MD, ANDREW S. TERRY, MD, TERRY F. DEER, MD, THANE F. COOPER, MD, DAVID BERKOP, MD, AMY S. RABINOVICH, MD, ROSE P. SOGAL, MD, PhD

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nAMD- Diagnosis

Expectation of typical findings

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CLASSIFICATION

- Type 1 (occult), CNV develops below the RPE.
 - The term occult comes from the pattern of leakage on fluorescein angiography
 - Polypoidal choroidal vasculopathy (PCV) is a subtype of Type 1 CNV that is characterized by the presence of polyp-like aneurysmal dilations of the branching vascular network.

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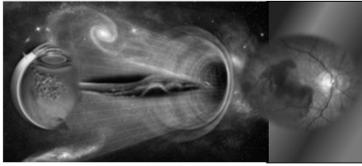
CLASSIFICATION

- Type 2 (classic), abnormal vessels invade the subretinal space by breaking through the RPE.
- These lesions have classic "hot spot" leakage in angiographic studies

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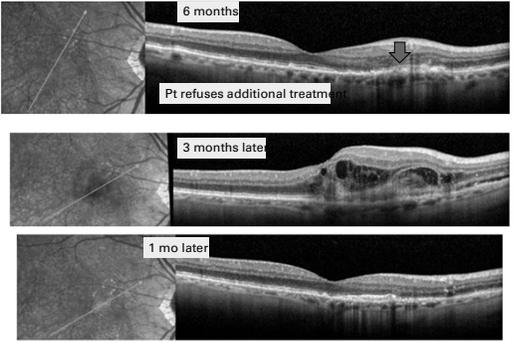
Wet, Exudative, Neovascular AMD (nAMD)

- Conversion of dry to nAMD has been under our radar for years
- There are almost as many GA as nAMD patients
- Burdens and Barriers
 - Frequent injections
 - Care provider issues
 - Patients Issues
- Patient education is very different



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Respond to Treatment



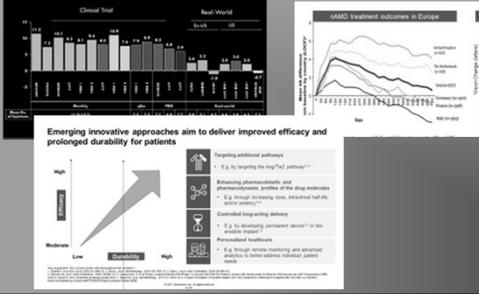
6 months
Pt refuses additional treatment
3 months later
1 mo later

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Drug	Bevacizumab (Avastin)	Ranibizumab (Lucentis)	Aflibercept (Eylea)	Brolucizumab (Beovu)	Faricimab (Vabysmo)
Format	Full IgG1 Ab	Fab Fragment	VEGFR1/2-Fc fusion protein	Single-chain Ab Fragment	First bispecific VEGF-A/Ang2
Initial FDA App	2004 Genentech	2006 Genentech	2011 Regeneron	2019 Novartis	2022 Genentech
Indications	Cancer	nAMD, RVO, DME, DR, mCNV	nAMD, RVO, DME, DR	nAMD	nAMD, DME, RVO, DR
Dosage	1.25 mg	0.5 mg or 0.3 mg	2 mg and 8 mg (HD)	6 mg	6mg
Formulation	Compounded	Single-use vial	Single-use vial	Single-vial use	Prefilled Single Dose
Administration	q 4-6 weeks PRN	Single-use vial Prefilled Syringe q 4-12 weeks	Single-use vial q 4-8 weeks after one year q12weeks	q 1 MOx3 then q 8-12W	q 4wksX4 Then extend

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Clinical Trial vs. Real-World VA Outcomes

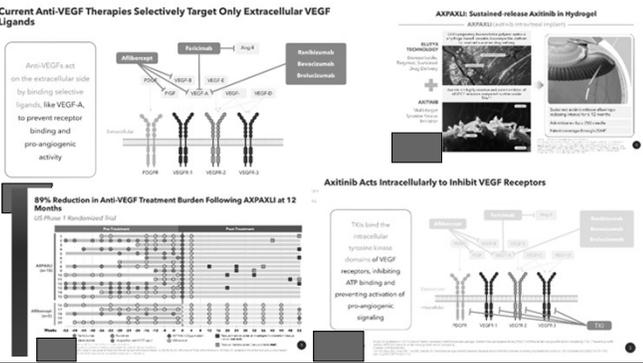


Emerging innovative approaches aim to deliver improved efficacy and prolonged durability for patients

- Targeting additional pathways (e.g. to targeting the Ang2 pathway?)
- Enhancing pharmacokinetics and pharmacodynamic profile of the drug molecules (e.g. through increasing size, intravitreal half-life, and potency?)
- Controlled long-syngy delivery (e.g. to decreasing treatment interval? or to extend treatment?)
- Long-term monitoring and advanced analytics to better assess individual patient

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Current Anti-VEGF Therapies Selectively Target Only Extracellular VEGF Ligands



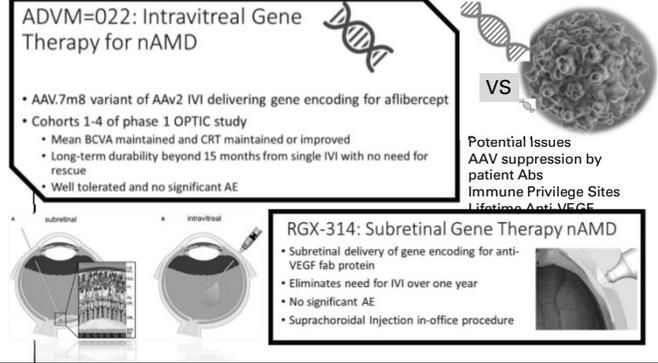
AXPAXU: Sustained-release Actinib in Hydrogel Ligands

89% Reduction in Anti-VEGF Treatment Burden Following AXPAXU at 12 Months

Axitinib Acts Intracellularly to Inhibit VEGF Receptors

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ADVM=022: Intravitreal Gene Therapy for nAMD



ADVM=022: Intravitreal Gene Therapy for nAMD

- AAV.7m8 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

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 fab protein
- Eliminates need for IVI over one year
- No significant AE
- Suprachoroidal Injection in-office procedure

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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 for AMD
 Temporary suspension was lifted

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78-year-old WM
 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 Asteroid

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Submacular Hemorrhage
 Recent Onset

PPV,
 Inject t-PA
 Under Retina
 With 41G Cannula,
 Fluid-Air Exchange,
 Anti-VEGF if CNV

To Avoid This

Supine for One Hour,
 Then Seated to
 Shift Liquefied Blood Clot
 Inferiorly

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65 Y/O WM 20/20

20/400
 Eccentric Fixation

SRH
 PED

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2 Weeks post-op 20/80

6 weeks post-op and Anti-VEGF 20/50

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FINAL THOUGHTS

AMD is a commonly encountered condition in optometric practices.

We should use our knowledge, experience, tools and evidenced based information to diagnose and manage patients with this potentially debilitating disease as best as possible.

Thank you!

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