Ask the "experts": retina edition

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WHEN WOULD YOU REFER A GA PT?

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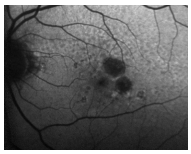
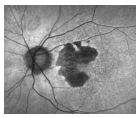
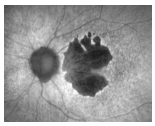
When to Refer?

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





Progression to subfoveal involvement 18 mo



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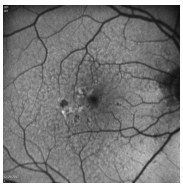
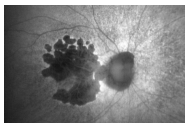
When to Refer?

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





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HOW SOON DOES A WET AMD PT NEED TO BE SEEN BY RS?

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Importance of Early Treatment: CNV Lesion Size

- Evidence from many trials is clear: smaller lesions respond better to treatment
- MARINA study[1]: larger CNV lesion size at baseline was associated with greater loss of letters in sham-treatment group and less gain of letters in ranibizumab-treated arms
- ANCHOR study[2]: smaller baseline CNVM lesion size was associated with greater gain of letters in those receiving ranibizumab
- CATT trial[3]: larger area of CNVM at baseline was associated with worse VA at 1 year, less gain in VA at 1 year, and lower proportion of patients gaining ≥3 lines of acuity

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Importance of Early Treatment: 2020 Analysis of IRIS Registry

- Real-world patients with neovascular AMD who underwent anti-VEGF treatment
- Study included 162,902 eyes
- Results
  - Patients who presented with VA of 20/40 or better at diagnosis maintained mean VA of 20/40 or better for 2 years after initiating treatment
  - Those who presented with VA worse than 20/40 never reached 20/40 at 1 or 2 years
- Conclusion: baseline VA at diagnosis of wet AMD predicts long-term VA outcomes

Early diagnosis before VA is adversely affected is a key factor in preserving vision in patients with wet AMD

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When Should Patients Be Referred to Retinal Specialist to Consider Treatment?

- Any change in vision or metamorphopsia in patients with AMD should be taken seriously
  - Assume "wet" AMD until proven otherwise
- Unless able to determine no fluid/CNVM, patient should be referred to retinal specialist
- Any patient with "wet" AMD deserves prompt referral to retinal specialist for consideration of treatment
  - Data show patients exhibiting CNVM do better with early detection and prompt treatment![1]

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DO YOU BELIEVE IN AREDS SUPPLEMENTATION?

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AREDS

- First large-scale study looking at nutrition and ocular health
- 3640 pts followed on average for 6.3 years
  - Results released October 2001
- Results showed that 25% risk reduction to developing advanced AMD in pts with intermediate (stage 3) AMD or worse
  - 500 mg vitamin C
  - 400 IU vitamin E
  - 15 mg vitamin A (25,000 IU beta carotene)
  - 80 mg zinc
  - 2 mg copper

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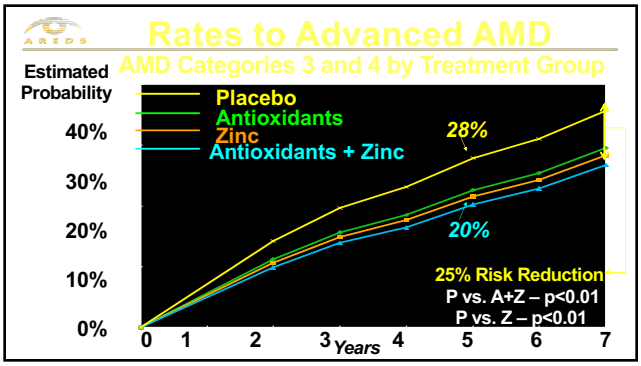

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AREDS: Shortfalls

- No apparent benefit in category 1 and 2
  - 80% fall into this group
- Unsure how long someone at risk should continue supplements
- Beta carotene associated with increased risk of lung cancer in smokers
  - substitution of other antioxidants (lutein) was unclear
  - how long a non-smoker was debatable

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AREDS: Shortfalls

- Did not evaluate the role of lutein/zeaxanthin, or omega 3's
- Benefit is modest, and all groups had progression despite treatment
- "The supplements are not a cure for ARMD, nor will they restore vision already lost from the disease"
  - AREDS press release 10/2001

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AREDS 2

- AREDS 2: Enrollment ended June 2008 with ≈4200 patients followed for six years
  - Effect of lutein, zeaxanthin and omega 3 on AMD
  - Effect of eliminating beta carotene on AMD
  - Effect of reducing zinc on AMD
  - Effect of supplements on cataracts
  - Validate the AMD scale from original AREDS
- Results released May 5, 2013

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AREDS 2

- Major Conclusions:
  - The addition of lutein and zeaxanthin, DHA and EPA or both to the AREDS formulation did not further reduce the risk of progression to advanced AMD
  - Substituting L/Z (10 mg/2 mg) for beta carotene is an appropriate substitution, because of potential increased incidence of lung cancer in former smokers

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Additional findings

- Lutein and zeaxanthin did provide an additional 10% reduced risk over current supplements
  - In patients with lowest dietary intake of l/z, additional 26% reduced risk
- Decreasing zinc from 80 mg to 25 mg had no significant effect
  - No change recommended (?)
  - Deserves further study
- Competitive absorption of carotenoids

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Additional findings

- Most positive effect was found on wet AMD patients, not GA patients
- Cataracts: no overall effect except in those patients with lowest l/z intake
- In general, patients were very well educated and well nourished and therefore may not reflect average patient
- Many were on multivitamins

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Age-Related Eye Disease Study 2
The Lutein/Zeaxanthin and Omega-3 Supplementation Trial

AREDS2 Formulation

Vitamin C (500 mg)

Vitamin E (400 IU)

~~Beta-Carotene (15 mg)~~

Lutein (10 mg)/Zeaxanthin (2 mg)

Zinc (80 mg zinc oxide)

Copper (2 mg cupric oxide)

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AREDS 10 year

Combined Arms Main Effect Progression to Late AMD – Hazard Ratio

	5 years	10 years
Lutein/Zeaxanthin	0.91 (*P* = 0.05)	0.91 (*P* = 0.03)
DHA/EPA	0.98 (*P* = 0.74)	1.01 (*P* = 0.91)
Low Zinc	1.06 (*P* = 0.32)	1.04 (*P* = 0.48)
Beta Carotene	1.07 (*P* = 0.31)	1.04 (*P* = 0.50)

- Key Takeaways:
  - Using a factorial study design, combining the arms that had Lutein/Zeaxanthin to increase sample size, the addition of Lutein/Zeaxanthin provided a similar ~10% reduction in progression to late AMD
  - Addition of Omega-3 FA DHA/EPA had no effect on progression
  - Reduction of Zinc level had no effect on progression
  - These results were sustained through 10 years

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GA and AREDS2

- New analysis in *Ophthalmology* looked at pts with late stage GA in AREDS/AREDS 2 study
- Showed that taking AREDS supplements slowed down lesion growth in non foveal GA by 55% over 3 years
  - Not as helpful for pts with central GA
- Consider recommending AREDS 2 supplementation for extra foveal GA pts

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Vitamins: Take Home

- Use AREDS 2 type formulation in suitable patients
  - Encourage proper dosing
  - Discourage use of similar products that differ from what you want
- Pick one or two products
- Review literature and additional AREDS 2 reports
- Discuss prevention in high risk patients

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Vitamins: Take Home

- The best intake is through diet/food
  - Not always realistic:
    - Average American gets only 2mg Lutein
    - Leading antioxidants for average American is coffee
    - French fries account for 25% of all vegetable intake in US
    - Vitamin E 13x, A and C 5x recommended daily dose
- Only 3% of Americans follow 4 basic health practices
  - No smoking
  - BMI 18.5 – 25
  - 5 or more FRUITS & VEGATABLES daily
  - > 30 minutes physical activity/ 5x times wk

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My thoughts…

- Discuss vitamins/nutrition and lifestyle changes with ALL AMD pts
  - Smoking, increased BMI, UV light, exercise, diet
- Decide which you feel should start vitamin therapy
- Make SPECIFIC recommendations based on your knowledge

- DO SOMETHING!!!

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WHEN DO YOU REFER A NEVUS?

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Nevus

- TFSOM: To Find Small Ocular Melanomas (1995)
  - T: Thickness: lesions > 2 mm
  - F: Fluid: any subretinal fluid suggestive of RD
  - S: Symptoms of photopsia or vision loss
  - O: Orange pigment overlying the lesion
  - M: Margin touching the optic nerve head
    - No factor= 3% risk of converting to melanoma in 5 yrs
    - 1 factor=8% risk
    - 2 or more factors =50% risk

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Update 2019

- Incorporates imaging and re-evaluates risk factors
- TFSOM-DIM
  - To Find Small Ocular Melanomas Doing Imaging
    - T: Thickness > 2mm (US)
    - F: Fluid, subretinal (OCT)
    - S: Symptoms of vison loss (VA)
    - O: Orange pigment (FAF)
    - M: Melanoma Hollowness (US)
    - DIM: diameter > 5 mm (photos)

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Update 2019

- M: Tumor Margin replaced with ultrasound
- S: Vision loss (VA < 20/50) rather than flashes/floaters
- Most important:
  - Thickness, Fluid, orange Pigment, Hollowness
- Least important:
  - Symptoms, Diameter

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Update 2019

- Risk of converting to melanoma over 5 years
  - 0 factors: 1 % risk
  - 1 factor: 11%
  - 2 factors: 22 %
  - 3 factors: 34%
  - 4 factors: 51%
  - 5 factors: 55%
  - 6 factors: who knows?
- Bottom line: Increasing number of risk factors imparts greater risk for transformation

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Nevus

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  - T: Thickness: lesions > 2 mm
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  - O: Orange pigment overlying the lesion
  - M: Margin touching the optic nerve head

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Gardner's Syndrome

- Multifocal CHRPE have been associated with Gardner's Syndrome
  - AKA FAP: familial adenomatous polyposis
  - Familial condition of colonic polyps that may be precursor to colon cancer
  - However, these lesions are bilateral, have more irregular borders, and are often scattered throughout the fundus

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WHEN/HOW DO YOU FOLLOW UP ON A NEW PVD?

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AAO Preferred Practice Patterns :
Retina Summary Benchmarks, 2023

- Posterior Vitreous Detachment, Retinal Breaks, and Lattice Degeneration (Initial and Follow-up
- Evaluation)
  - Ophthalmic Exam (Key elements)
    - Confrontation visual field examination
    - Visual acuity testing
    - Pupillary assessment for the presence of a relative afferent pupillary defect
    - Examination of the vitreous for hemorrhage, detachment, and pigmented cells
      - Examination of the peripheral fundus using scleral depression. The preferred method of evaluating peripheral vitreoretinal pathology is with indirect ophthalmoscopy combined with scleral depression.

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AOA Optometric Clinical Practice Guideline
Retinal Detachment and Related Peripheral Vitreoretinal Diseases

April 1995, review April 1998, revi9ed June 18999, reviewed 2004

Ocular Examination The examination for retinal detachment and related peripheral vitreoretinal disease may include, but is not limited to:

- Best corrected visual acuity
- Pupillary responses
- Biomicroscopy
- Binocular indirect ophthalmoscopy, with scleral indentation if indicated
- Tonometry
- Visual field screening (confrontation)
- Retinal drawing or photodocumentation, if indicated.

– Scleral depression may be needed to detect small, asymptomatic peripheral retinal detachments.

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Study: American Journal of Ophthalmology

- 50 eyes, 25 pts with symptoms of flashes floaters
- 50 eyes , 25 pts with no symptoms
  - Examination with scleral depression did not provide any additional benefit to an examination vs without in any of the 100 pts
  - Scleral depression did significantly increase pt discomfort

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DO YOU NEED TO DO A SYSTEMIC WORKUP FOR RETINAL PLAQUES? VEIN OCCLUSION? ARTERY OCCLUSION

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RVO Risk factors

- Age: most common after 65
- HTN (46%)
- Hyperlipidemia (20%)
- Diabetes (5%)
- Others: smoking, glaucoma, obesity
- Younger pts: Hypercoagulability, inflammatory disorders like lupus, contraceptives

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RVO Systemic testing

- In office BP
- Lipid profile, HGBA1c, CBC
- Refer for complete vascular workup including carotid doppler, TEE
- Might consider: Sarcoid testing, Syphilis, SLE , etc in younger pts or if suspected on exam
- Thrombolytic factors, homocysteine, antiphospholipid if needed

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RETINAL PLAQUES

- Several different types of plaques can often be visualized in the retinal vasculature
- Often totally asymptomatic and found on routine exam
- Three different types of plaques, but all share strong association to significant cardiovascular disease
  - HOLLENHORST PLAQUE (CHOLESTEROL) 80% > FIBRINO-PLATELET 14%> CALCIFIC 6%

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RISK FACTORS

- Age
- HTN
- Vascular disease
- Past vascular surgery
- SMOKING
- High TOTAL cholesterol
- Men> women

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Retinal Plaques: Work up

- Assess risk factors with PCP
  - DM, HTN, LIPID PANEL
- Carotid auscultation in clinic for bruit
- Carotid ultrasound/Duplex
  - Identifies flow rate and % stenosis OF Common, internal, and external carotid arteries
  - ORDER WITHIN TWO WEEKS!!

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Work up, cont.

- TEE: trans esophageal echocardiogram
  - invasive, probe into esophagus to image heart valves
    - Helpful with calcific
- CTA: Computed Tomographic angiography
  - CT scan of arteries construct 3D images
    - Useful for atypical /confounding findings or if surgery indicated

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treatment

- <50% stenosis: medical management with blood thinner/antihyperlipidemics
  - Aspirin, clopidogrel , warfarin, statins
- >70% stenosis: Surgical intervention
  - CEA: Carotid endarterectomy
  - Carotid angioplasty
- 50-69% stenosis: Depends on other risk factors if medical or surgical

ONLY 7-20% of Asymptomatic retinal plaques have significant stenosis

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Artery occlusion

- If acute, straight to ER
- **DO NOT SEND TO RS FOR CONSULT BEFORE OBTAINING STROKE WORK UP**
- Needs close follow up for NV

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WHEN DO YOU FOLLOW UP ON CSR? WHEN DO YOU REFER?

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Central Serous Retinopathy

- 80-90% of pts will undergo spontaneous resolution and return to normal (or near normal) VA within 1-6 mos.
  - >60% resolve back to 20/20
  - Rare to have vision remain < 20/40
- Approx 40% will get recurrence
- CNVM is VERY rare occurrence, but possible

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CSR

- **When to worry/refer**
  - If VA worse than 20/70
  - If pt demographics do not support
  - If does not resolve in 6 mos
  - If gets worse rather than better
  - FA/ OCT does not support diagnosis
  - "Just doesn't feel right"
  - Pt is unable to accept vision/prognosis

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Treatment

- Observation
- PDT
- Anti-VEGF
- Anti-corticosteroids
  - Rifampin
  - Mifepristone
  - Ketoconazole
  - Spironolactone/eplerenone
  - Finasteride
- Acetazolamide
- Aspirin
- Metoprolol
- H.pylori treatment
- Methotrexate
- Behavior Modification!

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WHEN WOULD YOU REFER AN ERM??

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Epi-retinal Membrane

- AKA macular pucker, cellophane maculopathy
- Can be secondary to peripheral retinal disease, such as detachment or tear; a retinal vascular disease such as BRVO; inflammation; trauma or idiopathic
- Idiopathic tend to be more mild and non-progressive vs. those after retinal tear

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Epi-retinal Membrane

- VA can range from 20/20 to 20/200 or worse
  - Studies show > 5% have worse than 20/200
- Often metamorphopsia is only complaint with idiopathic ERM
- Fewer than 20% of cases are bilateral
- Surgical removal is considered if severe vision loss or distortion

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ERM

AGE	INCIDENCE
< 60	1.7%
60-69	7.2%
70-79	11.6%
80+	9.3%

BLUE MOUNTAIN EYE STUDY, AUSTRALIA

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ERM

- Consider surgery if:
  - VA 20/40-ish or worse
  - Symptomatic
  - Visual need of patient
- Make sure you have an experienced surgeon!!

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AT WHAT STAGE DO YOU REFER A PT WITH DR TO A RETINAL SPECIALIST? HOW ABOUT DME??

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When to refer: DR

- Worse than Moderate NPDR: 2 weeks
  - Moderately severe to severe NPDR
    - 4/2/1 rule
- PDR: 1-2 weeks
- High risk PDR: 48 hrs
- However, really anytime exceeds your comfort level!
- REFER TO PCP AS NEEDED FOR A1C/HTN CONTROL

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DME

- Old definitions being replaced with newer ones based on OCT findings
  - Center involved
  - Non-center involved
  - OCT best way to evaluate retina for DME
- Can Occur at ANY level of DR

CSME
1. RT within 500 microns (1/3 DD) from FAZ
2. Hard exudates with associated thickening 500 microns from FAZ
3. RT > 1DD in area any part of which is within 1DD from FAZ

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When to refer: DME

- NON-CI DME, PT CAN BE MONITORED Q4-6 MOS
  - REFER IF NOT CONFORTABLE BUT RS MAY DEFER TX
- CI-DME WITH REDUCED VA, REFER TO RETINAL SPECIALIST 2-4 WEEKS
  - MOST COMMON TREATMENT IS ANTIVEGF
  - LASER STILL USED SPARINGLY
  - STEROID IMPLANTS IF NO RESPONSE
- CI-DME WITH GOOD VA (20/25 OR BETTER)
  - CONSIDER REFERAL BUT TX MAY BE DEFERED

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DO YOU BELIEVE IN GENETIC TESTING FOR AMD PATIENTS?

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Why do genetic testing?

- Increased surveillance for those at higher risk
  - Sooner/more frequent appointments
  - More diligent home monitoring
- More diligence with modifiable risk factors
- Consider earlier vitamin supplementation
- Potential treatments in the future

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Is AMD in our DNA?

- AMD is a genetic disease with known markers accounting for at least 70% of the population attributable risk
- Other 30% is environmental/lifestyle
- Risk factors
  - Non-modifiable: age, race, gender
  - Modifiable: Smoking, increased BMI, poor diet/nutrition, UV exposure

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AMD Genetic Testing: Arctic DX

Macula Risk NXG

Looks at 15 SNPs as well as smoking, BMI, age and AMD status to determine AMD patients who may progress to advanced AMD and vision loss in

- 2 years
- 5 years
- 10 years

Cheek Swab

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AMD Risk Testing for a Full Spectrum of Patients

AMDiGuard DNA Progression Assessment

For people ≥55yo with or without AMD findings

For people <55yo WITH AMD findings

- Assesses a patient's risk of progression to advanced AMD within 2, 5,10, 20 and 30 years
- Delaying progression to advanced AMD with secondary prevention including AREDS vitamins, increased surveillance (home monitoring)

AMDiGuard DNA Risk Assessment

For people <55yo without AMD findings

- Assesses a patient's lifetime risk of developing advanced AMD (GA or CNV) *allowing preventive lifestyle changes at younger age*
- Delaying onset of disease with primary prevention including lifestyle modifications, supplementation (i.e. nutrition) and nutritional intervention

Visible GENOMICS

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Visible Genomics AMD Gene Panel

- Based on the latest in AMD Genetics research
- Clinically Proven and Clinically Actionable to be the most impactful variations on AMD progression
- Combines both genetic + non-genetic markers

23andMe SNPs

Gene	SNP No.	Allele Variants	AMD Risk	Chromosome	Pathway
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	Rs10490924 (A69S)	GG	Lower Risk (Reference)	10q26	Immune/ inflammatory
		GT	Moderate Risk		
		TT	Higher Risk		
CFH (Complement Factor H)	Rs1061170 (Y402H)	TT	Highly Protective	1q31	Complement
		CT	Moderately Protective		
		CC	Higher Risk (Reference)		
	Rs121913059 (R1210C)	CC	Lower Risk (Reference)		Complement
		CT	Moderate Risk		
		TT	Higher Risk		
	Rs1410996 (IVS14)	AA	Highly Protective		Complement
		GA	Moderately Protective		
		GG	Higher Risk (Reference)		
C3 (Complement Component 3)	Rs2230199 (R102G)	GG	Lower Risk (Reference)	19p13	Complement
		GC	Moderate Risk		
		CC	Higher Risk		

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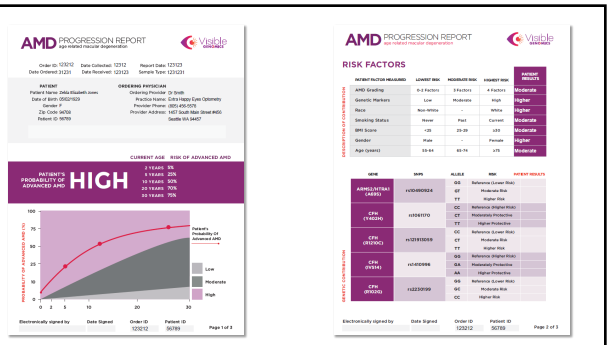

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WHAT NEW RETINAL DEVELOPMENT ARE YOU MOST EXCITED ABOUT?

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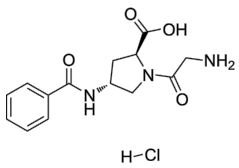
Danegaptide

- Breye Therapeutics
- Gap junction modifier
- Potential oral therapy for NPDR
- Phase 1 study:
  - 24 pts with NPDR and associated edema
  - Well tolerated
  - Imaging showed reduced retinal vascular leakage and "improvements in anatomical parameters"
- Phase 2 to begin soon



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