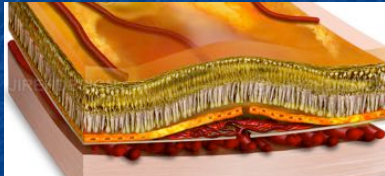
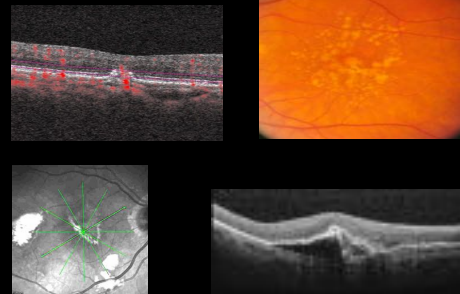


Age-related Macular Degeneration Update



Joseph J. Pizzimenti, OD, FFAO

pizzimen@uiwtx.edu



Financial Disclosures

- Honoraria
 - Review of Optometry
 - Optometric Management
 - Maculogix
 - Notal Vision
- Paid Advisory Board Member
 - Zeiss
 - EyePromise/Zeavision
 - Genentech
 - Regeneron



Financial Disclosures

- Proprietary Interests
 - None
- Consulting Fees
 - Zeiss
 - EyePromise/Zeavision
- Stockholder: Zeavision

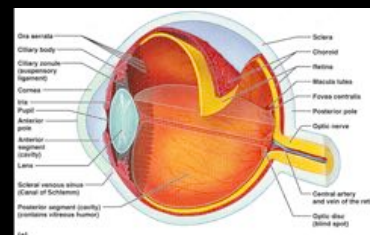


E-Newsletter



optometricretinasociety.org

Check out our E-newsletter



QUESTIONS?

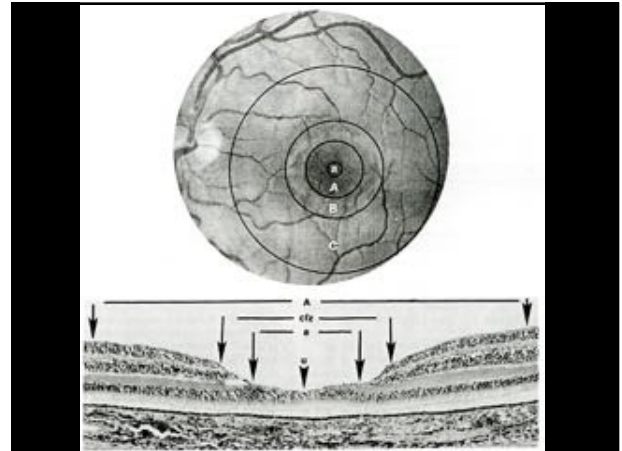
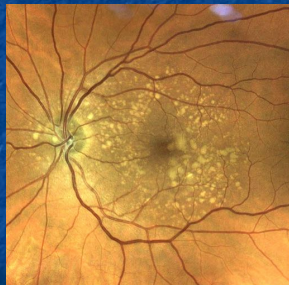


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Bob Marley
get up,
stand up

Course Goals

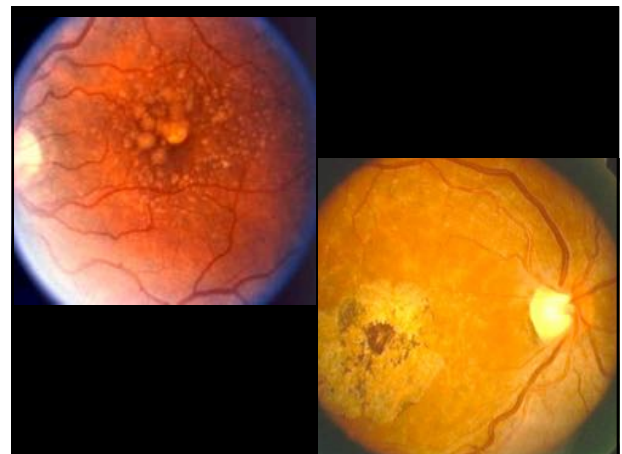
- To provide clinically useful information about AMD
- Prevention
- Early diagnosis
- Treatment and management



Statement of The Problem

- The AMD "Epidemic"
- AMD is the leading cause of blindness in individuals over the age of 50 in the developed world.

■ Klein R, Klein BEK, Linton KLP.
Prevalence of age-related maculopathy.
Ophthalmology. 1992;99:933-943.



The Burden of Disease



The Burden of Severe Vision Loss in AMD

- Patients, loved ones, caregivers, medical community.
- Consequences may be:
 - Social
 - Economic
 - Psychological
 - Physical



Prevalence of Ocular Diseases

- Glaucoma 4 million
- Diabetic Retinopathy 5 million
- Intermediate AMD 8 million¹

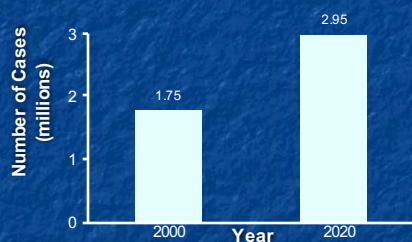
1. Age-Related Eye Disease Study 1 data

Epidemiology

- 2004 data: 15 million affected in the US¹
- 2012 17 million
- 2016 20 million
- Distribution (age)
 - 55–64: 17% of Caucasians have AMD
 - 65–74: 26%
 - >75: 42%¹

1. Congdon N, et al. *Arch Ophthalmol.* 2004;122:477.

Prevalence of Advanced AMD* in the United States



Friedman DS, et al. *Arch Ophthalmol.* 2004;122:564.

A recent review of the **global prevalence** of AMD showed that the number of people with any AMD in 2020 was ~196 million. This is projected to increase to 288 million in 2040.

AMD:

A Changing Environment

- *How will these dramatic changes and projections impact **your** practice?*

What is AMD?

- AMD is a heterogeneous disorder affecting the RPE/Bruch's membrane/choriocapillaris complex.
- Early disease is **classically** characterized by minor vision loss associated with focal or diffuse sub-RPE debris and changes in RPE pigmentation.
- Late, advanced disease is characterized by severe vision loss associated with extensive RPE atrophy with or without the sequelae of choroidal neovascularization.

■ Zafin MA. Age-related macular degeneration: review of pathogenesis. Eu. J Ophthalmol. 1998;199-206.

What is AMD?

- Continuum of Normal Aging and Disease
- Degenerative changes are observed in maculae of most elderly persons to some degree.



Terminology

- **Age Related Maculopathy (ARM)**
 - age related changes in central retina
 - Examples- drusen, RPE disturbances
- **Age Related Macular Degeneration (AMD)**
 - retinal status when vision deteriorates

What is AMD?

- Cell Death and Functional Loss *
 - Only in some individuals do age-related changes progress to this stage
- Transition From “Normal Aging” to Disease ?
 - Loss of Visual Acuity
 - Funduscopy Appearance
 - Measurable Loss of Functional Vision *

The 4 Seasons of AMD

- Oxidation
- Inflammation/Ischemia
- Atrophy
- Neovascularization



QUESTIONS?



Email me at pizzimen@uiwtx.edu

The AMD “Epidemic”

How should we as optometrists respond?

Prevention
Early Diagnosis
Early Intervention
Improved Visual Outcomes

Advanced AMD starts out like this:



Large, ill-defined, and confluent soft drusen**

AREDS 1 and AREDS 2



AREDS Studies



AMD and Nutrition

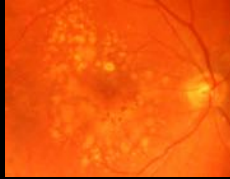


“The **AREDS 1 Study** resulted in a formulation of vitamin C, beta carotene, zinc, and vitamin E that reduced the risk of progression of advanced disease by **25%** at 5 years.”

Emily Chew, MD, from the National Eye Institute in Bethesda, Maryland

Intermediate Stage AMD

• AREDS Category 3



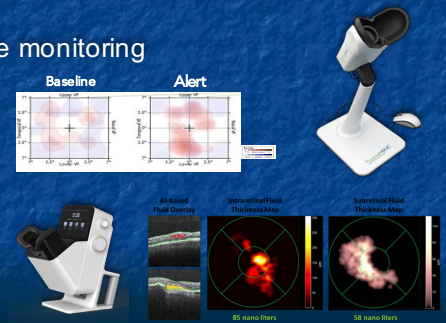
- Extensive intermediate drusen (63-124 μ diameter)
- At least one large druse (>125 μ)
- Geographic atrophy not involving the foveal center

Emerging Trend

■ Home monitoring

■ PHP

■ OCT



Set up and daily tests are quick and easy for patients



1 Patient uses mouse to click where artificial distortion (bump or wave in the dotted line) appeared on the screen



2 ForeseeHome uses PHP (Preferential Hyperacuity Perimetry) to detect tiny changes in the central visual field, including metamorphopsia and scotoma



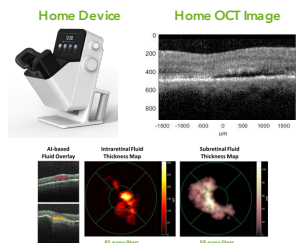
3 Data from each test is sent to the Notus Vision Diagnostic Clinic for evaluation and monthly reports are emailed to practice; available 24/7 on the ECP (Eye Care Professional) Portal

Alert is sent when a significant change compared to baseline occurs, indicating possible AMD progression

You control how data are managed

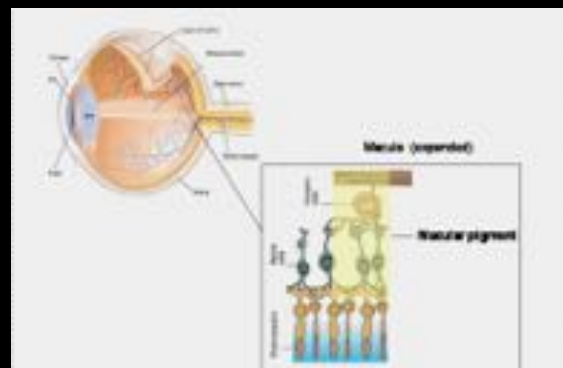
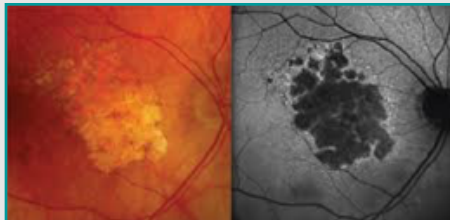
Home OCT for monitoring chronic therapy of neovascular AMD between office visits

- Monitoring of intra- and subretinal fluid based on daily patient self-imaging
- Easy-to-use, patient-operated device
- Takes less than one minute per eye
- AI algorithm analyzes images on cloud
- Remote diagnostic clinic, provider of monitoring program, reports changes meeting physician-selected fluid volume thresholds to referring physician
- 24/7 physician access to all data



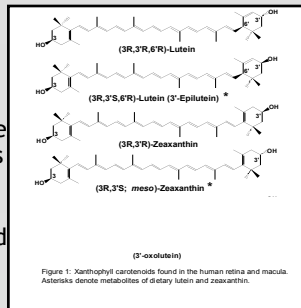
What are the four primary retinal pigments?

- Lutein and Zeaxanthin – found in the macula's sensory layers
- Melanin – found in the RPE
- Lipofuscin – found in the RPE



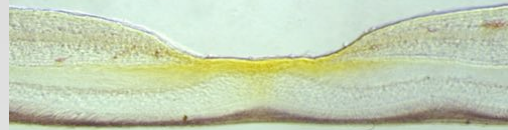
Xanthophylls and AMD

- Lutein, zeaxanthin, and their metabolites help form the macular pigment.
- Dietary sources include green leafy vegetables and orange-yellow fruits
- Act as antioxidants and blue light screening compounds



The Importance of Macular Pigment

- Filters blue light
- Acts as an antioxidant by quenching free radicals
- Provides support to sensory retina



Macular Pigment Optical Density (MPOD)

Heterochromatic Flicker Photometry (HFP)

Risk assessment, early detection and monitoring of AMD

- Macular Pigment Optical Density
- MPOD



Test Results

Macular Pigment Optical Density (du)

<u>Low</u>	<u>Average</u>	<u>High</u>
0.10- 0.30	0.30- 0.50	> 0.50

MPOD is the IOP for AMD

About AMD



“Dry”

Drusen, RPE clumping,
RPE atrophy

“Dry” ARMD = 85-90% of all cases

“Wet” ARMD = 10-15% of all cases
(90% of all cases of severe vision loss)



“Wet”

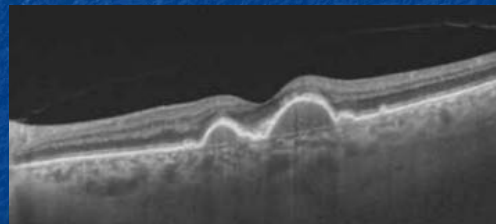
CNVM

Drusen are the
earliest clinically
detectable
ophthalmoscopic sign
of AMD. **

Mixed Drusen



OCT of Soft Drusen



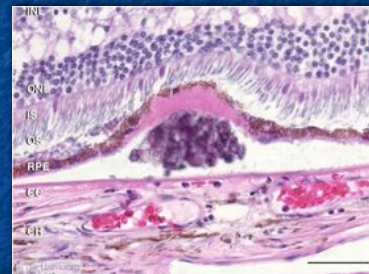
AMD and Drusen

- AMD is a disease resulting from poor “Waste Management”.

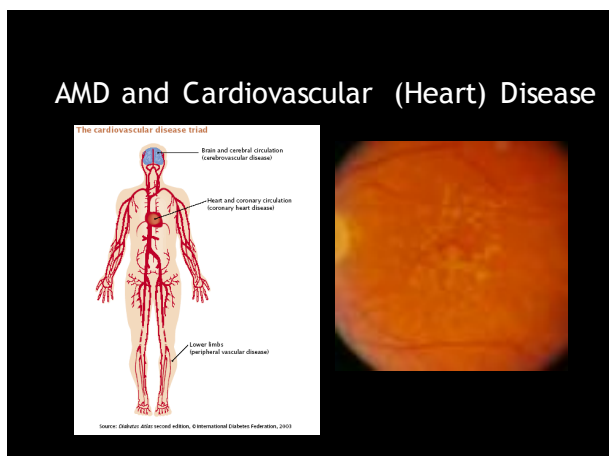
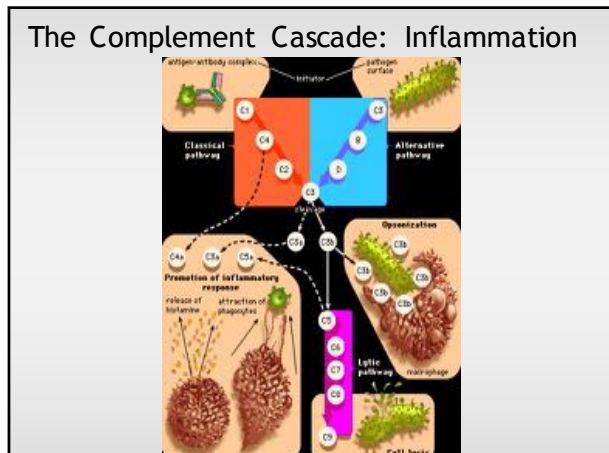
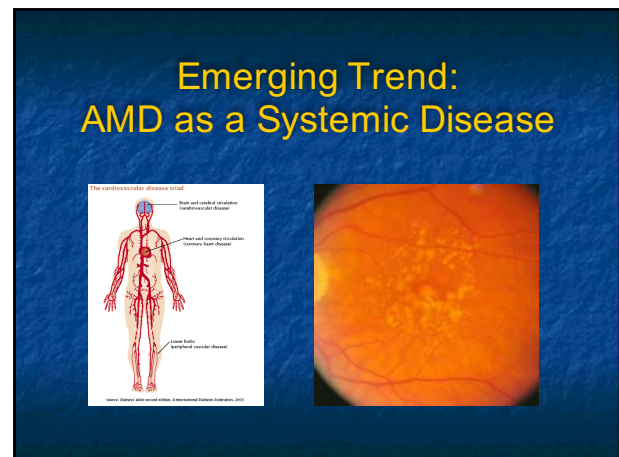
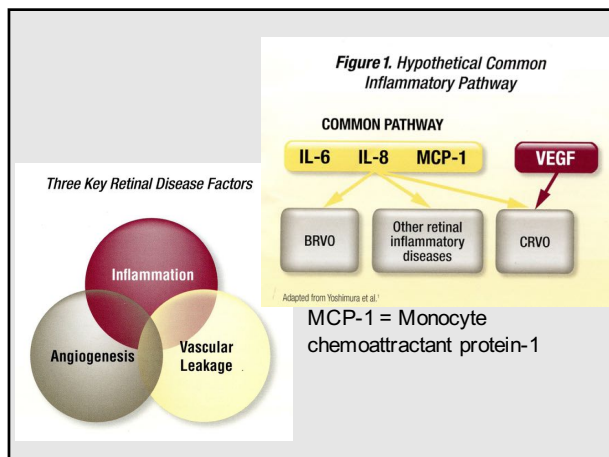


- Drusen are “pockets of inflammation”
 - Recent investigations show that proteins associated with inflammation and immune-mediated processes are prevalent in drusen.

Drusen



Drusen is the earliest clinically detectable feature of AMD. **



Parallel Worlds: Heart Disease and AMD

- Diet – Low fruit/vegetable consumption increases risk of AMD and CVD
- Obesity and physical inactivity
- C-reactive protein (elevated)
 - Inflammatory marker
- Homocysteine (elevated)
- Omega-3 EFA may be beneficial for AMD patients
- Cholesterol (elevated)
- Serum Iron – Increased amounts may increase AMD and CVD

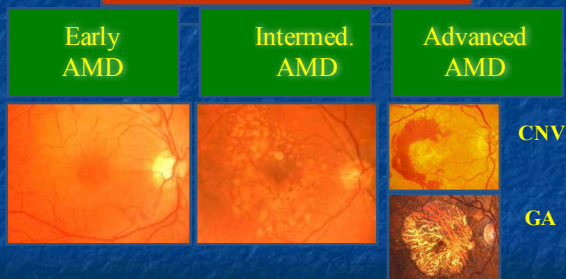
20% of eyes with dry AMD eventually convert to Wet AMD.**

Fundus Biomicroscopy



**The "gold standard" for the evaluation of new onset choroidal neovascularization (CNV) in AMD patients is Fluorescein Angiography.

Stages of AMD



Advanced AMD

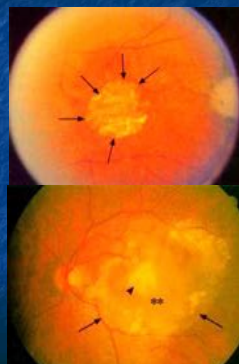
- Defined as either:
 - Geographic atrophy (GA)
 - Atrophy of the RPE and/or photoreceptors, CC
 - "End-stage" non-exudative (dry) AMD
 - Choroidal neovascularization (CNV)
 - Exudative "wet"
- 80-90% of advanced AMD cases are due to CNV.

Classification of AMD

- **Non-exudative (atrophic, "dry")**
 - Can be performance-degrading
 - Majority of AMD cases

- **Exudative (neovascular, hemorrhagic, "wet")**

- Choroidal NV –devastating to central VA
- Minority of AMD cases
 - Majority of vision loss

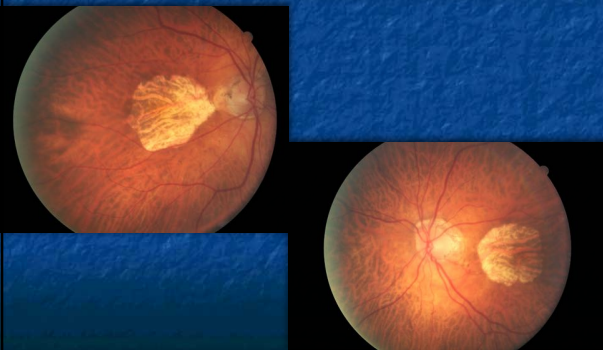


Prevention and treatment of GA remains an unmet need.



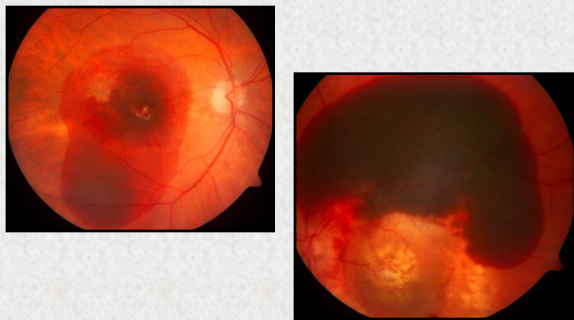
Ultimate hope is that innovations such as stem cell-based therapies provide an avenue for tissue regeneration or replacement.

Advanced Atrophic AMD



Dry AMD is the
new Wet AMD.

Advanced Neovascular AMD



Both Wet and Dry (Advanced x 2)



Unfavorable prognostic signs leading to CNVM, GA:

- Soft, large, confluent drusen
- Reticular (pseudo) drusen*
- Focal hyperpigmentation
- Disciform lesion in the fellow eye
- Older age
- Poor dark adaptation*

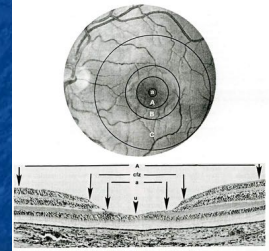
QUESTIONS?





A Rod-centric Model of Disease

- In maculae of healthy, young adults, rods outnumber cones by 9:1.
- Therefore, the macula may be described as cone-enriched but rod-dominated.
- In AMD, central rods die first, followed shortly by the nearby cones.



A Rod-centric Model of Disease

Patients with pre-AMD often complain of difficulty with activities performed at night and under low illumination (e.g., driving, reading).

Mangione CM, Gutierrez PR, Lowe G, Orav EJ, Seddon JM. Influence of age-related maculopathy on visual functioning and health-related quality of life. Am J Ophthalmol. 1999;128:45-53.

Early Detection of Degenerative Change in "Subclinical AMD" or "Pre-AMD"

- DA measures the time for retinal adaptation after exposure to a light stimulus.
- Poor DA is a functional manifestation of early disease.
- Rod intercept (RI) is analogous to A1C.



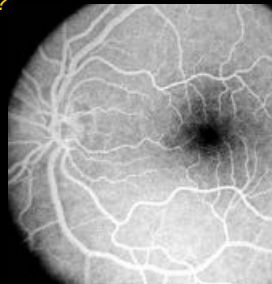
Dark Adaptation (RI)
is the
A1C
for AMD

Imaging the Macula

Invasive Methods

Fluorescein Angiography (FA)

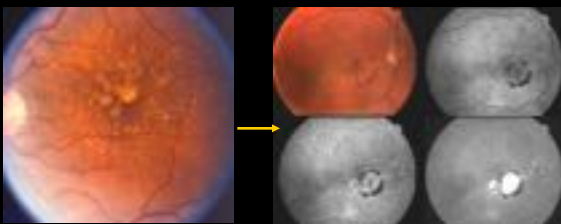
- *FA answers the question: is the blood-retinal barrier intact?*



FA

- The “gold standard” for the evaluation of new onset choroidal neovascularization (CNV) in AMD patients.

Conversion to Exudative AMD

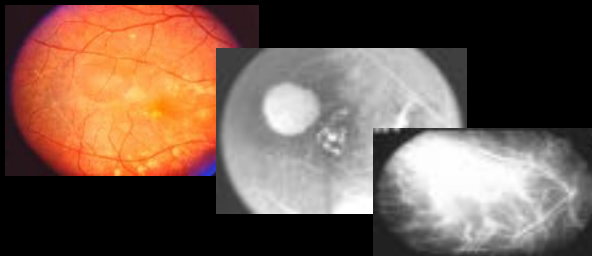


**20% of dry (non-exudative) AMD eyes progress to wet (exudative) AMD,

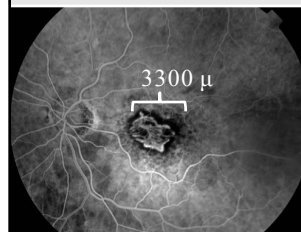
****Indocyanine green (ICG)** is a dye that is used as an alternative to fluorescein.

Indocyanine Green Angiography

- Clinical CNVM Case



CNVM Size and Progression



Average size CNV lesion @ diagnosis **3000-3300μm**

Growth = ~10-20 μm/day

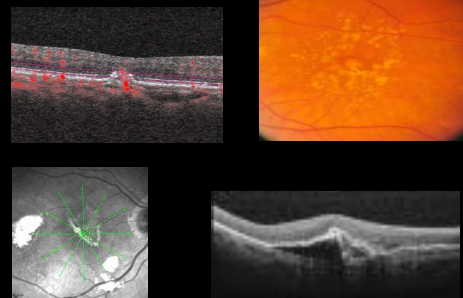
Too large, too late

Olsen, TW Ophthalmology Feb. 2004

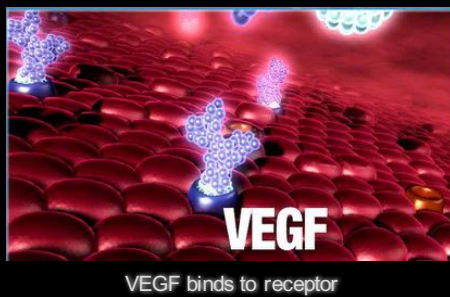
CNV ---> FV Scar



Treatment of nvAMD



Antiangiogenic Drugs: VEGF Inhibitors



~30% showed improved VA in ANCHOR, MARINA

New Therapy with a Fraternal Name: Brolucizumab

- Humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A.
- Phase III data from the HAWK and HARRIER trials.
- May allow for an extended interval between intravitreal injections for CNV, thus reducing the treatment burden.



1980's – Thermal Laser Photocoagulation

- Very few patients suitable for treatment*
- High recurrence rate (~50%)**

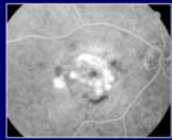


* Freund KB, Yannuzzi LA, Sorenson JA. Am J Ophthalmol 1993; 115:786-791.
** Macular Photocoagulation Study Group. Arch Ophthalmol 1990; 108:825-831.

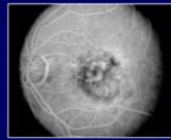
2000 – Photodynamic Therapy (PDT)

****Advantage of PDT: less scarring than thermal laser****

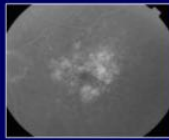
FDA-approved only for patients with subfoveal predominantly classic angiographic subtype



Predominantly classic
26%



Minimally classic
35%



Occult with no classic
40%

****PDT scars less than thermal laser****

75% with no FDA-approved therapy

Retina Quiz: CNV Tx

- Which of the following is the main advantage of Photodynamic therapy (PDT) over traditional laser photocoagulation?
 - a. Lower cost for PDT
 - b. More scar tissue formation in PDT
 - c. Less scar tissue formation in PDT
 - d. PDT uses a "hotter" laser

Retina Quiz: CNV Tx

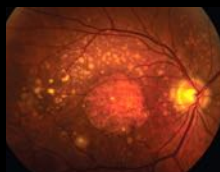
- Which of the following is the main advantage of Photodynamic therapy (PDT) over traditional laser photocoagulation?
 - a. Lower cost for PDT
 - b. More scar tissue formation in PDT
 - c. Less scar tissue formation in PDT *
 - d. PDT uses a "hotter" laser

Imaging the Macula

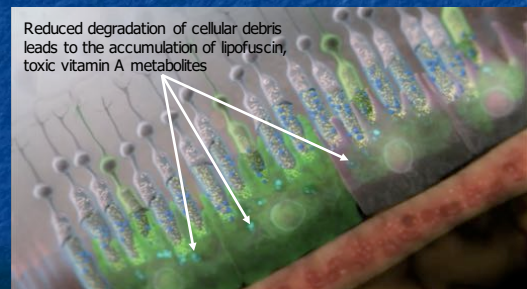
Non-invasive Methods

Autofluorescence (FAF)

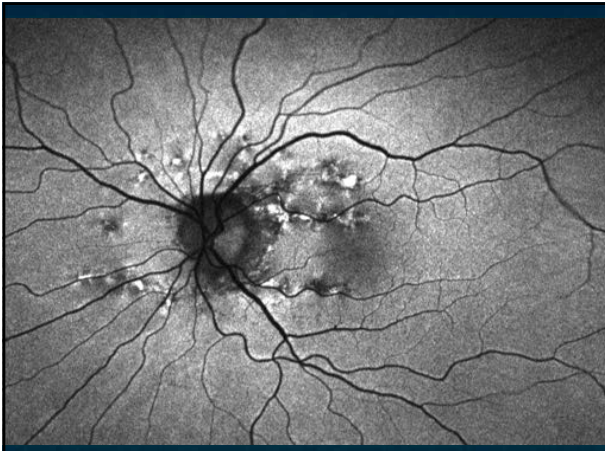
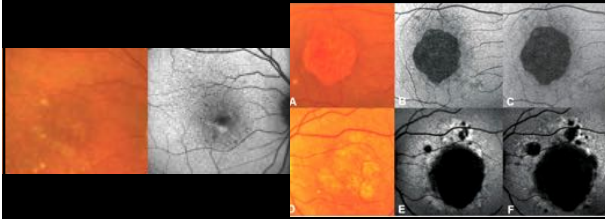
- Principle
 - When stimulated with light in the blue range, lipofuscin granules emit yellow fluorescence.
 - Patterns of fundus autofluorescence may predict which cases will progress more quickly.



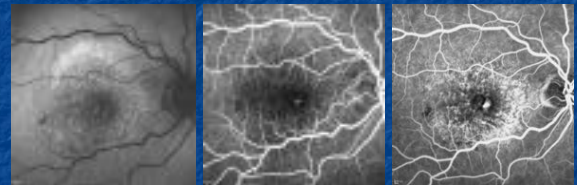
Early AMD: Accumulation of Lipofuscin and Vitamin A Metabolites



Autofluorescence



FAF and FA - Exudative AMD



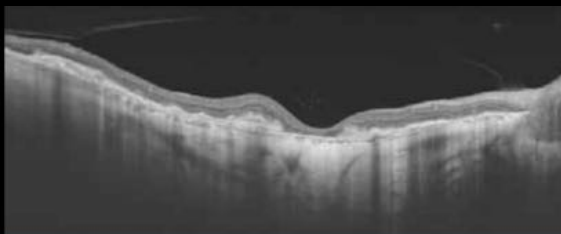
Hyperfluorescence
in FAF

FA 36 sec

FA 69 sec

Liakopoulos - Department of Ophthalmology at the University of Cologne

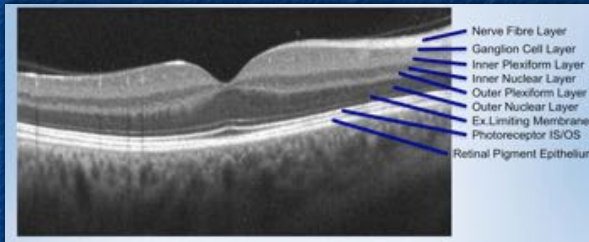
QUESTIONS?



Optical Coherence Tomography

OCT uses low-coherence interferometry to obtain real-time, cross-sectional histology of live tissue (virtual biopsy)

SD-OCT Healthy Macula w/Layers



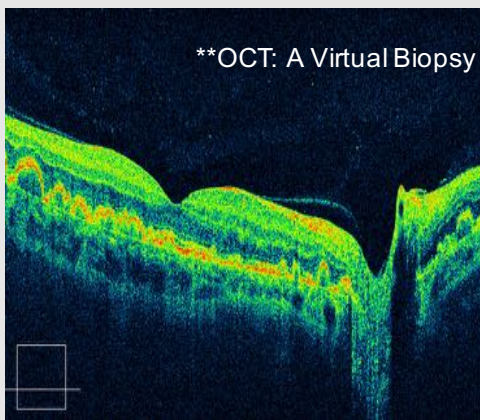
Current commercially available Spectral Domain OCT is capable of obtaining 3-5µm resolution**

****The earliest clinically detectable feature of AMD is Drusen.**



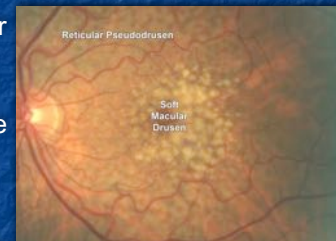
Drusen/
RPEDs

****OCT: A Virtual Biopsy**



Reticular (Pseudo)drusen (RPD)

- Seen as a reticular pattern of small yellow-white lesions often in the superior macula, RPD are a high-risk sign for advanced AMD.



Reticular (Pseudo)drusen

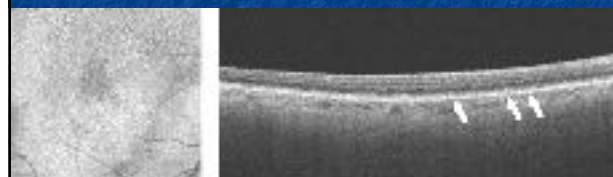


Reticular (Pseudo)drusen

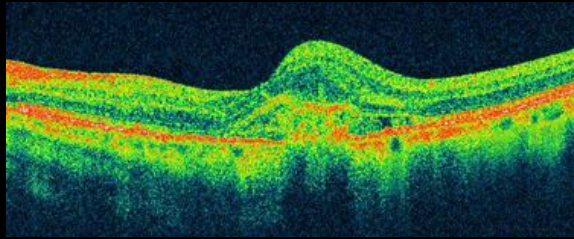
- Presence of RPD is a consistent risk factor for progression to both atrophy and CNV

■ IS/OS C-scan

B-scan

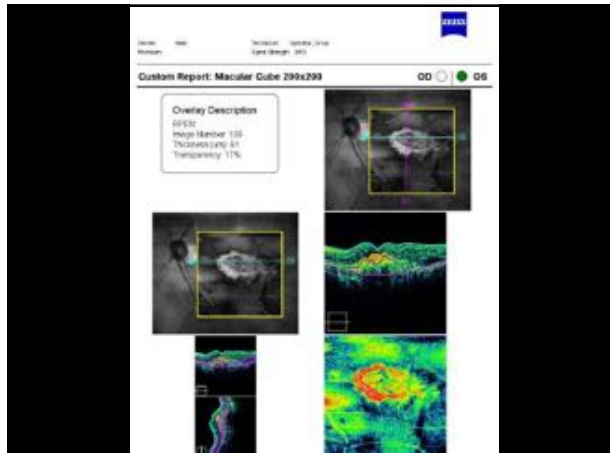
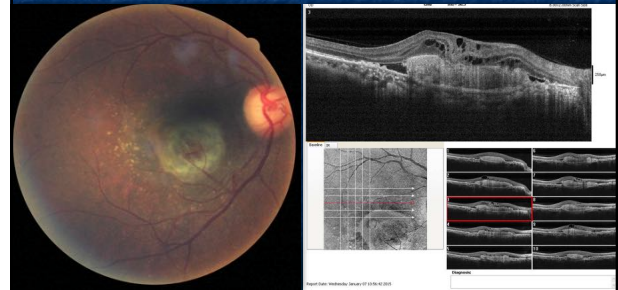


Spectral Domain OCT Shows CNV



****Current commercially available Spectral Domain OCT is capable of obtaining 3-5 μ m resolution**

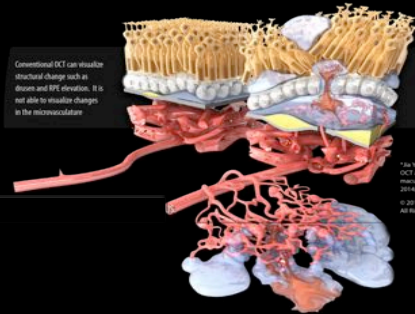
OCT Structural Changes: FV Scar



THE ARRIVAL OF OCT-ANGIOGRAPHY (OCTA)

A new way of visualizing ocular bloodflow in the vessels—identifies retinal microcirculation using the intrinsic motion of blood cells in the vessel

- Enables immediate assessment of microcirculation in ocular diseases with unprecedented microvascular detail



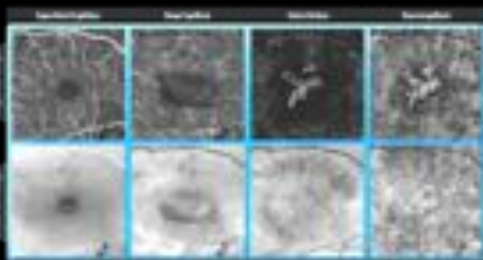
Conventional OCT can visualize structural change such as drusen and RPE elevation. It is not able to visualize changes in the microvasculature.

OCT Angiography can visualize ocular bloodflow in the vessels. Therefore, it can identify changes in the microvasculature such as choroidal neovascularization associated with wet AMD.

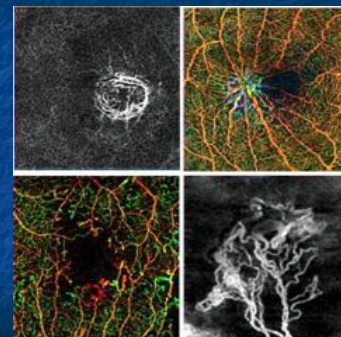
*Tak Y, Bailey S, Wilson D, et al. Quantitative OCT angiography of CNV in age related macular degeneration. *Ophthalmology* (2014) 121: 1433
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Imaging

OCTA IMAGES DEPICTING CHOROIDAL NEOVASCULARIZATION

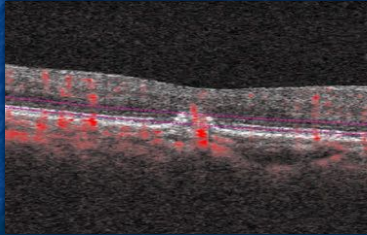


Imaging

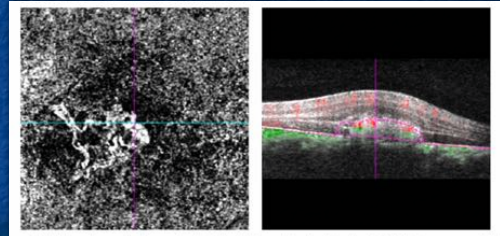


En face OCT angiograms

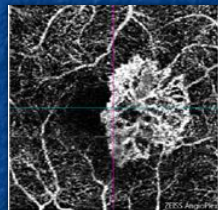
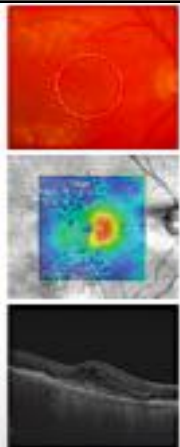
Emerging Trend: OCTA



OCTA reveals CNV Lesion in nAMD

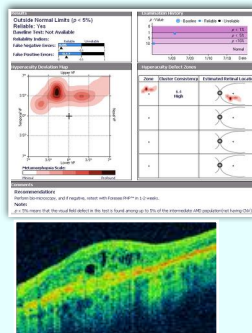
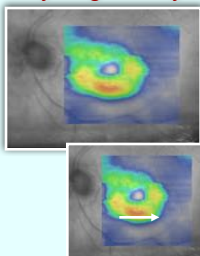


81 y/o WM OCTA at RPE Level



Structure and Function

- OCT and PHP work synergistically

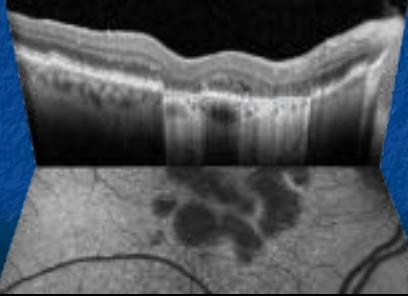


Multi-Modality Imaging

- Color photography
- Infrared
- Red-free
- FAF
- Fluorescein Angiography
- Indocyanine Green Angiography
- OCT/OCT-A

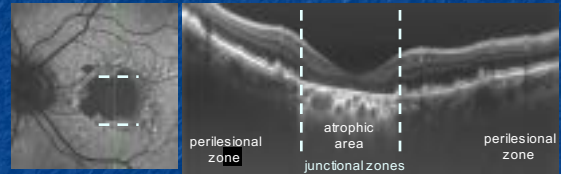
FAF + OCT

Offers a new perspective of the structure-function relationship within the retina



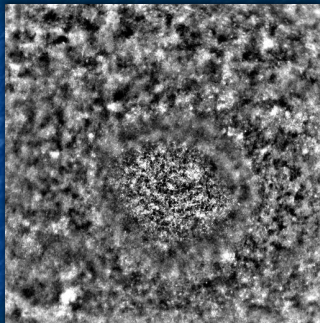
Simultaneous FAF and OCT

Geographic Atrophy



- FAF shows areas of hypo-autofluorescence in GA
- OCT outlines the corresponding photoreceptor dropout

Imaging



Adaptive Optics

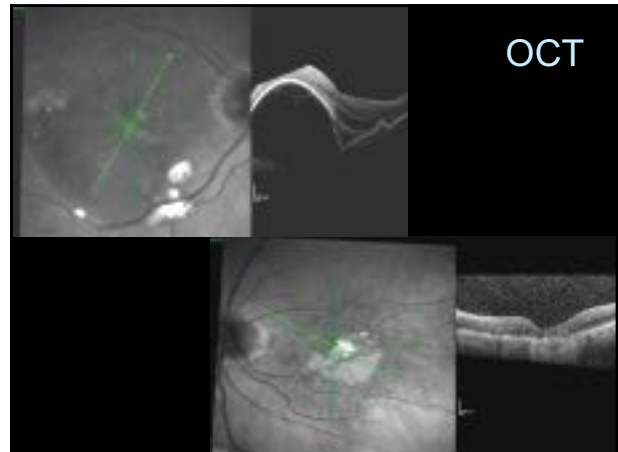
Case

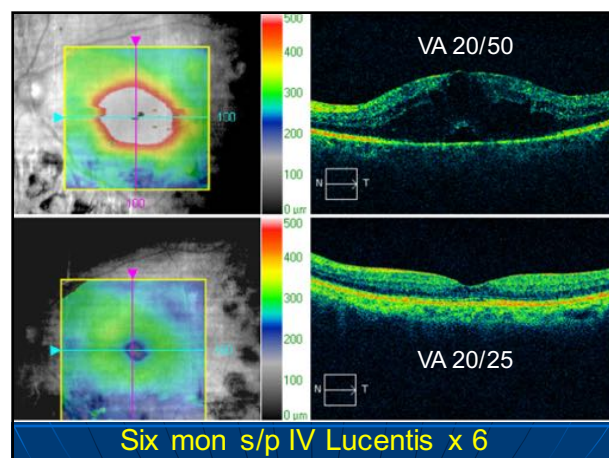
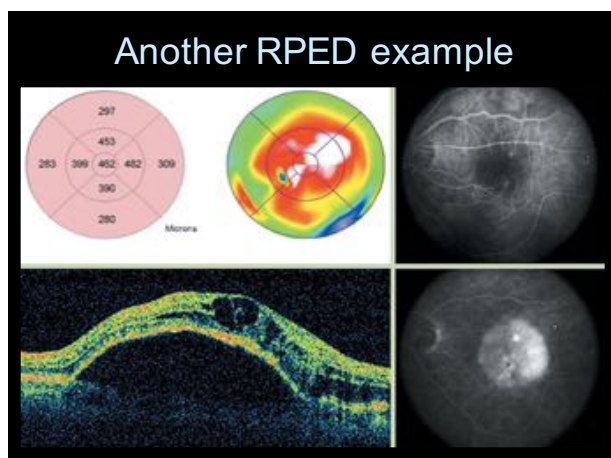
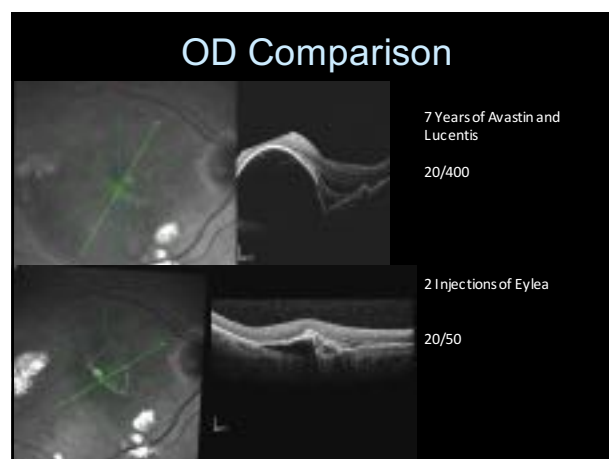
- 81 Year old Female with a history of arthritis.
- 7 year history of injections with Avastin or Lucentis
- PMH: AMD OU, Cataracts OU
- OCHx: Injections for Wet AMD in OD

Ophthalmic Exam

- VA:
 - OD: 20/400 OS: 20/80
- IOP
 - OD: 11 OS: 12
- SLE:
 - OD: NS +1 OS: NS + 1
- DFE:
 - RPED OD and Geographic Atrophy OS

OCT

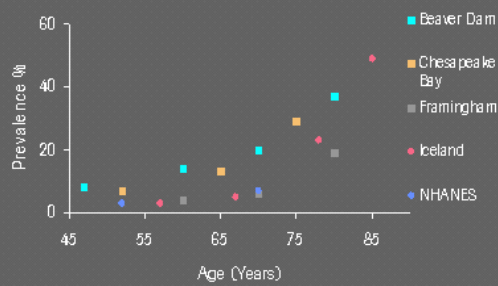




- ### AMD Risk Factors
- Non-modifiable
 - Age
 - Heredity
 - Sex
 - Pigmentation
 - Race
 - Iris color
 - Modifiable
 - Smoking
 - Cardiovascular disease
 - Blood lipid status
 - Hypertension
 - Alcohol consumption
 - Light exposure (UV, blue)
 - Nutrition
 - Obesity

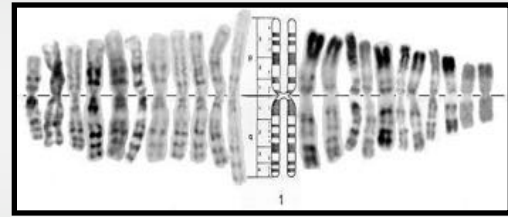
Epidemiology

Prevalence of AMD



Adapted from Vingerling et al., 1995

Genetics: ARMD-1



Chromosome 1
Region Displayed: 1q25-q31

Genetics and AMD

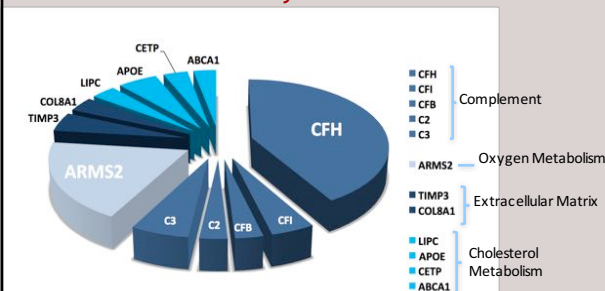
- Inherited variation in the **complement factor H gene** is a major risk factor for drusen.
- A single-nucleotide polymorphism (SNP) in the promoter region of **HTRA1** (a serine protease gene on chromosome 10q26) is a major risk factor for **Wet AMD**.
 - DeWan, A. Science, November 2006:Vol. 314. no. 5801, pp. 989 - 992

Genetics and AMD

Naturally occurring variations conferring AMD risk

Marker	Allele	Odds Ratio	Freq
CFH	H1+H3 (risk)	>15	0.202
	Average		0.495
	(H2+H4)		0.303
C3 rs2230199	G (risk)	2.6	0.18
	C		0.83
ARMS2 rs10490924	T (risk)	8.2	0.17
	G		0.83
Smoking	Current (risk)	3.14	0.17
	Never		0.55
mt. A4917G	G (risk)	2.2	0.09
	A		0.90

Key AMD-associated Genes



To whom should we recommend genetic testing to predict progression to advanced AMD?



Example of Genomics



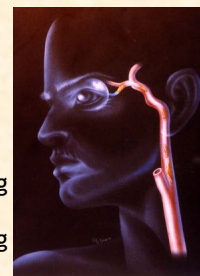
Smoking interacts with CFH Gene variants to increase AMD risk by 5X compared with genetically similar nonsmokers.



Am J Epidemiol. 2009 March 1; 169(5): 633-641.

Cigarette Smoking, Ocular & Vascular Disease

- Increased arteriolar stiffness (sclerosis)
- Increased Vascular Endothelial Growth Factor (VEGF) production
- Development /worsening of DR
- Development /worsening of AMD



AMD Gene Associations

- Mutations in the TIMP3 gene
 - metalloproteinase inhibitor 3 gene
- Two variants involved in the HDL cholesterol pathway.
 - Human hepatic lipase (LIPC) and cholesterol ester transfer protein (CETP).

● Proceedings of the National Academy of Sciences (4/2010)

AMD and Nutrition



"The **AREDS 1 Study** resulted in a formulation of vitamin C, beta carotene, zinc, and vitamin E that reduced the risk of progression of advanced disease by **25%** at 5 years."

Emily Chew, MD, from the National Eye Institute in Bethesda, Maryland

Johanna Seddon, MD (Tufts U)

"Don't smoke; follow a healthful diet rich in dark green leafy vegetables and low in fat; eat fish a few times a week; maintain a normal weight and waist size; exercise regularly; and control blood pressure and cholesterol."



"Anyone with signs of intermediate-level macular degeneration in both eyes or advanced macular degeneration in one eye should also take dietary supplements that contain lutein, zeaxanthin, vitamin C, vitamin E, and zinc."

Example of Genomics

A BMI over 30 increases AMD risk by 2.5X.

Clinical & Experimental
Ophthalmology

Celebiler et al., J Clin Exp Ophthalmol 2012, 3:5

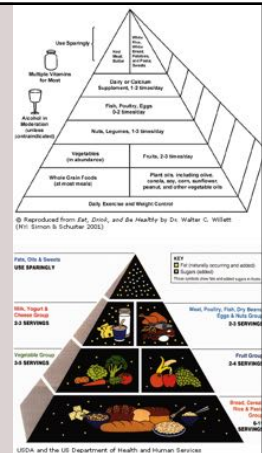




Questions?

Is There a Strategy?

- USDA Food Triangle/My Plate
- 5+ daily portions of fruits & veggies
 - at least 1 dark green, leafy veg (spinach, kale)
- Low saturated/trans fat, low cholesterol
- Antioxidant for at risk patients
 - L and Z
- CV Dx
- Physical Activity
- Low WL Blue, UV protection



USDA Replaces Food Pyramid



Behavior Modification

- Physical activity
- Fish consumption
- Greens
- Smaller portions
- Alcohol in moderation
- Nutritional supplements
- Blocking blue light from reaching retina



Behavior Modification

- Sedentary lifestyle
- Smoking
- Excess Alcohol
- High BMI
- HTN, Cholesterol
- Diet low in fish, green veggies



Conclusions

- AMD is on the rise, and it has systemic comorbidities and implications.
- Diet, nutrition, lifestyle matter.
- We must take proactive steps on behalf of our patients.



Thank you!

Joe