Optometric Education Consultants

Integrative and Functional Medicine

New Opportunities for Optometry

Greg Caldwell, OD, FAAO

Primary Eye Care Conference
Pittsburgh

Optometric Education Consultants

Saturday, February 17, 2024

Disclosures- Greg Caldwell, OD, FAAO

All relevant relationships have been mitigated

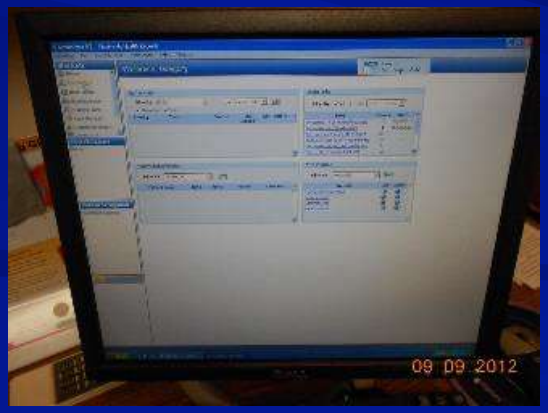
- Lectured for: Alcon, B&L, BioTissue, Dompé
  - Disclosure: Receive speaker honorariums
- Advisory Board: Dompé, ImmunoGen, Iveric
  - Disclosure: Receive participant honorariums
- I have no direct financial or proprietary interest in any companies, products or services mentioned in this presentation
  - Disclosure: Non-salaried financial affiliation with Pharmanex
- Healthcare Registries – Chairman of Advisory Council for Diabetes and AMD
- The content of this activity was prepared independently by me - Dr. Caldwell
- The content and format of this course is presented without commercial bias and does not claim superiority of any commercial product or service
- Optometric Education Consultants – Scottsdale, AZ, Pittsburgh, PA, Sarasota, FL , Barcelona, Spain, Orlando, FL, Mackinac Island, MI, Quebec City, Canada, and Nashville, TN- Owner

Optometric Education Consultants

My Practice

I am a clinician first then a scientist

- Some are scientists first then clinician
- I need to simplify for patient and patient care.
- Science is great, but not good if there isn't a clinical application.
- Some lectures are science based without clinical application.
- My lecture will be a hybrid. Showing clinical applications of the science



It is wonderful to have someone who's juggling so many aspects of optometry [scientific, clinical experience, teacher & lecturer]. It is refreshing and very informative. -Sarah

Ocular Disease Career
Allopathic

- OCT - Spectral domain
- OCT Angiography
- Visual Fields
- AMD, glaucoma, retinal degenerations, diabetic retinopathy
- Dark Adaptation

- Focusing on structure and function loss or damage

- Patients asking what about supplements
  - Reading about it on internet
- Promised I would do my due diligence

- Ocular disease optometrist to an Integrative Optometrist

Confidence
Capable
Courage
Commitment

Acute vs Chronic

- Corneal abrasion
- Marginal ulcer
- CL overwear
- Hordeolum
- HSV Keratitis
- Anterior Chamber Iritis

- Randomized Clinical Trials
  - Heterogenous input and arrive at a homogenous result
  - Evidence based medicine – we apply those average findings to everyone, that is an individual
- Everyone is not average
- The longest clinical trials are 5-10 years

- Thyroid Eye Disease
- Diabetes
  - Metabolic diseases
- Cardiovascular disease

- Rheumatoid Arthritis
- Macular degeneration
  - Geographic atrophy
  - Wet AMD

Chronic

- Not acute or binary
  - Complex processes
- Short term fixes don't work
- More of strategy
- Assessment of risk

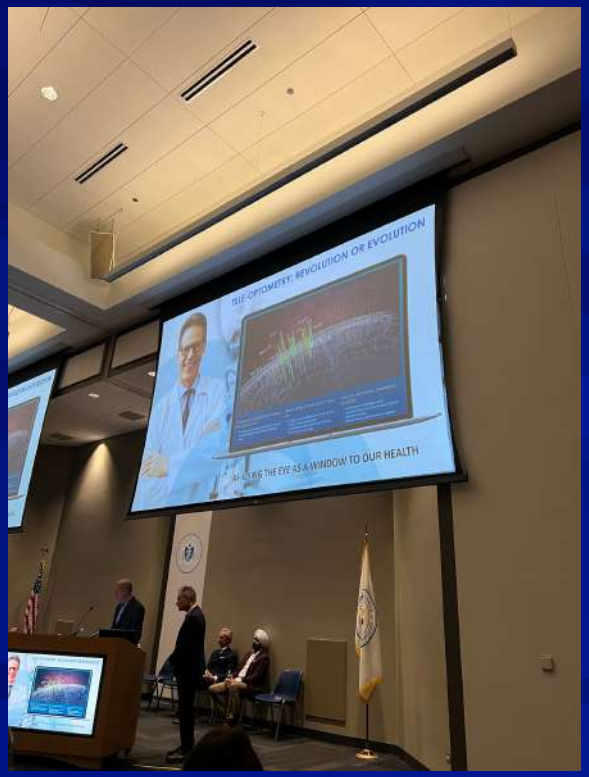
- We try to take complex processes and try to make them binary

- Thyroid Eye Disease
- Diabetes
  - Metabolic diseases
- Cardiovascular disease
- Alzheimer's Disease
- Rheumatoid Arthritis
- Macular degeneration
  - Geographic atrophy
  - Wet AMD

Chronic or Focus of Prevention
Shift from evidence based to
Evidence Informed Risk Adjusted Medicine

Tele-Optometry – AI and Risk

Evidence Informed Risk Adjusted Medicine



Using AI, retina, and blood vessels for “risk”
Cardiovascular Disease

Using AI, retina, and blood vessels for “risk”
Alzheimer's Disease

Nutrition

- Don't consume too many or too few calories
- Eat sufficient protein and essential fats
- Obtain the vitamins and minerals you need
- Avoid pathogens like E Coli
- Avoid toxins like mercury and lead
- Beyond this we know relatively little with complete certainty

Why?

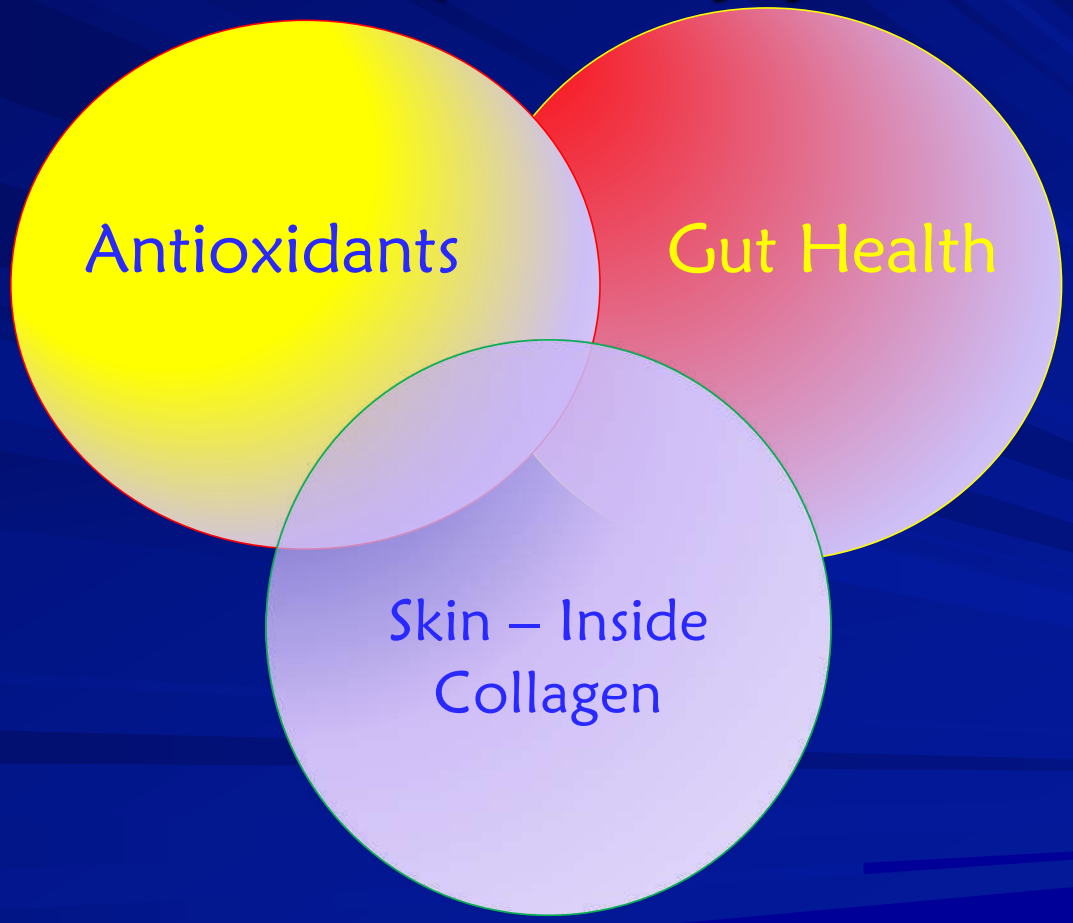
- Do not claim that a product will treat, cure, or prevent any disease or health condition (including COVID-19 or viruses) or that the product cured your own ailment

- Dietary supplements are not intended to treat, diagnose, mitigate, prevent, or cure disease

Comprehensive Antioxidant Support

- Cell membrane support
- Immune support
- Support to the oxidative stress to the extracellular matrix
- Support to cell signaling

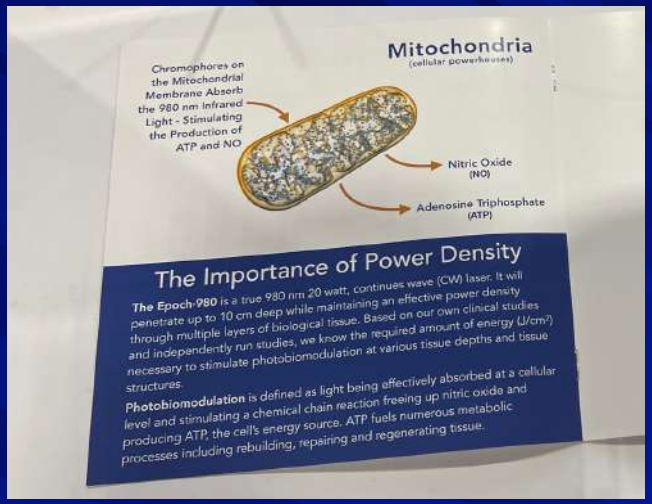
Optometry's Opportunity?



Exercise – 77% of Americans do not exercise

90 minutes per week decreases of dying of all causes by 14%


A4M
Longevity
FEST 2022
30TH ANNUAL WORLD CONGRESS
FRIDAY DECEMBER 9TH
10:30AM - 6:00PM


Mitochondria
(cellular powerhouses)
Chromophores on the Mitochondrial Membrane Absorb the 980 nm Infrared Light - Stimulating the Production of ATP and NO
Nitric Oxide (NO)
Adenosine Triphosphate (ATP)
The Importance of Power Density
The Epoch-980 is a true 980 nm 20 watt, continues wave (CW) laser. It will penetrate up to 10 cm deep while maintaining an effective power density through multiple layers of biological tissue. Based on our own clinical studies and independently run studies, we know the required amount of energy (J/cm²) necessary to stimulate photobiomodulation at various tissue depths and tissue structures.
Photobiomodulation is defined as light being effectively absorbed at a cellular level and stimulating a chemical chain reaction freeing up nitric oxide and producing ATP, the cell's energy source. ATP fuels numerous metabolic processes including rebuilding, repairing and regenerating tissue.


time—line
Mitochondrial health is key to healthy aging
90% of our cellular energy (ATP) is generated by our


ÉLEVÉ
HEALTH


"The Comfort Zone"
COMFORT ZONE
Feel safe and in control
Be affected by others' opinions
FEAR ZONE
Find excuses
Lack of self-confidence
Deal with challenges and problem
LEARNING ZONE
Acquire new skills
Extend your comfort zone
GROWTH ZONE
Find purpose
Live dreams
Set new goals
Conquer objectives

Credit to: James LaValle, RPh, CCN

Life Span versus Health Span

- If we are all "Human Beings: version 1600", why are we getting weaker and sicker than ever before? Why are we not continuing to evolve and get better and stronger, like our mobile phones have done in only 10 generations?

- Our average age or life span may be getting longer, but the average Health span, the number of healthy years we can expect to live is decreasing. Lifespan in the USA is now about 79 years while Health span is 63 years. In other words, we are living an average of 63 years of healthy life followed by a 16-year burden of chronic disease.

- Why is this happening to us? The answer is chronic diseases, most of which are self-inflicted. We have accepted unhealthy lifestyle and dietary choices, robbing our bodies of the tools and ingredients necessary to stay healthy, to repair itself and evolve. Only we can make ourselves healthy. Medications, especially those for chronic disease do NOT make us better. They just reduce the symptoms, whether it is pain, diabetes, high blood pressure or a wide range of eye disorders. Medications for chronic conditions like these do not treat our underlying medical conditions. They reduce the symptoms of the disease process by tampering with our internal body chemistry to reduce our symptoms or change the numbers on a lab test, without addressing the actual cause of the problem.

Barry Shuman O.D., M.P.H., F.A.A.O.
Eye Care Systems Consultant

Life Span versus Health Span

Today slow death has surpassed fast death.

Most can expect to live to be their 80s, but die from chronic disease or slow death

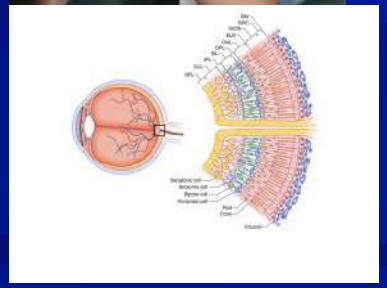
Patients Are Expecting

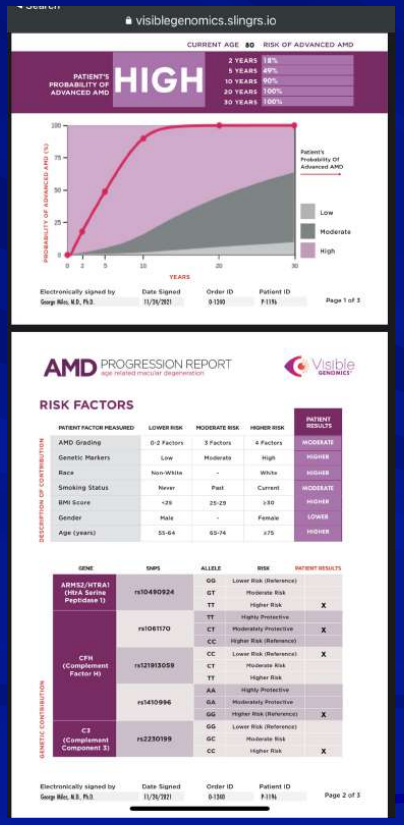
- Early detection
- Wellness
- Prevention

Early Detection and Allopathic Treatments

Rabin Cone Contrast Test

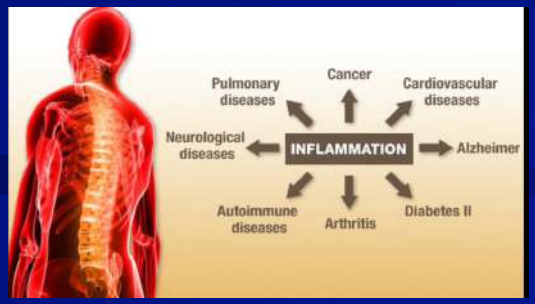
ERG and VEP





Evidence Informed Risk Adjusted Medicine

Measuring Carotenoids – Gives You the Patient's Over-All Antioxidant Status – In the Office – 30 Seconds



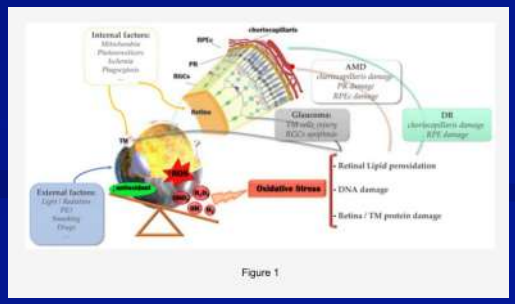
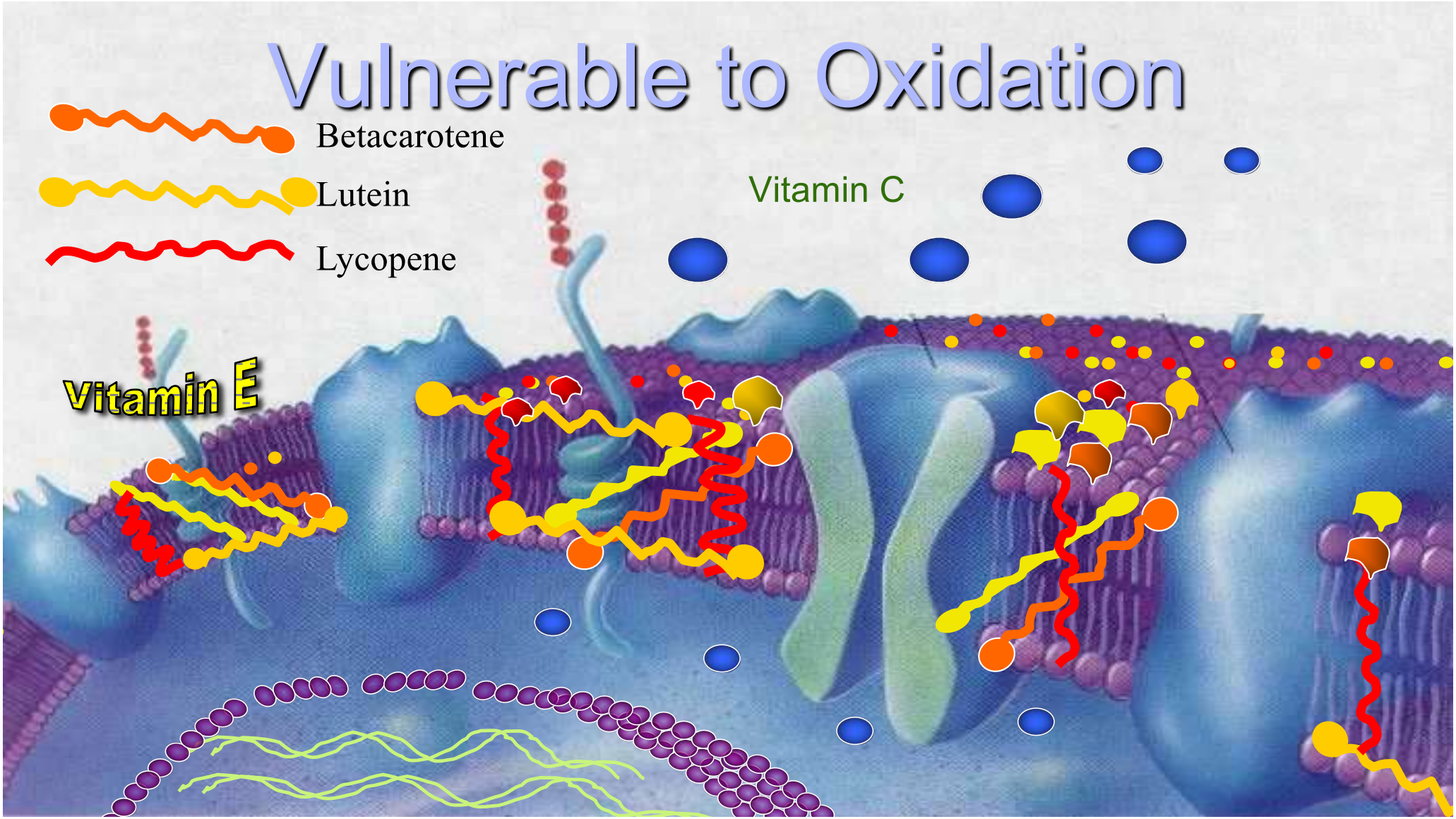


Figure 1

Vulnerable to Oxidation



OmegaQuant Analytics
5009 W. 12th St, Suite 7
Sioux Falls, SD 57106
omegaquant.com

Omega-3 Index Plus Report

NAME: Greg Caldwell
DOB: 04/03/1970
PATIENT ID: GCaldwell
SAMPLE ID: USAFS32022

COLLECTION DATE: 01/16/2023
RESULT DATE: 01/27/2023
PROVIDER:
ACCOUNT: Consumer

Your Omega-3 Index

Reference Range*: 3.00% - 14.10%

* Reference Ranges encompass about 99% of fatty acids levels measured in US adults. Visit our FAQ section for more information on ranges.

The Omega-3 Index is the proportion of long-chain omega-3s, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), of all fatty acids in your red blood cell membranes. It reflects the omega-3 status of your body over the last 4 months, similar to how hemoglobin A1C reflects long-term glucose blood levels. As a part of an overall healthy lifestyle, an Omega-3 Index in the 8-12% range may help to maintain heart, brain, eye and joint health. To increase your Omega-3 Index, eat foods rich in EPA and DHA, especially "oily" fish such as those in the accompanying table. They can also be obtained from dietary supplements (fish, krill, cod liver, algal oils) and functional foods (omega-3 enriched milk, eggs, etc.).

The amount of EPA and DHA needed to raise the Omega-3 Index into the desirable range is different for everybody. Many factors – age, sex, weight, diet, genetics, smoking habits, medications, and other medical conditions – can all influence the body's response to EPA and DHA. Still, we can provide an estimate, based on our own research, of how much EPA and DHA you may need to raise your level to the desirable range given your current Omega-3 Index level. Visit our Omega-3 Index Calculator on OmegaQuant.com to find out your personalized EPA and DHA recommendation.

The other main dietary omega-3 fatty acid, alpha-linolenic acid (ALA), is found in walnuts, flax and chia seeds. ALA can be converted to EPA and DHA in the body, but this happens at a very low rate in most people. An increase in ALA intake will have little to no effect on the Omega-3 Index.

Please consult with your healthcare provider before making any dietary changes. If you increase your intake of EPA and DHA, your Omega-3 Index will begin to slowly go up within a few days but will continue to change for 3-4 months. We recommend that you re-measure your Omega-3 Index in 3-4 months until you reach the desirable range. Once you reach the desirable range for Omega-3 Index, we recommend that you re-test every 6 months. Answers to commonly asked questions about your results can be found in the FAQ section on our website.

OmegaQuant Analytics
5009 W. 12th St, Suite 7
Sioux Falls, SD 57106
omegaquant.com

Omega Ratios Report

NAME: Greg Caldwell
DOB: 04/03/1970
PATIENT ID: GCaldwell
SAMPLE ID: USAFS32022

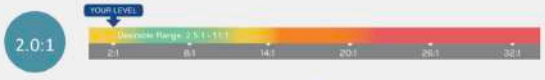
COLLECTION DATE: 01/16/2023
RESULT DATE: 01/27/2023
PROVIDER:
ACCOUNT: Consumer

Omega-6:Omega-3

Reference Range*: 2.1:1 - 13.6:1

AA:EPA

Reference Range*: 1.3:1 - 59.9:1



* Reference Ranges encompass about 99% of fatty acids levels measured in US adults. Visit our FAQ section for more information on ranges.

Omega-6:Omega-3 (n6:n3) ratio is calculated by dividing the sum of seven omega-6 fatty acids by the sum of four omega-3 fatty acids in whole blood. Only one omega-6 fatty acid, arachidonic acid (AA), and one omega-3 fatty acid, eicosapentaenoic acid (EPA), make up the AA:EPA ratio. The desirable range for the Omega-6:Omega-3 ratio is 3:1 to 5:1, and the desirable range for the AA:EPA ratio is 2.5:1 – 11:1. The desirable ranges for the ratios were calculated to correspond to the desirable range for the Omega-3 Index due to the strong relationship among these metrics.

Higher omega-3 blood levels are strongly related to improved health and longevity. Similarly, higher - not lower - blood levels of the main omega-6 fatty acid, linoleic acid, have been associated with better heart and metabolic health. AA blood levels alone are a poor predictor of health outcomes. However, there is considerable controversy regarding omega-6s in the diet and health, which is beyond the scope of this report.

Please consult with your healthcare provider before making any dietary changes. The most efficient way to lower both the Omega-6:Omega-3 and the AA:EPA ratios is to consume more omega-3 EPA and DHA from fish or supplements (see attached table). Omega-6 blood levels are less responsive to dietary changes than omega-3 blood levels. Therefore, lowering dietary omega-6s as a strategy to correct these ratios is typically less effective than raising intake of EPA and DHA. It will take 3-4 months for these ratios to reach their new levels and we recommend re-testing at that time.

OmegaQuant Analytics
5009 W. 12th St, Suite 7
Sioux Falls, SD 57106
omegaquant.com

Trans Fat Index Report

NAME: Greg Caldwell
DOB: 04/03/1970
PATIENT ID: GCaldwell
SAMPLE ID: USAFS32022

COLLECTION DATE: 01/16/2023
RESULT DATE: 01/27/2023
PROVIDER:
ACCOUNT: Consumer

Your Trans Fat Index

Reference Range*: 0.30% - 1.70%

* Reference Ranges encompass about 99% of fatty acids levels measured in US adults. Visit our FAQ section for more information on ranges.

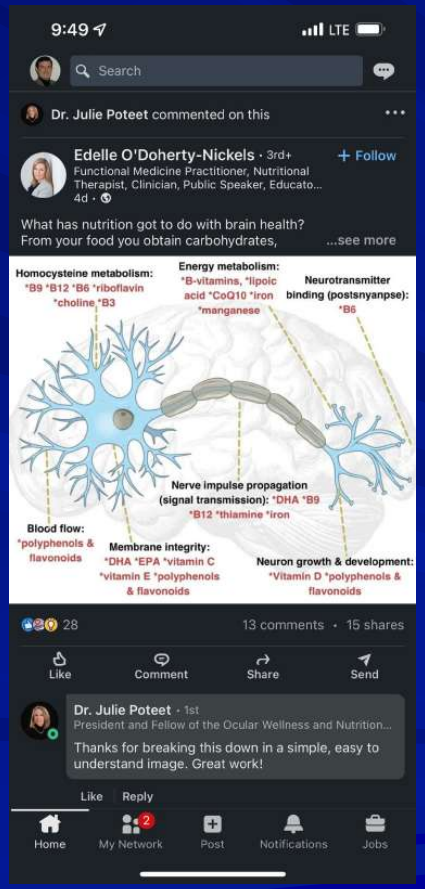
The Trans Fat Index is the percent of 18:1 and 18:2 trans fatty acids of total fatty acids in red blood cell membranes, and the desirable range is **<1%**. *Trans* fatty acids (or *trans* fats) in our blood come only from the food we eat because our bodies cannot make them. *Trans* fats in the diet come from two sources: 1) industrial production by the "partial hydrogenation" of vegetable oils, in which liquid oils are converted into solid fats to be used in processed foods, and 2) meat and milk products of ruminant animals, like cows and goats. The fatty acids that make up the Trans Fat Index were chosen because they were typically found in processed foods, but a small amount may come from ruminant sources.

Higher intakes of *trans* fats from processed foods have led to higher Trans Fat Index levels. Higher*trans* fat blood levels and intake have been strongly related to heart disease. As such, the World Health Organization (WHO) has called on all countries to remove*trans* fats from their food supplies by 2023, and many countries have already achieved this. The relationship between ruminant*trans* fats and heart disease is not as clear. The amount of ruminant *trans* fats typically present in meat and dairy are very low, so normal intakes of these foods probably will not result in a high Trans Fat Index.

Traditionally, *trans* fats were abundant in processed foods, like baked goods, chips, and microwave popcorn. As*trans* fats have been removed from the food supply, however, eating processed foods has become less connected to blood*trans* fat levels. For example, since 2009, the average Trans Fat Index measured at OmegaQuant has decreased by half (from 1.7% to 0.8%), and in 2017 more than half of the samples submitted to OmegaQuant have a Trans Fat Index of <1%. Still, if you ate a lot of processed food in the past, your Trans Fat Index may be elevated.

Please consult with your healthcare provider before making any dietary changes. If your Trans Fat Level is <1%, there is no need to change your diet. If your Trans Fat Level is >1%, you may still be releasing stored*trans* fats that have built up over the years. Eating less processed food ensures you will not be eating any "hidden" *trans* fats that may still be in the food supply. We recommend you re-test every 6 months until your levels are <1%.

Comprehensive versus Isolate



Ocular Nutrition

Tying Structure, Function, and Molecular Altogether

Is it really any different than systemic nutrition?

Tying Structure, Function, and Molecular Altogether

Organ and End Organ Damage from Oxidative Stress

- Dry eye
- Floaters
- AMD
- Glaucoma
- Diabetes
- Autoimmune disease

Comprehensive Antioxidant Support

- Cell membrane support
- Immune support
- Support to the oxidative stress to the extracellular matrix
- Support to cell signaling

Question?

- Who in here would consider themselves as an integrative optometrist?

- Who has done or recommended?
  - Supplements, vitamins, AREDS2
  - Omegas, EPA, DHA
  - Vital tears – ASED
  - Regener-Eyes
  - Tea tree oil – Cliradex
  - Amniotic membranes
  - Hypochlorous acid – Avenova
  - CBD
  - Probiotics

Allopathic vs Integrative Medicine

- "Allopathic medicine" is a term used for modern or mainstream medicine
  - Conventional medicine, mainstream medicine, Western medicine, biomedicine
  - Treating conditions and symptoms with its "opposite"
  - Health system in which medical doctors, nurses, pharmacists, and other healthcare professionals are licensed to practice and treat symptoms and diseases
  - Using medication, surgery, radiation, therapies, and procedures
- Complementary and integrative medicine are commonly used along with mainstream medicine
  - Homeopathy, naturopathy, chiropractic care, Chinese medicine
- Allopathic or modern medical schools have recently added more study and information on how food and nutrition can help prevent and treat disease
  - More education is being offered on integrative approaches and potential interactions with mainstream medicine

Medical Practices

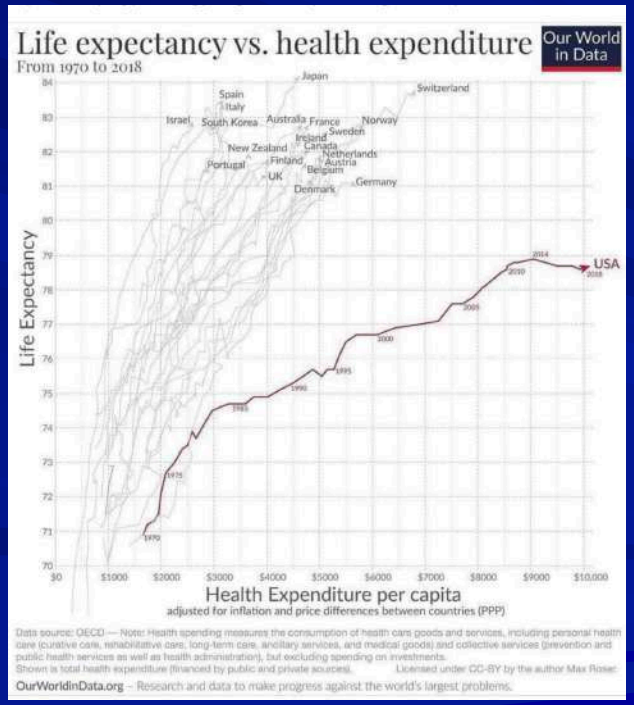
- Allopathic medicine
  - Western medicine
- Alternative "homeopathic"
- Functional
  - Medicine of why, treat the cause
- Integrative medicine
  - Complementary medicine - Eastern complimenting Western

What is integrative medicine?

The practice of integrative medicine refers to the **blending of conventional and evidence-based natural and complementary medicines and/or therapies with lifestyle interventions** to deliver holistic, patient-centred care.

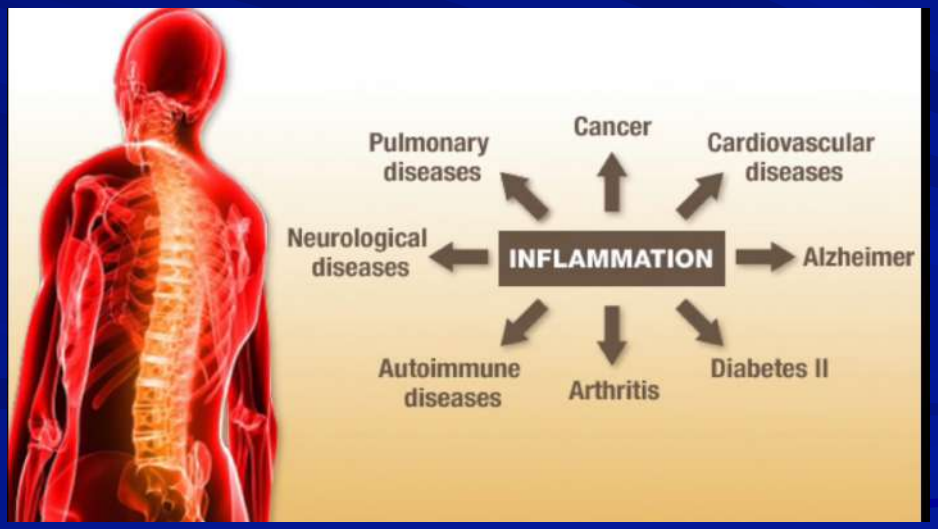
Chronic and Low-Grade Inflammation

Science has proven that chronic, low-grade inflammation can turn into a silent killer that contributes to cardiovascular disease, cancer, type 2 diabetes, diabetic retinopathy, cataracts, macular degeneration, and many other conditions



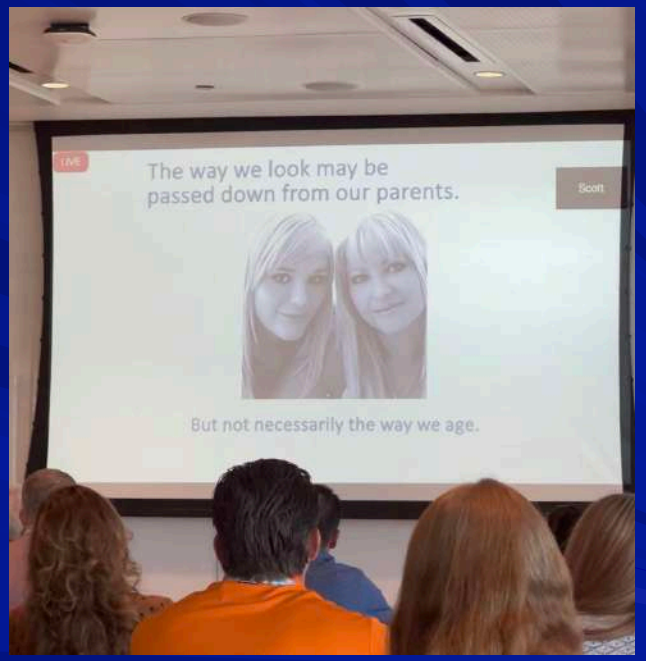
Chronic and Low-Grade Inflammation

Like cancers and other slow-burn diseases, identifying these conditions early can make the difference between full recovery or a dramatically reduced quality of life or even death (vision loss or blindness)



"Choose Your Parents Wisely"

- This just isn't as true as it's used to be
- Lifetime health
  - 8% genetics "Picking your parents wisely"
    - DNA in our nucleus
      - Can't be influenced
  - 92% epigenetics
    - Lifestyle choices = we can influence
    - Turn on/off gene expression

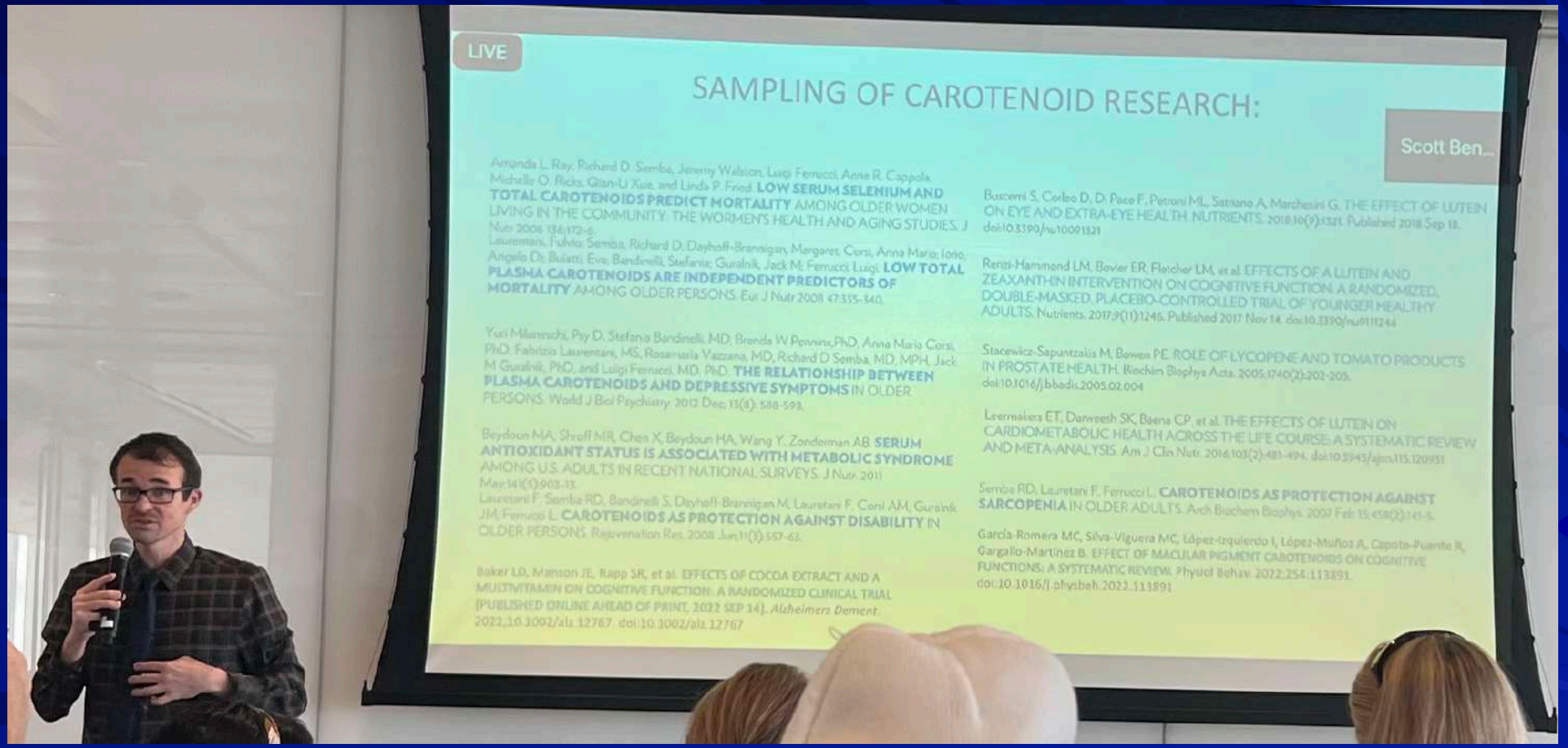


Biomarker

- Test that has meaning
- Biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease.
- A biomarker may be used to see how well the body responds to a treatment for a disease or condition
- Blood pressure, blood work, heart rate, genetic testing, IOP

Predictive Biomarker

- Used to identify individuals who are more likely to respond to exposure to a particular medical product or environmental agent
- The response could be a symptomatic benefit, improved survival, or an adverse effect
- A value that we can guide therapy around
  - HbAlc
  - C-Reactive Protein
  - Plasma Homocysteine
  - Vitamin D (25-HydroxyD)
  - Omega 3 index
  - Carotenoid – measure of all antioxidants


LIVE
SAMPLING OF CAROTENOID RESEARCH:
Scott Ben...
Amanda L. Ray, Richard D. Semba, Jeremy Walston, Luigi Ferrucci, Anne R. Cappola, Michelle O. Ricks, Qian-Li Xue, and Linda P. Fried. LOW SERUM SELENIUM AND TOTAL CAROTENOIDS PREDICT MORTALITY AMONG OLDER WOMEN LIVING IN THE COMMUNITY. THE WOMEN'S HEALTH AND AGING STUDIES. J Nutr 2008 136:172-6.
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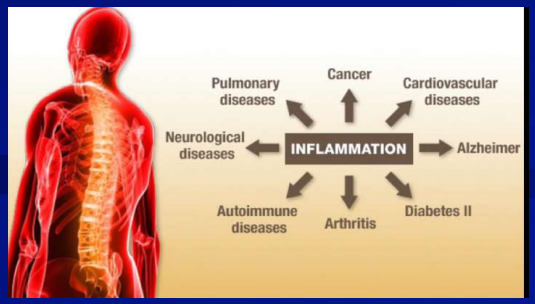
Predictive Biomarker – Gives You the Patient's Over-All Antioxidant Status – In the Office – 30 Seconds



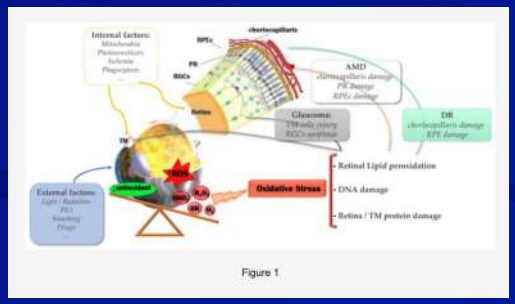
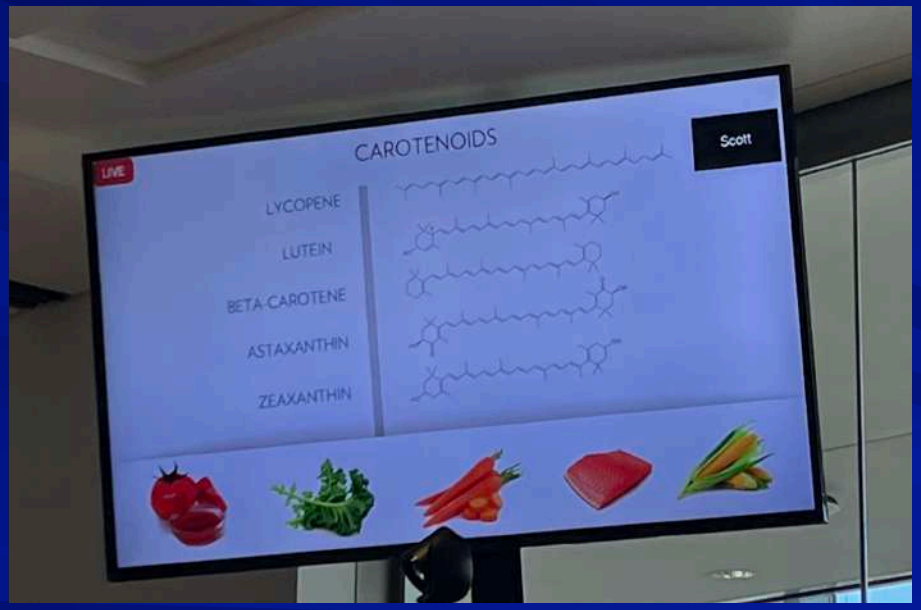
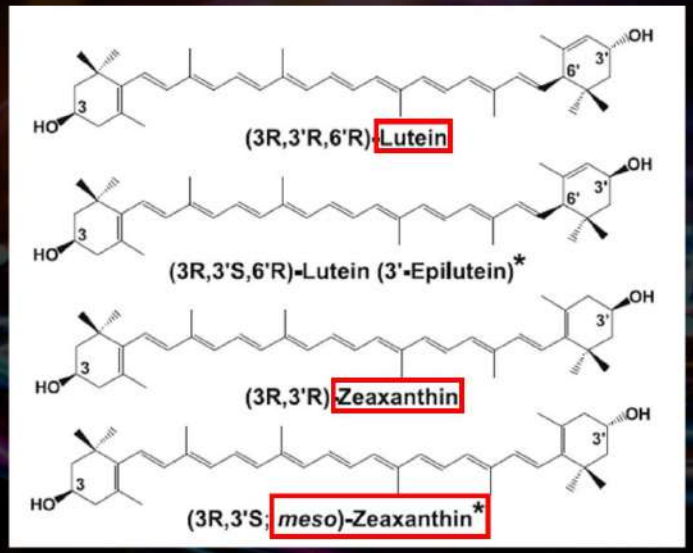


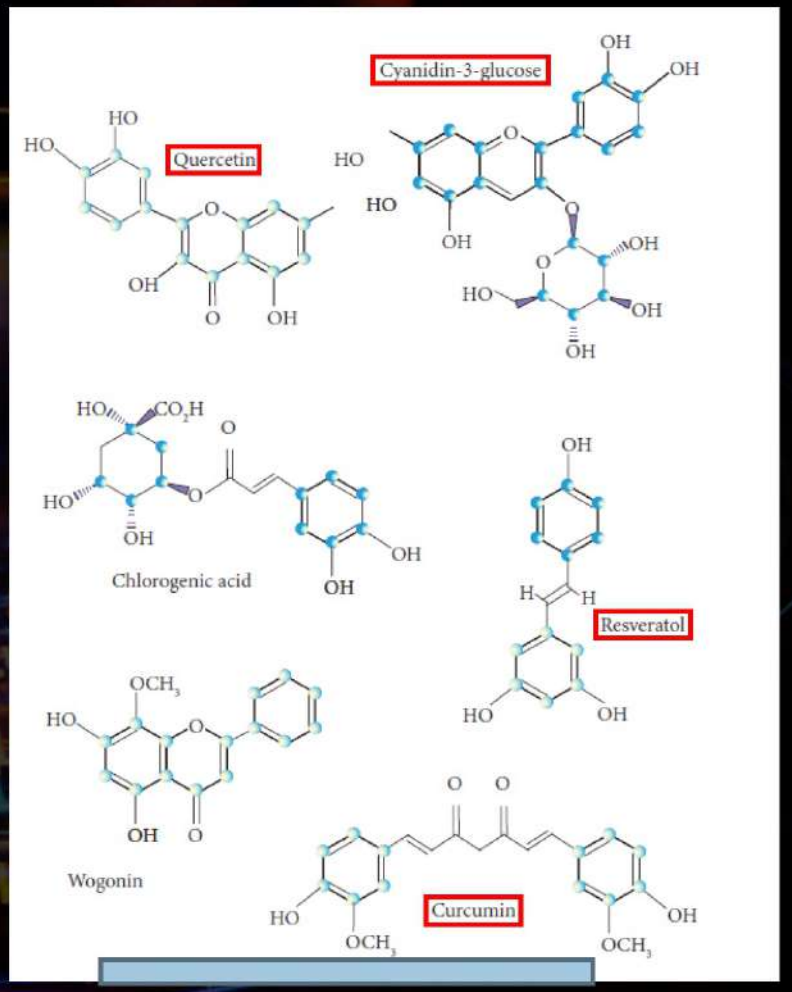
Figure 1

Carotenoids



Retinal nutraceuticals share a common thread....

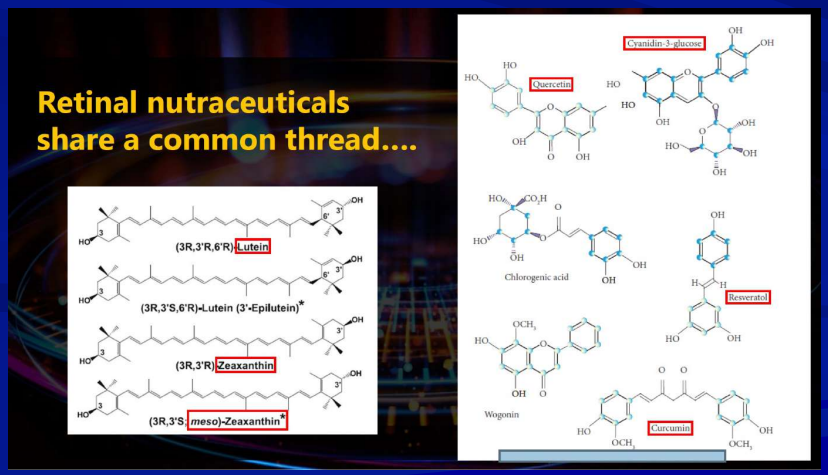




Thank you, Dr. Chris Putnam,

-OH

- -OH group donate an electron to mitigate the ROS and singlet oxygen generated from highly metabolic tissue
- -OH group is found on all of them and it's what makes them such a fantastic antioxidant



Polyphenols
Flavonoids
Quercetin

Thank you, Dr. Chris Putnam,

Evidence Informed Risk Adjusted Medicine

Quercetin inhibits choroidal and retinal angiogenesis *in vitro*.
Graefe's Arch Clin Exp Ophthal (2008) 246.3:373-378.

Singlet oxygen quenching-and chain-breaking antioxidant-properties of a quercetin dimer able to prevent AMD.
Biophysical chemistry 243 (2018): 17-23.

Quercetin and cyanidin-3-glucoside protect against photooxidation and photodegradation of A2E in RPE cells.
Experimental eye research 160 (2017): 45-55.

Neuroprotective effects of quercetin in diabetic rat retina.
J Bio Sciences. (2017) 24.6:1186-1194.

Protective effect of quercetin and chlorogenic acid, two polyphenols widely present in edible plant varieties, on visible light-induced retinal degeneration *in vivo*.
J Func Foods (2017) *33*, 103-111.

Polyphenols
Flavonoids
Anthocyanins

Thank you, Dr. Chris Putnam,

Evidence Informed Risk Adjusted Medicine

Antioxidant and anti-inflammatory effects of blueberry anthocyanins on high glucose-induced human retinal capillary endothelial cells.
Oxidative medicine and cellular longevity. (2018)

Protective effects of blueberry anthocyanins against H_2O_2-induced oxidative injuries in human retinal pigment epithelial cells.
J Agricultaral Food Chem. (2018) *66*(7):1638-1648.

Protective effect of anthocyanins and xanthophylls on UVB-induced damage in retinal pigment epithelial cells.
Food and Function (2016) *7*(2):1067-1076.

Effects of blueberry anthocyanins on retinal oxidative stress and inflammation in diabetes through Nrf2/HO-1 signaling.
J Neuroimmunology (2016) 301:1-6.

Identification of anthocyanins in the liver, eye and brain of blueberry-fed pigs
J Agric Food Chem (2008) 56.3:705-712

Polyphenols
Non-Flavonoids
Curcumin

Thank you, Dr. Chris Putnam,

Evidence Informed Risk Adjusted Medicine

Therapeutic potential of curcumin in major retinal pathologies.
Int ophth (2019) 39.3:725-734.

Vascular endothelial growth factor: An important molecular target of curcumin.
Crit Review Food Sci Nutrition (2019) 59.2:299-312.

Retinal protection and distribution of curcumin *in vitro* and *in vivo*.
Frontiers in pharmacology 9 (2018) 670.

Curcumin acts to regress macular drusen volume in dry AMD.
Invest Ophth Vis Sci (2020) 61.7:1036-1036.

Curcumin-Based Treatment for Macular Edema from Uncommon Etiologies: Efficacy and Safety Assessment.
Journal of Medicinal Food (2020) 23.8

Polyphenols
Non-Flavonoids
Resveratrol

Thank you, Dr. Chris Putnam,

Evidence Informed Risk Adjusted Medicine

Resveratrol based oral nutritional supplement produces long-term beneficial effects on structure and visual function in human patients.
Nutrients. (2014), 6.10:4404-4420.

Resveratrol suppresses expression of VEGF by human retinal pigment epithelial cells: potential nutraceutical for age-related macular degeneration.
Aging and disease (2014) 5.2:88.

SIRT1 mediated inhibition of VEGF/VEGFR2 signaling by Resveratrol and its relevance to choroidal neovascularization.
Cytokine 76.2 (2015):549-552.

Anti-oxidant, anti-inflammatory and anti-angiogenic properties of resveratrol in ocular diseases.
Molecules 21.3 (2016):304.

Toxic effects of A2E in human ARPE-19 cells were prevented by resveratrol: A potential nutritional bioactive for age-related macular degeneration treatment.
Archives of Toxicology 94.2 (2020): 553-572.

Measure?

ANNUAL REVIEWS

Annual Review of Nutrition

Ocular Carotenoid Status in Health and Disease

Lydia Sauer, Binxing Li, and Paul S. Bernstein

Department of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, Utah 84132, USA; email: lydia.sauer@hsc.utah.edu, Binxing.Li@hsc.utah.edu, paul.bernstein@hsc.utah.edu

Annu. Rev. Nutr. 2019. 39:95–120

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https://doi.org/10.1146/annurev-nutr-082018-124555

Keywords

macular pigment, macular carotenoids, carotenoid supplementation, ocular nutrition, retinal imaging

Abstract

Retinal carotenoids are dietary nutrients that uniquely protect the eye from light damage and various retinal pathologies. Their antioxidative properties protect the eye from many retinal diseases, such as age-related macular degeneration. As many retinal diseases are accompanied by low carotenoid levels, accurate noninvasive assessment of carotenoid status can help ophthalmologists identify the patients most likely to benefit from carotenoid supplementation. This review focuses on the different methods available to assess carotenoid status and highlights disease-related changes and potential nutritional interventions.

ASSESSMENT OF CAROTENOIDS

Impact of Carotenoid Assessment

Because carotenoids appear to play a key role in retinal diseases, intensive research has resulted in a variety of innovative carotenoid assessment techniques. The breadth of possibilities for assessing retinal carotenoids is often confusing because methodologies, units of measurement, and the presentation of results vary widely. Accurate readings of carotenoid status are important in order to correctly advise individuals with regards to supplementation. Furthermore, in diseases such as macular telangiectasia type 2 (MacTel), the assessment of carotenoids may be crucial to the diagnosis, as reduced MP levels as well as abnormal distributions are among the first signs of the disease. Therefore, the measurement of carotenoids can impact clinical practice, and the evaluation of MP may eventually become an integral part of comprehensive ophthalmological care. The following sections describe and aim to give an organized overview of different MP assessment techniques.

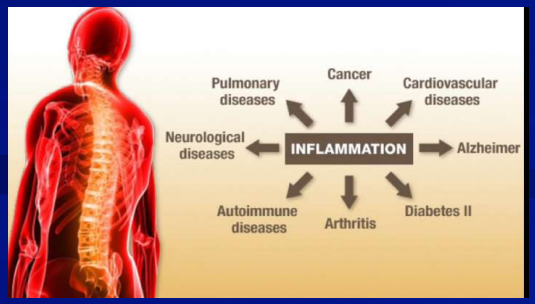
A large variety of methods are used to assess carotenoid status in humans, most of which are focused on the eye, but carotenoids can also be measured in tissue outside of the eye, such as the skin, blood, and the brain. Measurements of ocular carotenoids can be distinguished between subjective (psychophysical) and objective (optical) methods used to assess the amount of MP. In subjective methods, a direct answer from the patient is required, whereas objective measurement methods typically require just enough cooperation to generate an image (73).

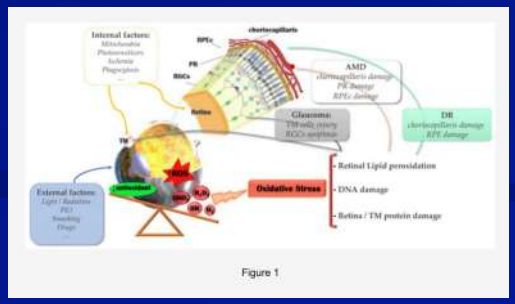
Carotenoids in Tissues Other Than the Eye

Carotenoids can be assessed noninvasively in the skin and by high-performance liquid chromatography (HPLC) of blood and tissue samples. It has been shown that RRS measurements of skin carotenoids show strong correlations ($r = 0.7$ to 0.9) with carotenoids in biopsies of human skin

(57, 96). Skin RRS and reflectometry are particularly useful to assess the carotenoid status of children, with skin carotenoid levels strongly associated with fruit and vegetable intake (123). Using HPLC, the carotenoid status in the plasma can also be assessed (77, 104), and higher L levels in the serum of patients have been associated with higher visual function. Similarly, carotenoid assessment in brain tissue suggests that higher carotenoid levels might be beneficial for overall cognitive performance (65, 74).

Chronic and Low-Grade Inflammation





DNA Sciences

- Genomics = all of our genes
- Genetics = individual genes

- Epigenetics – the study of how our cells control gene activity without changing the DNA
  - Internal and external environments

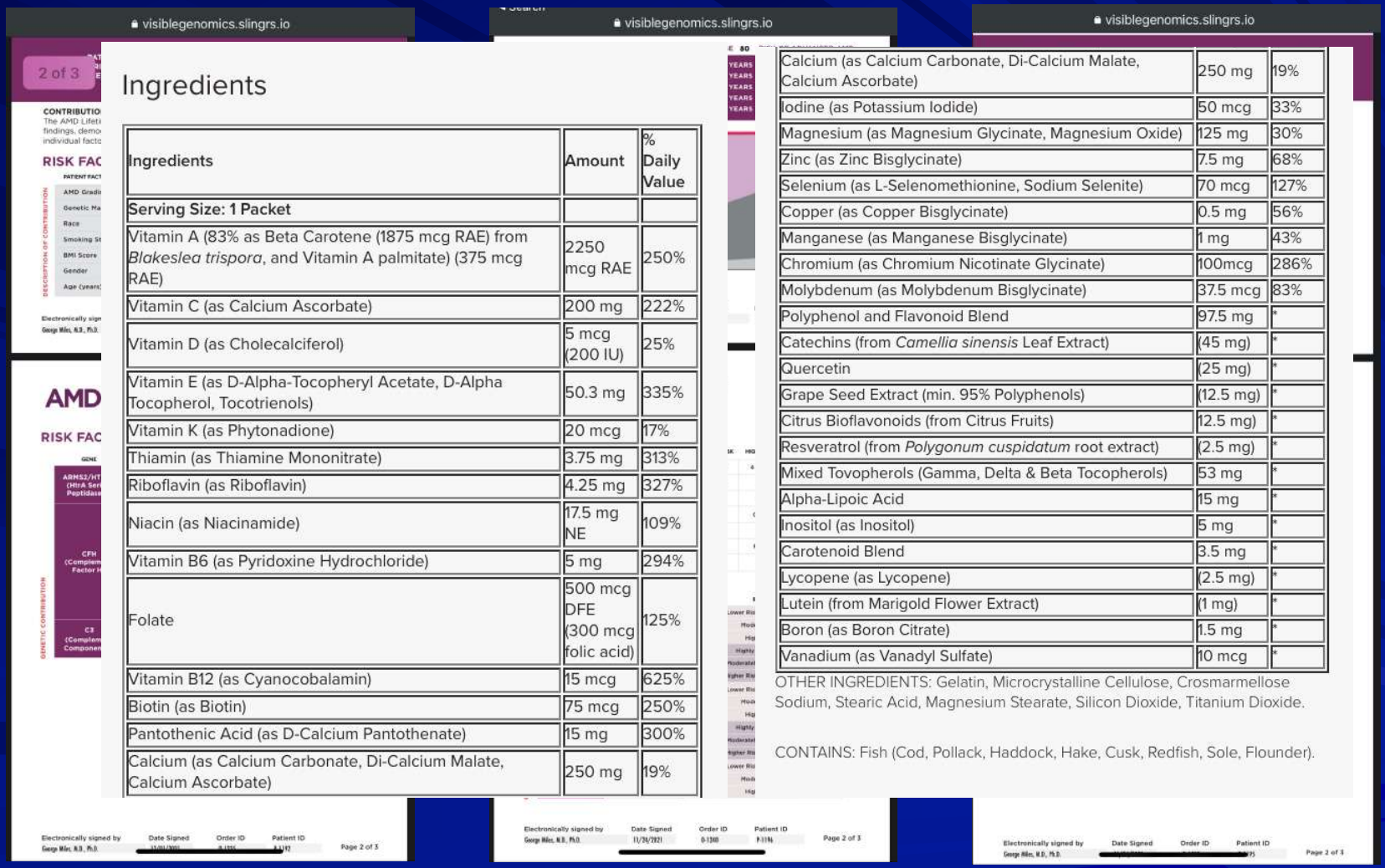
Exposome

The exposome can be defined as **the measure of all the exposures of an individual in a lifetime and how those exposures relate to health**. An individual's exposure begins before birth and includes insults from environmental and occupational sources. Understanding how exposures from our environment, diet, lifestyle, etc.

CDC https://www.cdc.gov › niosh › topics

Exposome and Exposomics - NIOSH Workplace Safety and Health Topic - CDC

Google Search Definition

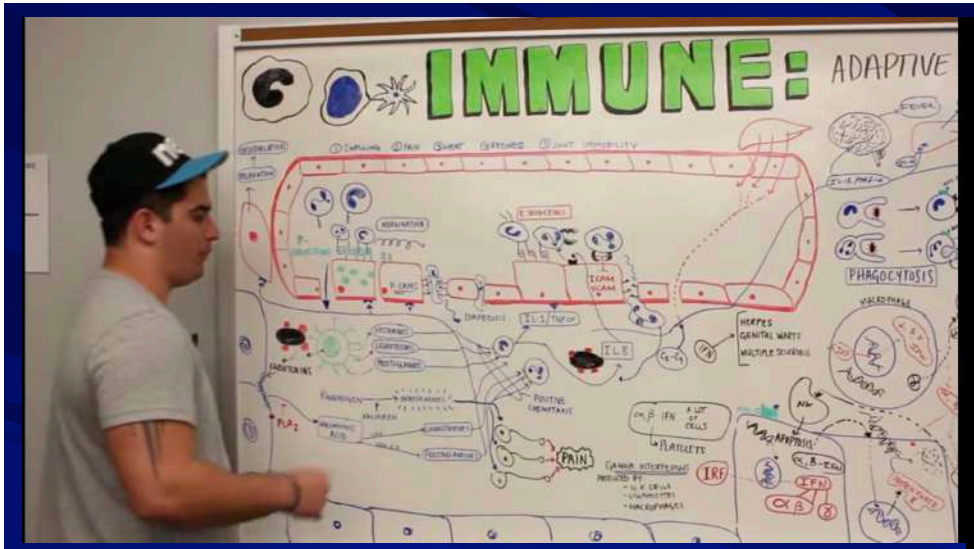


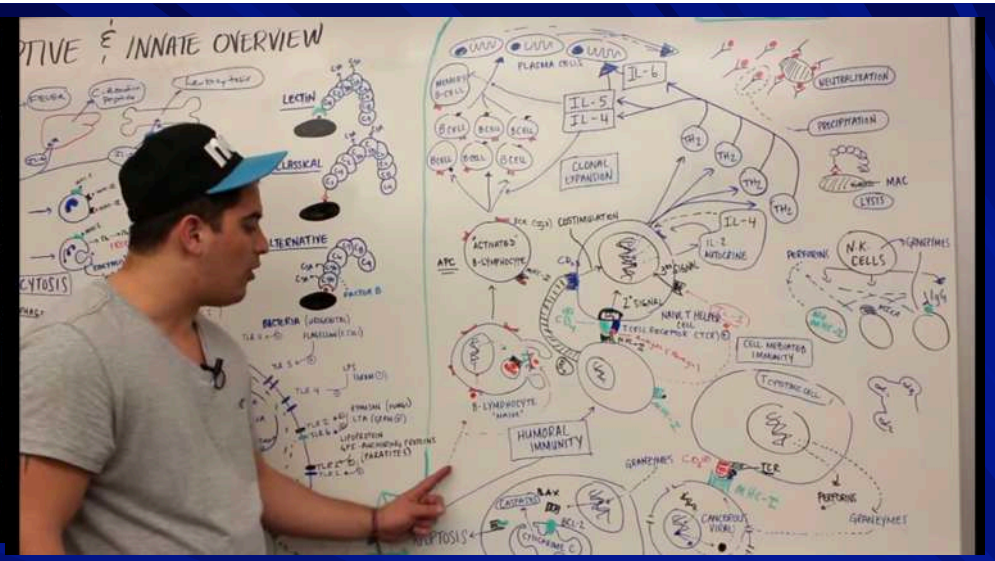
Ingredients

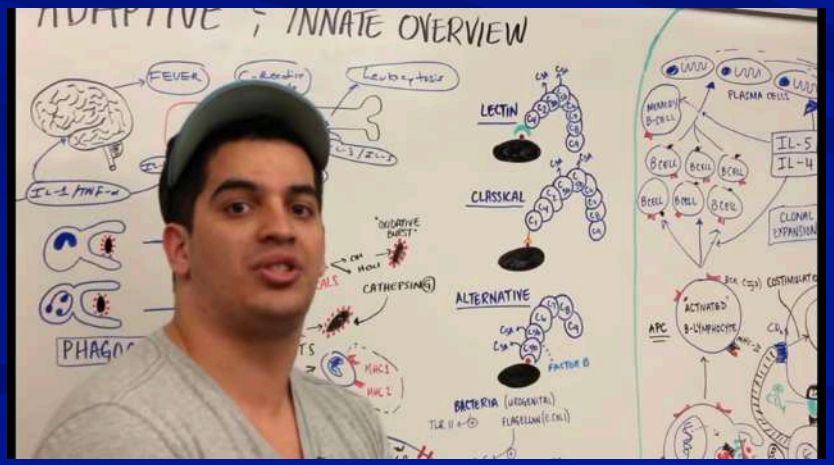
Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	7.5 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	*
Catechins (from *Camellia sinensis* Leaf Extract)	(45 mg)	*
Quercetin	(25 mg)	*
Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	*
Resveratrol (from *Polygonum cuspidatum* root extract)	(2.5 mg)	*
Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	3.5 mg	*
Lycopene (as Lycopene)	(2.5 mg)	*
Lutein (from Marigold Flower Extract)	(1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	10 mcg	*

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).







Ninja Nerd Science
YouTube

Complement factor H in AMD: Bridging genetic associations and pathobiology

Christopher B. Toomey [a, b, 1] ... Catherine Bowes Rickman [a, b]

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https://doi.org/10.1016/j.preteyeres.2017.09.001

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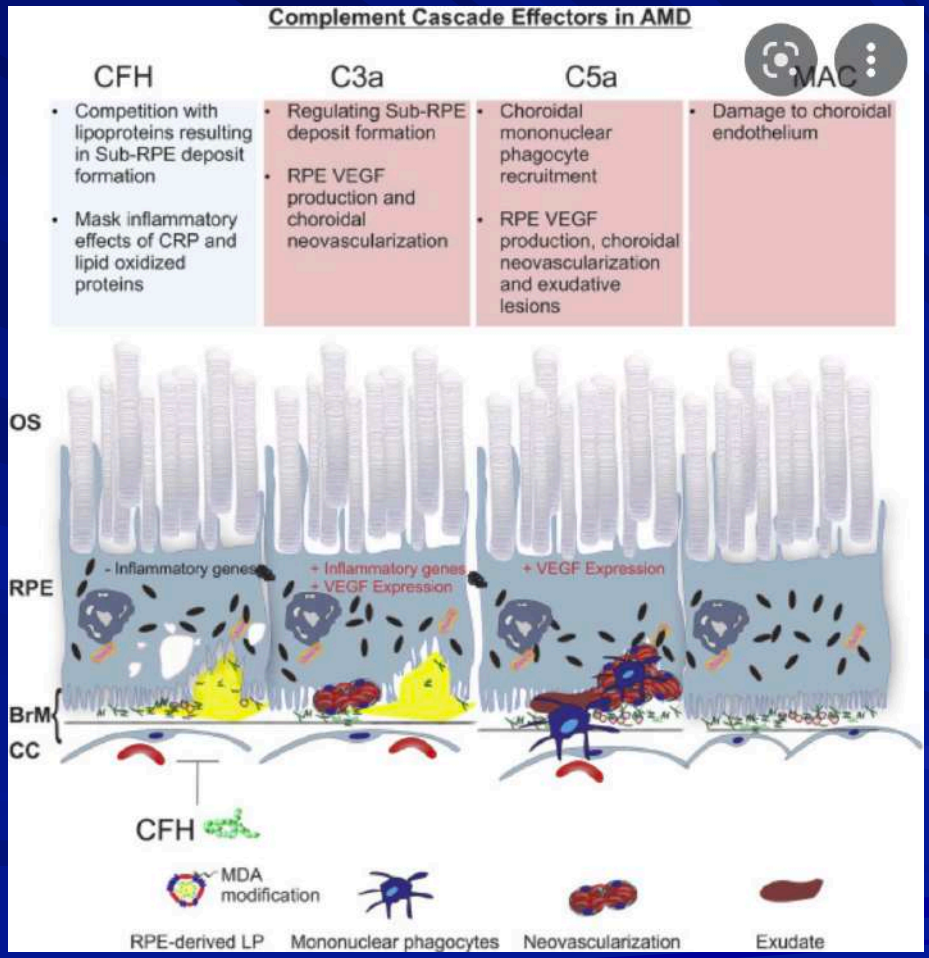
Abstract

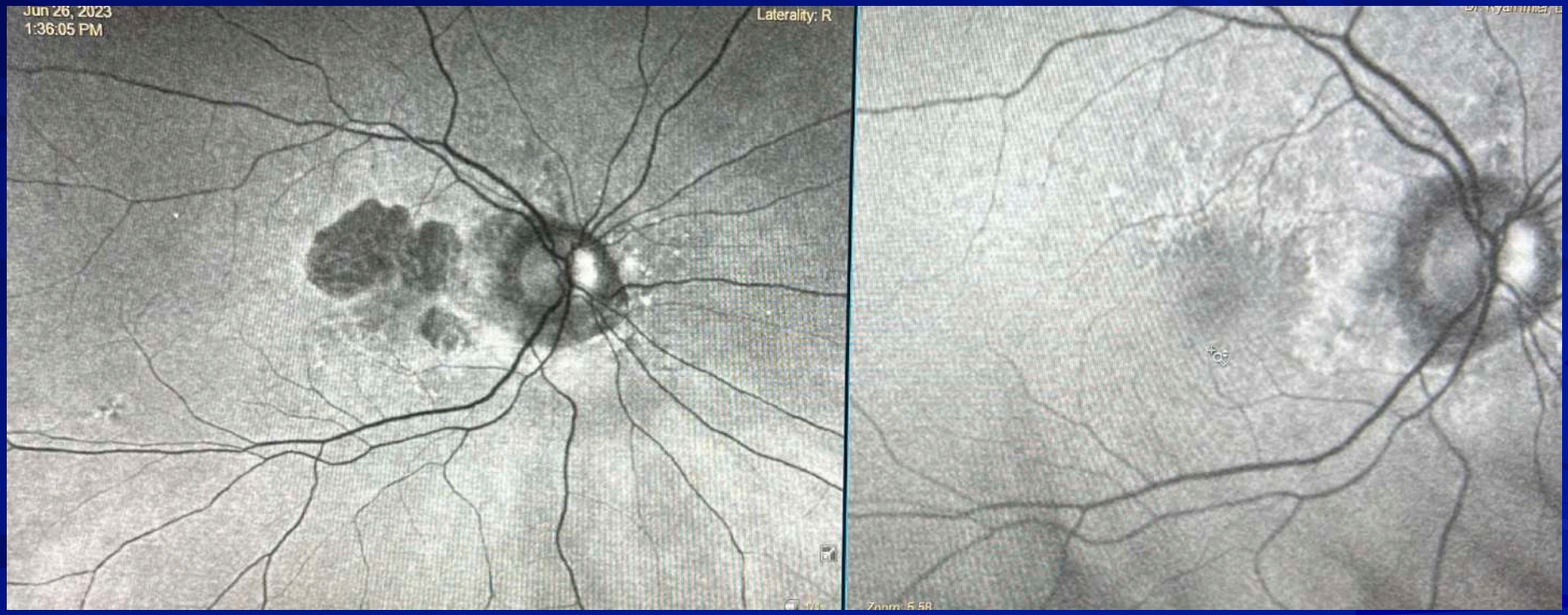
Age-Related Macular Degeneration (AMD) is a complex multifactorial disease characterized in its early stages by lipoprotein accumulations in Bruch's Membrane (BrM), seen on fundoscopic exam as drusen, and in its late forms by neovascularization ("wet") or geographic atrophy of the Retinal Pigmented Epithelial (RPE) cell layer ("dry"). Genetic studies have strongly supported a relationship between the alternative complement cascade, in particular the common H402 variant in Complement Factor H (CFH) and development of AMD. However, the functional significance of the CFH Y402H polymorphism remains elusive. In this

FEEDBACK

sciencedirect.com



Geographic Atrophy



Syfovre (pegcetacoplan injection)

- Apellis- indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)
  - First approved for treatment of GA
- Macular degeneration is associated with overaction of the complement system
- C3 activation – inflammation, phagocytosis, cell membrane disruption
- C3 inhibitor is mechanism of action (MOA)
  - Synthetic, peptide-based inhibitor of C3
  - Prevents overactivation

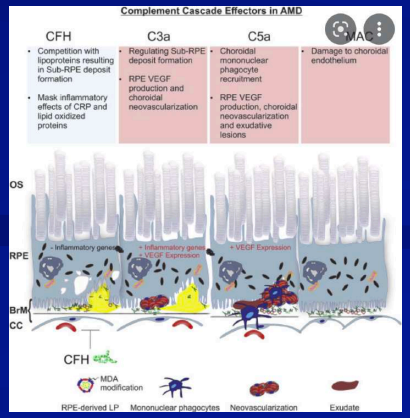
https://syfovreecp.com/how-syfovre-works/

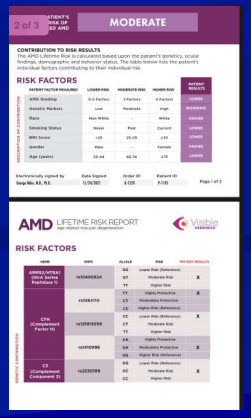
Avacincaptad pegol injection

- Iveric Bio - Research, preclinical, Phase 1, 2, 3, under FDA review for geographic atrophy
- PEGylated RNA aptamern
- Phase 3 for autosomal recessive Stargardt disease
- Mechanism of Action (MOA) inhibition of complement component C5
  - ★ Overaction or dysregulated complement system

Evidence Informed Risk Adjusted Medicine

Evidence Based Medicine





Ingredients

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Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
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Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
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Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
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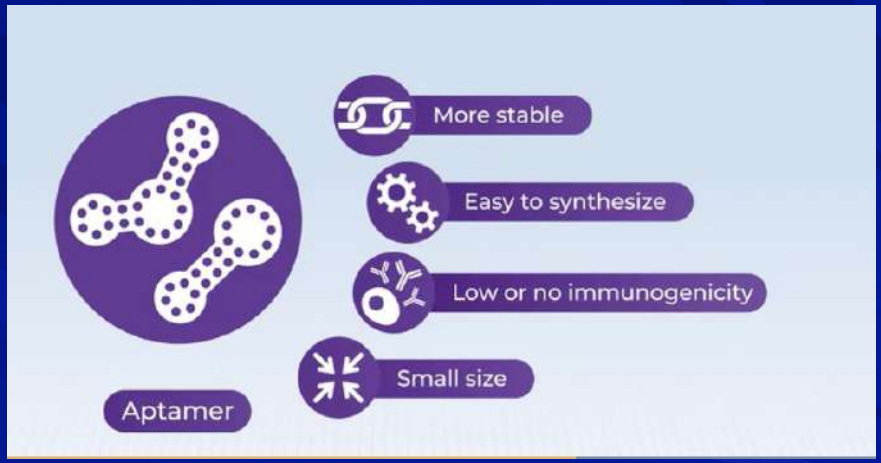
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	†
Catechins (from *Camellia sinensis* Leaf Extract)	(45 mg)	†
Quercetin	(25 mg)	†
Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	†
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg	†
Resveratrol (from *Polygonum cuspidatum* root extract)	12.5 mg	†
Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	†
Alpha-Lipoic Acid	15 mg	†
Inositol (as Inositol)	5 mg	†
Carotenoid Blend	3.5 mg	†
Lycopene (as Lycopene)	(2.5 mg)	†
Lutein (from Marigold Flower Extract)	(1 mg)	†
Boron (as Boron Citrate)	1.5 mg	†
Vanadium (as Vanadyl Sulfate)	10 mcg	†

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

Aptamer versus Antibody



Hope you enjoyed your lunch

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Home » Research at NEI » Clinical Trials » Age-Related Eye Disease Studies (AREDS/AREDS2) » AREDS/AREDS2 Frequently Asked Questions

AREDS/AREDS2 Frequently Asked Questions

Ingredients

Supplement Facts

Serving Size 2 Capsules — Servings per Container 30

Amount Per Serving		% Daily Value
Vitamin C (Ascorbic Acid)	500 mg	833%
Vitamin E (d-Alpha Tocopheryl Succinate)	200 IU	667%
Zinc (Zinc Gluconate)	25 mg	167%
Copper (Copper Gluconate)	2 mg	100%
Selenium (L-Selenomethionine)	70 mcg	100%
Lutein (from Marigold Flower Extract)	10 mg	*
Zeaxanthin (from Marigold Flower Extract)	2 mg	*

*Daily Values not established.

Other Ingredients: Gelatin, Microcrystalline Cellulose, Stearic Acid, Silicon Dioxide, Magnesium Stearate.

What is the basis for the concentration of zinc in the AREDS supplements? What concentration should I take?

In the AREDS trial, the 80 mg zinc dose (alone or in combination with antioxidant vitamins) was found to be effective compared to a placebo. Although zinc was found to be an essential component of the AREDS formulation, some nutritional experts recommended a lower dose. In the AREDS2 trial, there was no placebo control. Instead, participants were given the option to take the original formula or to be randomly assigned to receive a modified version, such as a formula containing 25 mg zinc. The investigators did not find a difference in the effects of 80 mg vs. 25 mg zinc. Because AREDS2 did not include a placebo control, results from AREDS, placebo-controlled trial, are still considered the gold standard.

Zinc is found in vegetables, grains, and meat. Vegetables and grains contain other molecules that can prevent zinc absorption and thus reduce its bioavailability. Supplements contain purified zinc, without these competing molecules. Although the chemical form of zinc affects its rate of absorption in the stomach, it is not clear how this affects bioavailability (i.e., the amount of zinc that reaches the retina). For more on this topic, please see the zinc fact sheet from the NIH Office of Dietary Supplements.

PubMed.gov

Advanced

Randomized Controlled Trial

Treatment response to antioxidants and zinc based on CFH and ARMS2 genetic risk allele number in the Age–Related Eye Disease Study

Carl C Awh et al. Ophthalmology. 2015 Jan.

Show details

Full text links | Cite | ...

Abstract

Objective: To evaluate the impact of complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) risk alleles on the observed response to components of the Age-Related Eye Disease Study (AREDS) formulation.

Design: Genetic and statistical subgroup analysis of a randomized, prospective clinical trial.

Participants: White patients from the AREDS with category 3 or 4 age-related macular degeneration (AMD) with available DNA (n = 989).

Results: Patients with 2 CFH risk alleles and no ARMS2 risk alleles progressed more with zinc-containing treatment compared with placebo, with a hazard ratio (HR) of 3.07 (P = 0.0196) for zinc and 2.73 (P = 0.0418) for AREDS formulation (AF). Seven-year treatment-specific progression rates were: placebo, 17.0%; zinc, 43.2% (P = 0.023); and AF, 40.2% (P = 0.039). Patients with 0 or 1 CFH risk alleles and 1 or 2 ARMS2 risk alleles benefited from zinc-containing treatment compared with placebo, with an HR of 0.514 for zinc (P = 0.012) and 0.569 for AF (P = 0.0254). Seven-year treatment-specific AMD progression rates were as follows: placebo, 43.3%; zinc, 25.2% (P = 0.020); and AF, 27.3% (P = 0.011). Zinc and AF treatment each interacted statistically with these 2 genotype groups under a Cox model, with P values of 0.000999 and 0.00366, respectively. For patients with 0 or 1 CFH risk alleles and no ARMS2 risk alleles, neither zinc-containing treatment altered progression compared with placebo, but treatment with antioxidants decreased progression (HR, 0.380; P = 0.034). Seven-year progression with placebo was 22.6% and with antioxidants was 9.17% (P = 0.033). For patients with 2 CFH risk alleles and 1 or 2 ARMS2 risk alleles, no treatment was better than placebo (48.4%).

Conclusions: The benefit of the AREDS formulation seems the result of a favorable response by patients in only 1 genotype group, balanced by neutral or unfavorable responses in 3 genotype groups.

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RESEARCH ARTICLE | OPEN ACCESS

CFH and *ARMS2* genetic risk determines progression to neovascular age-related macular degeneration after antioxidant and zinc supplementation

Demetrios G. Vavvas, Kent W. Small, Carl C. Awh, +2, and Rafal Kustra Authors Info & Affiliations

January 8, 2018 | 115 (4) E696-E704

https://doi.org/10.1073/pnas.1718059115

Genetic Polymorphisms of *CFH* and *ARMS2* Do Not Predict Response to Antioxidants and Zinc in Patients with Age-Related Macular Degeneration

Independent Statistical Evaluations of Data from the Age-Related Eye Disease Study

Melissa J. Assel, MS,[1,2] Fan Li, MS,[1,2] Ying Wang, PhD,[1,2] Andrew S. Allen, PhD,[1,2] Kirk A. Baggerly, PhD,[3,4] Andrew J. Vickers, PhD[1,2]

Purpose: Considerable controversy has erupted in recent years regarding whether genotyping should be part of standard care for patients with age-related macular degeneration (AMD) who are being considered for treatment with antioxidants and zinc. We aimed to determine whether genotype predicts response to supplements in AMD.

Design: Three separate statistical teams reanalyzed data derived from the Age-Related Eye Disease Study (AREDS), receiving data prepared by the AREDS investigators and, separately, data from investigators reporting findings that support the use of genotyping.

Participants: The population of interest was AREDS participants with AMD worse than category 1 and genotyping data available. Data from the 2 groups overlap imperfectly with respect to measurements made; the largest common set involved 979 participants for whom the same *CFH* and *ARMS2* single nucleotide polymorphisms were measured by both groups.

Methods: Each team took a separate but complementary approach. One team focused on data concordance between conflicting studies. A second team focused on replicating the key claim of an interaction between genotype and treatment. The third team took a blank slate approach in attempting to find baseline predictors of treatment response.

Main Outcome Measures: Progression to advanced AMD.

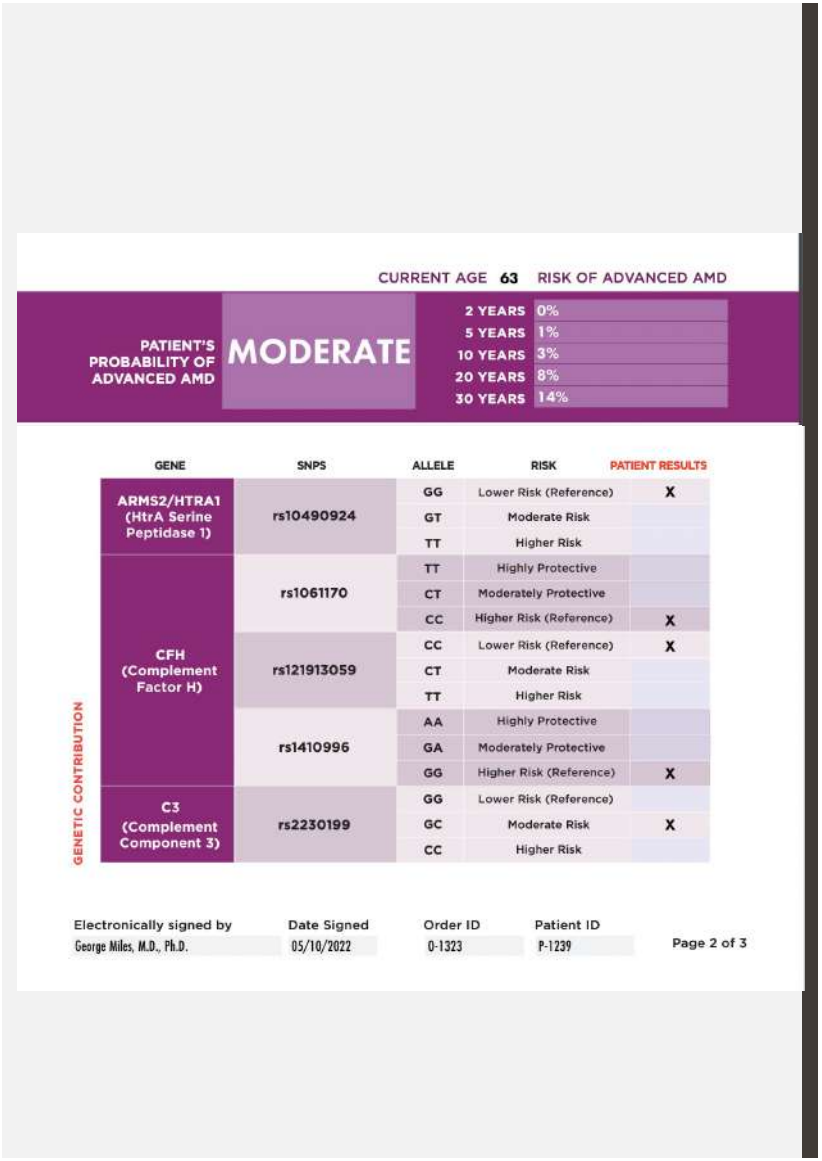
Results: We found errors in the data used to support the initial claim of genotype–treatment interaction. Although we found evidence that high-risk patients had more to gain from treatment, we were unable to replicate any genotype–treatment interactions after adjusting for multiple testing. We tested 1 genotype claim on an independent set of data, with negative results. Even if we assumed that interactions in fact did exist, we did not find evidence to support the claim that supplementation leads to a large increase in the risk of advanced AMD in some genotype subgroups.

Conclusions: Patients who meet criteria for supplements to prevent AMD progression should be offered zinc and antioxidants without consideration of genotype. Ophthalmology 2018;125:397–397 © 2017 by the American Academy of Ophthalmology

Supplemental material available at www.aaojournal.org.

The Age-Related Eye Disease Study (AREDS) was a large, multicenter, double-blind randomized trial to determine whether high-dose antioxidants, zinc, or their combination could reduce the risk of progression of age-related macular degeneration (AMD) in older patients. Excluding patients in AMD category 1, for whom the event rate was less than 1%, the combination of zinc and antioxidants was found to reduce the risk of progression to advanced AMD (odds ratio, 0.68; 95% confidence interval [CI], 0.49–0.93; $P = 0.002$).[1] The publication of the trial results led to rapid changes in practice, with at-risk patients routinely prescribed the zinc and antioxidant combination noted in the trial.

In 2008, Klein et al[2] published a pharmacogenomic study suggesting that the effects of antioxidants and zinc on AMD in AREDS may be influenced by genotype,



CURRENT AGE 63 RISK OF ADVANCED AMD

PATIENT'S PROBABILITY OF ADVANCED AMD: MODERATE

2 YEARS	0%
5 YEARS	1%
10 YEARS	3%
20 YEARS	8%
30 YEARS	14%

GENETIC CONTRIBUTION

GENE	SNPS	ALLELE	RISK	PATIENT RESULTS
ARMS2/HTRA1 (HtrA Serine Peptidase 1)	rs10490924	GG	Lower Risk (Reference)	X
		GT	Moderate Risk	
		TT	Higher Risk	
CFH (Complement Factor H)	rs1061170	TT	Highly Protective	
		CT	Moderately Protective	
		CC	Higher Risk (Reference)	X
	rs121913059	CC	Lower Risk (Reference)	X
		CT	Moderate Risk	
		TT	Higher Risk	
	rs1410996	AA	Highly Protective	
		GA	Moderately Protective	
		GG	Higher Risk (Reference)	X
C3 (Complement Component 3)	rs2230199	GG	Lower Risk (Reference)	
		GC	Moderate Risk	X
		CC	Higher Risk	

Electronically signed by	Date Signed	Order ID	Patient ID
George Miles, M.D., Ph.D.	05/10/2022	0-1323	P-1239

Page 2 of 3

Raise Your Hand

Would you recommend AREDS 2 or a supplement high dose Zinc?

A. Yes
B. No

Results: Patients with 2 CFH risk alleles and no ARMS2 risk alleles progressed more with zinc-containing treatment compared with placebo, with a hazard ratio (HR) of 3.07 (P = 0.0196) for zinc and 2.73 (P = 0.0418) for AREDS formulation (AF). Seven-year treatment-specific progression rates were: placebo, 17.0%; zinc, 43.2% (P = 0.023); and AF, 40.2% (P = 0.039). Patients with 0 or 1 CFH risk alleles and 1 or 2 ARMS2 risk alleles benefited from zinc-containing treatment compared with placebo, with an HR of 0.514 for zinc (P = 0.012) and 0.569 for AF (P = 0.0254). Seven-year treatment-specific AMD progression rates were as follows: placebo, 43.3%; zinc, 25.2% (P = 0.020); and AF, 27.3% (P = 0.011). Zinc and AF treatment each interacted statistically with these 2 genotype groups under a Cox model, with P values of 0.000999 and 0.00366, respectively. For patients with 0 or 1 CFH risk alleles and no ARMS2 risk alleles, neither zinc-containing treatment altered progression compared with placebo, but treatment with antioxidants decreased progression (HR, 0.380; P = 0.034). Seven-year progression with placebo was 22.6% and with antioxidants was 9.17% (P = 0.033). For patients with 2 CFH risk alleles and 1 or 2 ARMS2 risk alleles, no treatment was better than placebo (48.4%).

Conclusions: The benefit of the AREDS formulation seems the result of a favorable response by patients in only 1 genotype group, balanced by neutral or unfavorable responses in 3 genotype groups.

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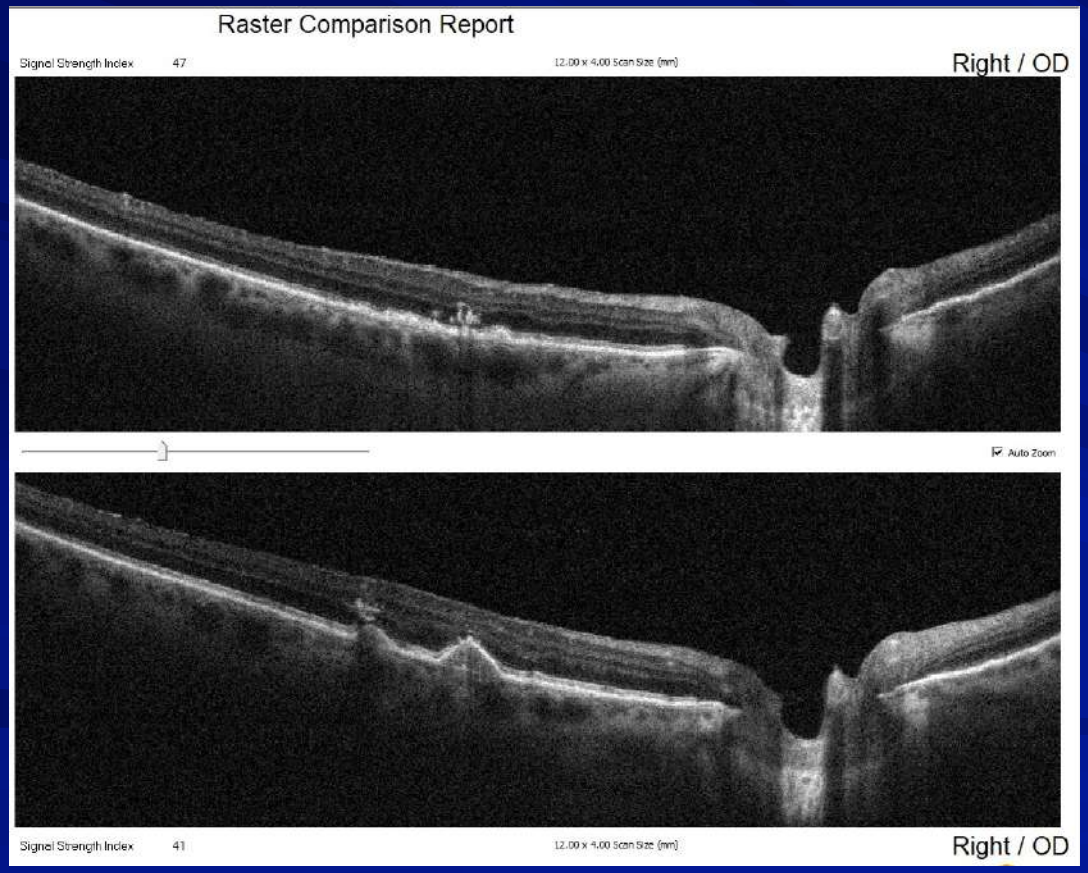
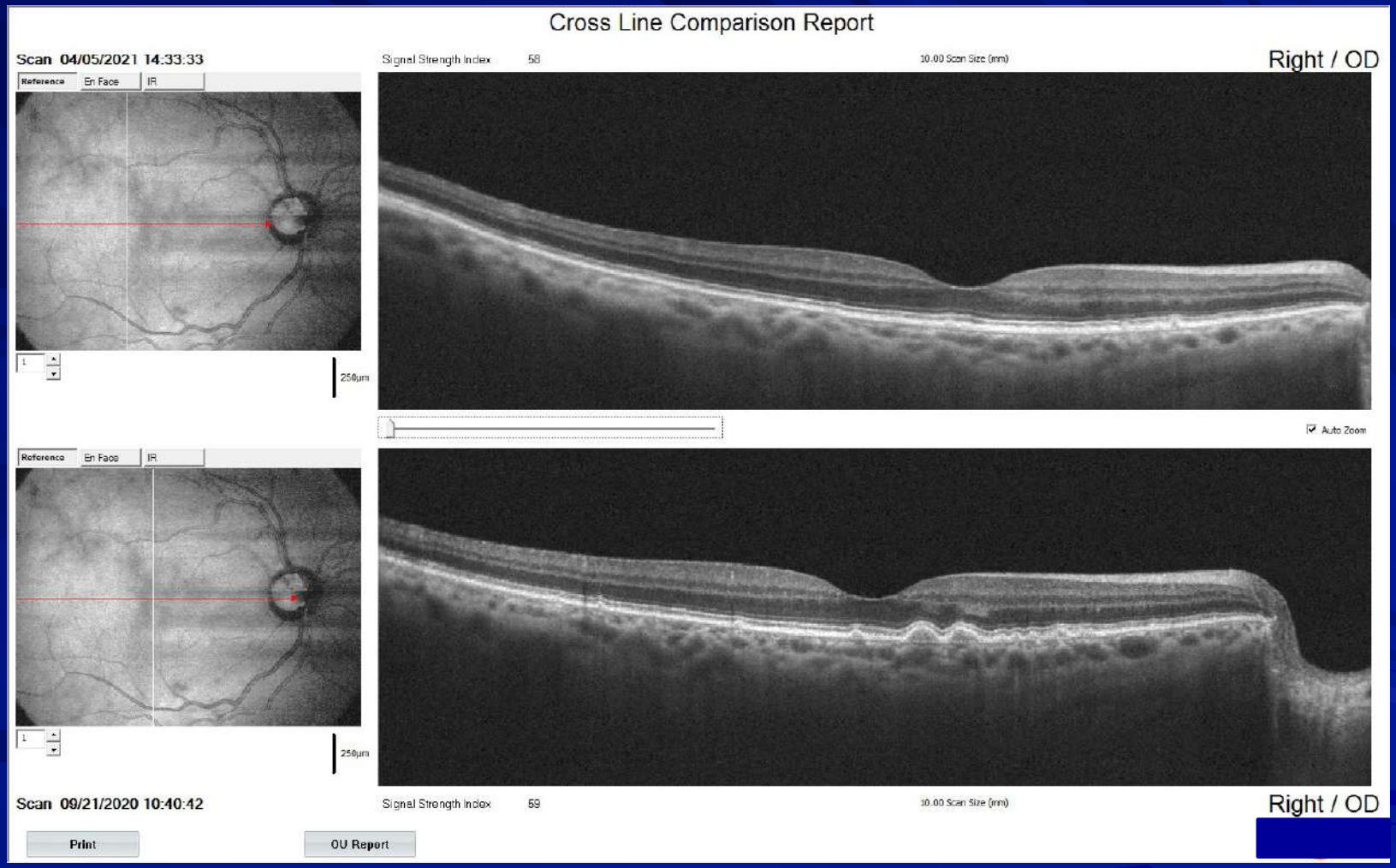
April 27, 2021 – January 26, 2022 (9 months)



Melonie Clemmons, OD
May 20, 2022 AACO Nashville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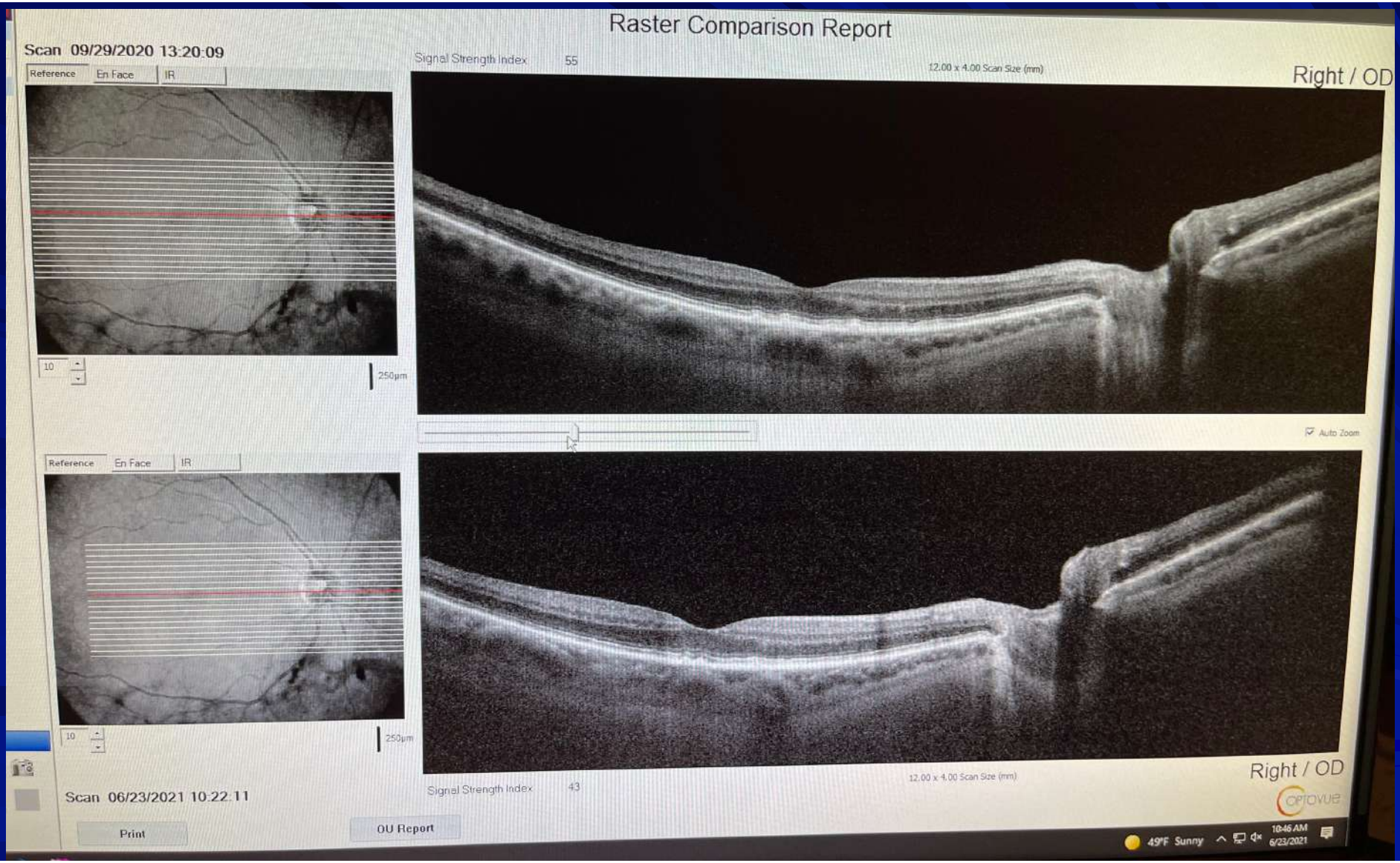
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IR
10
250µm
Scan 06/23/2021 10:22:11
Signal Strength Index 43
12.00 x 4.00 Scan Size (mm)
Right / OD
OPTOVUE
Print
OU Report
49°F Sunny
10:46 AM
6/23/2021

Ingredients

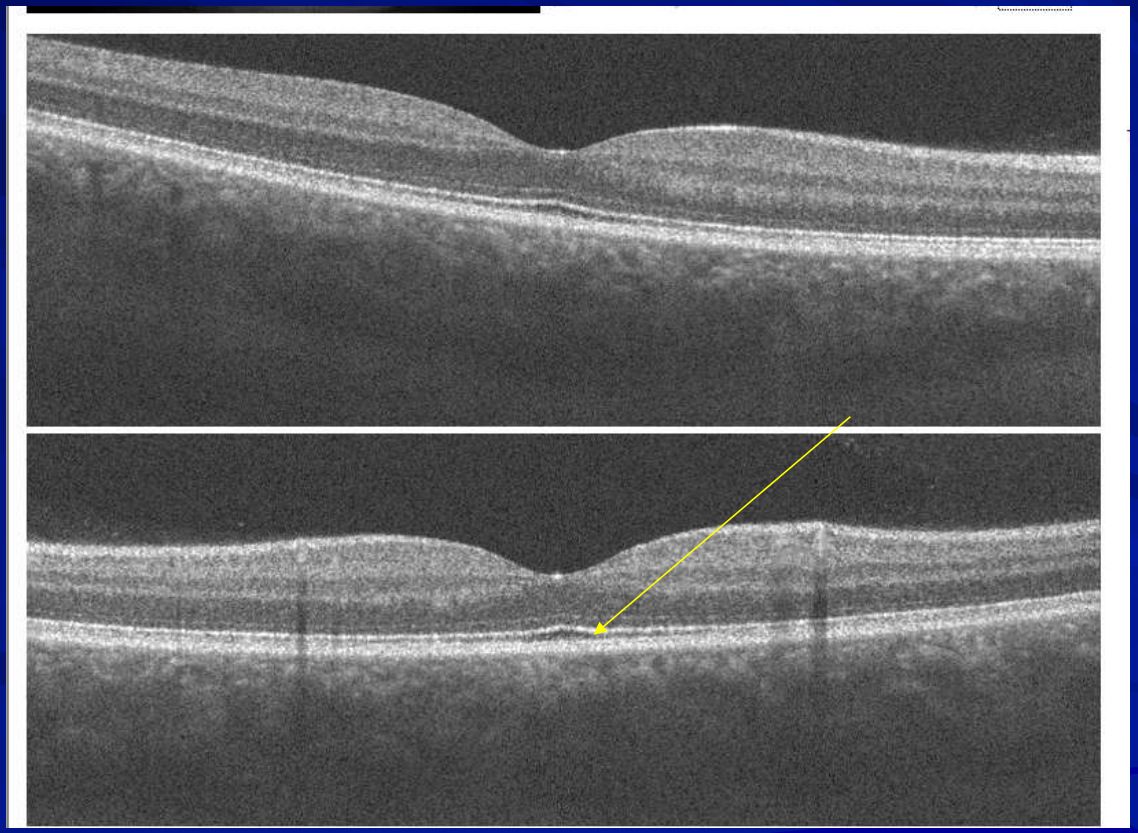
Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	7.5 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	*
Catechins (from *Camellia sinensis* Leaf Extract)	(45 mg)	*
Quercetin	(25 mg)	*
Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	*
Resveratrol (from *Polygonum cuspidatum* root extract)	(2.5 mg)	*
Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	3.5 mg	*
Lycopene (as Lycopene)	(2.5 mg)	*
Lutein (from Marigold Flower Extract)	(1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	10 mcg	*

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

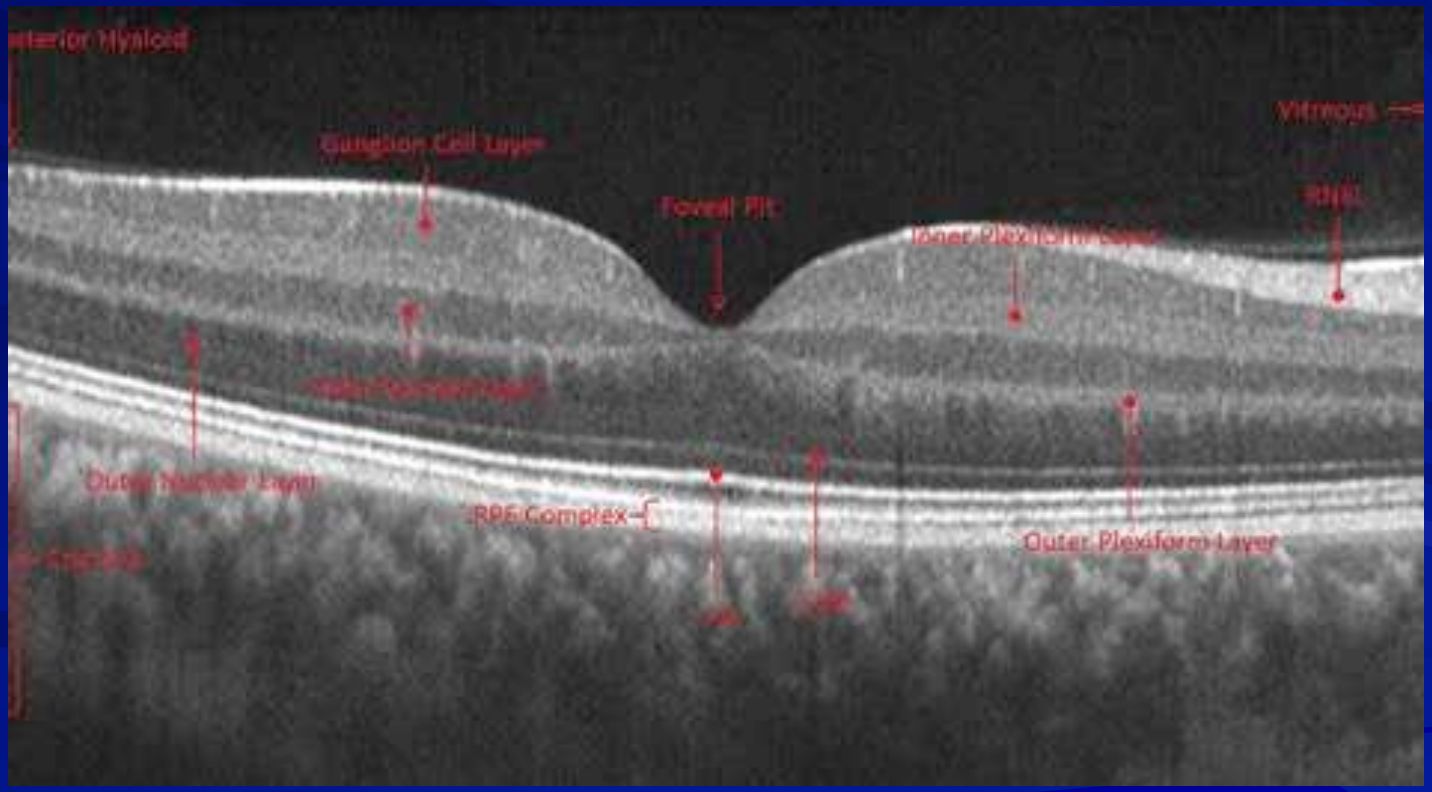
CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

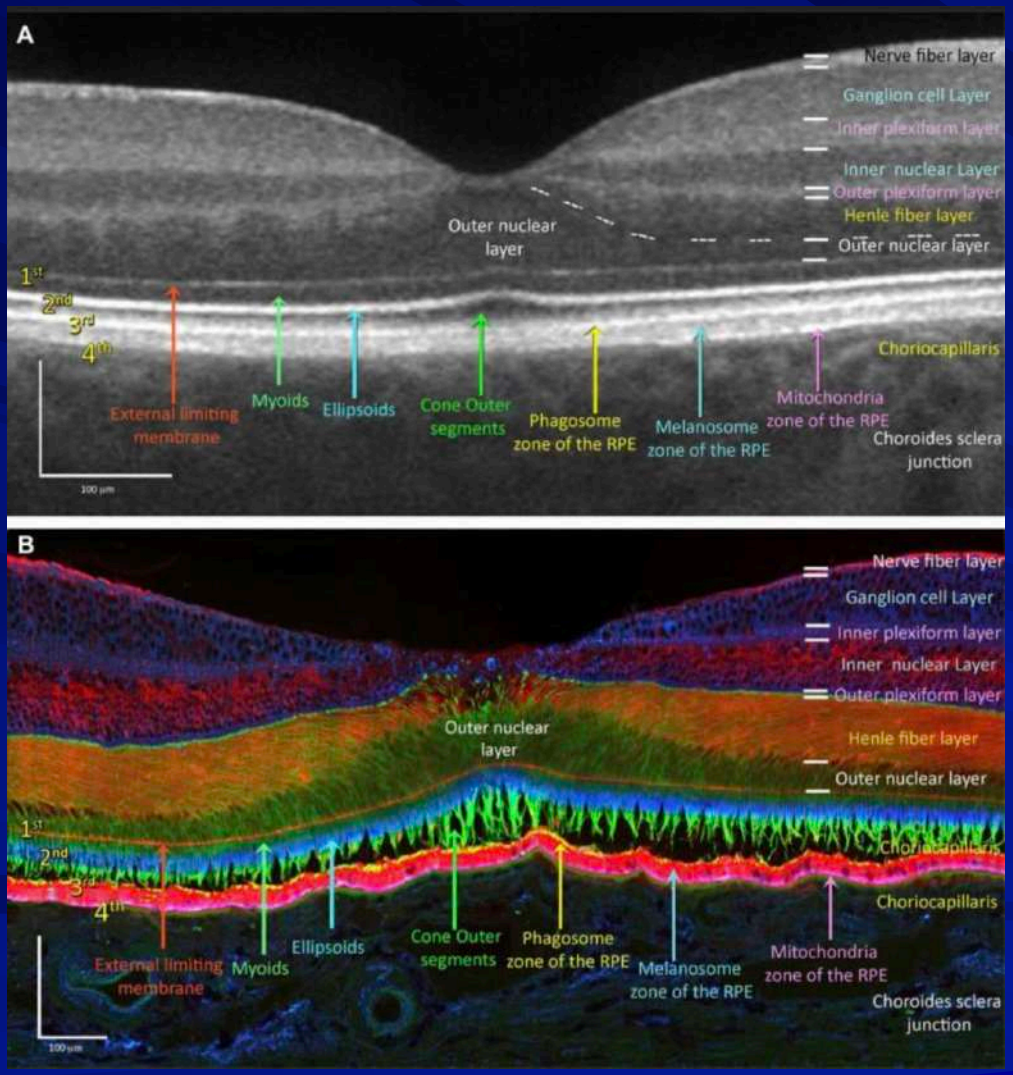
Credit to: James LaValle, RPh, CCN

What is this layer called?



The ellipsoid zone (EZ) is considered to be **formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors**. However, it was previously known as the junction between the photoreceptor IS/OS).





Progress in Retinal and Eye Research
Volume 77, July 2020, 100828

Interpretation of OCT and OCTA images from a histological approach: Clinical and experimental implications

Nicolás Cuenca [a, b, 1] ... Isabel Pinilla [f, 1]

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https://doi.org/10.1016/j.preteyeres.2019.100828

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Abstract

Optical coherence tomography (OCT) and OCT angiography (OCTA) have been a techn

FEEDBACK

Fun Facts I Have Learned About the Mitochondria

- Mitochondria produce energy from organic matter
- Live about 100 days
- They produce 90% of energy in the body
- In return they product 90% of the free radicals
- When they become dysfunction when get many clinical consequences
- Mitochondria are very sensitive to reactive oxygen and need antioxidant support
- Mitochondria are one of cellular organelles
  - Electron transport chain – uses co-enzyme 10, and many other micronutrients
  - Brain cell has 1-2 million/single neuron
  - Heart cell has 5,000/cell
  - Liver cell has 1000-2000/cell
  - Photoreceptors 498/cell
  - RPE cells >700/cell


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doi: 10.1016/j.neuron.2017.09.055

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NIHMSID: NIHMS909951
PMID: 29096078

Mitostasis in neurons: Maintaining mitochondria in an extended cellular architecture

Thomas Misgeld[1,2,3,4] and Thomas L. Schwarz[5,6]

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Article | Open Access | Published: 22 September 2021

The 3D organisation of mitochondria in primate photoreceptors

Matthew J. Hayes, Dhani Tracey-White, Jaime Hoh Kam, Michael B. Powner & Glen Jeffery

Scientific Reports 11, Article number: 18863 (2021) | Cite this article

913 Accesses | 21 Altmetric | Metrics

The ellipsoid contains a densely-packed array of mostly elongated mitochondria arranged broadly parallel to the long axis of the photoreceptor. The cell contained **498 individual mitochondria**

Mitochondria

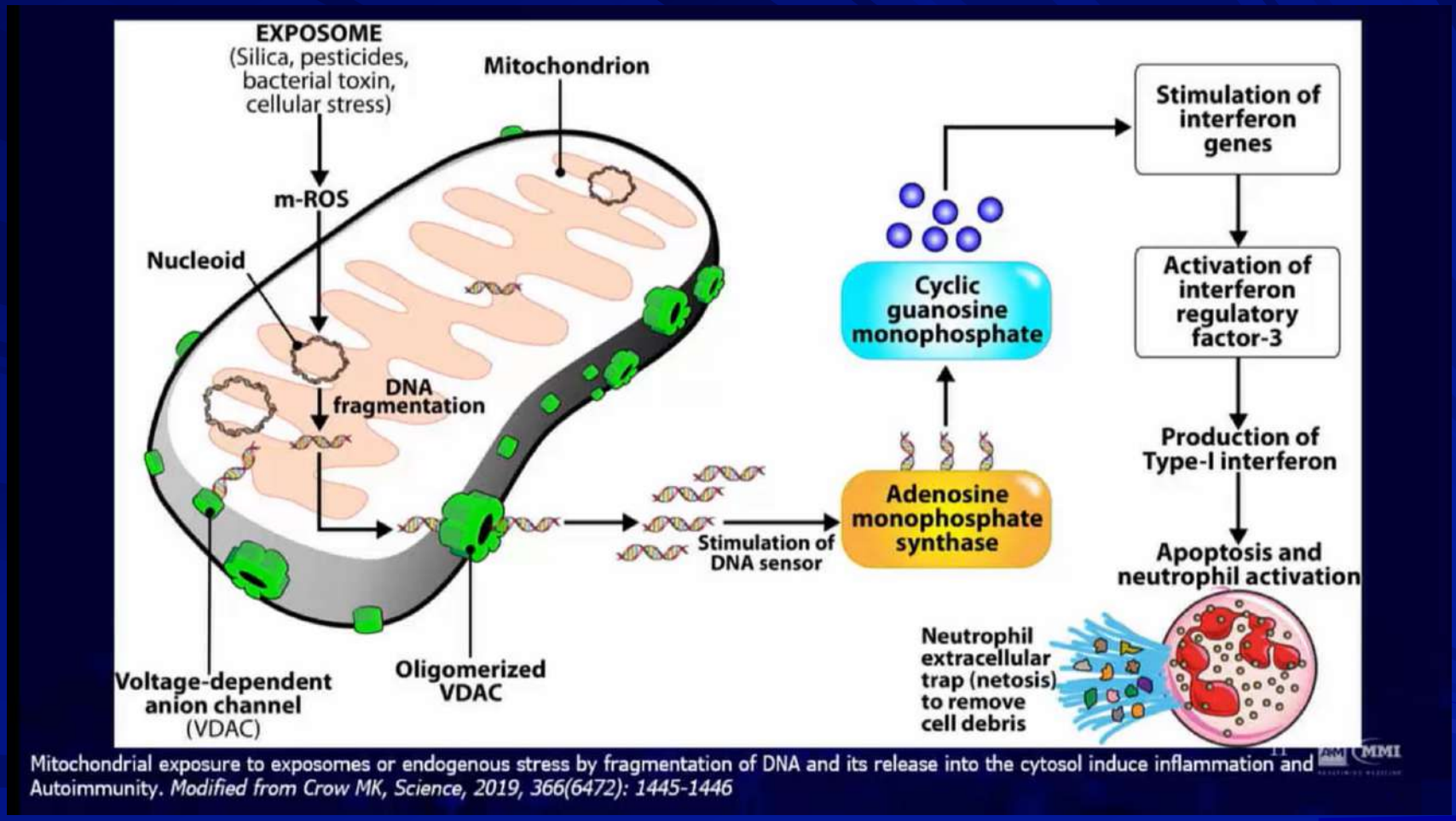
- Exercise help and increases the mitochondria
- Burn both glucose and fat
  - Metabolic flexibility
- Type 2 DM – does a number to the mitochondria
  - Burn only glucose and glycogen
  - Unable to access fat storage
- Great news they are plastic and malleable

Inflamm-aging

One of the consequences of failing mitochondria due to aging, beyond mtROS, is the release of mtDNA. Plasma levels of mtDNA increase gradually after the fifth decade of life, correlating with elevated levels of pro-inflammatory cytokines (i.e., TNF-α, IL-6, RANTES, and IL-1ra)

These data indicate that mtDNA may promote the production of pro-inflammatory cytokines in aging. Because cell stress, senescence and death are a part of the pathophysiology of aging designing new therapeutic strategies against circulating mtDNA, or other mtDAMPs, or their cognate receptors (e.g., TLRs or FPR1) may be a viable strategy to approaching IA and its associated conditions.

Credit to: Elroy Vojdani, MD - Dead Batteries: The Role of Mitochondrial Dysfunction in Immunological Decline - Emerging Diagnostic Tools and Nutraceutical Interventions



Mitochondrial exposure to exposomes or endogenous stress by fragmentation of DNA and its release into the cytosol induce inflammation and Autoimmunity. *Modified from Crow MK, Science, 2019, 366(6472): 1445-1446*

Credit to: Elroy Vojdani, MD - Dead Batteries: The Role of Mitochondrial Dysfunction in Immunological Decline - Emerging Diagnostic Tools and Nutraceutical Interventions

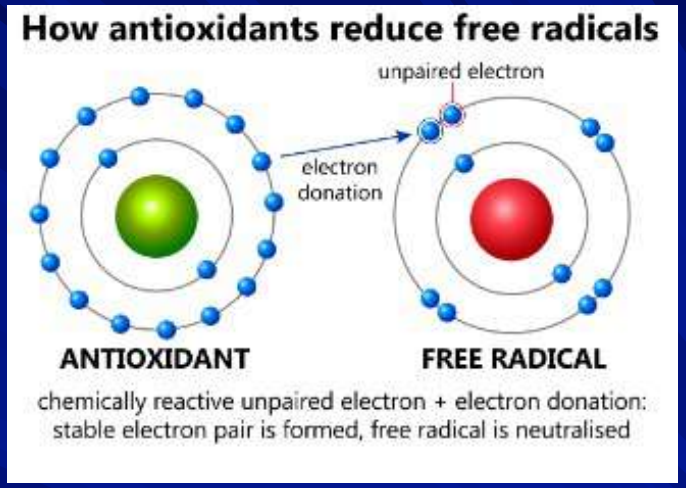
Optometric Education Consultants

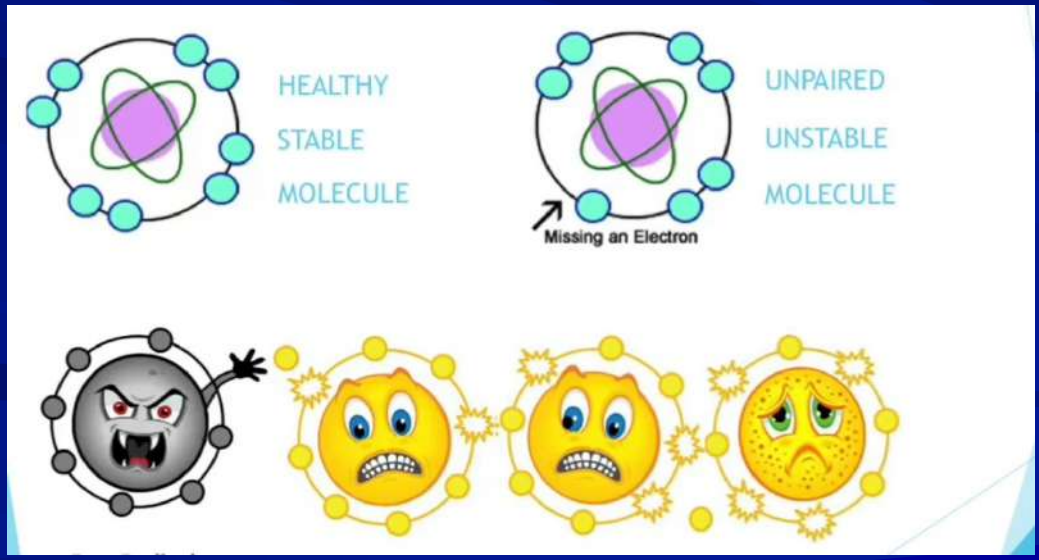
Raise Your Hand

Do you agree that free radical formation is a progressive process that leads to cell damage or death?

A. Yes
B. No
C. Hmmmm – I am not sure

Free Radials and Antioxidants

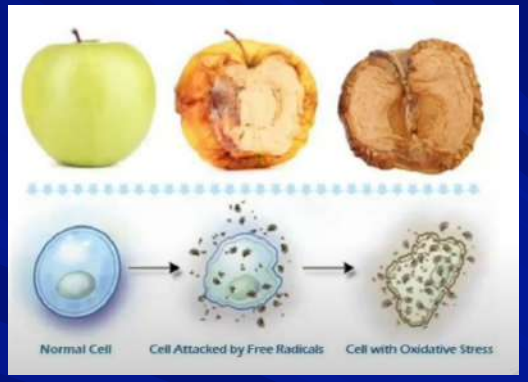


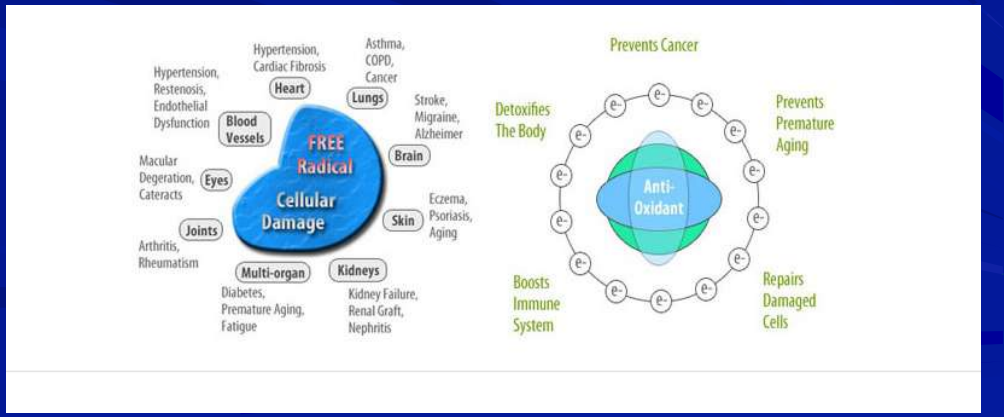


Oxidative Stress

- Small percentage of oxygen is not completely reduced
- Accumulation of free radicals
- Oxidative damage
- Oxidative stress
- Considered the starting of several diseases
- Responsible for epigenetic alterations
- Mitochondria – vulnerable

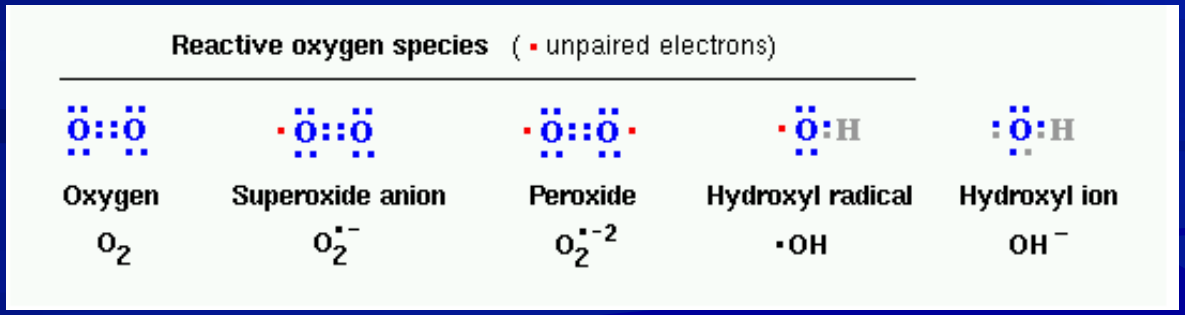
- Not going to make this apple new again
  - ★ Prevention is the one of the best medicines



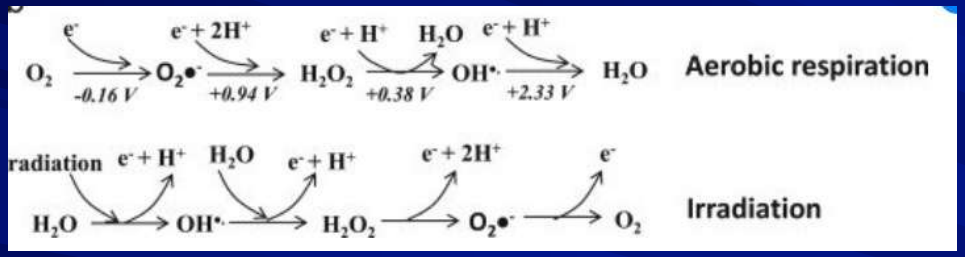


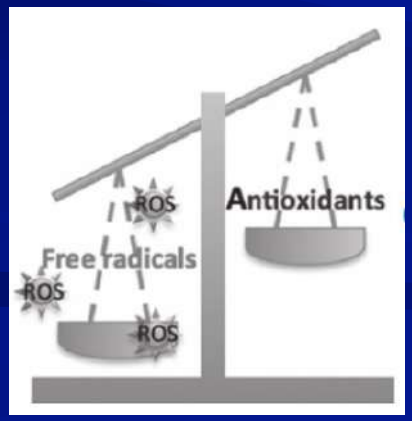
Free Radicals

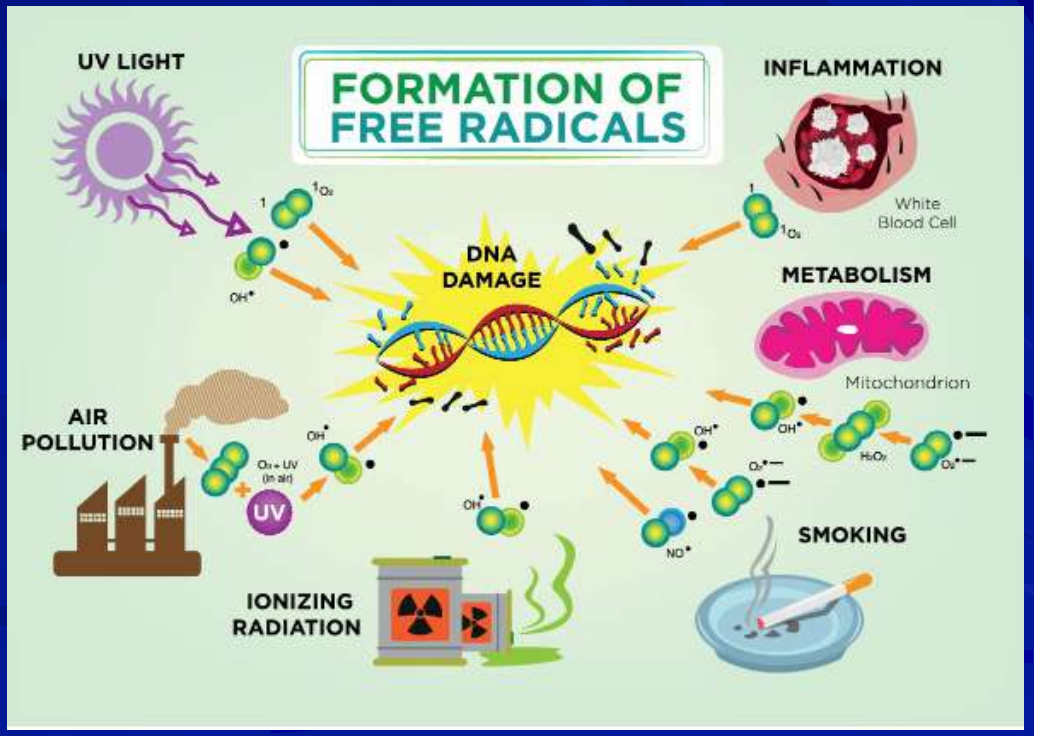
- During metabolism the O_2 molecule splits and energy is released
  - Endogenous free radical formation
- Regain stability the free single oxygen atom (oxygen free radical) seeks and steals electrons from other molecules
  - Superoxide anion – will accept one electron
  - Peroxide – will accept two electrons
- These molecules can be proteins, lipids, and DNA
  - Proteins (enzymes) – kinases, phosphatases, and transcription factors



Endogenous and Exogenous Free Radial Formation







Our Food Sources

Oh no

- Increasing exogenous free radicals
- Less antioxidant protection in our diet
- More bad and less good

Is an orange of the 1950's equivalent to 21 of today's oranges?

An orange from the 1950's was full of vitamin A, precious for our sight and our immune defenses. To attain the same amounts today, you would have to consume 21 of them. Onions and potatoes no longer contain any trace of it. The iron content in meat? Divided by 2. Calcium in broccoli? Divided by 4. To ingest the vitamin C contained in an apple from yesteryear, you would have to eat 100 today.

The Equalizer

American Rainbow

Standard American Diet (SAD)

Nutritional Antioxidants

- Exogenous antioxidants
  - Tocopherols (E), ascorbic acid (C), carotenoids, ubiquinone, and polyphenols
- Well know antioxidants
  - Vitamin C, E, Beta-carotene, lutein, zeathanin, selenium, quercetin, and resveratrol
- Mechanisms of action;
  - Neutralize free radicals
  - Repair oxidized membranes
  - Decrease reactive oxygen species
  - Neutral reactive oxygen species

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Raise Your Hand

Can our body manufacture these antioxidants? Vitamins A, C, and E, carotenoids, flavonoids, resveratrol, and quercetin

A. Yes
B. No
C. Hmmmm – I am not sure

Endogenous and Exogenous Antioxidants

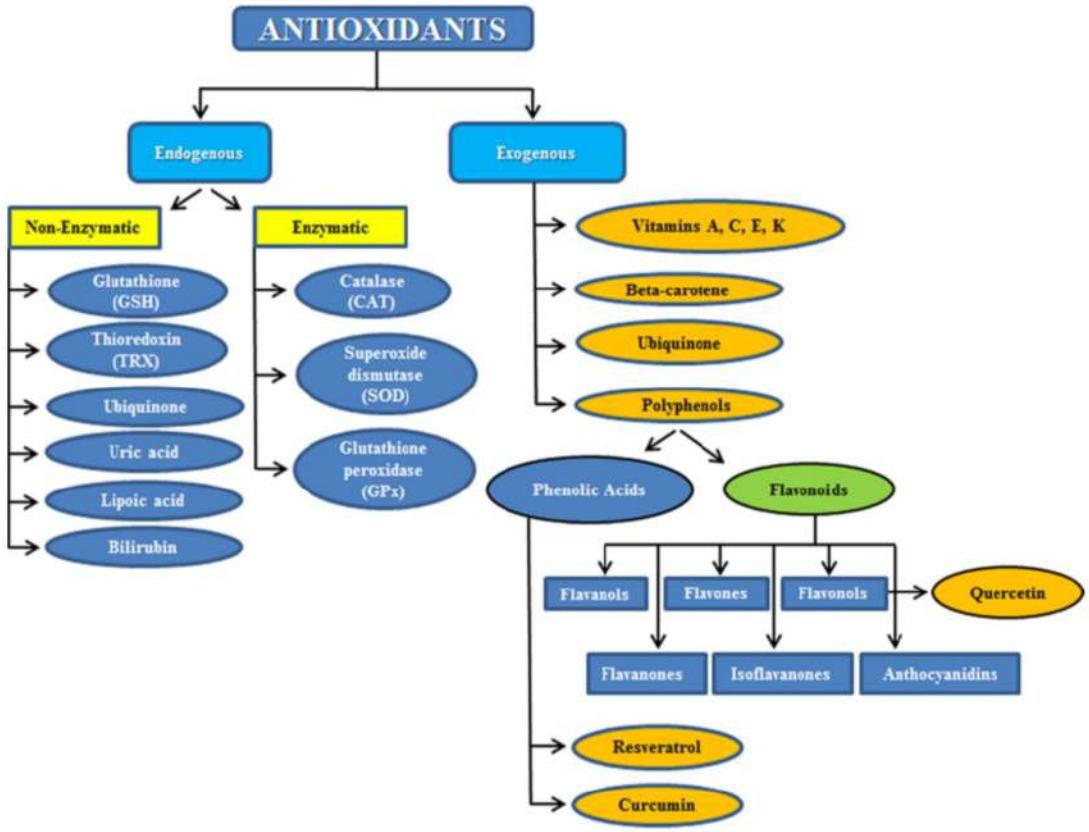

Figure 1: Subdivision between endogenous and exogenous antioxidants.

Comprehensive Antioxidant Support

- Cell membrane support
- Immune support
- Support to the oxidative stress to the extracellular matrix
- Support to cell signaling

Carotenoids

- Organic pigments produced by plants, algae, and bacteria
- Cannot be synthesized by the human body
  - Hydrophobic compounds
    - Important for the phospholipid bilayer
- 600 in nature – 50 human food chain – 15-20 human blood stream
- Macular carotenoids (L and Z) – highest concentration found in the human body
  - Diet derived
  - Henle fibers – between the inner and outer plexiform layers
  - Sequester or absorb blue light

Measure?

ANNUAL REVIEWS

Annual Review of Nutrition

Ocular Carotenoid Status in Health and Disease

Lydia Sauer, Binxing Li, and Paul S. Bernstein

Department of Ophthalmology and Visual Sciences, John A. Moran Eye Center, University of Utah, Salt Lake City, Utah 84132, USA; email: lydia.sauer@hsc.utah.edu, Binxing.Li@hsc.utah.edu, paul.bernstein@hsc.utah.edu

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Keywords

macular pigment, macular carotenoids, carotenoid supplementation, ocular nutrition, retinal imaging

Abstract

Retinal carotenoids are dietary nutrients that uniquely protect the eye from light damage and various retinal pathologies. Their antioxidative properties protect the eye from many retinal diseases, such as age-related macular degeneration. As many retinal diseases are accompanied by low carotenoid levels, accurate noninvasive assessment of carotenoid status can help ophthalmologists identify the patients most likely to benefit from carotenoid supplementation. This review focuses on the different methods available to assess carotenoid status and highlights disease-related changes and potential nutritional interventions.

ASSESSMENT OF CAROTENOIDS

Impact of Carotenoid Assessment

Because carotenoids appear to play a key role in retinal diseases, intensive research has resulted in a variety of innovative carotenoid assessment techniques. The breadth of possibilities for assessing retinal carotenoids is often confusing because methodologies, units of measurement, and the presentation of results vary widely. Accurate readings of carotenoid status are important in order to correctly advise individuals with regards to supplementation. Furthermore, in diseases such as macular telangiectasia type 2 (MacTel), the assessment of carotenoids may be crucial to the diagnosis, as reduced MP levels as well as abnormal distributions are among the first signs of the disease. Therefore, the measurement of carotenoids can impact clinical practice, and the evaluation of MP may eventually become an integral part of comprehensive ophthalmological care. The following sections describe and aim to give an organized overview of different MP assessment techniques.

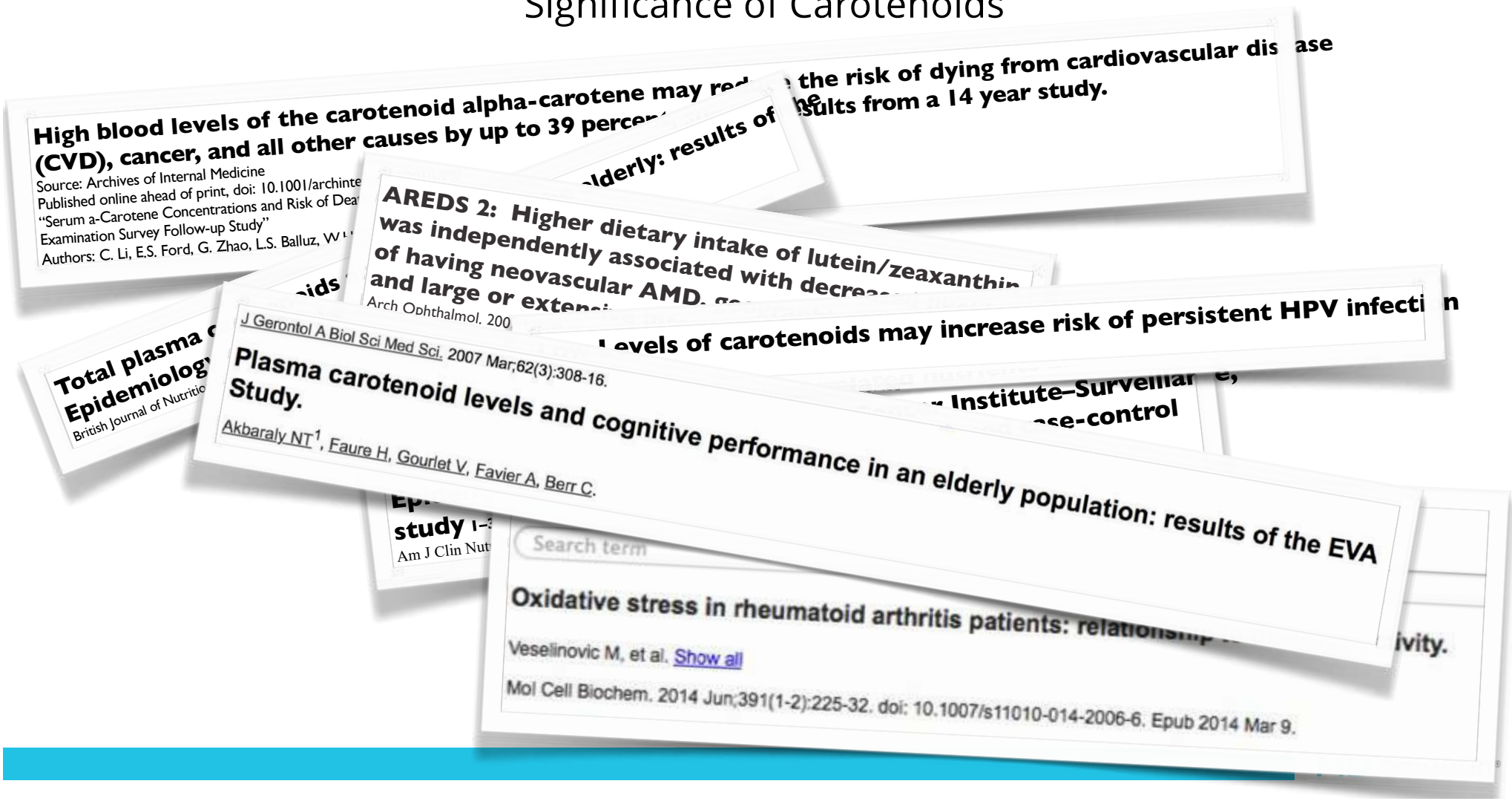
A large variety of methods are used to assess carotenoid status in humans, most of which are focused on the eye, but carotenoids can also be measured in tissue outside of the eye, such as the skin, blood, and the brain. Measurements of ocular carotenoids can be distinguished between subjective (psychophysical) and objective (optical) methods used to assess the amount of MP. In subjective methods, a direct answer from the patient is required, whereas objective measurement methods typically require just enough cooperation to generate an image (73).

Carotenoids in Tissues Other Than the Eye

Carotenoids can be assessed noninvasively in the skin and by high-performance liquid chromatography (HPLC) of blood and tissue samples. It has been shown that RRS measurements of skin carotenoids show strong correlations ($r = 0.7$ to 0.9) with carotenoids in biopsies of human skin

(57, 96). Skin RRS and reflectometry are particularly useful to assess the carotenoid status of children, with skin carotenoid levels strongly associated with fruit and vegetable intake (123). Using HPLC, the carotenoid status in the plasma can also be assessed (77, 104), and higher L levels in the serum of patients have been associated with higher visual function. Similarly, carotenoid assessment in brain tissue suggests that higher carotenoid levels might be beneficial for overall cognitive performance (65, 74).

Significance of Carotenoids



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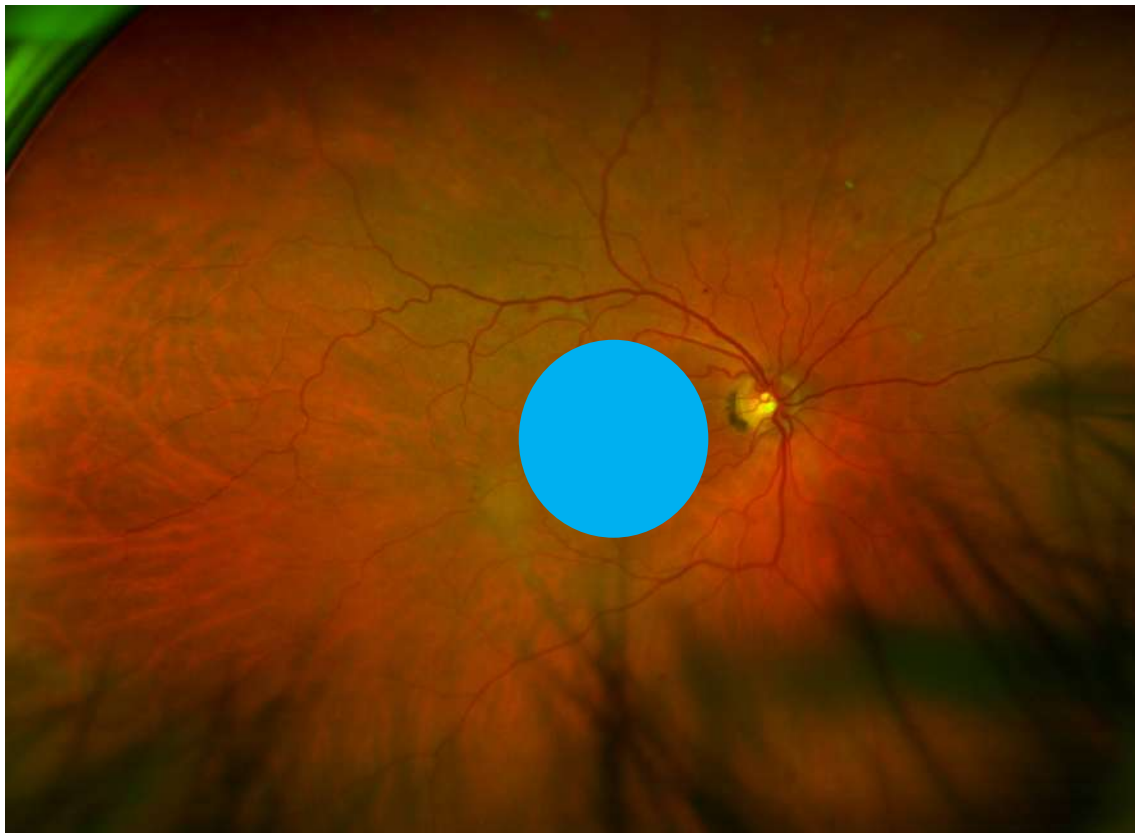
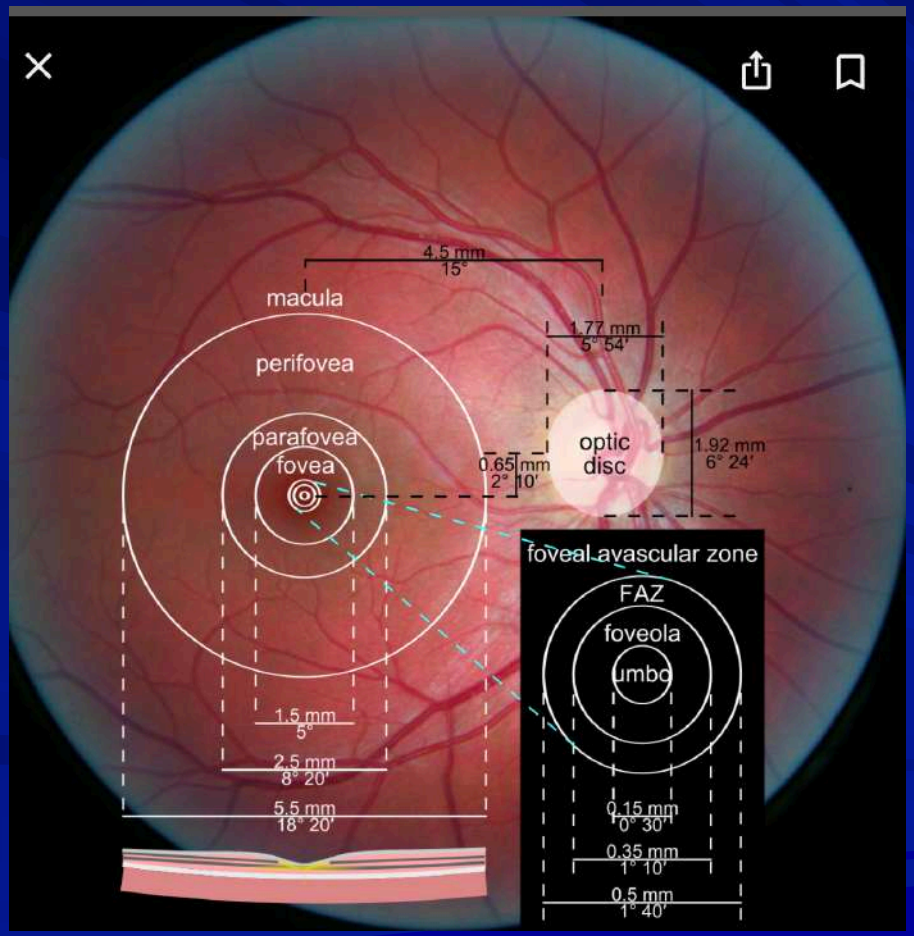
Where is the macula?

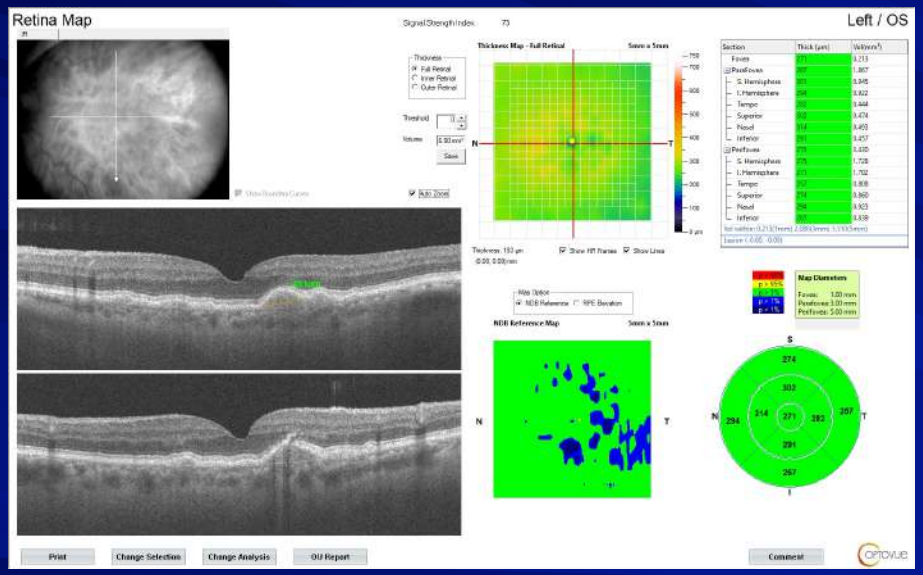
A. Blue
B. Orange

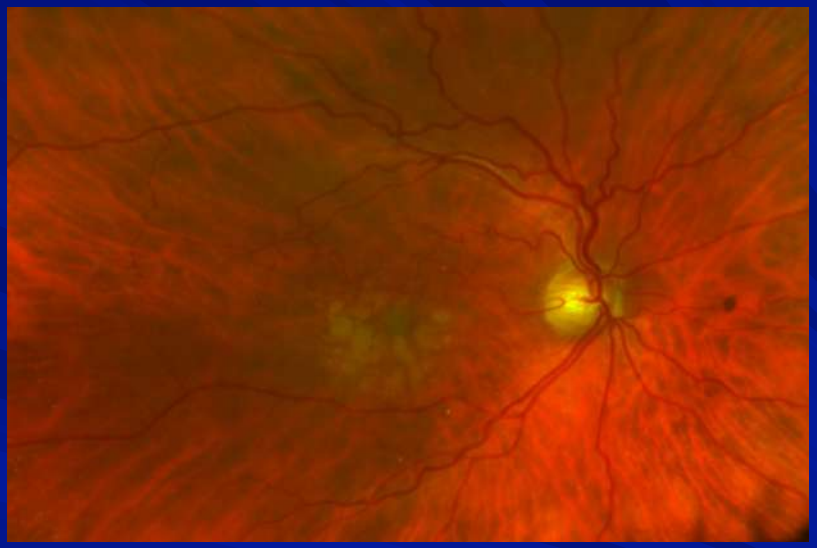


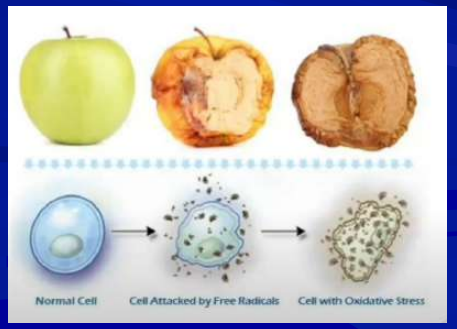
How large is the macula?



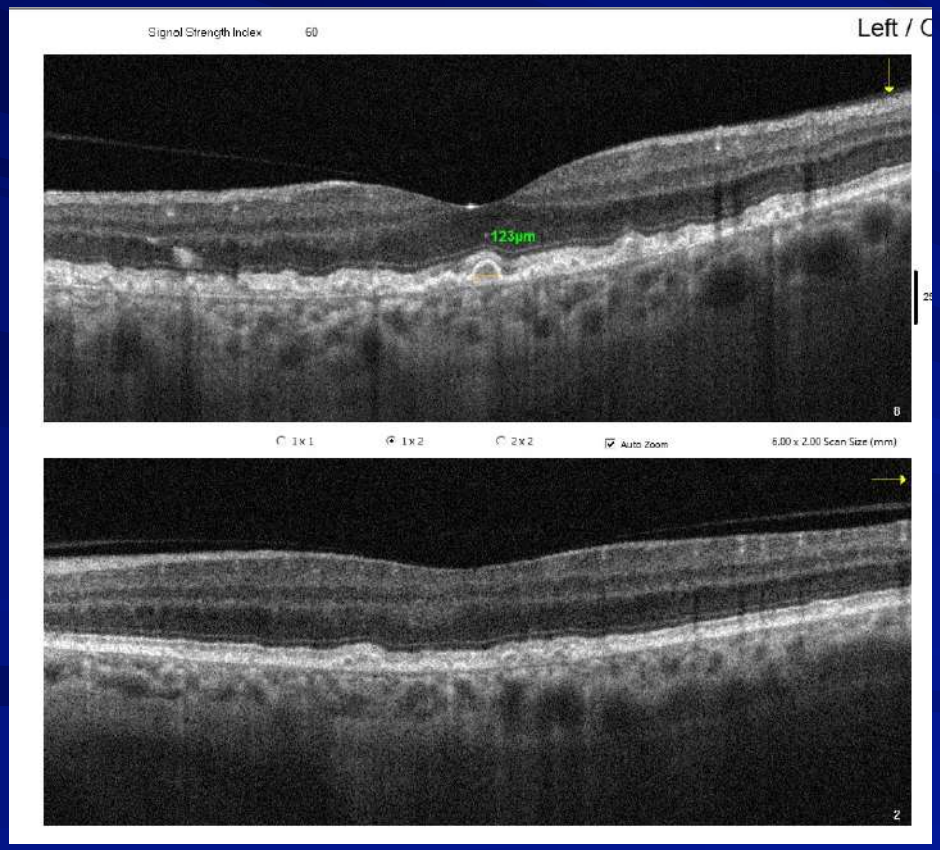
Oxidative Stress with Your OCT

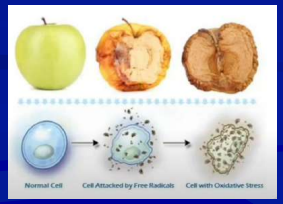




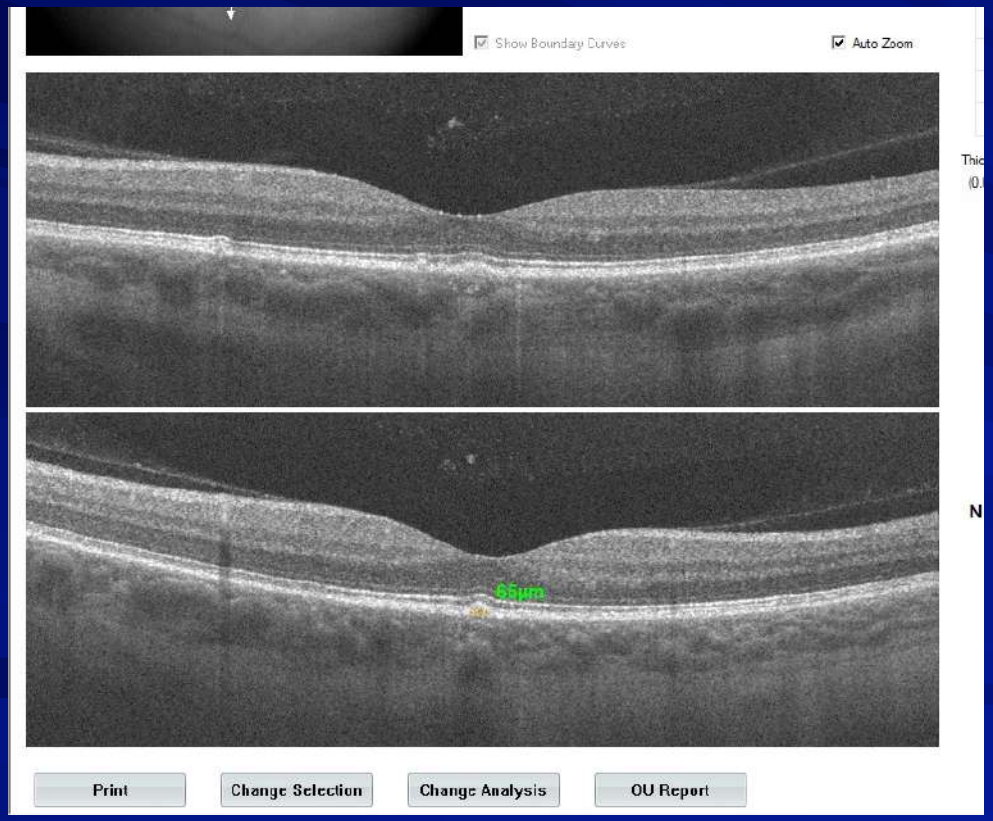


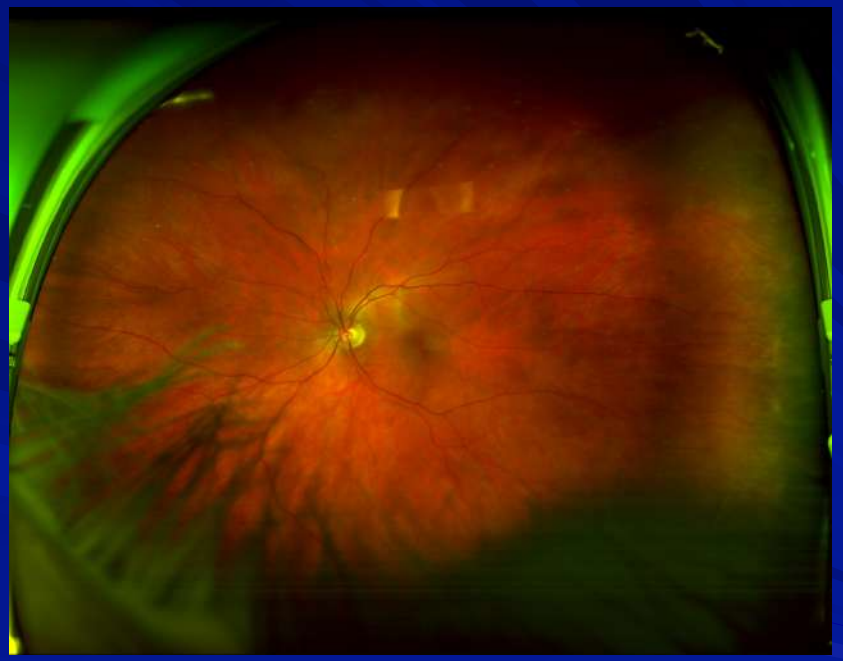
Oxidative Stress with Your OCT

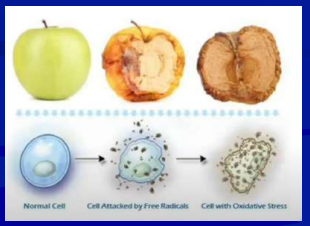




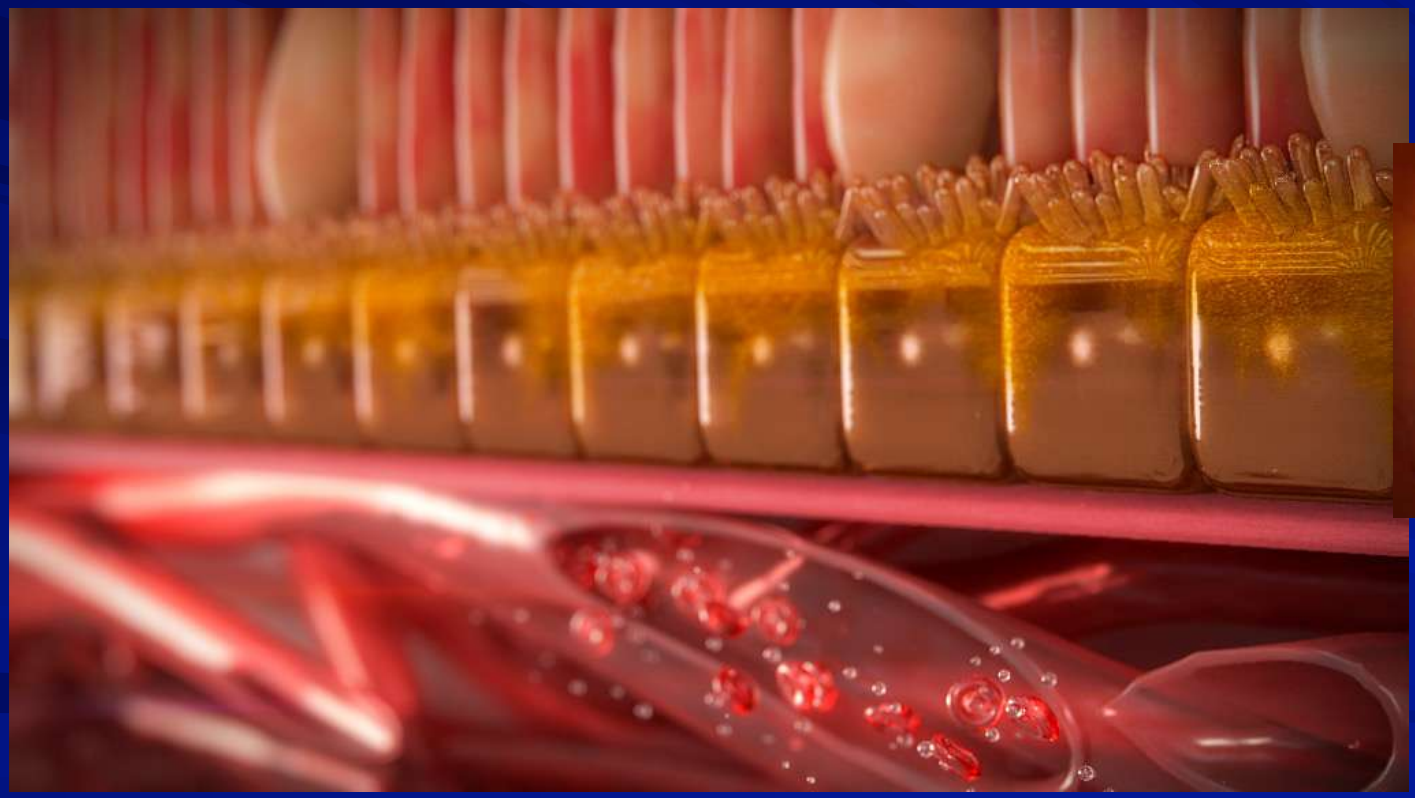
Oxidative Stress with Your OCT







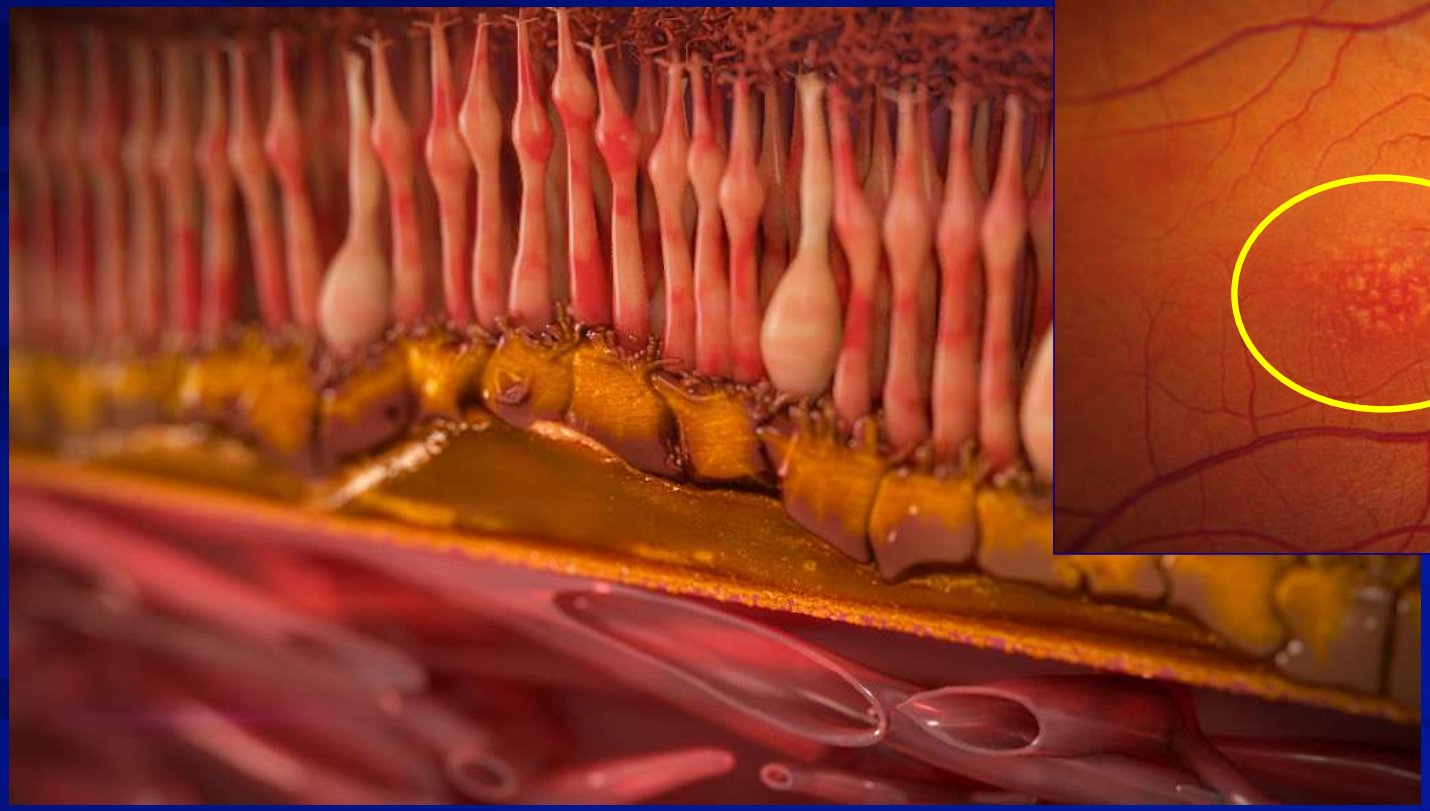
Healthy choriocapillaris, Bruch's, RPE, and Photoreceptors

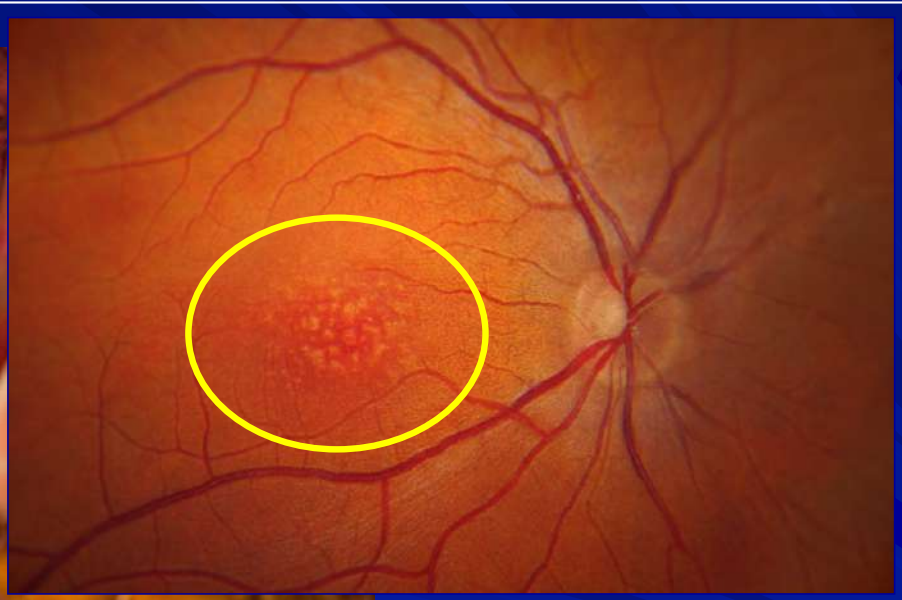


Cholesterol barrier deposited along Bruch's and RPE

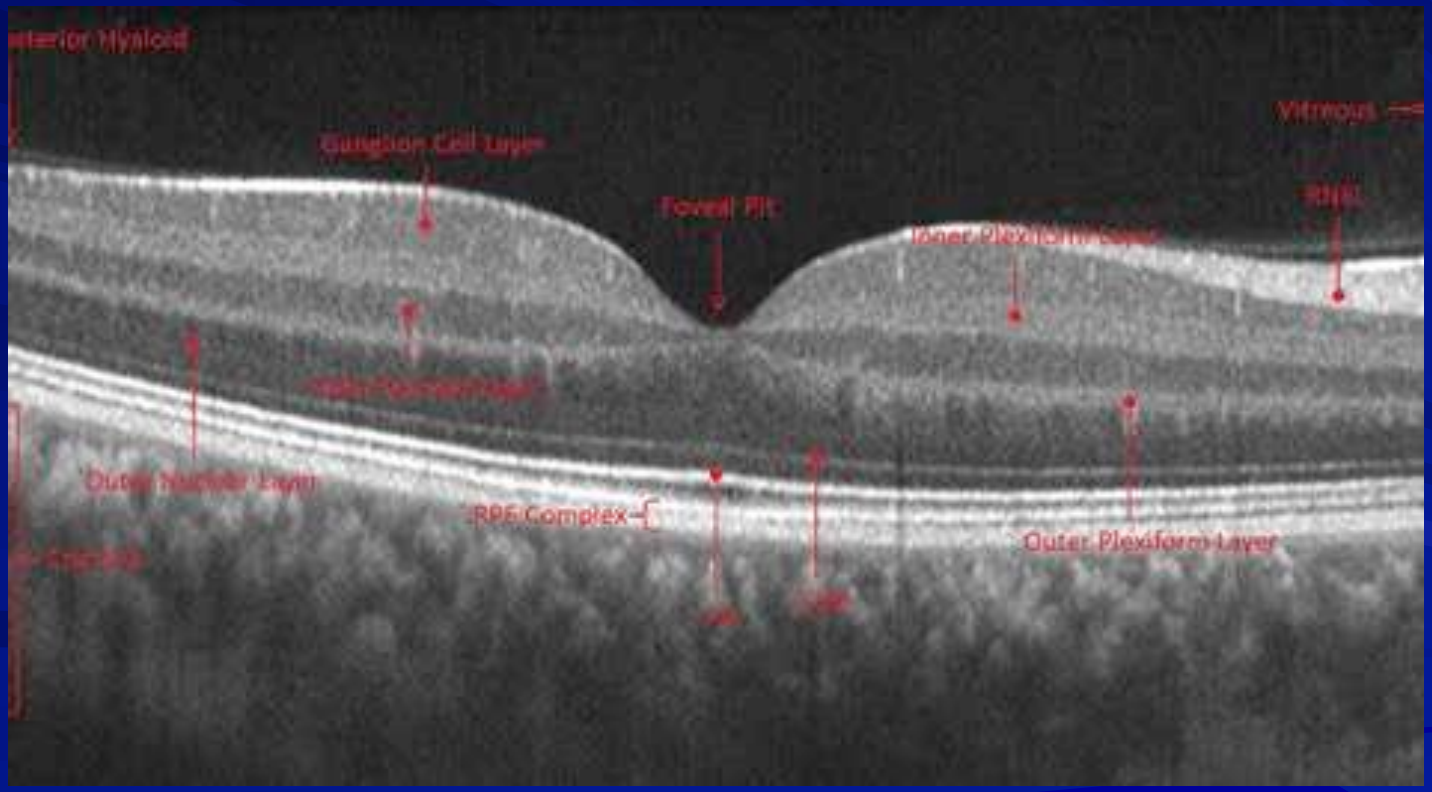
RPE Secretes even more cholesterol and degenerates

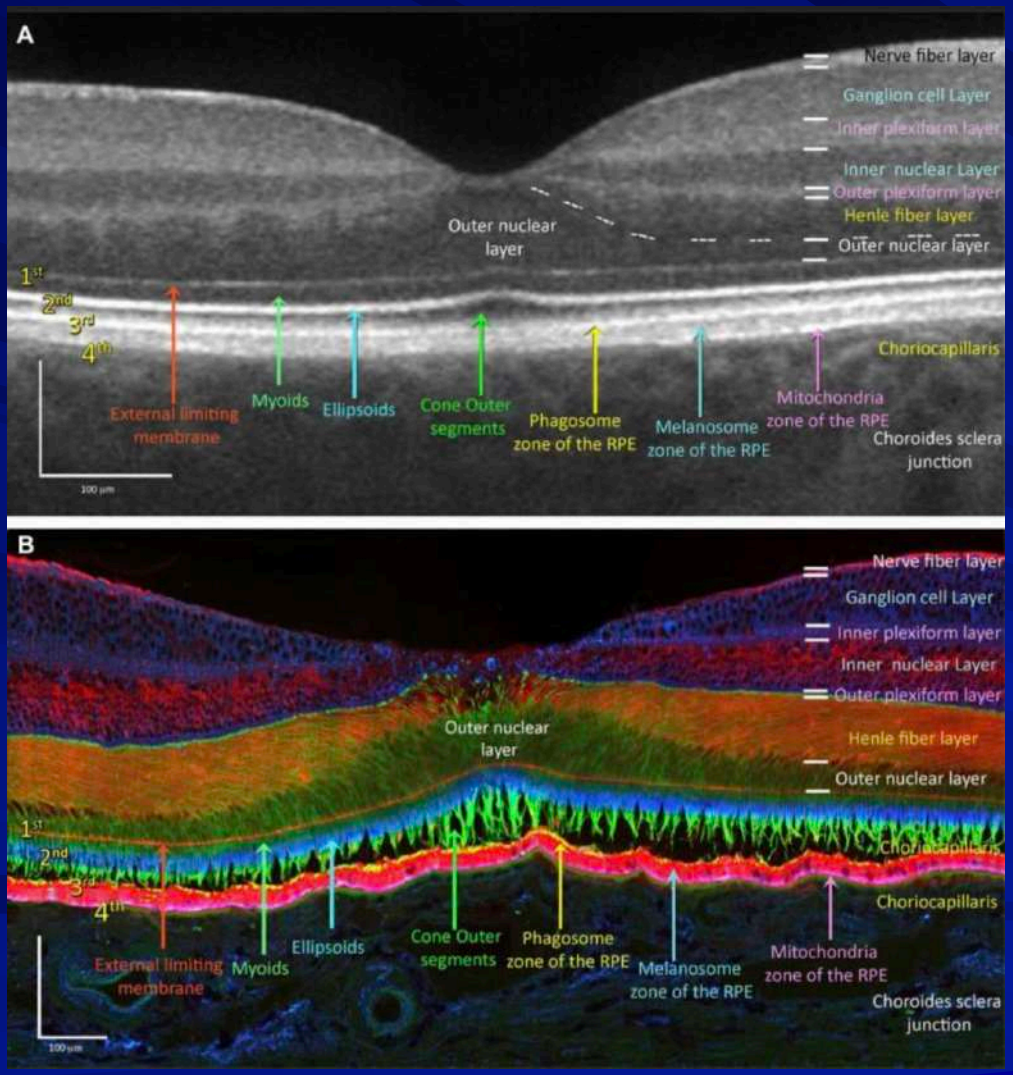
Finally, visibly evident drusen on fundus evaluation





The ellipsoid zone (EZ) is considered to be **formed mainly by mitochondria within the ellipsoid layer of the outer portion of the inner segments of the photoreceptors**. However, it was previously known as the junction between the photoreceptor IS/OS).





Progress in Retinal and Eye Research
Volume 77, July 2020, 100828

Interpretation of OCT and OCTA images from a histological approach: Clinical and experimental implications

Nicolás Cuenca [a, b, 1] ... Isabel Pinilla [f, 1]

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https://doi.org/10.1016/j.preteyeres.2019.100828

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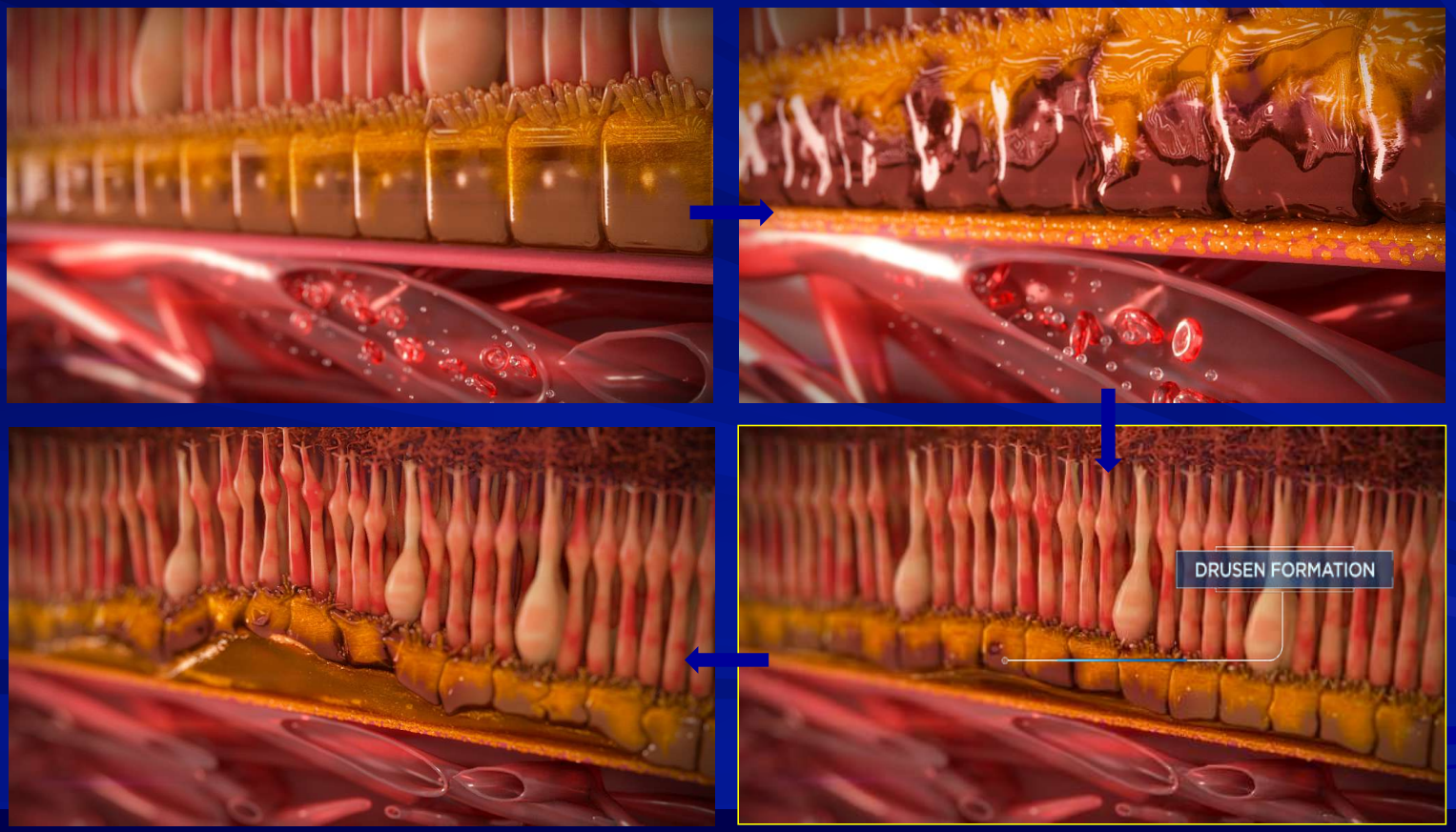
Abstract

Optical coherence tomography (OCT) and OCT angiography (OCTA) have been a techn

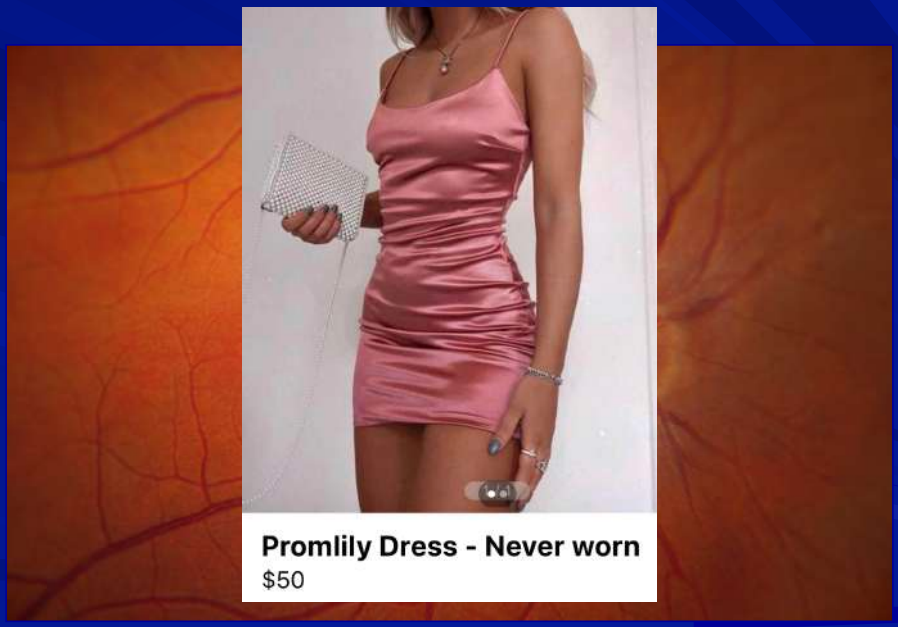
FEEDBACK

AMD is a Disease Process that Starts Below the Surface



Beckmann Committee Classification of AMD

- Based on presence of lesions within 2 DD of fovea in either eye
  - ★ No AMD
    - None or few small drusen, < 63 microns
    - No AMD pigmentary abnormalities
  - ★ Early AMD
    - Medium drusen, > 63 – <125 microns
    - No AMD pigmentary changes
  - ★ Intermediate AMD
    - 1 large drusen, > 125 microns
    - Any AMD pigmentary changes
  - ★ Advanced AMD
    - Any geographic atrophy
    - Choroidal neovascularization (CNV)



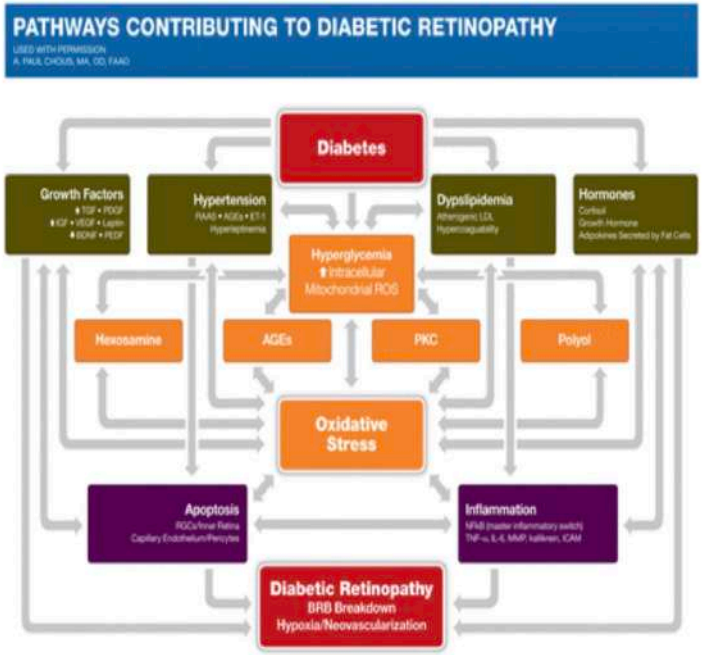
Randomized Controlled Trial > Br J Ophthalmol. 2016 Feb;100(2):227-34.
doi: 10.1136/bjophthalmol-2014-306534. Epub 2015 Jun 18.

The Diabetes Visual Function Supplement Study (DiVFuSS)

A Paul Chous [1], Stuart P Richer [2], Jeffry D Gerson [3], Renu A Kowluru [4]

Affiliations + expand

PMID: 26089210 PMCID: PMC4752618 DOI: 10.1136/bjophthalmol-2014-306534
Free PMC article



DiVFuSS Constituents	Mitigates DR in animal models	Blocks capillary cell apoptosis	Improves retinal capillary fragility	Reduces VEGF	Reduces oxidative stress	Reduces AGE activity	Reduces Polyol activity	Reduces PKC activity	Reduces NF-Kβ
Alpha-Lipoic Acid	•		•	•	•				•
Benfotiamine	•	•				•	•	•	
Vitamins C/E	•				•		•		•
Curcumin	•			•	•	•			•
Vitamin D3	•			•					
DHA/EPA	•	•			•				
Grape Seed Extract		•			•	•			
Resveratrol	•	•			•				
Green Tea Extract				•					
N-Acetyl Cysteine	•			•	•				
CoQ10					•				
Zinc	• (in ARDS)								
Pycnogenol	•		•		•				•
Lutein/Zeaxanthin	•			•	•				•

DiVFuSS Constituents	Improves visual function in humans	Reduces retinal edema in humans	Improves endothelial dysfunction in humans	Improves retinal blood flow in humans	Reduces HbA1c in humans	Improves Dyslipi-demia in humans	Reduces blood pressure in humans	Reduces DPN symptoms in humans
Alpha-Lipoic Acid			•	•				•
Benfotiamine			•			•		•
Vitamins C/E			•	•		•		
Curcumin	•	•		•				
Vitamin D3					•	•		
DHA/EPA			•			•	•	
Grape Seed Extract								
Resveratrol			•		•			
Green Tea Extract			•			•	•	
N-Acetyl Cysteine								
CoQ10			•					
Zinc						•		
Pycnogenol	•	•		•	•	•	•	
Lutein/Zeaxanthin	•	•						

Note: Suggested improvements marked by • include published evidence in animal and/or cell models, except as specifically noted, but do not reflect grading of that evidence.

Download figure

Review > Nutrients. 2019 Apr 2;11(4):771. doi: 10.3390/nu11040771.

Nutraceuticals for the Treatment of Diabetic Retinopathy

Maria Grazia Rossino [1], Giovanni Casini [2 3]

Affiliations + expand

PMID: 30987058 PMCID: PMC6520779 DOI: 10.3390/nu11040771

Free PMC article

Abstract

Diabetic retinopathy (DR) is one of the most common complications of diabetes mellitus and is characterized by degeneration of retinal neurons and neoangiogenesis, causing a severe threat to vision. Nowadays, the principal treatment options for DR are laser photocoagulation, vitreoretinal surgery, or intravitreal injection of drugs targeting vascular endothelial growth factor. However, these treatments only act at advanced stages of DR, have short term efficacy, and cause side effects. Treatment with nutraceuticals (foods providing medical or health benefits) at early stages of DR may represent a reasonable alternative to act upstream of the disease, preventing its progression. In particular, in vitro and in vivo studies have revealed that a variety of nutraceuticals have significant antioxidant and anti-inflammatory properties that may inhibit the early diabetes-driven molecular mechanisms that induce DR, reducing both the neural and vascular damage typical of DR. Although most studies are limited to animal models and there is the problem of low bioavailability for many nutraceuticals, the use of these compounds may represent a natural alternative method to standard DR treatments.

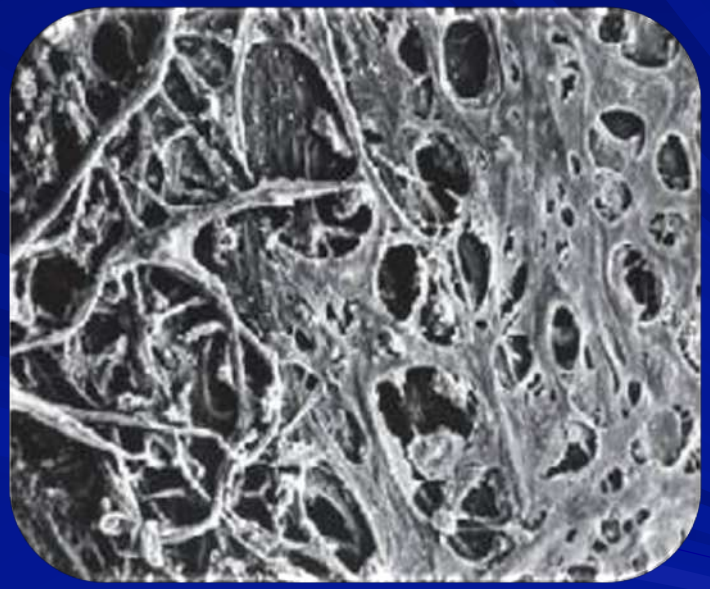
Keywords: carotenoids; flavonoids; inflammation; microvascular lesions; neoangiogenesis; oxidative stress; polyphenols; retina; saponins.

Disease at the TM is responsible for elevated IOP in glaucoma[1,2]

Healthy TM
Normal IOP

Cellular Damage
(eg, Oxidative Stress)

POAG TM Stiffness
Elevated IOP



Scanning electron microscopy (2000x) was used to examine human TM under physiological conditions and in patients with POAG.[2]
POAG, primary open-angle glaucoma; TM, trabecular meshwork.

1. He et al. *Invest Ophthalmol Vis Sci*. 2008;49:1447.
2. Saccà et al. *J Cell Physiol.* 2015;230:510.

Glaucoma

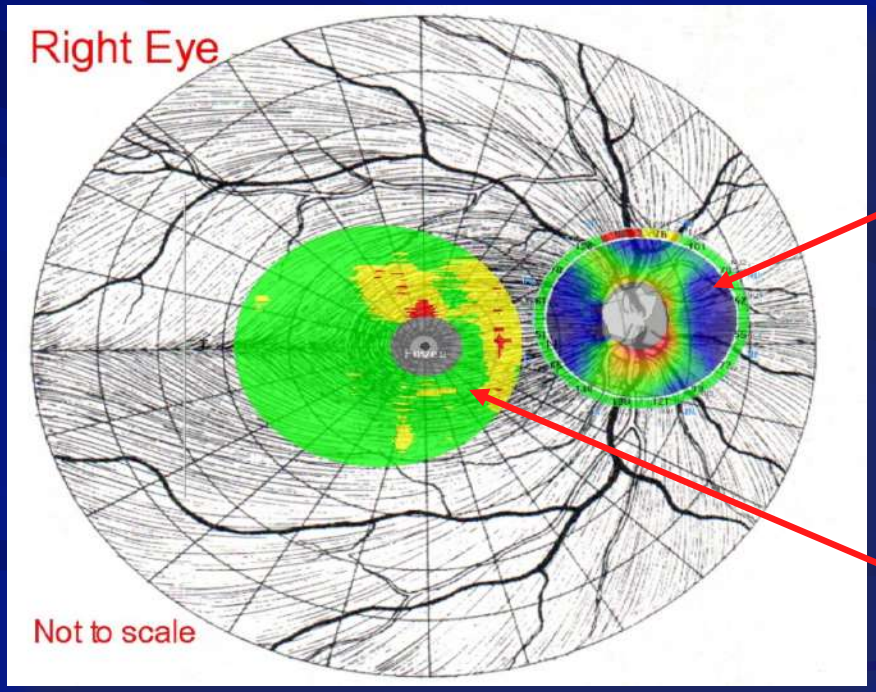
PERSPECTIVES ON GLAUCOMA

Antioxidants enhance ocular perfusion in Open Angle Glaucoma

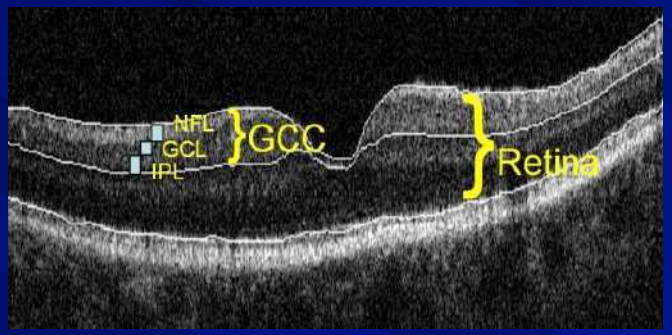
Harris A, et al. Acta Ophthalmol. 2018;doi:10.1111/aos.13530.

"In agreement with previous findings, our results indicate that the supplementation of certain antioxidants may increase blood supply to the orbit and within retinal capillary beds following 4 weeks administration," the authors wrote. "Our data suggest oral antioxidant supplementation may decrease vascular resistance over a longer period of time than previous trials investigated."

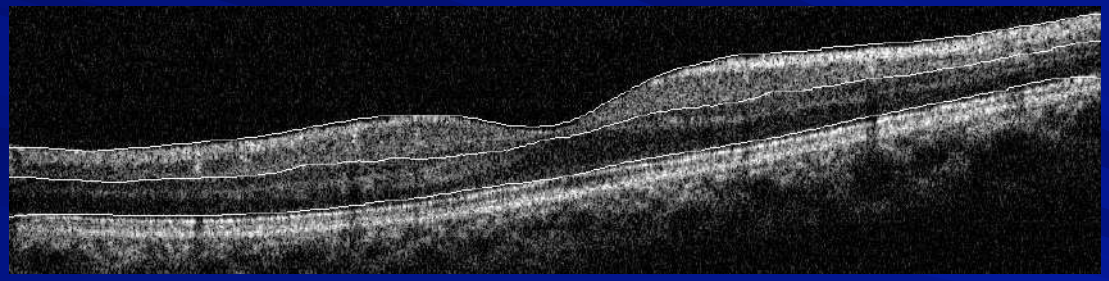
Overlay of the RNFL and GCC



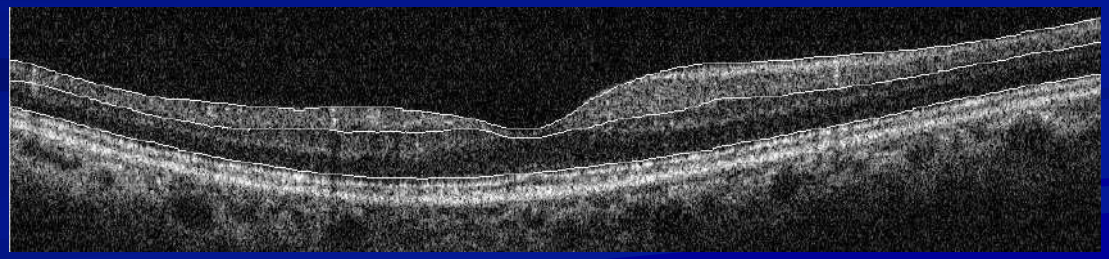
GCC Thinning in Glaucoma

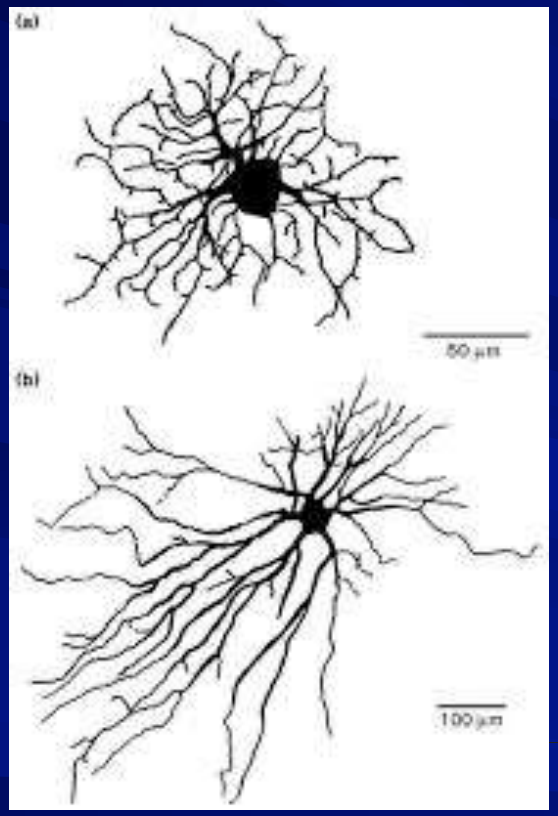


Normal

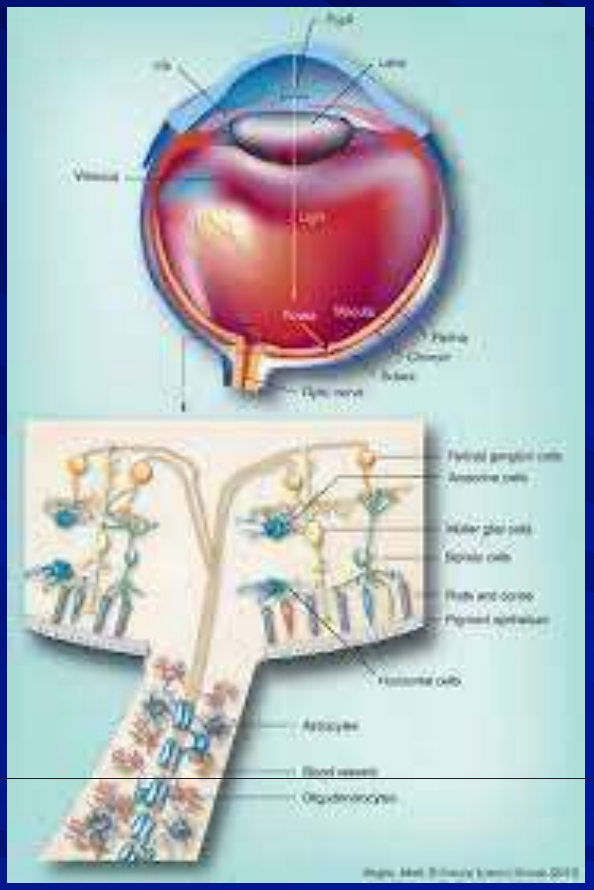


Glaucoma with thinner GCC

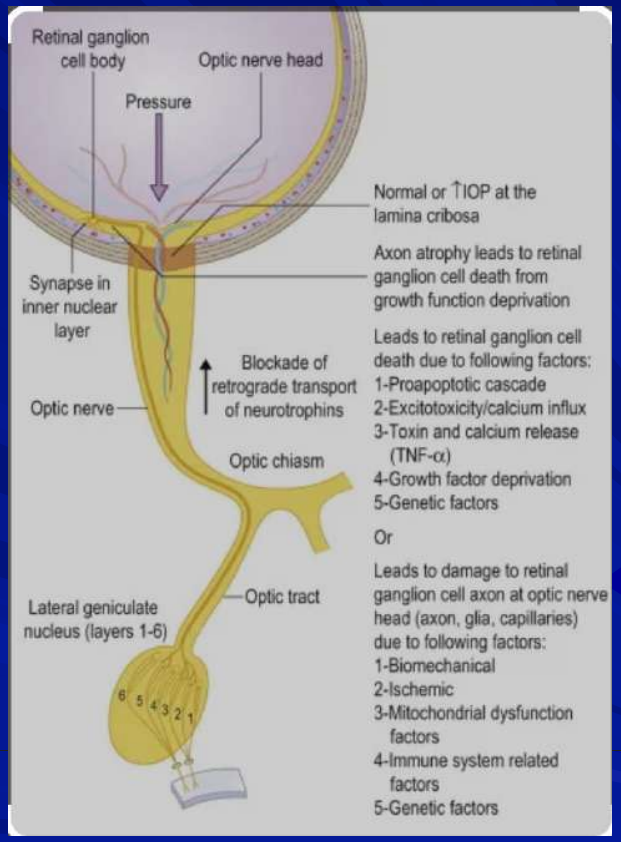




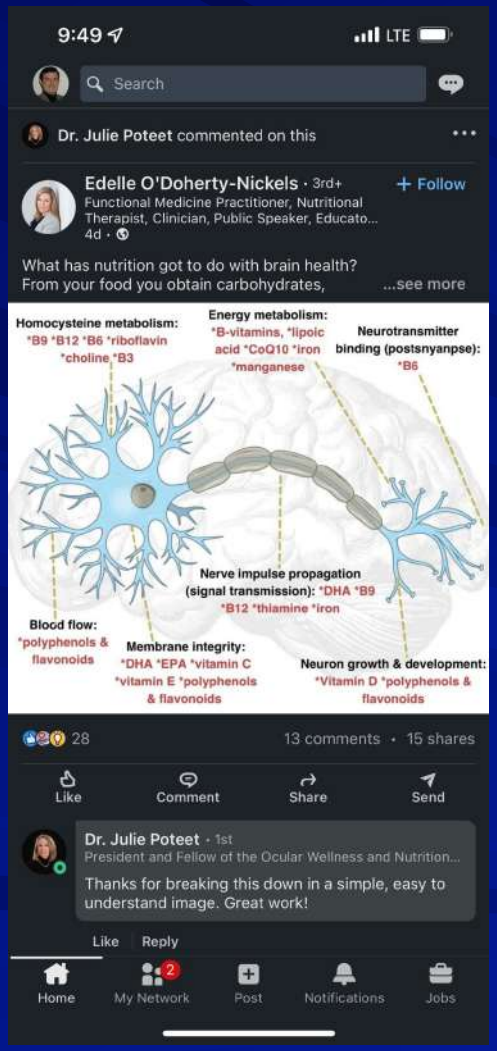
alpha and beta retinal ganglion cells ... cell.com



retinal ganglion cell regeneration ...futuremedicine.com



Pu Eble Rino
Retinal Ganglion Cells Optic Nerve


9:49
LTE
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Dr. Julie Poteet commented on this
Edelle O'Doherty-Nickels · 3rd+
Functional Medicine Practitioner, Nutritional Therapist, Clinician, Public Speaker, Educato...
4d ·
+ Follow
What has nutrition got to do with brain health?
From your food you obtain carbohydrates,
...see more
Homocysteine metabolism: *B9 *B12 *B6 *riboflavin *choline *B3
Energy metabolism: *B-vitamins, *lipoic acid *CoQ10 *iron *manganese
Neurotransmitter binding (postsnyanpse): *B6
Nerve impulse propagation (signal transmission): *DHA *B9 *B12 *thiamine *iron
Blood flow: *polyphenols & flavonoids
Membrane integrity: *DHA *EPA *vitamin C *vitamin E *polyphenols & flavonoids
Neuron growth & development: *Vitamin D *polyphenols & flavonoids
28
13 comments · 15 shares
Like
Comment
Share
Send
Dr. Julie Poteet · 1st
President and Fellow of the Ocular Wellness and Nutrition...
Thanks for breaking this down in a simple, easy to understand image. Great work!
Like
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Home
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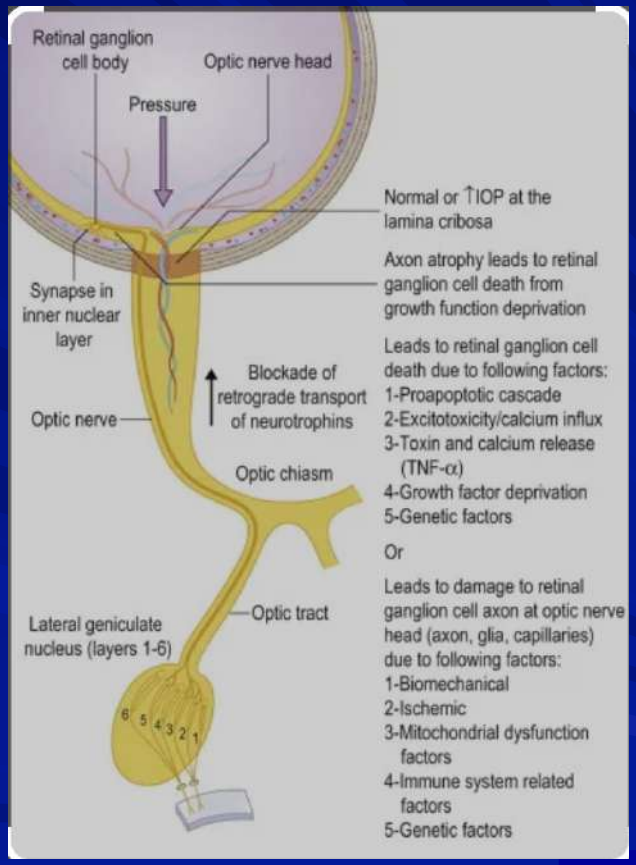
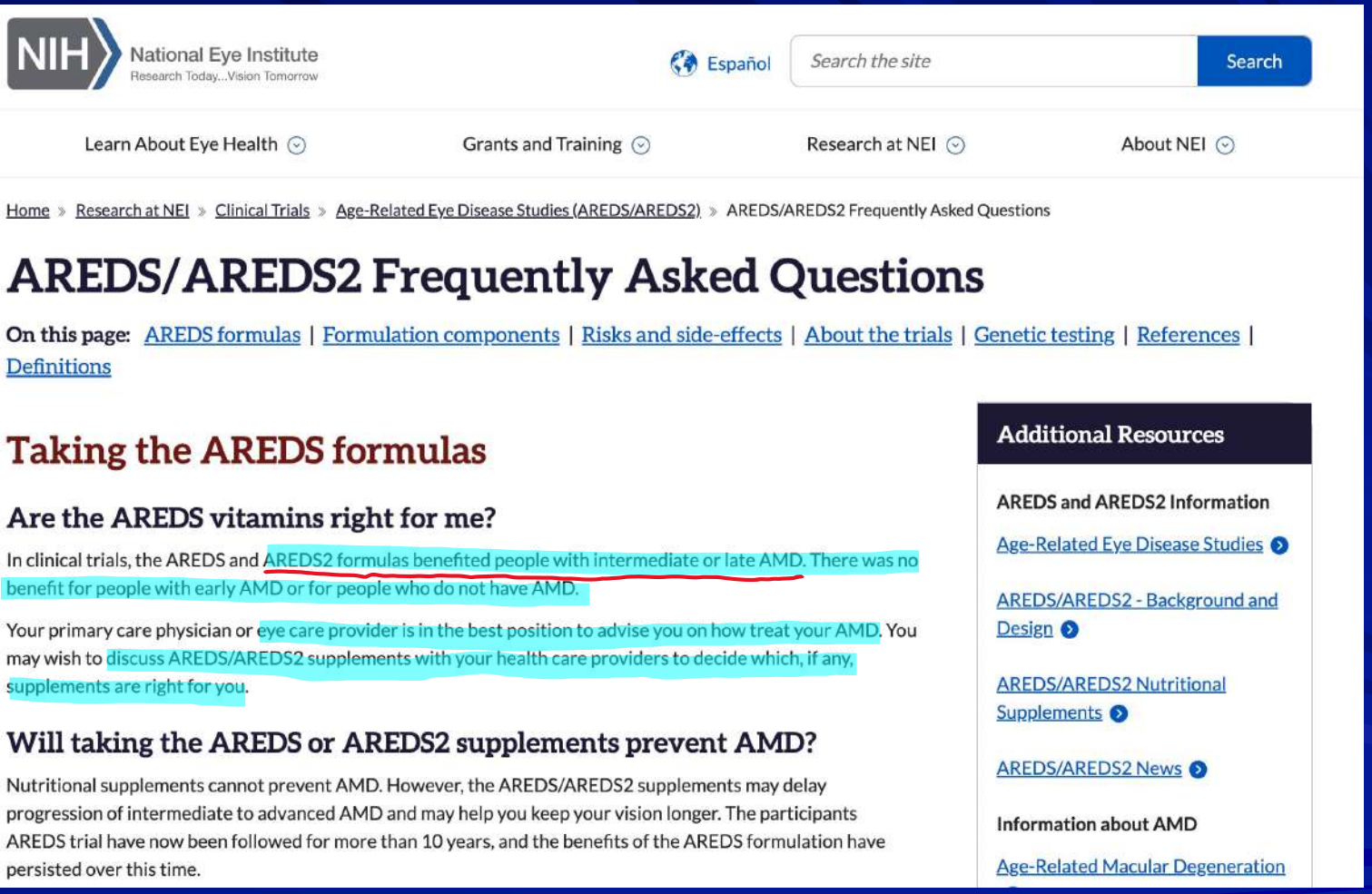

Retinal ganglion cell body
Optic nerve head
Pressure
Normal or ↑IOP at the lamina cribosa
Axon atrophy leads to retinal ganglion cell death from growth function deprivation
Synapse in inner nuclear layer
Leads to retinal ganglion cell death due to following factors:
1-Proapoptotic cascade
2-Excitotoxicity/calcium influx
3-Toxin and calcium release (TNF-α)
4-Growth factor deprivation
5-Genetic factors
Blockade of retrograde transport of neurotrophins
Optic nerve
Optic chiasm
Or
Leads to damage to retinal ganglion cell axon at optic nerve head (axon, glia, capillaries) due to following factors:
1-Biomechanical
2-Ischemic
3-Mitochondrial dysfunction factors
4-Immune system related factors
5-Genetic factors
Optic tract
Lateral geniculate nucleus (layers 1-6)
6 5 4 3 2 1

Treatments for AMD

- Early detection and meaningful treatments with significant value, do not cure, but have been shown to slow or halt progression. Not limited to early stages but all stages of AMD
  - Prescribe smoking cessation programs
    - Smoking and AMD
      - Depletes serum antioxidants
      - Decreases pigmentary density
      - Increases risk to advanced AMD
  - Lifestyle changes
    - Diet
    - Exercise
  - Systemic disease management
    - Cardiovascular disease, DM, obesity, high cholesterol

Evidence Informed Risk Adjusted Medicine



NIH National Eye Institute
Research Today...Vision Tomorrow

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Home » Research at NEI » Clinical Trials » Age-Related Eye Disease Studies (AREDS/AREDS2) » AREDS/AREDS2 Frequently Asked Questions

AREDS/AREDS2 Frequently Asked Questions

On this page: AREDS formulas | Formulation components | Risks and side-effects | About the trials | Genetic testing | References | Definitions

Taking the AREDS formulas

Are the AREDS vitamins right for me?

In clinical trials, the AREDS and AREDS2 formulas benefited people with intermediate or late AMD. There was no benefit for people with early AMD or for people who do not have AMD.

Your primary care physician or eye care provider is in the best position to advise you on how treat your AMD. You may wish to discuss AREDS/AREDS2 supplements with your health care providers to decide which, if any, supplements are right for you.

Will taking the AREDS or AREDS2 supplements prevent AMD?

Nutritional supplements cannot prevent AMD. However, the AREDS/AREDS2 supplements may delay progression of intermediate to advanced AMD and may help you keep your vision longer. The participants AREDS trial have now been followed for more than 10 years, and the benefits of the AREDS formulation have persisted over this time.

Additional Resources

AREDS and AREDS2 Information

Age-Related Eye Disease Studies

AREDS/AREDS2 - Background and Design

AREDS/AREDS2 Nutritional Supplements

AREDS/AREDS2 News

Information about AMD

Age-Related Macular Degeneration

Optometric Education Consultants

Raise Your Hand

During the AREDS2 Study – were patients allowed to take a multivitamins?

A. No – they were testing the efficacy of AREDS2
B. Yes – 10 % 1 of 10
C. Yes- - 50% 5 of 10
D. Yes – 90% 9 of 10

Will taking the AREDS or AREDS2 supplements prevent AMD?

Nutritional supplements cannot prevent AMD. However, the AREDS/AREDS2 supplements may delay progression of intermediate to advanced AMD and may help you keep your vision longer. The participants AREDS trial have now been followed for more than 10 years, and the benefits of the AREDS formulation have persisted over this time.

Can I take a daily multivitamin if I am taking one of the AREDS/AREDS2 formulas?

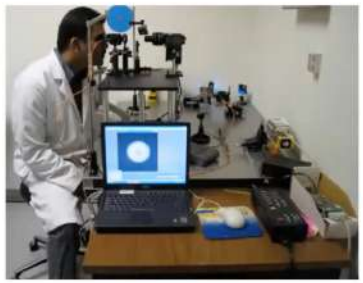
Yes. The AREDS and AREDS2 formulas do not substitute for multivitamins. In AREDS, two-thirds of the study participants took multivitamins along with the AREDS formulation. In AREDS2, almost nine of ten participants took multivitamins.

Treatment for AMD

- Nutritional supplements
  - Sub-clinical/sub-structural or early disease
    - Controversy flourishes
      - No definitive guideline exists
      - Despite consensus evidence suggests using supplements
  - Intermediate – advance disease
    - No controversy on advocating for supplements
  - AREDS 1
    - Contains Beta-carotene and no lutein or zeaxanthin, no longer recommended
    - Investigated early AMD, no statistically significant benefit
  - AREDS 2
    - Recommended for intermediate and advanced AMD, study protocol
  - The Practical Guide for the Treatment of AMD - 3 primary options
    - Macular pigment supplement
      - Carotenoids: lutein, zeaxanthin, meso-zeaxanthin
    - Carotenoids, antioxidants, zinc, and vitamins C & E
      - AREDS 2
    - Carotenoid macular supplement in subclinical and early AMD. Carotenoid and antioxidant is intermediate and AMD that is progressing

An Evening with Dr. Paul Bernstein

Measurement of Macular Pigment



- **HPLC**
- **Psychophysical**
  - Heterochromatic flicker photometry (HFP)
  - Minimum motion photometry
- **Image Based**
  - Autofluorescence attenuation
  - Reflectometry
  - Resonance Raman spectroscopy (skin and eye)

High Performance Liquid Chronography

ARVO STUDY

Interrelationships between Macula, Skin and Serum Carotenoids- Paul Bernstein, Werner Gellerman et al ARVO May 2016

Conclusions:

"Our results emphasize the importance of measuring the total amount of carotenoids in the macula region using an objective image based modality such as AFI w Spectralis rather than subjective MPOD."

Skin resonance Raman Spectroscopy of skin carotenoids is a reasonable biomarker of macula carotenoid status. and correlates better than than subjective MPOD tests.

The objective hand scanner is better than the subjective Macuscope, QuantifEYE, and Densitometer for estimating macula pigment.

An Evening with Dr. Paul Bernstein

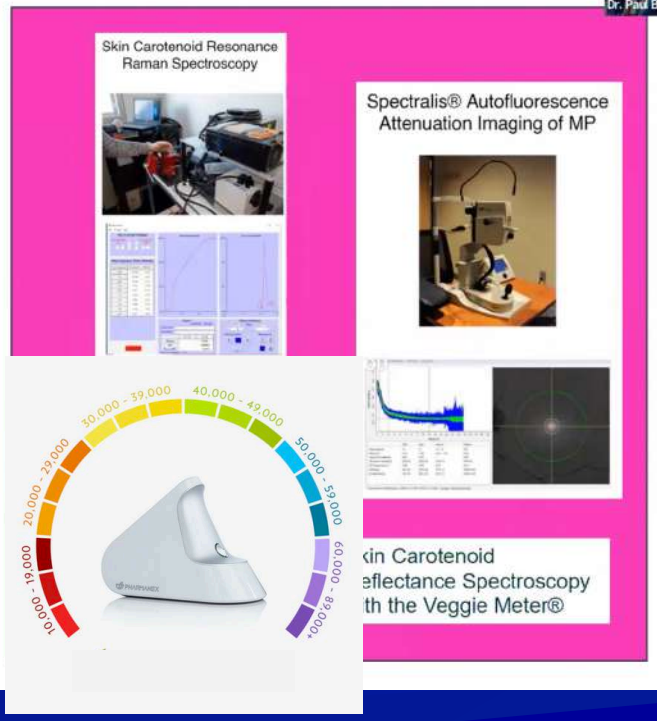
The Lutein and Zeaxanthin in Pregnancy Study: The L-ZIP Study

- Will addition of L and Z to standard-of-care prenatal vitamins combat maternal carotenoid depletion and improve maternal and infant ocular health?
- Randomized, controlled trial of 10 mg/d L and 2 mg/d Z v no L/Z
- Low-risk pregnancies
- Outcomes
  - Skin carotenoids by RRS in mother and infant
  - Maternal macular pigment by Spectralis AFI
  - Infant macular pigment and foveal structure by RetCam and Bioptigen OCT
- Fully enrolled
- NEI funded

An Evening with Dr. Paul Bernstein

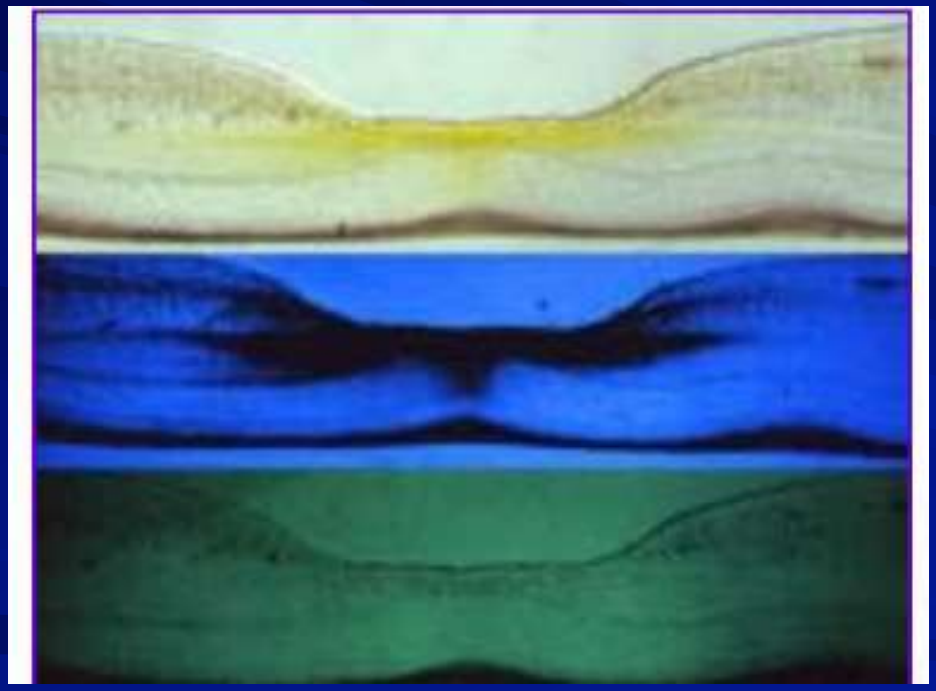
The Moran AMD Genetic Testing Assessment Study: The Magenta Study

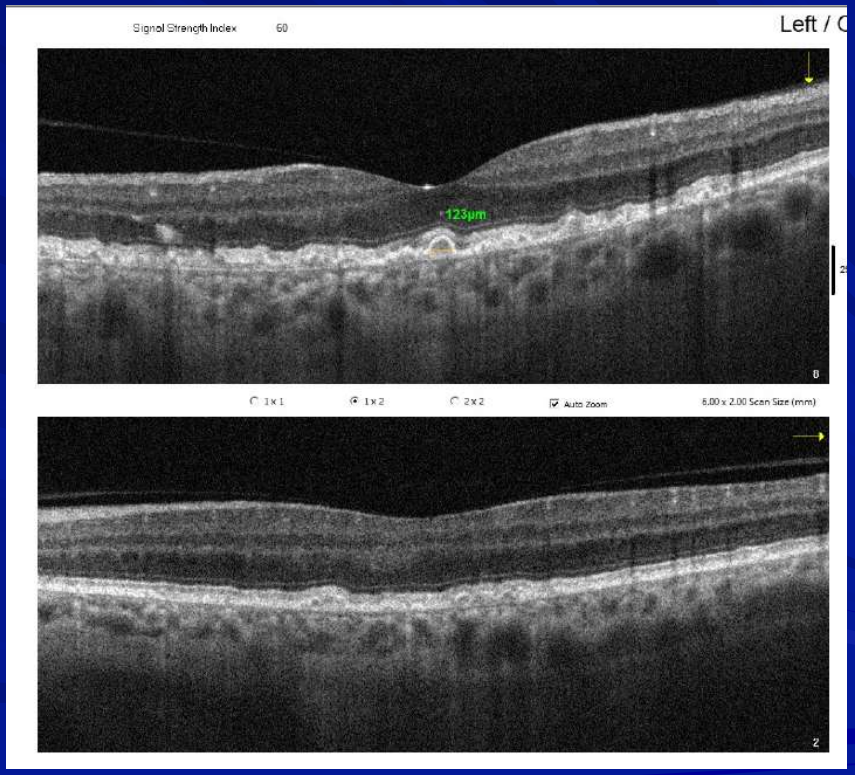
- Will knowledge of AMD genetic risk lead to quantifiable, sustained healthy changes in lifestyle?
- Randomized, controlled trial of pre-symptomatic genetic risk testing and counseling
  - immediate versus deferred disclosure
- 18-64 years-old w/o AMD
- Outcomes
  - Skin carotenoids by RRS and RS
  - Macular pigment by Spectralis AFI
  - Lifestyle surveys
- Awaiting NEI funding



Macular Pigment

Foveal Pigment?





Macular Pigment
Foveal Pigment?

Imaging lutein and zeaxanthin in the human retina with confocal resonance Raman microscopy

Binxing Li[a], Evan W. George[a], Gregory T. Rognon[a], Aruna Gorusupudi[a], Arunkumar Ranganathan[a], Fu-Yen Chang[a], Linjia Shi[a], Jeanne M. Frederick[a], and Paul S. Bernstein[a,1]

[a]Department of Ophthalmology and Visual Sciences, Moran Eye Center, University of Utah School of Medicine, Salt Lake City, UT 84132

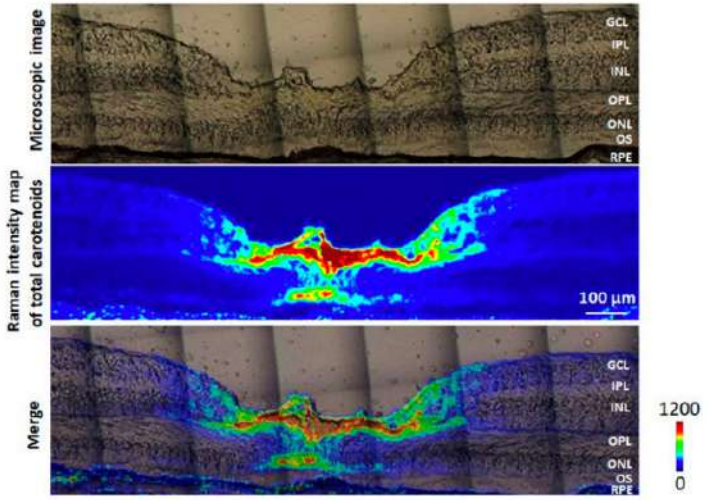
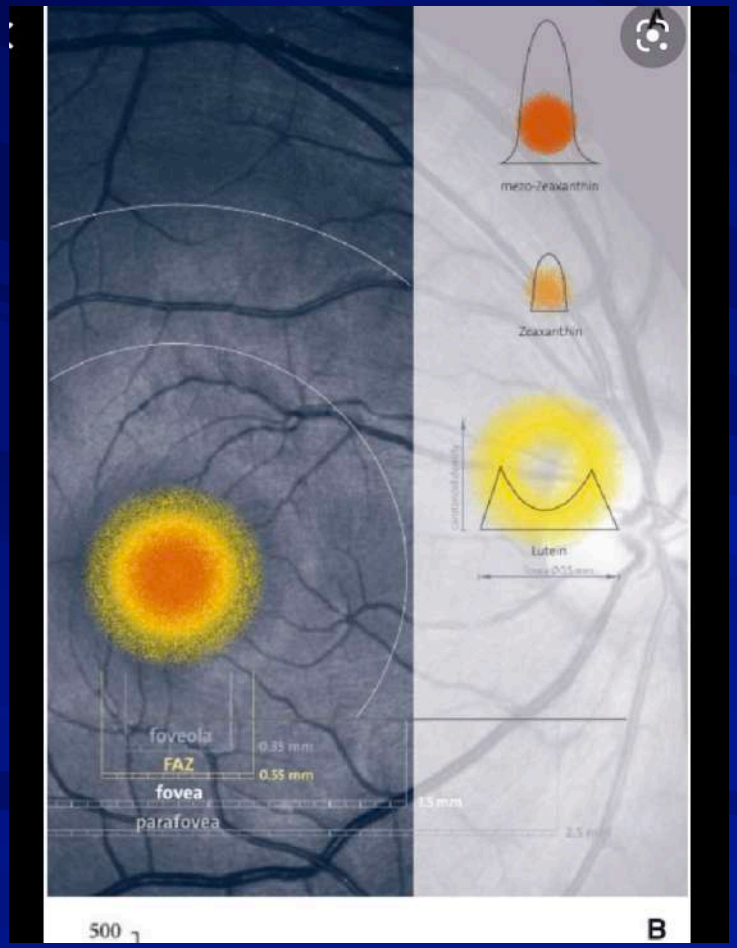
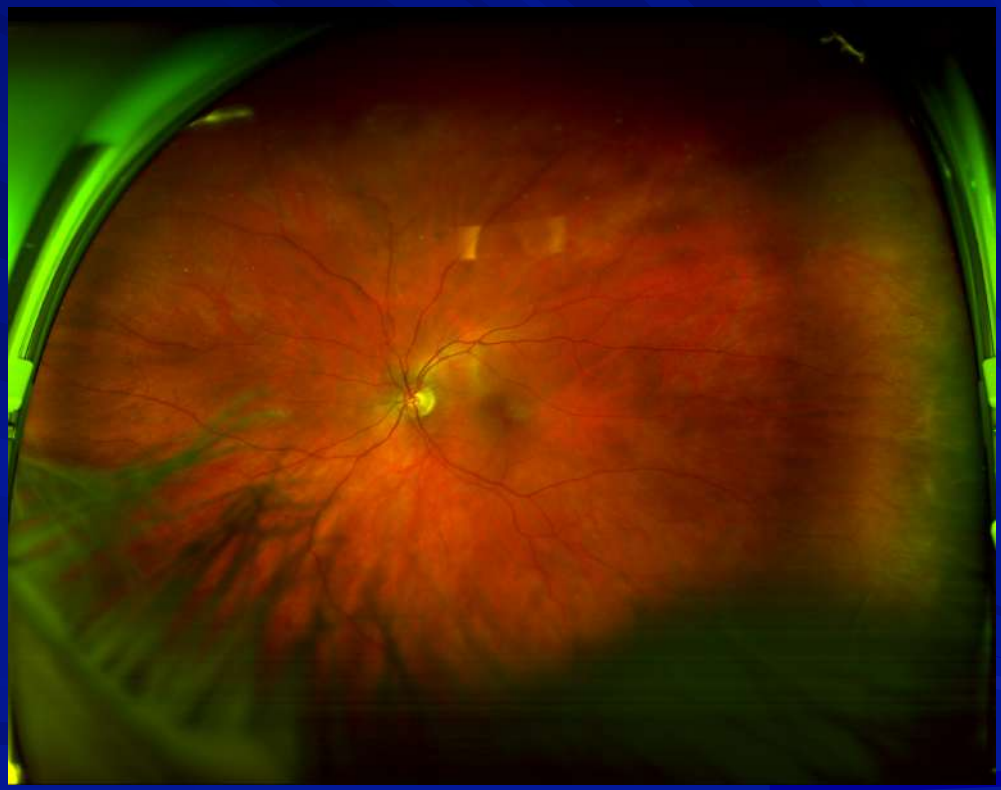


Fig. 4. Distribution of total carotenoids in a human retinal section. (*Top*) A

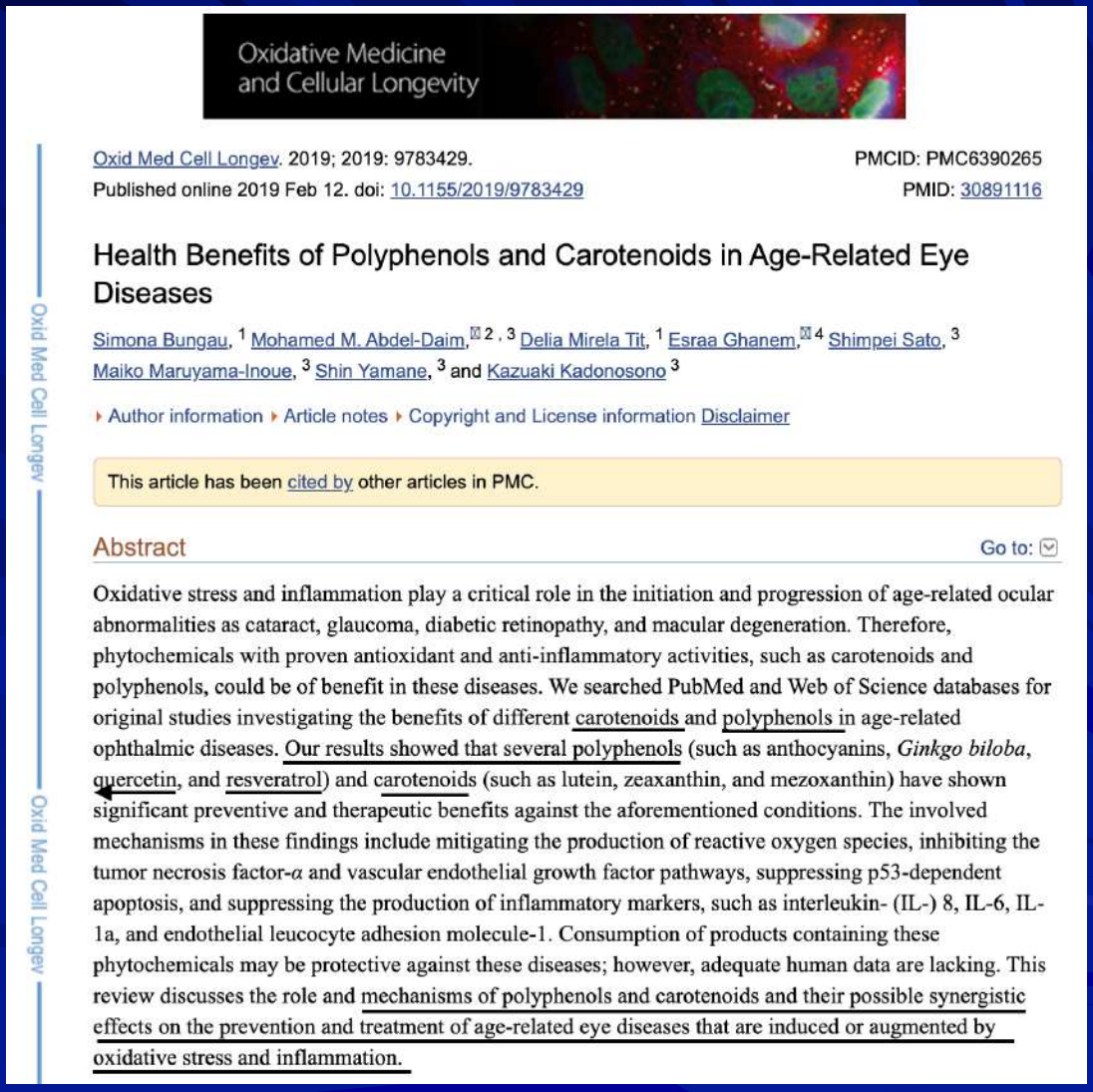

meso-Zeaxanthin
Zeaxanthin
Lutein
foveola
FAZ
0.35 mm
0.55 mm
fovea
1.5 mm
parafovea
2.5 mm
500
B



Question

- Do you recommend resveratrol and quercetin antioxidants when treating ocular/retinal conditions?
  - Yes
  - No

Why Are We Only Treating Half the Retina?



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PMCID: PMC6390265
PMID: 30891116

Health Benefits of Polyphenols and Carotenoids in Age-Related Eye Diseases

Simona Bungau, [1] Mohamed M. Abdel-Daim, [2,3] Delia Mirela Tit, [1] Esraa Ghanem, [4] Shimpei Sato, [3] Maiko Maruyama-Inoue, [3] Shin Yamane, [3] and Kazuaki Kadonosono [3]

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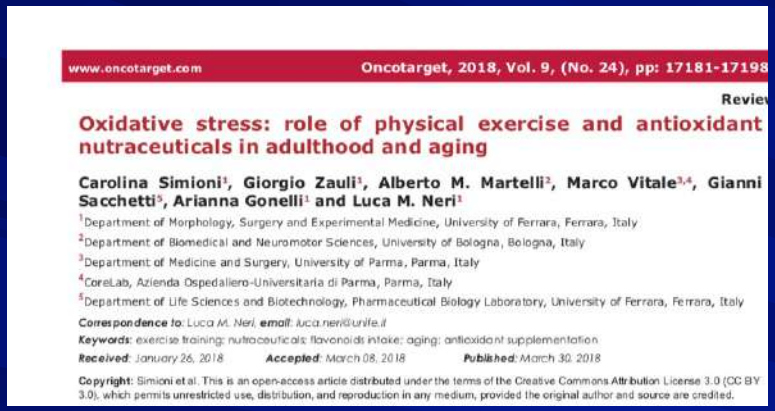
Abstract

Go to:

Oxidative stress and inflammation play a critical role in the initiation and progression of age-related ocular abnormalities as cataract, glaucoma, diabetic retinopathy, and macular degeneration. Therefore, phytochemicals with proven antioxidant and anti-inflammatory activities, such as carotenoids and polyphenols, could be of benefit in these diseases. We searched PubMed and Web of Science databases for original studies investigating the benefits of different carotenoids and polyphenols in age-related ophthalmic diseases. Our results showed that several polyphenols (such as anthocyanins, *Ginkgo biloba*, quercetin, and resveratrol) and carotenoids (such as lutein, zeaxanthin, and mezoxanthin) have shown significant preventive and therapeutic benefits against the aforementioned conditions. The involved mechanisms in these findings include mitigating the production of reactive oxygen species, inhibiting the tumor necrosis factor-α and vascular endothelial growth factor pathways, suppressing p53-dependent apoptosis, and suppressing the production of inflammatory markers, such as interleukin- (IL-) 8, IL-6, IL-1a, and endothelial leucocyte adhesion molecule-1. Consumption of products containing these phytochemicals may be protective against these diseases; however, adequate human data are lacking. This review discusses the role and mechanisms of polyphenols and carotenoids and their possible synergistic effects on the prevention and treatment of age-related eye diseases that are induced or augmented by oxidative stress and inflammation.

Carotenoids and Polyphenols



www.oncotarget.com Oncotarget, 2018, Vol. 9, (No. 24), pp: 17181-17198

Review

Oxidative stress: role of physical exercise and antioxidant nutraceuticals in adulthood and aging

Carolina Simioni[1], Giorgio Zauli[1], Alberto M. Martelli[2], Marco Vitale[3,4], Gianni Sacchetti[5], Arianna Gonelli[1] and Luca M. Neri[1]

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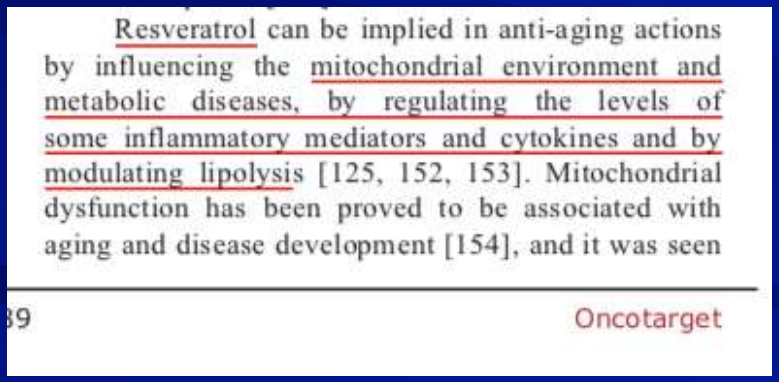
[2]Department of Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy
[3]Department of Medicine and Surgery, University of Parma, Parma, Italy
[4]CoreLab, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy
[5]Department of Life Sciences and Biotechnology, Pharmaceutical Biology Laboratory, University of Ferrara, Ferrara, Italy

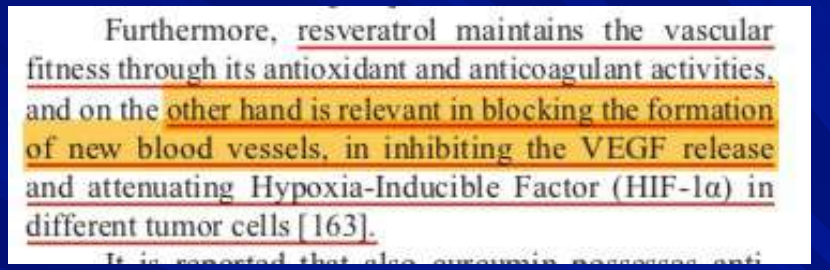
Correspondence to: Luca M. Neri, **email:** luca.neri@unife.it

Keywords: exercise training; nutraceuticals; flavonoids intake; aging; antioxidant supplementation

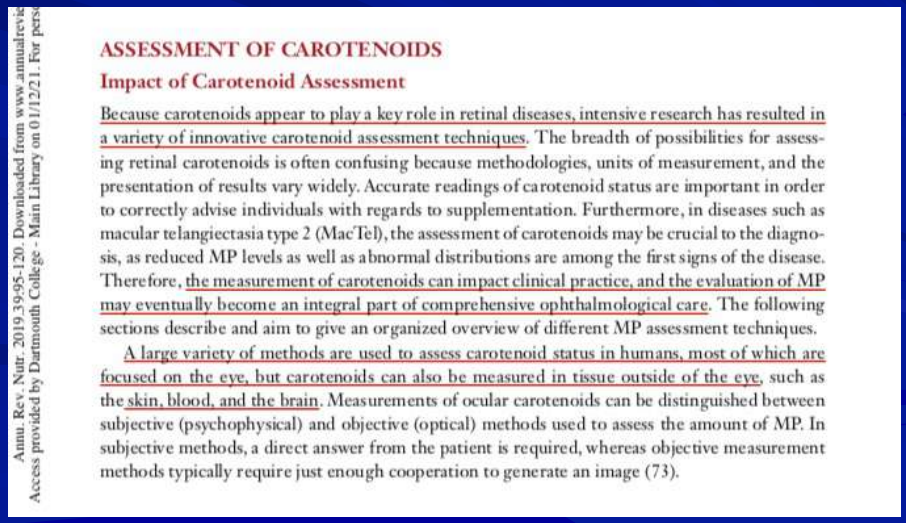
Received: January 26, 2018 **Accepted:** March 08, 2018 **Published:** March 30, 2018



Resveratrol can be implied in anti-aging actions by influencing the mitochondrial environment and metabolic diseases, by regulating the levels of some inflammatory mediators and cytokines and by modulating lipolysis [125, 152, 153]. Mitochondrial dysfunction has been proved to be associated with aging and disease development [154], and it was seen



Furthermore, resveratrol maintains the vascular fitness through its antioxidant and anticoagulant activities, and on the other hand is relevant in blocking the formation of new blood vessels, in inhibiting the VEGF release and attenuating Hypoxia-Inducible Factor (HIF-1α) in different tumor cells [163].



ASSESSMENT OF CAROTENOIDS

Impact of Carotenoid Assessment

Because carotenoids appear to play a key role in retinal diseases, intensive research has resulted in a variety of innovative carotenoid assessment techniques. The breadth of possibilities for assessing retinal carotenoids is often confusing because methodologies, units of measurement, and the presentation of results vary widely. Accurate readings of carotenoid status are important in order to correctly advise individuals with regards to supplementation. Furthermore, in diseases such as macular telangiectasia type 2 (MacTel), the assessment of carotenoids may be crucial to the diagnosis, as reduced MP levels as well as abnormal distributions are among the first signs of the disease. Therefore, the measurement of carotenoids can impact clinical practice, and the evaluation of MP may eventually become an integral part of comprehensive ophthalmological care. The following sections describe and aim to give an organized overview of different MP assessment techniques.

A large variety of methods are used to assess carotenoid status in humans, most of which are focused on the eye, but carotenoids can also be measured in tissue outside of the eye, such as the skin, blood, and the brain. Measurements of ocular carotenoids can be distinguished between subjective (psychophysical) and objective (optical) methods used to assess the amount of MP. In subjective methods, a direct answer from the patient is required, whereas objective measurement methods typically require just enough cooperation to generate an image (73).

Measuring Carotenoids and the Macular Pigment

- Biophotonic Scanner
  - ★ Measures carotenoids
  - ★ Based on an optical method known as Resonant Raman Spectroscopy (RSS)
    - Used for many years in research laboratories
  - ★ Skin RRS measurements
    - Noninvasive
    - Objective
    - Reliable methods to assess carotenoid levels
      - Ocular
      - Systemic

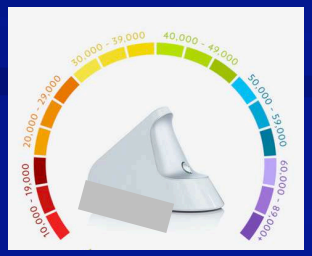
Carotenoid Levels

ARVO
The Association for Research in Vision and Ophthalmology

Scanner correlates to blood and macular pigment

read study

- Biomarker of health for diet and lifestyle
  - ★ Yale University
- Phospholipid bi-layer
- Carotenoids, flavonoids, and polyphenols



Clinical and Epidemiologic Research

Correlations Between Macular, Skin, and Serum Carotenoids

Christopher D. Conrady,[1] James P. Bell,[1] Brian M. Besch,[1] Aruna Gorusupudi,[1] Kelliann Farnsworth,[1] Igor Ermakov,[2] Mohsen Sharifzadeh,[2] Maia Ermakova,[2] Werner Gellermann,[1,2] and Paul S. Bernstein[1]

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[2]Image Technologies Corporation, Salt Lake City, Utah, United States

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Accepted: June 18, 2017

Citation: Conrady CD, Bell JP, Besch BM, et al. Correlations between macular, skin, and serum carotenoids. *Invest Ophthalmol Vis Sci*. 2017;58:3616–3627. DOI:10.1167/iovs.17-21818

Purpose. Ocular and systemic measurement and imaging of the macular carotenoids lutein and zeaxanthin have been employed extensively as potential biomarkers of AMD risk. In this study, we systematically compare dual wavelength retinal autofluorescence imaging (AFI) of macular pigment with skin resonance Raman spectroscopy (RRS) and serum carotenoid levels in a clinic-based population.

Methods. Eighty-eight patients were recruited from retina and general ophthalmology practices from a tertiary referral center and excluded only if they did not have all three modalities tested, had a diagnosis of macular telangiectasia (MacTel) or Stargardt disease, or had poor AFI image quality. Skin, macular, and serum carotenoid levels were measured by RRS, AFI, and HPLC, respectively.

Results. Skin RRS measurements and serum zeaxanthin concentrations correlated most strongly with AFI macular pigment volume under the curve (MPVUC) measurements up to 9° eccentricity relative to MPVUC or rotationally averaged macular pigment optical density (MPOD) measurements at smaller eccentricities. These measurements were reproducible and not significantly affected by cataracts. We also found that these techniques could readily identify subjects taking oral carotenoid-containing supplements.

Conclusions. Larger macular pigment volume AFI and skin RRS measurements are noninvasive, objective, and reliable methods to assess ocular and systemic carotenoid levels. They are an attractive alternative to psychophysical and optical methods that measure MPOD at a limited number of eccentricities. Consequently, skin RRS and MPVUC at 9° are both reasonable biomarkers of macular carotenoid status that could be readily adapted to research and clinical settings.

Keywords: macular pigment, carotenoids, macula

The New Standard

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Turning Discovery Into Health

- Quick Test (approx. 30 sec)
- Portable
- Cost Effective
- Remeasure in 60 days
- Reassurance to you and patient

Raman Spectroscopy

478nm PHOTONS ARE EMITTED FROM THE SCANNER

AS 478nm PHOTONS STRIKE CAROTENOIDS IN THE SKIN, THEY ARE REFLECTED BACK AS 518nm PHOTONS

Resonance Raman spectroscopic evaluation of skin carotenoids as a biomarker of carotenoid status for human studies

Susan T. Mayne [a,*], Brenda Cartmel [a], Stephanie Scarmo [a,b], Lisa Jahns [c], Igor V. Ermakov [d], Werner Gellermann [d]

[a] Yale School of Public Health and Yale Cancer Center, 60 College St., P.O. Box 208034, New Haven, CT 06520, USA
[b] Center for Science in the Public Interest, 1220 L Street, N.W., Suite 300, Washington, DC 20005, US
[c] USDA/ARS Grand Forks Human Nutrition Research Center, 2420 2nd Avenue North, Grand Forks, 58203,
[d] Department of Physics and Astronomy, University of Utah, Salt Lake City, UT 84

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100 STUDIES

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Keywords:
Carotenoids
Skin
Resonance Raman spectroscopy
Beta-carotene
Biomarker

ABSTRACT

Resonance man sproscopy RS) is a invasive method that has been developed to assess carotenoid statu human ues uding human skin *in vivo*. Skin carotenoid status has been suggested as a promising marker for human studies. This nuscript describes research done relevant to the development of th biomarker, including its repod ibility, lidity, feasibility for use in field settings, and factors that affect the biomark such a t, mok , and adiposity. Recent studies have evaluated the response of the ar r to on olli carotenoid interventions, both supplement-based and dietary [e.g., provision of a hi -ca ter id t and vegetable (F/V)-enriched diet], demonstrating consistent response to inter tio The totality of evidence supports the use of skin carotenoid status as an objective biomarker f/V intake, although in the cross-sectional setting, diet explains only some of the variation in this biomarker. However, this limitation is also a strength in that skin carotenoids may effectively serve as an integrated biomarker of health, with higher status reflecting greater F/V intake, lack of smoking, and lack of adiposity. Thus, this biomarker holds promise as both a health biomarker and an objective indicator of F/V intake, supporting its further development and utilization for medical and public health purposes.

*Arch Biochem Biophys. PMC 2014 Nov 15.

ARVO STUDY

Interrelationships between Macula, Skin and Serum Carotenoids- Paul Bernstein, Werner Gellerman et al ARVO May 2016

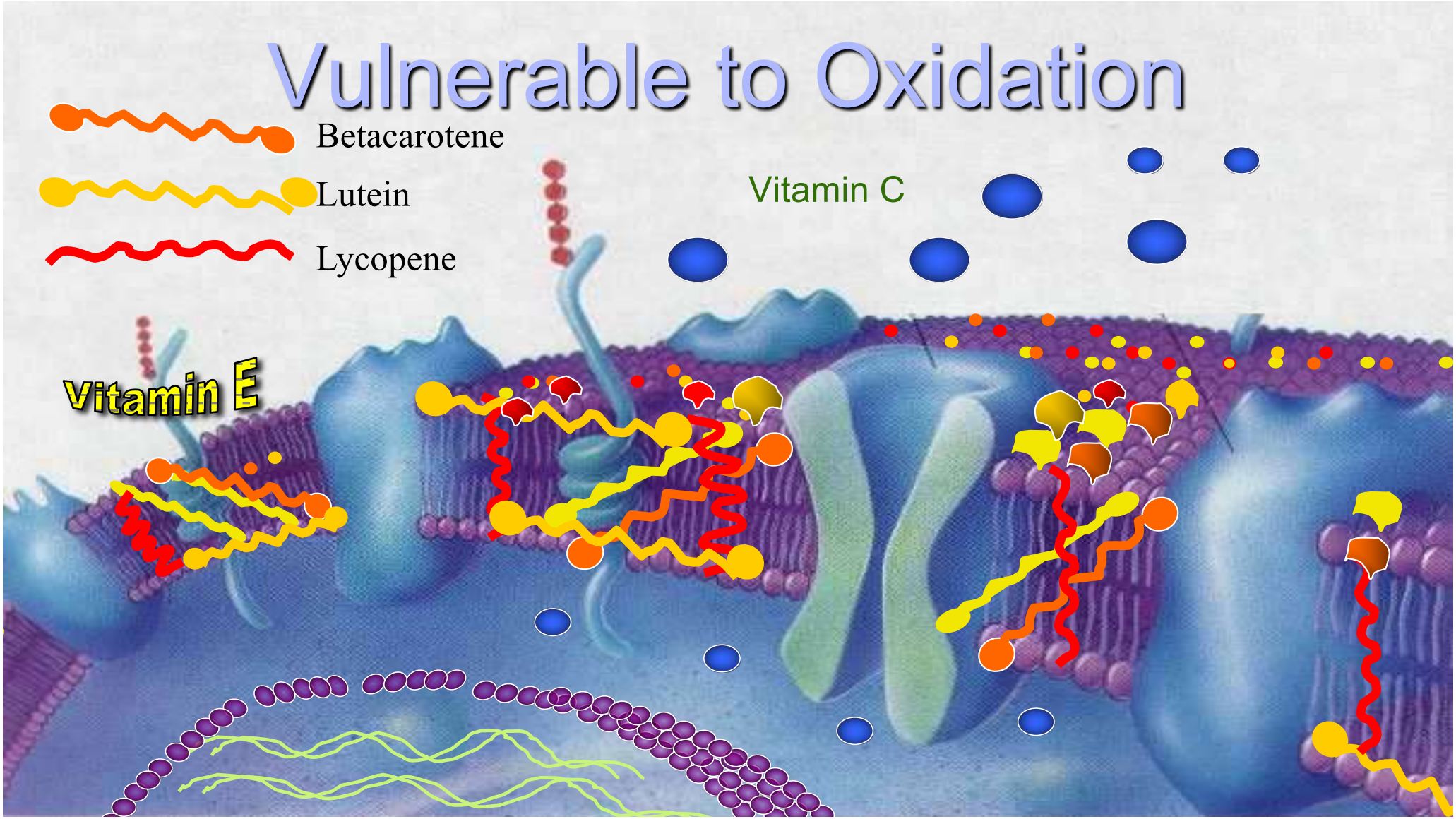
Conclusions:

"Our results emphasize the importance of measuring the total amount of carotenoids in the macula region using an objective image based modality such as AFI w Spectralis rather than subjective MPOD."

Skin resonance Raman Spectroscopy of skin carotenoids is a reasonable biomarker of macula carotenoid status. and correlates better than than subjective MPOD tests.

The objective hand scanner is better than the subjective Macuscope, QuantifEYE, and Densitometer for estimating macula pigment.

Vulnerable to Oxidation



Do We Need?


COMING SOON
Optic Nerve
& Eye Pressure Support
Supports Optic Nerve Health and Eye Pressure.
Promotes Optic Blood Flow & Retinal Health.
Dietary Supplement
30
Capsules
Optic Nerve and Eye Pressure Support

Are you taking a supplement?

53-year-old man

- Family history of AMD
  - Dad with 43 injections for AMD
- Pre-diabetic with borderline HbA1c
- Vision 20/20 OU
- DFE- retina clear
- OCT normal
- Passes dark adaptation

CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

Dear [redacted]

Recently, on 12/15/2020, you met with me and I scanned the palm of your hand with the [redacted] BioPhotonic Scanner. Your scan returned a Skin Carotenoid Score (SCS) of 26000.

This score represents the current carotenoid level of your skin. The higher the score, the more carotenoids your body is receiving.

Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
Vitamin A (83% as Beta Carotene (1875 mcg RAE) from *Blakeslea trispora*, and Vitamin A palmitate) (375 mcg RAE)	2250 mcg RAE	250%
Vitamin C (as Calcium Ascorbate)	200 mg	222%
Vitamin D (as Cholecalciferol)	5 mcg (200 IU)	25%
Vitamin E (as D-Alpha-Tocopheryl Acetate, D-Alpha Tocopherol, Tocotrienols)	50.3 mg	335%
Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Calcium (as Calcium Carbonate, Di-Calcium Malate, Calcium Ascorbate)	250 mg	19%
Iodine (as Potassium Iodide)	50 mcg	33%
Magnesium (as Magnesium Glycinate, Magnesium Oxide)	125 mg	30%
Zinc (as Zinc Bisglycinate)	7.5 mg	68%
Selenium (as L-Selenomethionine, Sodium Selenite)	70 mcg	127%
Copper (as Copper Bisglycinate)	0.5 mg	56%
Manganese (as Manganese Bisglycinate)	1 mg	43%
Chromium (as Chromium Nicotinate Glycinate)	100mcg	286%
Molybdenum (as Molybdenum Bisglycinate)	37.5 mcg	83%
Polyphenol and Flavonoid Blend	97.5 mg	*
Catechins (from *Camellia sinensis* Leaf Extract)	(45 mg)	*
Quercetin	(25 mg)	*
Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	*
Resveratrol (from *Polygonum cuspidatum* root extract)	(2.5 mg)	*
Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	3.5 mg	*
Lycopene (as Lycopene)	(2.5 mg)	*
Lutein (from Marigold Flower Extract)	(1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	10 mcg	*

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

SUPPLEMENT FACTS

Supplement Facts

Serving Size 2 Softgels — Servings Per Container 60

Amount Per Serving		% DV
Total Calories	15	
Total Fat	1 g	1%*
Saturated Fat	0 g	0%*
Trans Fat	0 g	
Vitamin D_3 (as cholecalciferol)	12.5 mcg (500 IU)	63%
Vitamin K_2 (as menaquinone-7)	20 mcg	17%
Ultra-pure fish oil concentrate:	1055 mg	**
EPA (Eicosapentaenoic acid)	300 mg	**
DHA (Docosahexaenoic acid)	200 mg	**
Citrus Bioflavonoids (including hesperidin and naringin)	100 mg	**
Purple corn (*Zea mays L.*) cob extract including anthocyanins	66.67 mg	**
Alpha Lipoic Acid	50 mg	**
Quercetin (from *Dimorphandra mollis* fruit extract)	37.5 mg	**
D-Limonene (from *Citrus sinensis* peel)	25 mg	**
Rosemary (*Rosmarinus officinalis L.*) leaf extract including carnosic acid	18.75 mg	**
Resveratrol (from *Polygonum cuspidatum* root)	15 mg	**
Coenzyme Q10	15 mg	**
Lycopene	2.5 mg	**
Lutein (from marigold flower (*Targetes erecta*))	2 mg	**
Astaxanthin (from *Haematococcus pluvialis* algae)	0.5 mg	**

* Percent Daily Values are based on a 2,000 Calorie Diet.
** Daily Value (DV) not established.

OTHER INGREDIENTS: Gelatin, Glycerin, Beeswax, Sunflower Lecithin, Vanillin.

CONTAINS: Fish (anchovies, sardines, mackerel).

53-year-old man

CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

Dear [redacted]

Recently, on 12/27/2020, you met with me and I scanned the palm of your hand with the [redacted] BioPhotonic Scanner. Your scan returned a Skin Carotenoid Score (SCS) of 33000.

This score represents the current carotenoid level of your skin. The higher the score, the more carotenoids your body is receiving.

33000

CONGRATULATIONS ON TAKING THE FIRST STEPS TOWARDS OPTIMIZING YOUR SCS

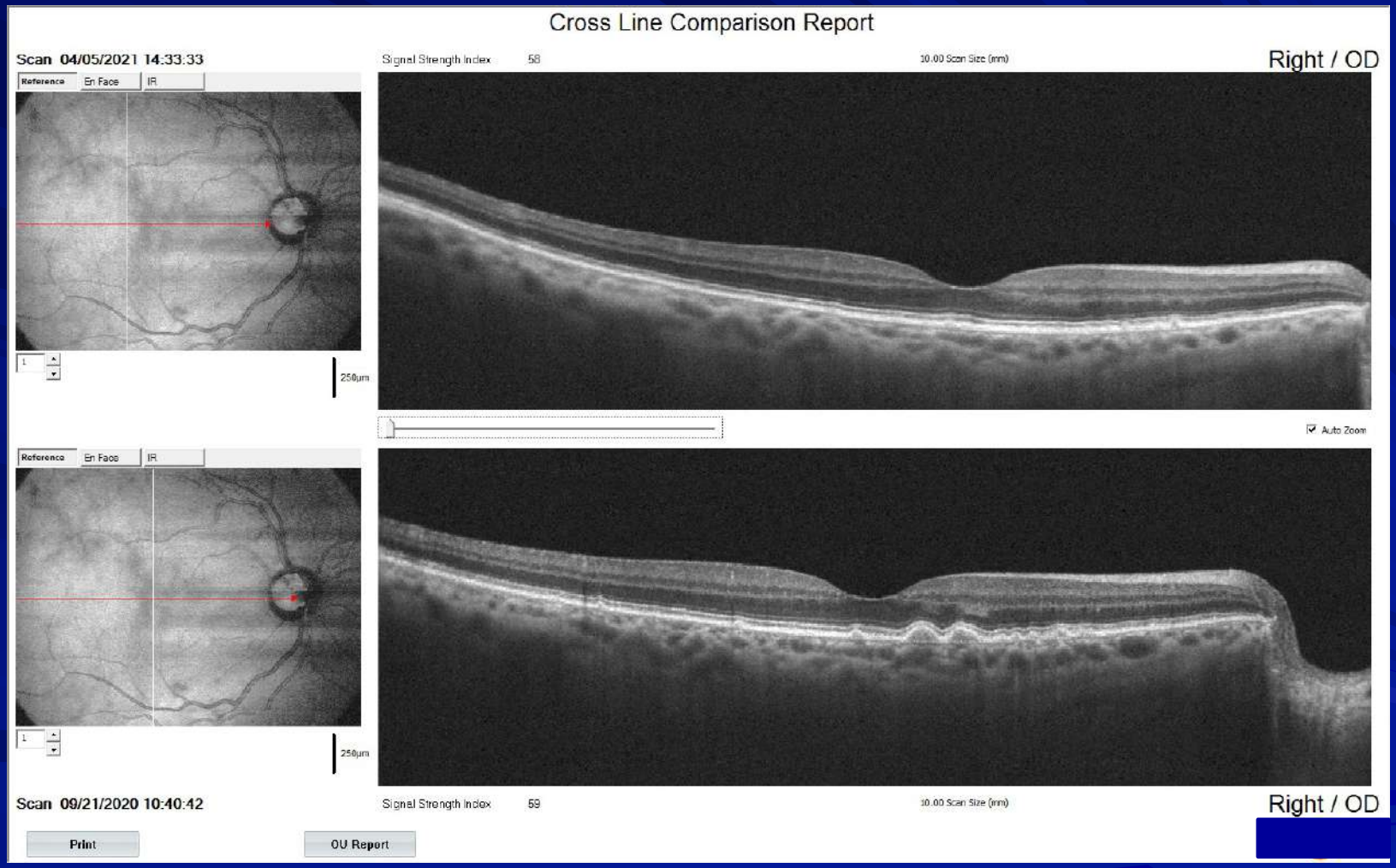
Dear [redacted]

Recently, on 01/23/2021, you met with me and I scanned the palm of your hand with the [redacted] BioPhotonic Scanner. Your scan returned a Skin Carotenoid Score (SCS) of 47000.

This score represents the current carotenoid level of your skin. The higher the score, the more carotenoids your body is receiving.

47000


Raster Comparison Report
Scan 09/29/2020 13:20:09
Reference
En Face
IR
Signal Strength Index 55
12.00 x 4.00 Scan Size (mm)
Right / OD
10
250µm
Auto Zoom
Reference
En Face
IR
10
250µm
Scan 06/23/2021 10:22:11
Signal Strength Index 43
12.00 x 4.00 Scan Size (mm)
Right / OD
OPTOVUE
Print
OU Report
49°F Sunny
10:46 AM
6/23/2021


Cross Line Comparison Report
Scan 04/05/2021 14:33:33
Signal Strength Index 58
10.00 Scan Size (mm)
Right / OD
Reference
En Face
IR
250µm
Auto Zoom
Scan 09/21/2020 10:40:42
Signal Strength Index 59
10.00 Scan Size (mm)
Right / OD
Print
OU Report

Ingredients

Ingredients	Amount	% Daily Value
Serving Size: 1 Packet		
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Vitamin K (as Phytonadione)	20 mcg	17%
Thiamin (as Thiamine Mononitrate)	3.75 mg	313%
Riboflavin (as Riboflavin)	4.25 mg	327%
Niacin (as Niacinamide)	17.5 mg NE	109%
Vitamin B6 (as Pyridoxine Hydrochloride)	5 mg	294%
Folate	500 mcg DFE (300 mcg folic acid)	125%
Vitamin B12 (as Cyanocobalamin)	15 mcg	625%
Biotin (as Biotin)	75 mcg	250%
Pantothenic Acid (as D-Calcium Pantothenate)	15 mg	300%
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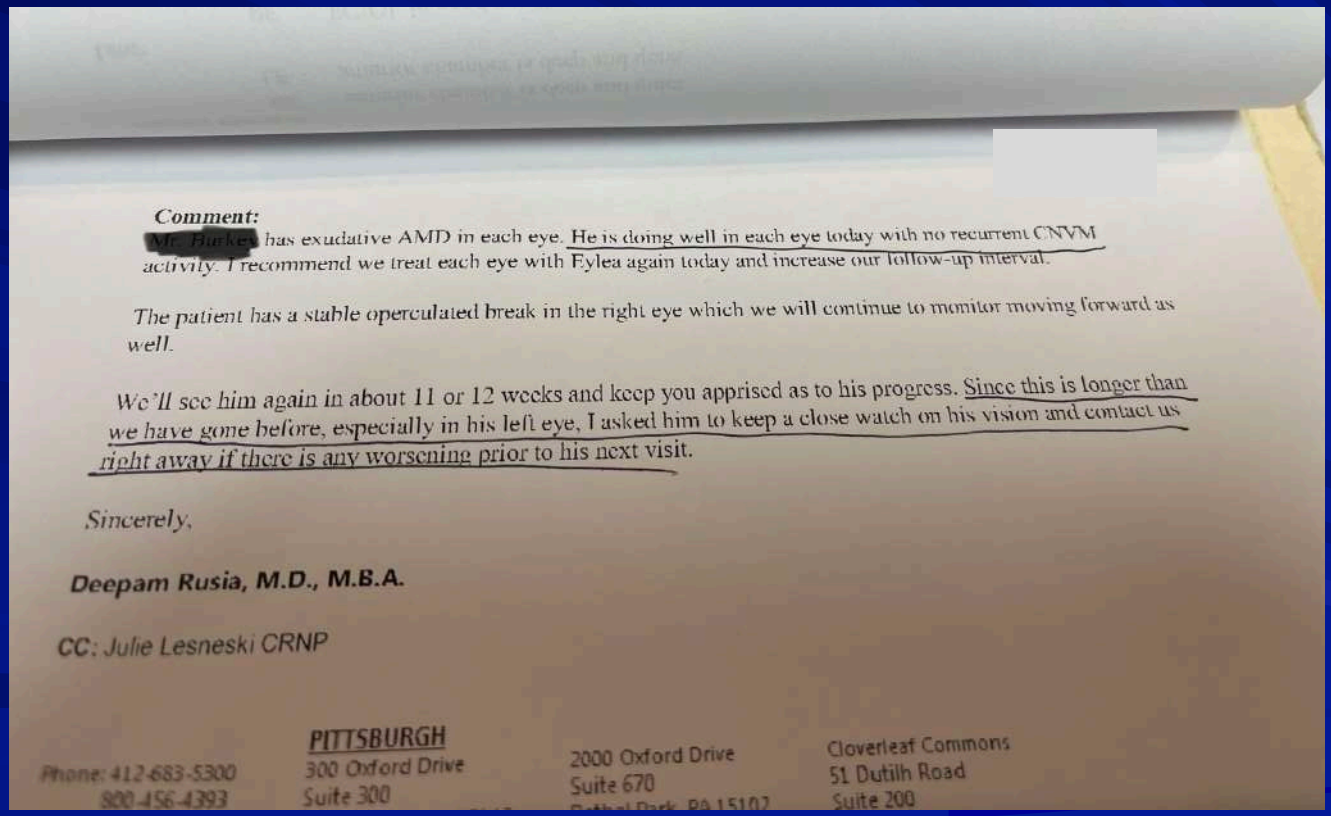
Quercetin	(25 mg)	*
Grape Seed Extract (min. 95% Polyphenols)	(12.5 mg)	*
Citrus Bioflavonoids (from Citrus Fruits)	12.5 mg)	*
Resveratrol (from *Polygonum cuspidatum* root extract)	(2.5 mg)	*
Mixed Tovopherols (Gamma, Delta & Beta Tocopherols)	53 mg	*
Alpha-Lipoic Acid	15 mg	*
Inositol (as Inositol)	5 mg	*
Carotenoid Blend	3.5 mg	*
Lycopene (as Lycopene)	(2.5 mg)	*
Lutein (from Marigold Flower Extract)	(1 mg)	*
Boron (as Boron Citrate)	1.5 mg	*
Vanadium (as Vanadyl Sulfate)	10 mcg	*

OTHER INGREDIENTS: Gelatin, Microcrystalline Cellulose, Crosmarmellose Sodium, Stearic Acid, Magnesium Stearate, Silicon Dioxide, Titanium Dioxide.

CONTAINS: Fish (Cod, Pollack, Haddock, Hake, Cusk, Redfish, Sole, Flounder).

Treat and Extend!



Comment:
[redacted] has exudative AMD in each eye. He is doing well in each eye today with no recurrent CNVM activity. I recommend we treat each eye with Eylea again today and increase our follow-up interval.

The patient has a stable operculated break in the right eye which we will continue to monitor moving forward as well.

We'll see him again in about 11 or 12 weeks and keep you apprised as to his progress. Since this is longer than we have gone before, especially in his left eye, I asked him to keep a close watch on his vision and contact us right away if there is any worsening prior to his next visit.

Sincerely,

Deepam Rusia, M.D., M.B.A.

CC: Julie Lesneski CRNP

PITTSBURGH

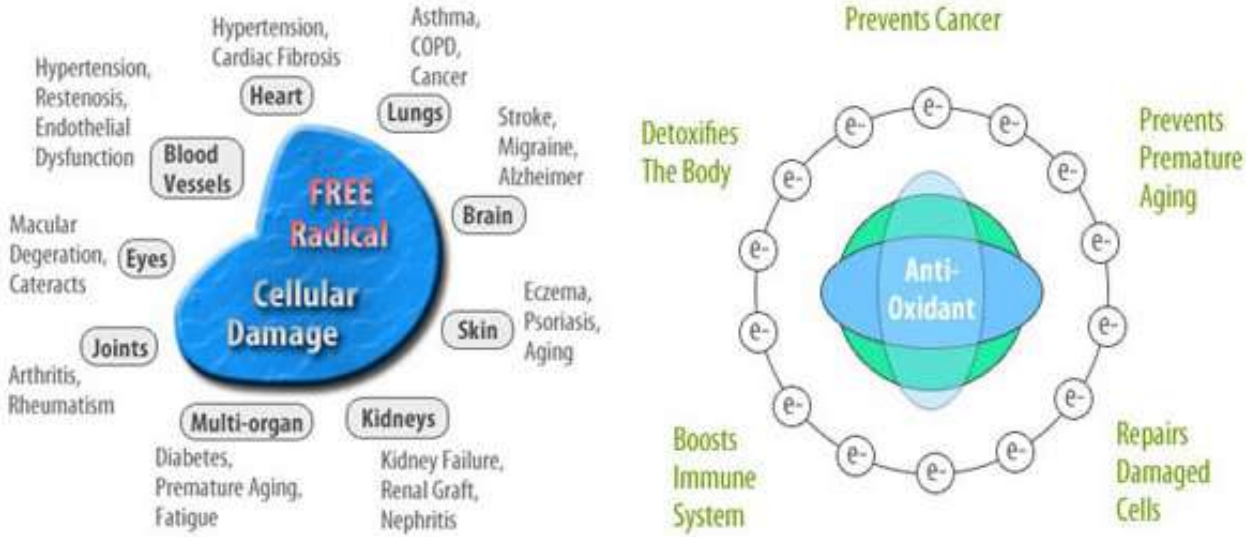
Phone: 412-683-5300
800-456-4393

300 Oxford Drive
Suite 300

2000 Oxford Drive
Suite 670

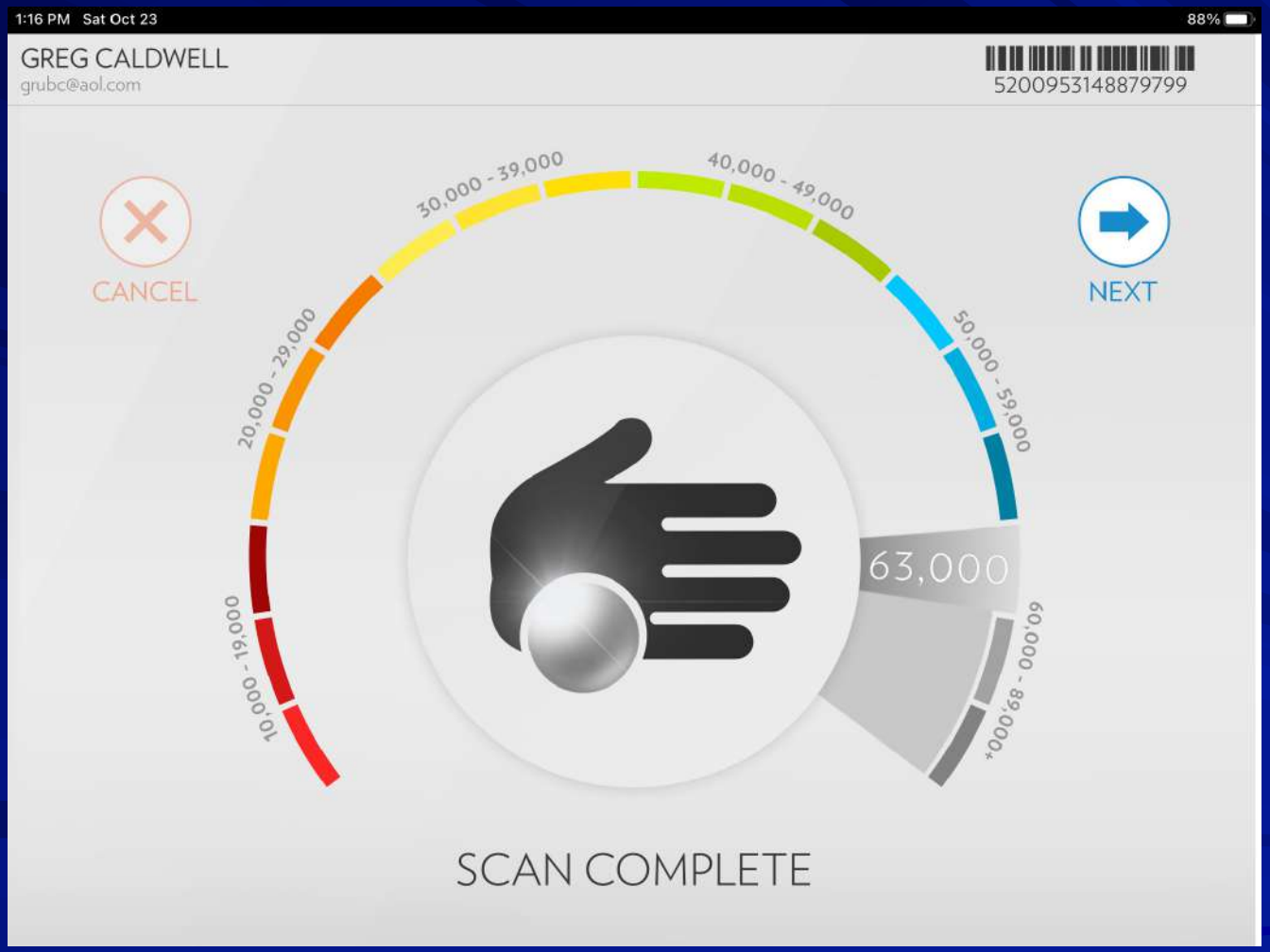
Cloverleaf Commons
51 Dutilh Road
Suite 200

Screen Everyone



Carotenoid and Antioxidant Levels in Ocular Disease and Systemic Health

- Plenty of evidence that carotenoids are beneficial in ocular and systemic prevention
- Patients are looking for guidance
  - Many are on supplements
    - Surprised what they are doing is minimally helping
- Measuring ensures the patient
- Antioxidants in the eye and body go beyond lutein and zeaxanthin
- Dr. Oz "Ultimate nutritional lie detector"
- Best benefit of all…


1:16 PM Sat Oct 23
88%
GREG CALDWELL
grubc@aol.com
5200953148879799
CANCEL
NEXT
10,000 - 19,000
20,000 - 29,000
30,000 - 39,000
40,000 - 49,000
50,000 - 59,000
60,000 - 89,000+
63,000
SCAN COMPLETE


"The Comfort Zone"
Find purpose
Deal with challenges and problem
Live dreams
Lack of self-confidence
COMFORT ZONE
Feel safe and in control
FEAR ZONE
Find excuses
Be affected by others' opinions
LEARNING ZONE
Acquire new skills
GROWTH ZONE
Set new goals
Extend your comfort zone
Conquer objectives

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Questions and Thank You!

Integrative and Functional Medicine
New Opportunities for Optometry

Greg Caldwell, OD, FAAO

Primary Eye Care Conference
Pittsburgh

Optometric Education Consultants

Saturday, February 17, 2024