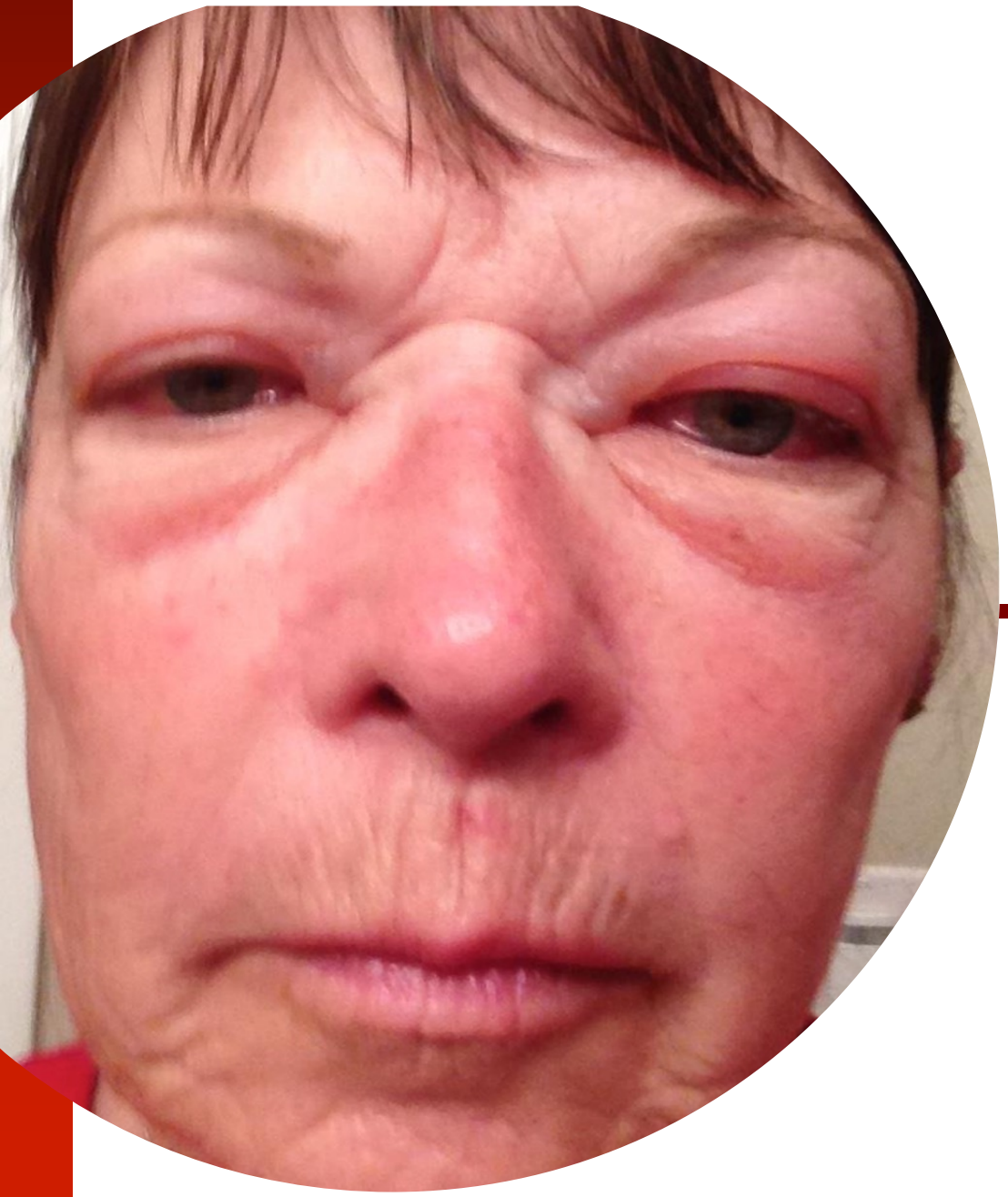
CASE STUDIES FOR THE 21ST CENTURY

Selina R. McGee, OD, FAAO



Case Presentation

65 y/o female with 4 months of eyelid swelling & redness

Diagnosed as allergy vs inflammation

- Treated with oral steroids x 8 weeks

She developed double vision

- Diagnosed with TED
- Treated with IV methylprednisolone 500 mg/week x 6 weeks then 250 mg

Developed loss of color vision

EYE EXAM

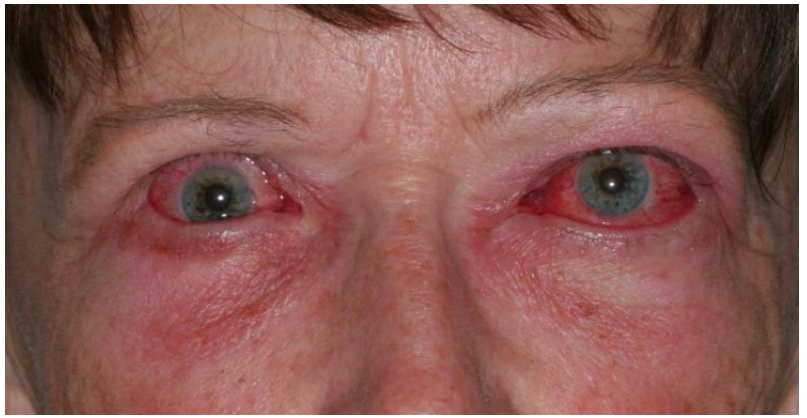
Vision:
- 20/80 OD 20/60 OS

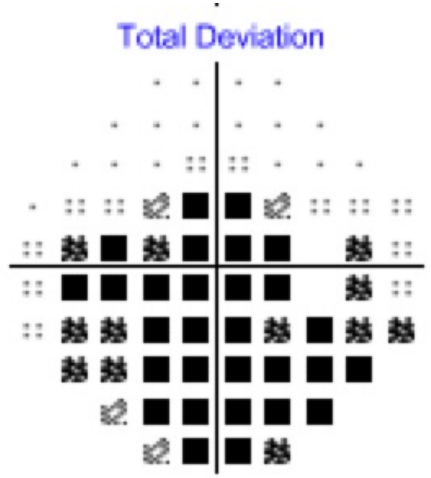
IOP: 28 OD, 26 OS
- Steroid response

EOM: -2 upgaze OD

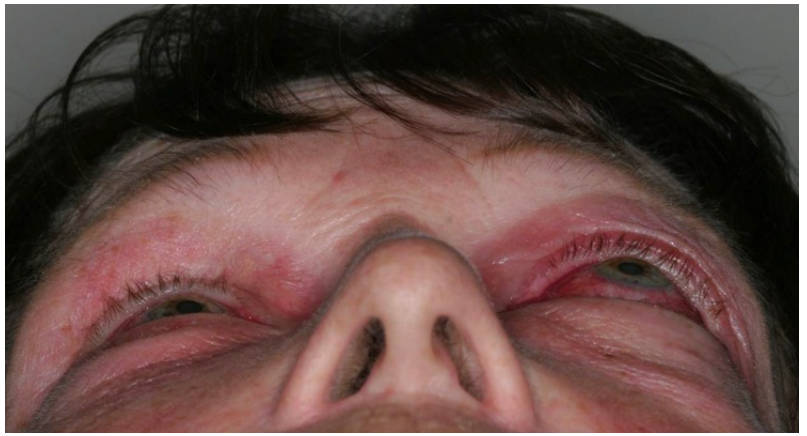
Pupils: 1+ RAPD OD

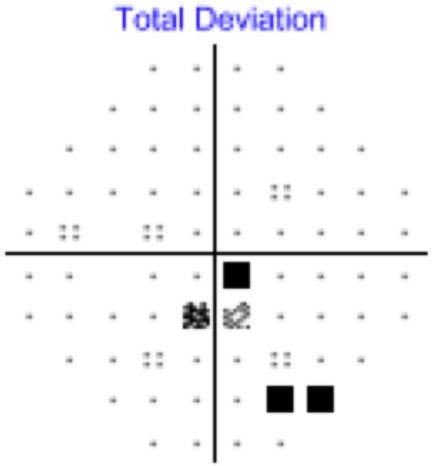
Color Vision 0/14 OD
- 14/14 OS





OD





OS

COMPRESSIVE OPTIC NEUROPATHY

Orbital decompression OD & IV steroids

- VA OD: 20/80 → 20/30

Active inflammation OS

- Treated with orbital XRT OS

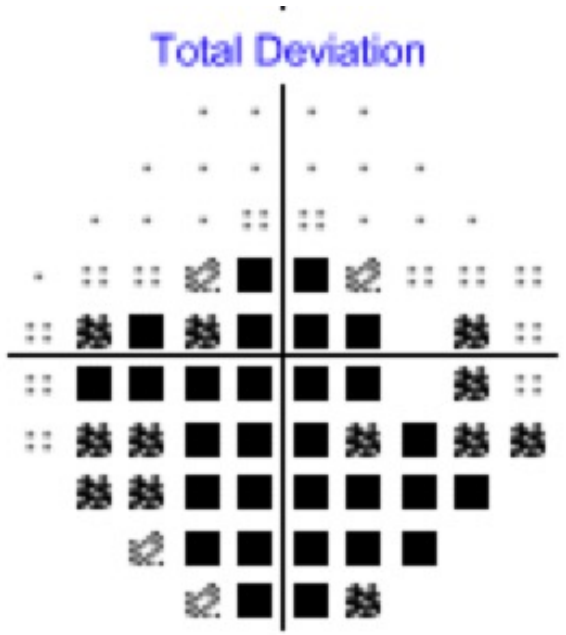
Developed CON OS

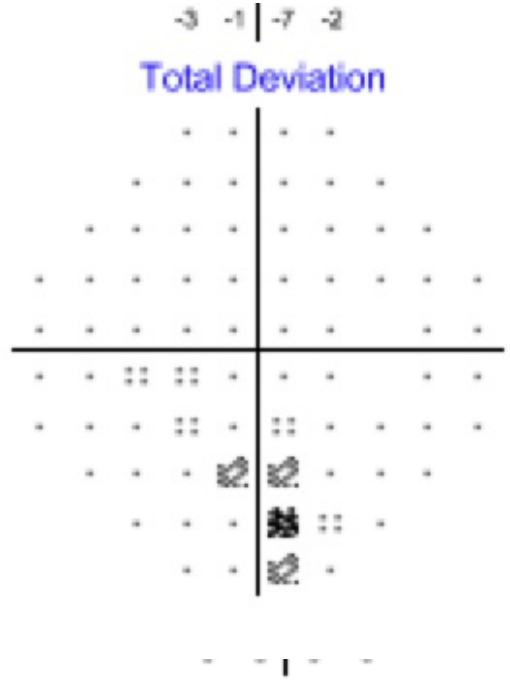
- + APD OS

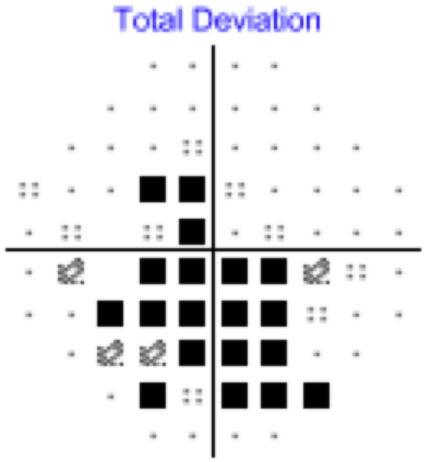
IV steroids 1g qd x 3

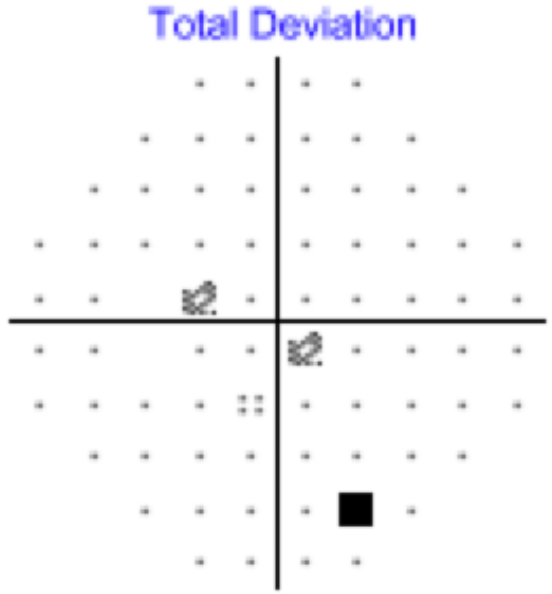
Orbital decompression OS

- VA OD: 20/30 → 20/25









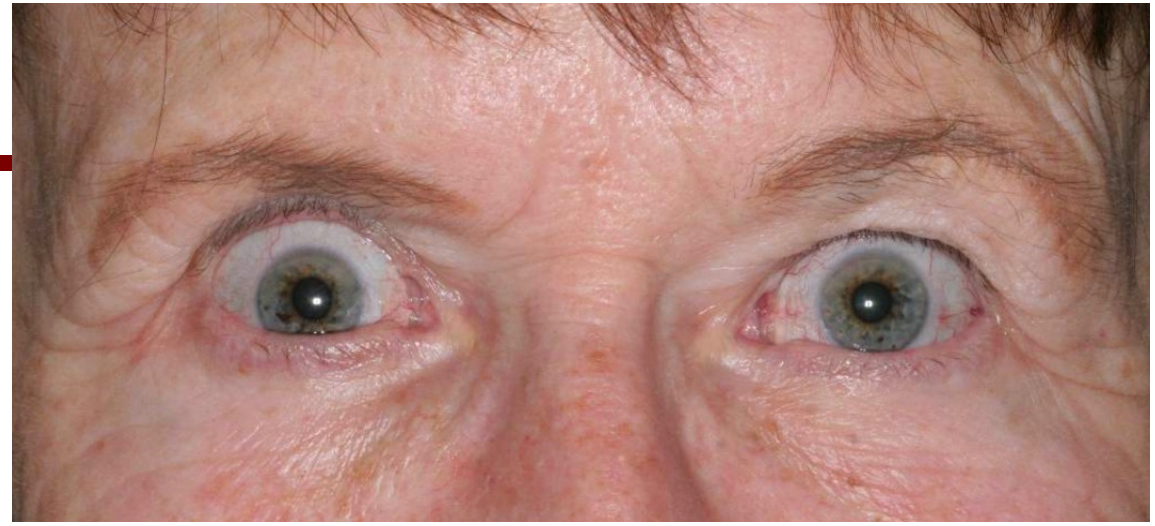
NEXT STEPS

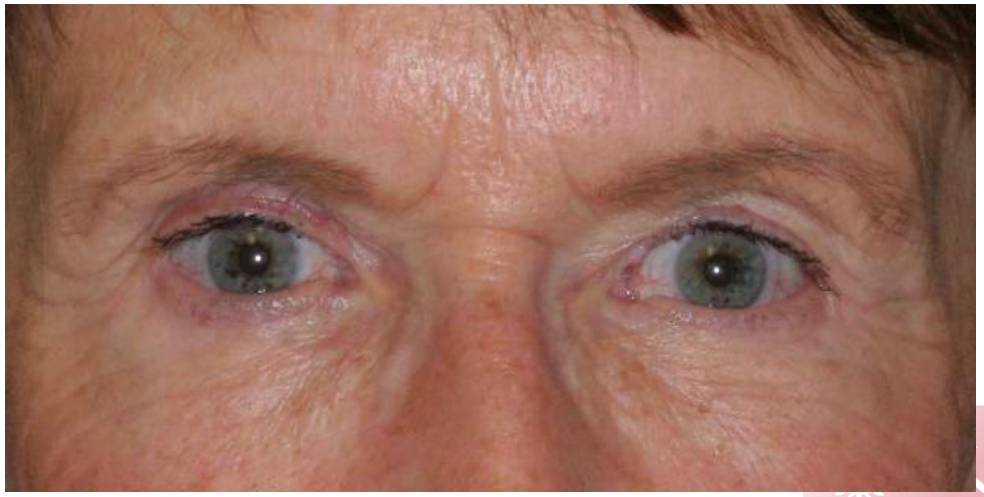
Restrictive strabismus

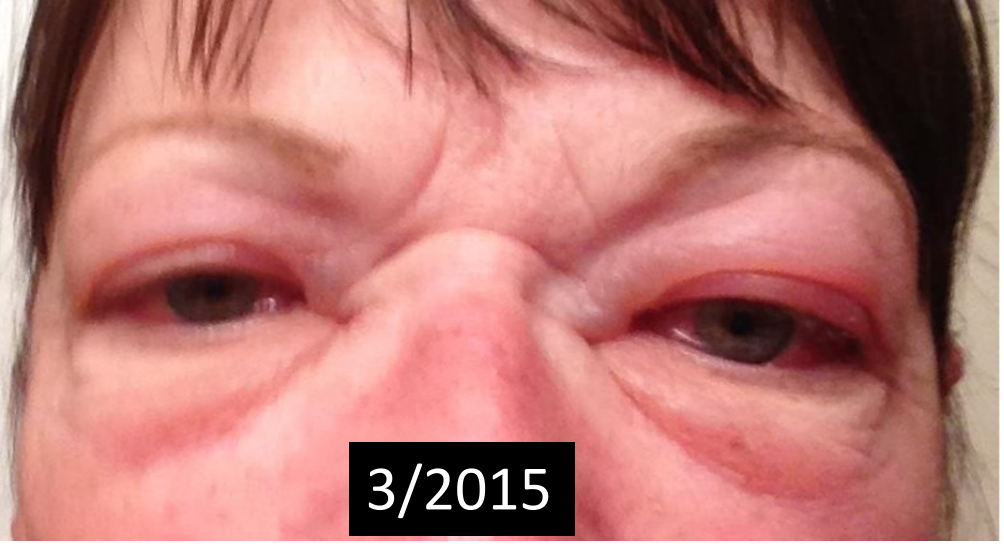
Eyelid retraction

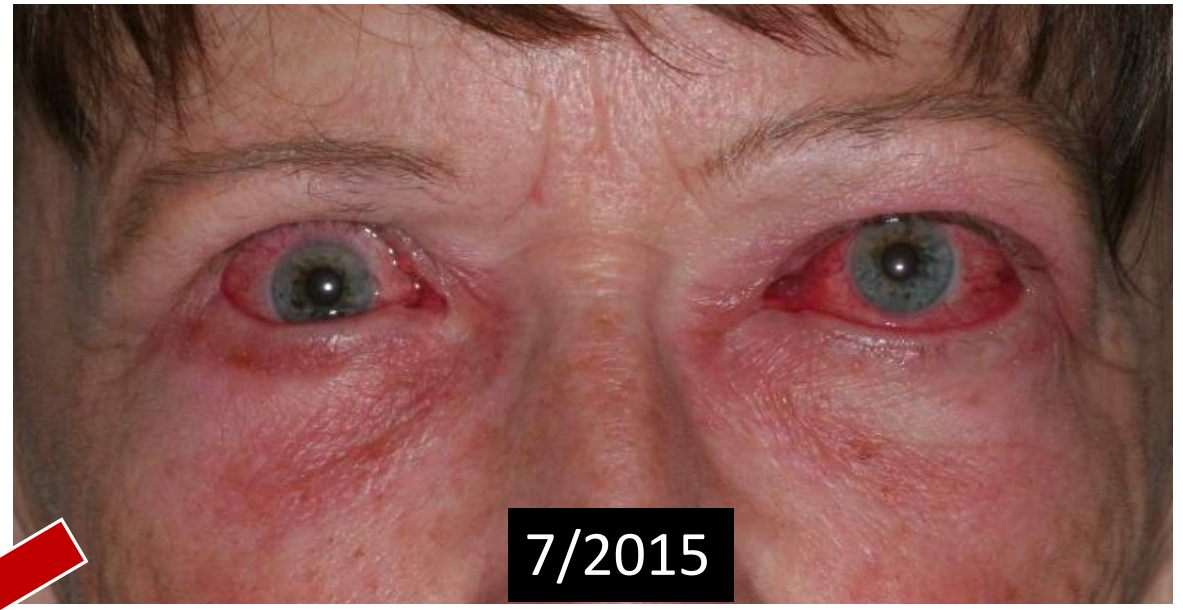
Treated with:

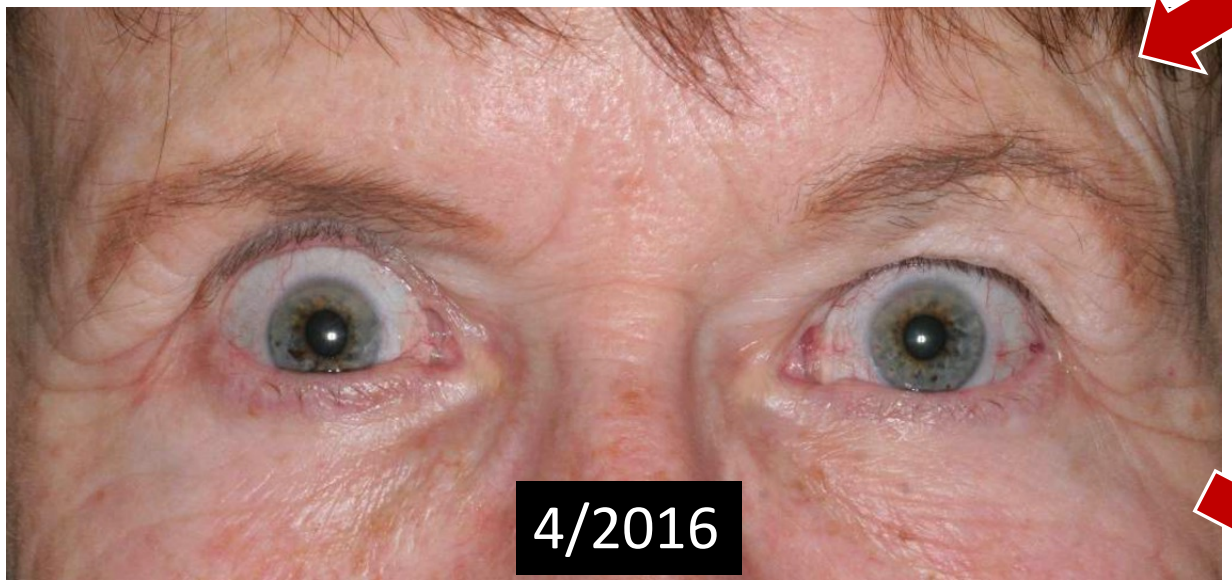
- Strabismus surgery
- Bilateral upper lid retraction repair






3/2015

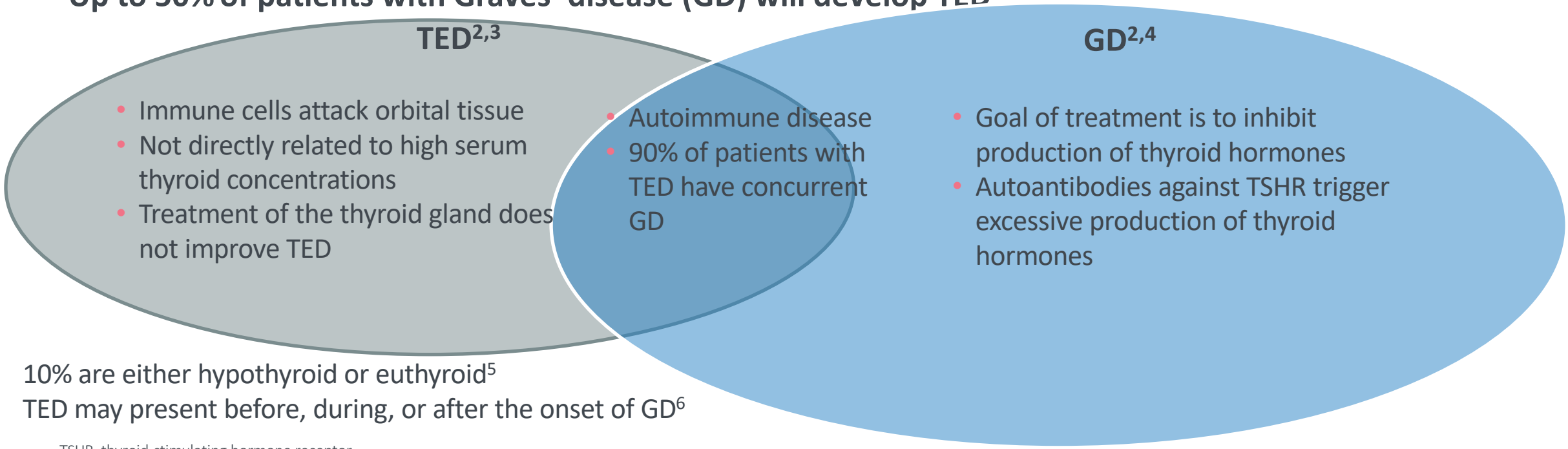

7/2015


4/2016


1/2017

TED IS THE MOST COMMON EXTRATHYROIDAL MANIFESTATION OF GRAVES' DISEASE

Up to 50% of patients with Graves' disease (GD) will develop TED[1]



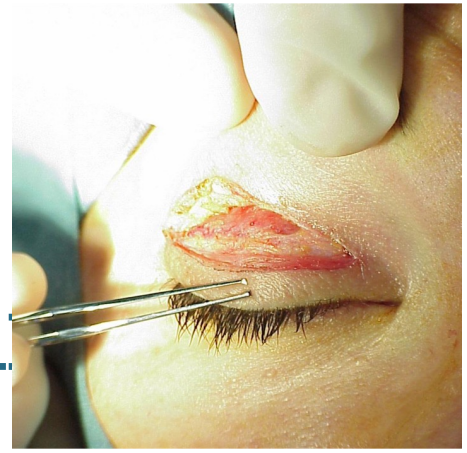
- 10% are either hypothyroid or euthyroid[5]
- TED may present before, during, or after the onset of GD[6]

TSHR, thyroid-stimulating hormone receptor.

1. Piantanida E, et al. *J Endocrinol Invest*. 2013;36(6):444-449. 2. Thyroid eye disease (TED or Graves' eye disease). https://www.umkelloggeye.org/conditions-treatments/thyroid-eye-disease. Accessed February 14, 2019. 3. Gwinup G, et al. *JAMA*. 1982;247(15):2135-2138. 4. Menconi F, et al. *Autoimmun Rev*. 2014;13(4-5):398-402. 5. Bartley GB, et al. *Am J Ophthalmol.* 1996;121(4):426-434. 6. Eckstein AK, et al. *Br J Ophthalmol.* 2009;93(8):1052-1056.

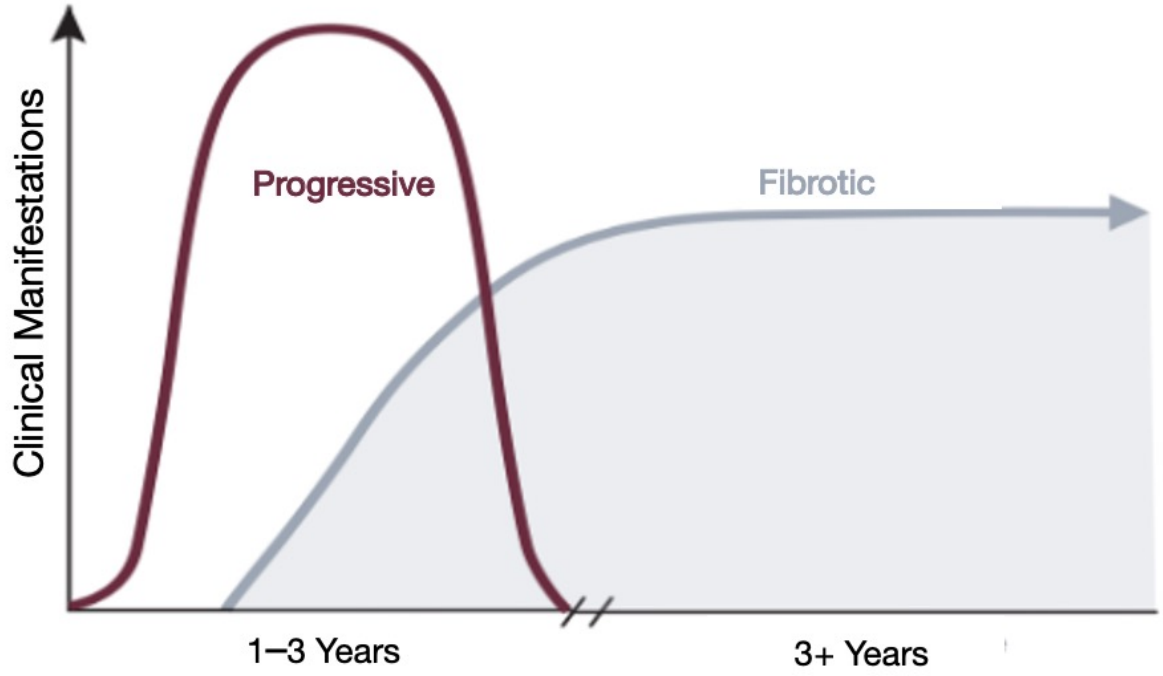
TED

- TED has long been a disease of "watching and waiting"
- Traditional treatments have been fraught with poor response rates and significant side effects.
- Surgical intervention is reserved for severe cases involving vision loss and focuses on controlling inflammation, but patients often still require surgical rehabilitation after reaching the fibrotic phase.

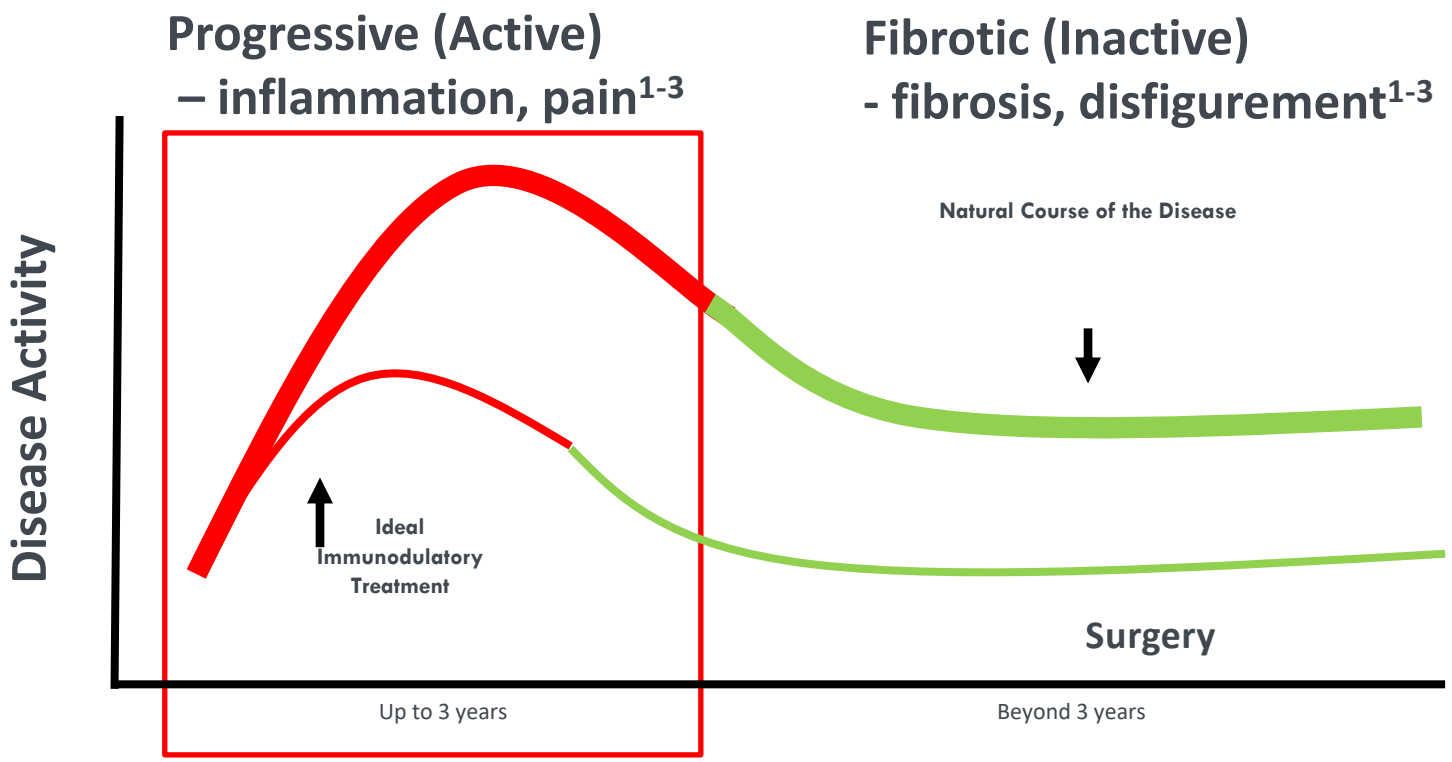


RUNDLE'S CURVE

The active phase is typically a self-limited process that lasts an average of **one** year in nonsmokers and **two to three** years in smokers



LIMITED WINDOW FOR TREATMENT DURING ACTIVE TED[1,2]



Once TED is inactive, medical therapy may not help.
Surgical intervention may be the only option, and, in some cases, it is also unsuccessful[2-5]

1. Bothun ED, et al. *Clin Ophthalmol.* 2009;3:543-551. 2. Barrio-Barrio J, et al. *J Ophthalmol.* 2015;2015:249125. 3. Dickinson AJ, et al. In: Wiersinga WM, Kahaly GJ, eds. Basel: Karger; 2017:1-25. 4. Bartalena L, et al. *Eur Thyroid J.* 2016;5(1):9-26. 5. Rootman DB, et al. *Ophthalmic Plast Reconstr Surg.* 2017;33(4):289-293.

AMERICAN THYROID ASSOCIATION TED SEVERITY GRADES

Grade*	Lid retraction	Soft tissues	Proptosis†	Diplopia	Corneal exposure	Optic nerve status
Mild	<2 mm	Mild involvement	<3 mm	Transient or absent	Absent	Normal
Moderate	≥2 mm	Moderate involvement	≥3 mm	Inconstant	Mild	Normal
Severe	≥2 mm	Severe involvement	≥3 mm	Constant	Mild	Normal
Sight threatening	—	—	—	—	Severe	Compression

*Mild TED: Patients whose features of TED have only a minor impact on daily life, generally insufficient to justify immunosuppressive or surgical treatment. Moderate-to-severe TED: patients without sight-threatening TED whose eye disease has sufficient impact on daily life to justify the risks of immunosuppression (if active) or surgical intervention (if inactive). Sight-threatening TED: patients with dysthyroid optic neuropathy and/or corneal breakdown. This category warrants immediate intervention.

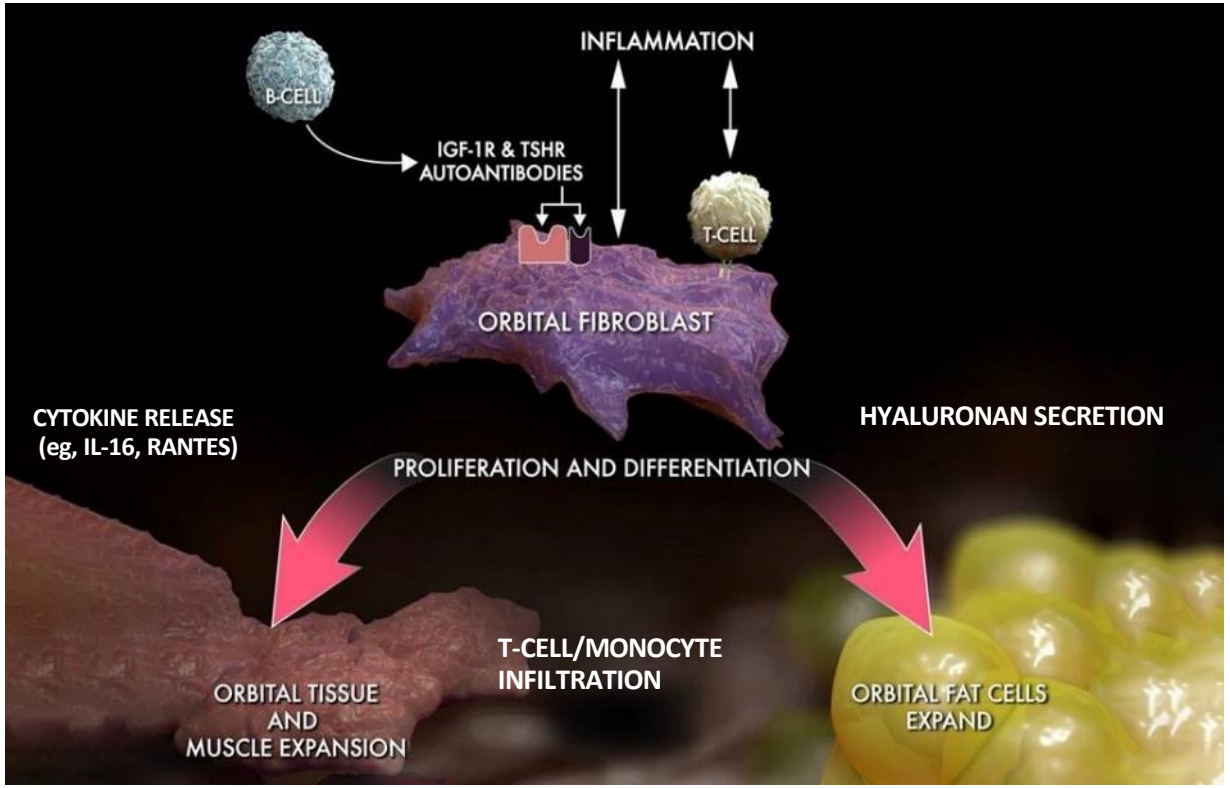
†Proptosis refers to the variation compared to the upper limit of normal for each race/sex or the patient's baseline, if available.

Ross DS, et al. *Thyroid*. 2016; 26(10):1343-1421.

TED IS DRIVEN BY AUTOANTIBODY ACTIVATION OF INSULIN GROWTH FACTOR-1 RECEPTOR (IGF-1R)

Orbital fibroblasts are the principal cells that drive the inflammation and expansion of orbital soft tissue, muscle, and fat[1-4]

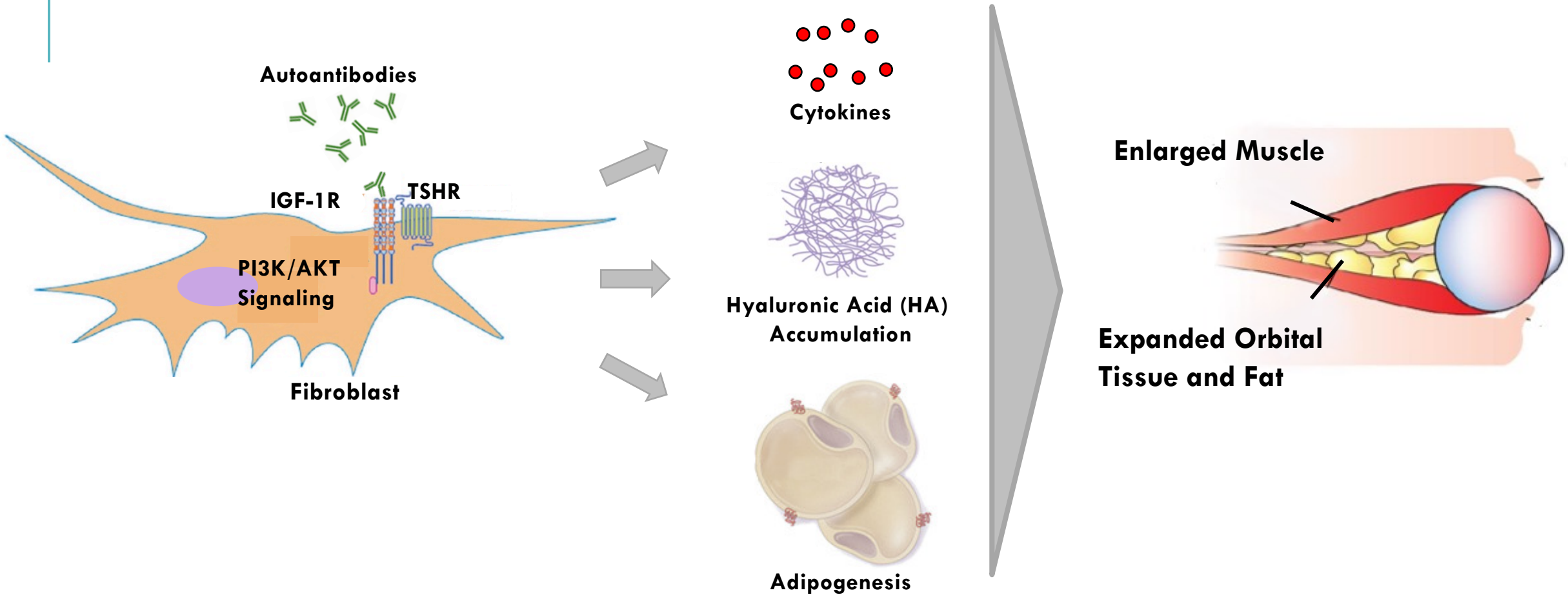
- IGF-1R and TSHR form a receptor-signaling complex and colocalize in orbital fibroblasts[5]
- IGF-1R is overexpressed in TED orbital fibroblasts[5]
- Activation of IGF-1R stimulates release of inflammatory cytokines and production of hyaluronan[6,7]



IGF-1R, insulin-like growth factor-1 receptor; IL-16, interleukin-16; RANTES, regulated on activation, normal T cell expressed.

1. Smith TJ, et al. *Thyroid*. 2008;18(9):983-988. 2. Smith T. *Pharmacological Rev*. 2010;62(2):199-236. 3. Bahn RS. *N Engl J Med.* 2010;362(8):726-738. 4. Shan SJ, et al. *J Neuroophthalmol.* 2014;34(2):177-185. 5. Tsui S, et al. *J Immunol*. 2008;181:4397-4405. 6. Pritchard J, et al. *J Immunol*. 2003;170:6348-6354. 7. Smith TJ, et al. *J Clin Endocrinol Metab*. 2004;89:5076-5080.

IGF-1R IS CENTRAL TO PATHOGENESIS OF TED

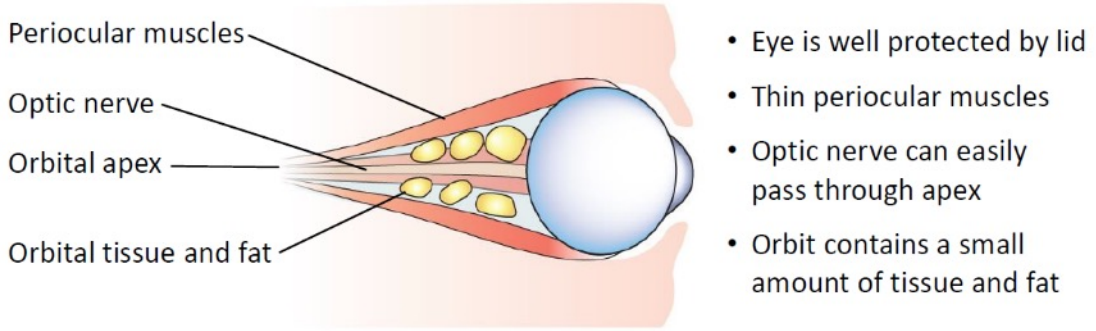


IGF-1R is necessary for downstream signaling and structural changes driving disease

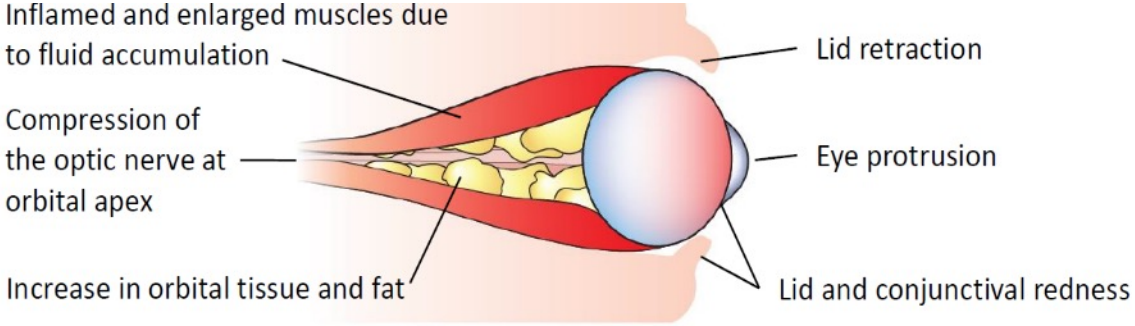
Smith TJ and Janssen J 2018 Endo Rev. DOI: 10-1210\er.2018\00066, Iyer S et al Prac Res Clin Endo Metab. 26:281, Douglas 2019 Eye 33:183

INFLAMMATION, TISSUE EXPANSION, AND EYE MUSCLE CHANGES LEAD TO THE CLINICAL MANIFESTATIONS OF TED

Healthy Eye and Orbital Tissue



In Presence of TED

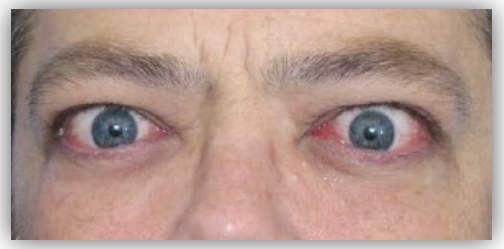


1. Pritchard J, et al. *J Immunol.* 2003;170(12):6348-6354. 2. Smith TJ, Hoa N. *J Clin Endocrinol Metab.* 2004;89(10):5076-5080. 3. Sorisky A, et al. *J Clin Endocrinol Metab.* 1996;81(9):3428-3431.
4. Valyasevi RW, et al. *J Clin Endocrinol Metab.* 1999;84(7):2557-2562.

THE MOST COMMON MANIFESTATIONS OF TED

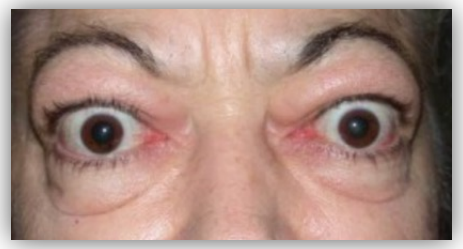
Conjunctiva and Cornea[1,2]

- Chemosis
- Conjunctival redness
- Epiphora
- Photophobia
- Foreign body sensation
- Pain
- Exposure keratopathy



From Novaes et al. *Clin Diabetes Endocrinol.* 2016;2:19. Reprinted with permission.[4]

Eyelid[1,3]

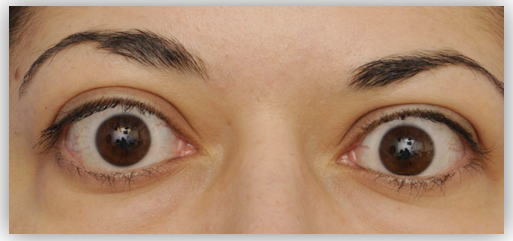


From Bartalena L. Graves' Disease: Complications. https://www.ncbi.nlm.nih.gov/books/NBK285551/?report=classic Reprinted with permission. Reprinted with permission.[5]

- Eyelid retraction:
  - **91% affected**
- Eyelid swelling
- Pain
- Lagophthalmos

Proptosis[2,3]

- Proptosis
  - **62% affected**
- Pain/deep ache
- Disfigurement



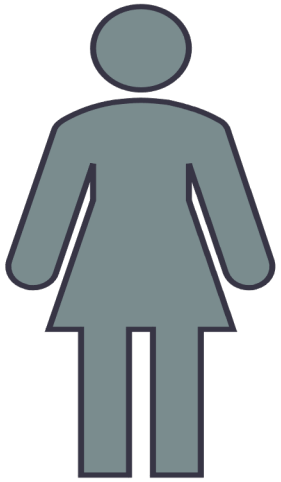
Extraocular Muscle[2,6]

- Diplopia
  - **51% affected**
- Strabismus
- Pain/deep ache

From Novaes et al. *Clin Diabetes Endocrinol*. 2016;2:19. Reprinted with permission[4]

1. WANG Y, ET AL. *THER CLIN RISK MANAG*. 2019;15:1305-1318. 2. PATEL A, YANG H, DOUGLAS RS. *AM J OPHTHALMOL*. 2019;208:281-288. 3. BARTLEY GB, ET AL. *AM J OPHTHALMOL.* 1996;121(3):284-290. 4. NOVAES, ET AL. *CLIN DIABETES ENDOCRINOL.* 2016;2:19. DOI: 10.1186/S40842-016-0037-5. 5. BARTALENA L. GRAVES' DISEASE: COMPLICATIONS. IN: FEINGOLD KR, ANAWALT B, BOYCE A, ET AL., EDITORS. ENDOTEXT [INTERNET]. HTTPS://WWW.NCBI.NLM.NIH.GOV/BOOKS/NBK285551/?REPORT=CLASSIC. ACCESSED DECEMBER 13, 2019. 6. TERWEE C, ET AL. *EUR J ENDOCRINOL.* 2002;146(6):751-757.

EPIDEMIOLOGY OF TED



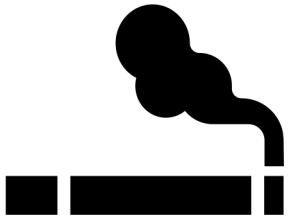
16 cases per 100,000 per person per year (PPPY)

3 cases per 100,000 PPPY

- Two peaks of incidence occur in patients at 40-49 and 60-69 years of age

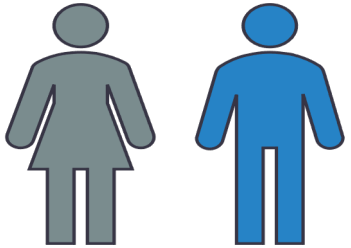
Bartley GB. *Trans Am Ophthalmol Soc.* 1994;92:477-588.

TED RISK FACTORS



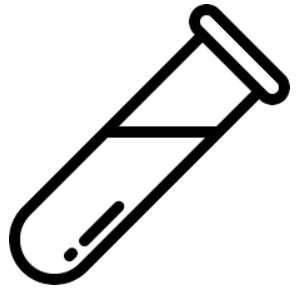
Increases the risk of developing TED by 2- to 8-fold[1-3]

Risk of developing new onset or worsening of TED is ≈20% after RAI treatment[4]



Women at higher risk but men have elevated risk for more severe TED[5,6]

Odds of TED increase by 17% with each decade of age progression[3]



TRAb levels may correlate with prognosis[7]

RAI, radioactive iodine; TRAb, thyroid autoantibodies.

1. Prummel MF, et al. *JAMA.* 1993;269(4):479-482. 2. Manji N, et al. *J Clin Endocrinol Metab.* 2006;91(12):4873-4880. 3. Khong JJ, et al. *J Clin Endocrinol Metab.* 2016;101(7):2711-2720.
4. Ponto KA, et al. *Thyroid.* 2010;20(7):785-793. 5. Perros P, et al. *Clin Endocrinol (Oxf).* 1993;38(4):367-372. 6. Bartley GB. *Trans Am Ophthalmol Soc.* 1994;92:477-588. 7. Roos JCP, et al. *Eye.* 2019;33:212-217.

TEPROTUMUMAB

- FDA approval of Teprotumumab (Tepezza, Horizon Therapeutics), an antigen-specific therapy designed to block IGF-1R and halt the signaling pathway.
- A Phase III trial found that teprotumumab could significantly reduce both proptosis and diplopia in patients with active, moderate-to-severe TED.
- At week 24, 83% of patients (10% of controls) experienced a reduction in proptosis.
- Each secondary outcome had also significantly improved with teprotumumab than with placebo. (Clinical Activity Score, Diplopia, Quality of Life Score)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Teprotumumab for the Treatment of Active Thyroid Eye Disease

R.S. Douglas, G.J. Kahaly, A. Patel, S. Sile, E.H.Z. Thompson, R. Perdok, J.C. Fleming, B.T. Fowler, C. Marcocci, M. Marinò, A. Antonelli, R. Dailey, G.J. Harris, A. Eckstein, J. Schiffman, R. Tang, C. Nelson, M. Salvi, S. Wester, J.W. Sherman, T. Vescio, R.J. Holt, and T.J. Smith

CONCLUSIONS

Among patients with active thyroid eye disease, teprotumumab resulted in better outcomes with respect to proptosis, Clinical Activity Score, diplopia, and quality of life than placebo; serious adverse events were uncommon. (Funded by Horizon Therapeutics; OPTIC ClinicalTrials.gov number, NCT03298867, and EudraCT number, 2017-002763-18.)

Contents lists available at ScienceDirect

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journal homepage: www.elsevier.com/locate/ajoc

Early experience with teprotumumab for chronic thyroid eye disease

Daniel J. Ozzello[a], Don O. Kikkawa[a,b], Bobby S. Korn[a,b,*]

[a] Division of Oculofacial Plastic and Reconstructive Surgery, UC San Diego Viterbi Family Department of Ophthalmology, La Jolla, CA, USA
[b] Division of Plastic and Reconstructive Surgery, UC San Diego Department of Surgery, La Jolla, CA, USA

ARTICLE INFO

Keywords:
Thyroid eye disease (TED)
Proptosis
Clinical activity score (CAS)
Teprotumumab
Inactive disease
Quiescent disease
Fibrotic disease

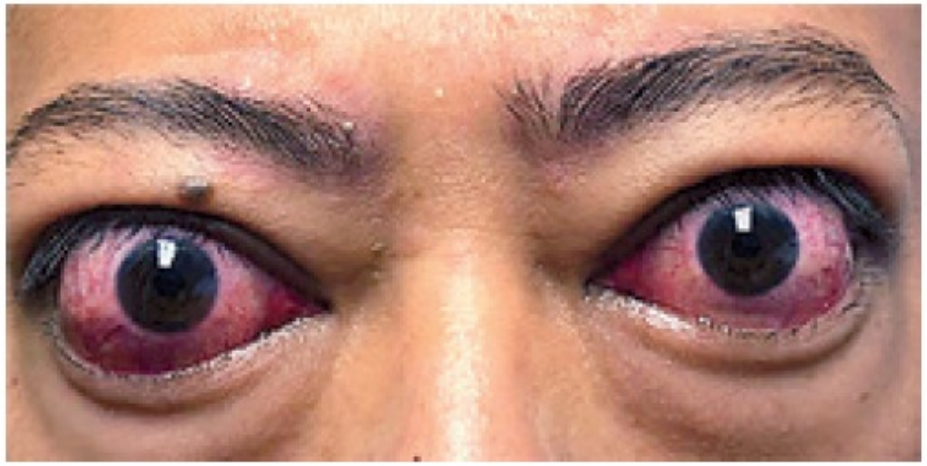
ABSTRACT

Purpose: To report the first case of a patient with chronic thyroid eye disease (TED) treated with teprotumumab.
Observations: A 50-year-old female with a 3-year history of Graves' disease presented with bilateral exophthalmos greatest on the left side. She was followed for 2 years with stable proptosis measurements (23mm OD, 28mm OS). Her clinical activity score (CAS) was 1 and there were no examination findings reflective of active inflammation. The patient underwent systemic treatment with teprotumumab and despite chronic TED and low CAS, she had notable improvement in proptosis (18mm OD, 22mm OS) and decrease in extraocular muscle volume as noted on orbital imaging.
Conclusion and importance: This case report suggests that teprotumumab may be used in patients with chronic TED and low CAS. Improvement in the proptosis and reduction in extraocular muscle volume suggest that teprotumumab may alter disease course even in patients with inactive or quiescent TED.

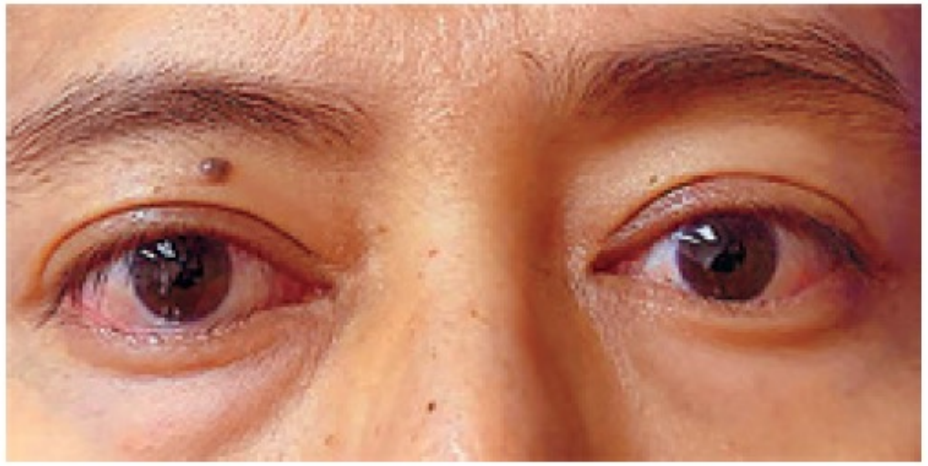
TEPROTUMUMAB

B Clinical Photographs of a Patient in the Teprotumumab Group

Baseline



24 Wk after Initial Dose



TEPROTUMUMAB SIDE EFFECTS

- The most common adverse events included muscle spasm, alopecia, nausea and fatigue, the majority of which were mild in severity and resolved after treatment.
- Adverse effects of special interest included
- Hyperglycemia in two patients
- Hearing impairment in five patients (two had hypoacusis, one had deafness, one had autophony and one had mild patulous eustachian tube) in the teprotumumab group, all of which resolved without treatment.

LABS FOR EYECARE

- TSH
- T3
- T4

TSI

- Thyroid-Stimulating Immunoglobulin, (Serum)
- The majority of TBAb assays detect both TSI and TBAb (Thyroid blocking antibodies)
- TSH, T3, T4 are measures of thyroid activity and this has LITTLE relevance with regard to TED

LABS FOR EYECARE

- IgG Antibody
- Mimics TSH
- Reacts with ocular tissues in TED

- Thyroid-Stimulating Immunoglobulin, (Serum)
- The majority of TBAb assays detect both TSI and TBAb (Thyroid blocking antibodies)
- TSH, T3, T4 are measures of thyroid activity and this has LITTLE relevance with regard to TED

REVIEW® OF OPTOMETRY

Published June 15, 2020

Racing the Rundle Against Thyroid Eye Disease

A new clinical approach to this condition may give patients a fighting chance at recovery.

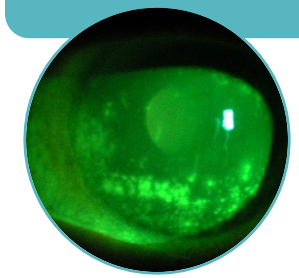
By Jacob Lang, OD, Nicole Harris, OD, and Sara Tullis Wester, MD

TED IS ASSOCIATED WITH SIGNIFICANT VISION-THREATENING IMPAIRMENTS

Consequences of TED can be devastating and can include:

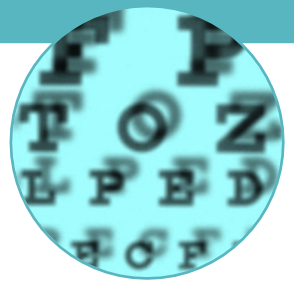
Vision impairment in patients with TED

Dry Eye Disease[1-3,a]



65%

Diplopia[4,5,b]

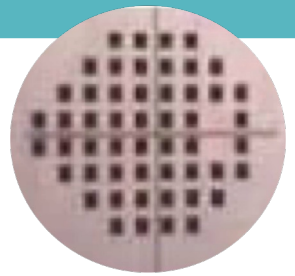


51%

Blurred Vision[5,6,b]

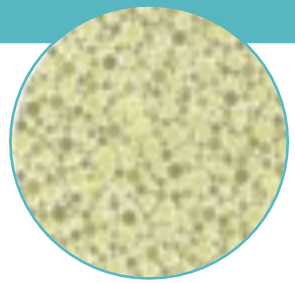
32%

Visual Field Defects[6,7,c]



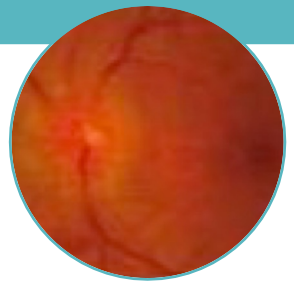
13%

Reduced Color Vision[6,8,d]



7%

Severe Sight-threatening Optic Neuropathy[7,9,10,c]



6%-9%

[a]From Pflugfelder SC. https://www.reviewofophthalmology.com/article/studies-yield-a-deeper-understanding-of-dry-eye. Reprinted with permission.[3] [b]From VSRN Vision Surgery Rehab Network website. http://www.visionsurgeryrehab.org/image-gallery/. Reprinted with permission.[5] [c]From Fernandez E, et al. *Ann Thyroid Res*. 2016;2:63-65. Reprinted with permission.[7] [d]From de Oliveira HM, et al. https://arxiv.org/ftp/arxiv/papers/1502/1502.03723.pdf. Reprinted with permission.[8]

1. Ismailova DS, et al. *Orbit*. 2013;32(2):87-90. 2. Selter JH, et al. *Clin Ophthalmol*. 2015;9:57-62. 3. Pflugfelder SC. Review of ophthalmology website. https://www.reviewofophthalmology.com/article/studies-yield-a-deeper-understanding-of-dry-eye. Accessed September 27, 2019. 4. Terwee C, et al. *Eur J Endocrinol*. 2002;146(6):751-757. 5. VSRN Vision Surgery Rehab Network website. http://www.visionsurgeryrehab.org/image-gallery/. Accessed September 27, 2019. 6. McKeag D, et al. *Br J Ophthalmol*. 2007;91(4):455-458. 7. Fernandez E, et al. *Ann Thyroid Res*. 2016;2:63-65. 8. de Oliveira HM, et al. Cornell University arXiv.org website. https://arxiv.org/ftp/arxiv/papers/1502/1502.03723.pdf. Accessed September 27, 2019. 9. Bartley GB. *Trans Am Ophthalmol Soc*. 1994;92:477-588. 10. Neigel JM, et al. Dysthyroid optic neuropathy. *Ophthalmology*. 1988;95(11):1515-1521.

CASE

72 year old Caucasian female

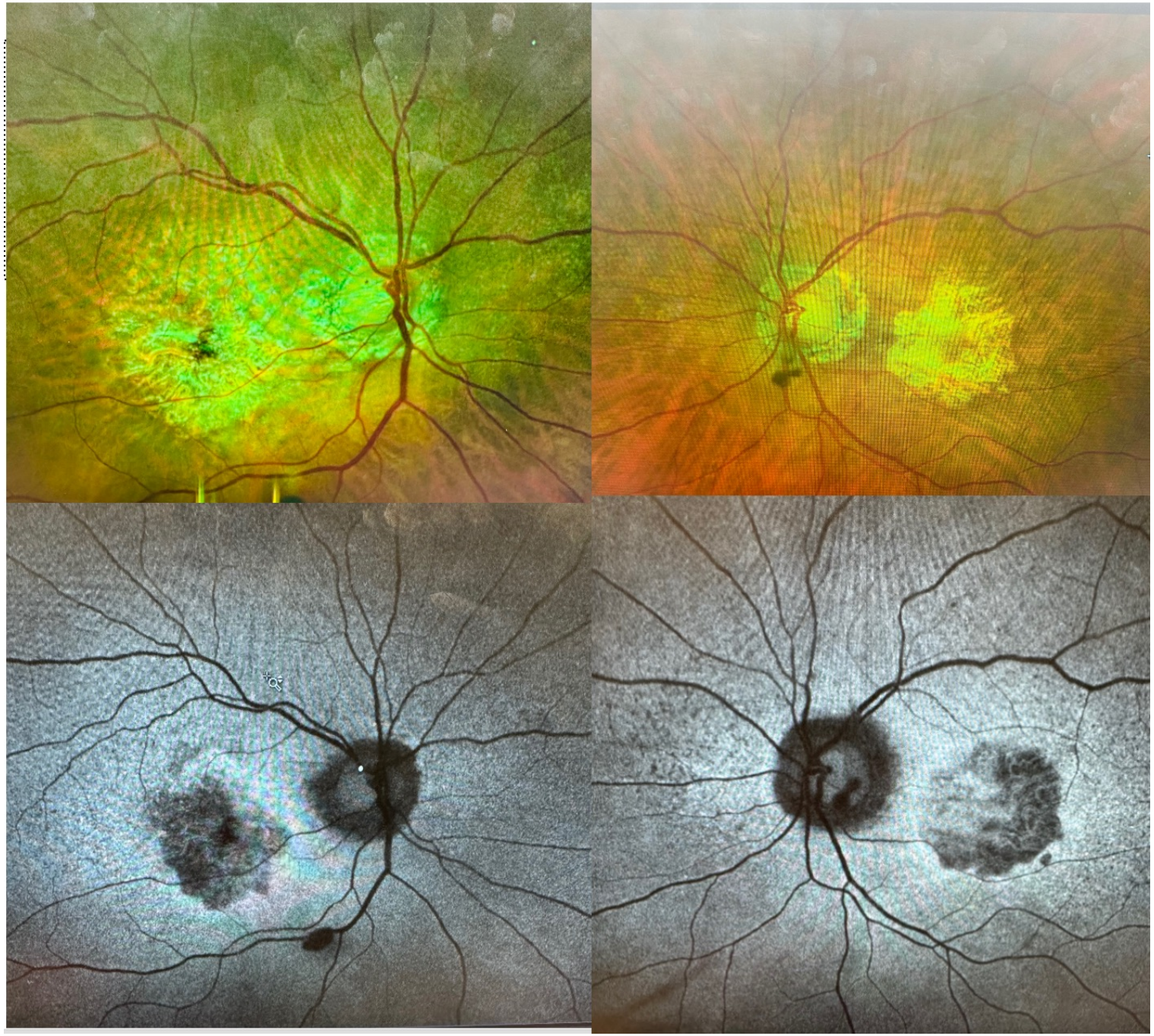
VA with best corrected Rx 20/200 OD, 20/30 OS, OU

MRx -4.00 and -4.50

Anterior Segment Unremarkable

PC IOL OU clear

See images of posterior pole/retina/optic nerve



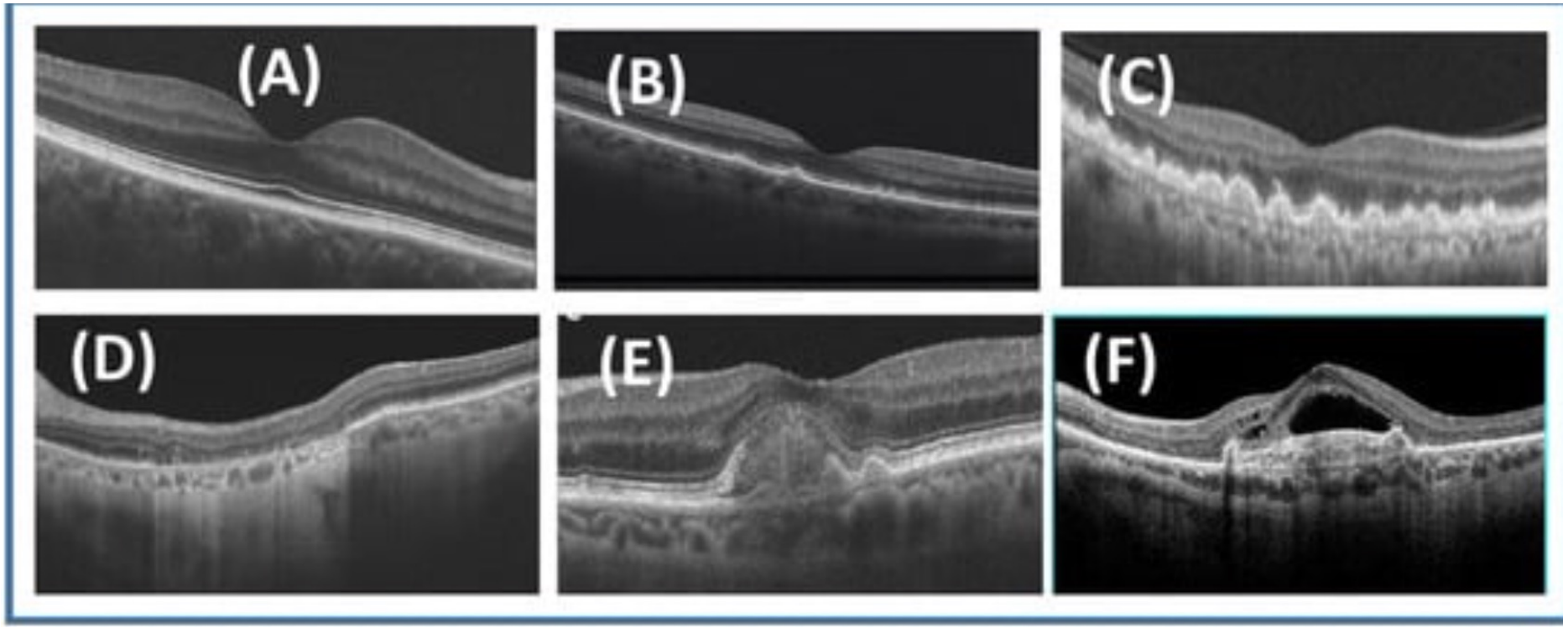


Figure 1. Examples of retinal OCT for (**A**) normal retina, (**B**) early AMD, (**C**) intermediate AMD, (**D**) geographic atrophy (GA), (**E**) inactive wet AMD, and (**F**) active wet AMD.

GEOGRAPHIC ATROPHY OVERVIEW

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Geographic Atrophy Overview

AGE-RELATED MACULAR DEGENERATION AND GEOGRAPHIC ATROPHY

AGE-RELATED MACULAR DEGENERATION (AMD) IS A PROGRESSIVE DEGENERATIVE DISEASE OF THE RETINA[1]

Leading cause of severe vision loss in individuals >55 years of age in the developed world, with **8.7% of the global population affected**[2,3]

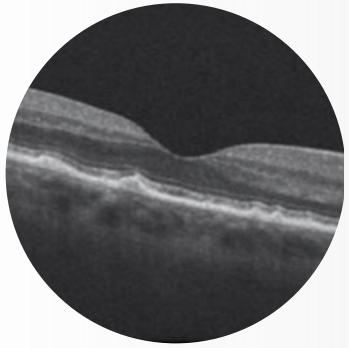
Affects the complex of **photoreceptors, retinal pigment epithelium (RPE), Bruch's membrane,** and the **choroid,** altering retinal homeostasis[1,3]

Clinical hallmark is the presence of **drusen**, which leads to **progressive degeneration** of photoreceptors and RPE and results in loss of central vision[3]

1. ARMENTO A, ET AL. *CELL MOL LIFE SCI.* 2021:78;4487-4505; **2.** Wong WL, et al. *Lancet Glob Health*. 2014;2:e106–e116; **3.** Fleckenstein M, et al. *Nat Rev Dis Primers.* 2021;7:31

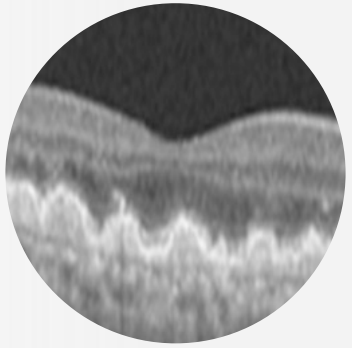
AMD IS A DISEASE SPECTRUM RANGING FROM EARLY AND LATE STAGES[1,2]

Early AMD



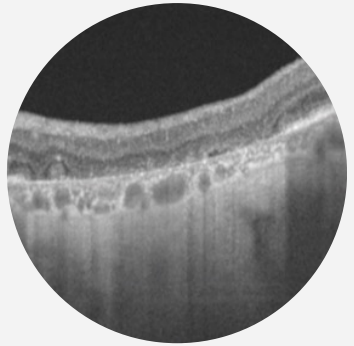
Characterized by multiple small drusen (<63 µm), few intermediate drusen (63-124 µm in diameter) or RPE abnormalities[2-4]

Intermediate AMD



Characterized by intermediate drusen, ≥1 large drusen (≥125 µm in diameter) that may be accompanied by hyper- or hypo-pigmentation of the RPE[3,4]

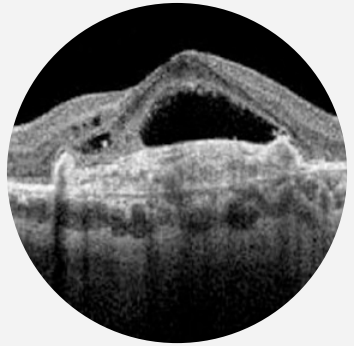
Late AMD



Dry AMD

Geographic Atrophy (GA)

Characterized by the progressive loss of photoreceptors, RPE, and underlying choriocapillaris, leading to **atrophic** lesions[2-4]



Wet AMD (nAMD)

Choroidal Neovascularization (CNV)

Characterized by the formation of CNV, which is the ingrowth of new blood vessels[1,2,4]

Images: Elsharkawy M, et al. *Diagnostics*,2021:11,2313.

AMD, age-related macular degeneration; RPE, retinal pigmented epithelium.

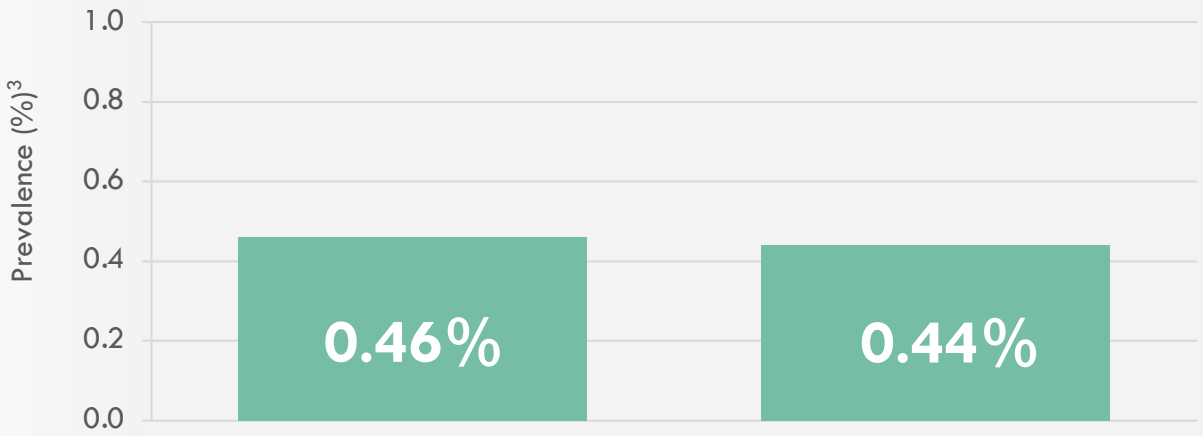
1. Holz FG, et al. *J Clin Invest.* 2014;124:1430-1438; **2.** Armento A, et al. *Cell Mol Life Sci.* 2021:78;4487-4505; **3.** Fleckenstein M, et al. *Ophthalmology.* 2018;125:369-390; **4.** Elsharkawy M, et al. *Diagnostics*,2021:11,2313.

PREVALENCE OF LATE AMD FORMS OF WET AMD AND GA ARE SIMILAR[1]

Late AMD can be classified as[2,3]

Wet AMD
(characterized by neovascularization)

GA
(characterized by atrophic lesions)



Overall prevalence of wet AMD and GA are similar[1]

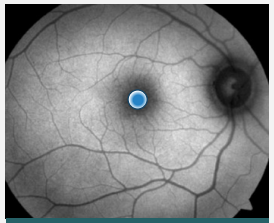
of diagnosed cases of AMD are considered **dry AMD,** which includes GA with early and intermediate AMD[4]

AMD, age-related macular degeneration; GA, geographic atrophy.

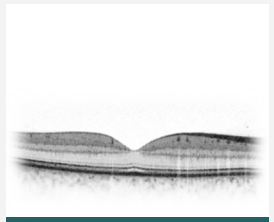
1. Wong WL, et al. *Lancet Glob Health.* 2014;2:e106-e116; **2.** Holz FG, et al. *Ophthalmology*. 2017;124:464-478; **3.** Gehrs KM, et al. *Ann Med.* 2006;38:450-471; **4.** Taylor DJ, et al. *Ophthalmic Physiol Opt.* 2018;38:98-105.

GEOGRAPHIC ATROPHY IS DEFINED BY THE PRESENCE OF SHARPLY DEMARCATED ATROPHIC LESIONS OF THE OUTER RETINA

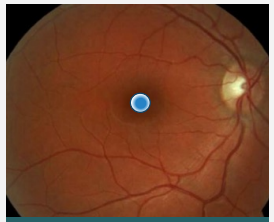
Normal Eye



FUNDUS AUTOFLUORESCENCE

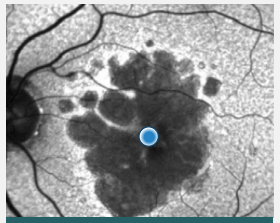


OPTICAL COHERENCE TOMOGRAPHY



COLOR FUNDUS PHOTOGRAPHY

Geographic atrophy



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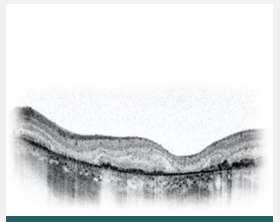
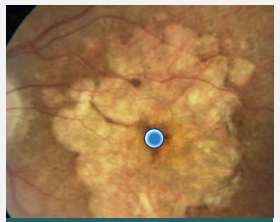


OPTICAL COHERENCE TOMOGRAPHY



COLOR FUNDUS PHOTOGRAPHY

Denotes approximate location of the fovea

Progressive loss of:

- Photoreceptors
- Retinal Pigment Epithelium (RPE)
- Underlying choriocapillaris

Irreversible loss of visual function

Images top left and right: Booysen D, South African Optometrist. 2013:72
Image top middle: https://www.know-the-eye.com/examinations/retinal-examinations/
Images bottom: Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.

AMD, age-related macular degeneration; GA, geographic atrophy.
Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.

GA SEVERELY AFFECTS VISION IN ~1.5 MILLION PATIENTS IN THE UNITED STATES ALONE[1-3]

Leading cause of central vision loss, accounting for ~20% of legal blindness in North America[1,4]

GA estimated to affect ~**1.5 million** individuals in the United States and **5 million** individuals worldwide[2,3]

Early AMD and signs of retinal changes are seen in individuals aged <**45 years old**[5,6]

Highest prevalence of GA seen in individuals >75 years old[7,8]

AMD, age-related macular degeneration; GA, geographic atrophy.

1. Holz FG, et al. *Ophthalmology* 2014;121:1079-1091; **2.** Boyer DS, et al. *Retina.* 2017;37:819-835; **3.** Friedman DS, et al. *Arch Ophthalmol.* 2004;122:564-572; **4.** Ferris FL, et al. *Ophthalmology*. 2013;120:844-851; **5.** Korb CA, et al. *Graefes Arch Clin Exp Ophthalmol.* 2014;252:1403-1411;

Geographic Atrophy Overview

PATHOGENESIS OF GEOGRAPHIC ATROPHY AND THE ROLE OF THE COMPLEMENT SYSTEM

THE PATHOPHYSIOLOGY OF GA IS MULTIFACTORIAL AND COMBINES ENVIRONMENTAL AND GENETIC RISK FACTORS[1,2]

Risk factors

Aging changes

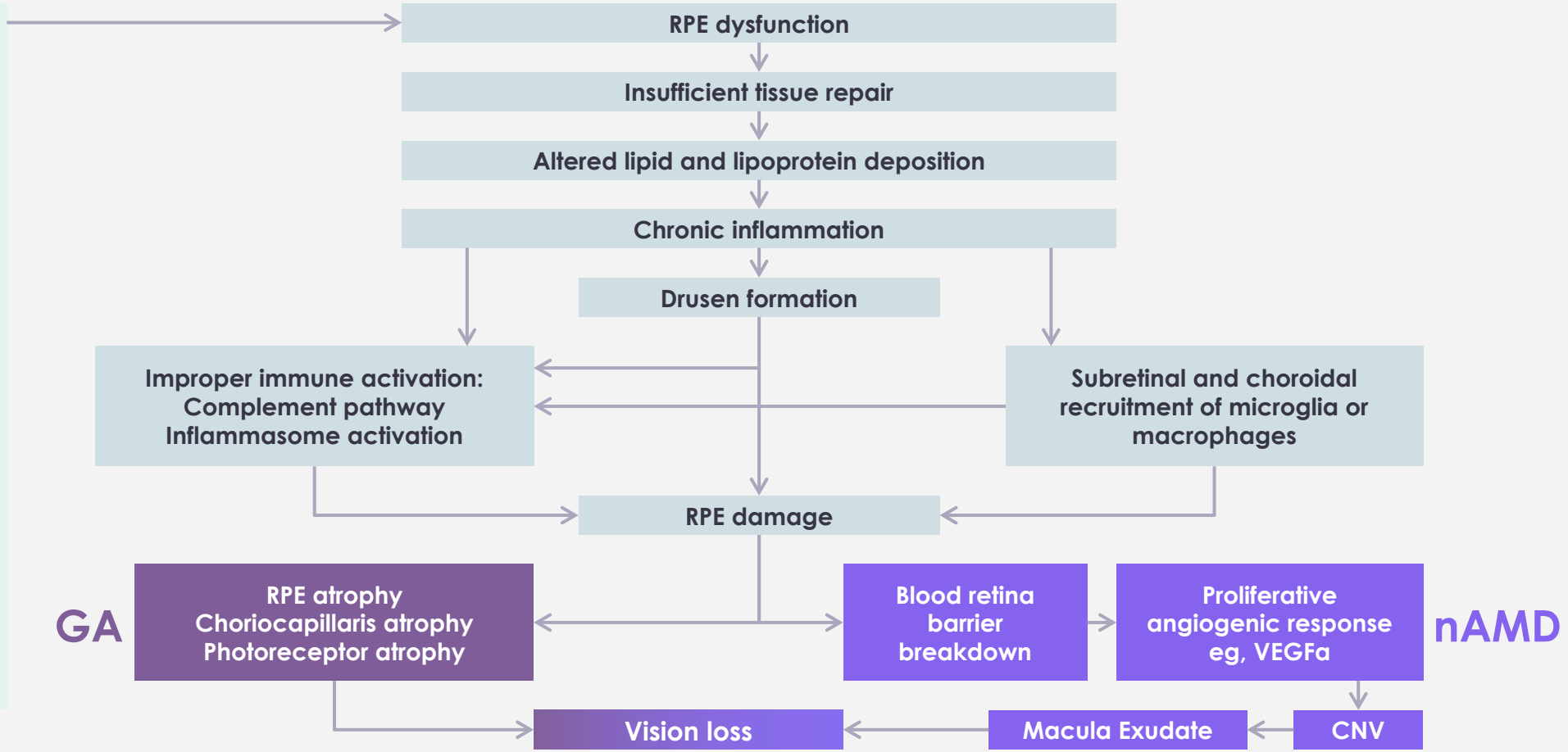
- Microangiopathy
- Lipid/lipoprotein deposition
- Oxidative/metabolic stress/ mitochondrial dysfunction

Genetics

- Complement pathway
- Lipid pathway
- Extracellular matrix pathways

Environmental factors

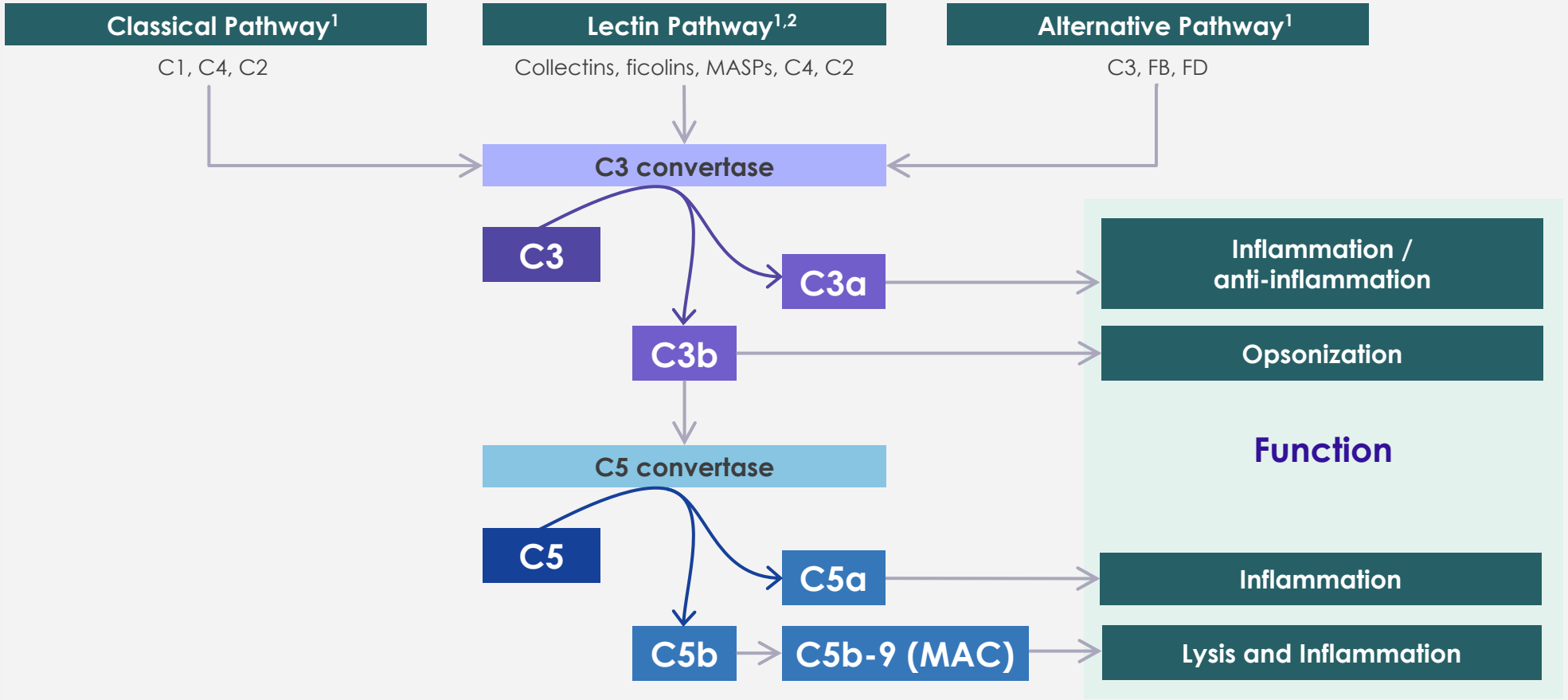
- Smoking
- Diet
- Comorbidities (hypertension, diabetes, cardiovascular disease)



CNV, choroidal neovascularization; GA, geographic atrophy; nAMD, neovascular age-related macular degeneration; RPE, retinal pigment epithelium; VEGF, vascular endothelial growth factor.

1. Ambati J, et al. *Nat Rev Immunol.* 2013;13:438-451; **2.** Fleckenstein M, et al. *Nat Rev Dis Primers.* 2021;7:31.

DYSREGULATED ACTIVATION OF THE COMPLEMENT SYSTEM CAN LEAD TO INFLAMMATION AND CELL DEATH AND MAY BE CENTRAL TO GA PATHOGENESIS[1]



FB, factor B; FD, factor D; MAC, membrane attack complex; MASP, MBL-associated serine protease; MBL, mannose-binding lectin.

1. Xu H, et al. *Eur J Pharmacol*. 2016;787:94-104; **2.** Bajic G, et al. *EMBO J*. 2015;34(22):2735-2757.

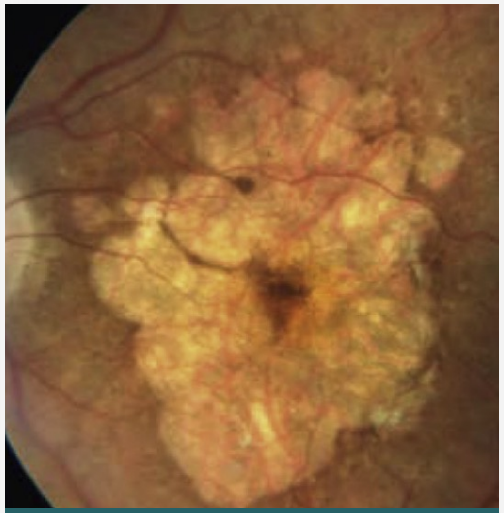
Geographic Atrophy Overview

DIAGNOSIS, IMAGING, AND PROGRESSION OF GEOGRAPHIC ATROPHY

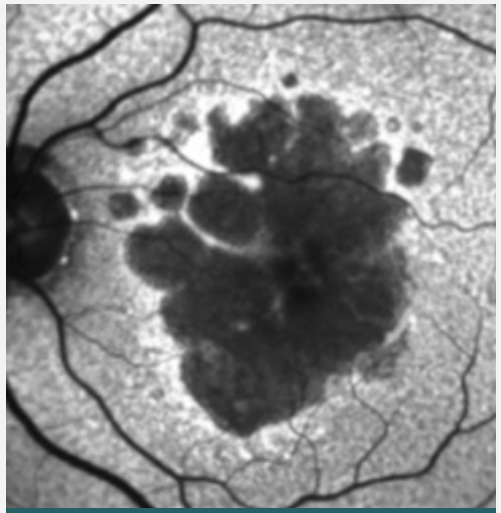
MULTIPLE IMAGING MODALITIES ARE USED TO VISUALIZE GA LESIONS[1,2]

Each modality has its strengths and weaknesses

Multimodal imaging may be needed to obtain the most reliable detection and measurement of atrophy



COLOR FUNDUS PHOTOGRAPHY



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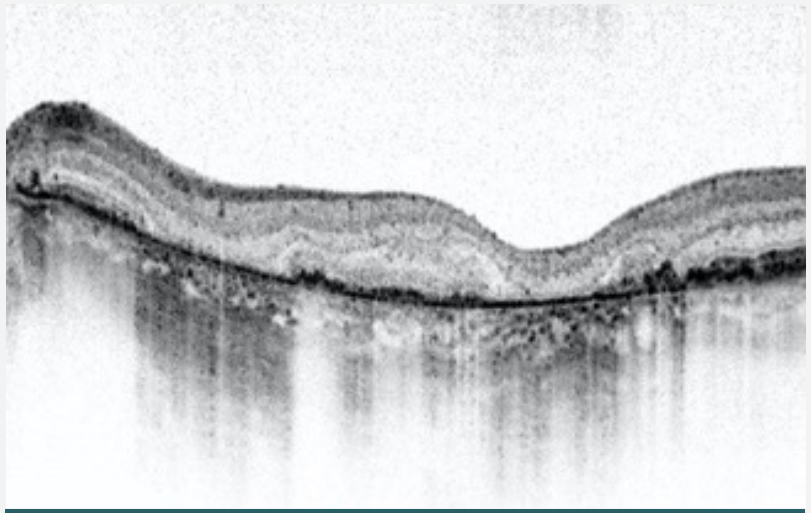


OPTICAL COHERENCE TOMOGRAPHY

Images: Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.

GA, geographic atrophy.

1. Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; **2.** Holz FG, et al. *Ophthalmology*. 2017;124:464-478.

CAM FINDINGS: OCT ESTABLISHED TO BE THE OPTIMAL IMAGING MODALITY FOR DEFINING AMD/ATROPHY

OCT: study of AMD progression and early end point development allows specific layers (photoreceptors, RPE) to be evaluated

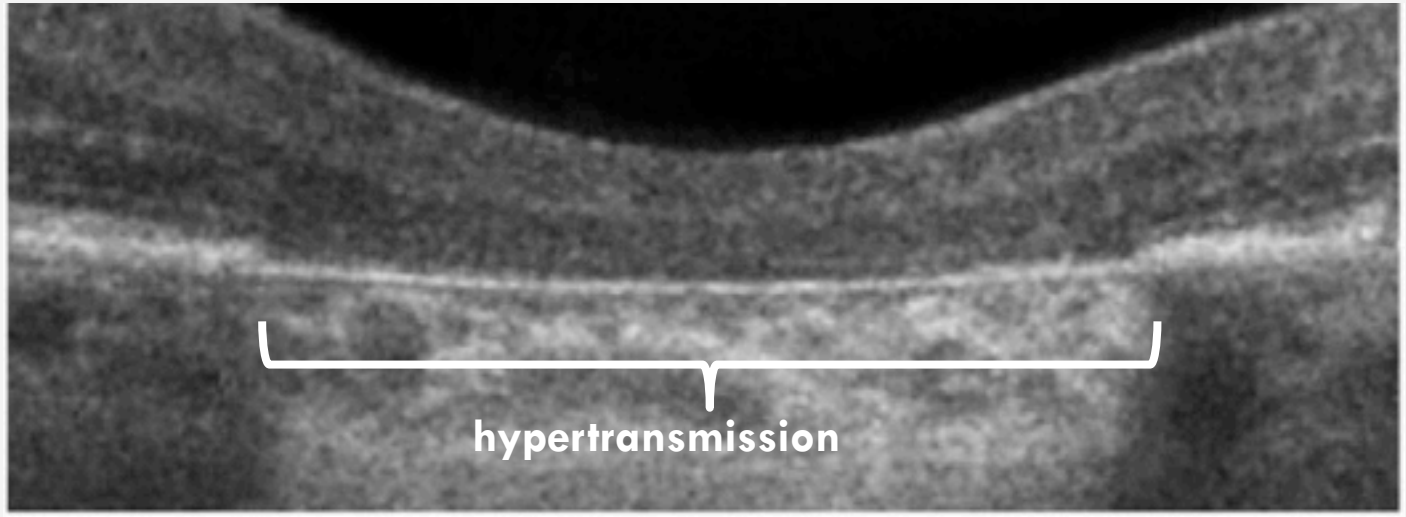


Image: Sadda SR, et al. *Ophthalmology*. 2018;125:537-548.

Other imaging methods would be used to corroborate or support OCT-based observations

AMD, AGE-RELATED MACULAR DEGENERATION; CAM, CLASSIFICATION OF ATROPHY MEETING; OCT, OPTICAL COHERENCE TOMOGRAPHY; RPE, retinal pigment epithelium.

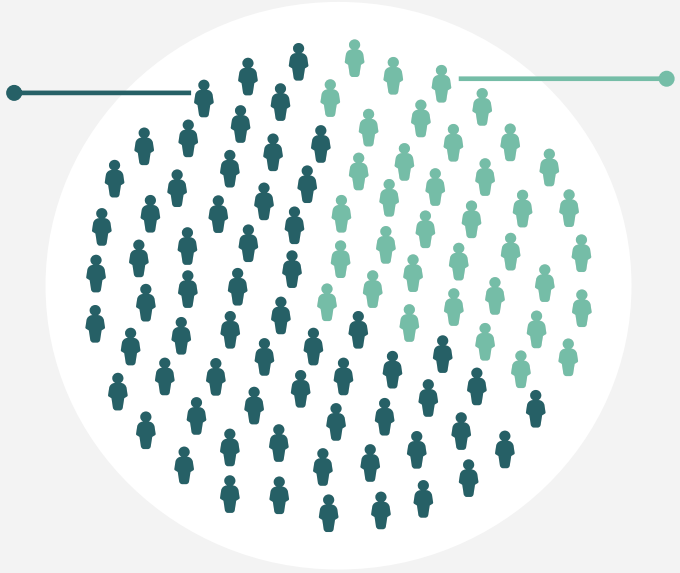
Sadda SR, et al. *Ophthalmology*. 2018;125:537-548.

MOST PATIENTS WITH GA PRESENT WITH NONFOVEAL LESIONS[1]

67%

Nonfoveal (noncentral)

At clinical examination, majority of participants with GA have nonfoveal lesions[1,2]



33%

Foveal (central)

When the fovea becomes involved, a **dramatic visual loss occurs**[1-3]

GA, geographic atrophy.

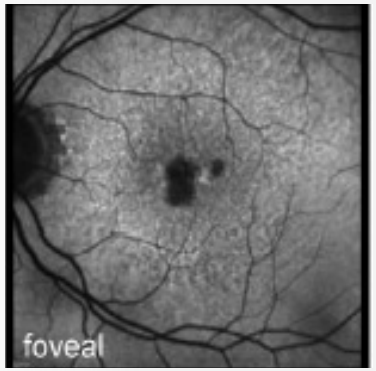
1. Schmitz-Valckenberg S, et al. *Invest Ophthalmol Vis Sci.* 2009;50:3915-3921; **2.** COLIJN JM, ET AL. *JAMA OPHTHALMOL.* 2021;139:743-750; **3.** Keenan TD, et al. *Ophthalmology*. 2018;125:1913-1928;

NONFOVEAL (EXTRAFOVEAL) GA LESIONS GROW AT A SIGNIFICANTLY GREATER RATE THAN FOVEAL LESIONS[1,2]

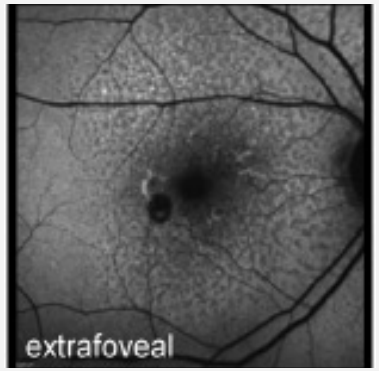
GA is a progressive disease, with an average growth rate of 0.33 mm per year or 1.66 mm^2 per year[3]

Growth rate of GA lesions:[1]

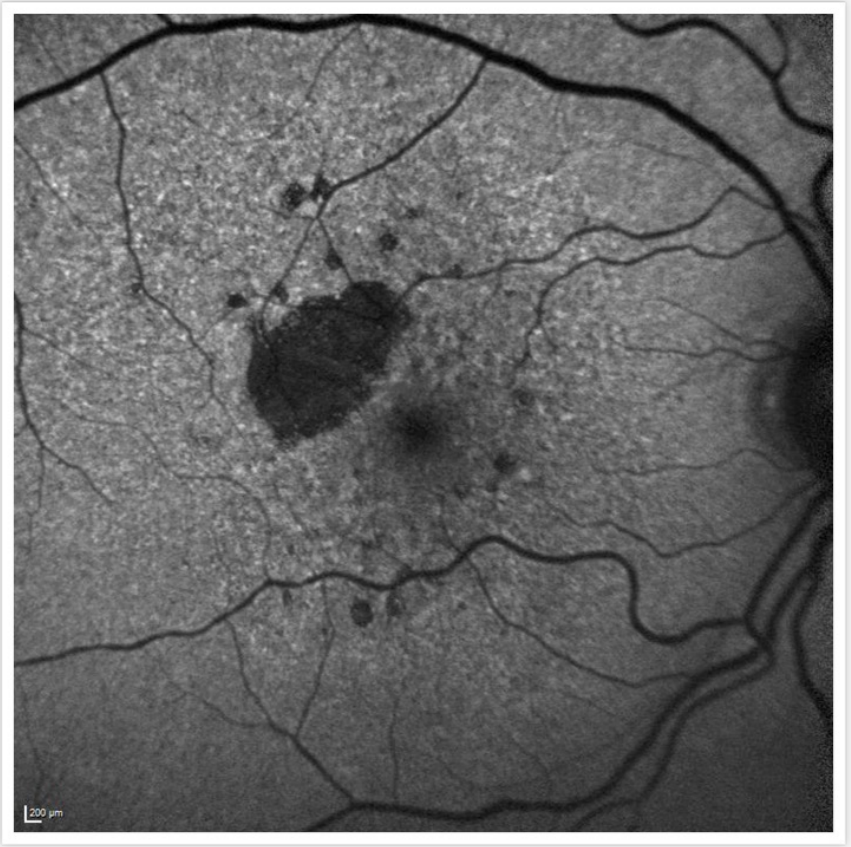
Foveal
1.28 mm^2 per year



Nonfoveal (extrafoveal)
2.05 mm^2 per year



Images: Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.



Courtesy: Frank Holz, MD

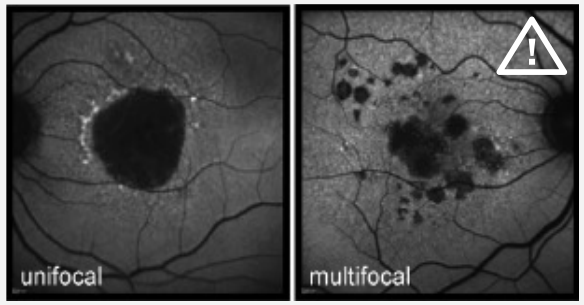
GA, geographic atrophy.

1. Keenan TD, et al. *Ophthalmology*. 2018;125:1913-1928; **2.** Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; **3.** Wang J, et al. *Ophthalmic Res.* 2021;64:205-215.

OTHER FACTORS ASSOCIATED WITH GA PROGRESSION

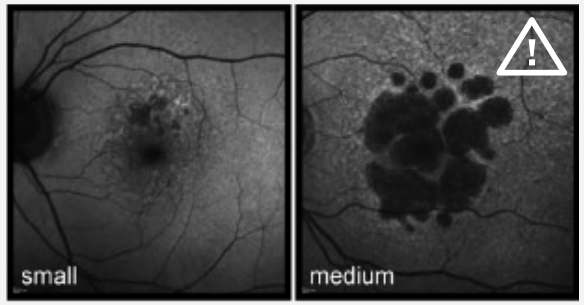
Lesion focality

Eyes with multifocal lesions have GA growth rates that are significantly higher than eyes with unifocal lesions[1]



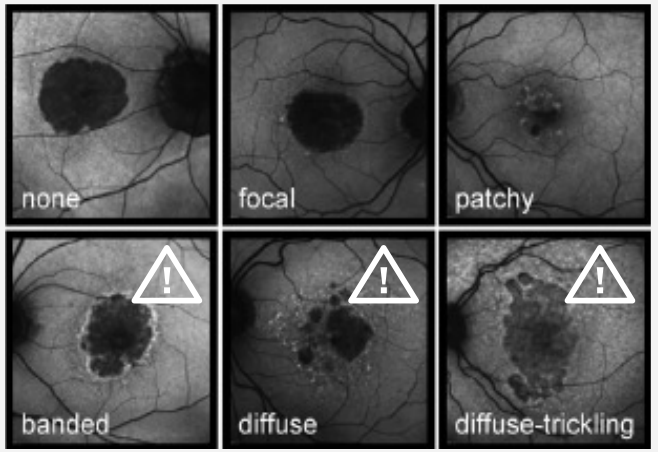
Lesion size

Baseline GA lesion size has consistently been associated with progression; ie, smaller baseline GA area in mm^2 have a lower GA growth rate[1,2]



Lesion characteristics and patterns

Lowest growth in eyes with no focal patterns; highest with banded or diffuse patterns. Diffuse-trickling pattern associated with rapid progression[1]



Bilateral GA (ie, GA in fellow eye)[1]

Images: Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390.

AMD, age-related macular degeneration; GA, geographic atrophy.

1. Fleckenstein M, et al. *Ophthalmology*. 2018;125:369-390; **2.** Wang J, et al. *Ophthalmic Res.* 2021;64:205-215.

ADVANCED FORMS OF AMD, GA AND CNV, WHILE PREVIOUSLY CONSIDERED DISTINCT ENTITIES, ARE NOT MUTUALLY EXCLUSIVE

CNV can occur in patients with GA. An eye with GA and CNV in the fellow eye has a significant risk of developing CNV in the eye with GA[1]

Macular neovascularization (MNV) has also been more commonly adopted in place of CNV; neovascularization does not necessary originate from the chorioid[2]:

MNV Type	Type 1	Type 2	Type 3
Replaces	Occult CNV	Classic CNV	Retinal angiomatous proliferation

Neovascularization can be in the exudative or nonexudative[3]

Signs of exudation include IRF, SRF, and sub-RPE fluid

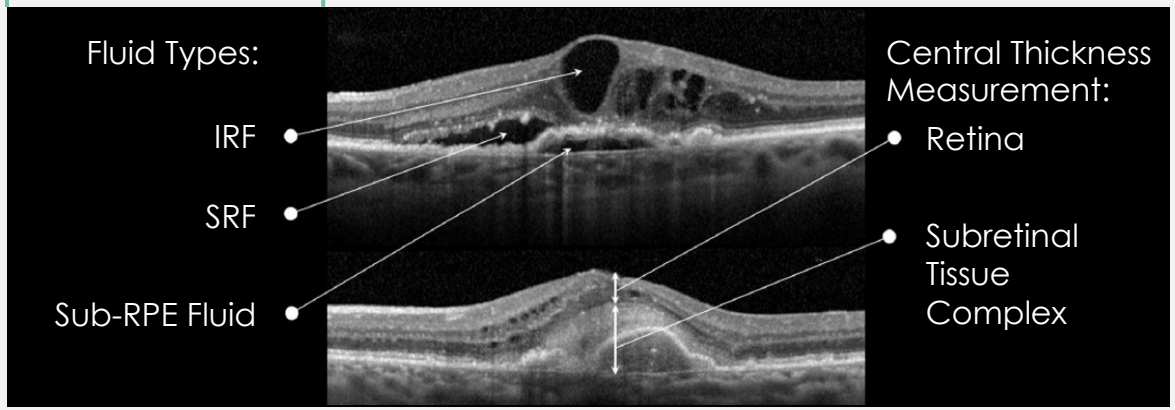


Image: Folgar FA, et al. *Ophthalmology*. 2014;121:1956-1965.

AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy; IRF, intraretinal fluid; SRF, subretinal fluid; Sub-RPE, subretinal pigment epithelial.

1. Sunness JS, et al. *Ophthalmology*. 1999;106:910-919; **2.** Spaide RF, et al. *Ophthalmology*. 2020;127:616-636; **3.** Sharma A, et al. *Graefes Arch Clin Exp Ophthalmol.* 2021;259:1381-1383.

PROGRESSION TO GA AND CNV IS OBSERVED FREQUENTLY IN EYES WITH EARLY OR INTERMEDIATE AMD

n=18,394 patients

Early or intermediate AMD in at least 1 eye

≥ 2 years of follow-up data

9.5% of patients progressed to GA, in a **median time of 2.57 years**

Study Eye	Fellow Eye	Rate of Progression
Early or Intermediate AMD	Early or Intermediate AMD	**7.6%**
Early or Intermediate AMD	CNV	**15.3%**
Early or Intermediate AMD	GA	**33.2%**

The status of the fellow eye affects the rate of progression

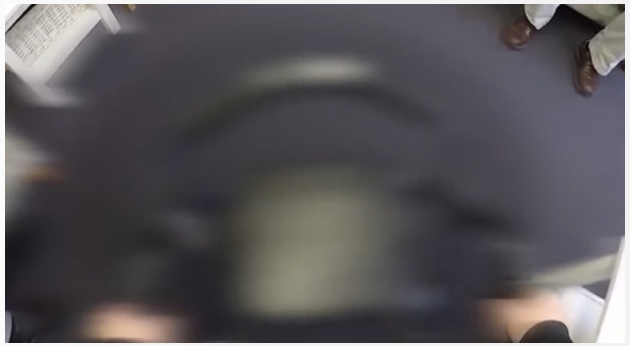
AMD, age-related macular degeneration; CNV, choroidal neovascularization; GA, geographic atrophy.
Chakravarthy U, et al. *Ophthalmol Retina*. 2020;4:662-672.

Geographic Atrophy Overview

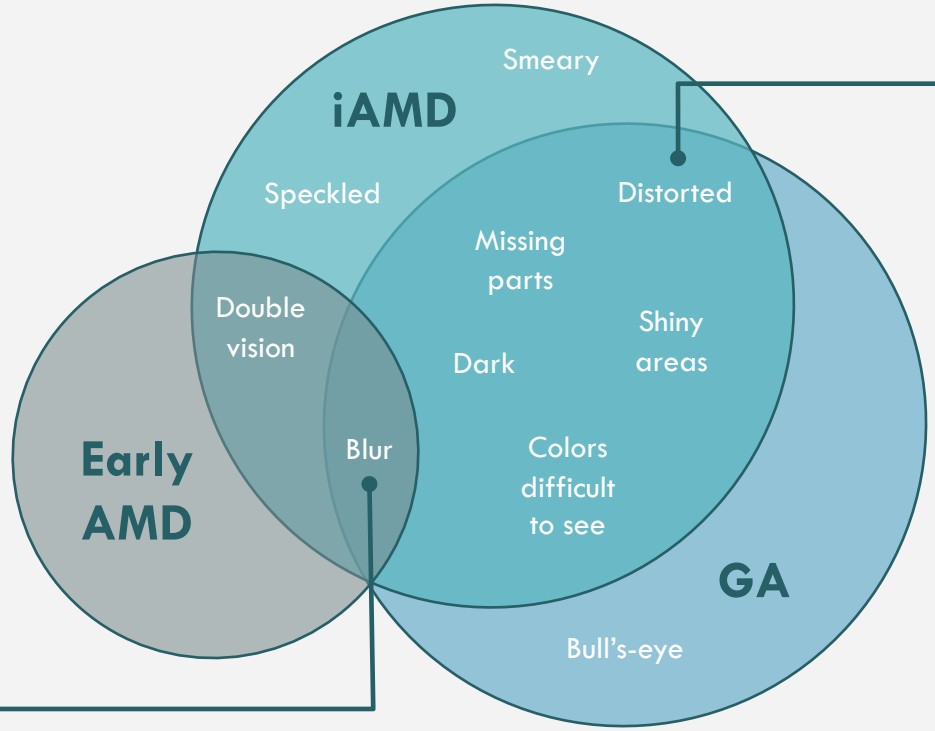
BURDEN OF DISEASE

LOSS OF VISUAL FUNCTION DUE TO GA IS IRREVERSIBLE, GREATLY AFFECTING QUALITY OF LIFE BECAUSE OF LOSS OF INDEPENDENCE AND MOBILITY[1]

Descriptors of Vision[2]



Blur



Distorted

Images: Macular Disease Foundation Australia. https://www.mdfoundation.com.au/about-macular-disease/age-related-macular-degeneration/how-do-you-know. Accessed 01/13/2023.

AMD, age-related macular degeneration; GA, geographic atrophy; iAMD, intermediate AMD.

1. Chakravarthy U, et al. *Ophthalmology*. 2018;125:842-849; **2.** Taylor DJ, et al. *Ophthalmic Physiol Opt*. 2018;38:98-105.

PATIENTS WITH GA EXPERIENCE INCREASED VISUAL IMPAIRMENT AND VISUAL ACUITY DEFICITS UNDER REDUCED ILLUMINATION[1,2]

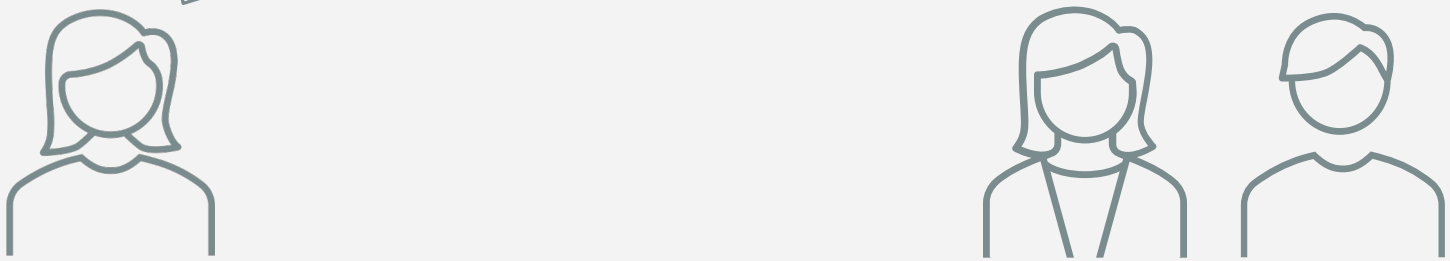
Patients with **nonfoveal lesions have preserved BCVA**; however, they have **visual impairment under low-light conditions**[1,3,4]

They have difficulties in **reading** and **recognizing faces** and have symptoms such as **blurring and distorted perception**[5-7]

"Can't read a menu if it's too small and it's too dark"[7]

"Real blurry to me… so it takes me forever to read this"[7]

"I look outside and, on the house opposite, I see 2 chimneys instead of 1"[8]



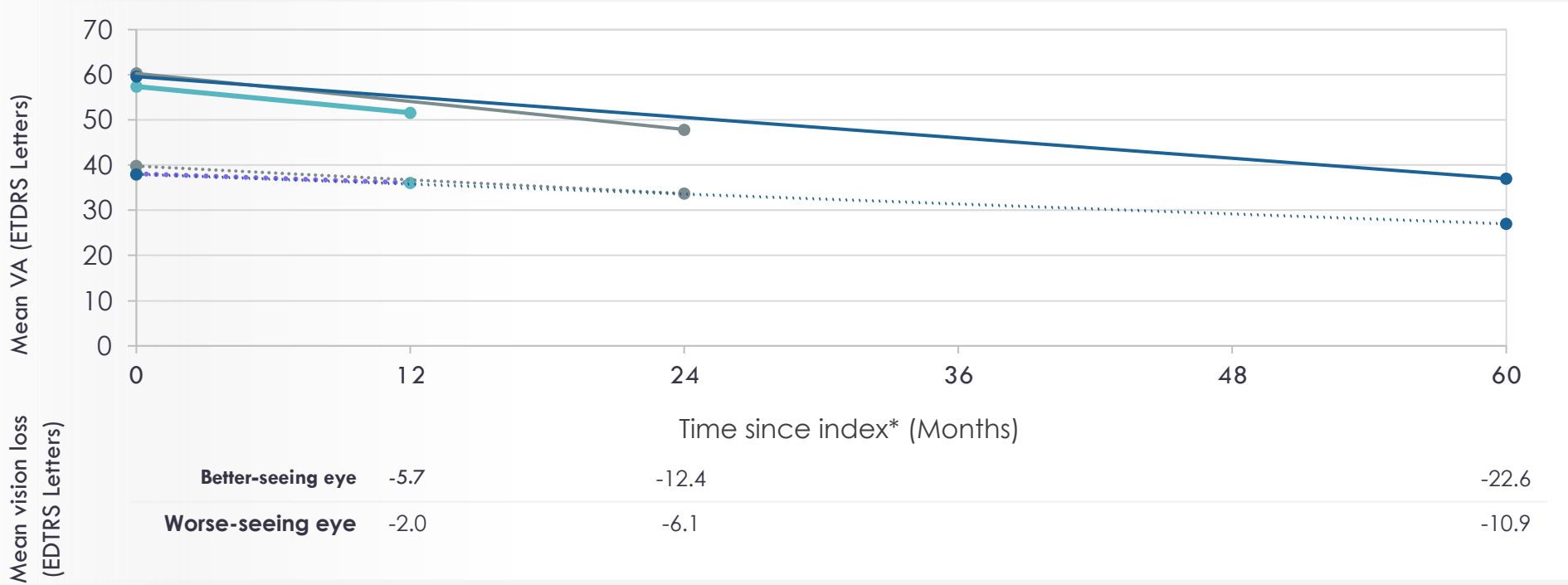
AMD, age-related macular degeneration; BCVA, best corrected visual acuity; GA, geographic atrophy; iAMD, intermediate AMD.

1. Boyer DS, et al. *Retina.* 2017;37:819-835; **2.** Sunness JS, et al. *Ophthalmology.* 1997;104:1677-1691; **3.** Sunness JS, et al. *J Vis Impair Blind.* 2008;102:600-610; **4.** Wu Z, et al. *Ophthalmology*. 2014;121:1612-1619; **5.** Patel PJ, et al. *Clin Ophthalmol.* 2020;14:15-28; **6.** Carlton J, et al. *Br Ir Orthopt J.* 2019;15:133-141; **7.** Sivaprasad S, et al. *Ophthalmol Ther.*

MEAN VISUAL ACUITY DECLINED BY MORE THAN 20 LETTERS OVER 5 YEARS, A LOSS OF NEARLY 4 LETTERS PER YEAR, IN PATIENTS WITH GA

From diagnosis of GA, there is a high risk of vision loss over time

Eyes with bilateral GA

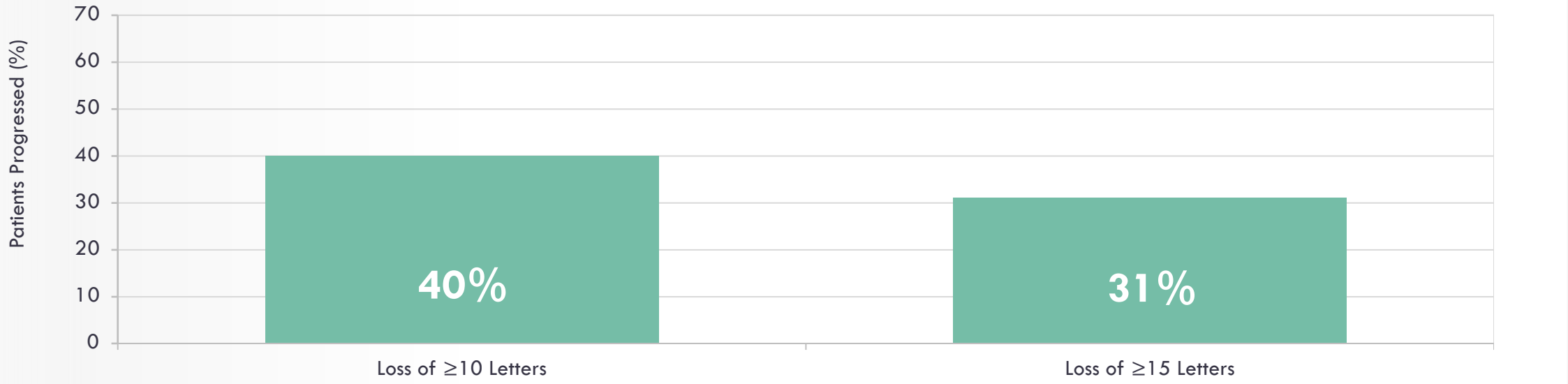


*Earliest record indicating the diagnosis of GA.
ETDRS, Early Treatment Diabetic Retinopathy Study; GA, geographic atrophy; VA, visual acuity.

Chakravarthy U, et al. *Ophthalmology*. 2018;125:842-849.

A LARGE PROPORTION OF PATIENTS CAN LOSE 10 LETTERS OR MORE WITHIN 2.4 YEARS

Visual impairment



Median time to progression
2.4 years (IQR: 1.1-5.0)

Median time to progression
3.3 years (IQR: 1.5–6.2)

GA, geographic atrophy; IQR, interquartile range.

Chakravarthy U, et al. *Ophthalmology*. 2018;125:842-849.

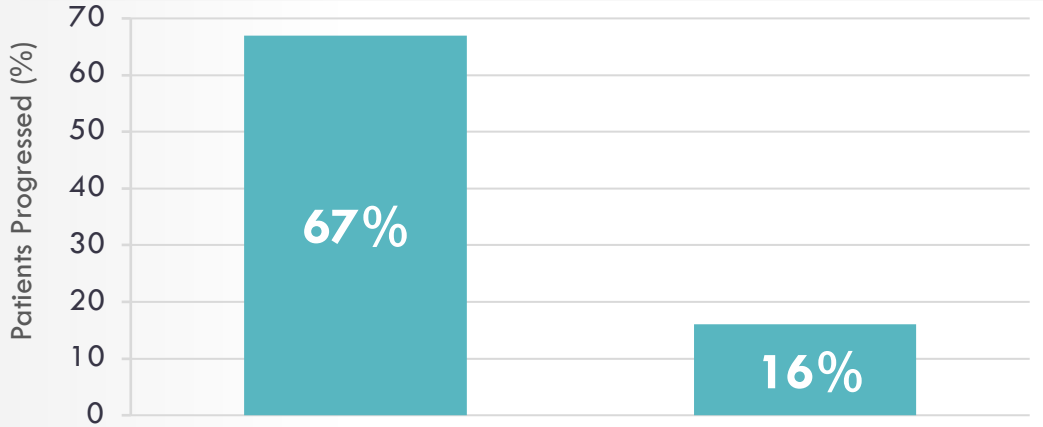
PATIENTS WITH GA SUFFER FROM POORER VISION-RELATED FUNCTION AND QUALITY OF LIFE COMPARED WITH THEIR PEERS WITHOUT GA[1]

Daily activities such as **driving, walking, traveling, reading, puzzles and watching TV** are affected, leaving a patient with GA feeling **frustrated**[1,2]

"I get frustrated when I can't do things what I used to do."[2]

"What upset me was I had to give up driving. I'm such an independent person.... I hate having to ask people."[2]

2/3 of patients with GA lost ability to drive, and 1/6 progressed to legal blindness[3]



Loss of Driving		Blindness
523	Study sample eligible for analyses (n)	1693
1.6 (0.7-2.7)	Median (IQR) time to outcome (years)	6.2 (3.3-8.5)

GA, geographic atrophy; IQR, interquartile range.

1. Patel PJ, et al. *Clin Ophthalmol.* 2020;14:15-28; **2.** Carlton J, et al. *Br Ir Orthopt J.* 2019;15:133-141; **3.** CHAKRAVARTHY U, et al. *Ophthalmology*. 2018;125:842-849.

THE UNMET NEED FOR GA IS THE LIMITED NUMBER OF APPROVED PHARMACOLOGICAL TREATMENTS[1]

GA leads to progressive and irreversible vision loss; therefore, preventive treatments to effectively slow or delay the progression to late AMD in the early stages of the disease are urgently needed to prevent irreversible vision loss[1]

On February 17, 2023, pegcetacoplan (Syfovre™) was approved by the FDA to treat GA. A number of other molecules are under investigation for the treatment of GA[a,b]

Product[2-8]	MOA/type of molecule[2-8]
Avacincaptad pegol	Complement C5 inhibitor (pegylated RNA aptamer)
NGM621	Complement C3 inhibitor (humanized Mab)
GEM103	Complement Factor H (recombinant human)
IONIS-FB-LR$_x$	Complement Factor B gene inhibitor (ligand-conjugated antisense oligonucleotide)
ANX007	Complement C1q inhibitor (humanized mAb)
Danicopan (ALXN2040)	Complement Factor D Inhibitor (small molecule, orally active)
FHTR2163/RG6147	HTRA1 inhibitor (antigen-binding fragment of humanized IgG - Fab)
Risuteganib	Integrin regulating therapy (small peptide)
Elamipretide	Mitochondria targeted therapy (small peptide)
OpRegen®	Cell therapy consisting of RPE cells
GT005	Complement Factor I modulator (AAV2 gene therapy)

[a]Focus is on clinical programs in Phase 2 or 3; [b]As of February 2022. AAV, ADENO-ASSOCIATED VIRUSES; GA, GEOGRAPHIC ATROPHY; FAB, FRAGMENT ANTIGEN BONDING; IGG, IMMUNOGLOBULIN G; MAB, MONOCLONAL ANTIBODY; MOA, MODE OF ACTION; RNA, RIBONUCLEIC ACID; RPE, RETINAL PIGMENT EPITHELIUM.

1. WU Z, ET AL. *OPHTHALMOLOGICA.* 2020;243:399-403; **2.** ARMENTO A, ET AL. *CELL MOL LIFE SCI.* 2021;78:4487-4505; **3.** RICHARD AJ, ET AL. *CURR OPIN OPHTHALMOL.* 2021;32:247-252; **4.** LOKTEV A, ET AL. PRESENTED AT: ARVO 2020; MAY 1-7, 2020; BALTIMORE, MARYLAND; **5.** HOLEKAMP N. PRESENTED AT: ASRS 2021; OCTOBER 8-12, 2021; SAN ANTONIO, TEXAS; **6.** BOYER D, ET AL. PRESENTED AT: ARVO 2021; MAY 2-6, 2021; SAN FRANCISCO CALIFORNIA. DENVER, CO; **7.** OPREGEN CLINICAL TRIAL. HTTPS://WWW.CLINICALTRIALS.GOV/CT2/SHOW/NCT02286089. ACCESSED APRIL 13, 2022. **8.** JAFFE GJ, ET AL. *IOVS.* 2020;61:4305.

KEY TAKEAWAYS

GA is a progressive and irreversible retinal disease. It is the largest unmet need in retina, with 5 million affected worldwide

GA is visualized by multiple imaging modalities. OCT is established to be the optimal reference modality to allow the study of AMD progression and early end point development (iRORA, cRORA)

GA is defined by the presence of sharply demarcated atrophic lesions of the outer retina, resulting from loss of photoreceptors, RPE, and underlying choriocapillaris, leading to irreversible visual loss

Patients with GA may struggle with everyday activities, such as reading, cooking, driving and recognizing faces, with significant impact on quality of life

Various lines of evidence, including genetic, histologic, and *in vitro*, link the complement system to AMD

As of February 17, 2023, one approved therapy for GA and several are under investigation

AMD, age-related macular degeneration; cRORA, complete RPE + outer Retinal Atrophy; GA, geographic atrophy; iRORA, incomplete RPE + outer Retinal Atrophy; OCT, optical coherence tomography; RPE, retinal pigment epithelium.

Table of contents

Efficacy and Safety of Avacincaptad Pegol in Geographic Atrophy

Avacincaptad pegol is under review with the FDA, and safety and efficacy have not been fully established. There is no guarantee that avacincaptad pegol will become commercially available.

Summary PDUFA Date: August 19, 2023

Primary endpoint

Avacincaptad pegol is the first investigational therapy in GA to achieve the 12-month, prespecified, primary objective vs. sham, coupled with a consistent safety profile, in two pivotal, phase 3 studies

Adverse events

The most common ocular TEAEs (≥5%) in the study eye for both studies were conjunctival hemorrhage, increased IOP, and CNV

CNV rates

In GATHER1, CNV rates were 9.0% in the avacincaptad pegol 2 mg group and 2.7% in the sham group

In GATHER 2, CNV rates were 6.7% in the avacincaptad pegol 2 mg group and 4.1% in the sham group

CNV, choroidal neovascularization; GA, geographic atrophy

CASE

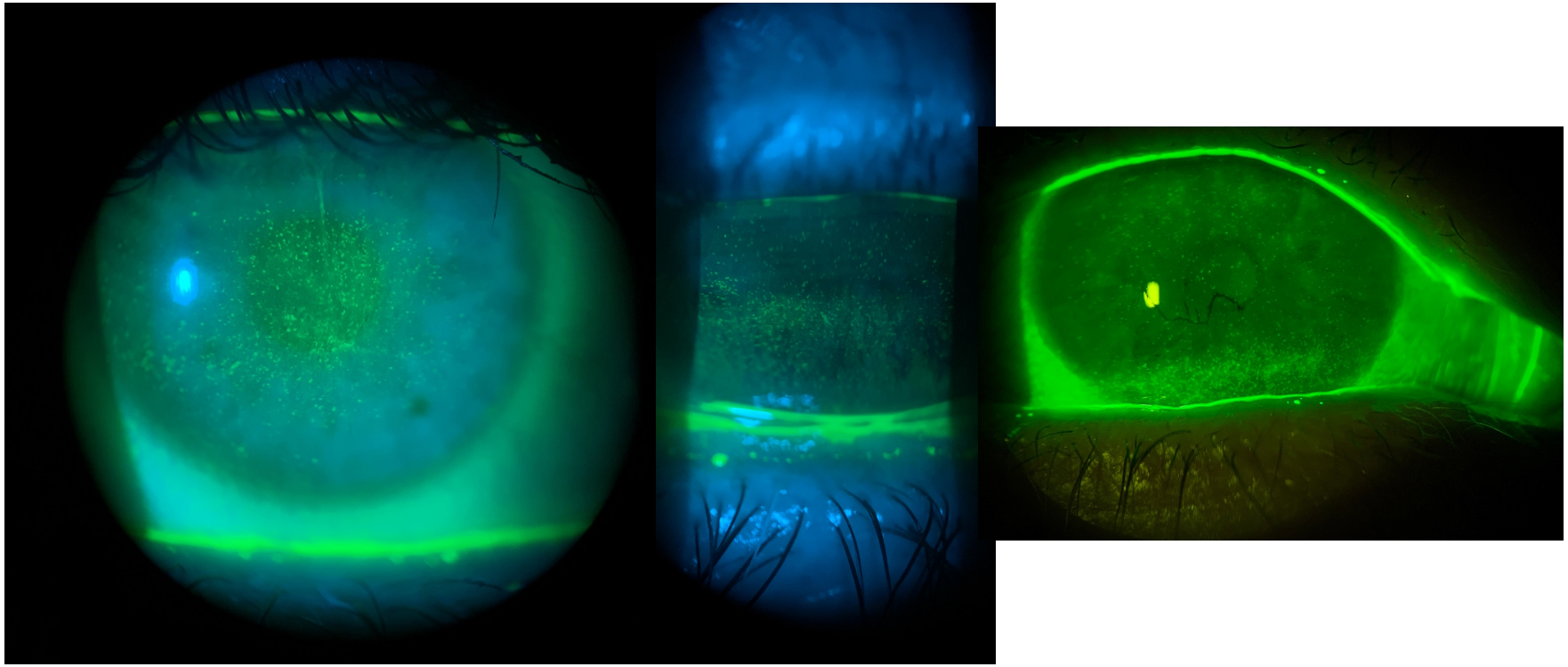
46 YOF presents for dry eye exam

Self referred

VA: 20/200 OD, 20/60 OS PHNI OU

PHI: Severe dry eye that has become incapacitating, difficult to work, tried everything and nothing seems to be helping

CASE



WHAT ELSE DO YOU WANT TO KNOW?

Ocular History

CORNEA SENSITIVITY TESTING

Testing Corneal Sensitivity: A Key Step in Diagnosing NK

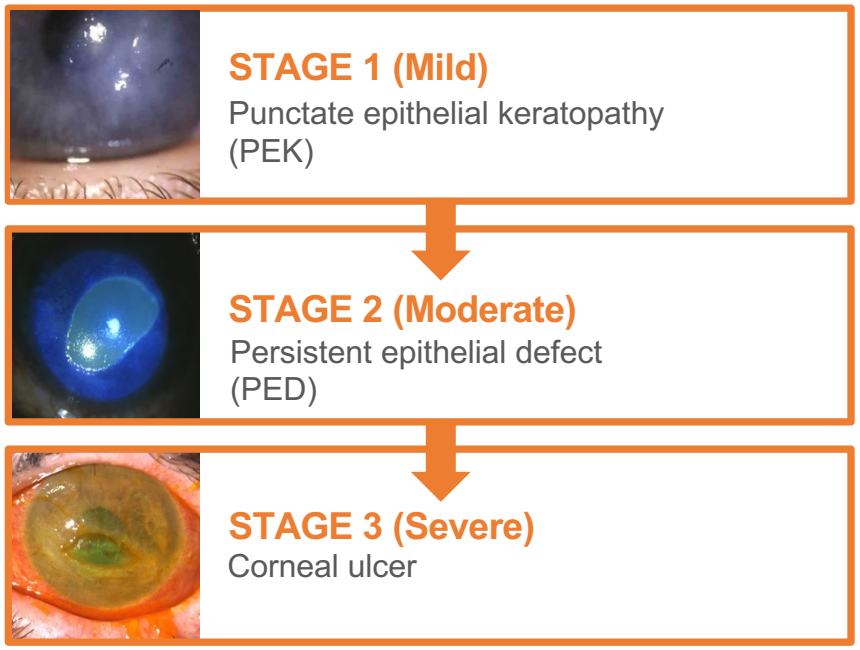
QUALITATIVE

- **Examples:** cotton swab, cotton wisp, dental floss, tip of a tissue
- Basic scoring systems may be developed using simple tests for sensation
- Descriptive scales: normal, hypoesthesia, anesthesia

QUANTITATIVE

- **Example:** Cochet-Bonnet esthesiometer
- Often used in basic research and clinical trial settings
- May be limited in general clinical practice

Milner M, Beckman K, Luchs J. Dysfunctional Tear Syndrome: Dry Eye Disease and Associated Tear Film Disorders - New Strategies for Diagnosis and Treatment. *Current Opinion in Ophthal.* Volume 28, Supplement 1. January 2017.



- Some vision loss can potentially be seen **in all stages of NK**[3]
- If untreated, **moderate NK progresses to severe disease** with associated risks of **profound vision loss** resulting from scarring and corneal perforation[3]

1. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018;66:107-131. **2.** Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica*. 2014;231:191-197.
3. Bonini S, Lambiase A, Rama P, et al. Phase II randomized, double-masked, vehicle-controlled trial of recombinant human nerve growth factor for neurotrophic keratitis. *Ophthalmology*. 2018;125:1332-1343.
4. Roussel T, Grutzmacher R, Coster D. Patterns of superficial keratopathy. *Aust J Ophthalmol*. 1984;12(4):301-316.

IMPAIRED CORNEAL TRIGEMINAL INNERVATION

Impairment of trophic supply

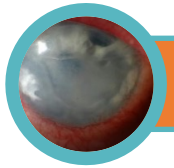
Impairment of trigeminal reflexes

Corneal epithelial alterations

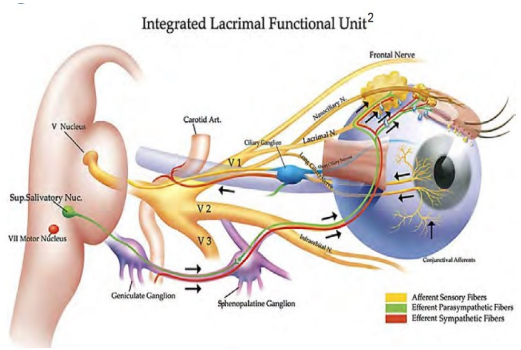
Impairment of corneal healing

Reduced tear film production & blink rate

Spontaneous corneal epithelial breakdown



NEUROTROPHIC KERATITIS



Mastropasqua L, Massaro-Giordano G, Nubile M, Sacchetti M. Understanding the pathogenesis of neurotrophic keratitis: the role of corneal nerves. *J Cell Physiol*. 2017;232(4):717-724.

Topicals	In-Office Procedures	Surgical Intervention
• Artificial tears • Corticosteroids • Autologous serum eye drops • Antibiotics • OXERVATE (cenegermin-bkbj ophthalmic solution 0.002% [20 mcg/mL])	• Therapeutic contact lenses • Punctal occlusion • Non-surgical eyelid closure • Amniotic membranes • Tissue adhesives	• Tarsorrhaphy • Conjunctival flap • Corneal transplant • Direct neurotization • Sutured AMT

Diagnostic Considerations

HISTORY

- Clinical history should be accurately collected and reviewed[1]

CORNEAL SENSITIVITY TESTING

- Can be confirmatory
- Qualitative: tissue, cotton swab, dental floss[2]
- Quantitative: Cochet-Bonnet[2]

SIGNS AND SYMPTOMS may not correlate: Stain, No Pain

- Advanced patients may be asymptomatic due to decreased corneal sensation[3]

MICROBIOLOGICAL EXAMINATION of large PEDs must be performed to exclude bacterial, fungal, or viral infection[4]

EVALUATION FOR SYSTEMIC IMMUNE DISORDERS should be considered[4]

1. Versura P, Giannaccare G, Pellegrini M, et al. Neurotrophic keratitis: current challenges and future prospects. *Eye Brain*. 2018 Jun 28;10:37-45.
2. Milner M, Beckman K, Luchs J. Dysfunctional Tear Syndrome: Dry Eye Disease and Associated Tear Film Disorders - New Strategies for Diagnosis and Treatment. *Current Opinion in Ophthal*. Volume 28, Supplement 1. January 2017.
3. Dua HS, Said DG, Messmer EM, et al. Neurotrophic keratopathy. *Prog Retin Eye Res*. 2018 Sep;66:107-131.
4. Semararo F, et al. Neurotrophic Keratitis. *Ophthalmologica*. 2014;231:191-197.

Chronic Comorbidities May Worsen the Prognosis of NK

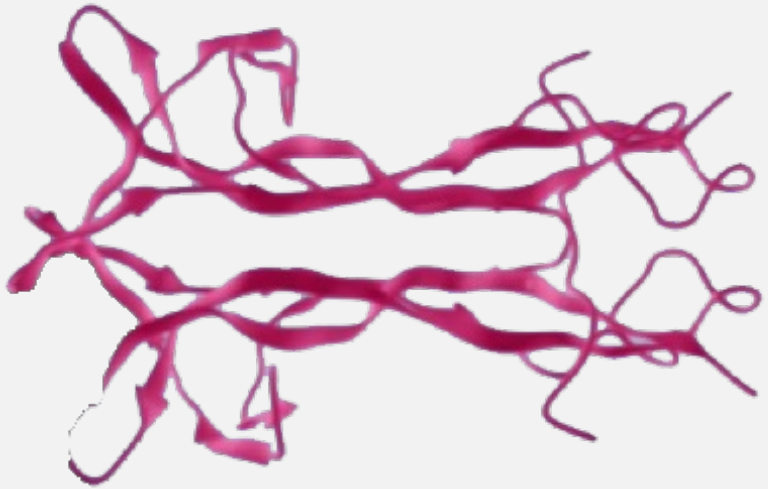
- Dry Eye
- Blepharitis
- Exposure Keratitis
- Topical Drug Toxicity
- Mild Chemical Injury
- Contact Lens-Related Disorder
- Limbal Cell Deficiency

They can also confound the diagnosis of NK, increasing the need for a thorough diagnostic workup, including a confirmatory test

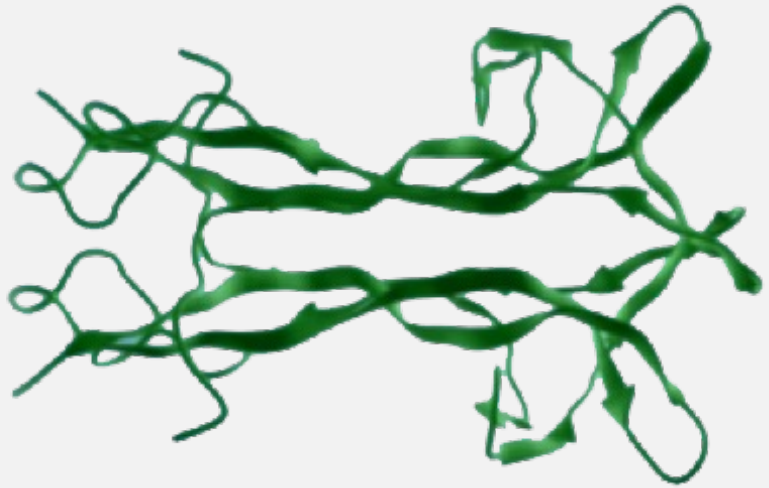
Sacchetti M, Lambiase A. Diagnosis and management of neurotrophic keratitis. *Clin Ophthalmol*. 2014;8:571-579.

CENEGERMIN, THE ACTIVE INGREDIENT IN OXERVATE, IS STRUCTURALLY IDENTICAL TO ENDOGENOUS NGF IN THE OCULAR TISSUES

Cenegermin

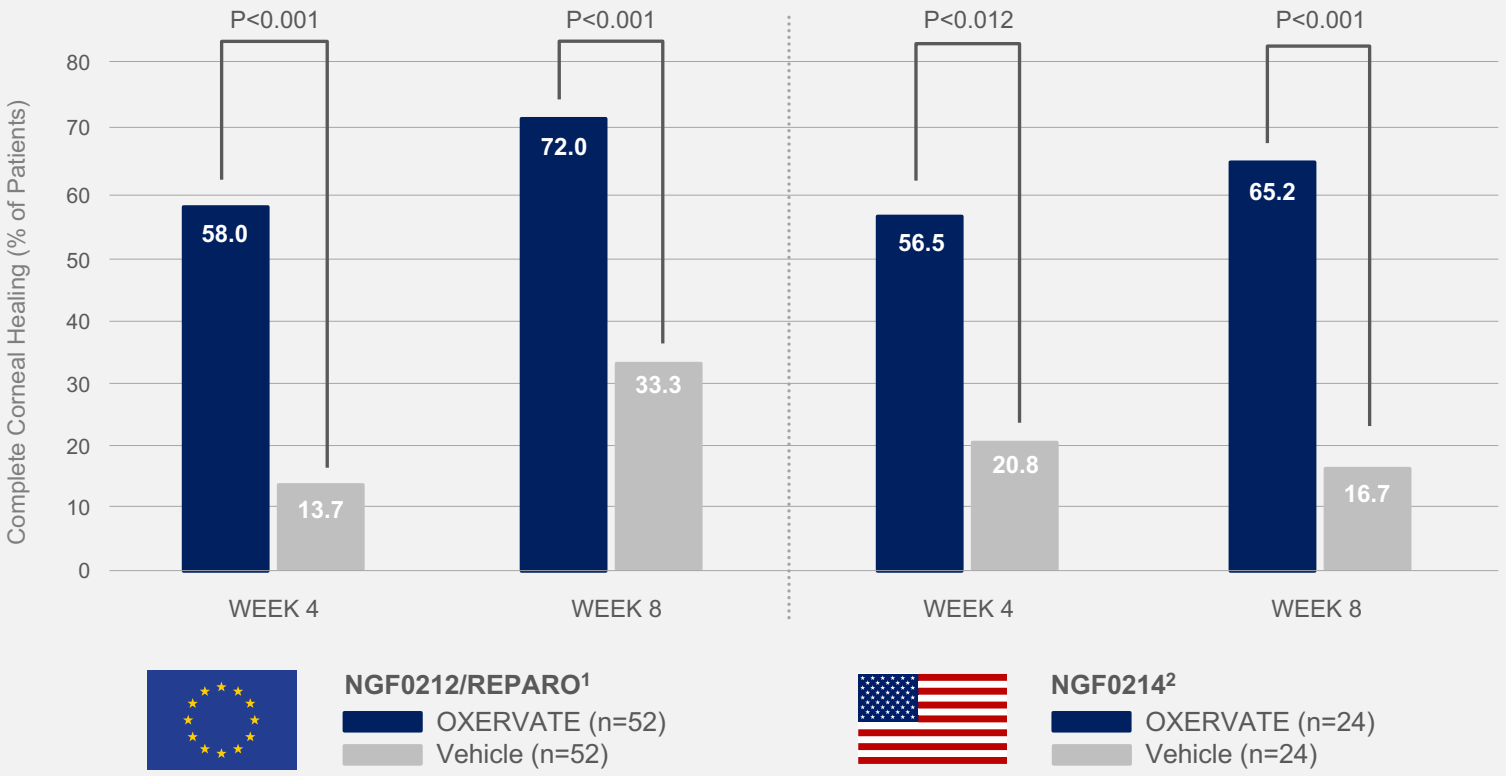


Endogenous NGF



Voelker R. New Drug Treats Rare, Debilitating Neurotrophic Keratitis. *JAMA*. 2018;320(13):1309.

UP TO 72% OF PATIENTS ACHIEVED COMPLETE CORNEAL HEALING AT 8 WEEKS



Up to

72%

of patients who received OXERVATE 20 mcg/mL were completely healed* after one 8-week course of therapy†

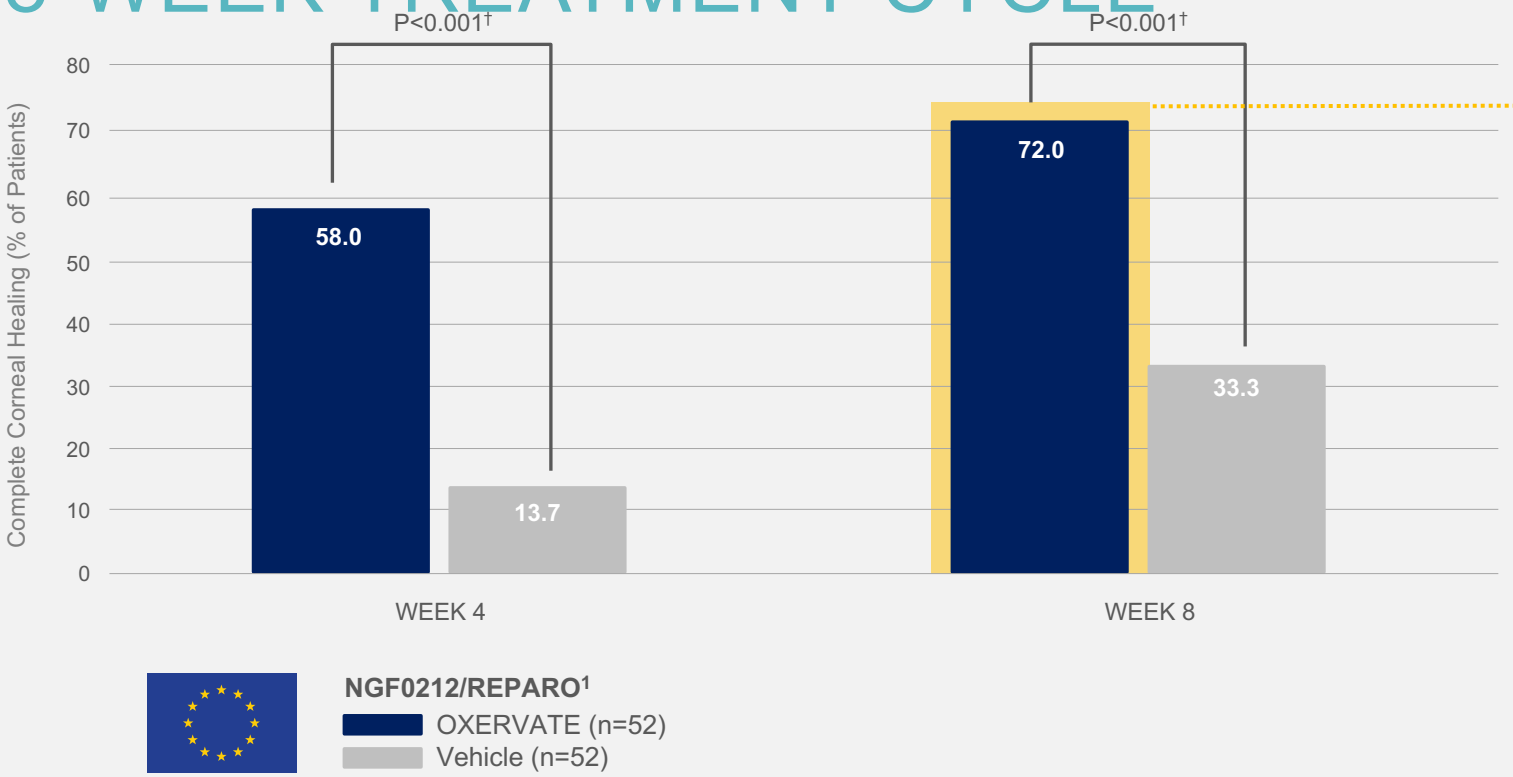
(*complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment)

The formulation that was tested in REPARO (Study NGF0212) did not include the antioxidant methionine and is not the final formulation that is marketed as OXERVATE. Methionine is an excipient added to the commercial formulation to improve its stability. More than one study was conducted with the final commercial formulation. No difference in safety was seen in either of the trials.

†Last post-baseline observation carried forward; chi-squared test

1. Bonini S, Lambiase A, Rama P *et al.* Phase II Randomized, Double-Masked, Vehicle-Controlled Trial of Recombinant Human Nerve Growth Factor for Neurotrophic Keratitis. *Ophthalmology.* 2018;125:1332-1343. **2.** Pflugfelder SC, Massaro-Giordano M, Perez VL et al. Topical Recombinant Human Nerve Growth Factor (Cenegermin) for Neurotrophic Keratopathy: A Multicenter Randomized Vehicle-Controlled Pivotal Trial. *Ophthalmology.* 2020;127(1):14-26.

MOST PATIENTS REMAINED COMPLETELY HEALED 48 WEEKS AFTER ONE 8-WEEK TREATMENT CYCLE[1,2]



80%

of patients who achieved complete corneal healing* in Study NGF0212/REPARO were still healed 48 weeks after completing one 8-week OXERVATE treatment cycle

(*complete corneal healing defined as absence of staining of the corneal lesion and no persistent staining in the rest of the cornea after 8 weeks of treatment)

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CASE

8 year old Caucasian male

VA with habitual Rx 20/40 OD, OS, OU -3.00 and -3.50, 6 months ago he was seen and Rx had changed from -1.50 to this.

MRx -4.00 and -4.50

Ocular health unremarkable

What should we do?

TREATMENT

New glasses Rx?

Recheck in 6 months or 1 year?

Contact lenses?

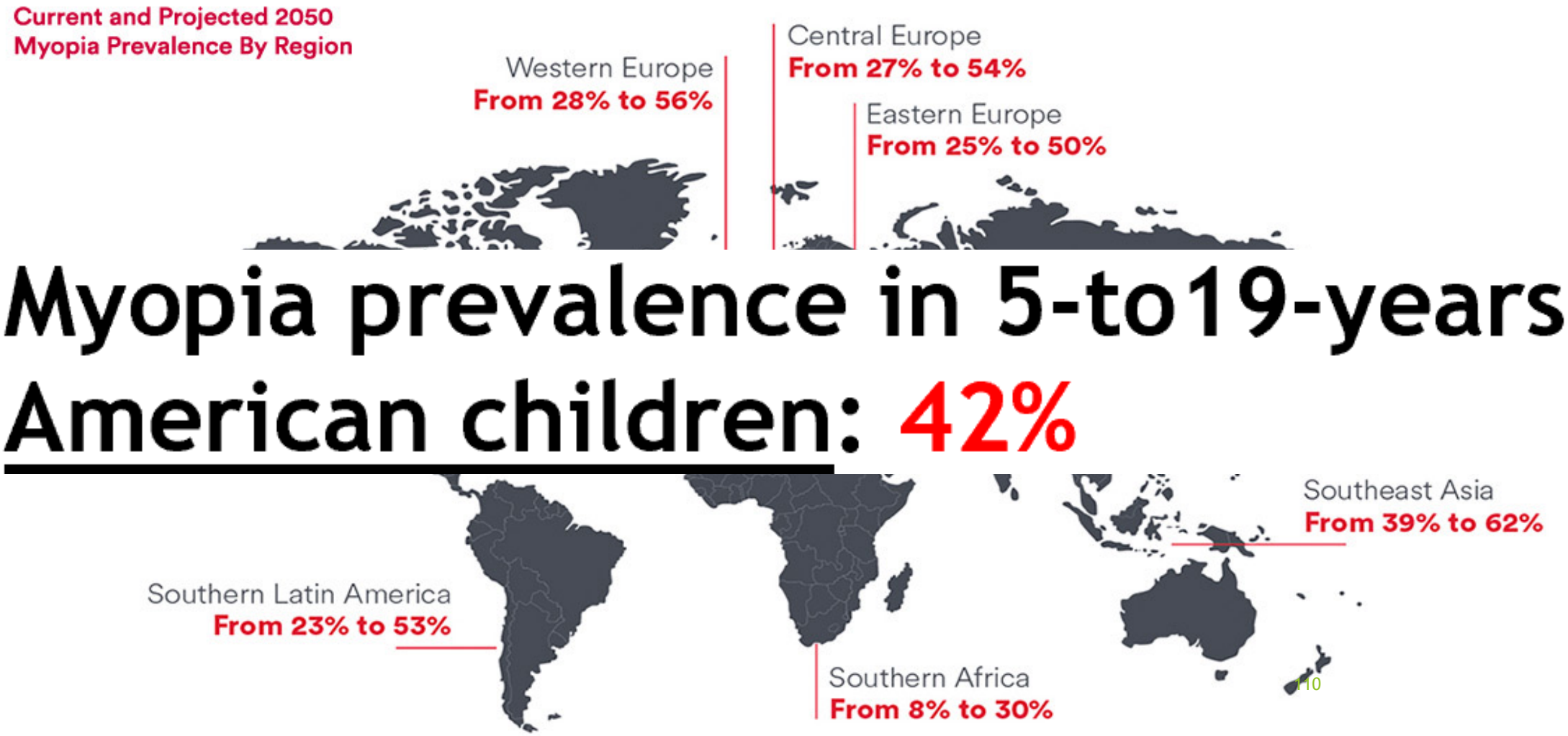
Options?

MYOPIA PROGRESSION

Clinical research spanning over 20 years has given us a new understanding of myopia. Evidence-based intervention strategies are now available which can delay the onset and slow the progression of myopia.

Overview

The global prevalence of myopia is increasing significantly. A 2016 study by Holden et al, reported that in 2010, myopia affected 1.9 billion people worldwide, or 28% of the world's population. By 2050, myopia is projected to affect almost 5 billion people or 50% of the world's population. They also reported that in 2010, 3% of the population had high myopia and that in 2050, 10% of the population or 1 billion people, will have high myopia and be at risk of vision impairment and blindness



Myopia prevalence in 5-to19-years old American children: 42%

Eye Disease	-2.00 D	-4.00 D	-6.00 D	-8.00 D
Myopic Maculopathy[2]	2.2 X higher	9.7 X higher	40.6 X higher	126.8 X higher
Retinal Detachment[3]	3.1 X higher	9.0 X higher	21.5 X higher	44.2 X higher
PSC Cataract[4]	1.6 X higher	3.2 X higher	5.4 X higher	12.3 X higher
Glaucoma[5]	1.7 X higher	2.5 X higher	2.5 X higher	N/A

Odds Ratio of Ocular Disease as a Function of Myopia Relative to Emmetropia[1]

1 Flitcroft, D. I. (2012). The complex interactions of retinal, optical and environmental factors in myopia aetiology. Progress in retinal and eye research, 31(6), 622-660.
2 Vongphanit, J., Mitchell, P., & Wang, J. J. (2002). Prevalence and progression of myopic retinopathy in an older population. Ophthalmology, 109(4), 704-711.
3 Ogawa, A., & Tanaka, M. (1988). The relationship between refractive errors and retinal detachment--analysis of 1,166 retinal detachment cases. Japanese journal of ophthalmology, 32(3), 310-315.
4 Chang, M. A., Congdon, N. G., Bykhovskaya, I., Munoz, B., & West, S. K. (2005). The association between myopia and various subtypes of lens opacity: SEE (Salisbury Eye Evaluation) project. Ophthalmology, 112(8), 1395-1401.
5 Marcus, M. W., de Vries, M. M., Montolio, F. G. J., & Jansonius, N. M. (2011). Myopia as a risk factor for openangle glaucoma: a systematic review and meta-analysis. Ophthalmology, 118(10), 1989-1994.

RISK ASSESSMENT

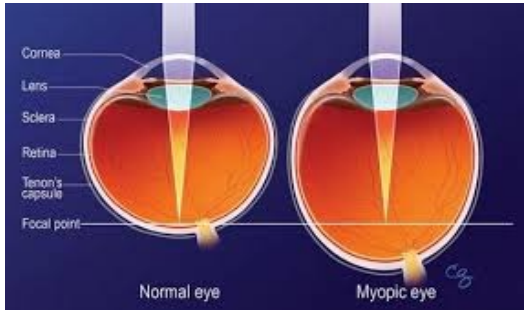
	Risk factors for developing myopia	Risk factors for fast progression
Age	9 years old or less	9 years old or less
Refractive error	Less plus refraction than expected for age	Not applicable
Current progression	Not applicable	> More than -1.00 D per year
Parental myopia	At least one myopic parent	At least one parent with myopia
Ethnicity	East Asian	East Asian
Time spent outdoors	< Less than 1.5 hours per day	Not applicable
Time spent on near work	> More than 2.5 hours per day	Not applicable

DEFINING MYOPIA

Talk about Myopia not nearsightedness

- Axial length of the eye is excessively long **(>23mm)**
- "The main reason to provide myopia management treatment is to prevent the child's eyes from growing too long. This is because the longer the eye, the higher the risk for associated ocular pathology"

Fuensanta A. Vera-Diaz, OD, PhD, FAAO
Review of Myopia Management 8/19



RISK ASSESSMENT

Calculator to assess risk: https://calculator.brienholdenvision.org

Delay onset -In order to try to prevent or delay the onset of myopia, increased outdoor time and regular breaks from near work is recommended.

Manage myopia progression

MYOPIA MANAGEMENT TREATMENT OPTIONS:

OrthoK/Corneal Reshaping*

Multifocal Daytime Wear CLs*

Atropine Therapy

Novel Spectacle Lenses**

Combination Treatments

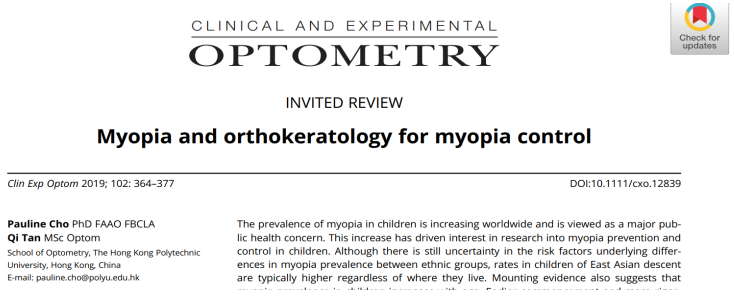
*Currently only modalities w/FDA approval for MM (Cooper's MiSight 11/19 // J&J Ability 5/21)

**Currently awaiting FDA approval (used outside US)

ORTHOK/CORNEAL RESHAPING AND MYOPIA PROGRESSION MANAGEMENT: EVIDENCE BASED DATA

- "Orthokeratology and Myopia"
  - **516 PubMed cited articles (10/21)**
- **More published every year**
  - Articles accepted in **both** optometry and ophthalmology peer reviewed journals
  - Eg:

PubMed.gov
US National Library of Medicine
National Institutes of Health



CLINICAL AND EXPERIMENTAL OPTOMETRY

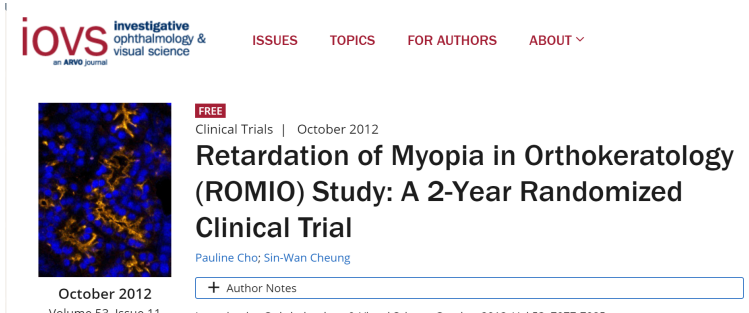
INVITED REVIEW

Myopia and orthokeratology for myopia control

Clin Exp Optom 2019; 102: 364–377 DOI:10.1111/cxo.12839

Pauline Cho PhD FAAO FBCLA
Qi Tan MSc Optom
School of Optometry, The Hong Kong Polytechnic University, Hong Kong, China
E-mail: pauline.cho@polyu.edu.hk

The prevalence of myopia in children is increasing worldwide and is viewed as a major public health concern. This increase has driven interest in research into myopia prevention and control in children. Although there is still uncertainty in the risk factors underlying differences in myopia prevalence between ethnic groups, rates in children of East Asian descent are typically higher regardless of where they live. Mounting evidence also suggests that



iovs investigative ophthalmology & visual science an ARVO journal

ISSUES TOPICS FOR AUTHORS ABOUT

October 2012

FREE

Clinical Trials | October 2012

Retardation of Myopia in Orthokeratology (ROMIO) Study: A 2-Year Randomized Clinical Trial

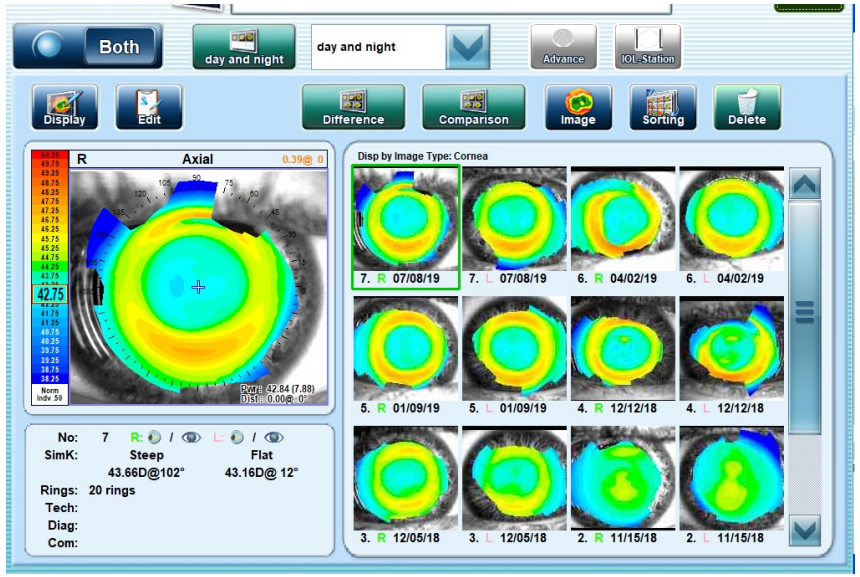
Pauline Cho; Sin-Wan Cheung

+ Author Notes

ORTHO-K

Average reduction in myopia progression: 30-57%.

Cho and Cheung, 2012 (ROMIO); Cho et al, 2005 (LORIC); Hiraoka et al, 2012; Kakita et al, 2011; Santodomingo et al, 2012; Walline et al, 2009; Zhu et al, 2014. Trials ranged from 1 to 5 years.



PREVENTION!!

Time spent in outdoor activities in relation to myopia prevention and control: a meta-analysis and systematic review.

Xiong S1,2, Sankaridurg P3,4, Naduvilath T3, Zang J5, Zou H1,2, Zhu J1, Lv M1, He X1,6, Xu X1,2. Based on 51 articles, Acta Ophthalmol. 2017 Sep;95(6):551-566. doi: 10.1111/aos.13403. Epub 2017 Mar 2.

Increased time outdoors is effective in preventing the onset of myopia as well as in slowing the myopic shift in refractive error. But paradoxically, outdoor time was not effective in slowing progression. Acta Ophthalmol. 2017 Sep;95(6):551-566. doi: 10.1111/aos.13403. Epub 2017 Mar 2.

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CASE

A 57-year-old Caucasian female presented on March 22, 2018 for examination with the complaint of blurry vision. She reported that the blurriness was in both eyes, and it was slowly progressive over the past few months.

Medical history of high blood pressure, high cholesterol, and rheumatoid arthritis.

Medications: 81 mg ASA, Atorvastin, Centrum Silver, Fish Oil, Hydroxychloroquine 200 mg QD, Isosorbife Mononitrate, Levetiracetam, Nitrostat, Restasis, Ranexa, Trexall, Citalopram, Losartan-hydrochlorothiazide, sulfamethoxazole-trimethoprim, topiratmate.

Habitual VA distance was 20/40 OD and 20/50-OS at near 20/40. Pinhole showed no improvement OD with OS improving to 20/40.

Pupils were equal, round and reactive to light, no afferent pupil defect noted OU.

Extraocular motility was full with no restrictions OU.

Intraocular pressures by Goldmann tonometry 14mm Hg OD and 13 mm HG OS at 15:01 pm.

Slit lamp biomicroscopy revealed dermatochalasis. Corneas were clear OU and anterior chambers were deep and quiet OU. Angles were 4x4 using the Von Herrick method.

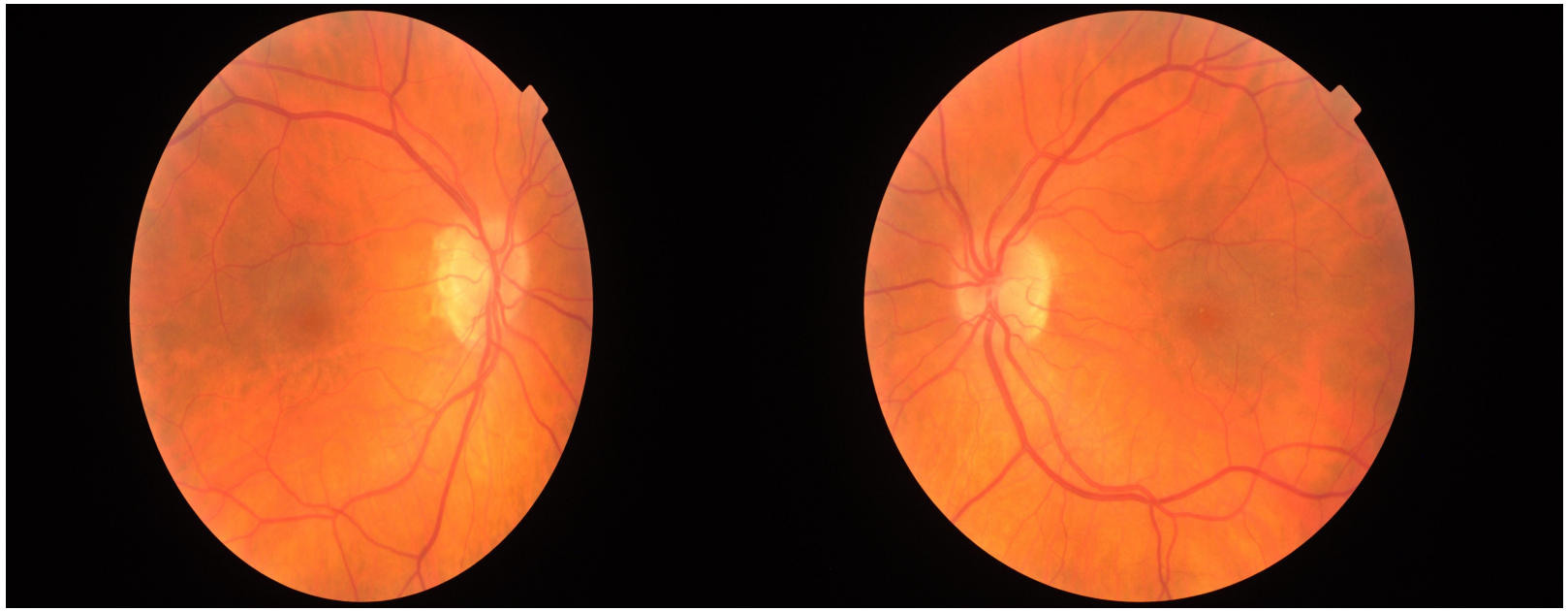
Pupils were dilated with one drop 1% Mydriacyl and one drop 2.5% phenylephrine.

Posterior exam showed 1+nuclear sclerosis of the lenses OU. Vitreous was clear of cell OU. Fundus exam showed OD and OS optic nerves were pink and distinct with a .15/.15 CD ratio.

Macula's were flat with absent foveal reflexes.

Peripheral retina was unremarkable OU.

FUNDUS PHOTOS, 10-2 VF WERE ORDERED AS WELL AS AN SD-OCT.

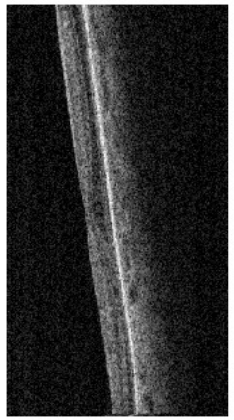


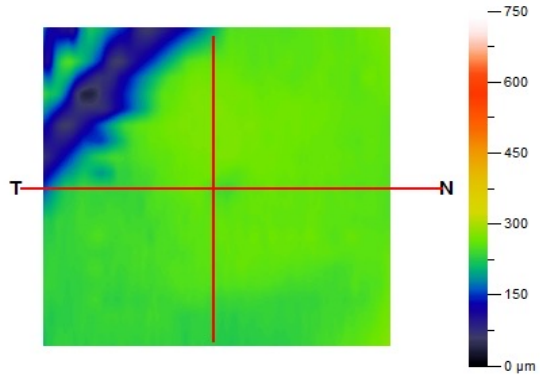
Right / OD

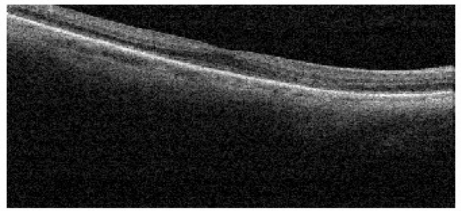
Retina Map OU Report

Left / OS

Full Retina Thickness Map

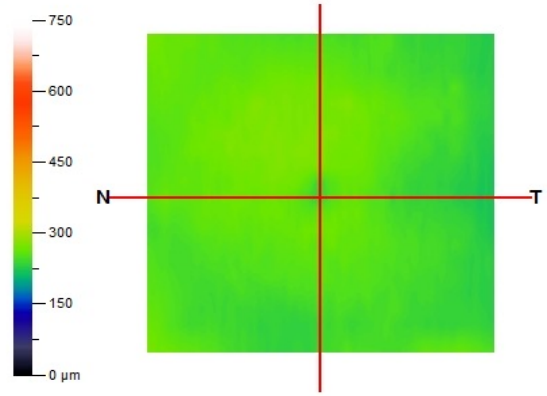


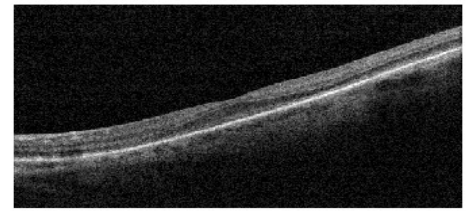




Exam Date: 03/20/2018, SSI = 52.4

Threshold 5





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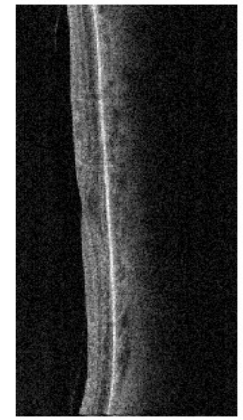

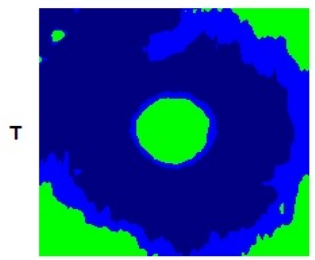

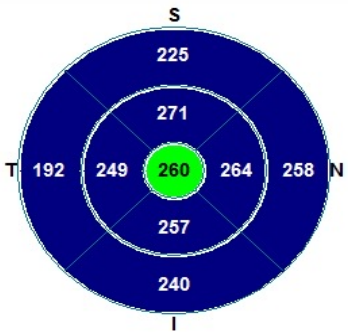

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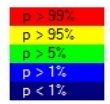

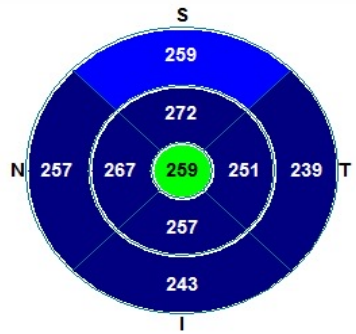

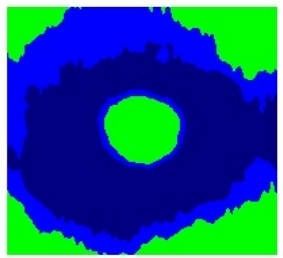

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Print

Change Analysis

optovue

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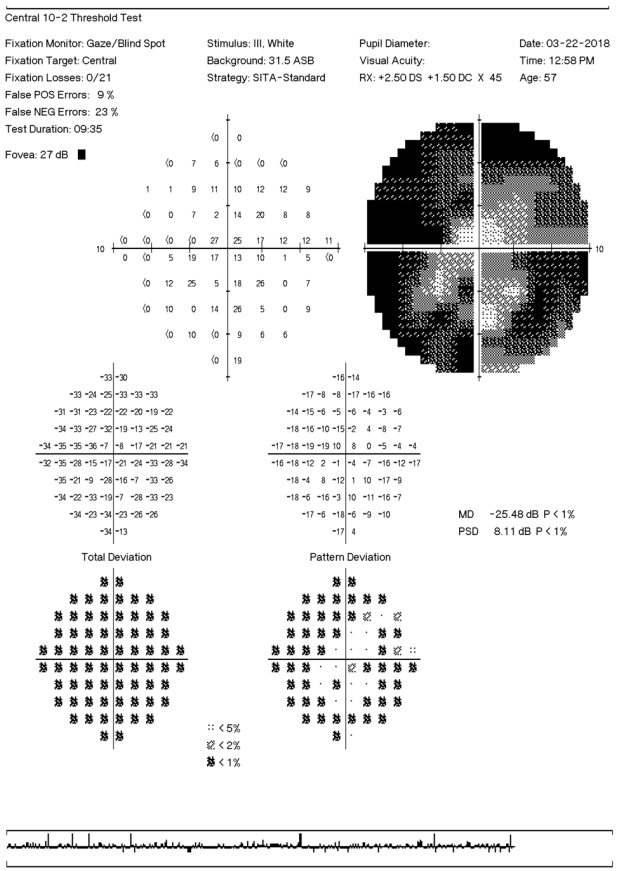
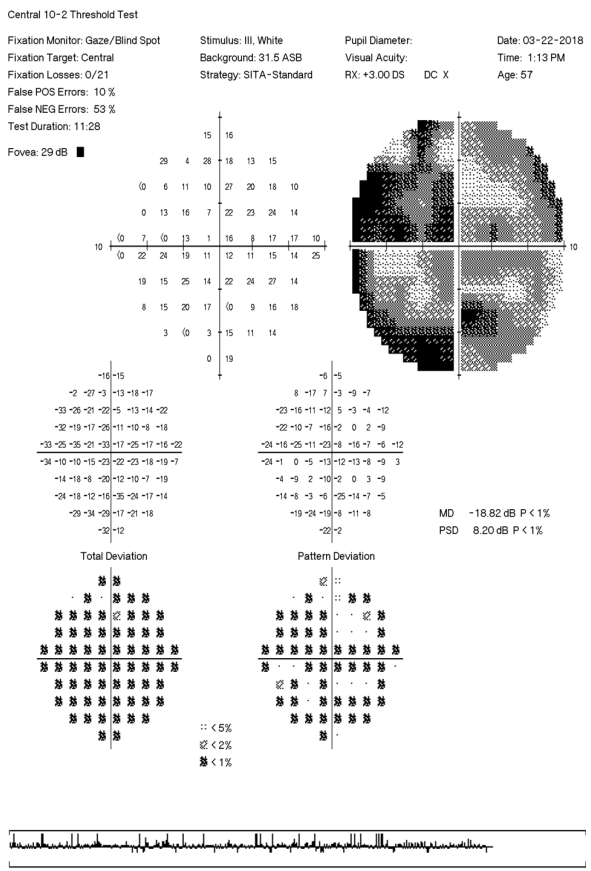

Central 10-2 Threshold Test
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/21
False POS Errors: 9 %
False NEG Errors: 23 %
Test Duration: 09:35
Fovea: 27 dB
Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Standard
Pupil Diameter:
Visual Acuity:
RX: +2.50 DS +1.50 DC X 45
Date: 03-22-2018
Time: 12:58 PM
Age: 57
MD -25.48 dB P < 1%
PSD 8.11 dB P < 1%
Total Deviation
Pattern Deviation
:: < 5%
< 2%
< 1%


Central 10-2 Threshold Test
Fixation Monitor: Gaze/Blind Spot
Fixation Target: Central
Fixation Losses: 0/21
False POS Errors: 10 %
False NEG Errors: 53 %
Test Duration: 11:28
Fovea: 29 dB
Stimulus: III, White
Background: 31.5 ASB
Strategy: SITA-Standard
Pupil Diameter:
Visual Acuity:
RX: +3.00 DS DC X
Date: 03-22-2018
Time: 1:13 PM
Age: 57
MD -18.82 dB P < 1%
PSD 8.20 dB P < 1%
Total Deviation
Pattern Deviation
:: < 5%
< 2%
< 1%

WHAT DO WE THINK?

The appearance of disruption of the photoreceptor integrity line, perifoveal thinning, and paracentral scotomas confirmed high likelihood of toxicity in this patient.

She was asked to stop the medication immediately which she did. She was educated that her vision could worsen until the medication was completely out of her system[1].

A referral for an FA for confirmation of bull's eye maculopathy was ordered.

FOLLOW UP #1 AT RETINA CONSULT

Uncorrected distance acuity OD and OS was 20/70 and PH was 20/50 OD and OS.

IOP was measured at 14 and 12 mm Hg in OD and OS. Anterior segment examination was normal OU. Patient was again dilated with 1% mydriacyl and 2.5% phenylephrine. Vitreous and optic nerve were normal. Macula showed very slight bull's eye macular changes.

FA showed subtle bull's eye maculopathy, and the repeated OCT showed slight parafoveal OCT EZ loss consistent with Plaquenil toxicity. She had already stopped the medication and was again educated that further progression and vision loss could happen. Vision loss did indeed stabilize at 20/50 6 months later.

- Hydroxychloroquine is a commonly used medication for rheumatoid arthritis, lupes, and other autoimmune conditions. In 2011 guidelines warned about cumulative dose of 1000g or exceeding 6.5 mg/kg/day. For a typical patient, most would reach the cumulative dose at 200 mg BID in five years[2]. It is rare for vision changes to occur.
- So what is rare? New information shows it occurs 7.5% of the time, which is actually not that rare. In those patients that are affected, their daily dose and duration of use varied widely. The new guidelines that came out in 2016 show the most critical determent of risk equals current excessive daily dose by actual weight. Under 5 mg/kg = 2% risk over 10 years and increases sharply to 20% at 20 years. ☐At 800mg daily risk was 25%-40% in 1-2 years.
- Who else is at high risk? Patients with renal disease, concomitant use of tamoxifen results in a 5 fold increase in toxicity, and patients who already have retinal and macular disease- mostly because it makes it very difficult to follow these patients with current testing[3]. Look at these additional risk factors carefully when screening patients.

Appropriate testing for screening patients is important because vision, once lost, is not reversible and may progress even after the medication is discontinued. A baseline exam should be performed within the first year of starting therapy, and SD OCT with visual fields are useful in that screening. Use a 10-2 for non-Asian patients. Asian patients can have manifests beyond the macula, so wider test patterns (24-2 or 30-2) should be utilized[4,5]. Screening frequency can be done again at 5 years unless there are higher risk factors then screening should be performed every year. Other useful screening tests are mfERG and FAF.

Do not utilize fundus photos, timed domain OCT, FA, Full field ERG, Amsler grids, color vision testing, or electro-oculogram. Some of these tests can show photoreceptor damage but only late in the disease

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CASE REPORT #3

A 57 year old Caucasian female presented on February 2, 2015 for examination with the complaint of a sudden black spot in central vision that began 3 weeks prior that was not improving. She reported that three days prior to the vision loss she had an intense headache and did not feel well for several days. The "black cloud" was in her central vision and was beginning to break up but vision was still very blurry remaining constant from day to day.

She had a medical history of breast cancer surgery in 2002, mild osteoarthritis, and suffered from depression and anxiety. She had a positive family history of glaucoma with her father being diagnosed later in life.

She was currently taking Alprazolam, Ambien, Xanax, Omeprazole, Venlafaxine XR, Olanzapine, and Zolpidem.

Her uncorrected visual acuity was 20/150-OD and 20/80-OS. Pinhole showed no improvement OD with OS improving to 20/40.

Pupils were equal, round and reactive to light, no afferent pupil defect noted OU. However, the technician dilated pupils before the doctor examined the patient. Due to the patients vision there was high suspicion for an APD that was missed by the technician and a red cap test was performed and was positive on OD.

Confrontational fields were full to finger count in both eyes. Extraocular motility was full with no restrictions OU.

Intraocular pressures by Goldmann tonometry 14mm Hg OD and 12 mm HG OS at 10:54 am.

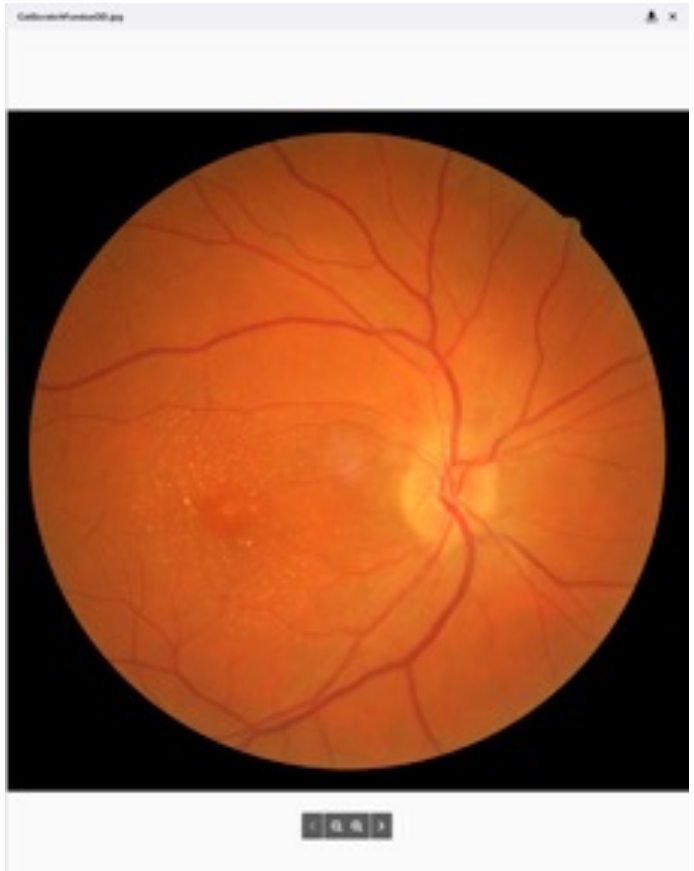
Manifest refraction was attempted on the OD with no improvement. OS was improved to 20/25 with +1.50 +0.50x 045.

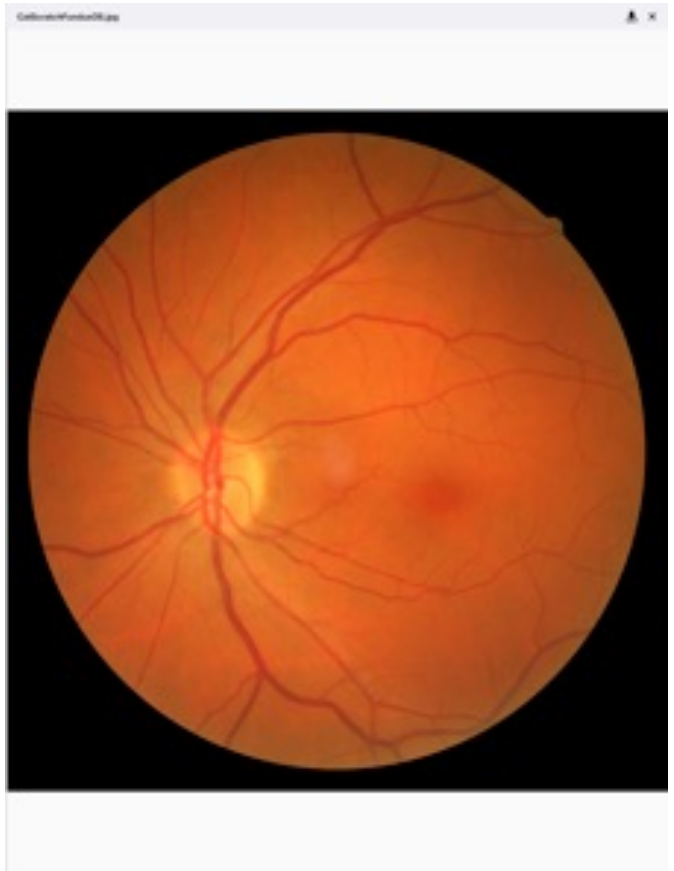
Slit lamp biomicroscopy revealed normal adnexae, lids, lashes, lacrimal drainage, bulbar and palpebral conjunctiva. Corneas were clear OU and anterior chambers were deep and quiet OU. Angles were 4x4 using the Von Herrick method.

Pupils were dilated with one drop 1% Mydriacyl and one drop 2.5% phenylephrine.

Posterior exam showed 1+nuclear sclerosis of the lenses OU. Vitreous was clear of cell OU. Fundus exam showed optic nerve swelling OD. OS optic nerve was pink and distinct with a .15/.15 CD ratio. There was a macular star OD. OS was flat with an absent foveal reflex. Peripheral retina was unremarkable OU.

Fundus photos were obtained as well as an SD-OCT. Blood pressure was also checked and was 136/106 in office. She was educated that she needed to see her PCP to evaluate the presence of hypertension. She did admit to having white coat syndrome but would follow up with her doctor.





DIFFERENTIALS

Hypertensive Retinopathy

Diabetic Papillopathy

Cat Scratch Disease

Lyme Disease

Syphilis

Toxoplasmosis

Tuberculosis

Hypertensive retinopathy presents with focal narrowing of the major retinal arterial branches. There can also be general retinal arteriole narrowing, A/V nicking, intraretinal hemorrhages, cotton-wool spots, or lipid exudates. With very high blood pressure, optic nerve head swelling can occur. Optic nerve head swelling could represent papilledema if bilateral. A macular star pattern of lipid exudate associated with optic nerve head swelling is classic but not a specific finding of severe systemic hypertension.

Diabetic Papillopathy is a transient swelling of the optic nerve head in the setting of a patient with diabetes regardless of the amount of diabetic retinopathy.

Cat Scratch Disease can present with unilateral optic nerve swelling, stellate macular exudates, vitreous cells, positive Bartonella serology, granulomatous conjunctivitis with preauricular lymphadenopathy (in cases of Parinaud's oculoglandular syndrome—POGS), systemic lymphadenopathy, uveitis or focal chorioretinitis.

Lyme Disease can present with decreased vision, double vision, pain, photophobia, optic neurititis, vitritis, iritis, choroiditis, third, fourth, or sixth nerve palsy, bilateral optic nerve swelling, other other inflammatory conditions. Patients may have a history of a prior tick bite, skin rash, Bell's palsy, or arthritis and may live in an endemic area.

Syphilis in it's secondary or tertiary stage can present with uveitis, optic neuritis, active chrorioretinitis, retinitis, retinal vasculitis, chronic iritis, Argyll Robertson pupil.

Toxoplasmosis presents with unilateral white-yellow retinal lesions with vitreous cells. An old chorioretinal scar can often be seen adjacent to a new white-yellow lesion. Optic disc swelling, neuroretinitis, cystoid macular edema or macular star may also be present.

Tuberculosis is caused by the bacteria *Mycobacterium tuberculosis*. It can present with neuroretinitis, retinal vasculitis, and serpiginous choroiditis.

The appearance of the macular star with unilateral optic nerve swelling and the absence of A/V nicking, CWS, or intraretinal hemorrhages was highly suggestive of CSD.

Upon further questioning the patient had brought home two new kittens 4 weeks before and had multiple scratches that had healed.

Although the disease is typically self-limiting, due to the patient's loss of vision she was started on Doxycycline 100 mg BID and a Medrol dose pack. *Bartonella Henselea* serology, ESR, CRP, and CBC with diff was ordered. Her Sed Rate was 16, CBC with diff all fell into the normal range, CRP was 0.37, and B.Henselae (IGG) was positive solidifying the diagnoses of CSD. The patient was to follow up in 1-2 weeks.

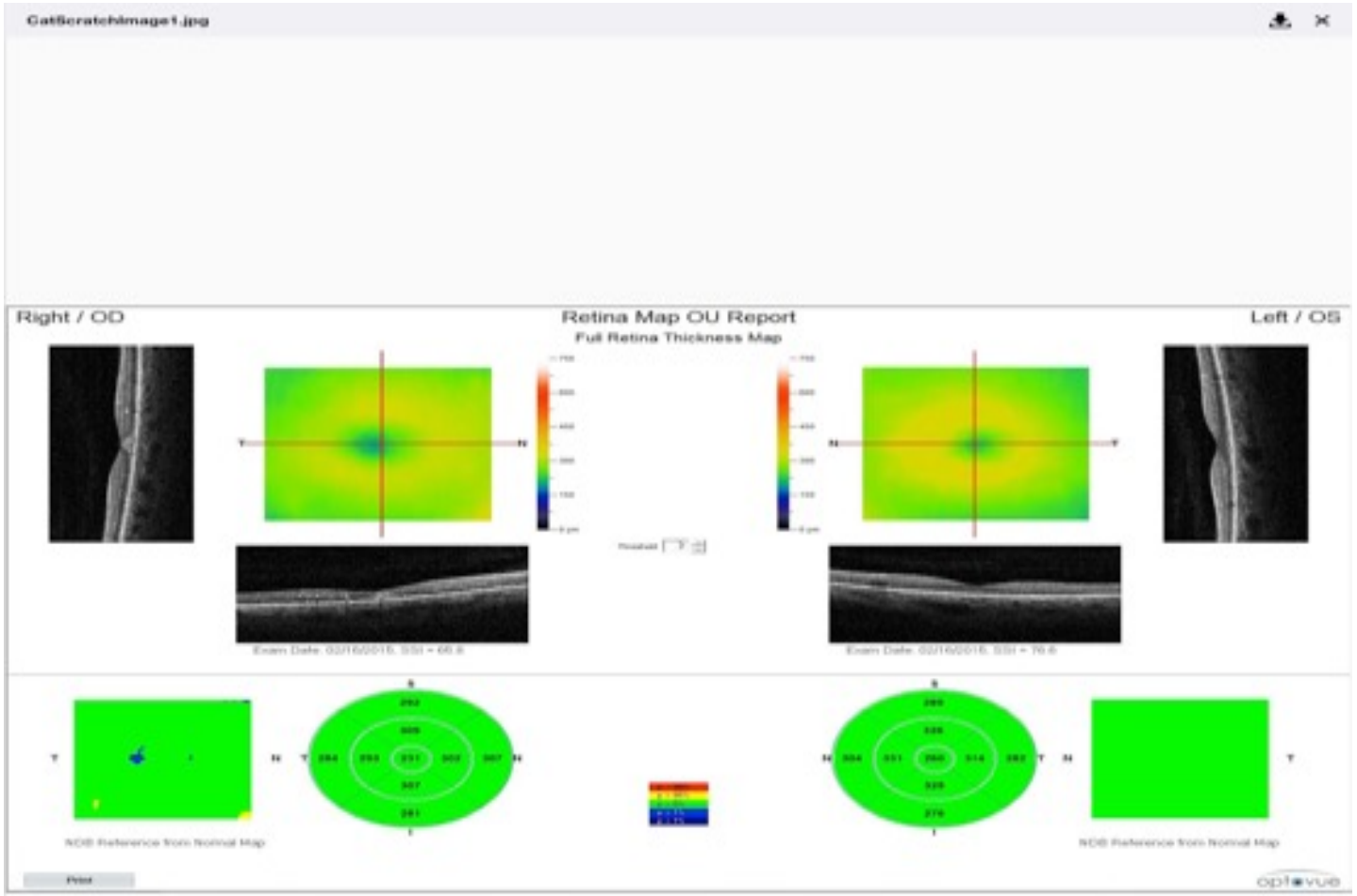
Cat scratch disease (CSD) is a self-limiting disease in immunocompetent individuals. It is caused by infections of *Bartonella henselae*, a gram-negative aerobic, fastidious, intracellular bacillus after contact with infected cats. CSD is transmitted to humans through a cat scratch, cat bite, cat saliva, or cat flea bite.

Typical presentation of CSD is fever and lymphadenopathy; Ocular manifestations occur in 1-2% of patients with CSD. It is a common cause of neuroretinitis, the least common type of optic neuritis. Neuroretinitis is a focal inflammation of the optic nerve and peripapillary retina or macula of either infectious or idiopathic etiology.

CSD is characterized by optic disc swelling with partial or complete macular star.

FOLLOW UP 1

The patient returned two weeks later on February 16, 2015 for further evaluation. She reported that she still had the large spot in her vision, had loss of color on the right eye, but was feeling better. She was compliant with her medications. Visual acuity in OD remained stable at 20/150 and PH showed NI. Uncorrected distance acuity OS was 20/70 and PH to 20/40. IOP was measured at 10 mm Hg in OD and OS. Anterior segment examination was normal OU. Patient was again dilated with 1% mydriacyl and 2.5% phenylephrine at 11:30 am. Posterior exam showed 1+nuclear sclerosis of the lenses OU. Fundus exam showed optic nerve swelling OD. OS optic nerve was pink and distinct with a .15/.15 CD ratio. The macular star OD was still present. OS was flat with an absent foveal reflex. Peripheral retina was again unremarkable OU. An SD-OCT was ordered and performed, which revealed intraretinal deposits OD, OS was normal and showed no evidence of intraretinal edema.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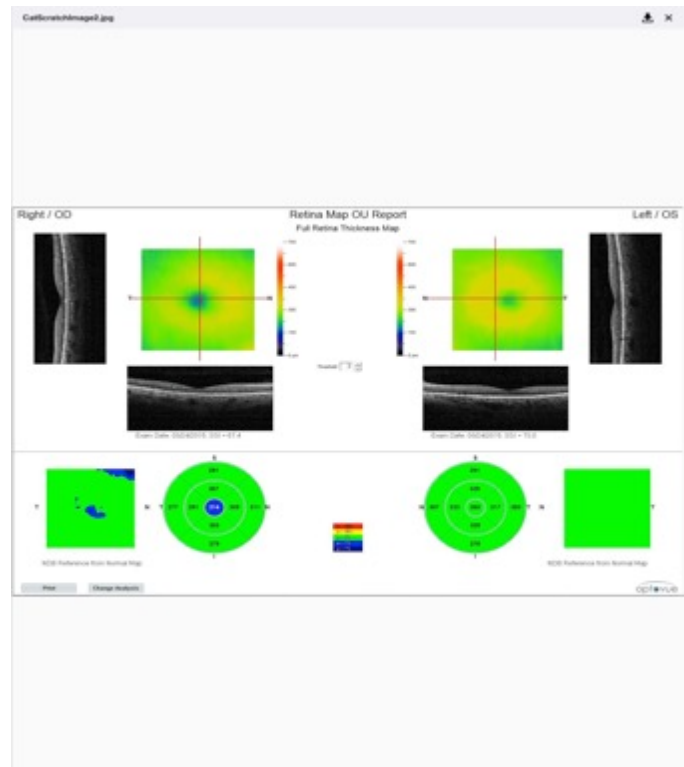
FOLLOW UP 2

The patient returned on March 24, 2015 and reported that vision was starting to improve. She still reported symptomatic color vision changes and reported glare bothering her at night. Unaided visual acuity had improved to 20/100 OD and OS was also 20/100 PH to 20/40. She had no glasses and asked for a glassed prescription today so that she could drive and continue functioning. MR was OD +0.50 +1.25 x 140 and vision remained at 20/100. OS was +1.50 +0.50 x 045 and she could see 20/25. With a +2.50 add she could read the 20/25 line with OU. IOP was performed and measured at 14mm Hg OU. Anterior segment exam was unremarkable and she was again dilated with 1%mydriacyl and 2.5% phenylephrine OU. Posterior exam showed 1+nuclear sclerosis of the lenses OU. Fundus exam showed optic nerve swelling OD. OS optic nerve was pink and distinct with a .15/.15 CD ratio. There was a macular star OD, but it was less prominent today. OS was flat with an absent foveal reflex. Peripheral retina was unremarkable OU. A SD-OCT was again performed, showing less intraretinal exudate. She was asked to return to clinic in 4 weeks. Unfortunately, she was lost to follow up after this visit.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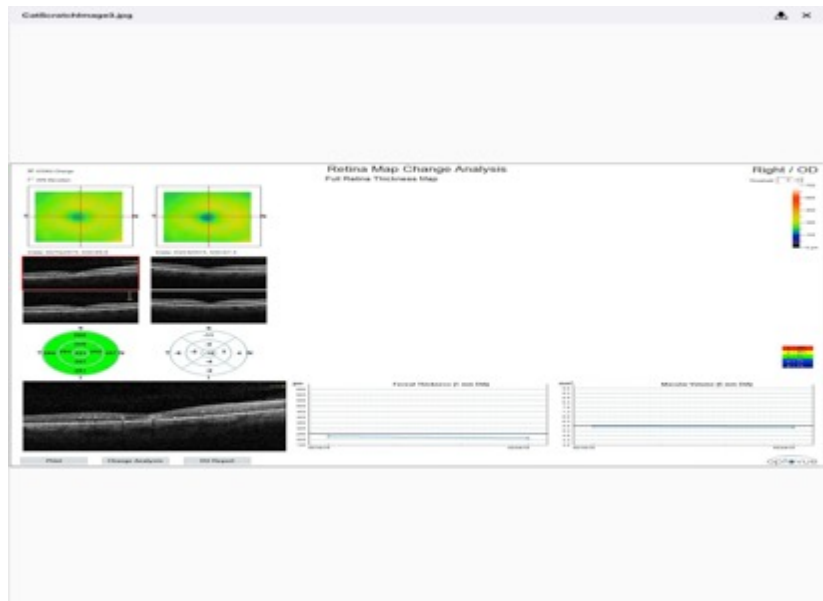
Retina Map Change Analysis
Full Retina Thickness Map
Right / OD

Neuroretinitis affects 1%-2% of patients with *B. henselae* and is characterized by optic disc swelling with partial or complete macular star.

CSD is generally self-limiting within 6-12 months, however it can be complicated by retinal vascular occlusion causing permanent vision loss.

Diagnosis of CSD is based on the history of exposure to cats, fundus findings of swollen optic nerve with a partial or complete macular star, and positive serology of *B. Henselae*[1,2].

In patients that present with marked decrease in vision a treatment of systemic antibiotics and steroids can improve vision more hastily. Typically the antibiotics that are used are doxycycline 100 mg BID for 2-4 weeks, azithromycin 250mg BID x 4 weeks, trimethoprim/sulfamethoxazole-Bactrim DS BID x 10 days, ciprofloxacin 500 mg BID x 10 days, and rifampin 300 mg BID x 4 weeks[1].

Treatment remains controversial because patients will almost always get better on their own. Antibiotics can shorten the duration of symptoms. Patients prognosis is generally good with 67% regaining >20/20 vision, and 97%>20/40 vision spontaneously.[5]

Disc edema resolves over 8-12 weeks and macular star resolves over 6-12 months.[5]

CONCLUSION

Ocular Bartonellosis is a rare manifestation of cat scratch disease. Neuroretinitis is the typical ocular presentation. The diagnosis can be made with a careful case history of exposure to cats and *B. henselae* serology. There is some suggestion that patients with vision threatening ocular manifestations can be improved with systemic antibiotics and steroids while other studies have shown improvement with no pharmacological intervention. Patients should be treated on a case-by-case basis with entrance acuities and presentation being taken into consideration. Patient follow up needs to be tailored to how severe the symptoms manifest initially and the resolution of signs and symptoms.

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CASE

An 62 year old Hispanic male presented on July 08, 2016 for examination with the complaint of sudden onset blurry vision that started 2 days prior. He stated his had not improved or worsened over the last two days. He said he had a black spot in the middle of his vision that did not move and had a "churning" pattern in the center of it.

He had a medical history of diabetes, Type I since 1995, hypertension, and past surgery for an abdominal aneurysm on February 5, 2016. His fasting blood sugar had been fluctuating between 70-206. His blood pressure today was 120/72 taken by him this morning.

He was currently taking Aciphex, Glucotrol, Lortab 5, allopurinol, aspirin, and gabapentin.

His visual acuity with habitual Rx was 20/25+2 OD and 20/60 OS. Refraction of OS improved with a more hyperopic shift -1.50+2.50 x 170 to 20/20.

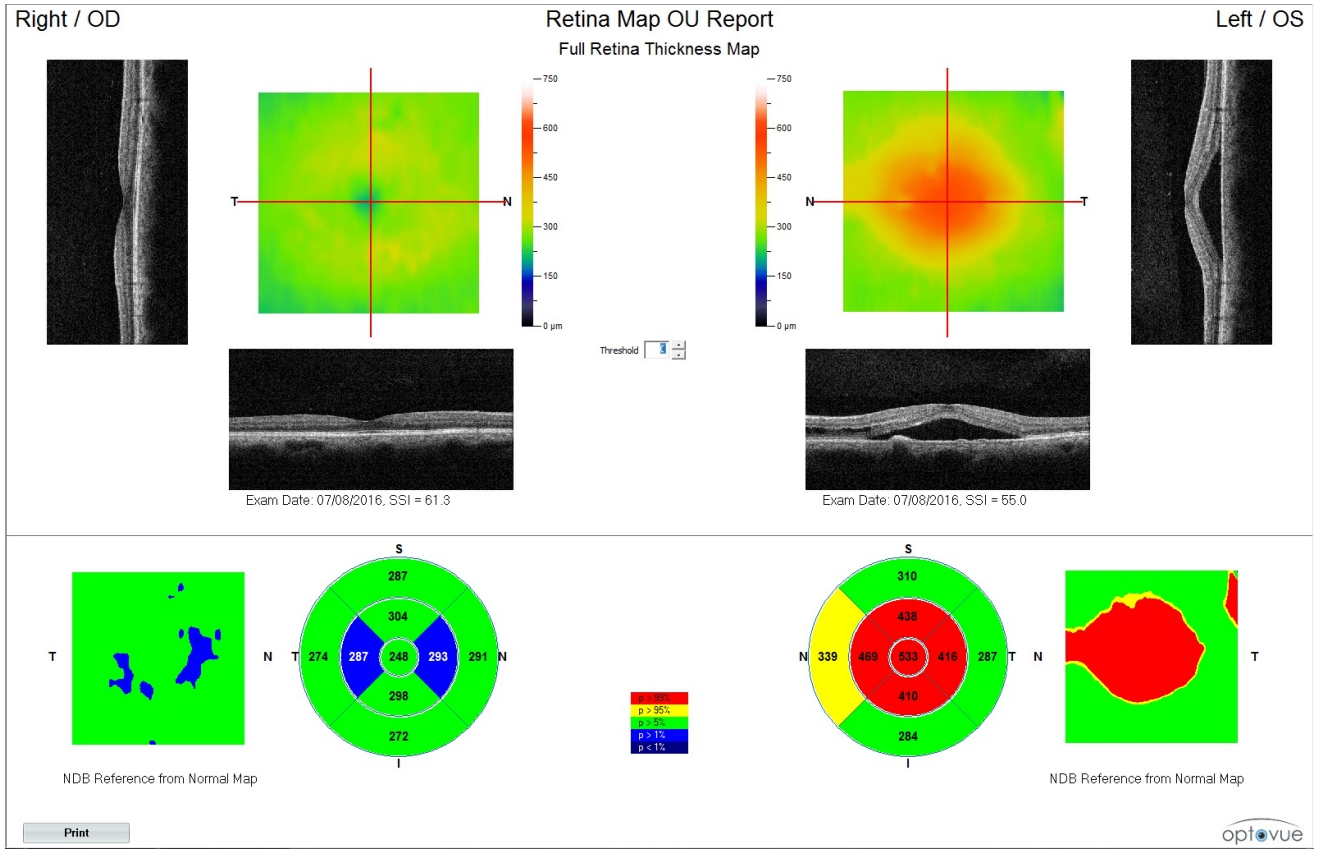
Pupils were equal, round and reactive to light, no afferent pupil defect noted OU. Confrontational fields were full to finger count in both eyes. Extraocular motility were full with no restrictions OU.

Intraocular pressures by Goldmann tonometry were 14mm Hg OD and 14 mm HG OS at 14:26.

Slit lamp biomicroscopy revealed normal adnexa with mild dermatochalasis, lids, lashes, lacrimal drainage, bulbar and palpebral conjunctiva. Corneas were clear OD and OS.

Anterior chambers were deep and quiet OU. Angles were 4x4 using the Von Herrick method.

Pupils were dilated with one drop 1% Mydriacyl and one drop 2.5% phenylephrine. Posterior exam showed +1 NSC OU. Fundus exam showed optic nerves to be pink and distinct with a .20/.20 CD ratio OU. Posterior pole was normal in OD, but there was subretinal fluid evident in his macula OS. Periphery of OU was unremarkable. Fundus photos were obtained as well as an OCT of his macula.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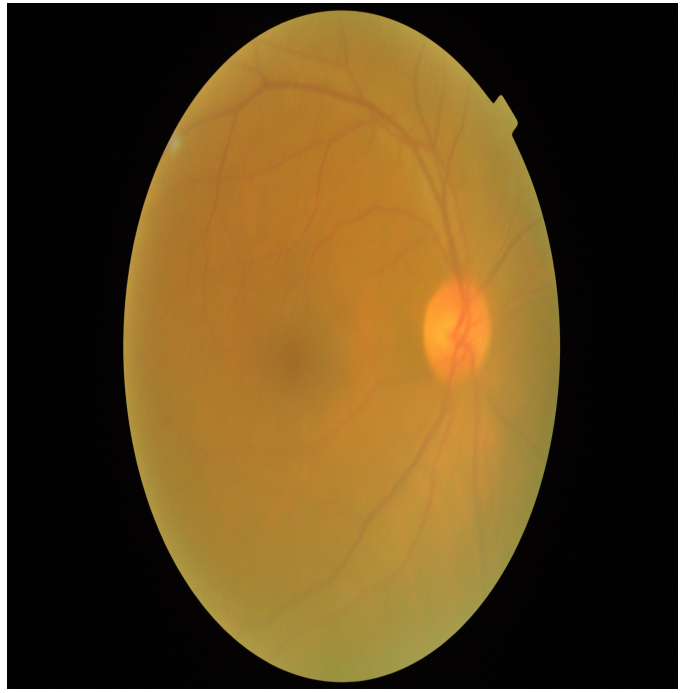

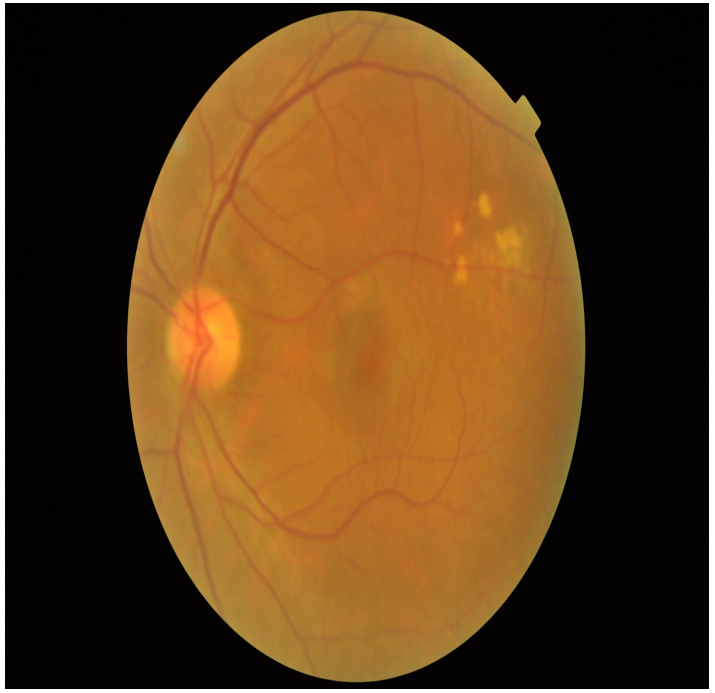

DIFFERENTIAL DIAGNOSIS

Choroidal neovascularization

Exudative Age Related Macular Degeneration (ARMD)

Nonexudative ARMD

Macular Hole

Central Serous Chorioretinopathy

Rhegmatogenous Retinal Detachment

Choroidal tumors

Optic nerve pit with serous macular detachment

Choroidal neovascularization (CNV)-CNV involves a new blood vessel that grows from the choroid through a break in Bruch's membrane and leaks into the subretinal space. Patients will present with painless vision loss, metamorphopsia, central scotoma, or changes in image size.

Exudative ARMD occurs when a choroidal neovascular membrane (CNVM) develops under the retina in the presence of ARMD. Patients describe a painless, progressive blur of their central vision, which can be acute or slow in onset. Patients will present with subretinal fluid, retinal pigment epithelial detachments, subretinal hemorrhage, and sometimes-subretinal lipid deposits.

Nonexudative ARMD patients complain about difficulty in night vision and slow adaption from changing light conditions, as well difficulty with near vision. Patients will present with drusen either soft or hard, RPE migration and atrophy.

DIFFERENTIAL DIAGNOSIS CONTINUED

Macular Hole is a condition in which there is a defect of the foveal retina and can involve the full thickness of retina from the internal limiting membrane to the outer segment of the photoreceptor layer. Patients can present with blurry central vision, metamophopsia, and a central scotoma. It usually has a slower onset but can present acutely especially if the patient covers their good eye and discovers the eye affected is blurry.

Rhegmatogenous retinal detachment occurs when there is a tear in the retina that allows fluid to accumulate and a separation of the neurosensory retina from the underlying RPE occurs. Patients can present with photopsia, visual field defects, floaters, or loss of central vision.

Choroidal tumors can also cause subretinal fluid to collect due to an abrupt disruption of the RPE. Patients will present with decreased vision, visual field defects, floaters, photopsias. The lesions will be elevated and appear gray-green or amelanotic.

Optic nerve pit is an abnormality of the optic nerve that can have an associated serous detachment of the macula.

Central serous chorioretinopathy (CSC) is a disease in which a serous detachment of the neurosensory retina occurs over an area of leakage from the choriocapillaris through the retinal pigment epithelium (RPE). It needs to be thought of as a diagnosis of exclusion as there are other disease states that cause fluid to leak at the level of the RPE. Other causes for RPE leaks, such as choroidal neovascularization, inflammation, or tumors, should be ruled out to make the diagnosis.

Historically, the stereotypical person diagnosed with CSC was a Type A middle-aged male. Studies suggest an annual incidence rate of 10 per 100,000 with it occurring six times more commonly in men than women[6]. Corticosteroid use can be a precipitating factor and can certainly exacerbate the condition[2]. Careful probing of the patients corticosteroid history use is important in managing the disease. The exact pathogenesis of CSC has yet to be determined. Evidence indicates that there are vascular abnormalities within the choroid that lead to hyperpermeability of the choroidal vessels, which can then cause a retinal pigment epithelial detachment[4].

The majority of patients with acute CSC will return to baseline without any type of intervention typically within 1-4 months. However, 30-50% of patients will recur within one year[3]. In recalcitrant cases or recurrence of CSC, focal laser and PDT are the current standard of care to facilitate reattachment of the neurosensory retina. Visual prognosis is usually good with returning vision 20/30 or better, but patients can be left with color defects, contrast sensitivity issues, and metamorphopsia.

Treatment is aimed at reattachment of the neurosensory retina through photocoagulation or photodynamic therapy (PDT). The available evidence suggests that retinal atrophy can be avoided if resolution of the detachment can be obtained within 4 months of the onset of symptoms. (Wang et al. 2002). Retinal photocoagulation using an argon laser is usually successful in reducing or stopping the RPE leakage that is causing the serous detachment, but it should be used with caution as it can induce subretinal neovascularization that can happen even years later[12]. This occurred in less than 10% of patients[6]. Argon laser is destructive to photoreceptors and cannot be used in subfoveal or juxtfoveal leaks and does not reach the choroidal layer. In these cases ICG guided half dose PDT is useful. In retrospective studies the success of PDT may depend on the degree of choroidal hyperpermeability, which is why ICG angiography is helpful in assessing who may benefit. Eyes that had intense hyperfluorescence on ICGA were much more likely to have resolution of subretinal fluid. If there was no hyperfluorescence there was no response in those eyes that had PDT. Other treatment modalities like micropulse diode laser, anti-VEGF agents, and oral medication that block systemic glucocorticoid have not been studied widely enough to be considered as therapy that has proven to be useful.

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CASE 5

An 85 year old Caucasian female presented on August 21, 2015 for examination with the complaint of dryness in both eyes that was constant. She had run out of her Restasis that she had been taking OU and felt her dryness symptoms were worse. She had a medical history of hypertension and hypercholesterolemia that were under good control. She also had history of basal cell carcinoma, osteoarthritis, suffered with GERD and was diagnosed with diabetes in 1994 that she currently controlled with her diet. She also had hypothyroidism. She had a positive history of cataract surgery OU in 2007. She had no positive family history of any eye diseases. She was currently taking Restasis, Vesicare, Alprazolam, Aspirin, Benzazepril-Hydrochlorthiazide, Citalopram, Furosemide, Levothyroxine, Meloxicam, Omeprazole, Polyethylene Glycol, Simvastatin, and Tramadol.

Her corrected visual acuity with habitual Rx was 20/20-OD and 20/30 OS.

Pupils were equal, round and reactive to light, no afferent pupil defect noted OU.

Confrontational fields were full to finger count in both eyes. Extraocular motility was full with no restrictions OU.

Intraocular pressures by Goldmann tonometry 15mm Hg OD and 15 mm HG OS at 11:27 am. Manifest refraction was -0.75 +0.50 x160 20/20 OD and -0.75+1.00x045 20/25 OS.

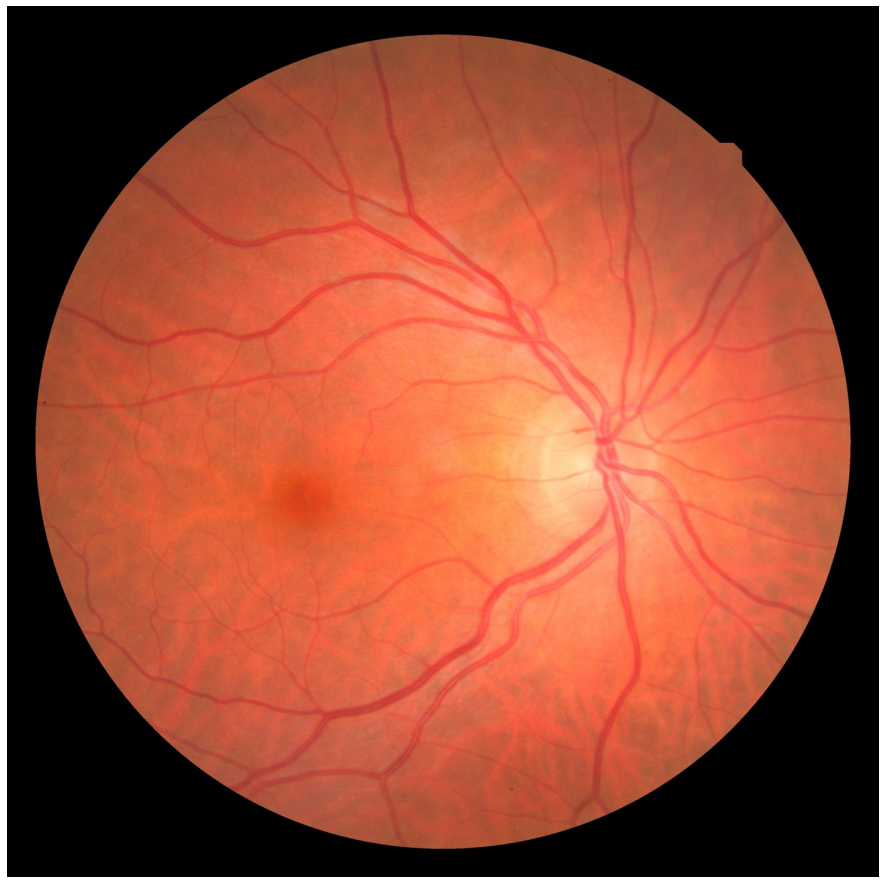
Slit lamp biomicroscopy revealed normal adnexae, lids, lashes, lacrimal drainage, bulbar and palpebral conjunctiva. Corneas were clear OU with no SPK but she had decreased tear volume OU and anterior chambers were deep and quiet OU. Angles were 4x4 using the Von Herrick method.

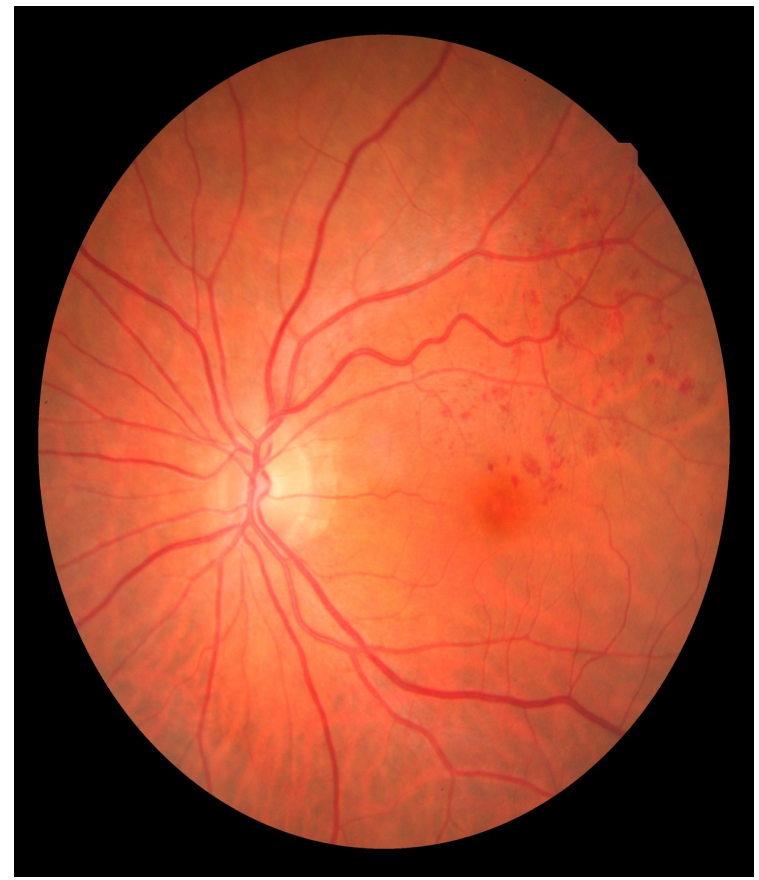
Pupils were dilated with one drop 1% Mydriacyl and one drop 2.5% phenylephrine.

Posterior exam showed PC IOL OD and PCIOL with trace PCO OS.

Fundus exam showed optic nerves to be pink and distinct with a .25/.25 CD ratio OU. Posterior pole was unremarkable OD, but OS showed multiple superficial retinal hemorrhages in a wedge shaped area. Periphery of OD was unremarkable and OS had an old hole with operculum that was stable with no RD or SR fluid. Fundus photos were obtained at this visit.

There was no baseline OCT performed at this visit as only fundus photos or OCT can be reimbursed in the same visit.





Hypertensive retinopathy

Diabetic retinopathy

Ocular Ischemic Syndrome

BRVO

Hypertensive retinopathy presents with focal narrowing of the major retinal arterial branches. There can also be general retinal arteriole narrowing, artery and vein nicking, intraretinal hemorrhages, cotton-wool spots, or lipid exudates. With very high blood pressure, optic nerve head swelling can occur. A macular star pattern of lipid exudate associated with optic nerve head swelling is classic but not a specific finding of severe systemic hypertension.

Diabetic retinopathy presents with bilateral hard and soft exudates, intraretinal hemorrhages, microaneurysms, venous beading, and intraretinal microvascular abnormalities throughout posterior pole and mid-periphery.

Ocular Ischemic Syndrome (OIS) is found in patients who have very severe stenosis, or complete occlusion, of the arterial lumen of the carotid artery. The retinopathy is ipsilateral to the more severely compromised artery. OIS presents with retinal arterial narrowing and venous dilation (not tortuous), retinal hemorrhages located in the midperiphery, microaneurysms, cotton-wool spots, disc or retinal neovascularization, and spontaneous pulsations of the retinal arteries. The retinal findings are quite similar to those found in diabetic retinopathy, except it corresponds to the more obstructed artery and occurs in the midperiphery of the retina rather than the posterior pole. Iris neovascularization and secondary neovascular glaucoma are common and are very important to diagnose as these can be sight threatening.

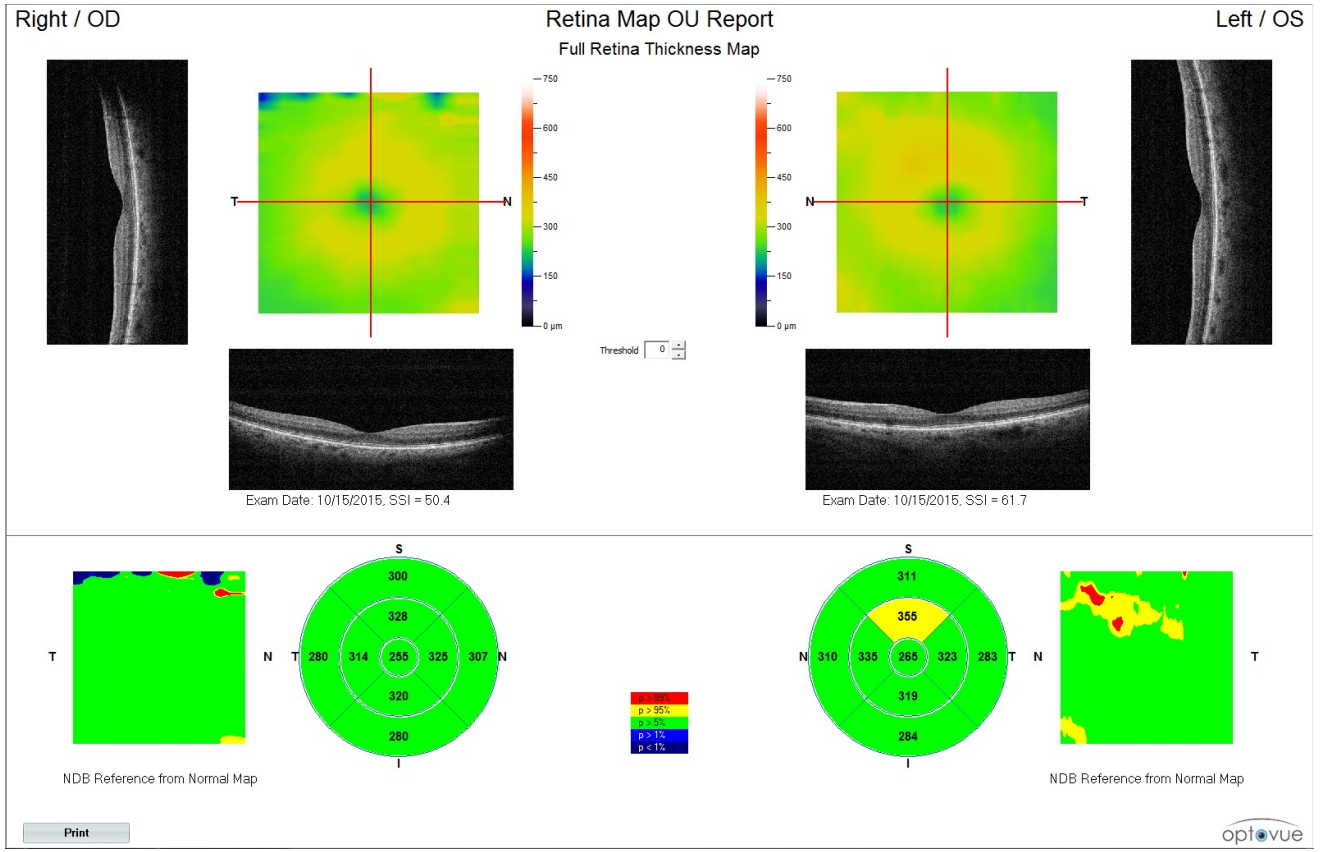
FOLLOW UP #1

Patient presented to clinic on 10/13/2015 for follow up. She presented with vision that was stable. Eyes were still burning and she had fallen approximately 6 weeks ago and hit her head on the right side.

Her visual acuity was stable at 20/25 OD and 20/30 with her habitual Rx.

IOP with Goldmann at 9:15 was 18 and 16. At 9:16 she was dilated with 1% Mydriacyl and 2.5% Neosynephrine.

Posterior pole still had hemorrhages OS across the branch retinal vein. A macular OCT was obtained today as well which showed no evidence of intraretinal edema. Patient was asked to return to clinic in 3 months.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FOLLOW UP #2

Patient presented to clinic on 02/18/16 for follow up. She had missed her follow up in early January.

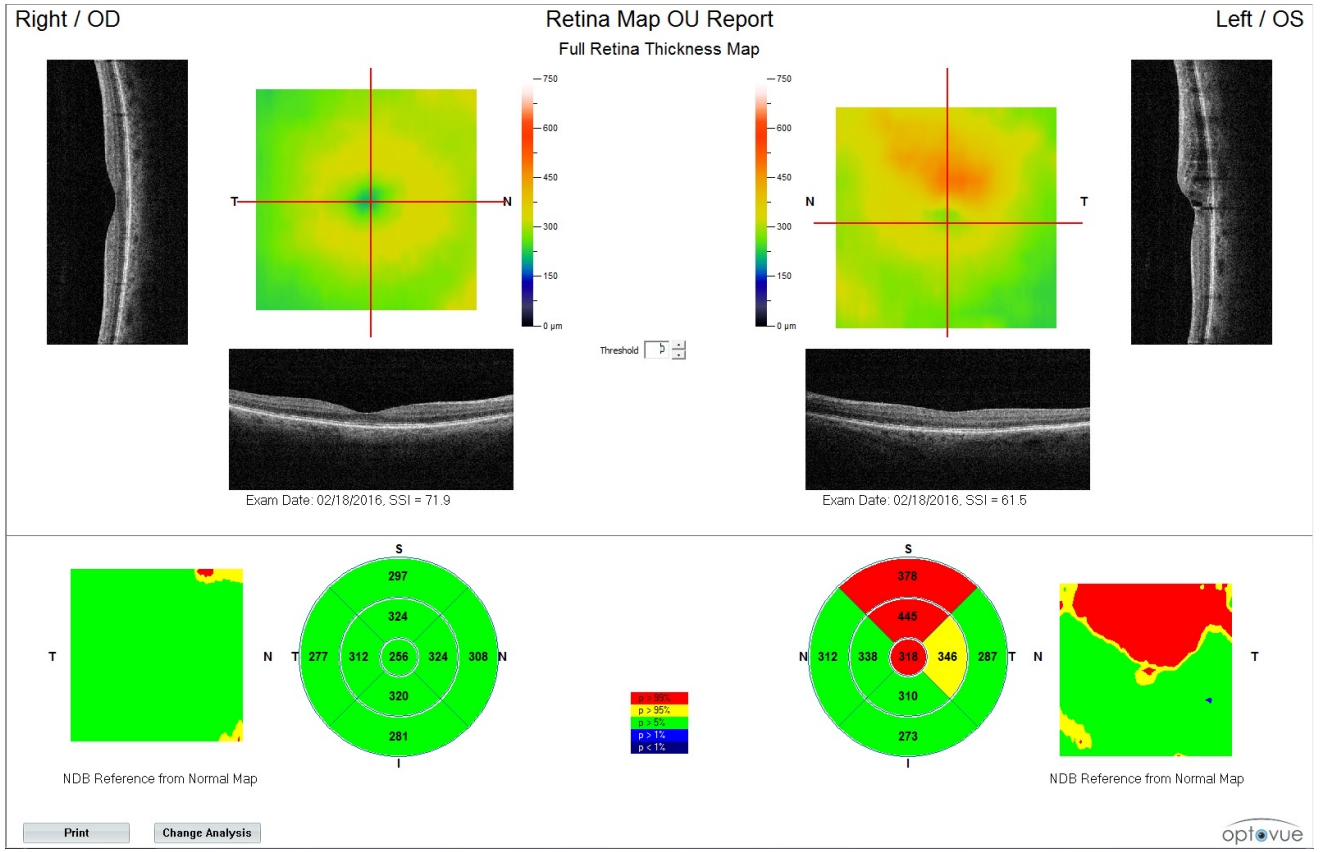
Patient presented with vision that had worsened in the last few weeks, which prompted her to reschedule the appointment.

Her visual acuity was stable at 20/20 OD and 20/30-2 with her habitual Rx.

IOP with Goldmann at 9:51 was 17 and 15. At 9:52 she was dilated with 1% Mydriacyl and 2.5% Neosynephrine.

Posterior pole still had hemorrhages OS across the branch retinal vein. A macular OCT was obtained today as well which now showed intraretinal edema and thickening.

Patient was referred to a retina specialist, Dr. Ryan Ridges.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Cup to disc ratio: OD: 0.3
OS: 0.3

OD:
Vitreous: noShafer's sign
Optic Nerve: pink with normal cupping
BV/Mac/Periph: fully attached, no RD, RH, RT

OS:
Vitreous: noShafer's sign
Optic Nerve: pink with normal cupping
BV/Mac/Periph: intraretinal hemorrhage at the superior border of the macula, intraretinal hemorrhage superior to the macula, w/ pigment, flat, no fluid operculated retinal tear temporal to the macula

Optical Coherence Tomography:
OCT OD: Good foveal contour, no fluid. Attached. OCT OS: central and superior intraretinal and subretinal fluid.

Fluorescein Angiography:
FA OD: no leakage. FA OS: venous transit delay. Blockage secondary to heme in superior macula, some leakage near fovea and superotemporal to fovea. No large areas cap dropout. No signs NV.

Impression:
OD posterior chamber intraocular lens
OS posterior chamber intraocular lens
OS branch retinal vein occlusion

Assessment and Plan: Dr. McGee, Mrs. Wilma Walters was referred for a retinal vein occlusion evaluation. She was found to have a branch retinal vein occlusion (BRVO) with cystoid macular edema in her left eye. Additional time was taken to educate the patient on her eye condition. The review of systems for BRVO risk factors includes hypertension and diet-controlled diabetes. I have emphasized the need to optimize control of blood pressure. I have recommended intravitreal anti-VEGF therapy. The risks, benefits, and alternatives of anti-VEGF therapy with off-label Avastin were discussed. A decision was made to proceed and informed consent was obtained. The procedure was performed without complication and post-injection precautions were provided. Laser and/or steroid treatment may also be required at a later date in order to reduce the risk for vision loss. I will update her PCP with this ocular finding and recommend ongoing vascular management.

Selina, thank you for the kind referral. Should you have any questions regarding Ms. Walters's care please feel free to contact me.

Best Regards,

RYAN RIDGES, M.D.
Retina Specialist

Typical patients that present with RVO's are older than 60.

According to the Eye Disease Case–Control Study risk factors include hypertension, diabetes, dyslipidemia, and open-angle glaucoma.

A retinal vein occlusion is essentially a blockage of the venous circulation that drains the retina. The pathophysiology essentially is caused by a thrombus formation that is associated with venous stasis[3].

It is suggested that primary open-angle glaucoma causes turbulence at the level of the retinal vein due to the narrowing it can cause with increased and decreased intraocular pressure. The central artery and vein travel in the same adventitial sheath and their lumina are smaller at the lamina cribosa than anywhere else. The lamina cribosa is a sievelike structure that can shift anterior or posterior depending on the shift in intraocular pressure. This shift could cause turbulence that can be associated with retinal vein occlusions.

Meta analysis has shown association with increased risk of future stroke and MI[1]. As primary eye care providers we can be first in line in preventing these future events.

Checking blood pressure in clinic and referring to their PCP for systemic evaluation of risk factors could help identify uncontrolled underlying systemic issues like hypertension, dyslipidemia, and diabetes.

Other systemic conditions including hyperviscosity states are rare.

Is it necessary to do a full systemic work up in patients with a retinal vascular occlusion?

Yes, in patients that are younger than 50 that have no other medical problems that can be identified or if it is bilateral.

Carotid ultrasound and transesophegeal echocardiograms are only necessary in a retinal artery occlusion because of the risk that it could be due to an embolism. Patients that have retinal vein occlusion do not need theses unnecessary tests.

Complications can arise that can cause additional vision loss.

Macular edema can occur as well as intraocular neovascularization.

Macular edema can be perfused, nonperfused, or mixed. In 40% of eyes with ischemic or nonperfused BRVO, disc or retinal neovascularization (neo) develops. In general, neo usually develops within the first 6-12 months after the onset of the occlusion but may develop anytime within the first 3 years[3].

Patients should be seen every 1 to 2 months at first then every 3 to 12 months checking for neovascularization and macular edema.

In the last 15 years there has been a paradigm shift in treatment.

Originally, the Collaborative Branch Vein Occlusion Study (BVOS) showed that 33% of eyes with macular edema had significant improvement in 3 months without treatment and so patients were watched for this period before grid laser photocoagulation was performed. In the BVOS, eyes with perfused macular edema of 3-18 months duration and visual acuity of 20/40 or worse were treated with grid laser photocoagulation or were watched. 63% of treated eyes gained two lines of visual acuity.

The Standard Care vs. Corticosteroid for Retinal Vein Occlusion (SCORE) study was conducted to evaluate the effectiveness of macular edema due to vein occlusion treated with grid laser versus corticosteroid injections. The conclusion of the SCORE BRVO trial suggested that the corticosteroids had similar impact on vision, as did the patients that were treated with grid laser. Due to the side effects of corticosteroids laser treatment remained a good option for macular edema due to BRVO.

Prior to anti-VEGF patients as shown in the BVOS were observed for 3 months then were treated with laser if they had a BRVO, patients with a CRVO were not treated at all based on the BVOS.

Patients treated with anti-VEGF therapy, steroids, and laser (grid and PRP) have outcomes that have improved significantly, particularly their visual acuity, decreased macular edema and neovascular glaucoma.

The landmark anti-VEGF trials include BRAVO, CRUISE, and HORIZON with Lucentis 0.5mg monthly for 6 months[13]. VIBRANT, GALILEO, and COPERNICUS were the trials with Eylea 2mg monthly for 6 mo[13].

Since our patient had a BRVO we will focus on the BRAVO and VIBRANT studies, which showed an 18 letter, gain and 17 letter gain respectively[13]. The landmark steroid studies were SCORE done with 1 mg intravitreal triamcinolone where 26% of patients gained 15+letter of VA for BRVO vs. 29% laser and GENEVA which used Ozurdex-0.7mg dexamethasone implant and 25% of patients gained 15+ letters of vision at 1-2 month visits vs. 7-12% of placebo[10]. Prognosis for patients was looked at in the RETAIN study and showed 56% of patients with a RVO needed some form of anti-VEGF treatment at 4 years to continue excellent vision outcomes[13].

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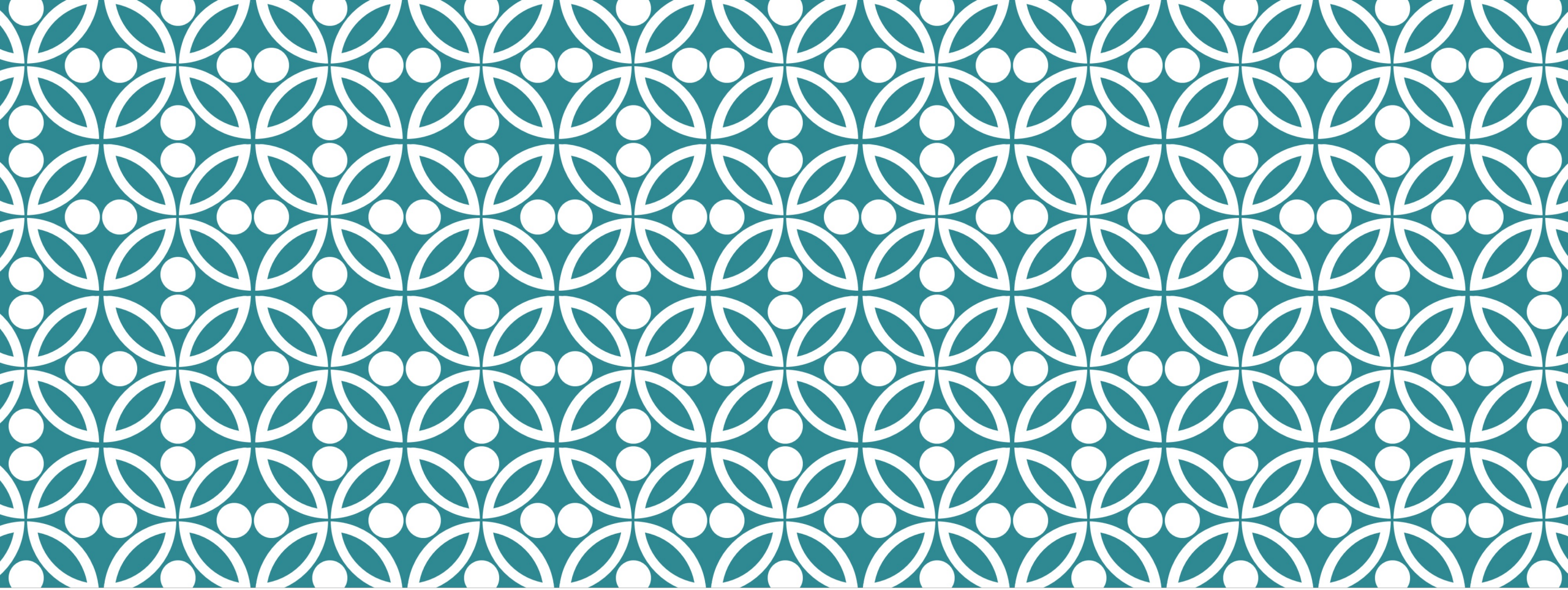


THE "DRY EYE" PATIENT

Selina R. McGee, OD, FAAO

40 YOF PRESENTS FOR "ANNUAL" EYE EXAM

CC: Eyes are gritty and irritated, seems to come and go but more consistent over the last year. Tried artificial tears that aren't much help.

Patient denies systemic disease, currently not taking medication, and NKDA

VA sc: 20/20 OD, OS, OU distance and near

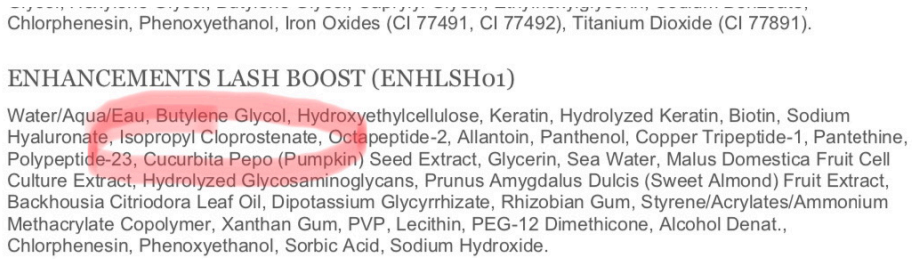
Anterior segment and posterior seg exam unremarkable.

A fairly straightforward patient?

LET'S TALK ABOUT PRODUCTS…

Are you using any new and different products around your eyes?

Only something for my eyelashes, but it's over the counter…



Chlorphenesin, Phenoxyethanol, Iron Oxides (CI 77491, CI 77492), Titanium Dioxide (CI 77891).

ENHANCEMENTS LASH BOOST (ENHLSH01)

Water/Aqua/Eau, Butylene Glycol, Hydroxyethylcellulose, Keratin, Hydrolyzed Keratin, Biotin, Sodium Hyaluronate, Isopropyl Cloprostenate, Octapeptide-2, Allantoin, Panthenol, Copper Tripeptide-1, Pantethine, Polypeptide-23, Cucurbita Pepo (Pumpkin) Seed Extract, Glycerin, Sea Water, Malus Domestica Fruit Cell Culture Extract, Hydrolyzed Glycosaminoglycans, Prunus Amygdalus Dulcis (Sweet Almond) Fruit Extract, Backhousia Citriodora Leaf Oil, Dipotassium Glycyrrhizate, Rhizobian Gum, Styrene/Acrylates/Ammonium Methacrylate Copolymer, Xanthan Gum, PVP, Lecithin, PEG-12 Dimethicone, Alcohol Denat., Chlorphenesin, Phenoxyethanol, Sorbic Acid, Sodium Hydroxide.

LOOK PAST THE HYPE-CARCINOGENIC AND SHOW UP IN THE BLOOD STREAM

There are no specific cosmetic safety tests that are required by the Federal Food, Drug, and Cosmetic Act of 1938

Sodium Laurel Sulfate

- Found in Shampoo, body wash, face wash, mouthwash, and toothpaste
  - Cancer, canker sores, eye irritant, cystic acne

BHA & BHT

- Found in exfoliants and perfume-carcinogenic

Triclosan and triclocarbon

- Found in toothpaste, deodorant, and antibacterial soap-hormonal disruption, bacterial resistance

Aminophenol, Diaminobenzene, Phenylenediamine-Coal Tar

- Hair Dye and shampoo-carninogenic

Parabens

- Preservative-mimic estrogen, linked to breast cancer, skin cancer, decreased sperm count

Polyethylene Glycol/PEG's

- Found in scrubs-carcinogenic

Retinal palmitate, retinyl acetate, retinoic acid, and retinol

- Moisturizer, lip products, anti-aging-carcinogenic in sunlight

Petroleum Distillers

- Mascara-contact dermatitis, cancer causing impurities

Isopropyl cloprostenate

- **Synthetic prostaglandin**

Oxybenzone

- Sunscreen-mimics estrogen

Dibutyl phthalate, toluene, and formaldehyde "Toxic Trio"

- Nail polish and other nail products-birth defects, endocrine disruption, headaches, respiratory problems

Hydroquinone

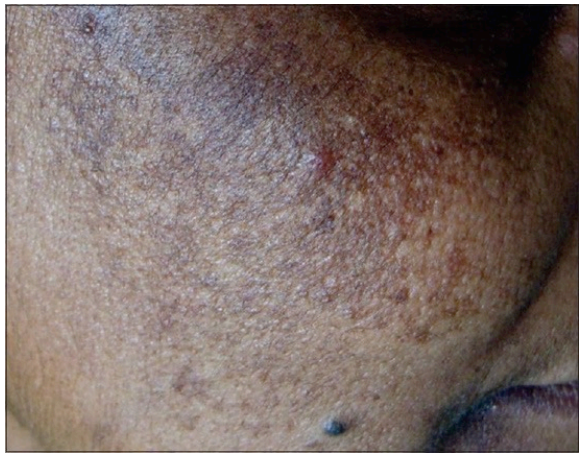
- Skin lighteners-ochronosis

Propylene Glycol

- Skin conditioning agent-contact dermatitis, hives

Fragrance

- Top 5 allergens in the world



SUNSCREEN

Completeness of Facial Self-application of Sunscreen in Cosmetic Surgery Patients

Nicole A. Langelier, MD, MBE; Jason Liss, MD; Sandra Stinnett, DrPH; Julie A. Woodward, MD

RACK CARDS


Sunscreen Application
Did you know that the eyelids are a common place to develop skin cancer?
Ingredients to Avoid
• Oxybenzone
Tips
• Minimum of SPF 35-Ideally SPF 50
• Active Ingredient: Zinc Oxide
• Apply liberally and evenly 15 minutes before sun exposure. Reapply at least every two hours.
• Wear UVA & UVB Sunglasses


Why do should I care about beauty ingredients?
The United States has not passed a major federal law to regulate the safety of ingredients used in personal care products since 1938. Shockingly, the FDA doesn't actually regulate this industry at all. Therefore the
Labels DON'T Mean Anything!
Companies are allowed to say whatever they want and label their product any way they choose.
Honestly, no products are perfect, We can learn what ingredients to avoid!
Apps we like to help identify problem ingredients
THINK DIRTY.
Mascara and eyeliner:
Glittery eyeshadows contain Mica which can clog delicate eye oil glands. Eyeliner applied inside the waterline is a No-No for the same reason.
CORRECT
INCORRECT
ZORIA
Mascara We
or visit BeautyCounter com for more products
Taking it off:
We like these to remove eye makeup safely.
we love eyes
eyeeco

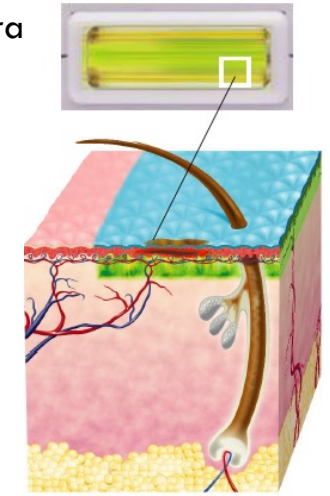

The Never List
by Beauty Counter
Sodium Laurel Sulfate
- Found in Shampoo, body wash, face wash, mouthwash, and toothpaste
BHA & BHT
- Found in exfoliants and perfume-carcinogenic
Triclosan and triclocarbon
-Found in toothpaste, deodorant, and antibacterial soap-hormonal disruption, bacterial resitance
Aminophenol, Diaminobenzene, Phenylenediamine-Coal Tar
-Hair Dye and shampoo-carminogenic
Parabens
-Preservative-mimic estrogen, linked to breast cancer, skin cancer, decreased sperm count
Polethylene Glycol/PEG's
- Found in scrubs-carcinogenic
Retinal palmitate, retinyl acetate, retinoic acid, and retinol
- Moisturizer, lip products, anti-aging-carcinogenic in sunlight *if you use retinol-sunscreen*
Petroleum Distillers
-Mascara-contact dermatitis, cancer causing impurities *DO NOT USE waterproof mascara.*
Isopropyl cloprostenate
-Synthetic prostaglandin (found in OTC eyelash growth serums)
Dibutyl phthalate, toluene, and formaldehyde "Toxic Trio"
-Nail polish and other nail products-birth defects, endocrine disruption, headaches, respirstory problems
Hydroquinone
-Skin lighteners-ochronosis
Oxybenzone
-Sunscreen-mimics estrogen
Propylene Glycol
-Skin conditioning agent-contact dermatitis, hives
Benzalkonium chloride
Preservative-Drying to the eye and allergy
EDTA
Synthetic Fragrance or Flavor-Top Five Allergy Causing Agent

SUN DAMAGE

IPL (INTENSE PULSED LIGHT)

How it works

- Emits a broad, continuous spectrum of light in the range of 515–1200 nm, with the ability to apply filters to target specific *chromophores* (i.e. melanin and hemoglobin).
- Melanin absorption is in the 400–700 nm range
- Blood absorption in the 900–1,200 nm range
- Role of oxyhemoglobin
  - The light that's emitted from the flashlamp is absorbed by the oxyhemoglobin in the blood vessels → genera coagulates the cells
- IPL in Dry Eye Disease and MGD
  - The generated heat also melts the meibomian secretions and opens the glands
  - Decrease release of inflammatory mediators from nearby blood-vessels, and decreased overgrowth of bacteria around the lid area.



MOST POPULAR COSMETIC LASER PROCEDURES PERFORMED

Photofacial

- #1 Cosmetic procedure performed in the United States
- 80 million Americans have some kind of venous disorder (80% of those are cosmetic)
  - Rosacea represents 16 million alone
- Hyperpigmentation is the 2nd largest skin disorder in the US (Acne #1)

American Academy of Dermatology

IPL PHOTOREJUVENATION-PHOTOFACIAL

Benign vascular lesions

- Red spider or thread veins (Telangectasias)
- Symptoms of rosacea
- Facial flushing
- Inflammatory acne
- Spider angiomas

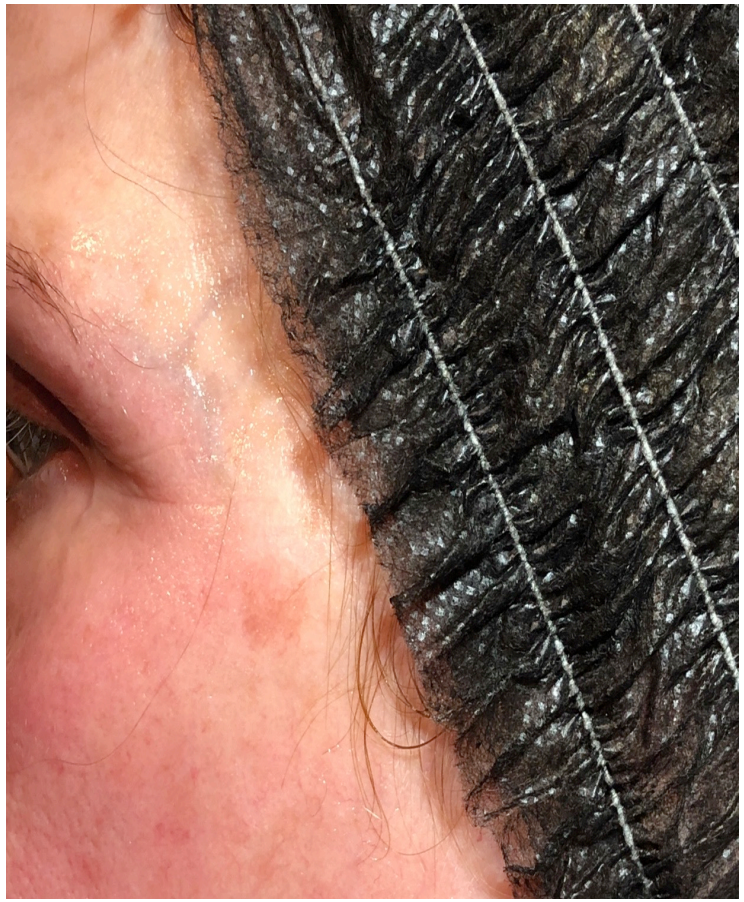
Hyperpigmentation (Abnormal melanocyte lesions)

Pigmentation: Sun damage (Liver/Age Spots)

Fine lines and wrinkles

Meibomian Gland Dysfunction

CLINICAL ENDPOINT FOR PIGMENT



RADIO-FREQUENCY REJUVENATION

Periocular Indications

- Skin tightening with modest reduction in fine lines & wrinkles

How it works

- Elevation of dermal layer temperature (of at least 42°C) leads to a transient denaturation of structural collagen fibrils → followed by contraction / tightening of the skin 42°C → Dermal fibroblasts to elicit a heat shock response → net increase in collagen production in upon cooling
- 2-3 treatments 4 weeks apart are generally needed to see a clinically measurable response.
  - Narins, D.J. and Narins, R.S. (2003) Non-surgical radiofrequency facelift. J. Drugs Dermatol. 2:495–500.

HOW RF REMODELS COLLAGEN AND IMPROVES ELASTIN

The Wound Healing Response

- Heat is applied to the epidermis creating an Inflammatory Phase (1-3 days)
  - a. Early contraction of blood vessels (5-10 minutes)
  - b. Vasodilation in order to increase blood supply (multiple hours to 1-3 days)
  - c. Cells (macrophages, neutrophils,etc) infiltrate the damaged area to remove dead/damaged tissue and destroy bacteria

Proliferative Phase – 3 weeks

- Ongoing Process to repair tissue
  - Day 2-3 – Fibroblast activity is induced in damaged tissue. Fibroblasts multiply, sending mediators to stimulate repair, combining with damaged tissue
  - Day 5-7 – Fibroblasts begin synthesis of collagen (Day 7-21)
  - Day 7-21 – Old collagen is removed by collagenase

Maturation Phase – 3 weeks to 6 months and beyond

- New collagen is generated
- Elastin becomes more uniform and its quality is improved

TREATMENT SETTINGS

Forehead
- 15mm, 25-30

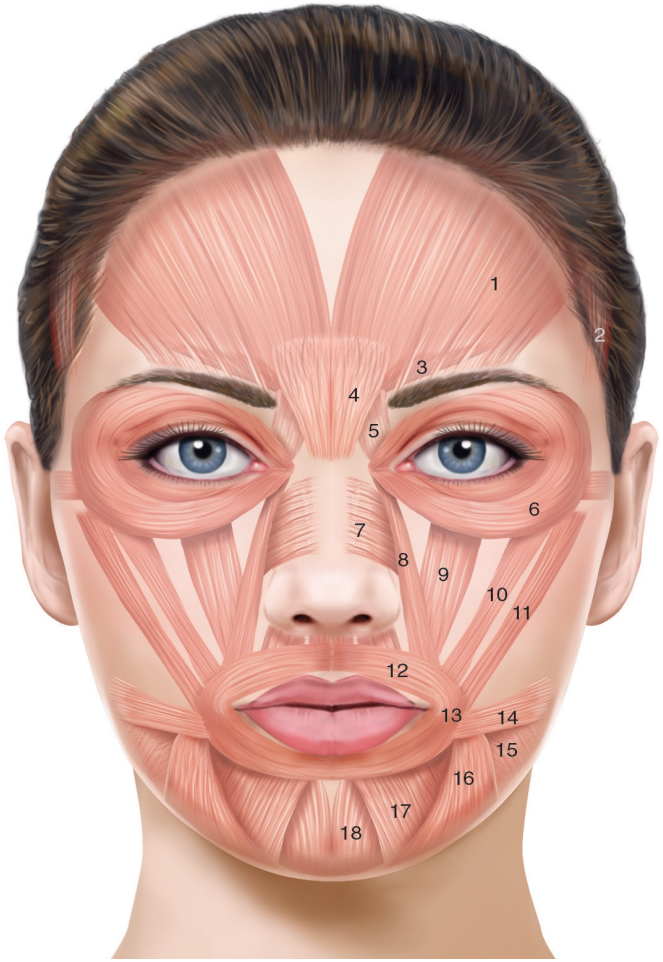
Periorbital
- 10mm, 15-20

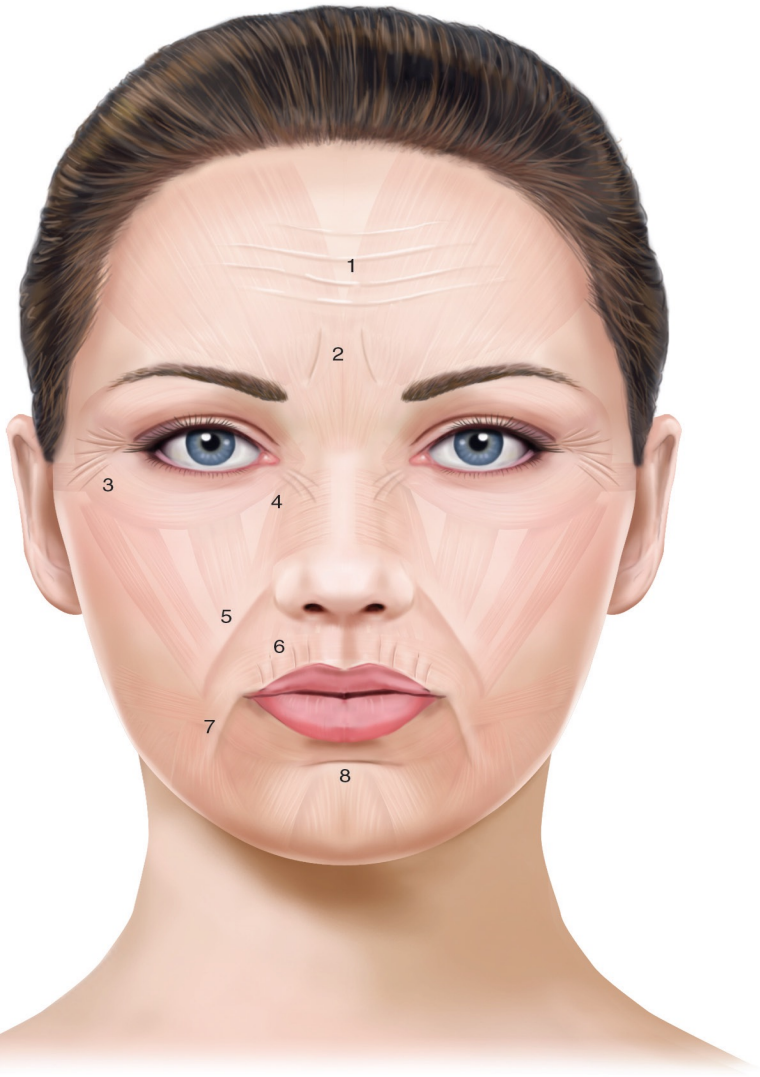
Mid and Lower Face
- 20 mm, 40-60

Treat to clinical endpoint: swelling
- and redness

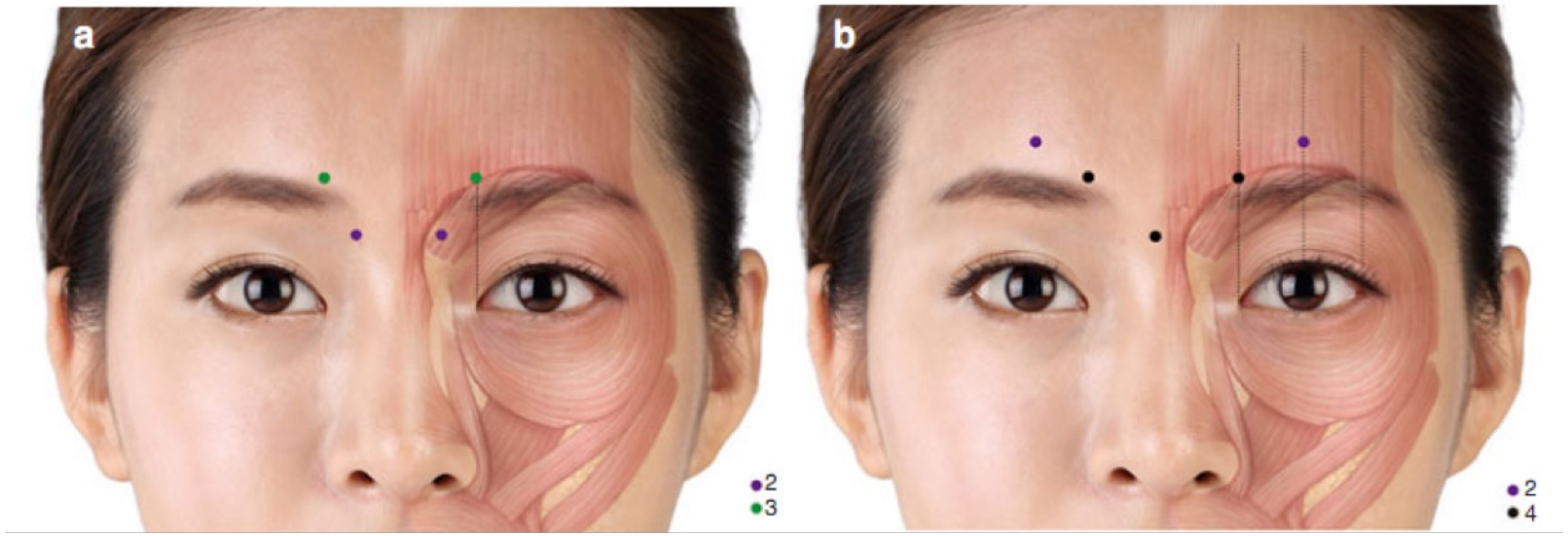
Typically 3:00 treatment times at 39-41°C

ANATOMY

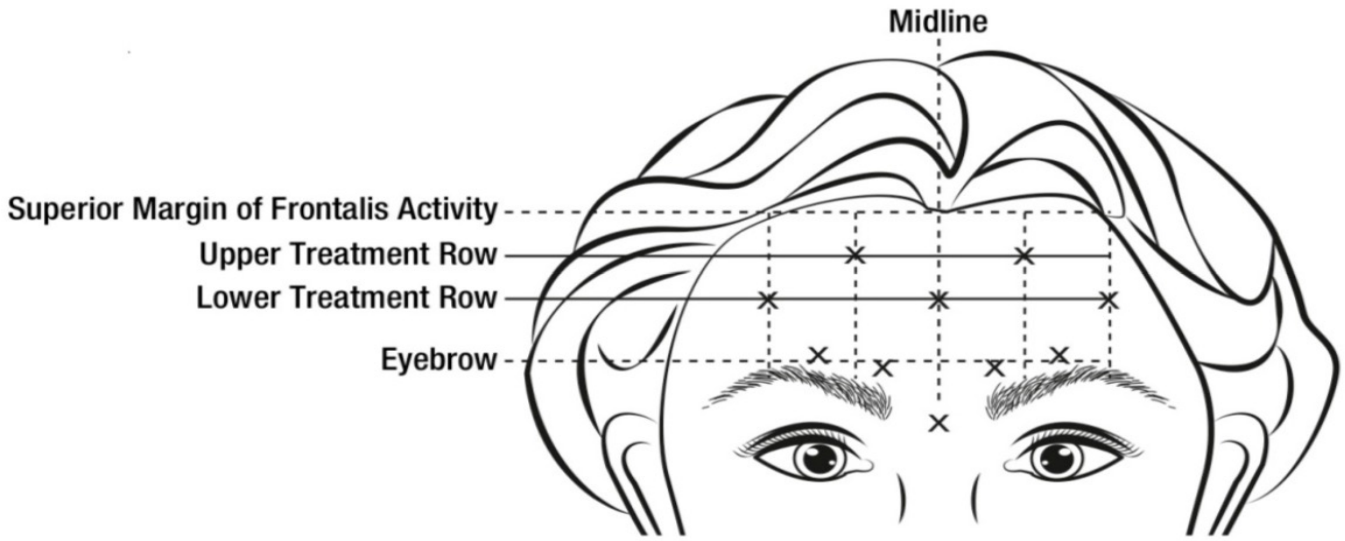




GLABELLA

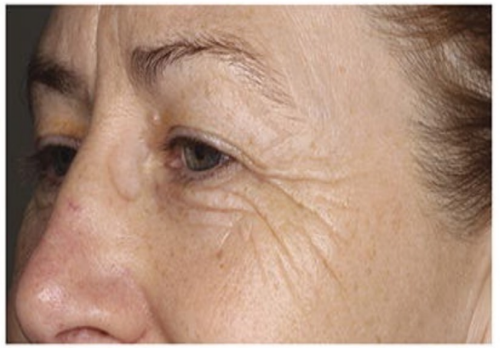


FRONTALIS

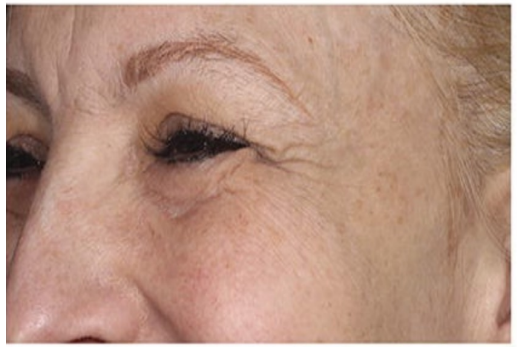

Midline
Superior Margin of Frontalis Activity
Upper Treatment Row
Lower Treatment Row
Eyebrow

LATERAL CANTHAL RHYTIDS

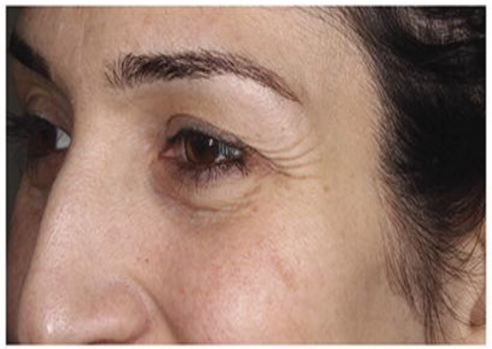
Full-fan Pattern: Lines that project from the lateral canthal area and extend into both the superior malar area and the tail of the brow



Lower-fan Pattern: Lines predominantly confined to the lateral canthal area and the superior malar area



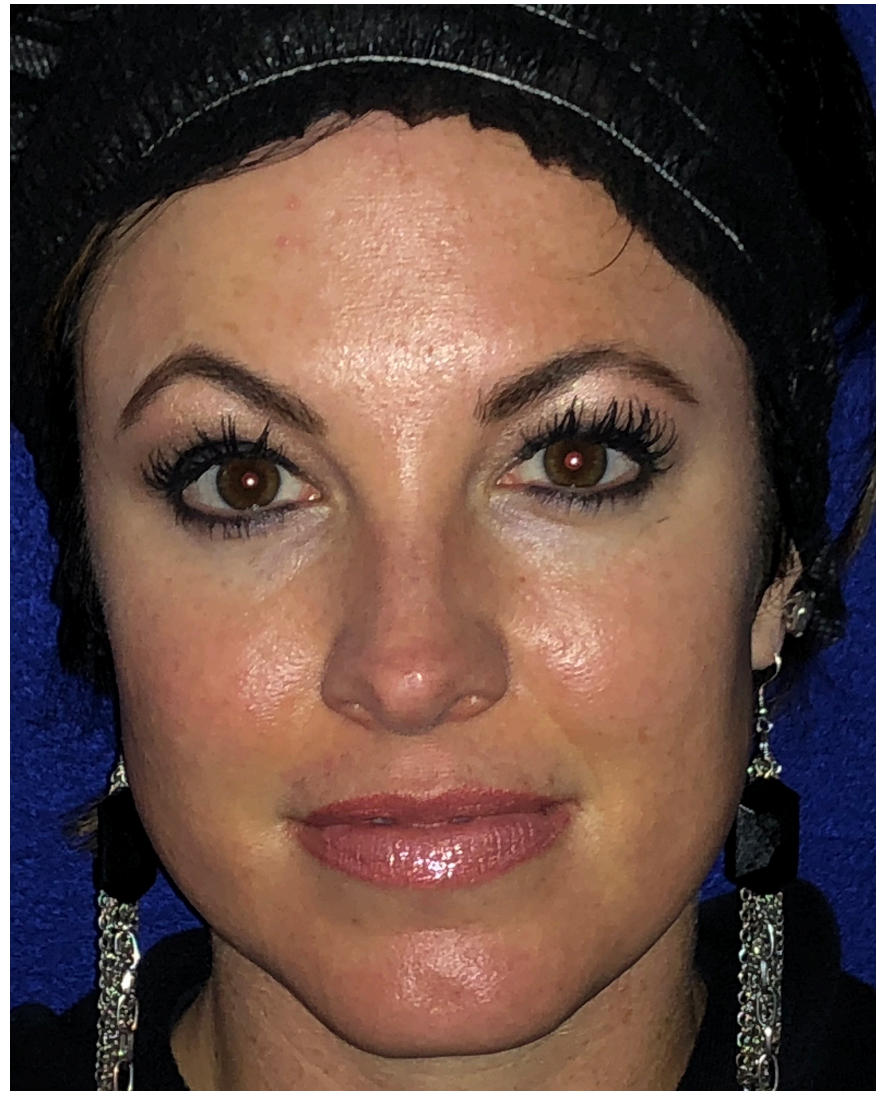
Central-fan Pattern: Lines predominantly confined to the lateral canthal area and not extending into the superior malar area or lateral third of the brow



Upper-fan Pattern: Lines predominantly confined to the lateral canthal area and extending toward or into the lateral third of the brow

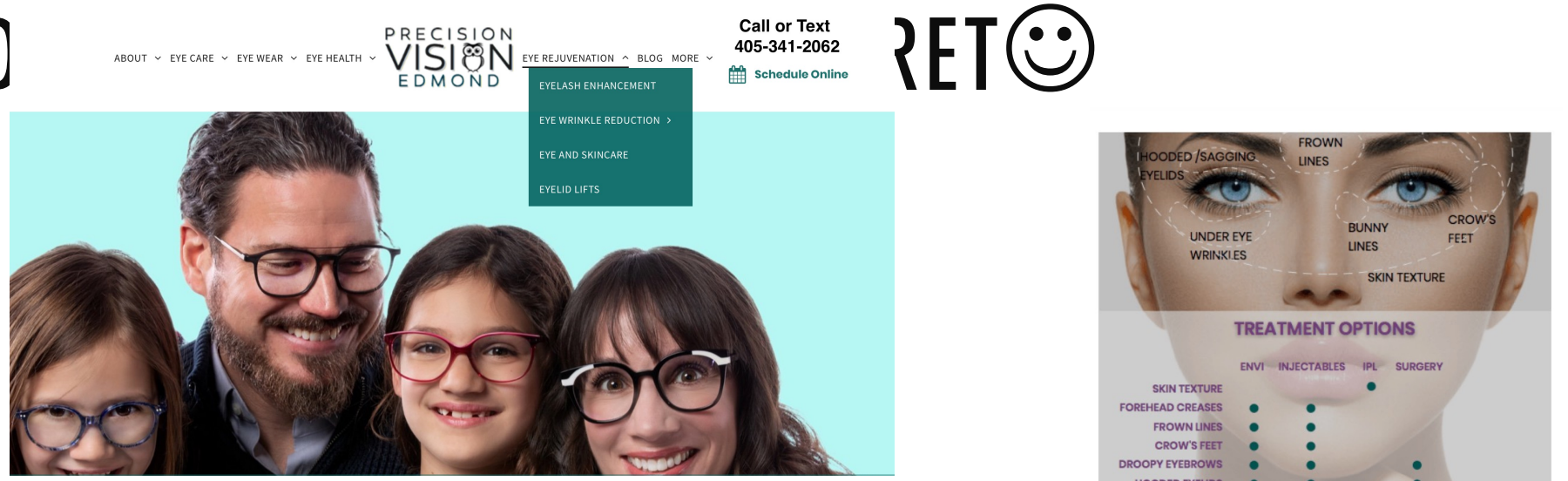
Figure 1. Classification of CFL patterns. Four patterns (full fan, lower fan, central fan, and upper fan) were identified in this study.

NEUROTOXIN

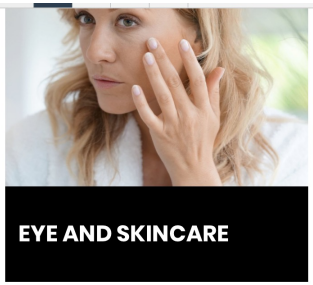


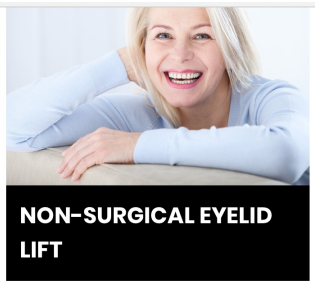
BECOME AN ASTUTE OBSERVER!

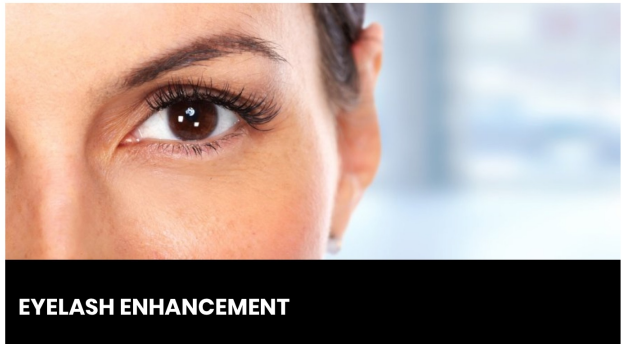
AND


ABOUT
EYE CARE
EYE WEAR
EYE HEALTH
PRECISION VISION EDMOND
EYE REJUVENATION
BLOG
MORE
Call or Text
405-341-2062
Schedule Online
EYELASH ENHANCEMENT
EYE WRINKLE REDUCTION
EYE AND SKINCARE
EYELID LIFTS


EYE WRINKLE REDUCTION

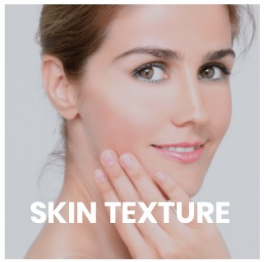

EYE AND SKINCARE


NON-SURGICAL EYELID LIFT


EYELASH ENHANCEMENT

HOODED /SAGGING EYELIDS
FROWN LINES
UNDER EYE WRINKLES
BUNNY LINES
CROW'S FEET
SKIN TEXTURE
TREATMENT OPTIONS
ENVI
INJECTABLES
IPL
SURGERY
SKIN TEXTURE
FOREHEAD CREASES
FROWN LINES
CROW'S FEET
DROOPY EYEBROWS
HOODED EYELIDS
SAGGING EYELIDS
EYE WRINKLE REDUCTION


BOTOX / XEOMIN / DYSPORT


SKIN TEXTURE


SKIN TIGHTENING

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Michael A. C. Kane, MD,* Sue Ellen Cox, MD,† Derek Jones, MD,‡ Xiaofang Lei, PhD,x and Conor J. Gallagher, PhDx . Heterogeneity of Crow's Feet Line Patterns in Clinical Study Patients. 2015 by the American Society for Dermatologic Surgery, Inc. Published by Wolters Kluwer Health, Inc. All rights reserved. ISSN: 1076-0512 ·Dermatol Surg 2015;41:447–456

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CASE #6

An 84 year old Caucasian male presented on January 16, 2014 for examination with the complaint of dryness that he was currently treating with over the counter artificial tears. He stated his vision was stable.

He had a medical history of diabetes and hypertension both of which he state were under good control. His fasting blood sugar on January 16 was 103; he was unsure what his HbA1C last was. He had no positive family history of eye diseases.

He had cataract surgery on Sept 15, 2008 right eye and left eye was subsequently performed on September 29, 2008.

He was currently taking HCTZ, metformin, omeprazole, glimepiride, Azor, losartan, Lialda, Centrum Performance and Co Q-10.

His uncorrected visual acuity was 20/60 right eye and 20/40-2 left eye. He pinholed to 20/30 right eye and 20/40+1 left eye. He declined refraction.

Pupils were equal, round and reactive to light, no afferent pupil defect noted in either eye. Confrontational fields were full to finger count in both eyes. Extraocular motility were full with no restrictions OU.

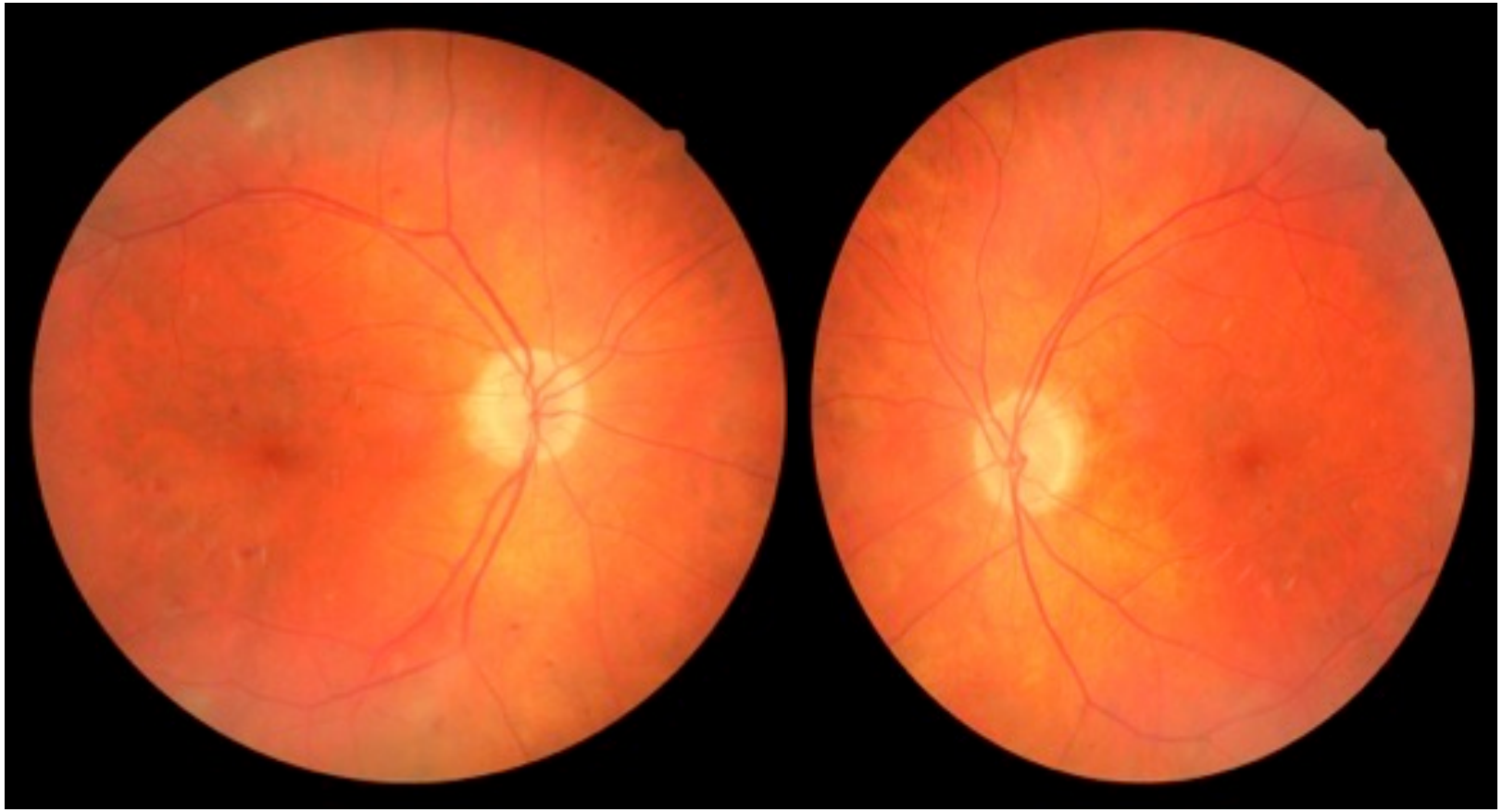
Intraocular pressures by Goldmann tonometry were 15mm Hg right eye and 13 mm Hg left eye at 15:03.

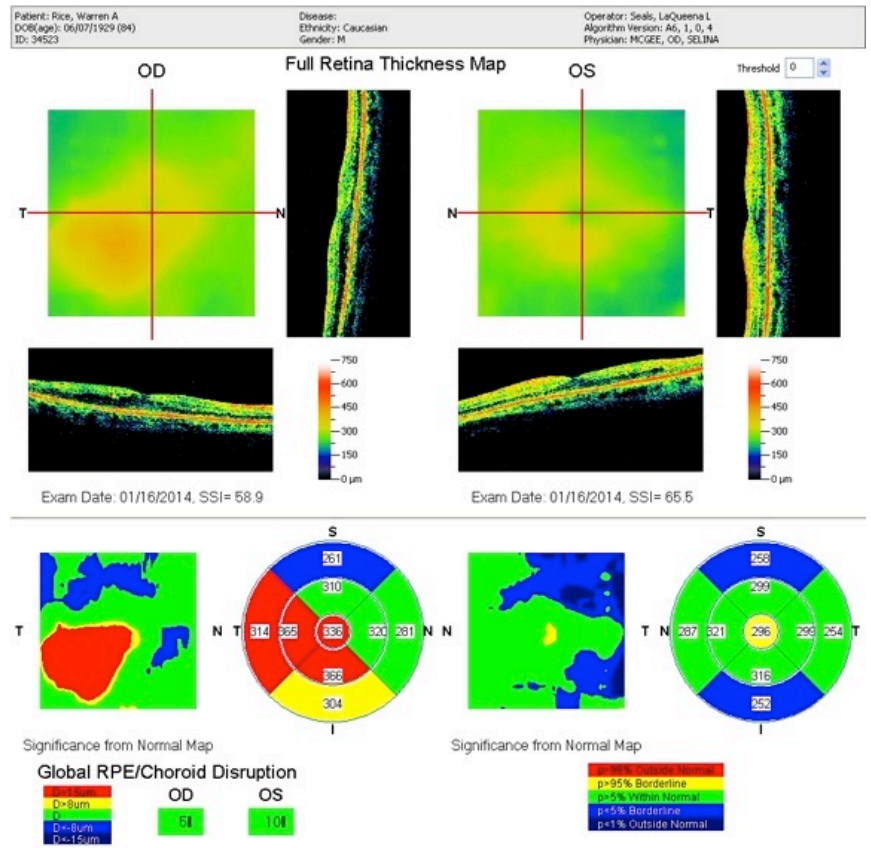
Slit lamp biomicroscopy revealed normal adnexa with mild dermatochalasis, lids, lashes, lacrimal drainage, bulbar and palpebral conjunctiva. Corneas were clear right eye and a small sub epithelial scar was noted in the left eye. Anterior chambers were deep and quiet in both eyes. Angles were 4x4 using the Von Herick method.

Pupils were dilated with one drop 1% Mydriacyl and one drop 2.5% phenylephrine.

Posterior exam showed trace nuclear sclerotic cataracts in both eyes. Fundus exam showed optic nerves to be pink and distinct with a .20/.20 cup to disc ratio in both eyes.

Posterior pole showed retinal thickening centrally and within the foveal zone with microanerurysms in right eye and scattered microaneurysms in the left eye. There was no evidence of neovascularization of the disc or neovascularization elsewhere. Periphery of both eyes was unremarkable. Fundus photos were obtained as well as an ocular coherence tomography (OCT) of his macula.




Patient: Rice, Warren A
DOB(age): 06/07/1929 (84)
ID: 34523
Disease:
Ethnicity: Caucasian
Gender: M
Operator: Seals, LaQueena L
Algorithm Version: A6, 1, 0, 4
Physician: MCGEE, OD, SELINA
Full Retina Thickness Map
OD
OS
Threshold 0
T
N
750
600
450
300
150
0 µm
Exam Date: 01/16/2014, SSI= 58.9
Exam Date: 01/16/2014, SSI= 65.5
S
I
261
310
814
365
332
320
281
368
304
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299
287
321
296
299
254
316
252
Significance from Normal Map
Significance from Normal Map
Global RPE/Choroid Disruption
OD
OS
D>8um
D<-8um
D<-15um
5
10
p>95% Borderline
p<5% Borderline
p<1% Outside Normal

DIFFERENTIAL DIAGNOSIS

Diabetic clinically significant macular edema is classified by any of the following: any edema within 500 microns of fovea, any hard exudate within 500 microns of fovea if associated with adjacent retinal thickening, or retinal edema>1disc diameter (DD) in diameter and extending to within 1 DD of center of fovea[2].

Hypertensive retinopathy presents with focal narrowing of the major retinal arterial branches. There can also be general retinal arteriole narrowing, A/V nicking, intraretinal hemorrhages (the hemorrhages tend to be more flame-shaped, cotton-wool spots, or lipid exudates. With very high blood pressure, optic nerve head swelling can occur; a macular star may also be present.

Ocular Ischemic Syndrome presents with retinal arterial narrowing and venous dilation, retinal hemorrhages, microaneurysms, cotton-wool spots, disc or retinal neovascularization, and spontaneous pulsations of the retinal arteries. Rubeosis is also common, the hemorrhages are larger and mostly in the midperiphery; exudate is absent.

Central retinal vein occlusion (CRVO) optic disc swelling is present, veins are more tortuous, and CRVO is usually unilateral with sudden onset.

Branch retinal vein occlusion (BRVO) has hemorrhages are distributed along the course of a vein, and does not extend across the horizontal raphe.

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetes. According to the International Diabetes Federation, about 1.5 million people worldwide have clinically significant macular edema[1]. The "one-third rule," is one-third of people with diabetes develop some form of retinopathy, one-third of patients with retinopathy have DME, and one-third of patients with DME have clinically significant macular edema (CSME).

DME is classified into focal DME, which is characterized by localized areas of retinal thickening, caused by leakage from microaneurysms, and areas of focal leakage often demarcated by a partial or complete ring of hard exudates (lipid). Diffuse DME is characterized by more generalized areas of vascular leakage from dilated, damaged retinal capillaries. There is non-center involving DME which happens away from the macular and center-involving DME that occurs in the central macula. CSME is classified by any of the following: any edema within 500 microns of fovea, any hard exudate within 500 microns of fovea if associated with adjacent retinal thickening, or retinal edema>1disc diameter (DD) in diameter and extending to within 1 DD of center of fovea[2].

Treatment for DME has changed in recent years with intravitreal Anti-VEGF therapy. Laser photocoagulation (focal/grid laser) technique has also changed. Focal laser is aimed at individual microaneurysms while grid laser is applied to an area with edema in a specific grid pattern. Today, there is less energy delivered and less thermal damage. Laser treatment is more commonly used today as a treatment for noncenter-involving DME (focal DME) and as adjunctive treatment with intravitreal anti-VEGF or steroids.

FOLLOW UP #1

Patient saw Dr. Phelps on 02/18/2016, vision remained stable at 20/30 and patient was still asymptomatic. Patient was found to have CSME of the right eye. Since there was center involving diabetic macular edema Dr. Phelps recommended focal laser photocoagulation to the leaking microaneursyms as guided by fluorescein angiography versus anti-VEGF therapy. The risks, benefits, and alternatives of the treatment were thoroughly discussed and patient proceeded with focal laser photocoagulation on 04/02/14. Follow up was scheduled in 3 months.

FOLLOW UP #2 & 3

Dr. Phelps saw patient on July 07, 2014. Vision remained stable at 20/30. OCT remained unchanged, no treatment was performed and the patient was asked to follow up in 4 months.

Dr. Phelps again saw the patient on 12/09/14. Vision remained unchanged at 20/30. No treatment was performed. Patient was asked to return to clinic in 6 months for follow up.

Diabetic macular edema (DME) is the most common cause of vision loss in patients with diabetes. Our focus with this case report is on those patients with clinically significant macular edema (CSME).

CSME is classified by any of the following: any edema within 500 microns of fovea, any hard exudate within 500 microns of fovea if associated with adjacent retinal thickening, or retinal edema>1DD in diameter and extending to within 1 DD of center of fovea[2].

Based on the EDTRS Study in 1985 patients that received focal laser had 50% reduction in moderate vision loss as stated by the doubling of the visual angle on two successive follow-up visits, from focal laser. Today, the technique has changed so that less energy is delivered and therefore there is less thermal damage. Focal laser is more commonly used as a treatment for center-involving DME and as adjunctive treatment with intravitreal anti-VEGF or steroids.

The RISE and RIDE studies with Lucentis 0.3 mg vs 0.5mg vs sham showed treated eyes gained 11.7 EDTRS letters vs 2.5 letters at 2 years. At 3 years visual acuity gains were 12.4 letters vs 4.5 for sham-to-0.5mg arm. The FDA approved the 0.3mg dose of Lucentis for treatment of DME in 2013. The sham arm did not experience similar gains after waiting 2 years to treat with Lucentis.

VIVID and VISTA trials were done with 5 loaded doses of 2mg Eylea followed by continuous doses every 4 weeks vs every 8 weeks. The control arm received focal laser. The results for VIVID and VISTA were similar. There was a gain of 11.5 letters gained with every 4 week injections and 11.1 with every 8 week injections, only 0.9 letter improvement was seen with control of focal laser.

The BOLT trial 2-year data was smaller with only 80 patients. There was an 8.6 letter gain with Avastin vs 0.5 letters lost in the focal group. Off label Avastin is effective in treating DME more effectively than laser.

The DRCR.net Protocol T Study compared all 3 anti-VEGF agents in DME. At one year the patients with baseline VA worse than 20/40 did better with Eylea. There was a 19 letter gain with Eylea vs 14 letter gain with Lucentis vs 12 letter gain with Avastin. The central standard thickness showed similar results. Avastin had less effect on reducing DME and resulted in more focal/grid laser treatments. The one year data suggests that Eylea is better for DME in eyes when VA is worse than 20/40. The two-year data was just released and there was a 12.8 letter gain with Eylea vs 12.3 letter gain with Lucentis vs 10 letters with Avastin for all patients. For patients whose VA was 20/50 or worse, there was an 18.1 letter gain with Eylea vs 16.1 Lucentis vs 13.3 Avastin. There were fewer injections in year two- 5 Eylea, 6 Lucentis, 6 Avastin. No advantage with Eylea over Lucentis was seen at year one. Eylea is still superior than Avastin at year 2.

Corticosteroids can also be utilized to treat DME. Triamcinolone (Kenalog and preservative free Triesence) have been used off-label for DME. There are two steroid intraocular implants that the FDA has approved for DME, dexamethasone (Ozurdex) and non-erodible flucinolone (Illuvien). For those patients with DME requiring steroids (they usually have a poorer response to anti-VEGF), 33% can expect IOP elevation of 10 mm Hg usually occurring after 2 months, and less than 5% may require incisional surgery for glaucoma.

The MEAD study utilized Ozurdex for DME. 60% of patients required cataract surgery. After surgery, patients demonstrated greater VA gains than sham treatment. 28% of Ozurdex patients experienced IOP elevation greater than or equal to 10mm Hg vs 4% in sham group. However, the IOP spikes appear to be predictable and the magnitude of spikes did not increase with repeat injections. IOP was well managed with drops. There was one patient that required glaucoma surgery. There appeared to be therapeutic benefit for 3 months or more with 4-5 injections in 3 years per MEAD study.

The FAME study was also thought to offer therapeutic benefit for 3 years. Fluocinolone Acetonide was dosed at 0.2 mcg/day, 0.5 mcg/day, and sham in the study. Almost all of the patients did develop a cataract and 4.8% at FDA dose required IOP-lowering surgery

Significant improvement in VA can be achieved with steroids with relatively fewer injections than is required for anti-VEGF agents. Most IOP increases can be managed with topical drops and cataract development of course is managed with cataract surgery.

Pars plana vitrectomy can also be effective for treating DME according to the DRCRnet protocol D study. It appears that resolving the mechanical tension in patients with vitreomacular traction and epiretinal membrane can help treat DME. This study came out before the anti-VEGF era, but in patients that have vitreomacular traction DME this approach is gaining acceptance. Of note, the half-life for anti-VEGF in vitrectomized eyes is markedly decreased.

IN SUMMARY

Diabetic retinopathy is a leading cause of blindness in working-age adults,[3] and diabetic macular edema is the most common cause of vision loss in patients with diabetes. Historically, macular laser (focal and grid) has been the standard of care in treating DME, yet despite adequate laser, up to 25% of patients at three years of follow up progressed to moderate vision loss[4].

Over the last decade, anti-VEGF has become first line treatment for DME, with steroids and macular laser used in conjunction or in combination when patients fail to respond or when DME becomes recurrent.

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CASE

50 Year Old Male

Works in Finance

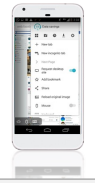
Likes to play golf, work out and stay fit

OD: -0.50-0.50x180, OS: -0.75-05.50x172 add power +1.50

Completely dependent on glasses now

Works on the computer typically 6-8 hours/day

CLASSIFYING PRESBYOPIA SEVERITY[1-5]



	Nutritional label, legal disclaimers, footnotes	**Smartphone (common text sizes),** Classified ads, Bible, toiletry labels, books, magazines	**Computer (common text sizes),** Children's books, newspaper sub-headlines
Unable to read font size*:	4 pt – 6 pt	8 pt – 12 pt	14 pt – 30 pt
PRESBYOPIA CLASSIFICATION	**MILD** PRESBYOPIA	**MODERATE** PRESBYOPIA	**ADVANCED** PRESBYOPIA
NEAR VISION CORRECTION†	≤ +1.25 D	> +1.25 – +2.00 D	> +2.00 D
DCNVA (photopic)	20/25 – 20/40	>20/40 – 20/80	>20/80
JAEGER EQUIVALENT (photopic)	<J4	J4 – J9	>J9
TYPICAL AGE	40 – 47 years	>47 – 55 years	>55 years

DCNVA = distance-corrected near visual acuity.
*Representation of differences in font size (actual size not shown). †Approximation of near vision correction relative to DCNVA.

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OUR CURRENT SOLUTIONS…

- **Spectacles**[1]
  - Single vision
  - Bifocal/Trifocal
  - Progressive
- **Contact Lenses**[2]
  - Soft Multifocal
  - Monovision
  - GP's
  - Scleral

Surgical Treatments

- Excimer laser[3]
  - Monovision
  - Modified Monovision
  - Multifocal ablation
- Femtosecond laser inlays[4]
- IOLs
  - Diffractive Technology-bifocals, trifocals, EDOF[3]
  - Nondiffractive Technology EDOF
  - Accommodating
  - Light Adjustable
  - Femtosecond laser-induced shape change
- Femtosecond laser[4]
  - Softening of the crystalline lens

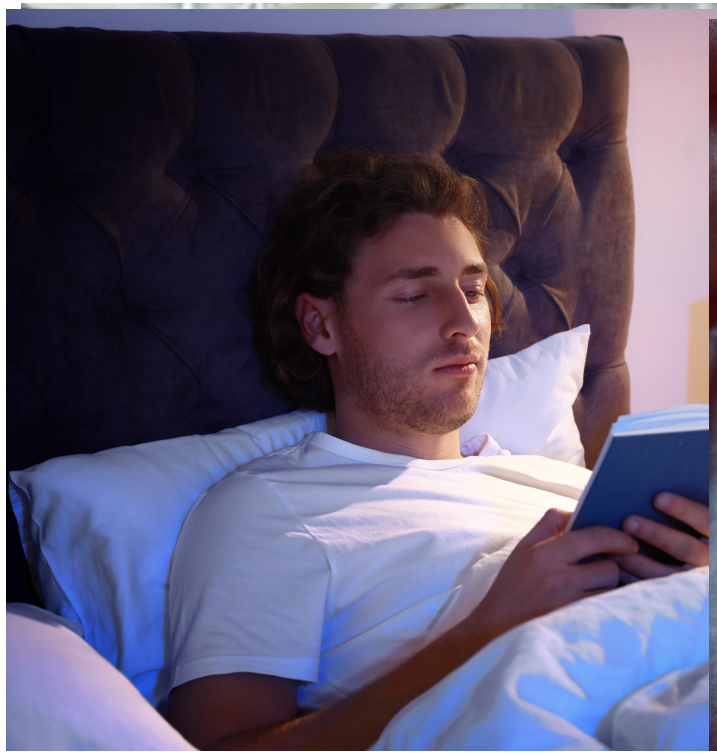
1. American Optometric Association website, Accessed 2020 2. American Academy of Optometry website, Accessed 2020. American Academy of Ophthalmology website, Accessed 2020 2. Liu et al. Int J Ophthalmol.2015; 3.Moarefi et al. Opthalmolo Ther. 2017 4. Sieburth and Chen. Taiwan J Ophthalmol. 2019.

PHARMACOLOGIC TREATMENTS FOR PRESBYOPIA ARE COMING, WITH MIOTIC DROPS OCCUPYING THE MAJORITY OF DEVELOPMENT

Topical Drops in Development	Active Ingredient(s)	Mechanism of Action
Brimochol™ (Visus Therapeutics) **Brimochol™ Preservative Free (Visus Therapeutics)**	Carbachol + brimonidine tartrate	Carbachol: Miotic Brimonidine tartrate: Prevents pupil dilation, inhibits contraction of ciliary muscle, increases bioavailability of carbachol[1,2], prevents redness[3]
CSF-1 (Orasis)	Pilocarpine	Miotic
PRX-100/Liquid Vision (LENZ Therapeutics)	Aceclidine	Miotic
AGN 190584 (Allergan) Vuity™	Pilocarpine	Miotic
MicroLine/OpteJet™ (Eyenovia)	Pilocarpine	Miotic
AcuStream™ (Kedalion)	Pilocarpine	Miotic
Nyxol® and Pilocarpine Combination Kit (Ocuphire)	Phentolamine mesylate and pilocarpine	Miotic (both pilocarpine and phentolamine mesylate products) Vasodilates small muscles (phentolamine mesylate product)[4]
True Vision Treatment® Contact lenses and Eye Drops Kit (Yolia Health)	Hyaluronidase and collagenase	Alters cornea[5]
UNR844 (Novartis)	Lipoic acid choline ester	Lens-softening agent
VP1-001 (Viewpoint Therapeutics)	Stabilizing alpha-crystallin molecule	Target's protein misfolding to restore native, functional shape[6]

1. Suzuki et al. Ocular and Systemic Pharmacokinetics of Brimonidine and Timolol After Topical Administration in Rabbits: Comparison Between Fixed-Combination and Single Drugs. *Ophthalmol Ther* (2020) 9:115–125; 2. Allergan patent application (Pub. No.: US 2018 / 0078500 A1). 3. LUMIFY® Product Insert www.fda.gov accessed 9/24/2020. 4. Pepose. Phentolamine Mesylate Ophthalmic Solution Provides Long Lasting Pupil Modulation And Improves Visual Acuity, ARVO 2020 Abstract: #3364450. 5. Yolia Health. 6. Viewpoint Therapeutics ,February 2021.

WHAT ARE SOME THINGS YOU'D REALLY LIKE TO DO… WITHOUT GLASSES? AND HOW WHEN, WHERE, AND HOW OFTEN DO YOU DO THEM?



HAVE THE CONVERSATION EARLY & OFTEN

IT'S NOT JUST ONE SOLUTION

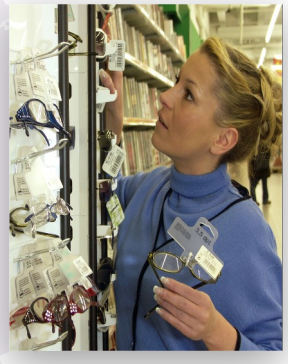
PRESBYOPIA:

How many people are affected globally?

~1.8 billion[1]

How many Americans are presbyopes?

128 million[2-4,*]



How many people buy their readers at the drugstore?

30.9 million[5]

*Determined based on U.S. Census data.

1. Fricke et al. Ophthalmology. 2018; 2. American Optometric Association website. Accessed 2019; 3. Zebardast et al. *Am J Ophthalmol*. 2017;
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PEARLS

Do Something, and don't be the "one and done" doctor

Talk to every patient about presbyopia age 37 and above

- Keep it simple

Don't Prescribe 1 and Done

Let the patient neuroadapt for 7-10 days

Follow-up

- Text
- Appointment
- Another visit reason, ie-dry eye, etc

Train your team for implementation strategy