Path to Earlier Intervention : Cone Contrast Testing

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Disclosures

Has a relevant financial relationship with:

Sanofi, Innova Systems, ZeaVision and Guardion health Sciences as a speaker and/or research consultant

The content and format of this course is presented without commercial bias and does not claim superiority and commercial product or service.

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Outline general

- How Cone Contrast Testing allows for earlier disease detection & better diagnosis
- Clinical benefits of using CCT in conjunction with OCT
- Clinical cases demonstrating CCT diagnostic yield beyond OCT
- How to easily implement CCT into AMD, diabetes, and glaucoma protocols
- How to adjust treatment plans & nutritional supplements from CCT results

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The common…

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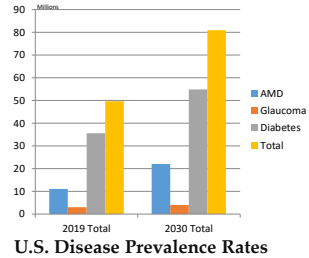
Medical management demands accurate diagnostic and monitoring equipment

- An estimated 50 million have disease that will affect their vision
- Half of those affected don't know they have the disease
- Prevalence rates expected to increase by roughly 50% by 2030



U.S. Disease Prevalence Rates

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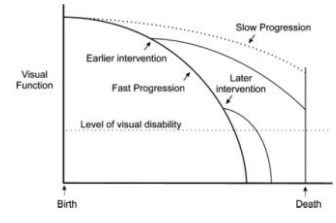
Early detection and prompt treating saves irreversible vision loss



J Caprioli; Am J of Ophthalmol, February 2008

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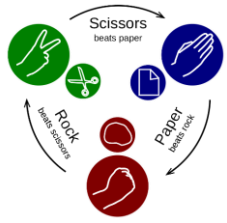
Ocular Structure and Visual Function

- Structure precedes functional damage
- Function precedes structural damage
- Both damage visible simultaneously



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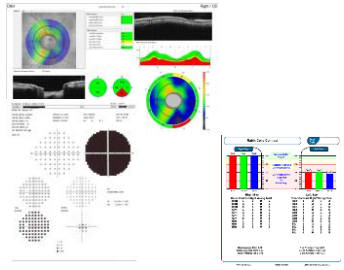
What is the diagnosis?



- What's the history?
- What's the clinical picture?
- What do other ancillary tests tell you?
  - Fundus, Visual fields, OCT, A1c???
  - All these tests may be needed to make the diagnosis

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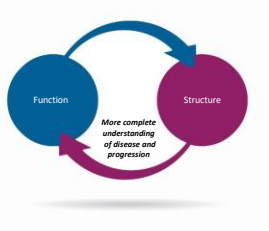
Value of Function *plus* Structure

- **Early Detection:** Function precedes structure in many conditions, highlighting problems before structural damage occurs
- **Progression:** Functional tests plays a critical role in detecting sub-clinical progression
- **Improvement:** Structural tests demonstrate stability; only functional tests can demonstrate improvement



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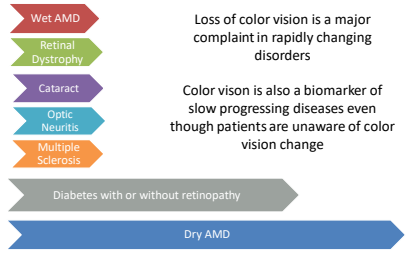
Color Vision as a Biomarker of Disease



Loss of color vision is a major complaint in rapidly changing disorders

Color vison is also a biomarker of slow progressing diseases even though patients are unaware of color vision change

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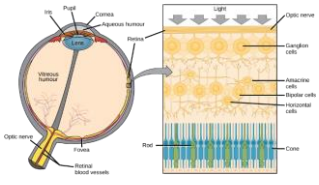
Color Processing Through the Visual Pathway



- Color perception (RGB) arises at the photoreceptor level
- Opponent color processing arises in inner nuclear layer via horizontal and bipolar cells and continues at retinal ganglion cells
- Damage to any part of the retina or visual pathway should affect color vision

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We have enjoyed our OCTs

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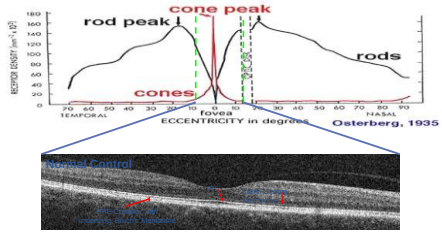
Cone Contrast Testing: Functional Compliment to the OCT



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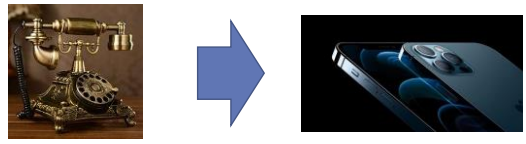
Color vision testing has seen some serious upgrade



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Rabin Cone Contrast Test

- Based in science
  - Co-developed between Innova Systems and US Air Force
- Combines Cone Isolation technology and Contrast Sensitivity
- Color vision technology sensitive enough to detect subtle changes from disease
- Threshold test, similar to visual field

But just faster…

- Patent No. US 9,883,794

Simulation

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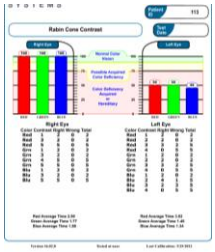
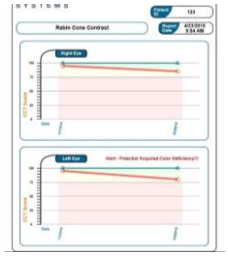
Rabin Cone Contrast Output





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Color Deficient Profiles

Hereditary	Acquired
• Specific to red or green cone type	• Not as selective to specific cone type
• Single cone type	• Multiple cone types
• Moderate to severe	• Mild to severe
• Symmetry	• Often asymmetry
• No blue	• Frequently blue

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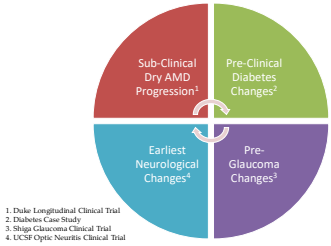
Cone Contrast Testing: Clinical Value Beyond OCT



1. Duke Longitudinal Clinical Trial
2. Diabetes Case Study
3. Shiga Glaucoma Clinical Trial
4. UCSF Optic Neuritis Clinical Trial

Rabin Cone Contrast identified:

- Progression in AMD when OCT showed no change
- Changes in diabetics prior to manifest retinopathy
- Earliest changes visible in ocular manifestations of multiple sclerosis
- Confirmation of pre-glaucomatous damage progression

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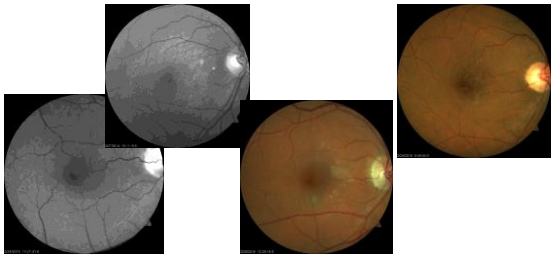
Structural changes



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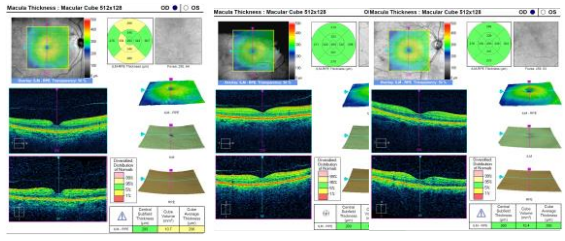
Do we always see thickness abnormalities?



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Structure & Function in AMD

- Drusen may occur first but visual acuity may be normal.
- But is 20/20 vision equals no

Glare Disability

Structure and function measurements should correlate and are not opposites

Not Structure or function BUT "StructuoFunction"

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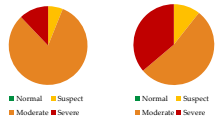
Cone Contrast Test Effectiveness in Staging Dry AMD

No AMD | Early Stage AMD | Intermediate AMD | Advanced AMD

"All patients in Early Stage AMD had abnormal Rabin Cone Contrast scores"



Duke University 12 Month Longitudinal Study

Unpublished Data

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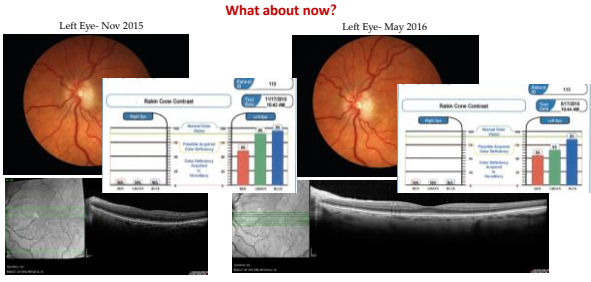
Intermediate Dry AMD Monitoring–What's Your Diagnosis?



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AMD: Reduces Cone Contrast

Detection of Progression

- Monitor more frequently
- Early intervention initiatives
  - ✓ Nutritional changes
  - ✓ Nutritional supplement changes
    - Early and greater amount
  - ✓ Medical management when needed

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Management of Dry-AMD… current practice

Category 1	Category 2	Category 3	Category 4
No AMD	*Early Stage AMD*	*Intermediate AMD*	*Advanced AMD*
A few small or no drusen	Several small drusen or a few medium-sized drusen in one or both eyes	Many medium-sized drusen or one or more large drusen in one or both eyes	In one eye only, either a break-down of light-sensitive cells and supporting tissue in the central retinal area (advanced dry form), or abnormal and fragile blood vessels under the retina (wet form)

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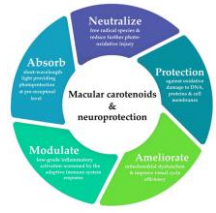
antioxidants

Systematic Review

A Systematic Review of Carotenoids in the Management of Age-Related Macular Degeneration

Drake W. Lem [1], Pinakin Gunvant Davey [1,*], Dennis L. Gierhart [2] and Richard B. Rosen [3]



- Carotenoid vitamin therapy can provide visual benefits at all stages of AMD.
- Albeit these benefits may vary among different stages of disease

Antioxidants 2021, *10*, 1255. https://doi.org/10.3390/antiox10081255

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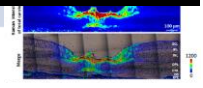
Imaging lutein and zeaxanthin in the human retina with confocal resonance Raman microscopy

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

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

Zeaxanthin	Lutein
• Mainly accumulates in the IPL, OPL, and ONL at the center of the human foveal pit • Concentrates highly in Fovea	• Distributed more diffusely across the retina at a much lower concentration relative to zeaxanthin
quenching	

Take home "the current AREDS2" formula's 10 mg of lutein and 2 mg of zeaxanthin may not be enough and greater amounts may be needed.



www.pnas.org/cgi/doi/10.1073/pnas.1922793117

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What Are You Going To Do Differently?

AMD Exam → Change >2L

- Monitor patient more frequently
- Review patient compliance
- Increase nutraceuticals

⇨ SLOW PROGRESSION

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How do you monitor treatment?

- Baseline fundus photos then OCT … then … do all over in 6 months?
- So you have measured structural damage…what about the function?

  - Color contrast changes
  - Contrast sensitivity changes
  - Dark adaptation changes
  - Visual field changes
  - Electrodiagnostics

  } Visual function changes observed in AMD

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Diabetes and Color Vision

Old dog new tricks

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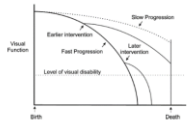
Diabetes and the Eye

Diabetic Retinopathy

- 4.2 million adults have DR in USA
- 655,000 have vision-threatening DR
- 1/3 patients with diabetes will develop retinopathy

Retina takes a good 10-15 years of beating

- During this time "looks normal" but probably not really
- Elevated blood glucose is the culprit
- Metabolic control is a must



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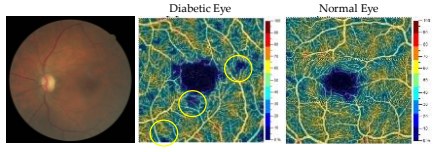
Diabetes and OCT angiography

- Vascular changes



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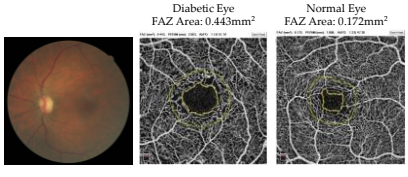
Identify Early Vascular Changes in Diabetic Eyes

Patients with DM more likely to have a larger FAZ than healthy eyes.



Mean Foveal avascular zone is larger in more advanced diabetic retinopathy

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Clinical Trials Show Color Vision as Biomarker in Diabetes

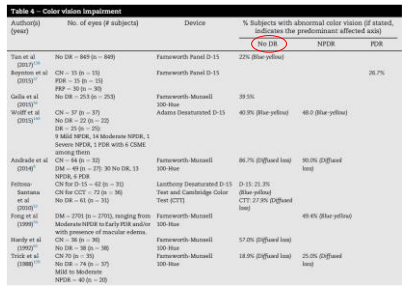

Table 4 – Color vision impairment

Author(s) (year)	No. of eyes (# subjects)	Device	% Subjects with abnormal color vision (if stated, indicates the predominant affected axis)		
			No DR	NPDR	PDR
Tan et al (2017)[139]	No DR = 849 (n = 849)	Farnsworth Panel D-15	22% (Blue-yellow)		
Boynton et al (2015)[37]	CN = 35 (n = 35) PDR = 35 (n = 35) PRP = 30 (n = 30)	Farnsworth Panel D-15			26.7%
Gella et al (2015)[38]	No DR = 253 (n = 253)	Farnsworth-Munsell 100-Hue	39.5%		
Wolff et al (2015)[140]	CN = 37 (n = 37) No DR = 22 (n = 22) DR = 25 (n = 25) 9 Mild NPDR, 14 Moderate NPDR, 1 Severe NPDR, 1 PDR with 6 CSME among them)	Adams Desaturated D-15	40.9% (Blue-yellow)	48.0 (Blue-yellow)	
Andrade et al (2014)[5]	CN = 64 (n = 32) DM = 49 (n = 27): 30 No DR, 13 NPDR, 6 PDR	Farnsworth-Munsell 100-Hue	86.7% (Diffused loss)	90.0% (Diffused loss)	
Fetissov Santana et al (2010)[42]	CN for D-15 = 62 (n = 31) CN for CCT = 72 (n = 36) No DR = 61 (n = 31)	Lanthony Desaturated D-15 Test and Cambridge Color Test (CCT)	D-15: 21.3% (Blue-yellow) CCT: 27.9% (Diffused loss)		
Fong et al (1999)[39]	DM = 2701 (n = 2701), ranging from Moderate NPDR to Early PDR and/or with presence of macular edema.	Farnsworth-Munsell 100-Hue		49.4% (Blue-yellow)	
Hardy et al (1992)[40]	CN = 36 (n = 36) No DR = 38 (n = 38)	Farnsworth-Munsell 100-Hue	57.0% (Diffused loss)		
Trick et al (1988)[141]	CN 70 (n = 70) No DR = 74 (n = 37) Mild to Moderate NPDR = 40 (n = 20)	Farnsworth-Munsell 100-Hue	18.9% (Diffused loss)	25.0% (Diffused loss)	

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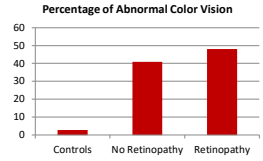
Color Vision and Neuroretinal Function in Diabetes

Wolff et al. investigates how T2DM and DR affect color vision and mfERG
84 subjects; participants included diabetics with and without retinopathy plus controls



CLINICAL STUDY RESULTS

CV Affected in patient with T2DM even without DR
Central DR increases likelihood of CV deficit

mfERG Less frequently abnormal than CV in the absence of DR

2014 *Documenta Ophthalmologica*

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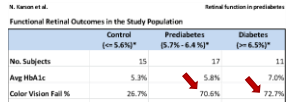
Functional Retinal Outcomes: Prediabetes & T2DM

Karson et al. investigates how T2DM affect color vision and mfERG
43 subjects; 3 groups: Prediabetics, Type II diabetics, Controls



N. Karson et al. — Retinal function in prediabetes

Functional Retinal Outcomes in the Study Population

	Control (<= 5.6%)*	Prediabetes (5.7% - 6.4 %)*	Diabetes (>= 6.5%)*
No. Subjects	15	17	11
Avg HbA1c	5.3%	5.8%	7.0%
Color Vision Fail %	26.7%	70.6%	72.7%

CLINICAL STUDY RESULTS

CV Prediabetic group had measurable functional changes before diabetes
Color vision is the strongest biomarker

mfERG No change in prediabetic group

CS No change in prediabetic group

2020 *Ophthalmic & Physiological Optics*

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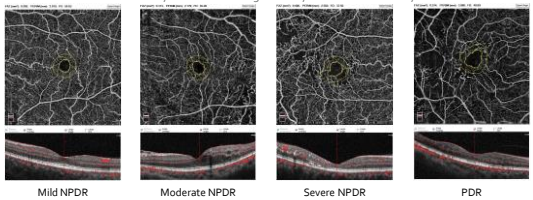
FAZ Measurements in diabetic eye disease

FAZ size and FAZ vessel density are correlated significantly with disease severity in DR.[1]



1. Nesper PL, Roberts PK, Onishi AC, et al. Quantifying Microvascular Abnormalities With Increasing Severity of Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Investigative Ophthalmology & Visual Science. 2017;58(6):BIO307-BIO315. doi:10.1167/iovs.17-21787.

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Case: Diabetes Exam- What's Your Diagnosis?

Courtesy of Pinakin Davey OD, PhD

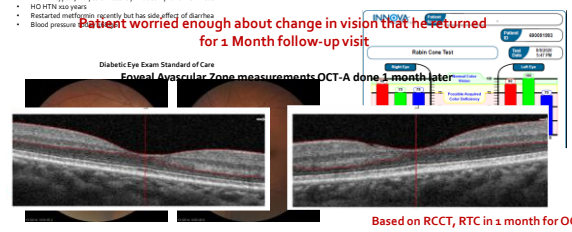
- 19 YO Asian male,
- HO DM type 2, 10 years "recently" not compliant with meds
- HO HTN xio years
- Restarted metformin recently but has side effect of diarhea
- Blood pressure [illegible]

What about now?

Patient worried enough about change in vision that he returned for 1 Month follow-up visit

Diabetic Eye Exam Standard of Care

Foveal Avascular Zone measurements OCT-A done 1 month later



Based on RCCT, RTC in 1 month for OCT

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Case: Diabetes Exam- What's Your Diagnosis?

Courtesy of Pinakin Davey OD, PhD

FAZ size and FAZ ve[illegible] [1]

Foveal Avascular Zone measurements OCT-A done 1 month later

Adding Rabin Cone Contrast:

- Revealed changes from early diabetic eye disease which otherwise would have been missed
- Motivated patient to follow-up with 1 month visit
- Allowed for detailed discussion about diet, lower blood pressure
- Patient began diabetes nutritional supplements

0.285 0.313 0.400 0.574

1. Nesper PL, Roberts PK, Onishi AC, et al. Quantifying Microvascular Abnormalities With Increasing Severity of Diabetic Retinopathy Using Optical Coherence Tomography Angiography. Investigative Ophthalmology & Visual Science. 2017;58(6):BIO307-BIO315. doi:10.1167/iovs.17-21787.

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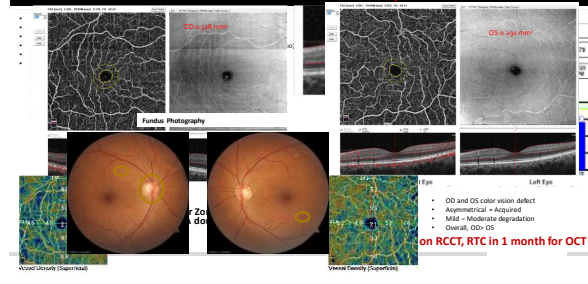
Case: Another Diabetes Exam- What's Your Diagnosis?

Courtesy of Pinakin Davey OD, PhD

Patient returned for 1 Month follow-up visit



- OD and OS color vision defect
- Asymmetrical – Acquired
- Mild – Moderate degradation
- Overall, OD> OS

on RCCT, RTC in 1 month for OCT

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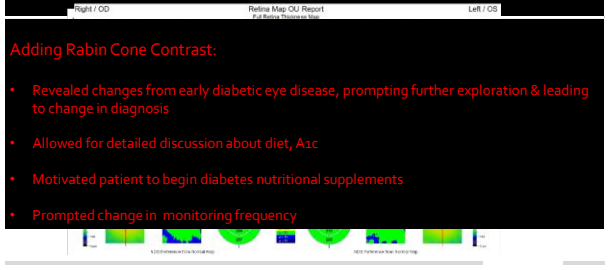
Case: Another Diabetes Exam- What's Your Diagnosis?

Courtesy of Pinakin Davey OD, PhD



Adding Rabin Cone Contrast:

- Revealed changes from early diabetic eye disease, prompting further exploration & leading to change in diagnosis
- Allowed for detailed discussion about diet, A1c
- Motivated patient to begin diabetes nutritional supplements
- Prompted change in monitoring frequency

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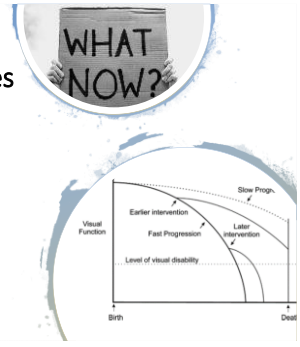
Diabetes & DR: Reduces Cone Contrast



Detection of Progression

- Monitor more frequently
- Health initiatives
  - ✓ Weight management
  - ✓ Exercise
  - ✓ Nutritional changes
  - ✓ Medical management when needed
- Nutritional supplements

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nutrients

Review

A Systematic Review of Carotenoids in the Management of Diabetic Retinopathy

Drake W. Lem [1,†], Dennis L. Gierhart [2] and Pinakin Gunvant Davey [1,*,†]

of DR, specifically in patients with type 2 or poorly managed type 1 diabetes. Meanwhile, early interventional trials with dietary carotenoid supplementation show promise in improving their levels in serum and macular pigments concomitant with benefits in visual performance. These findings provide a strong molecular basis and a line of evidence that suggests carotenoid vitamin therapy may offer enhanced neuroprotective effects with therapeutic potential to function as an adjunct nutraceutical strategy for management of diabetic retinopathy.

Nutrients 2021, *13*, 2441. https://doi.org/10.3390/nu13072441

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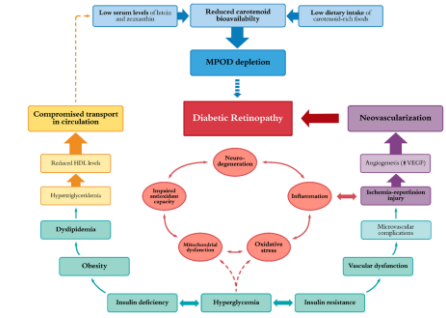

Nutrients 2021, *13*, 2441. https://doi.org/10.3390/nu13072441

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The Diabetes Visual Function Supplement Study (DiVFuSS)

The Diabetes Visual Function Supplement Study (DiVFuSS) was designed to test the effects of a novel, multi-component nutritional supplement on visual function. Participants included patients with both type 1 and type 2 diabetes.

- 2016 *British Journal of Ophthalmology*
  - six-months
  - placebo controlled

CLINICAL STUDY RESULTS WITH DVS

Randomized, placebo-controlled study demonstrated:

- 21% improvement in color vision**
- 19% improvement in contrast sensitivity (easier to read ink on an newspaper)**
- 12% improvement in central and peripheral vision**

**improvements were made without significantly affecting blood glucose levels

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What Are You Going To Do Differently?

(Pre) Diabetic Exam → Screen ~65

- Initiate A1C testing in suspect patients & alert PCP
- Discuss lifestyle modifications earlier
- Motivate patient to begin carotenoid vitamin supplements & Omega 3's

→ PREVENT ONSET

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Glaucoma and color vision defects

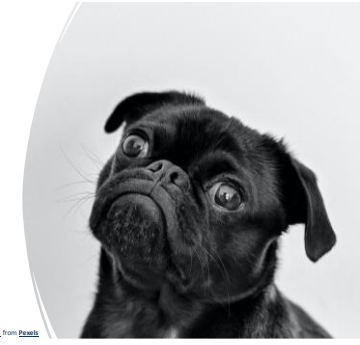

Photo by Charles from Pexels

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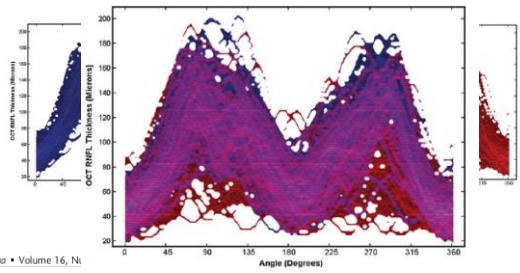
RNFL in a population with and without glaucoma



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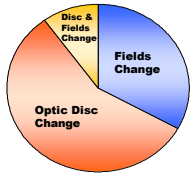
Does structural loss always precede functional loss in glaucoma?

- OHTS reports
- 55% of subjects reached endpoint (POAG) based on changes in the optic disc only.
- 35% of glaucoma was found by visual field changes.
- Only 10% of subjects had concurrent optic disc and visual field changes.



Kass et al., Arch Ophthalmol. 2002;120:701-703

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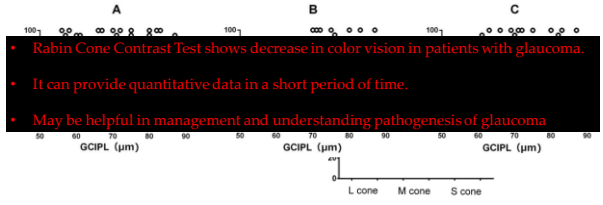
Glaucoma

Evaluation of Acquired Color Vision Deficiency in Glaucoma Using the Rabin Cone Contrast Test

Yuichi Niwa, Sanae Muraki, Fumiyuki Naito, Takayuki Minamikawa, and Masahito Ohji



- Rabin Cone Contrast Test shows decrease in color vision in patients with glaucoma.
- It can provide quantitative data in a short period of time.
- May be helpful in management and understanding pathogenesis of glaucoma

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What Are You Going To Do Differently?

Glaucoma Exam → Change >10 → •Begin treatment in borderline cases •Adjust treatment plan ⇨ REDUCE VISION LOSS

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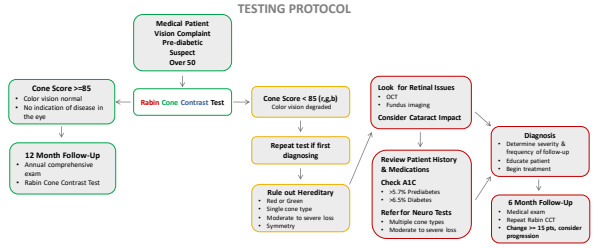
How Are You Going To Test?



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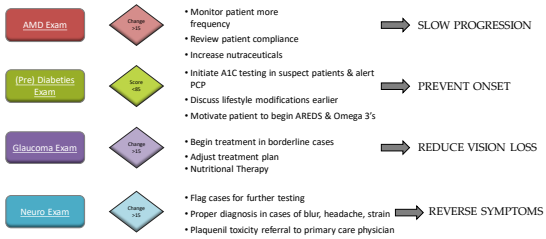
To clinically summarize…



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Summary

- Adding Rabin CCT completes the comprehensive exam
- Rabin CCT allows for early detection and progression of disease
- Rabin CCT demonstrates improvement with treatment

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