


Being a Bridge

Paul Palmberg, MD, PhD
Professor Emeritus-Active
Bascom Palmer Eye Institute
University of Miami School of Medicine

Each of us is Potentially a Bridge in Several Ways

My Parents:
Laura Palmberg, BS,MS (School Psychologist)
Karl Palmberg, MD (Ophthalmologist)

My wife Carol and our 3 daughters

Being a Bridge Between:

- Your parents and your children
- Your teachers and your students
- Your knowledge -- teaching your patients
- Horizontally: colleagues, siblings, friends

What Moves Across these Bridges?

- Family: Genes, language, religion, culture, opportunity, inheritance
- Mentors: Clinical skills, strategies, ethical behavior
- Stories "tag" short-term memory for long-term storage and recall.
- Example: Avoiding hand tremor—watching a jeweler

Turning Points and Consequences

At 9: Learned from my father's example
to do the right thing, even if you face opposition.

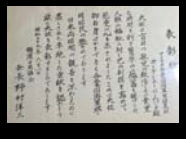
(In 1952-4, he operated upon cataract-blind children in Japan, trained a Japanese ophthalmologist)

The head of the Naval Hospital asked him to stop.

"How can we claim we need more staff if you have time for this? I can't order you to stop, but if you don't stop, I will give you jury duty."

Stop? Not my dad!

A Japanese Prince presented a scroll of thanks at the Imperial Palace.



Turning Points and Consequences

- At 12: Miss Squire taught "Eyes on speaker's eyes or the board" helped me become a better student!
- Took 4 of us to UC Berkeley to see possible paths to take
- At 14: Watched father in clinic and OR—decided on ophthalmology (he listened and explained!)
- At 14: Met Carol Crone (now married 62 years, 3 daughters)

Turning Points and Consequences

- Always a "guinea pig"--High school "More Able Program"
- At 18: Entered inaugural class of Northwestern University's 6-year Med Program
- At 20: Decided to be a bridge between science and medicine and entered inaugural Medical Scientist (MD-PhD) Training Program.

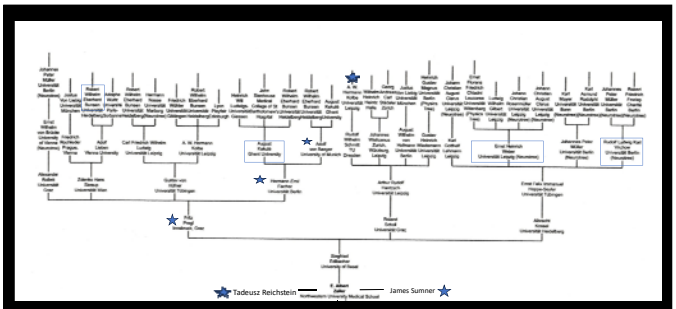
American Medical News Story on the new Medical Scientist Training Program at Northwestern University

1965-1970

Mentor and Role Model:

E. Albert Zeller, MD, PhD (worked with Nobel Laurates Tadeusz Reichstein James Sumner)

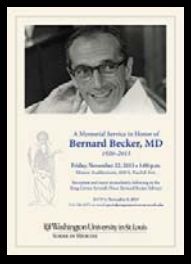
Preparing for combined degree at Northwestern University, Paul Palmberg, 21, plans to be both an eye surgeon and ocular chemist. He is shown here studying mechanisms and kinetics of lens enzymes as a basis for further study of cataract formation.



In Biochemistry my PhD thesis advisor was E Albert Zeller, MD, PhD, at Northwestern.
He named and studied Monoamine Oxidase and recognized the importance of serotonin and dopamine in depression
His mentors included Nobel Laureates Reichstein (cortisol) and Sumner (enzyme isolation)

Washington University in St. Louis: Residency and Clinical and Research Fellowships in Glaucoma and Chief Residency 1971-7

Mentors:



Bernard Becker, MD

Michael Kass, MD

Clinical Mentors at Washington University in St. Louis

Bernard Becker, MD
1920-2013
Introduced Acetazolamide
Trained with Friedenwald
Editor IOVS
NOAO 1957, 1966

Michael Kass, MD, MS
1942-
PI of the OHTS
NOAO 1996

Allan Kolker, MD
1933-2020

Steven Podos, MD
1937-2009
NOAO 1974

Theodore Krupin MD
1942-2015
Krupin-Denver Valve, the first Aqueous Drainage Device

Chief Residency at Washington University:

Washington University in St. Louis Ophthalmology Graduation 1977
Yes, only one woman, Elizabeth Hodapp, MD

To instill confidence and achieve competence in the first year Residents (that I had picked):

I had a list of skills to master during the year:

Refraction, slit lamp exam, tonometry, gonioscopy, neuro exam, VF testing, optic nerve exam, indirect ophthalmoscopy, cataract surgery

Changed the Residency by having each of them perform 6 cataract operations *in the first year,* doing it on 2nd eyes as I assisted. Better than do first operations well into the second year.

Steroid Sensitivity in Glaucoma

- At WUMS 1971 Arrived to find that *the lens research guy had left*
- *Had to do research in glaucoma instead*
- Study of steroid sensitivity in the blood lymphocytes of glaucoma patients vs normals and those steroid tested in their eyes

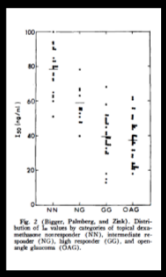


Fig. 2 (Bigger, Palmberg, and Zink). Distribution of I_{50} values by categories of topical dexamethasone nonresponder (NN), intermediate responder (NG), high responder (GG), and open-angle glaucoma (OAG).

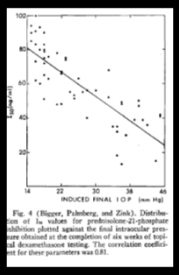


Fig. 4 (Bigger, Palmberg, and Zink). Distribution of I_{50} values for prednisolone-21-phosphate inhibition plotted against the final intraocular pressure obtained at the completion of six weeks of topical dexamethasone testing. The correlation coefficient for these parameters was 0.81.

Then the Research Fell Apart!

- First, another group confirmed our work.
- Then another found no difference and had much higher and non-physiologic I-50 values
- *Then suddenly the assay would no longer work! WHY?*
- Found out from John Baxter that stress-induced release of Epidermal Growth Factor had a strong permissive effect on corticosteroid action

Then the Research Fell Apart!

- The calves (source of 15% fetal calf serum used in the assay) were no longer being exsanguinated, but now electroshocked first—no stress experienced!
- We were studying a stress-artifact! (9 Years of research down the drain!
- When we studied the *corticosteroid receptor affinities and numbers per cell* there were no differences between POAG and controls.
- Palmberg PF, Nakanishi, M., Coit, D., Matulich, D.T., Lan, N.C., Hajek, A.S., Hajek, S., Becker, B., Baxter, JD: Cellular sensitivity to glucocorticoids in patients with primary open angle glaucoma: steroid receptors and biological responsiveness of cultured skin fibroblasts. Invest Ophthalmol Vis Sci 26:805 809, 1985.
- By the way, one day when I was visiting him, he ran to the OR to get a Human Growth Hormone secreting tumor. Soon after he launched Cal Bio and Genentech was started, the beginning of the biotech industry.

Why am I telling you about this?

Because we were able to harvest fruit from failure!

- Consequences:
  - (because of tissue culture work)
  - Introduced HEPES buffer and the color indicator In corneal transplant media

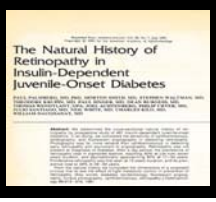
Because of work with Medicine Department tissue culture folks, I volunteered to see the Juvenile Diabetics (exam, photos, angiograms)

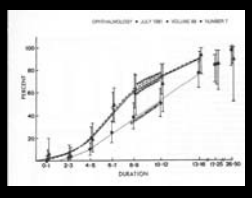
Dr. David Kipnis, Chair of Medicine at Washington University in St. Louis and Editor of Diabetes asked me to write a review article on Diabetic Retinopathy

- Diabetic retinopathy. Palmberg PF Diabetes 1977;26:(7):703-9
- Screening for diabetic retinopathy. Palmberg P. Diabetes Care. 2001 Mar;24(3):419-20.

Harvesting Fruit From Failures:

- Because of work with Medicine Department tissue culture folks, volunteered to see the Juvenile Diabetics (exam, photos, angios)
- Consequence: ***Accidentally*** constructed the Natural History of JODM Diabetic Retinopathy that was the basis for the Primary Prevention part of the Diabetes Control and Complications Trial!


The Natural History of Retinopathy in Insulin-Dependent Juvenile-Onset Diabetes



Diabetes Control and Complications Trial

On the DSMB for 13 years I presented the eye findings at each meeting

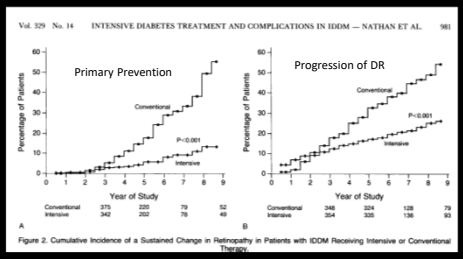


Figure 2. Cumulative Incidence of a Sustained Change in Retinopathy in Patients with IDDM Receiving Intensive or Conventional Therapy.

Diabetes Control and Complications Trial

I asked for and insisted on doing this analysis—43% lower risk of DR progression, 33% more hypoglycemic episodes per point lower HbgA1c. NOW that we have glucose measuring patches that can be worn on the skin, smart phone apps can use that to control an insulin pump and achieve great control without as much risk of hypoglycemia!

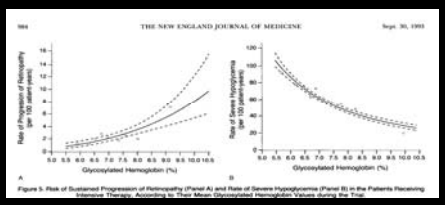


Figure 5. Risk of Sustained Progression of Retinopathy (Panel A) and Rate of Severe Hypoglycemia (Panel B) in the Patients Receiving Intensive Therapy, According to Their Mean Glycosylated Hemoglobin Values during the Trial.

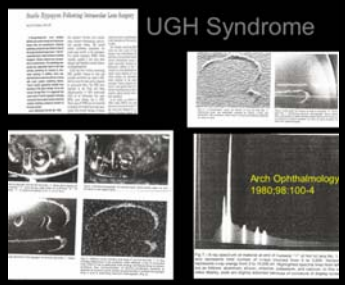
Only with the Advent of Continuous Glucose Monitors, Smart Phones and Insulin Pumps Can we take Full Advantage of the Risk/Benefit Information from the DCCT

Other Interactions: I picked David Meltzer, previous astrophysicist, to be a Resident in Ophthalmology. He had predicted Pulsars! He saved the intraocular lens industry.

David Meltzer, MD, PhD

The original report of a Pulsar quotes Meltzer.

David asked me to ask Dr. Becker for funding.
David helped eliminate UGH Syndrome causes with EDXA Analyses



In Academia Many Things you Start Don't Work Out
It's a High Risk, High Return Adventure

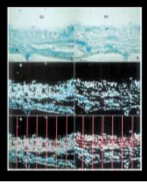
Bridge to Nowhere

Trabecular Meshwork Biology

- Conclusions: The data provided the first quantitative biochemical profiles of GAGs of individual normal and POAG TM, and suggested that a depletion of hyaluronic acid and increase of chondroitin sulfates likely increases aqueous outflow resistance in the POAG TM.
- These findings suggest that **the trabecular cells in the drain are prematurely senescent (as similar changes occur normally in other organs with aging)**, but we don't know why. We could culture TM cells from normals, but not from POAG—another dead end in my career.

Glycosaminoglycans of the human trabecular meshwork in primary open-angle glaucoma. Knepper PA, Goossens W, Hvizd M, Palmberg PF. Investigative Ophthalmol Vis Sci 1996;37(7):1360-7

Glycosaminoglycan stratification of the juxtacanalicular tissue in normal and primary open-angle glaucoma. P A Knepper; W Goossens; P F Palmberg Ophthalmol. Vis. Sci.. 1996; 37(12):2414-2425.



We studied drugs (timolol, epinephrine, brimonidine) that affect cyclic nucleotide metabolism and are used to treat glaucoma, but found that there were no differences in aqueous levels of cyclic nucleotides in glaucoma

- The Additive Effect of Topical Epinephrine and Topical Timolol, ARVO, 1980.
- Cyclic Nucleotide Concentrations in Aqueous Humor
  - Underwent a diurnal variation, but ***no difference in POAG vs Cataract***
  - ***Presented at ARVO.***

National Visual Acuity Impairment Survey:

Technique validation: Photos of the anterior segment and of the disc and macula, along with a VF, reliably allowed remote masked determination of the cause of impairment.

This demonstrated that a form of tele-ophthalmology could be feasible if portable photography and VF testing could be developed.

- Sperduto, R.D., Hiller,R., Podgor, M.J., Palmberg PF, Ferris, F.L., Wentworth, D. and The Visual Acuity Impairment Survey Research Group. Comparability Of Ophthalmic Diagnoses By Clinical And Reading Center Examiners In The Visual Acuity Impairment Survey Pilot Study. Am. Journal of Epidemiology, 124:994-1003, 1986.

NEI Study Section

- Johanna Seddon: Study of dietary yellow-green vegetables and of serum lutein in AMD (let to AREDS)
- Alfred Sommer Baltimore Eye Survey
  - (had to fight hard for this one as it was expensive, "only grant I need this time, need to know epidemiology of POAG by IOP and race"
  - Added an automated perimeter to the study.

Bascom Palmer Glaucoma Faculty and Fellows

Martha Araujo Deborah Darnley Elizabeth Hodapp
Rich Parrish Douglas Anderson Paul Palmberg

Found my Place in Clinical Research

- At BPEI: Richard Parrish, Mark Blumencranz and 5-FU in filtering surgery in 1982
- 1988 Safety Valve trabeculectomy (Ophthalmology 1997)
- Introduced term "Target Pressure" in the AAO POAG PPP
- Two sets of stitches for repair of hypotony maculopathy (Ophthalmology 1997)
- Bleb compression sutures for painful blebs and leaks
- Trans-corneal needling of scleral flap and bleb
- 30g needle paracentesis to clear cornea in AACG
- Relaxing incisions to get under Tenons tissue, avoid bleeding and leaks
- AGIS analysis that progression of VF can be halted (AJO 2000)—World Glaucoma Prize
- CIGTS analysis showing partial VF recovery at IOP <13 mm Hg (AJO 2014)
- Training: 260 Residents, 107 Fellows, 108 Foreign Fellows
- Medical Monitor and/or Consultant for AADI, XEN and MicroShunt

Resolving Paradoxes

A classical paradox in physics:

Light is a particle
Light is a Wave

Light is a particle that moves in a wave!

The Paradox of Treatment

- My surgery can help the patient.
- My surgery can harm the patient.
- Much of my career has been focused on solving the simultaneous equations in risk/benefit

Peng Khaw Visited as a Student

Thank you Sir Peng Khaw!

After change

Fornix based
Large Area
MMC 0.5 mg/ml

Before Change

Limbus based
Small Area
MMC 0.4 mg/ml

Bleb related problems inc leaks / blebitis / endophthalmitis

0% **20%**

My bleb problems reduced from 8% to 1% at 5 years.

5 Questions With Peng T. Khaw, MD, PhD
Glaucoma Today, May/June 2008

As a junior resident, while passing through Miami, I took a chance and called the department of glaucoma at Bascom Palmer Eye Institute. Paul Palmberg, MD, PhD, invited me to visit during his lunch break. He gave me a copy of his meta-analysis of several studies showing that, the lower the average IOP, the lower the rate of glaucomatous progression.

When I finished my ophthalmology training, I decided to pursue a doctoral degree...Based on my clinical observations and the understanding of what was happening in the bleb from our laboratory studies, we showed that making the surface area larger produced dramatically healthier blebs.

Our rate of complications in the high-risk group of children and young adults decreased from approximately 20% to 0.5%.

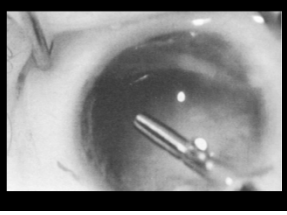
Interestingly, one of the people who were most instrumental in popularizing the technique in the US was Dr. Palmberg. After seeing my video, he began using a larger surface area in his trabeculectomies, and he noticed a dramatic decrease in bleb-related complications within weeks. He became a strong advocate for the surgery internationally. At a later meeting, he came up and hugged me. He said he always hugged people who made a difference for his patients. I told him, years ago, you gave up your lunchtime to meet with a resident you didn't know. That was me, and that meeting was one of the reasons I began researching wound healing, which led to the improved technique.

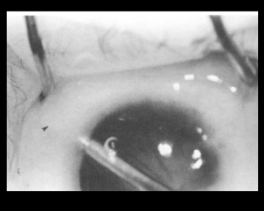
- Moraczewski AL, Lee RK, Palmberg PF, Rosenfeld PJ, Feuer WJ. Outcomes of treatment of neovascular glaucoma with intravitreal bevacizumab. Br J Ophthalmol. 2009 May;93(5):589-93. Epub 2008 Dec 15
- Our use of Avastin in 63 cases of Neovascular Glaucoma

REGRESSION OF RETINAL AND IRIS NEOVASCULARIZATION
AFTER INTRAVITREAL BEVACIZUMAB (AVASTIN) TREATMENT
AVERY, ROBERT L. MD (also reported AAO October 2005)
Retina 2006;26(3):352-354

An early attempt at Minimally Invasive Surgery

- Brown, R.H., Lynch, M.G., Denham, D.B., Parel, J.M., Palmberg, P., Brown, D.D. Internal sclerectomy with an automated trephine for advanced glaucoma. Ophthalmology. 95:728-734, 1988.





Suggested that OHTS was the perfect test of the monocular treatment trial; the result was disappointing as spontaneous changes in eye pressure are somewhat independent of each other

- Bhorade AM, Wilson BS, Gordon MO, Palmberg P, Weinreb RN, Miller E, Chang RT, Kass MA; Ocular Hypertension Treatment Study Group. *The utility of the monocular trial:* data from the ocular hypertension treatment study. Ophthalmology. 2010 Nov;117(11):2047-54. Epub 2010 Aug 12.

- Palmberg P, Kim EE, Kwok KK, Tressler CS; Canada and United States Fixed Combination Latanoprost/Timolol Study Group. A 12-week, randomized, double masked study of fixed combination latanoprost/timolol versus latanoprost or timolol monotherapy. Eur J Ophthalmol. 2010 Jul-Aug;20(4):708-1.

- My brilliant idea of studying the combo drug in timolol "responders" did not work and cost Pfizer millions!

- JUDGE ACQUITS WOMAN OF GROWING POT ILLEGAL DRUG MEDICAL NECESSITY, COURT RULES Sun Sentinal Aug 16, 1988
- Dr. Paul Palmberg of the Bascom Palmer Eye Institute of the University of Miami Medical School testified that Musikka has undergone at least 14 eye operations since childhood for cataracts and glaucoma. Musikka lost the sight in her right eye after surgery last year, he said.

32 Year Study of Marijuana for Glaucoma

- Required FDA IND #31534
- RP DEA License Class I for Marijuana Cigarettes
- UM IRB 1988 0353
- Order forms sent to NIDA, then RTI International
- Annual reports to the FDA

Effects of Marijuana on Aqueous Humor Dynamics in a Glaucoma Patient
April 2005Journal of Glaucoma 14(2):175-7
Zhan G-L, Camras CB, Palmberg P, Toris C

Marijuana and IOP

- Shown to lower IOP by Hepler, tachyphyllaxis
- Smoked: onset 30 minutes, lasts 2-3 hours
- Studies in animals gave conflicting mechanisms

- My patient studied by flourophotometry:
  - Doubling of uvealscleral outflow (like PGA)
  - Uses ten 5.6% THC cigarettes a day, oral or smoked

- IOP reduced from 50s to low 20s + Tim to 18
- Mental effects, heart rate, BP no longer affected, IOP lowered
- VF stable from 1988 till 2013 (on only 2.4% THC)
- Now stable again back on 5.6% THC

- Consultant, Workshop on the Medical Utility of Marijuana
- National Institutes of Health and National Institute on Drug Abuse, February 1997

- Eight experts in clinical studies and therapeutics who convened for a two-day meeting at the National Institutes of Health (NIH) in February 1997 to review and discuss current scientific evidence of medical uses for marijuana have issued their 40-page report (For background, see "NIH Panel Suggests More Research of Medical Marijuana," News Briefs, March-April 1997). The report, released August 8, concludes that marijuana appears to be an effective medicine, but that more rigorous studies of the therapeutic use of marijuana are needed.

- Harbour JW, Rubsamen PE, Palmberg P. Pars plana vitrectomy in the management of phakic and pseudophakic malignant glaucoma. Arch Ophthalmol 1996;114:1073-1078.

- An early report showing that making the eye unicameral, with a vitrectomy, hyaloidotomy and opening in the zonular diaphragm and iris, is needed to achieve lasting cure.

- Palmberg, P. April Consultation # 8. Journal of Cataract and Refractive Surgery; 2006; 32:553-4.
- What to do for a phaco burn at the limbus? My surprising answer? One horizontal 10-0 deeper than the tunnel!

- Kim WI, Larar JG, Cheson BD, Lee RK, Palmberg PF. Resolution of lymphoma-associated open-angle glaucoma by rituximab. J Glaucoma. 2011 Aug;20(6):398-400.
- A bilateral secondary glaucoma caused by lymphoma around the limbus in both eyes. The patient thought of the cure (and asked for and got authorship!)

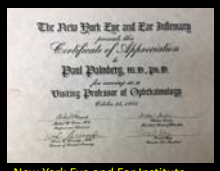
Be Fair with Others!

Association of International Glaucoma Societies Award 2000

American Academy of Ophthalmology Life Achievement Award

Association of International Glaucoma Societies Award 2000

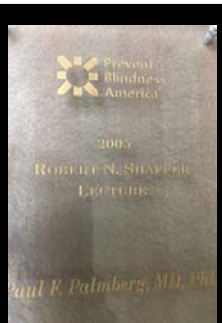
Duke University



New York Eye and Ear Institute

Wills Eye Institute

Washington University



Shaffer Lecture AAO 2015

Aravind AADI Launch

American Glaucoma Society
Surgery Day Lecture 2014

Fellows Roast Paul at AGS 2014
Surgery Day Lecturer
Cosmos Club, Washington, D.C.

Flashmob of Fellows at AGS 2018 in NYC
Receiving Educator of the Year for AGS

BPEI Fellows Dinner at AGS in 2023--Annual Meeting Honoree

James Robinson | Douglas Anderson | David Greenfield | Darryll WuDunn | Rich Parrish | Don Budenz | Paul Palmberg | Nauman Imami | Jorge Lynch | Quang Nguyen | Paul, Carol, | Anna Galanopalous | Eleonore Savatovsky

Some of the 107 Clinical Fellows and 107 Foreign Observer Fellows at BPEI

Who were your mentors/role models?

- Do you have a favorite mentor/role model/teacher?
- Have you thanked them?
- Have you ever asked them about *their* life story?

- Ms Squire— "All eyes on my eyes or the board" helped me become a much better student. Trip to UC Berkeley Campus.
- I returned to find her in a retirement home and showed her that I dedicated my PhD Thesis to my mentors, including her.

- Palmberg's Hug List: From Ridley, Kelman, Schjernshantz, to Baerveldt, Molteno, Ahmed, I Howard Fine…

How Might YOU be More Intentional About Being a Bridge?

- Don't miss the joy!
- Don't miss the satisfaction!

My wish for all of us is that at the end of our careers, and life, we will hear a voice saying, "Well done, good and faithful servant!"

Also, Don't Forget to Have Fun

Don Johnson in Costa Rica

New Orleans Academy of Ophthalmology

Micro Zorro at AGS 2016

George H W Bush

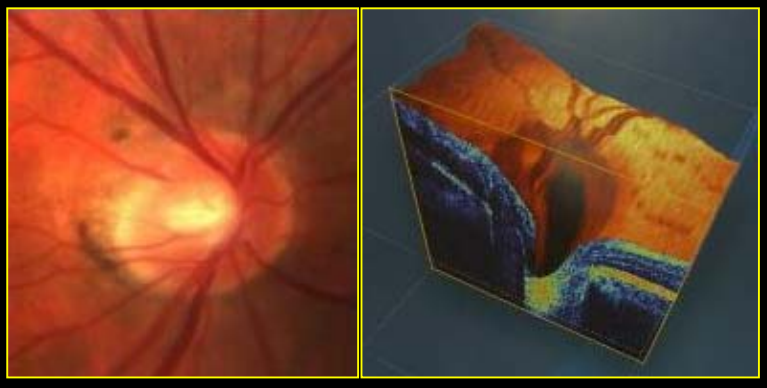
Elvis, New Orleans House of Blues

Teresa C. Chen, MD
Associate Professor of Ophthalmology, Harvard Medical School
Glaucoma Service, Massachusetts Eye and Ear Infirmary

2/2/2024

1

Using OCT to Help Diagnose Glaucoma and to Determine Progression + OCT Artifacts



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Financial Disclosures

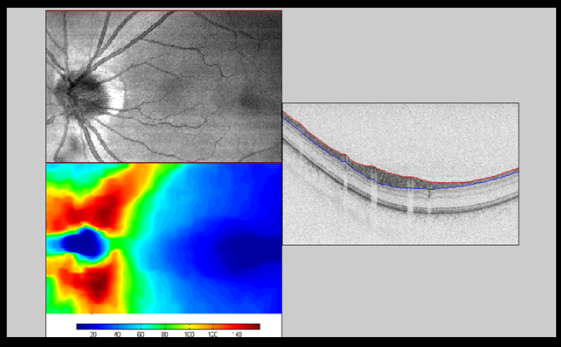
NIH R01 EB033321
NIH R44EY034409
NIH UG1 EY033703

Alcon Laboratories

Harvard Foundation
(Fidelity Charitable Fund)

3

Anniversary Disclosures



- *White BR, Pierce MC, Nassif N, Cense B, Park BH, Chen TC, de Boer JF…Imaging Using Ultra-High-Speed Spectral Domain Optical Doppler Tomography. Optics Express 2003; 11 (25): 3490-7.*
- *Nassif N, Cense B, Park BH, Yun SH, Chen TC, Bouma BE, Tearney GJ, de Boer JF. In vivo Human Retinal Imaging by Ultrahigh-Speed Spectral Domain OCT. Opt Lett 2004;29(5):480-482.*
- *Nassif N, Cense B, Park BH, Pierce M, Yun SH, Bouma BE, Tearney GJ, Chen TC, de Boer JF. In vivo High-resolution Video-Rate Spectral Domain OCT of the Human Retina and Optic Nerve. Opt Express 2004;12(3):367-376.*
- *Cense B, Nassif N, Chen TC, Pierce MC, Yun SH, Park BH, Bouma BE, Tearney GJ, de Boer JF. Ultrahigh-resolution High-speed Retinal Imaging Using Spectral Domain OCT. Opt Express 2004;12(11):2435-2447.*

4

Interpreting Glaucoma Imaging

Lecture Aerial View

- **Pros**
  - many SDOCT machines
  - diagnosis
  - progression analysis
- **Cons**
  - how to recognize artifacts

2/2/2024

5

Interpreting Glaucoma Imaging

Lecture Aerial View

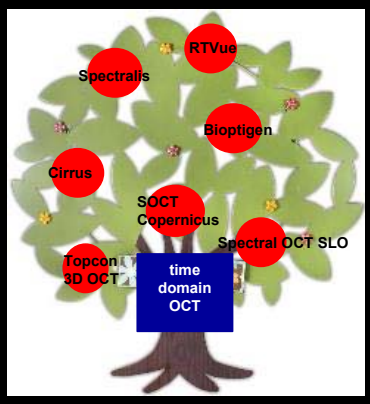
- **Pros**
  - many SDOCT machines
  - diagnosis
  - progression analysis
- **Cons**
  - how to recognize artifacts?

2/2/2024

6

Many SD-OCT machines

- Cirrus HD-OCT (Carl Zeiss Meditec, Inc, Dublin, California)
- RTVue (Optovue, Inc, Fremont, California)
- Spectralis SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany)
- 3D-OCT (Topcon Medical Systems, Inc, Paramus, New Jersey)
- Bioptigen Envisu SD-OCT (Bioptigen, Inc, Research Triangle Park, North Carolina)
- SOCT Copernicus HR (Optopol Technology, SA, Zawiercie, Poland)



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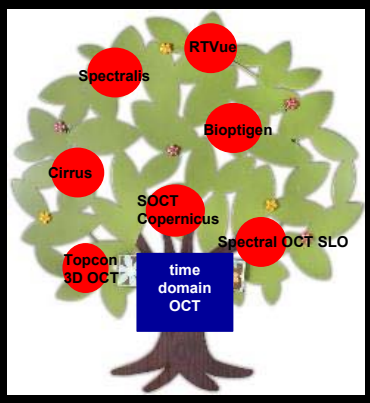
Many SD-OCT machines

- Cirrus HD-OCT (Carl Zeiss Meditec, Inc, Dublin, California)
- RTVue (Optovue, Inc, Fremont, California)
- Spectralis SD-OCT (Heidelberg Engineering GmbH, Heidelberg, Germany)
- 3D-OCT (Topcon Medical Systems, Inc, Paramus, New Jersey)

SDOCT machines appear to have similar clinical diagnostic abilities[1-4]

1. Akashi et al. IOVS 2013;54(7):4478-4484.
2. Akashi et al. IOVS 2013;54(9):6025-6032.
3. Leite et al. Ophthalmology 2011:118(7):1334-1339.
4. Lee, et al. Optom Vis Sci 2011:88(6):751-758.



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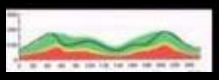
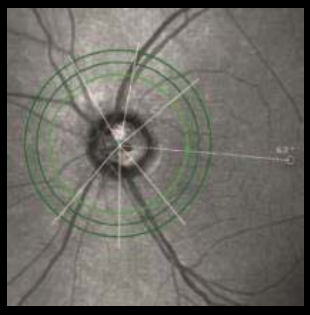
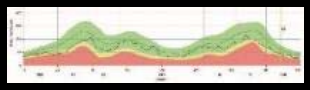
SD-OCT Software Differences

RNFL  | optic nerve  | macula 





- Spectralis Glaucoma Module Premium Edition (GMPE) FDA approved in 2016
- RNFL scan protocol:
  - 12°/14°/16° arc
  - centered over BMO
  - 3.5 mm, 4.1 mm, and 4.65 mm*

* *Gmeiner et al. IOVS 2016;57(9):575-584.*

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SD-OCT Software Differences

RNFL  | optic nerve  | macula 

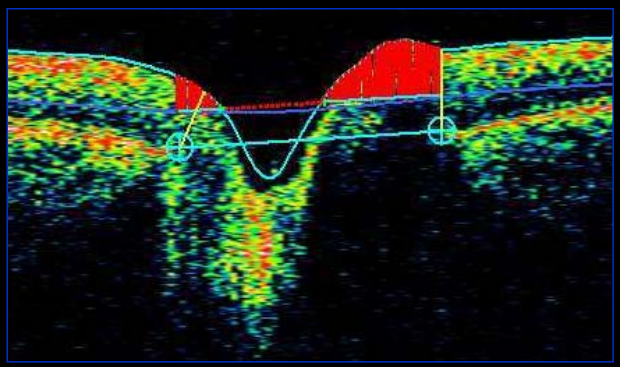

Table 1.
reference plane vs. reference plane independent…

Chen TC, Hoguet A, Junk A, Nouri-Mahdavi K, Radhakrishnan S, Takusagawa H, Chen PP. Spectral Domain OCT: Helping the Clinician Diagnose Glaucoma. Ophthalmology 2018;125:1817-1827.

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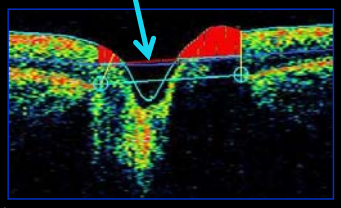
SD-OCT Software Differences

RNFL | optic nerve | macula

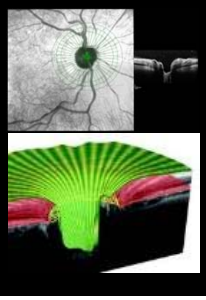
old way → new way

- reference plane dependent parameters
  - Cirrus - 200 microns above RPE
  - RTVue – 150 microns above RPE
  - 3D OCT – 120 microns above RPE



- reference plane independent parameters
  - Spectralis – BMO-MRW (GMPE*)

*Chen TC. Trans Am Oph Soc 2009;107:254-81.
Chen TC, Zeng A, Sun W, Mujat M, de Boer JF. SDOCT in Glaucoma. International Ophthalmology Clinics 2008 Fall; 48 (4): 29-45.



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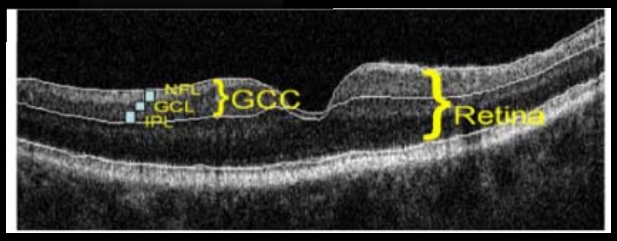
SD-OCT Software Differences

RNFL | optic nerve | macula



NFL: Nerve fiber layer (ganglion cells axons)
GCL: Ganglion Cell Layer (ganglion cells bodies)
IPL: Inner Plexiform Layer (ganglion cells dendrites)
Retina: total retinal thickness

RTVue
GCC: Ganglion Cell Complex = NFL + GCL + IPL

Cirrus GCA: Ganglion Cell Analysis
GCC = NFL + GCL + IPL
GCIPL = GCL + IPL

3D OCT
GCC
GCIPL
NFL

Spectralis
Total retina thickness

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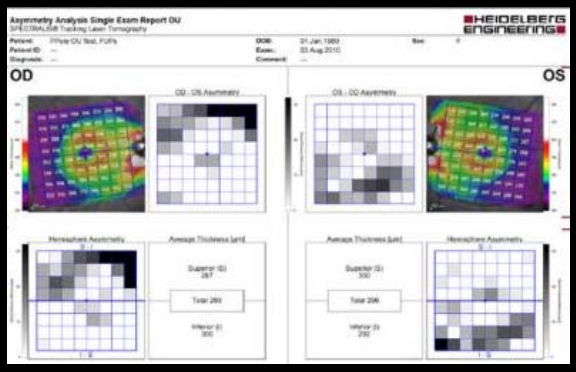
SD-OCT Software Differences

RNFL  optic nerve  macula 



Spectralis Glaucoma Module Premium Edition (GMPE)
GMPE FDA approved in 2016

Posterior Pole Asymmetry Analysis (PPAA)

- 8 X 8 array or superpixel 3°X3°
- 30°X25° volume scan
- 61 horizontal Bscans (120 microns apart)

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Interpreting Glaucoma Imaging

Lecture Aerial View

- **Pros**
  - many SDOCT machines
  - diagnosis
  - progression analysis
- **Cons**
  - how to recognize artifacts

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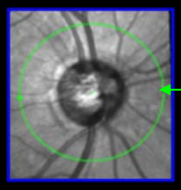
SD-OCT Software Differences

principles → similar across machines

Cirrus, RTVue, Spectralis, 3D OCT



- Most important parameters …
  1) RNFL thickness
  2) Macula
     - GCC
     - GC/IPL
  3) Disc
     - rim area
     - vertical cup-disc ratio
     - BMO-MRW (in 3D space)

Chen TC, Hoguet A, Junk AK, Nouri-Mahdavi K, Radhakrishnan S, Takusagawa HL, Chen PP. Spectral domain optical coherence tomography: helping the clinician diagnose glaucoma. A report by the American Academy of Ophthalmology. Ophthalmology. 2018 Nov;125(11):1817-1827.

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SD-OCT Software Differences

principles → similar across machines

Cirrus, RTVue, Spectralis, 3D OCT

- Better AUROC values for…
  - greater disease severity
  - better signal strength
- Diagnosis
  (RNFL ~ macula ~ disc)
  - maybe macula for myopes
- Combining parameters improves diagnostic performance

Chen TC, Hoguet A, Junk AK, Nouri-Mahdavi K, Radhakrishnan S, Takusagawa HL, Chen PP. Spectral domain optical coherence tomography: helping the clinician diagnose glaucoma. A report by the American Academy of Ophthalmology. Ophthalmology. 2018 Nov;125(11):1817-1827.

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SD-OCT Software Differences

principles → similar across machines

Cirrus, RTVue, Spectralis, 3D OCT

- Most important regions …
  - average
  - inferior & superior
  - inferior temporal & superior temporal

Chen TC, Hoguet A, Junk AK, Nouri-Mahdavi K, Radhakrishnan S, Takusagawa HL, Chen PP. Spectral domain optical coherence tomography: helping the clinician diagnose glaucoma. A report by the American Academy of Ophthalmology. Ophthalmology. 2018 Nov;125(11):1817-1827.

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Interpreting Glaucoma Imaging

Lecture Aerial View

- **Pros**
  - many SDOCT machines
  - diagnosis
  - progression analysis
- **Cons**
  - how to recognize artifacts

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What is progression?

What is clinically significant change…

Event based analysis

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What is progression?

What is clinically significant change…

Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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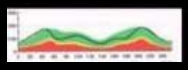
What is progression?

What is clinically significant change…

RNFL 

optic nerve 

macula 

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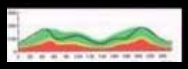
What is progression?

What is clinically significant change…

RNFL 

optic nerve 

macula 

Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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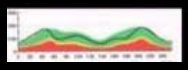
What is progression?

What is clinically significant change…

RNFL | optic nerve | macula



Normal OCT test variability ("noise")

RNFL thinning: 5 µm or more

Sw = 0.43 µm – 4.33 µm (or standard deviation)
(User Manual; Wu Huijuan 2011; Lange 2012; Gardiner 2015)

COV (%) = 0.44 – 5.04%
(User Manual; Langenegger IOVS 2011; Arthur Eye 2011; Pierro IOVS 2012; Lange ISRN 2012; Wu Huijuan J Glaucoma 2011)

ICC = 0.87 - 0.99
(Langenegger IOVS 2011; Arthur Eye 2011; Pierro IOVS 2012; Wu Huijuan J Glaucoma 2011)

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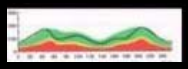
What is progression?

What is clinically significant change…

RNFL | optic nerve | macula



Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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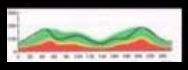
What is progression?

What is clinically significant change…

RNFL | optic nerve | macula



RNFL change from normal aging (1-2 microns/decade)

…or 0.05 to 0.36 µm/ year (normal aging)

…or less than the ± 4 µm (inter-test variability)

RNFL thinning: 5 µm or more

RNFLT (3.5 mm circle diameter)

	$\bar{r}$ [µm]	σ_r [µm]	s_{lin} [µm/year]
RNFLT Global	98.7	9.2	-0.1906
RNFLT T	70.0	10.0	-0.0503
RNFLT TS	127.1	21.0	-0.1460
RNFLT TI	149.2	17.9	-0.3155
RNFLT N	82.1	13.2	-0.1726
RNFLT NS	117.3	24.0	-0.3119
RNFLT NI	112.7	23.0	-0.3578

Spectralis User Manual GMPE Software Version 6.6

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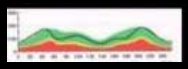
What is progression?

What is clinically significant change…

RNFL | optic nerve | macula

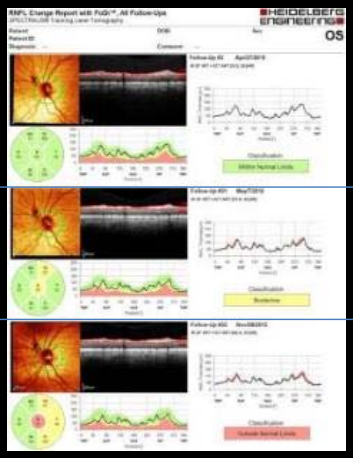


Determining change by numbers…

April 2010
G = 80 µm
TS = 106 µm

May 2012
G = 76 µm
TS = 101 µm

Nov 2012
G = 72 µm
TS = 91 µm



- Is there clinically significant RNFL thinning OS?

Abe et al. Open Ophthalmology Journal 2015

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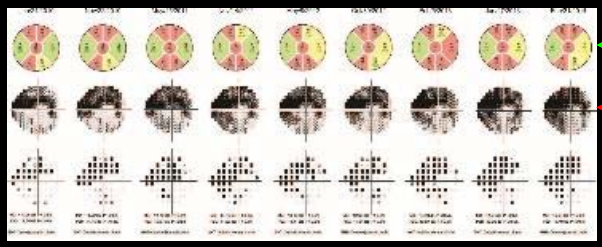
What is progression?

What is clinically significant change…

RNFL | optic nerve | macula

RNFL thickness…

- stop looking for OCT progression when you hit the "floor" (i.e. RNFL 49.2 to 52.6 µm)[1-2]



OCT can be stable

HVF is progressing

Abe et al. IOVS 2016.

[1]Mwanza et al. IOVS 2015:56(11):6344-51.
[2]Tsikata et al. IOVS 2016.

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What is progression?

What is clinically significant change…

RNFL | optic nerve | macula

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What is progression?

What is clinically significant change…

Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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What is progression?

What is clinically significant change…

Normal OCT test variability ("noise")

BMO-MRW thinning: 13 µm or more

Sw = 1.2 µm – 12.09 µm* (or standard deviation)
(Spectralis User Manual; Schrems-Hoesl 2018; *Park JOG 2017)

COV (%) = 0.42 – 6.46%
(Spec User Manual; Schrems-Hoesl J of Glaucoma 2018; Park J of Glaucoma 2017)

ICC = 0.974 - 0.997
(Park K, Kim J, and Lee J. J of Glaucoma 2017; 26(11):1041-1050)

*inferior nasal sector in glaucoma subjects

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What is progression?

What is clinically significant change…

Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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What is progression?

What is clinically significant change…

BMO-MRW change from normal aging (10-15 microns/decade)

…or 0.97 to 1.92 µm/ year (normal aging)[1-2]

…or less than the ± 12 µm (inter-test variability)

BMO-MRW thinning: 13 µm or more

	$\bar{r}$ [µm]	σ_r [µm]	s_{ra} [µm/year]
BMO-MRW Global	333.3	54.10	-1.2653
BMO-MRW T	234.4	44.79	-0.9863
BMO-MRW TS	319.4	62.69	-1.2923
BMO-MRW TI	352.2	61.22	-1.4375
BMO-MRW N	370.2	67.04	-1.2565
BMO-MRW NS	374.3	74.20	-1.3932
BMO-MRW NI	408.3	71.50	-1.5892

- $\bar{r}$ = mean BMO-MRW in the reference database (age- and BMO area-adjusted)
- σ_r = standard deviation of BMO-MRW in the reference database (age- and BMO area-adjusted)
- $\bar{a}$ = mean age of the subjects in the reference database
- $\bar{b}$ = mean BMO area of the eyes in the reference database
- s_{ra} = slope of the regression of BMO-MRW versus age
- s_{rb} = slope of the regression of BMO-MRW versus BMO area

[1]Spectralis User Manual GMPE Software Version 6.6
[2]Vianna et al. Ophthalmology 2015;122:2392-2398.

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What is progression?

What is clinically significant change…

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What is progression?

What is clinically significant change…

Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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What is progression?

What is clinically significant change…

Normal OCT test variability ("noise")

Sw = 0.98µm – 2.88µm (or standard deviation)
(Spectralis User Manual; Menke AJO 2009)

COV (%) = 0.0 – 1.9%*
(Spec User Manual; *Kochendorfer et al Klin Monatsbl 2014; Menke AJO 2009; Wolf-Schnurrbusch IOVS 2009)

ICC = 0.94 - 0.99
(Kochendorfer et al Klin Monatsbl 2014; Pierro et al AJO 2010)

total retinal thickness:
~ 5µm or more

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What is progression?

What is clinically significant change…

Event based analysis:

- Change greater than normal test variability
- Change greater than normal aging

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What is progression?

What is clinically significant change…

RNFL | optic nerve | macula

Retinal thickness change from normal aging (1.9 to 4.2 µm/decade)

…or 0.19 to 0.42 µm/ year (normal aging)[1-3]

…or less than the ± ~5 µm (inter-test variability)

total retinal thickness:
~ 5µm or more

[1]Sung et al. Ophthalmology 2009;116:1119-24.
[2]Patel et al. Ophthalmology 2016;123:829-40.
[3]Gupta et al. Invest Ophthalmol Vis Sci 2013;54:7968-76.

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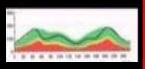
What is progression?

RNFL 	~ 5µm or more	[1]Tatham et al. Detecting Structural Progression in Glaucoma with OCT. Ophthalmology 2017.
optic nerve 	~ 13µm or more	[1]Spectralis User Manual GMPE Software Version 6.6 [2]Vianna et al. Ophthalmology 2015;122:2392-2398.
total macula 	~ 5µm or more	[1]Sung et al. Ophthalmology 2009;116:1119-24. [2]Patel et al. Ophthalmology 2016;123:829-40. [3]Gupta et al. Invest Ophthalmol Vis Sci 2013;54:7968-76.
GCC 	~ 4µm or more	[1]Tatum et al. Ophthalmology 2017;124:S57-S65. [2]Pearce et al. Optom Vis Sci 2017;94:404-410. [3]Rosenberg et al. J Fr Ophtalmol 2015;38:832-843.

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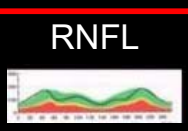
What is progression?

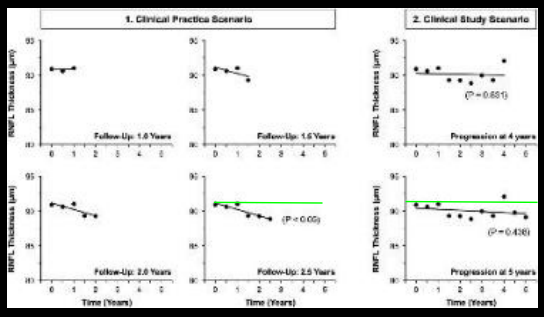
What is clinically significant change…

RNFL | optic nerve | macula



Trend based analysis

1. stat sig negative slope (i.e. slope different from zero p<0.05)
2. stat sig negative slope, with slope more negative than the 5% lower limit of the normal range
3. stat sig negative slope relative to mean normal estimate, with slope being more negative than 5% lower limit of normal
4. stat sig negative slope relative to the 5% lower limit of the normal range



1. High rates of false positive detection of progression
2. With 5 years of annual testing, up to 25% of normal eyes falsely progressed

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Interpreting Glaucoma Imaging

Lecture Aerial View

- **Pros**
  - many SDOCT machines
  - diagnosis
  - progression analysis
- **Cons**
  - how to recognize artifacts

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Artifacts in OCT Imaging

- Top 10 artifacts
- OCT diseases
  - red disease
  - yellow disease
  - green disease
- Variations between machines
  - different measurements
  - different normative databases

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Artifacts in OCT Imaging

83.8 – 87.3% of RNFL and macular artifacts were obvious on the printout

1,118 patients with Spectralis RNFL
Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015.

213 patients with Spectralis RNFL
Steven Mansberger, Shivali Menda, Brad Fortune, Stuart Gardiner, Shaban Demirel. *Am J Ophthalmol* 2017.

277 patients with Spectralis RNFL
Sanjay Asrani, Luma Essaid, Brian Alder, Cecilia Santiago-Turla.
JAMA Ophthalmology 2014.

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Artifacts in OCT Imaging

Cut edge

(0.17% of RNFL scans)…

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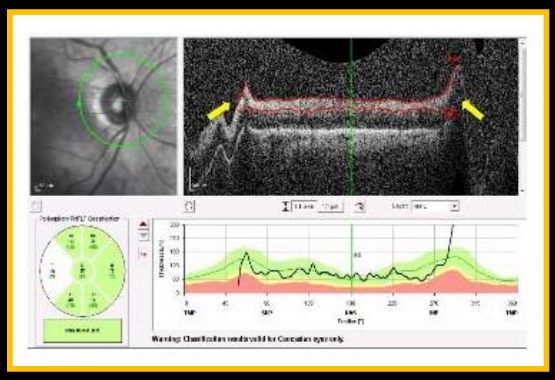

Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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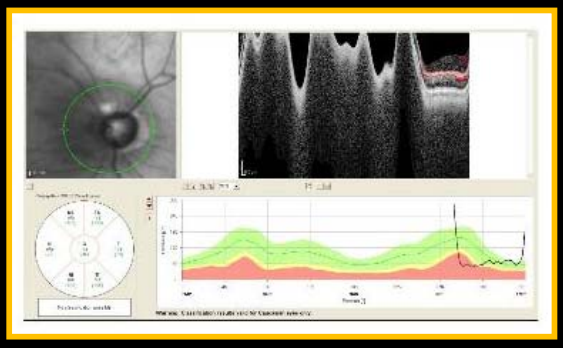
Artifacts in OCT Imaging

Motion artifact

(0.2% of RNFL scans)…

9



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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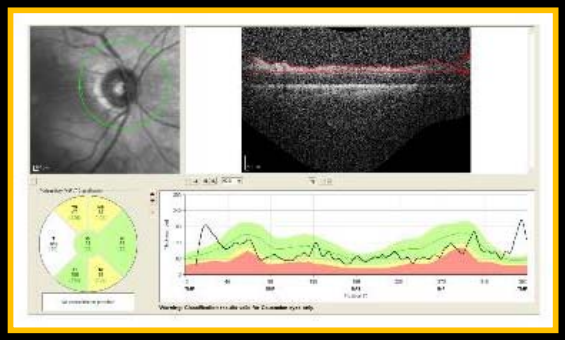
Artifacts in OCT Imaging

Incomplete segmentation
(0.6% of RNFL scans)……

8



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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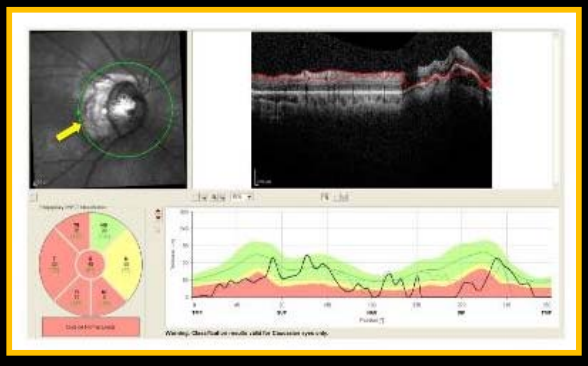
Artifacts in OCT Imaging

PPA-associated error
(1.2% of RNFL scans)…

7

optimal scan circle size



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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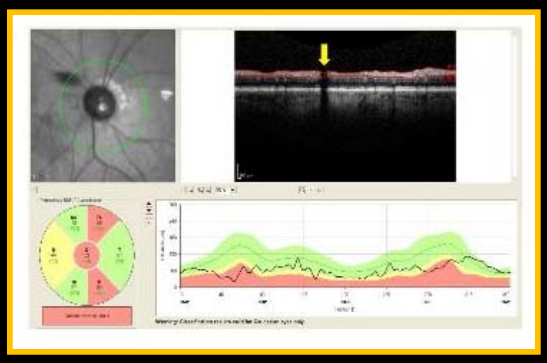
Artifacts in OCT Imaging

Missing parts
(1.5% of RNFL scans)…

6



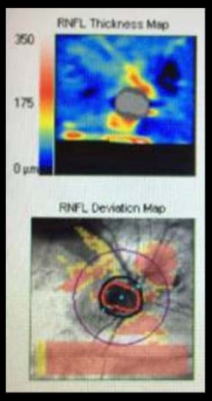
Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

47

Artifacts in OCT Imaging

Missing parts
(1.5% of RNFL scans)…

6



Eye Wiki by Anjum Cheema, MD and Daniel Moore MD

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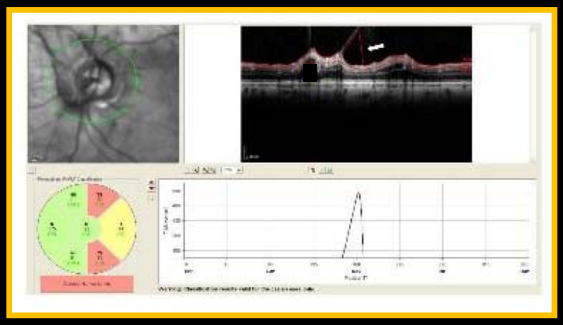
Artifacts in OCT Imaging

Anterior mis-identification of RNFL (3.2% of RNFL scans)…

5



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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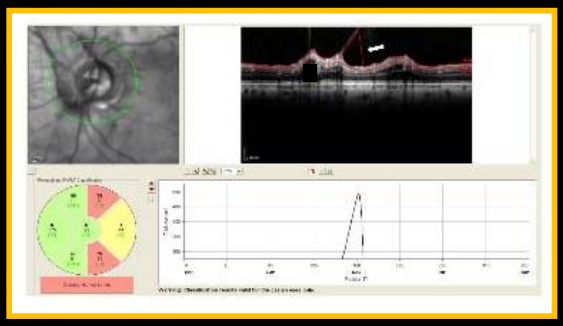
Artifacts in OCT Imaging

Anterior mis-identification of RNFL (3.2% of RNFL scans)…

5



23.1% ERM in macular scans

Artifacts in SDOCT Measurements in Glaucoma. Sanjay Asrani, Luma Essaid, Brian Alder, Cecilia Santiago-Turla. *JAMA Ophthalmology* 2014; 132:396-402.

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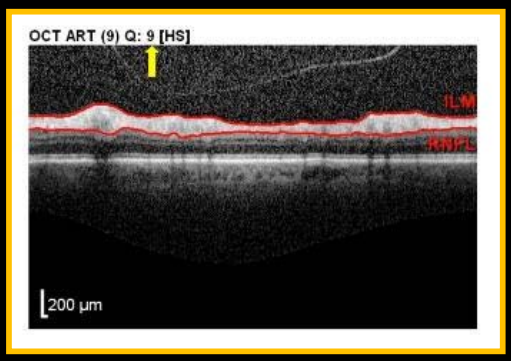
Artifacts in OCT Imaging

Poor signal (5.1% of RNFL scans)…

4



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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Artifacts in OCT Imaging

image quality indices different for different machines
image quality affects RNFL thickness measurements

SDOCT Machine	Scan Quality Index
Cirrus HD-OCT	Signal Strength > 6 (max. 10)
RTVue	Signal Strength Index (SSI) ≥ 30 (max. 100)
3D-OCT	Image quality > 45 (max. 160)
Spectralis SD-OCT	Quality (Q) > 15 (max. 40)

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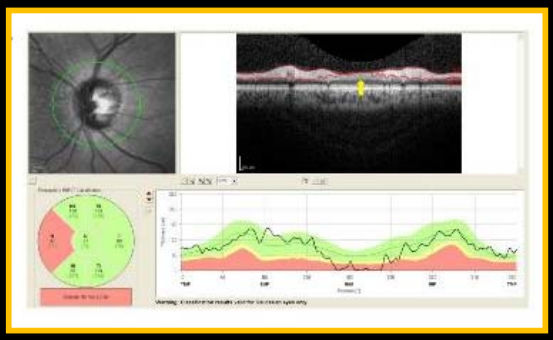
Artifacts in OCT Imaging

Posterior RNFL misidentification (7.7% of RNFL scans)……

3



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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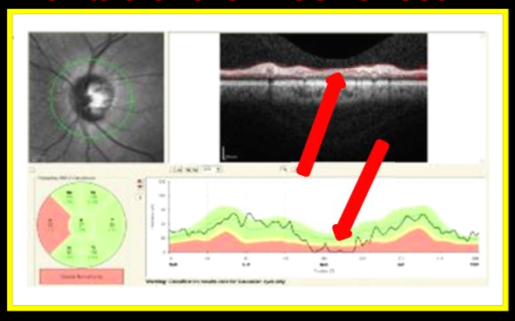
Artifacts in OCT Imaging

Posterior RNFL misidentification (7.7% of RNFL scans)……

3

Beware of the "floor effect"…

Spectralis 49.2 microns
Cirrus 57 microns
RTVue 64.7 microns



Comprehensive Three-Dimensional Analysis of the Neuroretinal Rim in Glaucoma…. Edem Tsikata, Ramon Lee, Eric Shieh, Huseyin Simavli, Christian Que, Rong Guo, Ziad Khouier, Johannes de Boer, Teresa Chen. *Invest Ophthalmol Vis Sci* 2016.

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Artifacts in OCT Imaging

PVD-associated error (14.4% of RNFL scans)…

2

Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

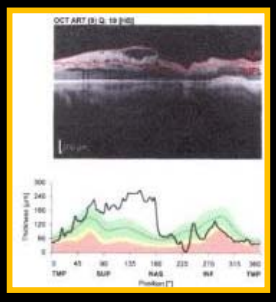
55

Artifacts in OCT Imaging

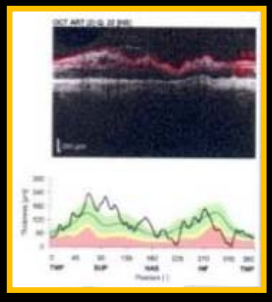
PVD-associated error (14.4% of RNFL scans)…

2

RNFL too "thick"….



RNFL too "thin"….



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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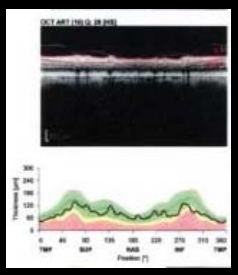
Artifacts in OCT Imaging

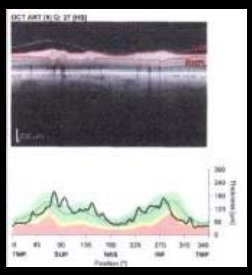
PVD-associated error
(14.4% of RNFL scans)…

2

…or just "right"….



…or just "right"….



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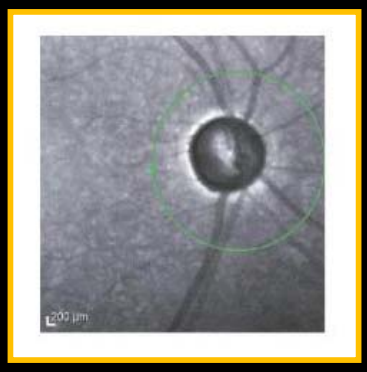
Artifacts in OCT Imaging

De-centration
(27.8% of RNFL scans)……

1



Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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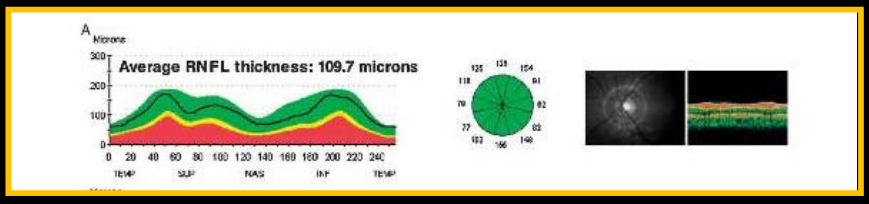
Artifacts in OCT Imaging

De-centration
(27.8% of RNFL scans)……

1



Effect of Improper Scan Alignment on RNFL Thickness Measurements Using Stratus OCT. Gianmarco Vizzeri, Christopher Bowd, Felipe Medeiros, Robert Weinreb, Linda Zangwill. Journal of Glaucoma 2008; 17: 341-349.

59

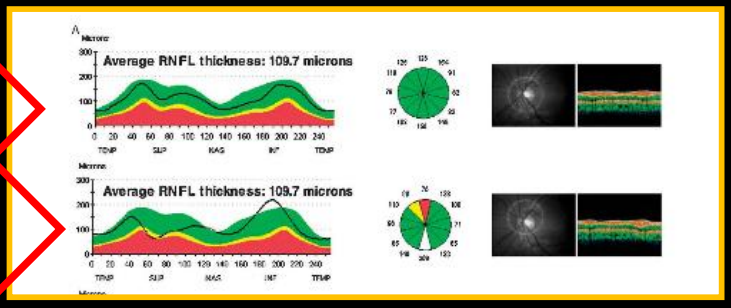
Artifacts in OCT Imaging

De-centration
(27.8% of RNFL scans)……

1

well-centered

superiorly de-centered

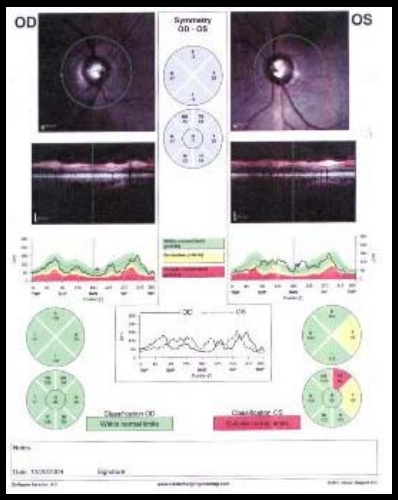


Effect of Improper Scan Alignment on RNFL Thickness Measurements Using Stratus OCT. Gianmarco Vizzeri, Christopher Bowd, Felipe Medeiros, Robert Weinreb, Linda Zangwill. Journal of Glaucoma 2008; 17: 341-349.

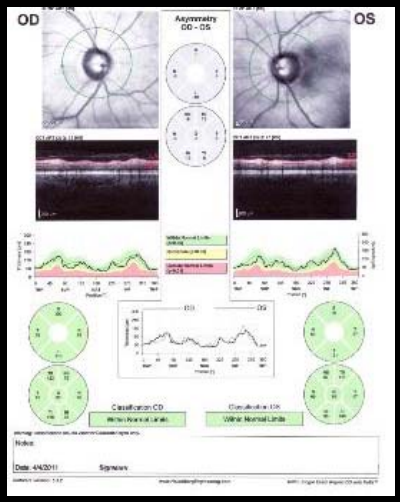
60

Artifacts in OCT Imaging

glaucoma
vs. "de-centered"



"cured!"



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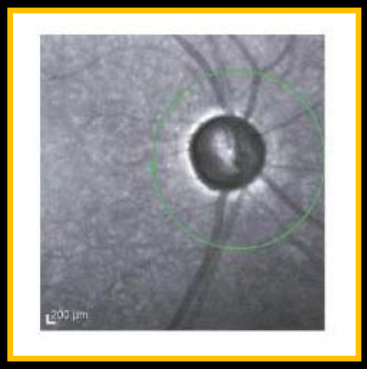
Artifacts in OCT Imaging

De-centration
(27.8% of RNFL scans)……

1



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e.g. Cirrus automatically "centers" RNFL scan via software

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OCT ARTIFACTS: Glaucoma or not?

Top Ten Reasons for OCT Artifacts

1. de-centration
2. PVD-associated error
3. posterior RNFL mis-identification
4. poor signal
5. anterior RNFL mis-identification
6. missing parts
7. PPA-associated error
8. incomplete segmentation
9. motion artifact
10. cut edge

Patient Characteristics Associated with Artifacts in Spectralis OCT Imaging of the Retinal Nerve Fiber Layer. Yingna Liu, Huseyin Simavli, Christian Que, Jennifer Rizzo, Edem Tsikata, Rie Maurer, Teresa Chen. *Am J Ophthalmol* 2015; 159:565-576.

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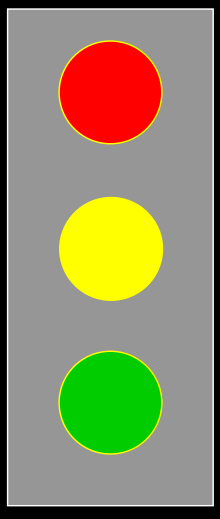
OCT Diseases



red = glaucoma

yellow = maybe glaucoma

green = normal

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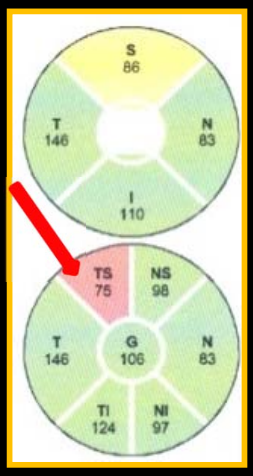
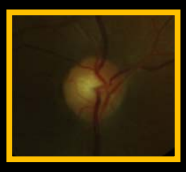
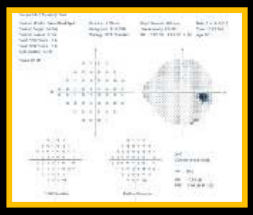
OCT-diseases

OD afflicted by red disease…







Gabriel Chong, Richard Lee. Glaucoma versus red disease: imaging and glaucoma diagnosis. Current Opinion 2012.

65

OCT-diseases

yellow disease = false borderline

146 or 617 (23.7 %) borderline classifications became normal with manual correction

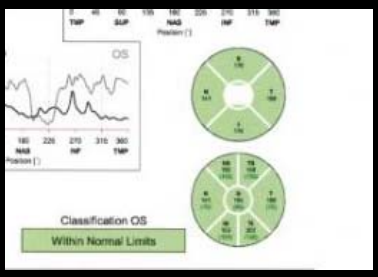
Steven Mansberger, Shivali Menda, Brad Fortune, Stuart Gardiner, Shaban Demirel. Am J Ophthalmol 2017; 174:1-8.

66

Artifacts in OCT Imaging

….OCT-diseases….

green disease



moral: don't use the OCT's brain (color scheme)

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Artifacts in OCT Imaging

….different doctors….

….different machines….

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Artifacts in OCT Imaging

RNFL "thinning" due to different SDOCT machines…

Stratus	Cirrus	Spectralis
110.1 ± 12.8	98.7 ± 10.9	106.6 ± 12.8

RTVue

112.8± 13.2

Comparison of RNFL Thickness in Normal Eyes Using TDOCT and SDOCT.
Leonard Seibold, Naresh Mandava, Malik Kahook. *Am J Ophthalmol* 2010.

40 normals

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Artifacts in OCT Imaging

Normative Databases

- limited refractive errors
- limited ethnicities

Model	Carl Zeiss Meditec	Topcon Medical Systems	Heidelberg Engineering	Optovue
Number of subjects	282	182	201	480
Ages (years)	19 to 84	19 to 84	18 to 78	18 to 84
Gender (M/F)	133 M 149 F	Disc: 54 M / 92 F Macula: 112 F/ 61 M	111 M 90 F	N/A
Ethnicity	43% Caucasian 24% Asian 18% African American 12% Hispanic 1% Indian 6% Mixed ethnicity	64% Caucasian 21% African American 15% Hispanic	Caucasian	33% Caucasian 22% Asian 20% African American 12% Hispanic 12% Indian 1% Other
Anatomy evaluated	pRNFL thickness Optic nerve Parameters GCL + IPL thickness Macular thickness	Optic disc Macula	RNFL Thickness	RNFL Thickness Ganglion cell complex Macular thickness
Study locations	United States, China	United States	Germany	11 clinical sites worldwide

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Artifacts in OCT Imaging

SUMMARY

- Top 10 artifacts
- OCT diseases
  - red disease
  - yellow disease
  - green disease
- Variations between machines
  - different measurements
  - different normative databases

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Interpreting Glaucoma Imaging

Lecture Aerial View

- **Pros**
  - many SDOCT machines
  - diagnosis
  - progression analysis
- **Cons**
  - how to recognize artifacts

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AAO Position Papers

Free on PubMed

Chen TC, Hoguet A, Junk AK, Nouri-Mahdavi K, Radhakrishnan S, Takusagawa HL, Chen PP. Spectral domain optical coherence tomography: helping the clinician diagnose glaucoma. A report by the American Academy of Ophthalmology. Ophthalmology. 2018 Nov;125(11):1817-1827.

WuDunn D, Takusagawa HL, Sit AJ, Rosdahl JA, Radhakrishnan S, Hoguet A, Han Y, Chen TC. Optical coherence tomography angiography for the diagnosis of glaucoma: a report by the American Academy of Ophthalmology. Ophthalmology. 2021 Aug;128(8):1222-1235.

Takusagawa HL, Hoguet A, Junk AK, Nouri-Mahdavi K, Radhakrishnan S, Chen TC. Swept source optical coherence tomography for evaluating the lamina cribrosa: a report by the American Academy of Ophthalmology. Ophthalmology. 2019 Sep;126(9):1315-1323.

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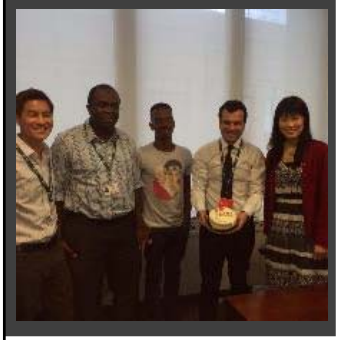
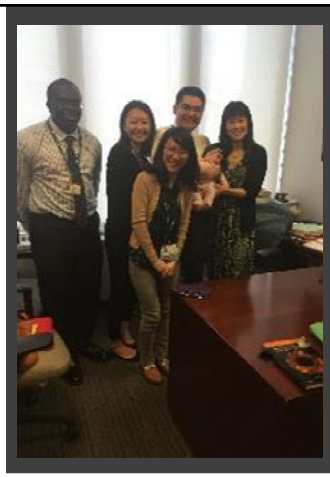

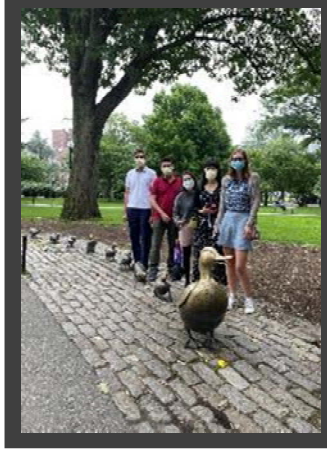

teresa_chen@meei.harvard.edu

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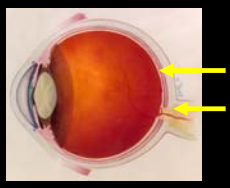
Getting Your Patients to Play on the Glaucoma Team

Paul Palmberg, MD, PhD
Bascom Palmer Eye Institute
University of Miami Miller School of Medicine
No relevant disclosures for this talk

Glaucoma Training Camp

- Explaining the Nature of the Game
- The Referees and Scoring System
  - Watching the Optic Nerve
  - Testing its Function
- A Winning Plan for Each Condition of the Field
- Drills: Three-step Drops
- Visual field tips
  - Keeping Appointments (Team Meetings)
- Good Players Overcome:
  - Understand their role, communicate, adjust to changes in strategy

What is Glaucoma?



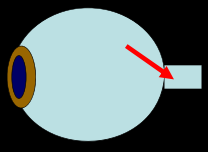
•Glaucoma is an illness of the optic nerve, the nerve that carries the electrical signals for sight from the retina to the brain.

What is Glaucoma?

- The exact cause is not known, but usually glaucoma is associated with a higher than average pressure inside the eye, which may reduce the blood flow that nourishes the nerve where it exits the eye at the “optic nervehead”.

What Damages the Optic Nerve in Glaucoma?

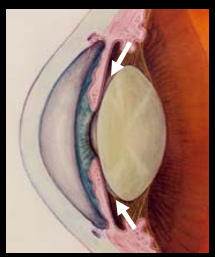
- **Pattern of Loss tells us the site of damage: the optic nervehead**
- **A likely mechanism: A pressure-related blockade of axoplasmic transport**
- **Anderson 1974**



Blockade of material (white) at the optic nerve head in a monkey with high eye pressure

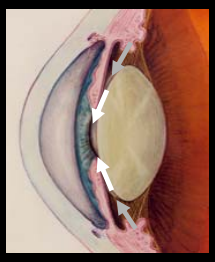
What is Glaucoma?

- The eye pressure depends upon the amount of a clear nourishing fluid that is transferred into the eye



What is Glaucoma?

- The eye pressure depends upon the amount of a clear nourishing fluid that is transferred into the eye to inflate it and to feed the lens and cornea (which have no blood vessels to feed them)



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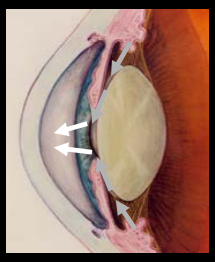

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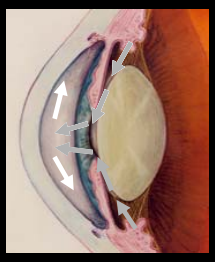
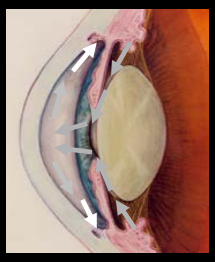


What is Glaucoma?

- The eye pressure depends upon the amount of a clear nourishing fluid that is transferred into the eye to inflate it and to feed the lens and cornea (which have no blood vessels to feed them) and upon the resistance to the exit of fluid through a drainage area.



What is Glaucoma?

- There are many types of glaucoma, each named for special features. Most are chronic conditions which can be treated successfully, but not cured, by lowering the eye pressure to prevent additional loss of sight.
- Some people have an elevated eye pressure, but not yet any nerve damage, a condition named "ocular hypertension". They require monitoring and sometimes treatment is a good idea if the risk of developing damage is high enough.
- The Glaucoma Foundation has nicely illustrated information available on the Internet at: glaucoma.org

The Scoring System

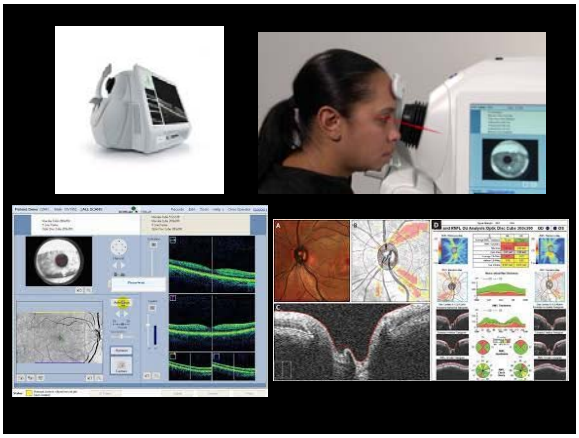
- Structure of the Optic Nerve

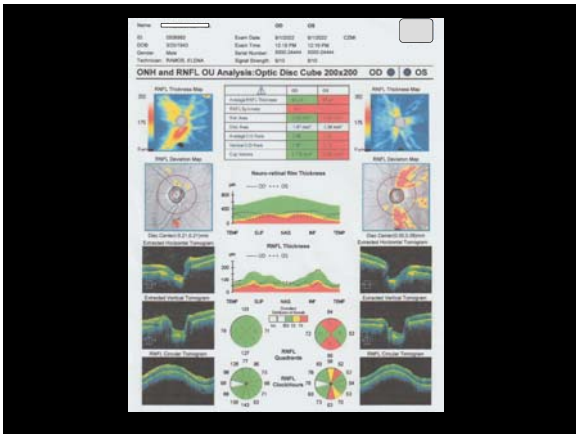
Obsolete way: Optic disc drawings—inaccurate, not done 50% of time

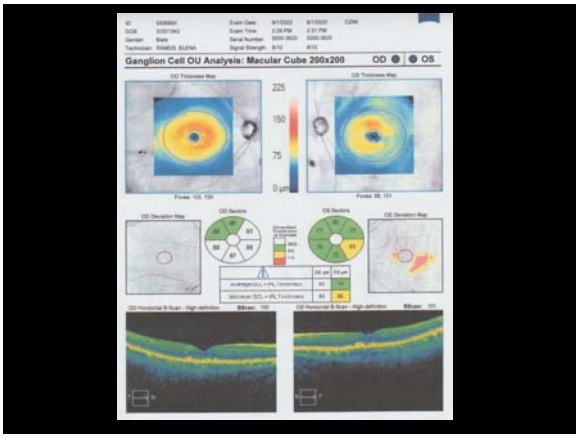
Optic disc stereophotography—semi-quantitative, still useful

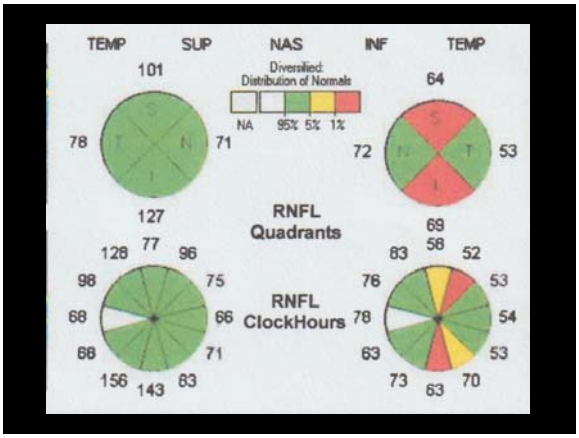
GDx (Laser Polarimetry)—out of favor now
optical rotation, generally proportional to structure
Heidelberg Retinal Tomography—out of favor now
(confocal reflectance from surface), shape rather than tissue depth

Optical Coherence Tomography (laser interferometry)
true structure—4 micron resolution
(Technique offers the huge advantage that it can also be used to monitor macular disease)





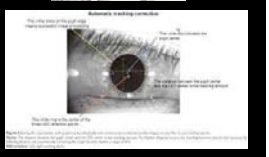




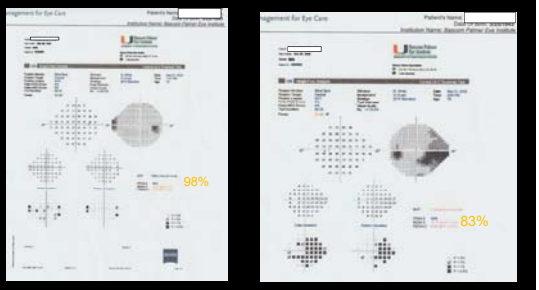
The Scoring System

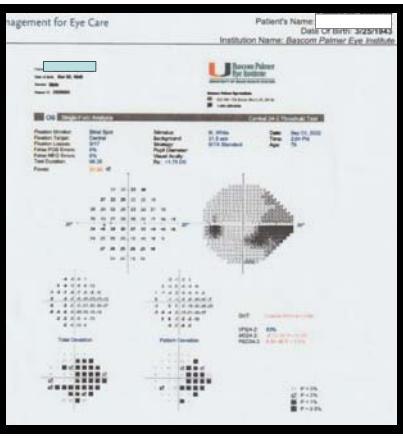
- Function of the Optic Nerve
  - Obsolete ways:
    - Tangent screen
    - Goldmann Kinetic Perimetry
  - Standard Automated Perimetry
  - Experimental ways:
    - Frequency Doubling Perimetry
    - Short-wavelength Perimetry
    - Pattern Electroretinogram (PERG)

Automated Perimetry



Perimetry Pearl: Tell the patient "You can control the test! Holding down the clicker pauses the test. Your speed of response controls the testing rate.





Which is Lost First, Structure or Function?

Several papers in the 1970s reported that structural damage generally preceded visual field loss. A mythical paradigm was adopted that it was always so

- Reed RM, Spaeth GL. TAAOO 1974;78:255
- Sommer A, Pollack I, Maumenee AE. Arch Ophthalmol 1979;97:1444
- Shiose Y. Glaucoma 1979;1:41
- Grant WM, Burke JF. Ophthalmol 1982;89:991

The Paradigm was Updated by Quigley and then Weinreb with Quantitative Methods

Once Vision Loss Is Detected
Substantial Structural Damage Has Already Occurred

- "Patients may lose up to 40% of their optic nerve fibers before damage can be detected."
- "Patients may lose up to 90% of their nerve fibers before they notice symptoms."

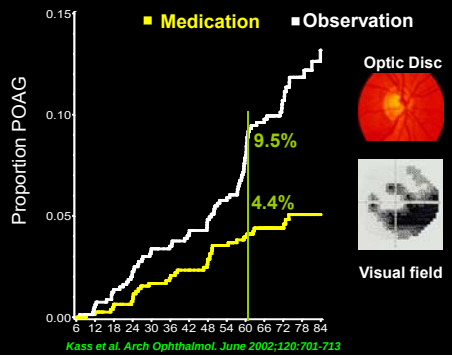
Quigley HA, et al. *Arch Ophthalmol.* 1982;100:135-146.

Consequences of Adopting the Myth

- It brought proper attention to looking for structural changes—a big plus
- It led to an inappropriate aggressiveness with medication and even surgery to treat ocular hypertension for fear of "losing half of the optic nerve" and fear that "once damage occurs it is difficult to halt progression"

OHTS Primary POAG Endpoints*

Log Rank P-value <0.001, Hazard Ratio 0.40, 95% CI (0.27, 0.59)



Kass et al. Arch Ophthalmol. June 2002;120:701-713

First POAG Endpoint per Participant
Structural Change Does Not Always Happen First

	Medication		Observation	
	N	%	N	%
Visual Field	15	41.7	29	32.6
Optic Disc	18	50.0	51	57.3
Concurrent Visual Field and Optic Disc	3	8.3	9	10.1
Total	36	100	89	100

55% detected only in disc, 35% only in field

Long-term Follow Up – Not so Benign

OHTS began with 1,636 patients, ran from Feb 1994 to Dec 2008.
Mean age 55 years, 57% women, White 70%

OHTS 20 year follow-up till April 2019. (515 had died)
After a median 20.2 years: The cumulative incidence was:
Black incidence 55%
White incidence 43%
.
Of the 46% with POAG, 25% had field loss.

The OHTS prediction model: OHTS@WUSL.org
Low risk: 32%
Medium risk: 48%
High risk: 60%

As a disc reader I was disappointed to see that many of the patients had advanced glaucoma, despite having been followed the whole time

What Was Said About Glaucoma Management 65 Years Ago

The New Orleans Academy of Ophthalmology 1957

In "What is Good Medical Control" by AE Maumenee:

"Good medical control is that treatment which will prevent a patient with glaucoma from losing visual function."
"Once the diagnosis has been established miotics should be prescribed in sufficient amount to maintain an intraocular pressure of below 24 mm Hg throughout the day." (Pilocarpine, Epinephrine and Acetazolamide).

However, in Normal Tension Glaucoma, 12-15 or operate

Back to the Future

Paul Chandler said it best (AJO 1960):

- "Eyes with advanced glaucoma…require a pressure below the average normal…"
- "Eyes with limited cupping , confined to one pole of the disc, appear to withstand tension better…"
- "Eyes with a normal disc appear to withstand pressure well…over many years…"
- "The appearance of the disc may serve as an important guide to the management of glaucoma."

What Was Said About Glaucoma Management 50 Years Ago

- In the VI International Symposium on glaucoma , 1973, in "When and How to Change Therapy" Bernard Schwartz suggests "control of less than 21 mm Hg", with progression then attributable to "spikes in pressure" or "non-compliance".
- Douglas Anderson: "We like to see the intraocular pressure below 20 in most cases, and …if there is severe damage to the optic nerve, less than 15."

Glaucoma Outcomes
How Well Had we Done?
(with Target Pressures in the Upper Teens

•VISUAL FIELD PROGRESSION

•:Hart and Becker, 1982: 73% worse in 10 years
•Chauhan and Drance, 1992: 58% worse in 7.4 yr
•Tezel, et al., 2001: up to 60% worse in 5 years

•BLINDNESS

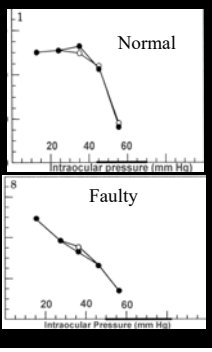
•Hattenhauer, 1999: **12% blind** in 12 years
•Royal Leicester Clinic, 2000: 34% blind in 20 yr
•COULD WE DO BETTER THAN THAT?
•Does pressure really matter all that much?

What Damages the Optic Nerve in Glaucoma?

If axoplasmic transport blockade is due to faulty auto-regulation of optic nerve blood flow

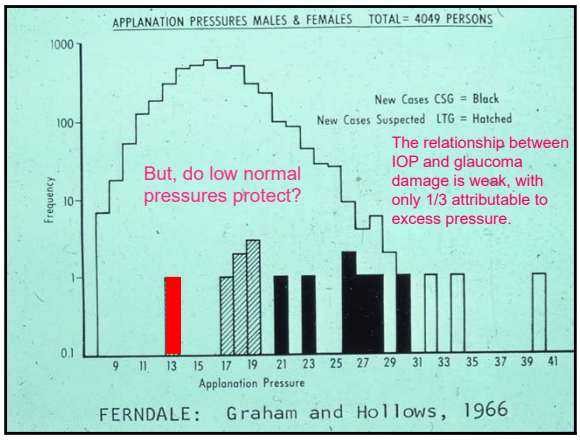
We might be able to compensate for it by reducing the IOP to venous pressures, 8-12 mm Hg

This would be unlike diabetes or systemic hypertension, where upper normal is optimal



The Pressure-Dependence of Glaucoma Damage

- Why would anyone need a low-normal pressure?
- Epidemiological studies suggest that only a third of glaucoma damage is associated with an excess pressure
- Yet, they also suggest that the lower the IOP, the lower the prevalence of glaucoma, so that low-normal pressures may protect the most vulnerable nerves, and that nearly all glaucoma is pressure-dependent
- Thus, IOP values near episcleral venous pressure may compensate for whatever else is wrong in glaucoma, by improving blood flow to the optic nerve, or equalize the pressure gradient at the optic nervehead.

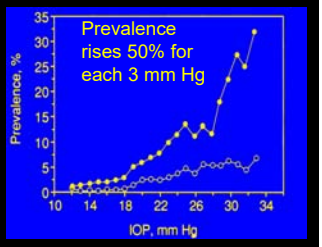


Nature's Experiment-Epidemiology

The lower the better?

- There is a "dose-response relationship" between the IOP and the risk of VF damage
- In the general population: Baltimore Eye Study Data

Prevalence of POAG in Relation to Screening IOP



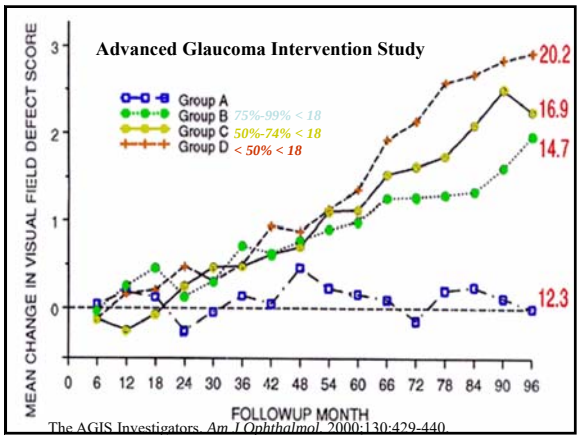
Sommer A, et al. *Arch Ophthalmol.* 1991;109:1090-1095.

How Much of Glaucoma Damage is Pressure-Dependent?

- **1987 Eddy and Billings pointed out that we had very little information about how much patients were benefited by medical therapy of glaucoma versus the natural history**
- **1989 American Academy of Ophthalmology Preferred Practice Pattern for POAG 1989 outlined the rationale and effectiveness of glaucoma therapy, and I introduced the term "target pressure"**
- **1999-2003 Results of Clinical Trials have clarified the effect of IOP and given us evidence-based guidance for treatment of patients with specific glaucoma conditions**

What Pressure Reduction is Suitable?

- **Advanced Glaucoma Intervention Study (AGIS) supports a 35-50% IOP reduction, CSI-Miami confirms**
- **Collaborative Normal-Tension Glaucoma Study (CNTGS) supports a 30% IOP reduction**
- **Collaborative Initial Glaucoma Treatment Study (CIGTS) supports a 30-35% IOP reduction.**
- **Ocular Hypertension Treatment Study (OHTS) supports a 20-30% IOP reduction and a consideration of the CCT**



The AGIS Investigators. *Am J Ophthalmol.* 2000;130:429-440.

The Collaborative Normal Tension Glaucoma Study:

Observation versus 30% reduction (Ta 16 to11 mm Hg)

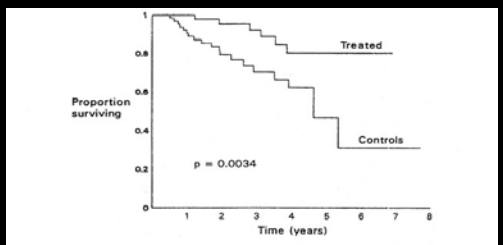
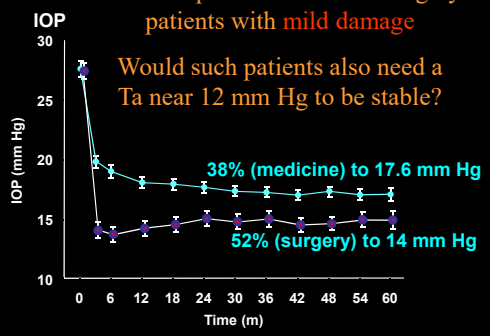


FIGURE 4. Survival curves of untreated control subjects and treated patients from randomization using the "four-of-five" end points after eyes that developed a cataract were censored.

Collaborative Initial Glaucoma Treatment Study (CIGTS)

- CIGTS is comparing initial medical treatment to initial surgery in newly diagnosed patients with glaucoma (with only minimal damage, HVF MD -5 dB).
- In the medical arm, a **38% reduction** of IOP from 27 to 17.5 mm Hg resulted in **no net visual field progression**, and a better quality of life than in the surgical arm.
- Surgical patients had IOP reduced 52% to 14 mm Hg, and also had on average stable visual fields.

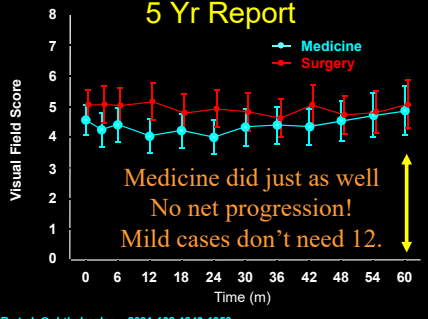
CIGTS compared medicine to surgery in patients with mild damage



Lichter PR et al. *Ophthalmology.* 2001;108:1943-1953.

Collaborative Initial Glaucoma Treatments Study CIGTS

Visual Field Score 5 Yr Report



Lichter PR et al. *Ophthalmology.* 2001;108:1943-1953.

OHTS Primary POAG Endpoints*

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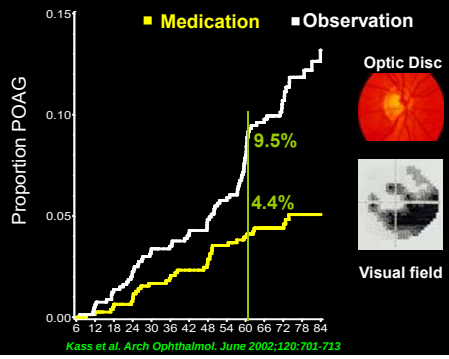


Kass et al. Arch Ophthalmol. June 2002;120:701-713

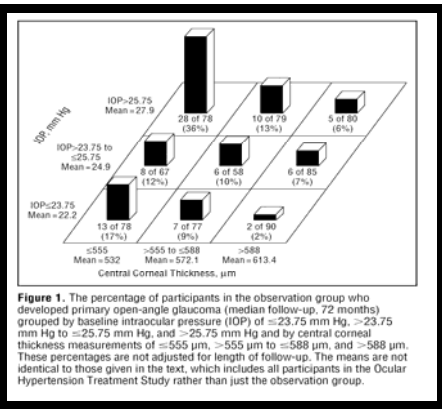
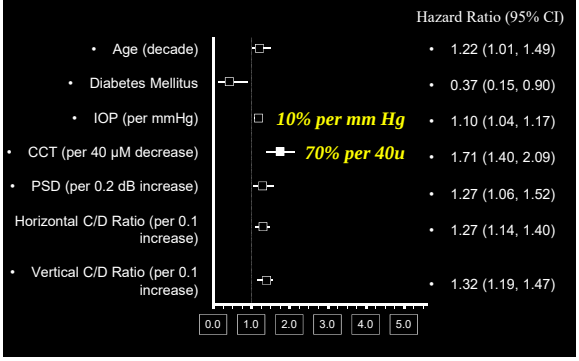


Figure 1. The percentage of participants in the observation group who developed primary open-angle glaucoma (median follow-up, 72 months) grouped by baseline intraocular pressure (IOP) of ≤23.75 mm Hg, >23.75 mm Hg to ≤25.75 mm Hg, and >25.75 mm Hg and by central corneal thickness measurements of ≤555 µm, >555 µm to ≤588 µm, and >588 µm. These percentages are not adjusted for length of follow-up. The means are not identical to those given in the text, which includes all participants in the Ocular Hypertension Treatment Study rather than just the observation group.

Significant Baseline Predictive Factors from Multivariate Proportional Hazard Models



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- **Ocular Hypertension Treatment Study (OHTS) supports a 20% IOP reduction (better if 30%)**

What can give us this much pressure reduction?

Medical Therapy of Glaucoma

CLASS	IOP reduction	Duration
Prostaglandins	25-33%	>24 hour action
Beta-blockers	18-27%	24 hour action
Alpha$_2$ Agonists	25% peak, 15% trough	8 hour action
CA Inhibitors	22% peak, 10% trough	8 hour action
DP Epinephrine	20% peak	12 hour action
Miotics	15-25% peak	6-12 hour action

Achieving Target Pressures at the High End of Response

	Latanoprost	Travaprost	Bimatoprost
13 mm Hg	11%	12%	10% AGIS
14 mm Hg	19%	19%	18%
15 mm Hg	27%	26%	29%
16 mm Hg	40%	33%	43%
17 mm Hg	52%	46%	59% CIGTS
18 mm Hg	65%	60%	68%
19 mm Hg	77%	72%	77%
20 mm Hg	84%	80%	82%
21 mm Hg	90%	83%	90% OHTS

Laser in Glaucoma and Ocular Hypertension (LiGHT) Trial at 6 Years

	SLT first	Drops first
IOP < target IOP (s meds)	68%	-------
Progression	20%	27%)
Trabeculectomy	2%	7%
Phaco	10%	17%

- Gazzard G, et al. Ophthalmology 2023;130:139-151

Compliance

- Meltzer-Kass Study—Electronic Monitor in Bottle

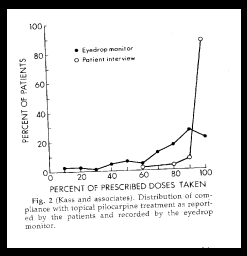


Fig. 2 (Kass and associates). Distribution of compliance with topical pilocarpine treatment as reported by the patients and recorded by the eyedrop monitor.

Subjects averaged 76% of prescribed doses

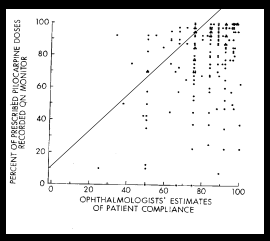
Subjects claimed 97%

6% took less than a quarter

15% took less than half

Doctors Can't Guess Compliance

- Meltzer-Kass Study—Electronic Monitor in Bottle Arch Ophthalmol 1984;102:1550; AJO 101:515
- Ophthalmologists estimated 92%, actual 76%, poor correlation of estimate and fact



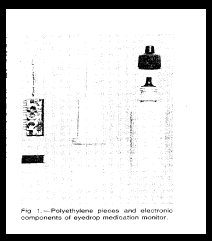
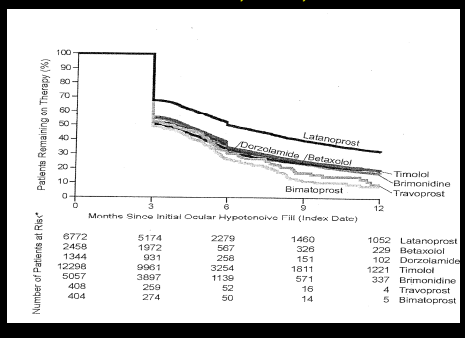
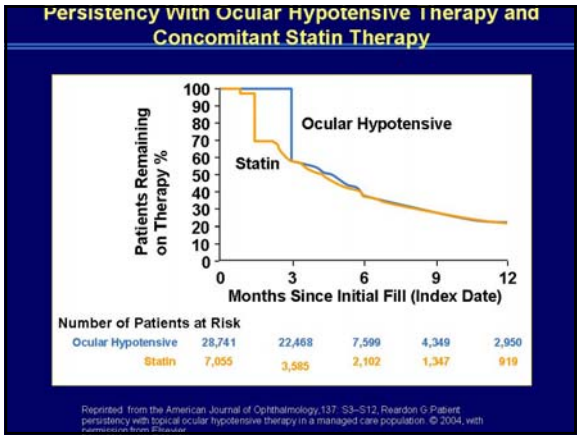


Fig. 1.—Polyethylene pieces and electronic components of eyedrop medication monitor.

Persistency in Drug Plan

- Data from Reardon, et al, AJO





Glaucoma History

- Personal or family history of glaucoma, elevated eye pressure, blindness
- History of eye injury, surgery, ocular disease, eye medication use, and systemic or local steroid use
- Visual disturbance, eye pain
- History of diabetes
- General review of symptoms (shortness of breath, cough), diseases (asthma, irregular heart beat, heart failure), meds use

Calcium Channel Blockers and Glaucoma in the UK Biobank

Kastner A, et al., JAMA Ophthalmology 2023;141(10):956-964

- Dihydropyridines (i.e. amlopidine, a calcium channel blocker), but not other classes of anti-hypertensive medications found to be a risk factor for glaucoma (diagnosis, thinner RNFL and mGCIPL) , but not IOP. RR=1.39 [95% CI 1.14 to 1.69].

- Amlopidine was begun in this case in 2020—relevant?
- Another class substituted in Jan 2024
- Patient said re amlopidine use "Not gonna do it, wouldn't be prudent".

Improving Compliance and Adherence Give a Written Plan!

- Written plan, using color coding:

Dorzolamide/Timolol twice a day, at breakfast and evening meal

Latanoprost daily at evening meal

Next appointment: October 7, 9 AM

The Bottle Cap Color System

- In existence for many years for Pilocarpine (green) and dilating drops (red).
- Expanded in about 1980 by American Academy of Ophthalmology Therapy Committee, suggested by Lee Duffner, MD, Hollywood, FL
- Yellow and blue: beta-blockers
- Orange, Purple for future antiglaucoma meds
- Gray, Brown, Pink for other classes of meds

Cap Colors for Glaucoma Meds

- Beta-blockers (yellow and blue)
- Carbonic Anhydrase inhibitors (orange)
- Alpha-agonists (purple)
- Pilocarpine (green)
- Prostaglandin analogues (teal)
- Post-operative meds: dilating (red) and steroids (pink or white)

How to Apply Eye drops

1. Pull down the lower lid to make a sack.
2. Grasp bottle (finger and thumb)
3. Rest palm of bottle hand on knuckles of hand holding lower lid down (aims, and avoids bottle tip touch to eye)
- Simple eyelid closure or compress NLD
- Wait 5 minutes between drops in an eye

1. Pull down eyelid

How to Apply Eye drops

1. **Pull down the lower lid to make a sack.**
2. Grasp bottle (finger and thumb)
3. Rest palm of bottle hand on knuckles of hand holding lower lid down (aims, and avoids bottle tip touch to eye)
- Simple eyelid closure or compress NLD
- Wait 5 minutes between drops in an eye

2. Grasp open bottle

How to Apply Eye Drops

1. Pull down the lower lid to make a sack.
2. Grasp bottle (finger and thumb)
3. **Rest palm of bottle hand on knuckles of hand holding lower lid down (aims, and avoids bottle tip touch to eye)**
- Simple eyelid closure or compress NLD
- Wait 5 minutes between drops in an eye

3. Palm on knuckles steadies hand, avoids touch

How to Apply Eye Drops

- Pull down the lower lid to make a sack.
- Grasp bottle (finger and thumb)
- Rest palm of bottle hand on knuckles of hand holding lower lid down (aims, and avoids bottle tip touch to eye)
- **Simple eyelid closure or compress NLD**
- **Wait 5 minutes between drops in an eye**

Simple eyelid closure for 5 minutes (induced by my lecture)

Nasolacrymal Duct Compression (Most people miss ducts, not worth it) If one squeezes, it pumps fluid into nose!

Inquire at Follow Up Visit

- What drops are you taking and when?
- Are you having any trouble remembering to take them?
- What are you using to remind yourself to take the drops? (Meals, alarm?)
- Are the drops causing you any discomfort, or do you have any new medical problems?
- Have you run out of any of them? Is cost a problem?
- Do you need someone to put them in, or to remind you to take them, or to get refills for you?

Patient-Related Factors

Personal
- Knowledge/skill
- Memory
- Motivation
- Comorbid disease
- Physical disabilities

Situational/Environmental
- Support
- Major life events
- Travel/away from home
- Competing activities
- Change in routine



Tsai JC et al. J Glaucoma 2003;12:393–398.

Systemic Medications and Glaucoma

- There are numerous warnings on over the counter and prescription medications regarding risk to glaucoma patients.
- With the exception of warnings about steroid ointments entering the eye or prednisone or cortisone by mouth, these are ridiculous! (Apply only to angle closure before a laser iridotomy, a non-existent group of people!)

Who Can Play on the Team

- Who can play on the team
  - Compliant patients
  - Ocular Hypertensives
- When do we send in a substitute?
  - Initial laser treatment for some with physical or mental disabilities and no one to assist
  - The patient who shows up with one eye already blind from glaucoma, and those who are non-compliant with meds or visits—OPERATE!

Getting Your Patients to Play on the Glaucoma Team

- Take the time at diagnosis to explain to the patient the disease, the reduction in risk of vision loss with treatment, and treatment options, and give written material or a website address.
- Develop a treatment plan that reaches an appropriate target pressure and makes adherence possible, with color-coded written instructions.
- Train patients or caregivers how to give drops, and check their ability and ask about compliance at next visit.
- Ask about impediments to adherence – side effects, cost, memory.
- Monitor the patient's condition with optic nerve imaging and visual fields, and discuss the results.
- That is a plan for a WINNING TEAM!