Technology in early glaucoma detection

GLAUCOMA

Over 3 million Americans are estimated to have glaucoma

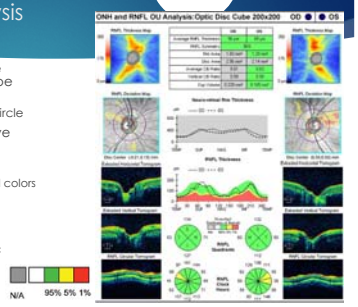
But…

OVER 64 MILLION SUSPECTED CASES WORLDWIDE

Leading cause of irreversible blindness

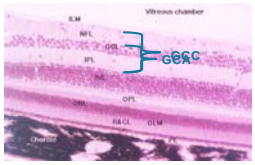
To review: ONH and RNFL Analysis

- Based on 6mmx6mm data cube captured by the "Optic disc cube 200x200" scan
  - 3.46mm diameter Calculation Circle
- Color coded based on normative database
- RNFL thickness map
  - Hourglass shape of yellow and red colors in normal eyes
- RNFL deviation map
  - Deviation from "normal"
  - Shows boundaries of cup and disc
- RNFL Quadrants/clock hours



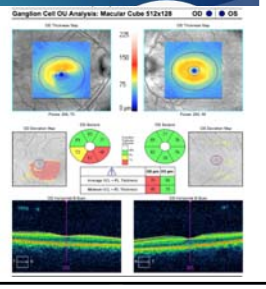
What is the "ganglion cell complex"?

- Ganglion Cell Complex (Optovue)
  - Inner plexiform layer
  - Ganglion cell layer
  - Nerve fiber layer
- Ganglion Cell Analysis (Zeiss Cirrus)
  - Inner plexiform layer
  - Ganglion cell layer



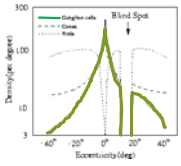
Ganglion Cell Analysis

- Derived from a macular cube scan
- Color-coded thickness based on normative database
- Thickness map
- Deviation map
- Sectors/cross-sections



Macular ganglion cell thickness in early glaucoma detection

- Densest population of ganglion cells is within the central macula
- Less variability, more reproducibility than optic disc RNFL scan
- May be easier to obtain reliable, high quality scan



http://utw10503.utweb.utexas.edu/research/eyefix/index.php

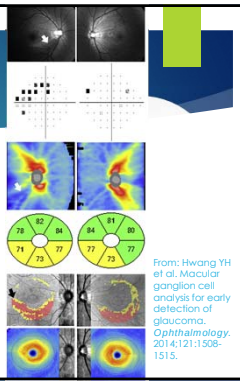
But… it can be misleading!

- "Normal" GCA in glaucomatous eyes
  - Small areas RNFL thinning (superior)
  - Mild visual field loss
- "Abnormal" GCA in healthy eyes
  - May occur in high myopia
  - Most often within inferior sectors

GCA in myopes

- Myope **with** glaucoma (left)
- Myope **without** glacuoma (right)

- Both eyes show abnormal GCA
  - Horizontal raphe
  - Nasal vs. temporal defects



From: Hwang YH et al. Macular ganglion cell analysis for early detection of glaucoma. *Ophthalmology*. 2014;121:1508-1515.

Case example: GCA scan for a glaucoma suspect

- P.C., a 63-year-old AA male, presented for a glaucoma w/u due to suspicious optic nerve appearance at initial exam
- Medical Hx:
  - High cholesterol (atorvastatin)
  - Anxiety (unknown med)
- Drug allergies: codeine

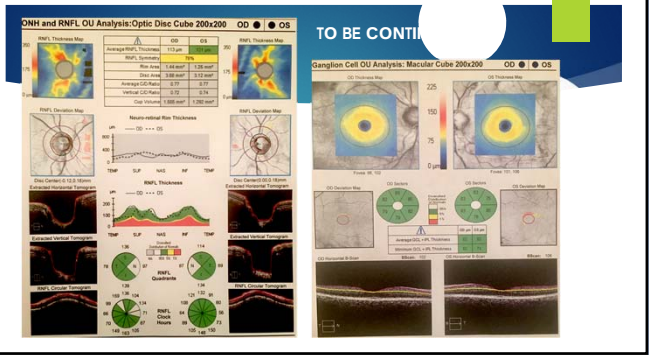
- Vitals
  - BP: 100/60
  - 208 lbs, 6'1

Entrance testing & SLE

- VAcc: 20/20 OD, 20/20-1 OS
- PERRL (-) APD OU
- Confrontations FTFC, EOMs FROM OU
- IOP: 14/14 mmHg (consistent w/ previous exam 1 yr ago)
- Pachymetry: 476/477 µm
- SLE:
  - Unremarkable except for 1+ NS OU
  - VH 1+ OD, OS
  - Gonio: posterior TM 3 quads OU

DFE

- Optic nerve:
  - 2.5 mm in height OU
  - Large, deep cups
  - Symmetrical rim tissue (-) notching
  - C/D 0.8/0.8 OD, 0.75/0.75 OS
- Macula: flat with even pigment, (+) FLR OU
- Vasculature: good caliber OU



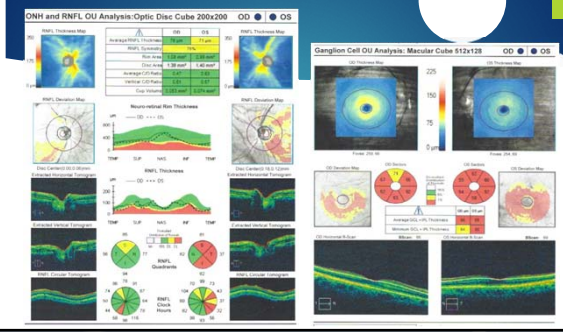
OCT GCA: Just for glaucoma?

- J.H., a 60-year-old AA female
  - Presented to UMSL Patient Care Center for a glaucoma work up (suspicious ONH appearance)
  - Pt had no complaints except for "blur at near"
- Medical Hx
  - Hypertension (controlled with amlodipine), hypercholesterolemia (controlled with atorvastatin, HCTZ), borderline diabetic (diet-controlled, last A1C 7%)
- Social Hx/Vitals
  - Social drinker, non-smoker
  - BP: 135/78

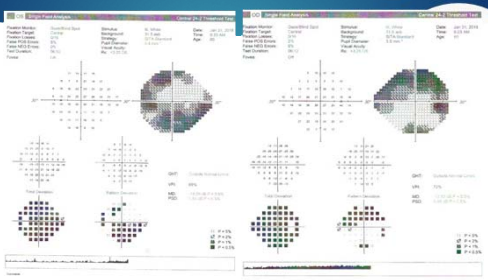
Entrance testing/SLE

- VAsc: 20/20 OD, OS
- Pupils: PERRLA (-) APD OU
- EOM's FROM; Confrontations FTFC OU
- HRR Color testing: 4/6 OD, OS → mild R/G defect OU
- IOP: 18/16 mmHg
- Anterior segment evaluation: Unremarkable
  - PCIOL OU, clear, well-positioned

DFE:



24-2 SITA-Standard Visual field



Assessment and Plan

- Is this glaucoma?
- Referral to neuro-ophthalmology
  - Ordered MRI of brain and orbit with and without contrast
- Diagnosis
  - Large sphenoidal meningioma encasing both optic nerves with effects on chiasm
  - Patient underwent surgery for removal

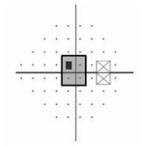
GCA in summary

- Additional puzzle piece when evaluating patients for early glaucoma
- May suggest closer monitoring
- Consider patient's refractive error in the presence of "abnormal" findings

10-2 perimetry in early glaucoma detection

- 24-2 testing: what are we missing?
  - Only 4 test points within the macula
  - Points spaced 6 degrees apart
  - Paracentral scotoma: common early field defect

VF 24-2



From: Park HL et al. Clinical clues to predict the presence of parafoveal scotoma on Humphrey 10-2 Visual Field using a Humphrey 24-2 Visual Field. *Am J Ophthalmol.* 2016;161:150-159.

10-2 testing in the literature

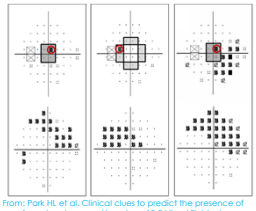
- Traynis et al. (2014)
  - **22%** of open-angle glaucoma suspects showed clear 24-2 but abnormal 10-2 fields
- De Moraes et al. (2017)
  - **35%** of ocular hypertensives showed abnormal 10-2 fields
- Detecting *progression* of paracentral loss
  - **70%** of eyes with central progression were missed by 24-2 testing (Park et al. 2013)

Predicting a 10-2 defect

- Park et al. (2016)
  - 75% of glaucomatous eyes found to have a paracentral scotoma on 10-2 VF test
- **Predictive factors of 24-2 VF:**
- Any central points at **p<0.5%**
- Abnormal **PSD** greater than the MD
- Any central points correlating to **GCA OCT**

VF 24-2

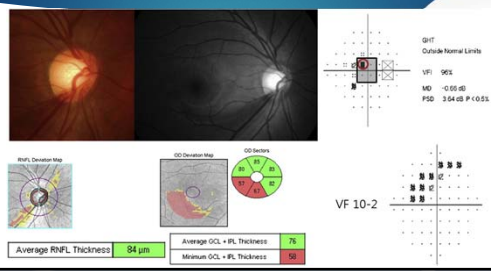
VF 10-2



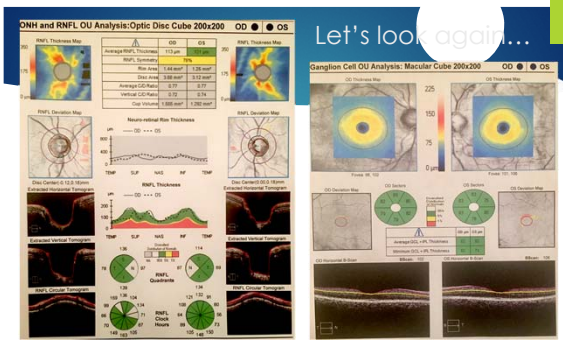
From: Park HL et al. Clinical clues to predict the presence of parafoveal scotoma on Humphrey 10-2 Visual Field using a Humphrey 24-2 Visual Field. *Am J Ophthalmol.* 2016;161:150-159.

Applying the interpretation: an example

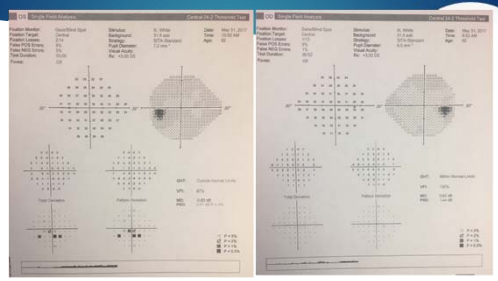
From: Park HL et al. Clinical clues to predict the presence of parafoveal scotoma on Humphrey 10-2 Visual Field using a Humphrey 24-2 Visual Field. *Am J Ophthalmol.* 2016;161:150-159.



Let's look again...



24-2 SITA-Standard VF



Assessment/Plan

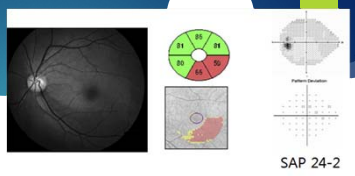
- Dx: Megalopapilla OU; Glaucoma suspect OU
- Continue to monitor closely
  - RTC 3 months repeat 24-2 SS VF, **10-2 SS VF OS**

Frequency doubling technology (FDT)

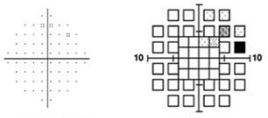
- Humphrey Matrix
  - May detect glaucoma earlier than traditional SAP
  - Isolates small population of ganglion cells (M-cells) through *spatial contrast sensitivity* testing
- Jung et al. (2017)
  - Paracentral damage detected **earlier with FDT 10-2** vs. SAP 10-2 in eyes with preperimetric glaucoma
  - 10-2 FDT correlated better with **GCA OCT results** compared to SAP
- FDT not as accurate as SAP for monitoring *change over time*

https://www.sciencedirect.com/science/article/pii/S0002939498000464

10-2 Visual Field: SAP vs. FDT



SAP 24-2



SAP 10-2 III

FDT 10-2

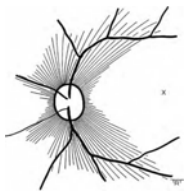
From: Jung KI, Park CK. Detection of functional change in preperimetric and perimeteric glaucoma using 10-2 Matrix perimetry. *Am J Ophthalmol.* 2017;182:35-44.

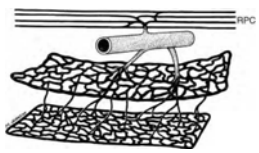
10-2 perimetry in summary

- Multiple field types for every glaucoma patient = impractical!
  - Consider 10-2 testing for dense central defect on 24-2 with high PSD
  - Look for **correlation** with RNFL/GCA thinning on OCT
- Once detected, consider alternating field types for best follow-up
- Consider 10-2 Matrix if available
  - Helpful for suspicious patients with normal SAP but GCC thinning on OCT

OCT Angiography in early glaucoma detection

- Radial Peripapillary Capillary Network

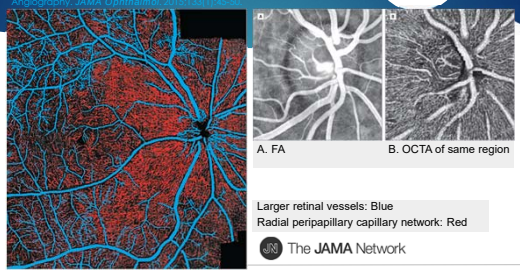




From: Henkind P. Radial Peripapillary capillaries of the retina. I. Anatomy: Human and comparative. Br J Ophthalmol. 1967;51(2):115–123.

Radial peripapillary capillary network

From: Retinal Vascular Layers Imaged by Fluorescein Angiography and Optical Coherence Tomography Angiography. *JAMA Ophthalmol.* 2015;133(1):45-50.



The JAMA Network

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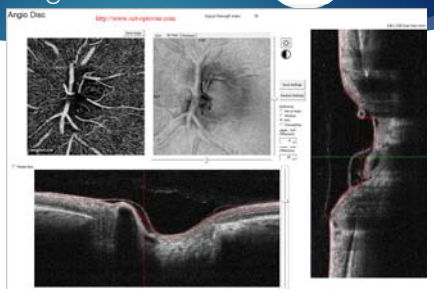
OptoVue Angio Disc

- Radial peripapillary capillary visualization



Glaucoma: Peripapillary vascular network

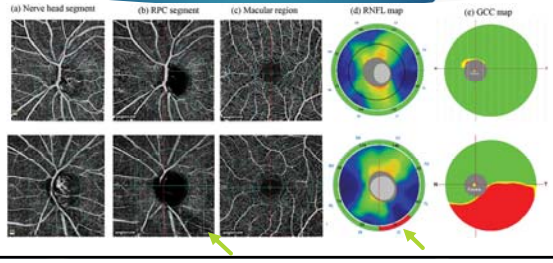
- Jia Y et al. (2014): **Optic disc flow index is reduced by 25% in glaucomatous eyes** - SS OCTA imaging
  - Flow index was highly correlated with visual field pattern standard deviation (PSD)
  - OCTA detected reduced perfusion in early glaucoma with 100% sensitivity and specificity
- Chen CL et al. (2016): Showed that **reduced peripapillary blood flux index had diagnostic ability** comparable to peripapillary RNFL thickness in glaucoma and glaucoma suspects
  - Again, significant correlation to visual field indices was observed
- Rao HL et al. (2017): Found **standard OCT parameters** (rim area, RNFL thickness, GCC) to have greater diagnostic abilities than the corresponding vessel densities in eyes with POAG
- Yarmohammadi A et al. (2017): **Vessel density measurements** showed stronger association with VF sensitivity measurements than did RNFL or GCC thickness

Glaucoma: Peripapillary vascular network

- Still unclear whether the structural damage or vascular abnormality comes first.
  - Lee EJ et al. (2016): Vascular change is a **consequence** of glaucomatous damage
  - Chen CL et al. (2017): Vascular damage **precedes** RNFL defect
- Conflicting data on diagnostic/predictive power of OCTA
  - Many discrepancies in methods, study design, OCT model used

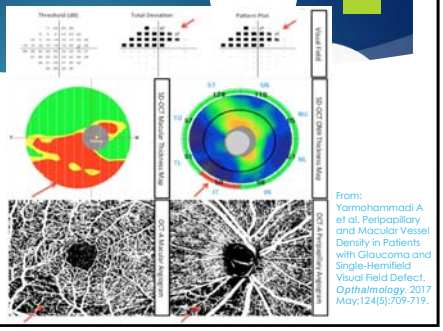
Vessel density compared to RNFL/GCC

From: Rao HL, et al. A comparison of the diagnostic ability of vessel density and structural measurements of optical coherence tomography in primary open angle glaucoma. *PLoS One*. 2017; 12(3): e0173930.

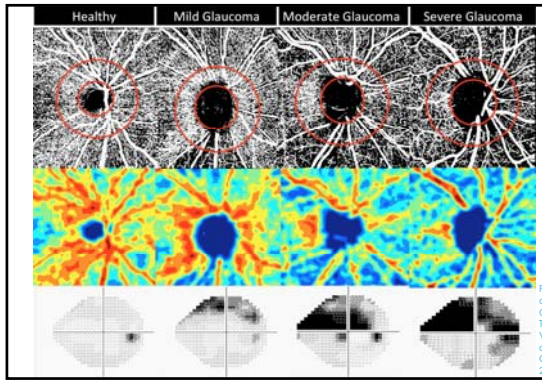


Vessel density corresponding to VF loss

- Yarmohammadi et al. (2017)
  - Vessel density was found to correlate better than RNFL thickness to visual field loss in glaucoma



From: Yarmohammadi A et al. Peripapillary and Macular Vessel Density in Patients with Glaucoma and Single-Hemifield Visual Field Defect. *Ophthalmology*. 2017 May;124(5):709-719.



From: Yarmohammadi A et al. Relationship between Optical Coherence Tomography Angiography Vessel Density and Severity of Visual Field Loss in Glaucoma. *Ophthalmology*. 2016;123(12):2498-2508.

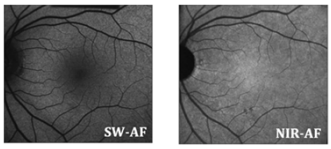
Fundus Autofluorescence (FAF)

BASED ON THE FLUORESCENCE OF "FLUOROPHORES" NATIVE TO THE EYE

Primarily within choroid/RPE

General principles of FAF

- Primary endogenous fluorophores of the eye
  - Melanin
  - Lipofuscin ***
- Two main types of FAF imaging
  - **Short-wavelength (SW-AF)**
  - Near-infrared (NIR-AF)



From: Greenstein VC, Schuman AD, Lee W, et al. Near-Infrared Autofluorescence: Its Relationship to Short-Wavelength Autofluorescence and Optical Coherence Tomography in Recessive Stargardt Disease. *Investigative Ophthalmology & Visual Science*. 2015;56(5):3226-3234.

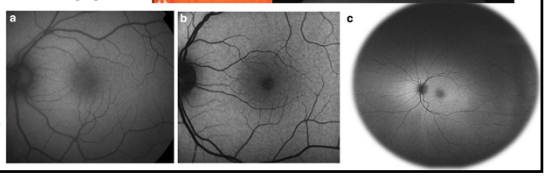
FAF: healthy retina

FAF interpretation

- Lipofuscin
  - Normal levels in all RPE
  - Increases with **age**
  - Increases in **retinal disease**
- General interpretation:
- Lipofuscin will ***hyperfluores*s on FAF**
- Non-functioning or missing RPE cells will ***hypofluores*s**
  - ***HYPER-***fluorescence: "sick/dying" RPE
  - ***HYPO-*** fluorescence: "Dead" (atrophic) RPE

FAF in Clinical Practice

- Confocal scanning laser ophthalmoscopy (cSLO)
- Digital fundus photography
- Ultra-widefield imaging



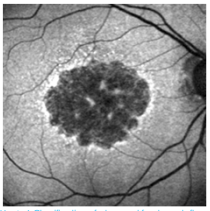
Yung et al. Clinical applications of fundus autofluorescence in retinal disease. Int J Retin Vitr (2016) 2:12.

When is FAF useful in a clinical setting?

Tsui I, et al. A practical approach to retinal dystrophies. *Retinal Physician*. 2007. Available at: https://www.retinalphysician.com/issues/2007/april-2007/a-practical-approach-to-retinal-dystrophies

FAF & Age-related macular degeneration

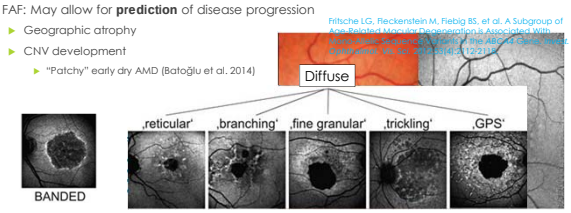
- Appearance with FAF
  - Focal hyperfluorescence (drusen)
  - Areas of hypofluorescence (RPE atrophy)
- Geographic atrophy: 10% of all vision loss
- FAF allows for visualization of full extent of the disease
- What about wet AMD?



Bindewald A, Schmitz-Valckenberg S, Jorzik JJ, *et al*. Classification of abnormal fundus autofluorescence patterns in the junctional zone of geographic atrophy in patients with age related macular degeneration. *British Journal of Ophthalmology* 2005;**89**:874-878.

FAF & Age-related macular degeneration

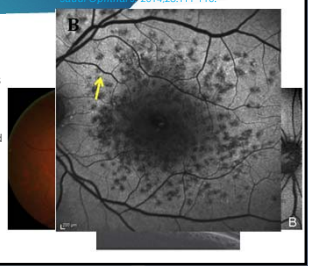
- FAF: May allow for **prediction** of disease progression
  - Geographic atrophy
  - CNV development
    - "Patchy" early dry AMD (Batoğlu et al. 2014)



Fritsche LG, Fleckenstein M, Fiebig BS, *et al*. A Subgroup of Age-Related Macular Degeneration is Associated With Monoallelic Sequence Variants in the ABCA4 Gene. *Invest Ophthalmol Vis Sci*. 2012;53(4):2112-2118.

FAF & Diabetic retinopathy

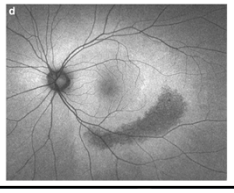
- Hyperglycemia in diabetes → free radicals → oxidative stress
- Reactive oxygen species (ROS) buildup leads to excess lipofuscin formation
- Calvo-Maroto et al. (2016)
  - Diabetic fundus changes more easily visualized with **FAF** than with **color fundus photography** (MA's, hemes)
- Vujosevic et al. (2011)
  - FAF showed 81% sensitivity in detecting cystoid macular edema (**hyperfluorescence**)



From Olsepah YJ et al. Fundus autofluorescence imaging: Fundamentals and clinical relevance. *Saudi Ophthal J*. 2014;28:111-116.

FAF & Hydroxychloroquine toxicity

- Plaquenil
  - May cause irreversible, parafoveal loss of photoreceptors → "Bull's eye" maculopathy
- FAF
  - Hyperfluorescent parafoveal ring
  - Hypofluorescence over time (RPE atrophy)
- Sensitivity of ~74% compared to mERG
- Early changes are often subtle
  - Best used as supplementary testing



Elsevier: Ophthalmolog, "Pericentral retinopathy and racial differences in hydroxychloroquine toxicity," 2015, pp. 110–116, Melles and Marmor, Fig. 1

Consider FAF imaging…

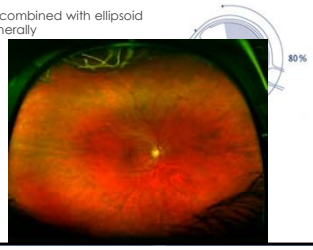
- In the case of unexplained vision loss
- For patients with macular degeneration or other retinal disease
- When patients are taking Plaquenil or other medications with known retinal toxicity

http://imagebank.asrs.org/file/7389/optic-disc-drusen

Ultra-Widefield (UWF) Imaging

Ultra-Widefield Imaging

- Uses confocal scanning laser technology combined with ellipsoid mirror for fundus imaging up to **200°** peripherally
  - **82.5%** of the retina
  - Dilation not required
- Available instruments
  - Heidelberg
    - Ultra-widefield contact lens (150°)
    - Ultra-widefield attachment (105°)
  - Zeiss CLARUS 500 (200°)
  - Optos OptoMap (200°)



Ultra-Widefield Imaging

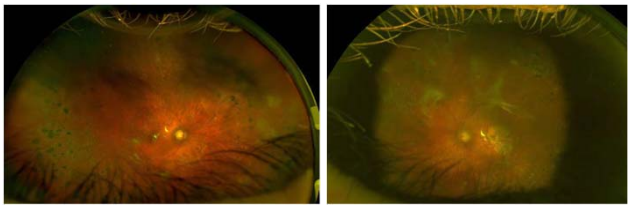
- "Pros"
  - Great way to document and aid in evaluation of peripheral retinal pathology
  - Look at the "big picture" all at once
  - Filters: FAF, red-free, choroidal visualization
- "Cons"
  - Lid/lash artifact
  - Pseudocoloration, peripheral distortion, low contrast
  - Still not imaging the ***entire*** retina!

Wessel MM et al. Ultra-Wide-field Angiography improves the detection and classification of diabetic retinopathy. *Retina*. 2012;32(4):785-791.

UWF Imaging: Diabetic retinopathy

- Silva et al. (2012)
  - Retinopathy classification (ETDRS): Optomap imaging vs. dilated fundus exam
- Wessel et al. (2012)
  - FA using Optos compared to traditional FA (75° field of view)
- Silva et al. (2014)
  - Ultrawide field imaging vs. non-mydriatic fundus photography for Telehealth program

PDR patient… deferred dilation



UWF Imaging: A dilation substitute?

- Not quite…
- Dilation: essential for stereoscopic evaluation of the entire fundus
  - Required for all new patients
  - Malpractice considerations
- UWF imaging
  - Great supplement to dilation or "in between" dilated visits
- It's all in the presentation
  - Give the patient the "full story"

Consensus-Based Action Statement (AOA):
Pharmacologic dilation of the pupil is generally required for thorough stereoscopic evaluation of the ocular media, retinal vasculature, macula, optic nerve, and the peripheral retina.

Thank you!

"Doctor and physician are outdated terms. I'm your biological tech support specialist."

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