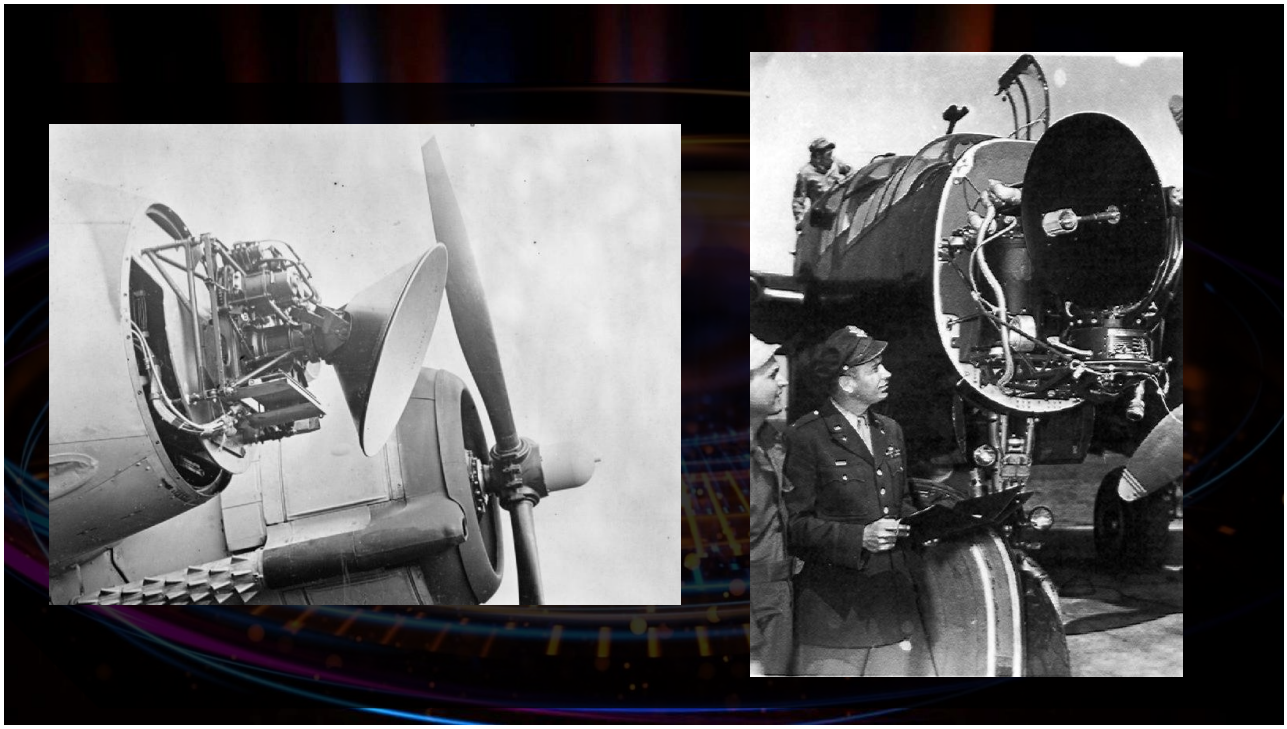

ICES 1 & 2
BRITISH PATHÉ
CARROTS
1D each
DOCTOR CARROT
the Children's best friend
VITA
NIGHT SIGHT
can mean LIFE or DEATH
EAT carrots and leafy green or yellow vegetables ... rich in Vitamin "A" essential for night sight.
SAVE

4



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The effect of bilberry nutritional supplementation on night visual acuity and contrast sensitivity

Alternative Medicine Review (2000) 5(2):164-173.

Purpose:
Investigation on the effects of bilberry on night visual acuity (VA) and night contrast sensitivity (CS).

Methods:
- Double-blind, placebo-controlled, crossover design using male subjects (25-47 years) with BCVA ≥ 20/20
- 8 received placebo and 7 received active capsules for 3 weeks.
- Active capsules contained 160 mg of bilberry extract (25% anthocyanosides)
- Subjects ingested one active or placebo capsule three times daily for 21 days.
  - After the 3-wk treatment period, 1-month washout period was employed to allow any effect of bilberry on night vision to dissipate.
  - In the second 3-week treatment period, the 8 subjects who first received placebo were given active capsules and the 7 who first received active capsules were given placebo.
- Night VA and night CS was tested throughout the 3-month experiment

Results:
- ***No difference in mesopic VA during any of the measurement periods***
- ***No difference in mesopic CS during any of the measurement periods***

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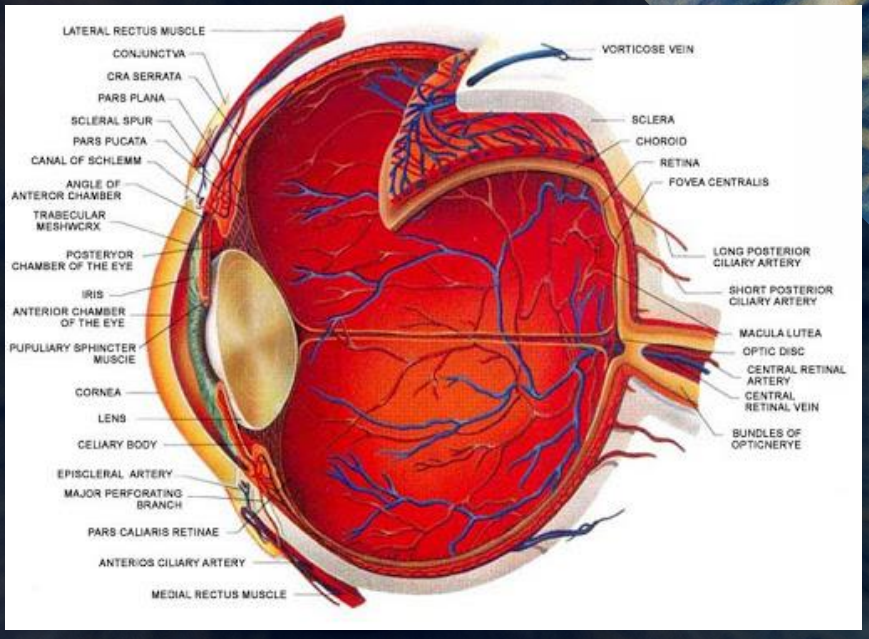
Ocular Anatomy and Physiology is…



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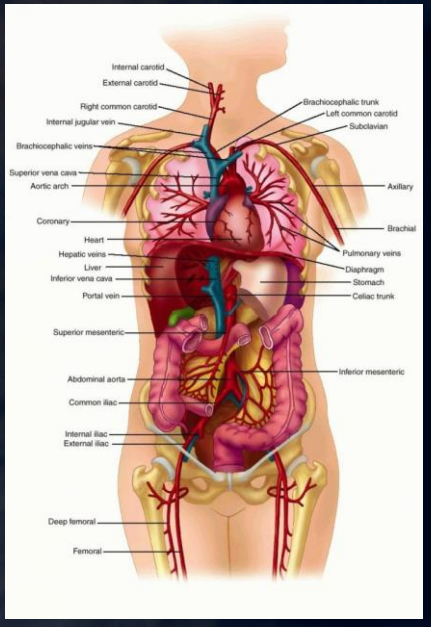
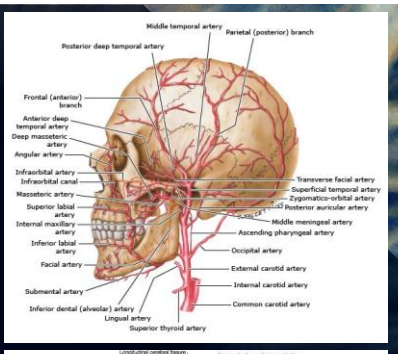
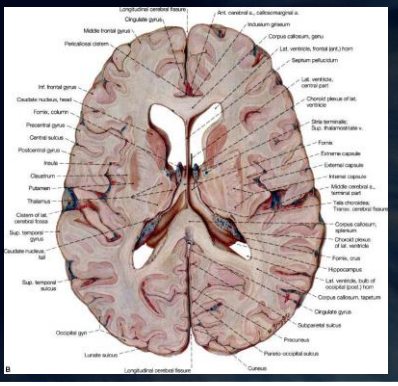
…Systemic Anatomy and Physiology







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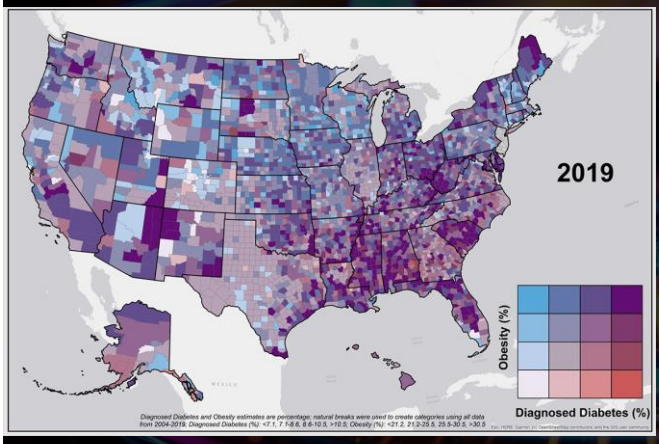
Clinical Retinopathy
Prevalence



20M Americans show clinical macular degeneration
- Estimated 5M persons undiagnosed

27M Americans diagnosed with diabetes
- Estimated 8M persons undiagnosed

- ***35% of patients >65 have diabetes and/or AMD clinical findings***

88M Americans have clinical retinopathy risk
- Age
- Family History ***(Genetic Predisposition)***
- Ethnicity
- Smoking
- CVD ***(Advanced / Exudative retinopathy)***
- Obesity
- Diet low in fruits/vegetables and Ω-3 FAs

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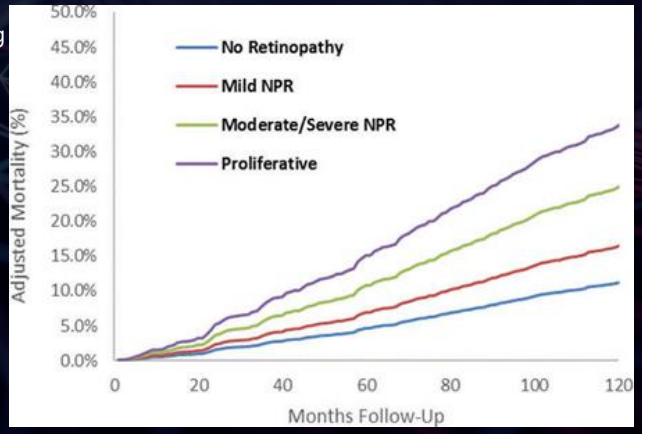
Clinical Retinopathy
Pathogenesis

Methods
- Data were obtained from the US National Health and Nutrition Examination Surveys from 2005 to 2008, with linked mortality through 2015. Severity of retinopathy was defined as no retinopathy, mild NPDR, moderate-severe NPDR and PDR

Results
- 5,543 participants (mean age 56±12) with retinal imaging
  - 696 showed retinopathy
  - 289 suffered a stroke
  - 597 developed dementia
- Retinopathy was associated
  - ***Higher risk of stroke (adj OR 2.39)***
  - ***Dementia (adj OR 1.68)***
- Over median duration of 118 months, dose-dependent relationship between severity of retinopathy and all-cause mortality.



Conclusions
- ***Retinopathy confers higher risk of morbidity and mortality after adjusting for age and vascular risk factors***

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OCULAR PHYSIOLOGY + SYSTEMIC DISEASE

- Retina is a ***highly metabolic neurological tissue*** with a ***microvascular supply*** originating at the internal common carotid artery
- Retinal imaging can be achieved ***in vivo with resolution limits of ~5µm***
  - ***Compare 4T MRI spatial limits of ~1mm***
- Subclinical vascular and neurological changes that manifest as retinal dysfunction can ***precede clinical symptoms by months to years***
- Although the diversity of systemic disease is broad, shared characteristics with the eye include:
  - ***Inflammation***
  - ***Oxidative Stress***
  - ***Mitochondrial dysfunction***

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Clinical Retinopathy

Pathogenesis – Microvascular insults

Retinal Microvascular Abnormalities and MRI-Defined Subclinical Cerebral Infarction: Atherosclerosis Risk in Communities Study

Stroke (2016) 37: 82-86

Methods

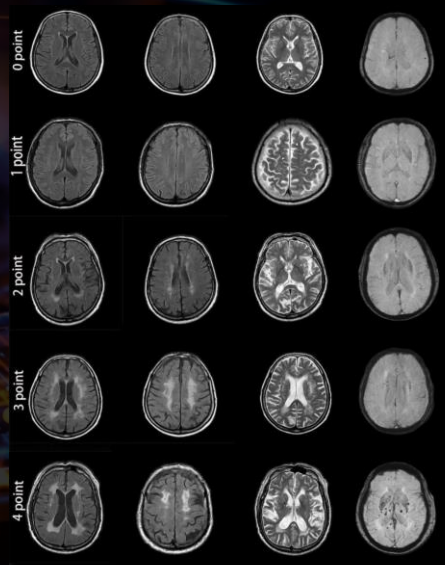
- 1684 persons 55 to 74 years of age ***without*** history of clinical stroke
- Retinal photographs were graded for microvascular abnormalities, A/V nicking, arteriolar narrowing, retinal hemorrhages, soft exudates and MA
- MRI scans graded for presence of cerebral infarct imaging characteristics

Results

- Total of 183 MRI cerebral infarcts adjusted for age, gender, race, 6-year MAP, DM and other stroke risk factors, cerebral infarcts were associated with retinal microvascular abnormalities
- **Odds Ratios**
  - **A/V nicking = 1.90**
  - **Focal arteriolar narrowing = 1.89**
  - **Blot hemorrhages = 2.95**
  - **Soft exudates = 2.08**
  - **Microaneurysms = 3.17**

Conclusions

- ***Retinal microvascular abnormalities are associated with MRI-defined subclinical cerebral infarcts independent of stroke risk factors***



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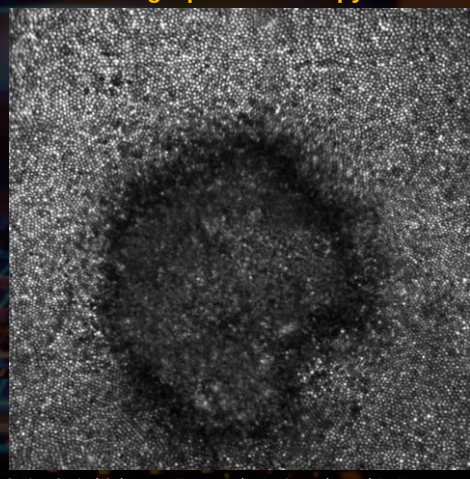
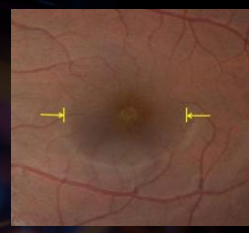
Clinical Retinal Imaging

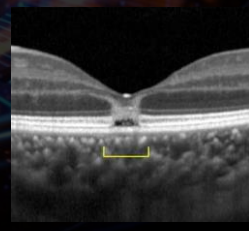
Solar Retinopathy viewed through Adptive Optics

Photographic Image of Solar Eclipse

AO Scanning Ophthalmoscopy







Wu, Chris Y., et al. "Acute Solar Retinopathy Imaged With Adaptive Optics, Optical Coherence Tomography Angiography, and En Face Optical Coherence Tomography." *JAMA Ophthal* (2017).

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Systemic Diagnosis and Mangement

- **Vasculopathies**
- Neurodegenerative
- Autoimmune
- Collagen Vascular Disease

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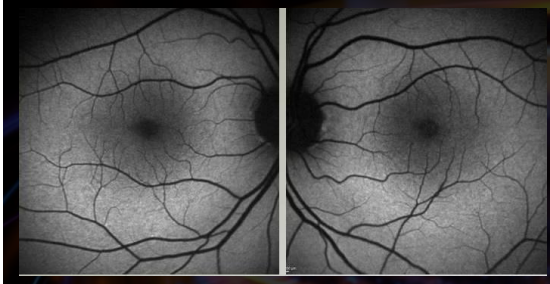
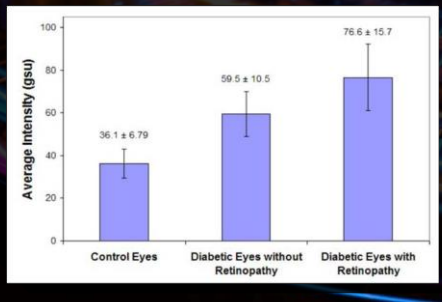
Vasculopathies
Diabetes Mellitus





- Worldwide prevalence is estimated at 483M
  - ~50% of diabetics are undiagnosed
- Estimated 5M diabetes related deaths in 2019
  - ~50% were < 60 years old

Retinal flavoprotein FAF as a measure of retinal health
*Transactions Am Ophthal Society (*2018) 106:215

- ***6-hour transient hyperglycemia results in significant 6-day increase in mitochrondrial ROS***
  - ***Underlying cause of diabetic retinopathy***
- FAF imaging of retinal flavoproteins can detect *in vivo* mitochondrial ROS
- Zeiss FF4 fundus camera using 467nm excitation and 535nm emission filters with electron-multiplying, charge-coupled device (EMCCD)

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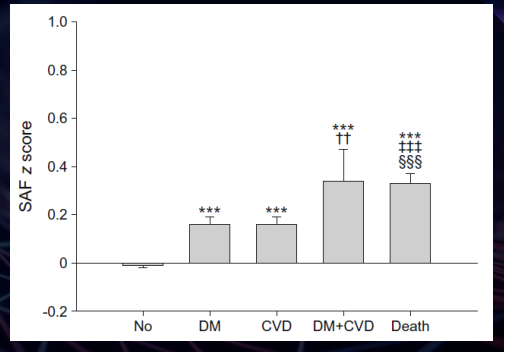
Vasculopathies
Diabetes Mellitus

Skin autofluorescence predicts incident DMII, CVD and mortality in the general population
Diabetologia (2019) *62*:269-280

Methods
- 72,880 participants ***without*** DM or CVD underwent baselin skin AF values
- Participants were diagnosed with incident DMII by a fasting blood glucose ≥126mg/dL or HbA1c ≥ 6.5% at follow-up.
- Participants were diagnosed as having incident CVD
  - MI, coronary interventions, CVA, TIA or vascular surgery

Results
After a median follow-up of 4 years, 1056 participants (1.4%) developed DMII 2, 1258 individuals (1.7%) were diagnosed with CVD while 928 (1.3%) had died.
- Baseline skin AF was elevated in participants with incident DMII, CVD and mortality compared with individuals who survived and remained free of the two diseases
- ***Skin AF predicted the development of DMII, CVD and mortality independent of metabolic syndrome, glucose and HbA1c.***

Conclusions/interpretation
- ***Non-invasive skin AF measurement shows clinical value for screening for future risk of DMII, CVD and mortality independent of glycemic measures and metabolic syndrome***



Baseline SAF at *4-year* follow-up shown as mean ± SE
No DMII/CVD: 69,749 **DM**: 977 **CVD**: 1171
DM+CVD: 55 **Death**: 928

***p < 0.001 vs no type 2 diabetes/CVD group;
††p < 0.005 (women only) vs DM group;
‡‡‡p < 0.001 vs DM group;
§§§p < 0.001 vs CVD group

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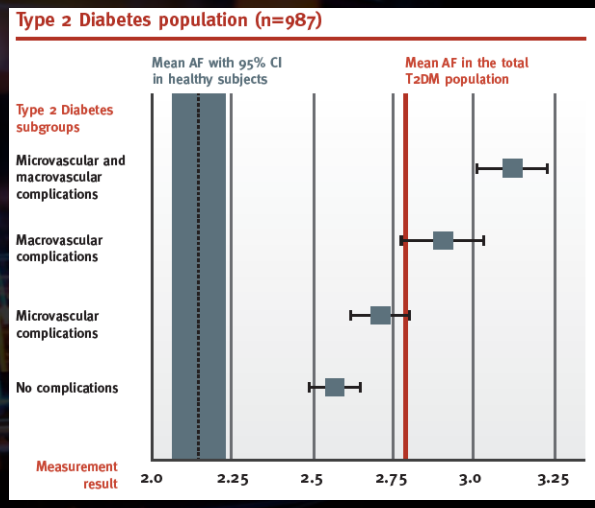
Vasculopathies

Diabetes Mellitus

Diagnoptics *Advanced glycation end-products (AGE) reader*



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Vasculopathies

Diabetes Mellitus

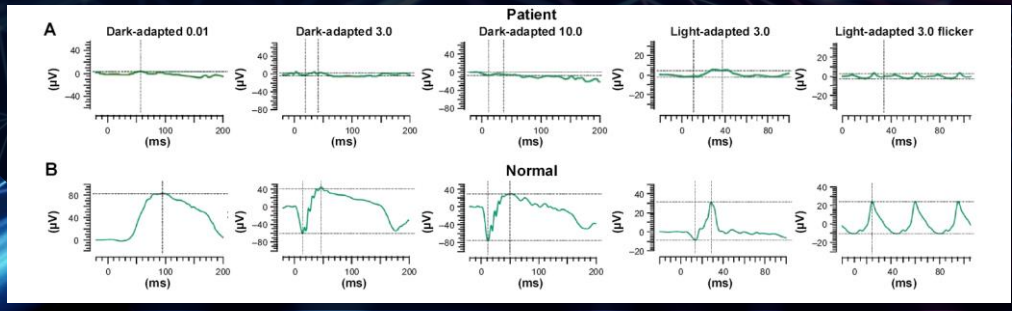
Screening for DR using new mydriasis-free, full-field flicker ERG recording

Scientific Reports Volume 6, Article number: 36591 (2016)

- Hand-held, mydriasis-free, full-field flicker ERG device called RETeval can be used to screen for DR
  - Full-field flicker ERGs using constant flash retinal luminance by adjusting luminance to compensate for pupil size
  - ***48 normal eyes and 118 eyes with different severities of DR***

Results

- ***Significant correlations between the severity of DR and the implicit times (r=0.55)***
- Area under the ROC curve was ***0.84 for detection of DR*** and ***0.89 for detection of VTR requiring treatments***
- Flicker ERG implicit time recorded by RETeval can be used as an adjunctive tool to screen for DR



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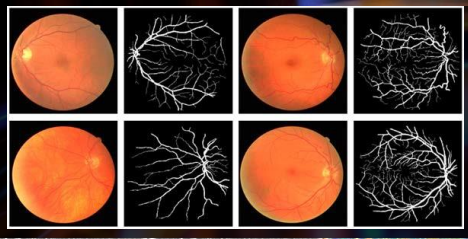
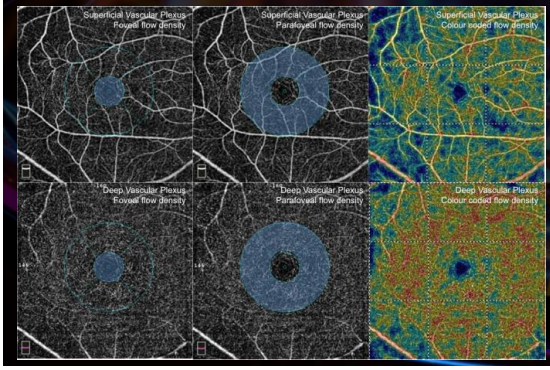
Vasculopathies
Hypertension





- US prevalence is estimated at 116M (~45% of adults)
  - ***Leading modifiable risk factor for cardiovascular disease and premature death***
- ***Clinically-evident hypertensive retinopathy signs typically develop late in the disease***
- High-resolution retinal microvascular imaging
  - Lumen caliber changes
- Retinal capillary rarefaction and flowrate
  - Density relative to normative database

Hypertensive retinopathy identification through retinal fundus image using back-propagation neural network.
Journal of Physics: Conference Series (2018) 978(1): 012106

Systemic hypertension associated retinal microvascular changes can be detected with OCTA
Scientific Reports (2020) 10: 9580

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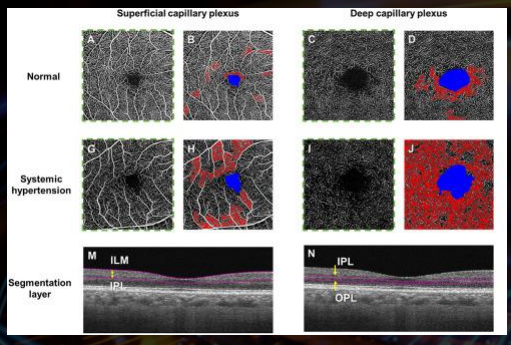
Vasculopathies
Hypertension



Devices utilized across studies:
AngioVue (Optovue) [SD-OCT]
Cirrus 5000 AngioPlex (Zeiss Meditec) [SD-OCT]
PLEX Elite 9000 (Zeiss Meditec) [SS-OCT]

Application of OCTA in Systemic HTN: Meta-Analysis
Front Med (2021) 8:778-789

Methods
- Literature search comparing OCTA parameters in non-diabetic participants with systemic hypertension vs. controls including minimumof 3 studies

Results
- At the macula, 9 studies analyzed vessel density at the superficial capillary plexus (SCP), 7 analyzed vessel density at the deep capillary plexus (DCP), and 6 analyzed area of superficial foveal avascular zone (FAZ)
- Participants with systemic hypertension
  - ***Significantly lower SCP***
  - ***Significantly lower DCP***
  - ***Significantly larger superficial FAZ***

Conclusion
- Patients with systemic hypertension have robustly lower superficial and deep vascular densities at the macula when compared to control eyes
- OCTA can provide information about pre-clinical microvascular changes related to systemic hypertension

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Systemic Diagnosis and Mangement

- Vasculopathies
- **Neurodegenerative**
- Autoimmune
- Collagen Vascular Disease

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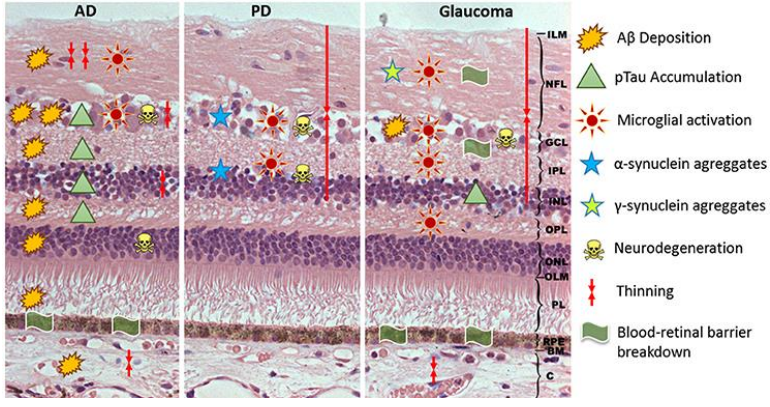
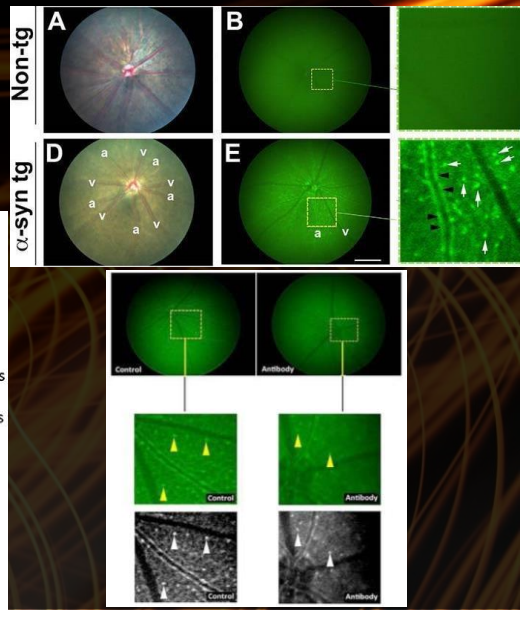
Neurodegenerative disease

Parkinson's disease

- Motor disorders associated with degeneration of dopaminergic neurons in the substantia nigra associated with high levels of ***α-synuclein***
  - Abnormalities in visual function have been reported in PD and LBD patients correlated with changes in retinal tissue to include:
    - Retinal thickness decrease
    - Inner retinal involvement
    - Protein deposits (***α-synuclein***) within retina





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Neurodegenerative disease

Parkinson's disease

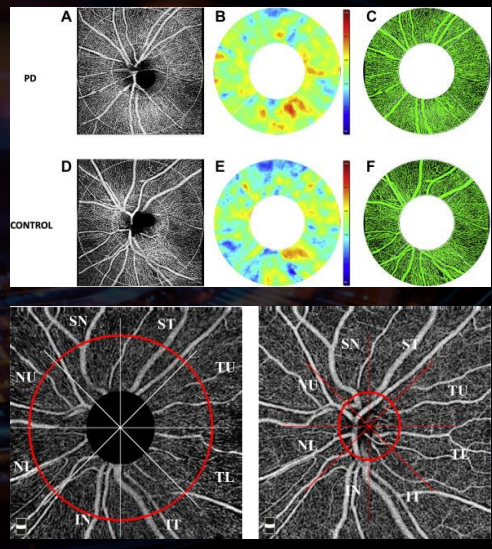
Identifying peripapillary radial capillary plexus alterations in Parkinson's disease using OCTA

Ophth Retina (2021) 6(1):29-36

Methods
- Participants underwent OCTA imaging (Cirrus HD-5000 AngioPlex)
- Capillary perfusion density (CPD) and capillary flux index (CFI) were assessed using a 4.5x4.5 mm peripapillary scan, and RNFL thickness was assessed using a 200x200µm cube OCT scan

Results
- Average CPD and CFI were significantly higher in PD eyes while average RNFL thickness was similar between groups.
- ***Significant correlations between Hoehn and Yahr stages and OCTA parameters were not observed***

Conclusions
- ***Increased peripapillary microvascular density and flux were detected in a large cohort of individuals with PD compared to controls***
  - ***RNFL thickness was similar between groups***



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Neurodegenerative disease

Parkinson's disease

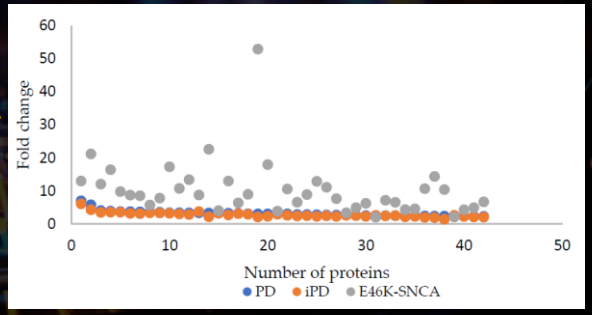
Tear Proteins as Possible Biomarkers for Parkinson's Disease

IOVS (2018) 59:4909

Methods
Tear samples from 60 diagnosed PD patients of varying severity and 30 matched non-PD controls were collected and pooled from both eyes for analysis. α-synuclein and MMP9 were measured using a human magnetic luminex assay kit while lactoferrin was measured using a human lactoferrin ELISA kit. Oligomeric α-synuclein was measured using a human α-synuclein oligo ELISA kit.

Results
- ***Total α-synuclein decreased significantly in PD patients relative to healthy controls***
- ***Oligomeric α-synuclein increased significantly in PD patients relative to healthy controls***
- Neither MMP9 or LF varied significantly between PD and controls

Conclusions
- ***Total tear α-synuclein and oligomeric synuclein may have potential to discriminate between tears of PD patients and healthy controls***
- ***Elevations in oligomeric α-synuclein are found in early, intermediate and late-stage PD***



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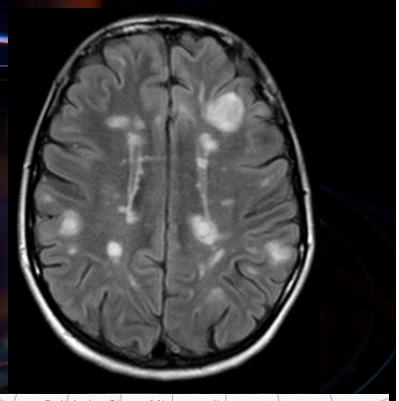
Neurodegenerative disease
Multiple Sclerosis

- Autoimmune disease represented by axon demyelination, disruption of inflammatory homeostasis and neuronal death
  - ***Cerebral pathology may mirror ocular manifestations***
  - ***Disease progression governed by the slow, subclinical injury accumulation of neuroaxonal structures***
- MRI is pivotal in clinical management/diagnosis of MS
  - ***Several limitations:***
    - ***Low sensitivity of conventional MRI in grey-matter involvement***
    - ***Diffuse damage in white matter***
    - ***Conventional MRI shows limited associations with clinical status***
- Etiology remains unclear with no definitive cure
  - MS cases (within United States) are more frequent above the 37th parallel than below
    - ***Above – 125 case per 100,000***
    - ***Below – 65 cases per 100,000***

  ****Risk is defined AFTER the age of 15***



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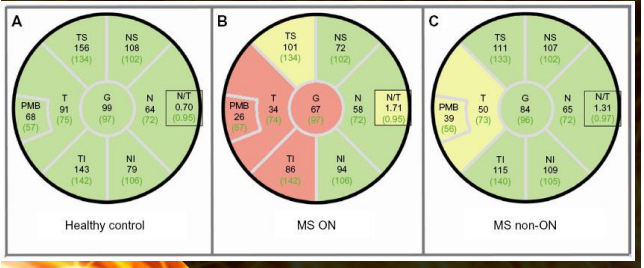
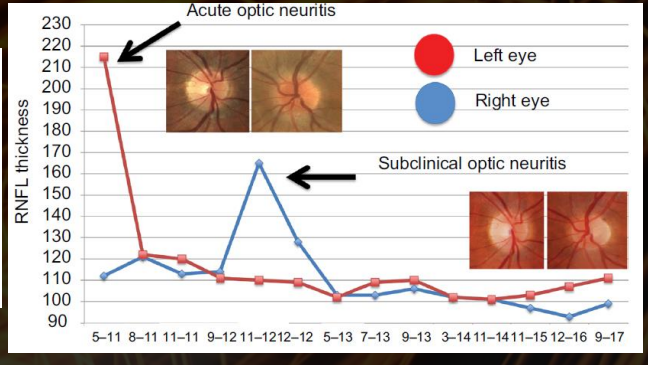
Neurodegenerative disease
Multiple Sclerosis

Retinal imaging with OCT: Biomarker in MS?
Eye and Brain (2018) 8:701-706

- Associated with RNFL thinning and neuronal degeneration
- OCT imaging has demonstrated a significant differences of average and temporal RNFL thickness was found in:
  - MS patients with optic neuritis
  - MS patients without optic neuritis





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Neurodegenerative disease

Multiple Sclerosis

Retinal asymmetry in multiple sclerosis

Brain (2021) 144(1):224-235

Abstract

Feasibility of OCT measures of retinal asymmetry as a diagnostic test for MS across 72,120 subjects for inter-eye percentage difference (IEPD) and inter-eye absolute difference (IEAD) were calculated for the macular GCC, ganglion cell inner plexiform layer (GCIPL) complex and ganglion cell complex.

- ***OCT macular GCC inter-eye difference may be considered as supportive MS diagnostic criteria in a young patient without relevant co-morbidity***
- ***Does not allow separation of multiple sclerosis from neuromyelitis optica***

Table 4 The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the mGCIPL IEPD and IEAD as a supportive diagnostic test for multiple sclerosis

mGCIPL	Cut-off	References	Specificity	Sensitivity	PPV	NPV
IEPD	20 %	Petzold *et al.*, 2014	99.4	2.7	0.998	0.01
IEPD	4 %	Coric *et al.*, 2017	82.8	51.7	0.6	99.9
IEAD	4 µm	Nolan-Kenney *et al.*, 2019	86.8	43.5	0.7	99.9

The levels were calculated for the published cut-off levels for the Heidelberg Spectralis OCT (Petzold *et al.*, 2014; Coric *et al.*, 2017; Nolan-Kenney *et al.*, 2019). All values presented in the table were calculated from the comparison of patients with multiple sclerosis to all controls (as summarized in Table 1).
The IEPD/IEAD qualifies as a supportive test for diagnostic criteria, but would not yet be sustainable as a screening test on a population level.

Table 5 Subgroup analysis multiple sclerosis compared to NMSOD

mGCIPL	Cut-off	References	Specificity	Sensitivity	PPV	NPV
IEPD	20 %	Petzold *et al.*, 2014	2.7	100	29.2	100
IEPD	4 %	Coric *et al.*, 2017	72.8	51.7	82.6	37.7
IEAD	4 µm	Nolan-Kenney *et al.*, 2019	76.3	43.5	35.2	82.1

All values presented in the table were calculated from the comparison of patients with multiple sclerosis to patients with NMOSD (as summarized in Supplementary Table 1). NPV = negative predictive value; PPV = positive predictive value.

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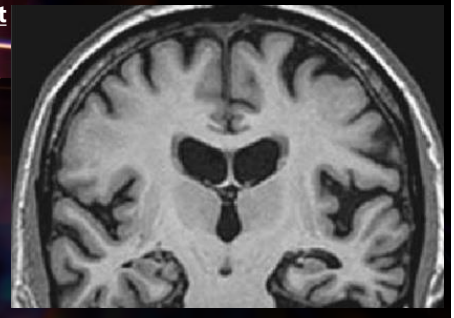
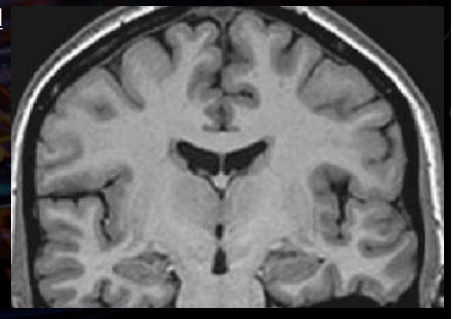
Neurodegenerative disease

Alzheimer's disease (AD)

AD subject



Control



- AD is characterized by an insidious onset of cognitive decline beginning with deficits in episodic memory:
  - forgetting recent personal and family events
  - losing items around the house
  - repetitive questioning
- As the disease progresses, other deficits gradually arise including:
  - Aphasia **(Loss of ability of understand or express speech)**
  - Apraxia **(Difficulty performing voluntary movements)**
  - Agnosia **(Inability to recognize or identify objects)**
  - Visuospatial difficulties
  - Executive dysfunction
- Clinical diagnosis criteria:
  - Definite AD (established by postmortem or biopsy),
  - Probable AD
  - Possible AD (other cognitive syndromes equally likely)

*****Average AD survival is typically 8-12 years from symptom onset*****

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Neurodegenerative disease
Alzheimer's disease (AD)

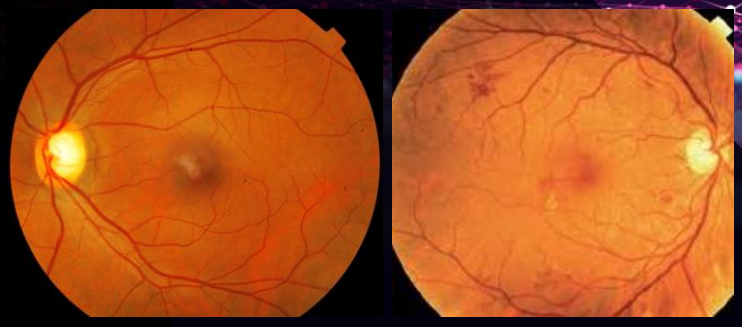
Associations between recent and established ophthalmic conditions and risk of AD
Alzheimer's and Dementia (2019) 15:34-41

Glaucoma 5-yr HR:
Recent 1.46
Established 0.87

AMD 5-yr HR:
Recent 1.20
Established 1.50

DR 5-yr HR:
Recent 1.50
Established 1.50

Glaucoma, AMD and DR are associated with increased AD risk



Shared characteristics:
1) ***Progressive neurodegeneration***
2) ***Chronic microvascular insults***
3) ***Protracted oxidative stress***

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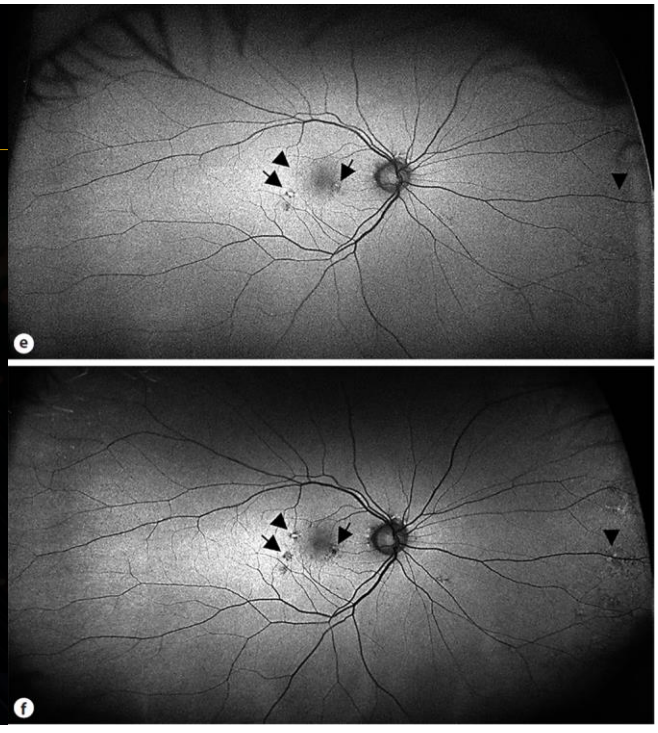
Neurodegenerative disease
Alzheimer's disease (AD)

Peripheral Retinal Imaging Biomarkers for Alzheimer's Disease: A Pilot Study
Ophthalmic Research (2018) 24.5

Results:
- Baseline analysis showed significantly higher prevalence of peripheral hard drusen
  - ***AD subjects (25%)***
  - ***Control subjects (4%)***
- Marked increase in drusen number at the 2-year follow-up in AD subjects vs. control subjects

Conclusions:
- ***UWF retinal imaging revealed a significant association between AD and peripheral hard drusen formation beyond the posterior pole at baseline and over 2-year progression***



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Systemic Diagnosis and Mangement

- Vasculopathies
- Neurodegenerative
- **Autoimmune**
- Collagen Vascular Disease

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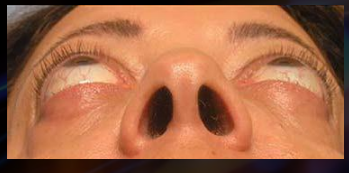
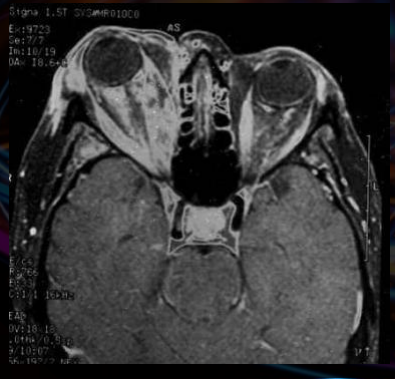
Automimmune disease

Grave's disease





- Hyperthyroidism caused by thyroid-stimulating antibodies to the TSH receptor
- Most commonly affects females ages 30-50
  - ***8X more common in women*** than men and risk increases if other family members affected
- Other system conditions linked to Graves:
  - ***RA***
  - ***SLE***
  - Celiac
  - Addison's disease (hypocortisolism)

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Automimmune disease

Grave's disease –> Thyroid Eye Disease

***In vivo* confocal microscopy assessment of MG microstructure in patients with Graves' orbitopathy**
BMC Ophthal. (2021) 21:261

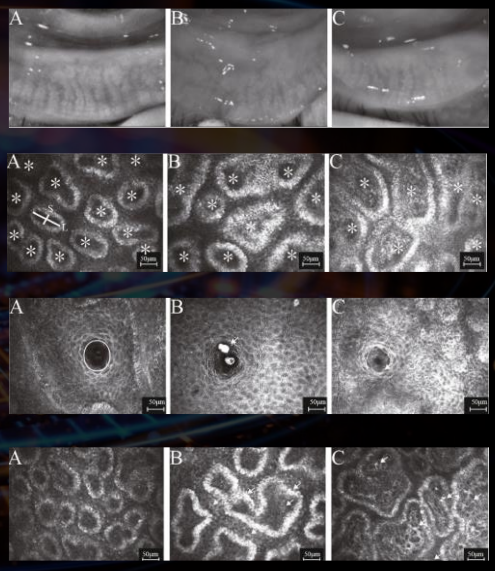
Methods
40 patients with GO (34 with active GO, 46 with inactive GO) and 31 matched control participants (62 eyes) were enrolled. A complete ophthalmic examination was then performed including external eye, ocular surface and MGs including *in vivo* confocal ophthalmoscopy

Results
All confocal microscopy assessments MGs significantly differed among groups

- ***GO groups showed significant differences in all measures***
- ***Active GO had higher degrees of acinar irregularity and inhomogeneity***
- ***Inactive GO had higher degrees of secretion reflectivity and fibrosis***

Conclusions

- ***IVCM effectively revealed MG microstructural changes in eyes with GO***
- ***Revealed discernible patterns of MG abnormalities in eyes with active GO and inactive GO, which are not easily distinguishable by clinical examinations.***



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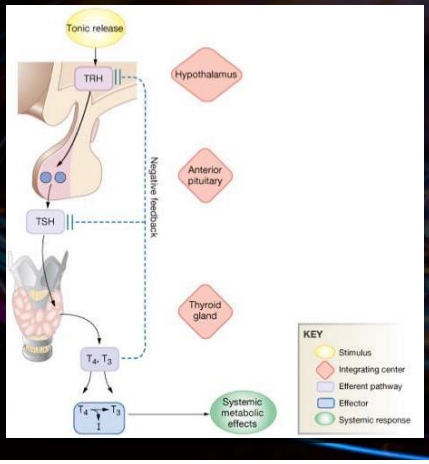
Automimmune disease

Thyroid Eye Disease… just when it seemed easy

Thyroid

- Largest endocrine gland
- Controlled by hypothalamus and pituitary
- Primary function is T4, T3 and calcitonin production



Thyroid Panel Test (Standard vs. Full)

- **T3 (Free T3)**
- **T4 (Free T4)**
- **TSH**
- **T7 [(T4 * T3 Uptake)/100]**
- **TPO (thyroid peroxidase antibodies)***
- **Tg (thyroglobulin antibodies)***
- **TR (thyroid antibodies)***

- **Thyroid Eye Disease**
- **~80%** = autoimmune hyperthyroid disorder
  - Graves' disease
- **~10%** = autoimmune hypothyroidism
  - Hashimoto's thyroiditis, atrophic thyroiditis or Hashitoxicosis
- **~10%** = normal thyroid function
  - Euthyroid Graves' disease
    - Some euthyroid Graves' disease never develop thyroid dysfunction

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Automimmune disease

Grave's disease –> Thyroid Eye Disease

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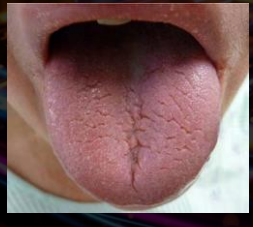
Automimmune disease

Sjogren's disease



- 2nd most common chronic autoimmune rheumatic disease and associated with a high burden of illness.
- Common clinical manifestations include xerostomia and keratoconjunctivitis sicca also ***including the development of non-Hodgkin's lymphomas***
- Diagnosis requires objective evidence of dry eyes and/or objective evidence of dry mouth associated with autoimmunity
- Sjo® Test as clinical point-of-care testing for KCS or recalcitrant DES in patients meeting the demographic

Prevalence of primary Sjögren's syndrome in a US population-based cohort.
Arthritis care & research (2017) 69(10:1612-1616
- Female (~85%)
- 65±15 years old
- Symptoms duration of 10±8 years

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Automimmune disease

Sjogren's disease

Early detection of Sjogren's syndrome: sensitivity and specificity of the Sjo Diagnostic Test

Invest Ophtahl Vis Sci (2016) 57:5681

Methods

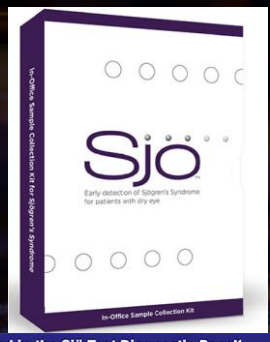
Antibodies to the traditional markers (SSA, SSB, ANA and RF and the novel biomarkers (salivary protein-1 [SP1], carbonic anhydrase-6 [CA6] and parotid secretory protein [PSP]) in patient sera samples were detected using the Sjö panel were assessed from 267 confirmed SS patients across 3 clinical studies were analyzed against 125 matched controls

Results

- ***Complete Sjö panel***
  - ***Sensitivity = 91.4% (SSA/SSB alone = 74.9%)***
  - ***Specificity = 79.8%***

Conclusions

Sjö panel increases the sensitivity in SS diagnosis over 25% without compromising specificity



Biomarkers Measured in the Sjö Test Diagnostic Panel[1]

	Biomarker	Diagnostic Characteristics
Novel, proprietary	Salivary protein-1 (SP-1, IgA, IgC, IgM)	Provides high specificity and sensitivity for early Sjögren's syndrome
	Carbonic anhydrase (CA-6, IgA, IgC, IgM)	Offers additional sensitivity for an early diagnosis
	Parotic secretory protein (PSP, IgA, IgC, IgM)	Expressed early in disease course
Traditional	SS-A (Ro)	Expressed in about 70 percent of patients; typically appears later than the novel biomarkers
	SS-B (La)	Less frequently expressed than Ro; typically appears later than novel biomarkers
	Antinuclear antibody (ANA) by HEp-2	Expressed in about 60 percent of Sjögren's sydrome patients
	Rheumatoid factor (RF) levels (IgA, IgC, IgM)	Found in many rheumatic conditions—not unique to Sjögren's syndrome

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Autoimmune disease

Prevalence of Autoimmune Disease in POAG

Prevalence of Autoimmune Diseases in Patients with Primary Open-Angle Glaucoma Undergoing Ophthalmic Surgeries

Ophthalmology Glaucoma (2022) 5(2):128-136

Results

172 patients with POAG and 179 controls were included

- Overall prevalence of AiD
  - ***17% in the POAG group vs. 10% in the controls***
  - 6.4% of POAG patients and 3.4% of controls had >1 AiD
  - Most prevalent AiD in POAG were ***RA (4.6%)*** and ***psoriasis (4.1%)***
  - AiD associated with ***OR: 2.62*** of POAG relative to controls

Conclusions

- ***Higher prevalence of AiD was found in POAG patients compared with control patients undergoing ophthalmic surgery***
- ***Presence of AiD was associated with increased risk for POAG after adjusting for covariates***

Demographic and Ophthalmic Information	*POAG (n = 62)*	*Controls (n = 97)*	*p-value*
Age (years)	74.56 ± 7.97	70.92 ± 11.14	**0.027**
Gender (% male)	45%	38%	0.38
Race (% Caucasian)	60%	81%	**0.003**
BMI (kg/m²)	27.38 ± 4.48	27.62 ± 5.48	0.773
Type 2 Diabetes (%)	37%	25%	0.096
BCVA (LogMAR)	0.36 ± 0.41	0.66 ± 0.87	**0.012**
HVF MD (decibels)	-11.06 ± 8.00	—	—
IOP (mmHg)	15.90 ± 4.50	15.42 ± 2.89	0.414
Cup to Disc Ratio	0.76 ± 0.15	0.33 ± 0.13	**< 0.0001**
Any history of systemic steroid use (%)	18%	14%	0.413
Any history of inhaled steroid use (%)	10%	20%	0.168
Autoimmune disease (%)	27%	9%	**0.003**

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Systemic Diagnosis and Mangement

- Vasculopathies
- Neurodegenerative
- Autoimmune
- **Collagen Vascular Disease**

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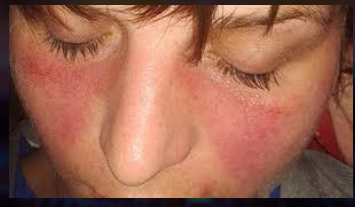
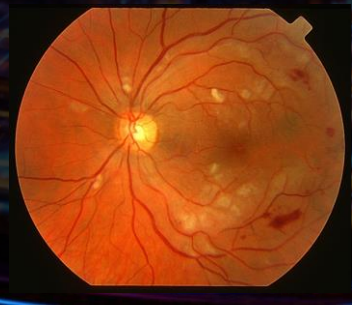
Collagen Vascular Disease

Systemic Lupus Erythematosus

- US prevalence of ~250 per 100,000
- Female : Male ratio of 6 : 1





Orbit	Myositis / proptosis / ptosis
Eyelids	Discoid rash
Anterior segment: • Cornea • Episclera/sclera • Iris/ciliary body	• KCS / SPK / PUK • Chemosis / scleritis / episcleritis • Uveitis (uncommon)
Posterior segment: • Retina • Choroid	• CWS / HE / hemes / vascular tortuosity / pigmentary changes • Choroidal ischemia
Neuro-ophthalmological	Optic neuritis / optic neuropathy/ INO / EOM dysfunction / diplopia

- ***KCS is most common ophthalmic manifestation***
  - ***Most develop secondary Sjogren's syndrome***

Condition	**Differentiating** Characteristics
Bechet's disease	• H/O genital or oral ulcers
Sarcoidosis	• Uveitis common
Lyme disease	• Annular skin lesions • Endemic area
HTN retinopathy	• A/V nicking • Copper wire vessels
DR	• H/O elevated A_1C
Polyarteritis nodosa	• More common in males • ANCA negative
Syphilis	• Uveitis common • Uniform retinal inflammation

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Collagen Vascular Disease
Rheumatoid arthritis

- Annual U.S. incidence of ~50 per 100,000 individuals
- Onset is most frequent ages 40-50 and ***women are affecting 2.5X more frequently than men***
- Early diagnosis and treatment can substantially slow progression of joint damage in up to 90% of patients
  - ***KCS is most common ophthalmic manifestation***
- Current understanding of disease is a combination of genetic and environmental factors
  - Elevated ESR and CRP (non-specific)
  - Elevated RF and anti-CCP (not definitive)
- Three phases of progression
  - Initiation phase due to non-specific inflammation
  - Amplification phase due to T-cell activation
  - Chronic inflammatory phase with tissue injury resulting from the ***cytokines, IL–1, TNF-α and IL–6***

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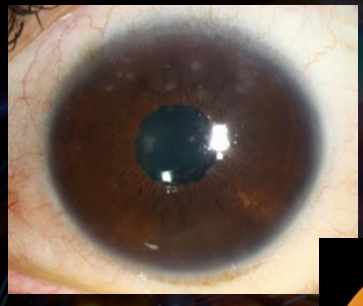
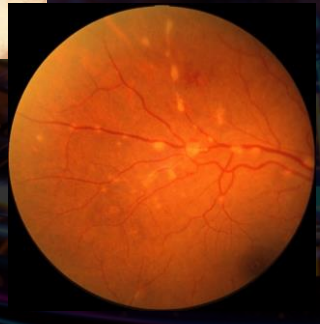
Collagen Vascular Disease
Sarcoidosis





- Annual U.S. incidence
  - 8 per 100,000 in Caucasians
  - ***18 per 100,00 in African Americans***
- More common in women 20-40
- 30-40% have ocular presentation as initial symptoms
  - ***Bilateral uveitis (most common)***
  - KCS
  - Choroidal granulomas
  - Periphlebitis
  - Perivascular exudates (candle-wax drippings)
- Systemic testing
  - Chest x-ray or CT (hilar lymphadenopathy)
  - Elevated ACE and lysozyme

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What is the role of primary care optometry in autoimmune and collagen vascular disease management?

Every primary care OD's bad penny…

Idiopathic anterior uveitis

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Autoimmune and Collagen Vascular Disease

Targeted Laboratory Ordering

Patterns of Laboratory Testing Among Uveitis Specialists

Am J Ophthal (2016) 170:161-167

- 13 patient scenarios evaluated by 11 specialists
- Mean number of tests was 5.5±2.7
- Average testing: ***$282.80***
- Most tests within each scenario were ordered by ***<50% of respondents***
- Only ***1 test (ANA)*** in a single scenario (unilateral scleritis) yielded ***universal consensus***
- ***No relationship*** between years in-practice and # of tests ordered

Top labs ordered:

1) Syphilis Ab [79.7%]
2) Chest x-ray [63.6%]
3) CBC [39.8%]
4) RPR [33.6%]
5) ***FA*** [27.3%]
6) CMP [25.2%]
7) ACE [23.8%]
8) ***OCT*** [23.1%]
9) HLA-B27 [22.4%]
10) Lyme titer [20.3%]
11) PPD [19.6%]
12) ANA [15.9%]
13) ESR [15.9%]

Diagnostic Test	Number of Orders	Cost per Order ($)	Total Cost ($)
Tests With No Diagnostic Value			
CBC	57	8.9	507.3
CMP	36	14.5	522
Creatinine	9	7	63
Hgb A1C	1	13.3	13.3
Liver panel	2	11.2	22.4
Hepatitis panel	1	20.1	20.1
ESR	22	3.7	81.4
CRP	6	7.1	42.6
Ocular Tests			
Fundus photo	10	69.2	692
FA	39	199.2	7768.8
ICG	5	199.2	996
OCT	33	56.5	1864.5
HVF	2	75.1	150.2
GVF	1	50.5	50.5
ERG	2	121.9	243.8
Viral PCR	10	196	1960
Non-Ocular Tests			
ACE	34	20.1	683.4
Lysozyme	11	25.8	283.8
ANA	22	16.6	365.2
ANCA	13	17.8	231.4
RF	13	7.8	101.4
anti-CCP	6	17.8	106.8
anti-RNP	1	24.7	24.7
anti-SS	1	49.3	49.3
HLA-B27	32	37.7	1206.4
HLA-A29	10	33.1	331
HLA-B51	2	81.9	163.8
Syphilis ab	114	18.2	2074.8
RPR	48	6.1	292.8
HIV	6	33.1	198.6
HTLV	3	11.5	34.5
Bartonella	6	48.2	289.2
Lupus ab	1	11.7	11.7
Lyme ab	29	23.4	678.6
Toxocara ab	1	17.9	17.9

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Table 3 Comparison between clinical diagnosis and automated diagnosis by Bayesian belief network in 10 typical cases of anterior uveitis

Case	Age	Sex	Chronicity	Laterality	Findings	Clinical diagnosis	Predicted probability (%)									
							Idiopathic	B27+/AS	Sarcoidosis	JIA	TB	IBD	Posner	Fuchs	RA	PA	Behçet
1	63	Female	Chronic	Bilateral	Granulomatous KPs, vitritis, cataract, synechiae, CMO	Sarcoidosis	2	0	86	1	5	6	0	0	0	0	0
2	28	Male	Acute	Unilateral	Flare 4+, synechiae, back pain, HLA-B27+	Ankylosing spondylitis	0	97	0	2	0	0	0	0	0	0	0
3	41	Female	Acute	Unilateral	Flare 4+, hypopion, panuveitis, vasculitis, VA < 20/200, B51+	Behçet's disease	1	0	0	0	0	0	0	0	0	0	99
4	57	Female	Acute	Unilateral	Posterior synechiae, B27+, chronic diarrhea and rectal bleeding	IBD	28	9	0	0	1	59	0	0	2	1	0
5	36	Male	Chronic	Unilateral	Stellate KPs, glaucoma, cataract	Fuch´s	17	0	1	10	1	5	0	61	0	5	0
6	14	Male	Chronic	Bilateral	Fine KPs, Flare 3+, vitritis, glaucoma, cataract, synechiae, VA < 20/200, arthritis	JIA	11	0	22	52	0	1	0	0	1	0	14
7	55	Female	Acute	Unilateral	Glaucoma, IOP 42 mm Hg	Posner	25	1	0	0	1	1	69	1	0	1	0
8	58	Female	Acute	Bilateral	Skin plaques, itching, nail pitting	Psoriasic arthritis	3	0	0	0	0	0	0	0	0	97	0
9	17	Male	Acute	Bilateral	Vitritis, urethritis, joint pain	Reactive arthritis	10	0	0	0	0	0	0	0	89	0	0
10	50	Female	Chronic	Unilateral	Granulomatous KPs, Vitritis, CMO, positive PPD	TB	4	0	31	0	59	6	0	0	0	0	0

Abbreviations: AS, ankylosing spondylitis; IBD, inflammatory bowel disease; JIA, juvenile idiopathic arthritis; KPs, keratic precipitates; PA, psoriasic arthritis; RA, reactive arthritis; TB, tuberculosis.

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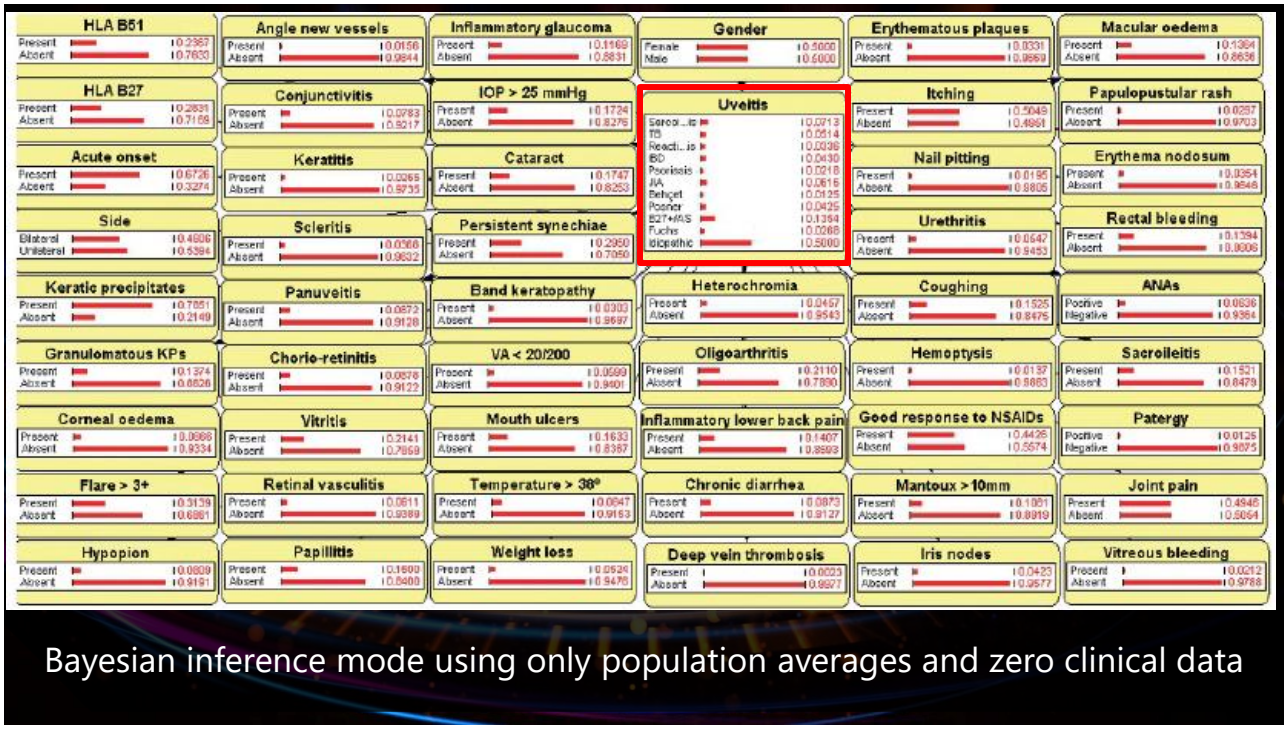

Bayesian inference mode using only population averages and zero clinical data

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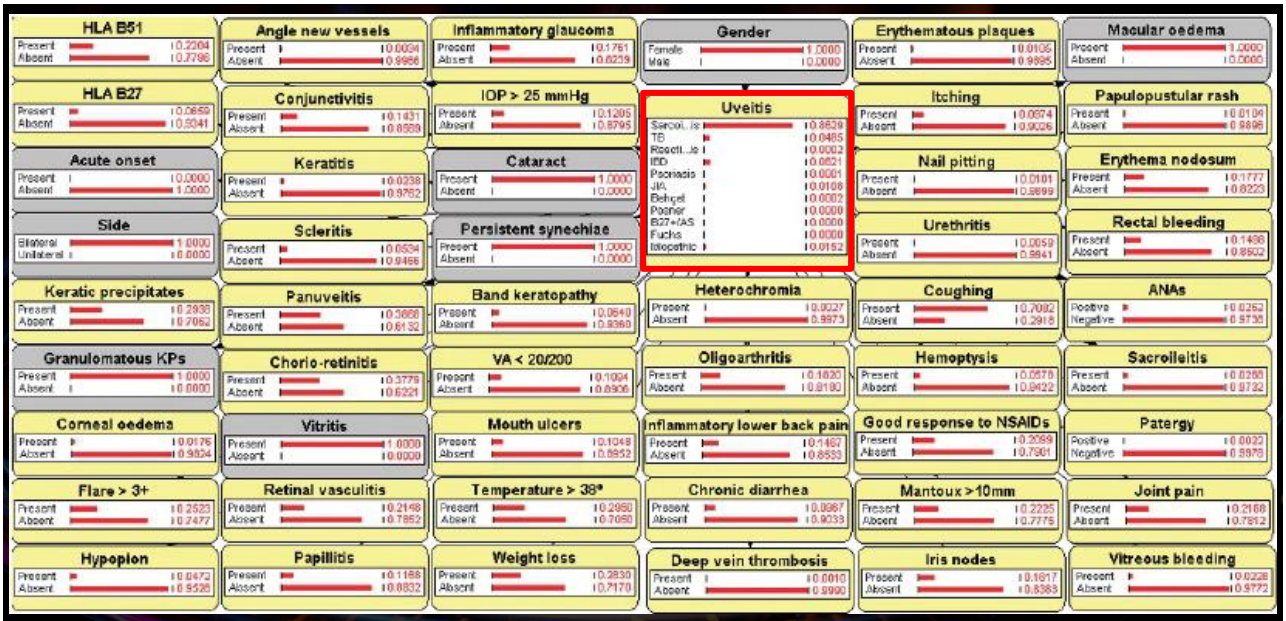

Inference mode after entering observed clinical data

Probabilities for each changed finding noted in gray making sarcoid the most likely diagnosis

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What does this mean clinically?

12 Total

Uveitis Laboratory Work Up: Making Smart Choices

Understanding Bayesian statistics and Implications

Disease X has a 0.1% prevalence rate in the population
- Diagnostic test with 99% sensitivity and 95% specificity (1- specificity)
- Patient with no findings would therefore have 0.1% pretest probability (1-probability)

PPV = (0.99*0.001) / (0.05*0.001+0.05*0.999) = 0.019

Only *1.9% of cases that were tested positive might actually have that disease.*

Using Bayes' theorem: Only way to increase post-test probability is to narrow the general prevalence by performing the diagnostic test in cases with *specific clinical findings*

Anterior Uveitis (90% of all uveitis)
- Classic symptoms: pain, redness, and photophobia.
- Classic signs include circumlimbal flush, fine/mutton-fat KPs and AC reaction

Tests to include:
1) HLA-B27,
2) RPR (confirmatory FTA-ABS),
3) serum ACE and lysozyme (confirmatory chest radiography) and
4) Quantiferon tests

Tests to omit: RF, ANA and ANCA are *unlikely related to anterior uveitis in adult population*

Intermediate Uveitis
- Common features include adherent, vitreal WBCs near inferior retina (snowbanks / snowballs)

Tests to include:
1) RPR (confirmatory FTA-ABS),
2) serum ACE and lysozyme (confirmatory chest radiography),
3) Lyme serology
4) Quantiferon tests

Tests to omit: HLA-B27, RF, ANCA and ANA

Posterior/Panuveitis
- "fog in headlights" complaint of decreased vision and floaters *without* the classic symptoms of pain and photophobia associated with anterior uveitis

Tests to include:
1) RPR (confirmatory FTA-ABS),
2) serum ACE and lysozyme (confirmatory chest radiography),
3) Lyme serology
4) Quantiferon tests

Tests to omit: HLA-B27, RF, ANCA and ANA *If NO vasculitis or related systemic involvement.*

Infectious Uveitis

Differential diagnosis of infectious etiologies are crucial
- Bacterial (**cat-scratch disease**),
- Viral (**HSV, VZV, CMV**)
- Parasitic (**toxoplasmosis, toxocariasis, oncocercosis**) infections should be investigated.
- Hematuria and proteinuria are assessed in **retinal vasculitis, scleritis and PUK.**

Tuberculosis. Hypothetically, if all patients were screened for tuberculosis with purified protein derivatives (PPD) or detection of IFN-γ expression following antigen stimulation (Quantiferon®) tests, PPVs would be less than 10%. PPVs of these tests would increase (up to 96%), only when performed at an endemic area or for a patient with clinical findings suggestive of tuberculosis such as serpiginous lesions.

Syphilis. Non-treponemal venereal disease research laboratories (VDRL) and rapid plasma reagin (RPR) are used to screen active syphilitic disease, whereas treponemal (FTA-ABS, MHA-TP, TPHA, EIA and syphilis IgG) tests recognize T. pallidum specific antibodies and demonstrate previous syphilitic exposure.
- 30% of RPR and VDRL tests may give false negative results for latent disease and neurosyphilis. In tertiary referral centers, where the prevalence is higher due to selection bias, initially a specific test (Syphilis IgG or FTA-ABS) is recommended in order to avoid false negative results.

Non-infectious Uveitis

Human Leukocyte Antigen B27 (HLA-B27). With 5% prevalence in a normal population, the expressivity of HLA-B27 increases from 50 to 80% in cases with *unilateral acute anterior uveitis*. PPV of the test varies depending on the anatomic location with anterior uveitis being highest.

Antinuclear antibodies (ANA). With a positive predictive value of 1%, it has very limited use in diagnosis of uveitic syndromes, which includes only *juvenile inflammatory arthritis, scleritis, peripheral ulcerative keratitis and vasculitis.*

Antineutrophil cytoplasmic antibodies (ANCA). These are exclusively beneficial for differential diagnosis of necrotizing scleritis, peripheral ulcerative keratitis and retinal vasculitis.

Angiotensin converting enzyme (ACE). ACE has a moderate sensitivity and specificity: an increase in ACE level has a PPV around 47% in diagnosing sarcoidosis-associated uveitis, which is thought to increase up to 72% when combined with increased *serum lysozyme* levels.

Putnam Preferred Practice Pattern – Uveitis Worksheet
- FHx of collagen vascular disease
  - 1st degree relative
  - Age of onset
- Review of Systems
  - Collagen vascular disease (RA / SLE / sarcoid)
  - Vascular disease (DM / HTN / dyslipidemia)
  - Inflammatory Bowel Disease (Crohn's / UC)
  - Current febrile illness
  - Dermatologic involvement
  - Recent travel
- Non-infectious laboratory testing
  - **RPR** (need confirmatory FTA-ABS (+))
  - **HLA-B27** (AS / reactive arthritis / IBD / psoriatic arthritis / Bechet's [prognostic if HLA-B27 (+)]
  - **ANA** (*ONLY* if suspected SLE / PUK / scleritis / JIA)
  - **ACE + lysozyme** (*ONLY* if suspected sarcoid)
  - **ANCA** (*EXCLUSIVELY* for necrotizing scleritis / PUK / retinal vasculitis)
  - **Quantiferon gold** (*ONLY* is suspected or endemic TB)
  - **ELISA / Western blot** (*ONLY* if suspected or endemic Lyme disease)
  - **Chest x-ray** (*ONLY* if suspected TB, sarcoid
- BCVA
  - ETDRS
  - Pelli-Robson or PV 5%
- Pupils:
  - Sluggish response or anisocoria
  - Consensual photo-oculodynia
- SLE
  - Presence of KPs (acute or chonic)
  - Presence of Koeppe or bussaca nodules
- Baseline Imaging
  - Full color fundus
  - OCT 5-line Raster
    - Identification of CME and chronic RPE changes
  - OCTA
    - Create baseline vascular appearance
    - Identify early vasculitis (deep plexus / choriocapillaris / Bruch's / intraretinal)

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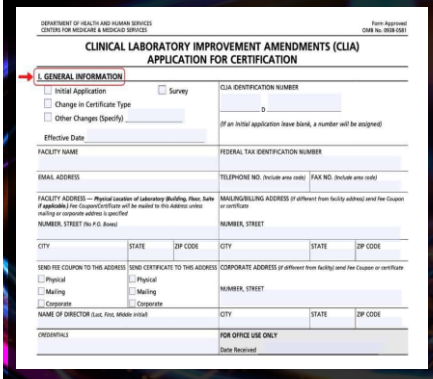
Autoimmune and Collagen Vascular Disease

Targeted Laboratory Ordering



DEPARTMENT OF HEALTH AND HUMAN SERVICES
CENTERS FOR MEDICARE & MEDICAID SERVICES

Form Approved
OMB No. 0938-0581

CLINICAL LABORATORY IMPROVEMENT AMENDMENTS (CLIA)
APPLICATION FOR CERTIFICATION

I. GENERAL INFORMATION

Initial Application ☐ Survey
Change in Certificate Type
Other Changes (Specify)

CLIA IDENTIFICATION NUMBER

(If an initial application leave blank, a number will be assigned)

Effective Date

FACILITY NAME

FEDERAL TAX IDENTIFICATION NUMBER

EMAIL ADDRESS

TELEPHONE NO. (Include area code) FAX NO. (Include area code)

FACILITY ADDRESS — Physical Location of Laboratory (Building, Floor, Suite if applicable.) Fee Coupon/Certificate will be mailed to this Address unless mailing or corporate address is specified

NUMBER, STREET (No P.O. Boxes)

CITY STATE ZIP CODE

MAILING/BILLING ADDRESS (If different from facility address) and Fee Coupon or certificate

NUMBER, STREET

CITY STATE ZIP CODE

SEND FEE COUPON TO THIS ADDRESS
Physical
Mailing
Corporate

SEND CERTIFICATE TO THIS ADDRESS
Physical
Mailing
Corporate

CORPORATE ADDRESS (If different from facility) and Fee Coupon or certificate

NUMBER, STREET

CITY STATE ZIP CODE

NAME OF DIRECTOR (Last, First, Middle Initial)

CREDENTIALS

FOR OFFICE USE ONLY

Date Received

- **Osmolarity System (TearLab)** [Class I CLIA]
  - Measurement of tear film osmolality
  - ***Non-differential KCS marker***
- **Lactoferrin (Advanced Tear Diagnostics)** [Class II CLIA]
  - Protein produced by the acinar cells of the lacrimal gland
  - ***Differential KCS marker***
- **IgE (Advanced Tear Diagnostics)** [Class II CLIA]
  - ***Presence of ocular allergen***
- **InflammaDry (RPS)** [Class I CLIA]
  - ***Detection of inflammatory marker MMP-9***
  - Qualitative marker
- **AdenoPlus® (RPS)** [Class II CLIA]
  - FDA-approved with CLIA-waiver
  - **In vivo detection of adenoviral antigen**
- **Sjo® Test**
  - RF and ANA
  - ***SS-A and SS-B with immune markers PSP-1, CA-6 and SP-1***

https://www.cms.gov/Medicare/CMS-Forms/CMS-Forms/downloads/cms116.pdf

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What can be done to bridge the gap from ocular management to systemic management?

If only there were a ubiquitous device with a widely-used platform that could make evidence-based research accessible to clinicians…

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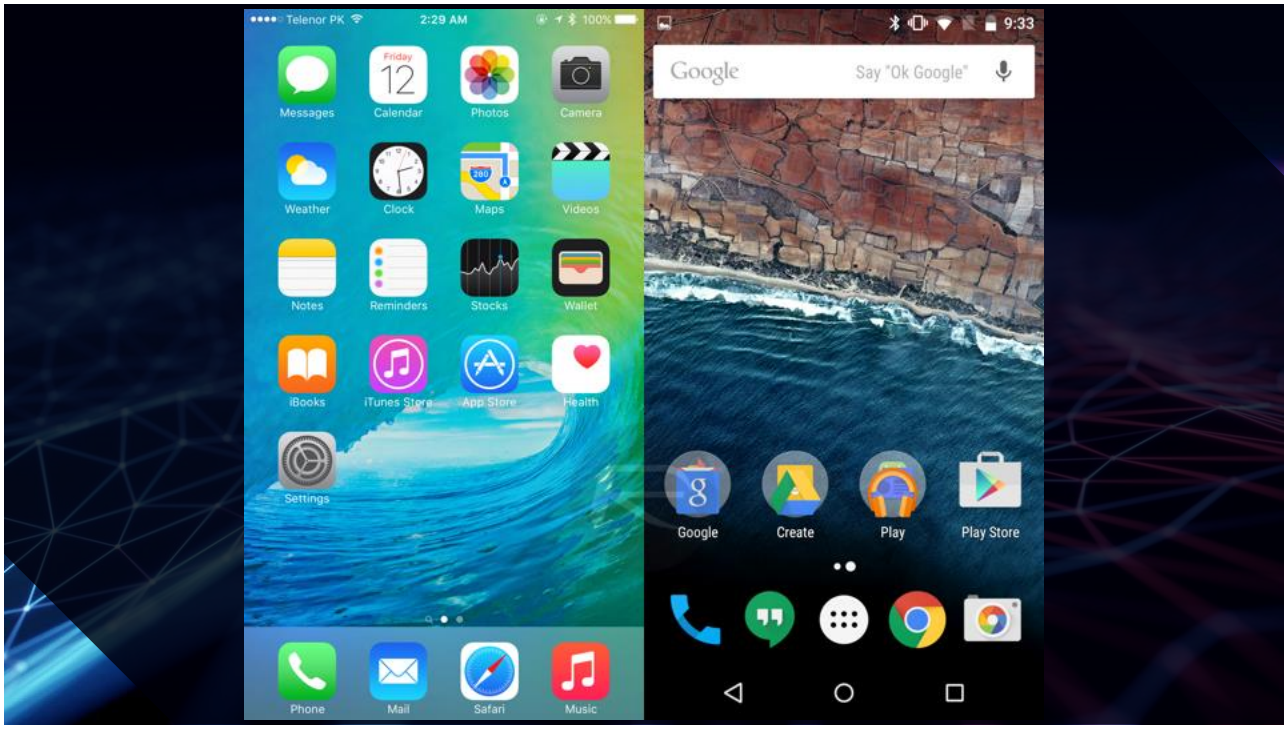

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Clinical Biomarkers of Retinal Injury

Smart Phone Applications

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Preventative Medicine + Systemic Disease Smartphone Applications

- *OHTS + EMGT Calculators**
- ASCVD Calculator
- Retinal Risk Calculator
- *Cradle*
- *StrabPix*
- *Aberrometry*
- *Periocular melanoma*
- MS Monitoring
- ASD Screening
- *mTBI (Concussion)*
- *NITBUT Screening*
- DryEyeRhythm
- *Myopic Progression*
- Smart Optometry
- *Epocrates*
- *Doc in a Box DDx Calculator*
- *Austere Retinal Imaging*

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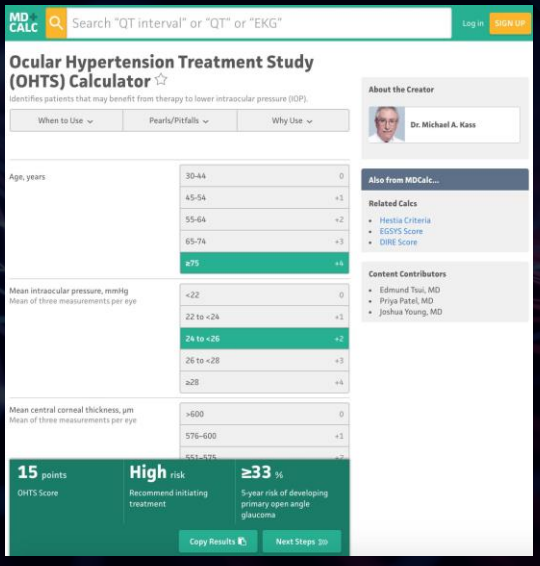
Clinical Systemic Disease Management

Smart Phone Applications – POAG Risk

- MDCalculator
  - OHTS calculator
    - Age
    - Mean IOP
    - Mean CCT
    - Mean vertical C/D ratio
    - Mean SITA Standard 30-2 or 24-2 PSD
  - Recommendation for observation vs treatment
  - Estimated 5-year risk of developing POAG
    - Provides supporting references

CAVEAT: OHTS IOPS inclusion criteria
- ***24 – 32 mmHG in one eye***
- ***21 – 32 mmHg in other eye***



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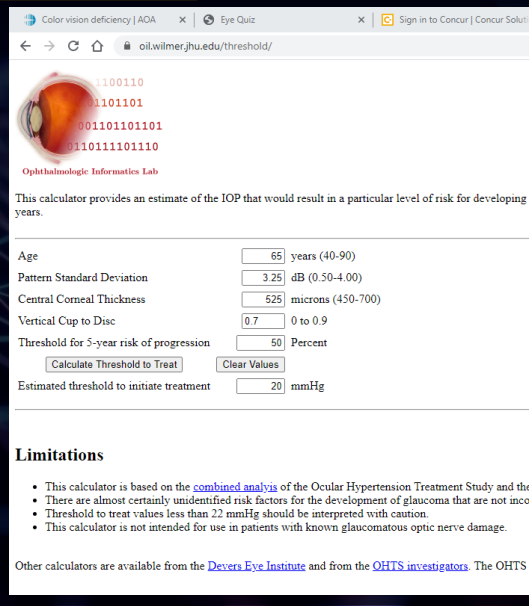
Clinical Systemic Disease Management

Smart Phone Applications – IOP Threshold

- **Ophthalmic Informatics Lab**
  - OHTS + EMGT calculator
    - Age
    - SITA Standard 30-2 or 24-2 PSD in dB
    - CCT
    - Vertical C/D ratio
    - Estimated 5-year risk of progression

- ***Estimated Threshold to Initiate Treatment****
  - ***LIMITATIONS…***



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Clinical Systemic Disease Management

Smart Phone Applications

Degree of Myopia and Glaucoma Risk: Dose-Response Meta-Analysis
Am J Ophthalmol (2022) 235:107-119

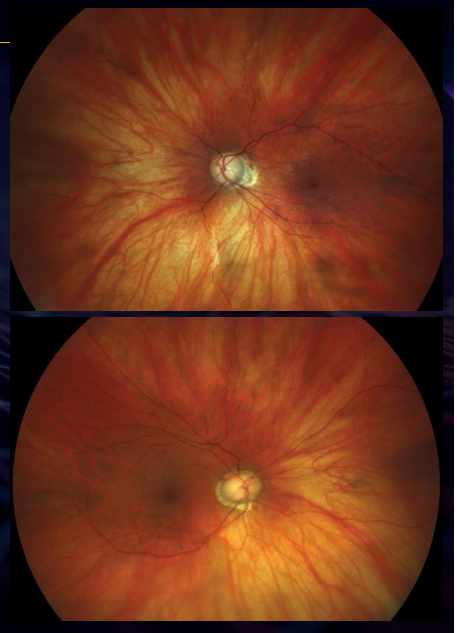
Results

- 24 studies in 11 countries (514,265 individuals) made up the meta-analyses. Pooled OR with OAG:
  - Low 1.50
  - Moderate 1.69
  - ***Moderate-to-high 2.27***
  - ***High myopia 4.14***

- ***OAG risk accelerated at around –6 D, and further accelerated from –8 D, showing a non-linear concave upward slope***

Conclusions

- ***For each 1D increase in myopia, the risk of OAG increases by ~20%***
- ***Risk increases steeply in high-degree myopia***



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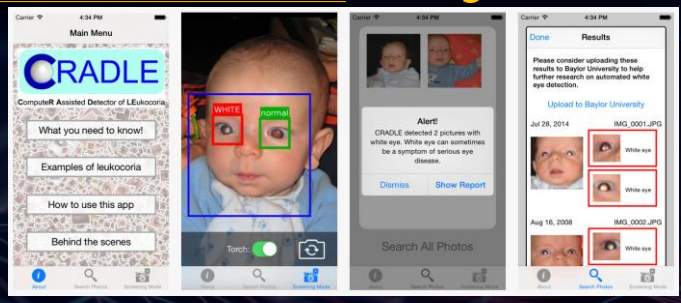
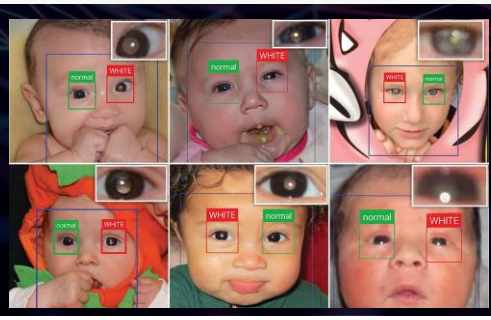
Clinical Systemic Disease Management

Smart Phone Applications - Leukocoria Screening

- **Cradle**
  - Leukocoria screener
    - Congenital cataracts
    - Coats disease
    - Retinoblastoma
    - ROP
    - Toxocariasis
    - Retrolental fibroplasia
  - 50K images incorporated
  - Mean detection ~1.3 years prior to diagnosis
  - False positive rate: ~1%
  - Database is heavily weighted with Caucasian children





Evaluation of a free public smartphone application to detect leukocoria in high-risk children aged 1 to 6 years.
J Ped Ophthal & Strab (2019) *56*(4):229-232

Clinical Systemic Disease Management

Smart Phone Applications – Strabismus Screening

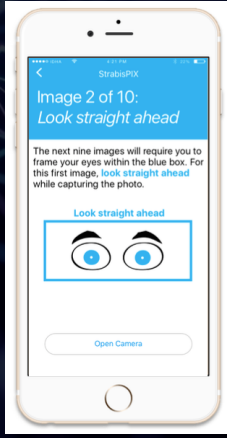
Validation of StrabisPIX, a mobile application for home measurement of ocular alignment
Trans Vision Science & Tech. (2019) *8*(2), 9-9

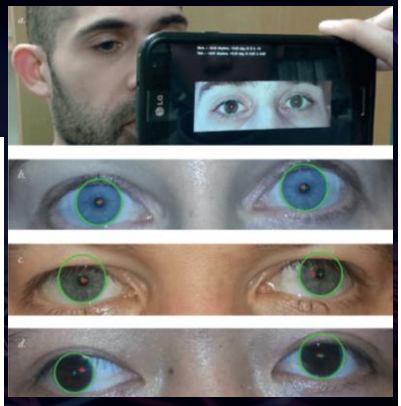
Methods:
- In this cross-sectional study, 30 strabismus patients aged ≥2 years were evaluated. Participants received standardized instructions and used StrabisPIX to obtain images as prompted. During the same visit, standard clinical images with a professional camera were taken All 60 image sets were evaluated by three observers.

Results:
- Clinic photographs had significantly higher acceptability for:
  - Horizontal versions (81% vs. 67%)
  - Vertical versions (76% vs. 60%)
  - Head posture (93% vs. 81%)

- **StrabisPIX had significantly higher detection of alignment abnormalities (89% vs. 77% for clinical photos)**

Conclusions:
- ***StrabisPIX images had similar quality and were as useful as images obtained in the clinic in detecting abnormalities***





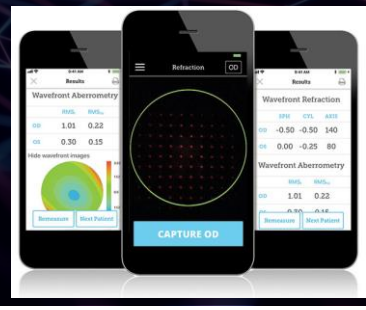
Clinical Systemic Disease Management

Smart Phone Applications - Aberrometry

Evaluation of SVOne: Handheld, smartphone-based autorefractor
Optometry and Vision Science (2015) 92(12): 1133

Methods
- Refractive error was assessed both with and without cycloplegia in 50 visually normal, young adults. Further, to assess repeatability of the instruments, the entire procedure was repeated in a subgroup of 10 subjects.

Results
- No significant difference was observed between the mean values of SE for the different techniques
- Retinoscopy and subjective refraction showed the best repeatability for pre-cycloplegic and post-cycloplegic measurements
- High and significant linear correlations were observed between the subjective findings and SVOne



Conclusions
- ***SVOne handheld aberrometer provides measurements of RE in normal, young individuals that are not significantly different from other subjective and objective procedures***

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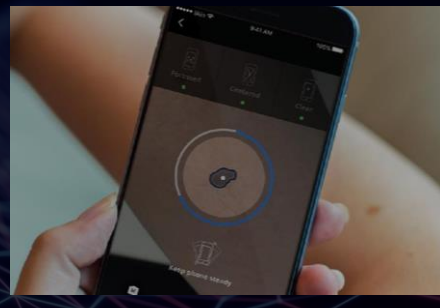
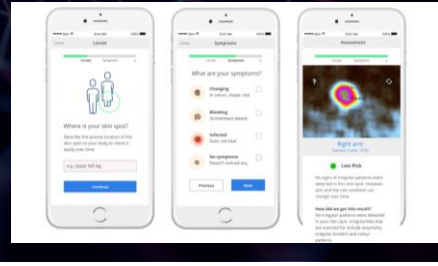
Clinical Systemic Disease Management

Smart Phone Applications – Periocular Melanoma

Accuracy of a smartphone application for triage of skin lesions based on machine learning algorithms
J European Acad Derm and Venereology (2020), 34(3), 648-655.



Methods
- Algorithm is trained on 131,873 images taken by 31,449 users and rated for risk by dermatologists.
- Evaluate sensitivity of the algorithm using 285 histopathologically validated skin cancer cases (138 malignant melanomas)
- Calculated the specificity on a separate set containing 6000 clinically validated benign cases



Results
- ***95.1% sensitivity in detecting pre-malignant conditions***
  - ***93% for malignant melanoma and 97% for keratinocyte carcinomas***
- ***78.3% specificity***

Conclusions
- ***High sensitivity to detect skin cancer with room for improvement in terms of specificity***

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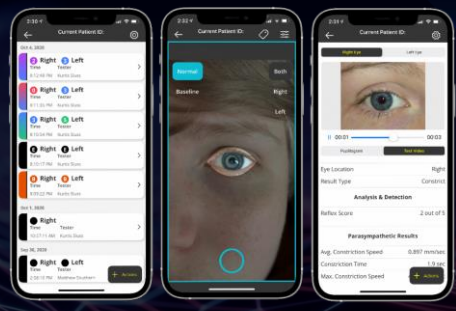
Clinical Systemic Disease Management

Smart Phone Applications – Concussion Screening

Utility of pupillary light reflex metrics as a physiologic biomarker for adolescent sport-related concussion

JAMA ophthalmology (2021)138(11), 1135-1141



DESIGN, SETTING, AND PARTICIPANTS

- Prospective cohort of adolescent athletes between ages 12 and 18 years included healthy control individuals (n=134) and athletes with a diagnosis of sport-related concussion (n=98).

RESULTS

- Pupillary light reflex metrics of 134 healthy control individuals and 98 athletes with concussion were obtained a median of 12 days following injury
- ***8 of 9 metrics were significantly greater with concussion after Bonferroni correction:***
  - ***Maximum pupil diameter***
  - ***Minimum pupil diameter***
  - ***Percentage constriction***
  - ***Average constriction velocity***
  - ***Peak constriction velocity***
  - ***Average dilation velocity***
  - ***Peak dilation velocity***
  - ***T75***
- Sex-based differences were observed, with girls with concussion exhibiting longer T75
- ***Among healthy control individuals, diminished PLR metrics were observed after exercise***

CONCLUSIONS AND RELEVANCE

- ***Quantifiable measures of the PLR may serve in the future as objective physiologic biomarkers for concussion in the adolescent athlete.***

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Clinical Systemic Disease Management

Smart Phone Applications - NITBUT Screening

Reliability and clinical applicability of a novel tear film imaging tool

Clin Exp Ophthalmol (2021) **259:** 1935–1943

METHODS

264 videos of TBUT were analyzed by three different examiners: two masked observers and a third investigator using the automatic software application. Subjective evaluation was conducted only once on an online software designed for this protocol where videos were presented in random masked order

RESULTS

- Substantial correlation was observed among the examiners
  - ***Statistical difference between observer 1 and 2 evaluations*** whereas data provided by the ***software showed no significant differences from those of the observers***
  - Similar results to the whole data set analysis were obtained when the sample was reassessed only considering mean BUT values ≤15 seconds.

CONCLUSIONS

- ***Acceptable clinical results for the software application designed to objectively measure the TBUT***

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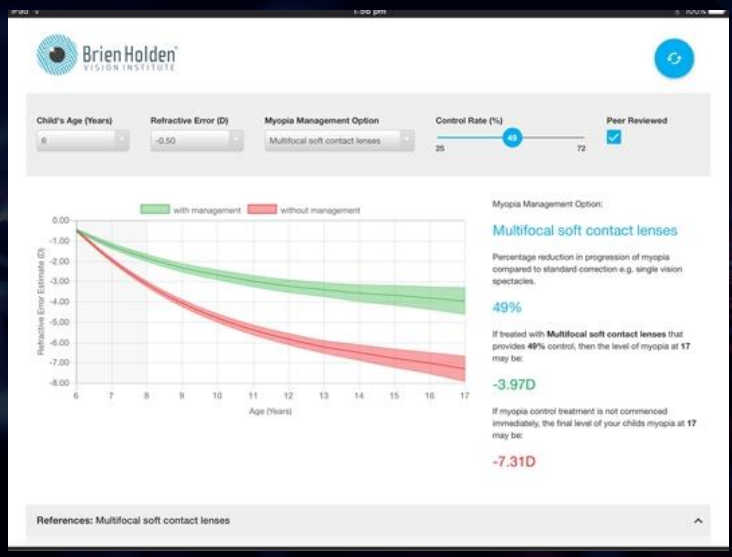
Clinical Systemic Disease Management

Smart Phone Applications – Pediatric Myopic Progression

Myopia: Should We Treat It Like a Disease? The research is mounting…
Rev Optom (2020) 157(10):32-38

- In 2015, the WHO and Brien Holden Vision Institute gathered for a global scientific summit on myopia.
- Current models project that by 2050, myopia (52%) and high myopia (10%) will reach epidemic proportions
- WHO identified the increase in myopia as the number one health threat facing vision worldwide, in part because of its association with
  - ***Myopic macular degeneration***
  - ***Cataracts***
  - ***Glaucoma***



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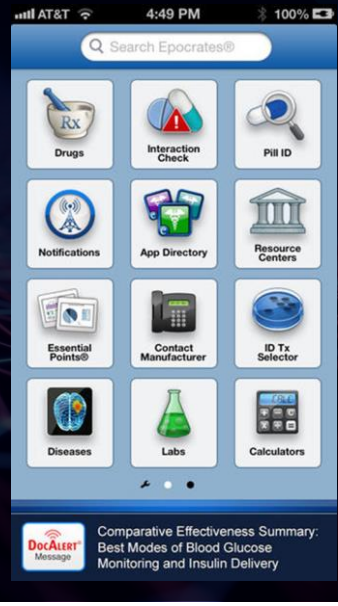
Clinical Systemic Disease Management

Smart Phone Applications – Drug Interactions / Contraindications

Mobile Medical Applications for Dosage Recommendation, Drug Adverse Reaction and Drug Interaction: Review and Comparison
Therapuetic Innov & Reg Sci (2018) 51(4)

Results
8 mobile medical apps were included and used to compare their features and functionalities. The 4 apps that scored the highest (14/17 points) are: Lexicomp®, ***Epocrates®***, Micromedex®, and Drugs.com®. Lexicomp and Micromedex do not provide the image of the drug and have an access subscription fee. Epocrates does not provide interaction classification and clinical teaching advice and occupies a large space in the memory to be installed.

Conclusion
- Based on the features assessment criteria of each mobile medical application, Lexicomp, Epocrates, Micromedex, and Drugs.com are the apps that scored the highest
- ***Epocrates® is useful for checking drug interactions and has additional features for the DoReADI criteria, dose calculator and interaction classification***



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Clinical Systemic Disease Management

Smart Phone Applications – Doc in a Box

- **Smartphone-based AI in primary care medicine**

How accurate are digital symptom assessment apps for suggesting conditions and urgency advice: Clinical vignettes comparison to GPs

BMJ Open (2020) 10:e040269

Intervention/comparator

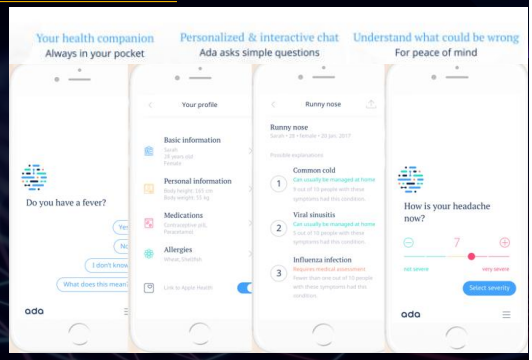
For eight apps and seven general practitioners (GPs): breadth of coverage and condition-suggestion and urgency advice accuracy measured against the vignettes' gold-standard.

Results

- ***Condition-suggestion coverage***
  - ***Ada: 99%***
- ***Top-3 suggestion accuracy for GPs (average): 82%±5%***
  - ***Ada: 71%***
- ***Safe urgency advice for GPs had an average of 97%±3%***
  - ***Ada: 97%***

Conclusions

- ***No digital tool outperformed GPs, some came close, and the nature of iterative improvements to software offers scalable improvements to care***



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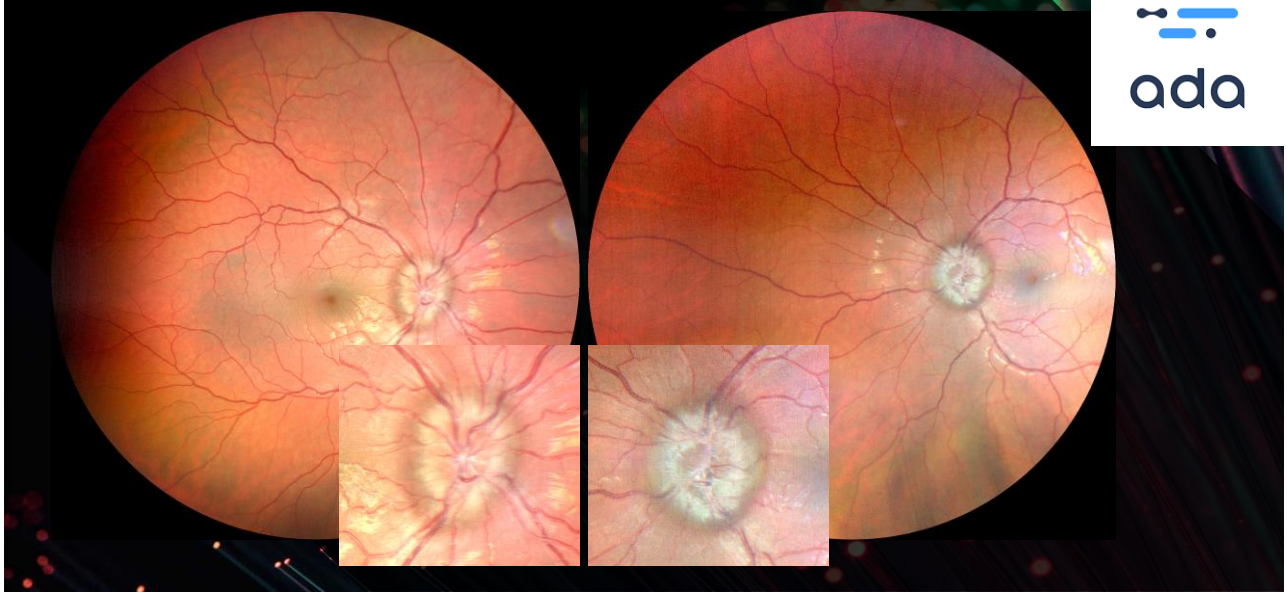
Clinical Systemic Disease Management

Smart Phone Applications – Case Report



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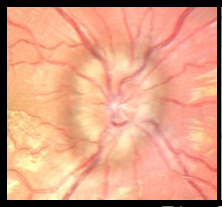
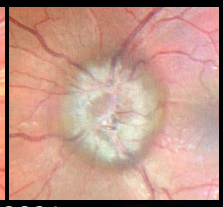
Clinical Systemic Disease Management

Smart Phone Applications – Case Report

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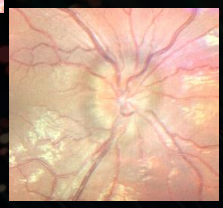
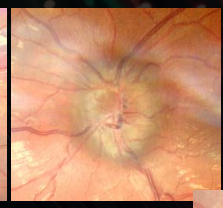

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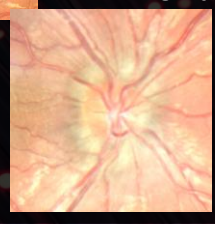
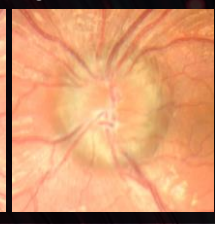

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Clinical Systemic Disease Management

Smart Phone Applications – Case Report

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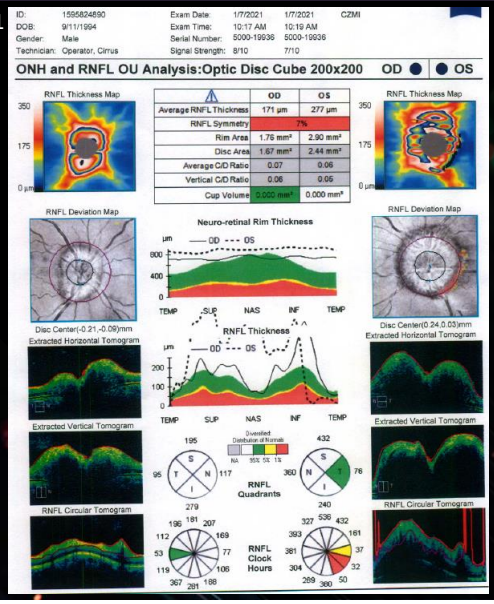

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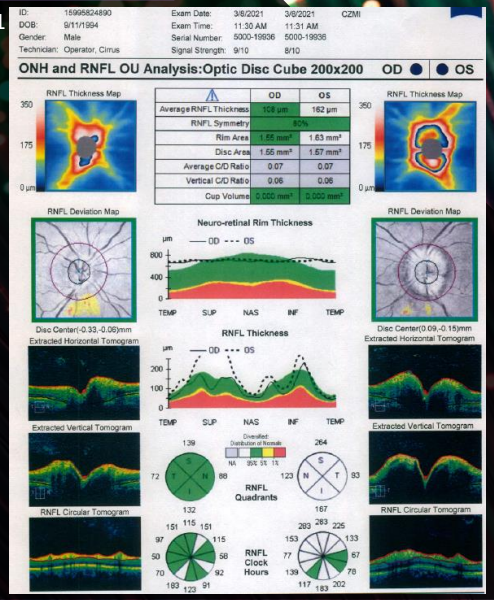

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Clinical Systemic Disease Management

Smart Phone Applications – Austere Retinal Imaging

oDocs VisoScope 20D CAD Files

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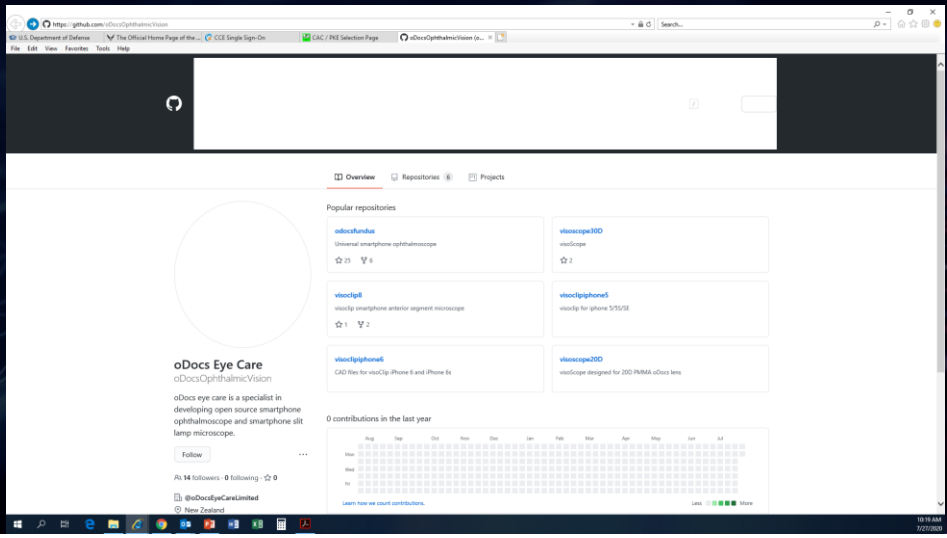
Clinical Systemic Disease Management

Smart Phone Applications – Austere Retinal Imaging

https://odocseyecare.shop/collections/all



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Opportunity and Limitations

- What's now?
- What's next?

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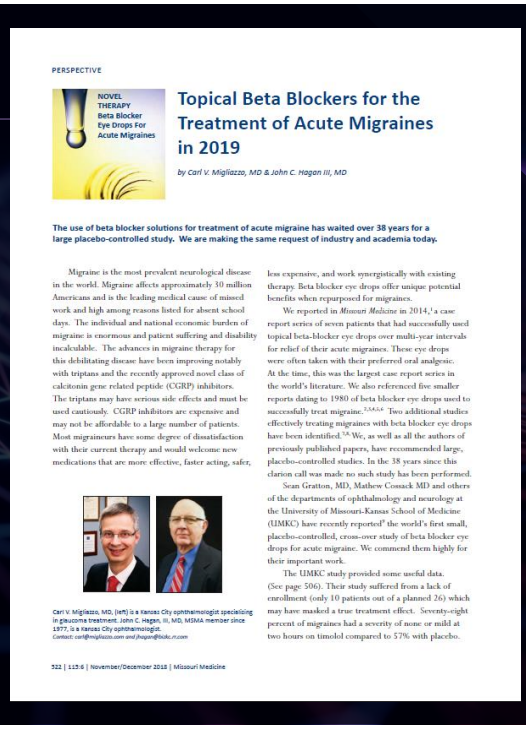
What's now?

Timolol eyedrops in the treatment of acute migraine attacks: Randomized cross-over study
JAMA Neurology (2018) 75(8):1024-1025

University of Missouri-Kansas School of Medicine reported the first small, placebo-controlled, cross-over study of topical β-blockers for acute migraine.

- Initial enrollment of 26 established migraine patients
  - ***78% of migraines had a severity of none or mild at two hours on timolol 0.5% compared to 57% with placebo***.
- Subject-rated overall effectiveness of timolol 0.5% was 2.4 out of 4 compared to 1.4 with placebo. Notably ***40% patients found β-blockers very effective while only 1 of placebo patients did***
- Vital component: ***Instillation OU at the first sign of an aura or migraine and a second set within 15 minutes***



PERSPECTIVE

NOVEL THERAPY
Beta Blocker Eye Drops For Acute Migraines

Topical Beta Blockers for the Treatment of Acute Migraines in 2019

by Carl V. Migliazzo, MD & John C. Hagan III, MD

The use of beta blocker solutions for treatment of acute migraine has waited over 38 years for a large placebo-controlled study. We are making the same request of industry and academia today.

Migraine is the most prevalent neurological disease in the world. Migraine affects approximately 30 million Americans and is the leading medical cause of missed work and high among reasons listed for absent school days. The individual and national economic burden of migraine is enormous and patient suffering and disability incalculable. The advances in migraine therapy for this debilitating disease have been improving notably with triptans and the recently approved novel class of calcitonin gene related peptide (CGRP) inhibitors. The triptans may have serious side effects and must be used cautiously. CGRP inhibitors are expensive and may not be affordable to a large number of patients. Most migraineurs have some degree of dissatisfaction with their current therapy and would welcome new medications that are more effective, faster acting, safer, less expensive, and work synergistically with existing therapy. Beta blocker eye drops offer unique potential benefits when repurposed for migraines.

We reported in *Missouri Medicine* in 2014,[1]a case report series of seven patients that had successfully used topical beta-blocker eye drops over multi-year intervals for relief of their acute migraines. These eye drops were often taken with their preferred oral analgesic. At the time, this was the largest case report series in the world's literature. We also referenced five smaller reports dating to 1980 of beta blocker eye drops used to successfully treat migraine.[2,3,4,5,6] Two additional studies effectively treating migraines with beta blocker eye drops have been identified.[7,8] We, as well as all the authors of previously published papers, have recommended large, placebo-controlled studies. In the 38 years since this clarion call was made no such study has been performed.

Sean Gratton, MD, Mathew Cossack MD and others of the departments of ophthalmology and neurology at the University of Missouri-Kansas School of Medicine (UMKC) have recently reported[9] the world's first small, placebo-controlled, cross-over study of beta blocker eye drops for acute migraine. We commend them highly for their important work.

The UMKC study provided some useful data. (See page 506). Their study suffered from a lack of enrollment (only 10 patients out of a planned 26) which may have masked a true treatment effect. Seventy-eight percent of migraines had a severity of none or mild at two hours on timolol compared to 57% with placebo.

Carl V. Migliazzo, MD, (left) is a Kansas City ophthalmologist specializing in glaucoma treatment. John C. Hagan, III, MD, MSMA member since 1977, is a Kansas City ophthalmologist.
Contact: carl@migliazzo.com and jhagan@bcbc.rr.com

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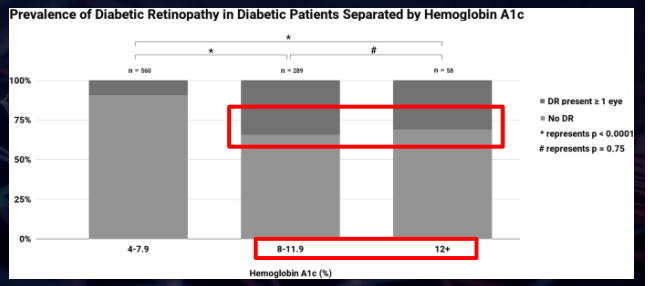
What's now?

15-Month Experience with Primary Care-based Telemedicine Screening Program for Diabetic Retinopathy
BMC Ophthal (2021) 21: 1-9

Methods:
- Review of 15 months of data investigating how many patients were screened, how often the photographs generated DR diagnosis and how many patients followed-up for an exam in the office

Results:
- 689 digital retinal screening exams of DR patients were conducted. Among all of the screening exams, 52% triggered a request for a referral to ophthalmology.
- 33% of photos were uninterpretable
- 10% suspected to have alternate condition

Conclusions:
- ***~50% of the patients required a referral***
  - ***Only 9.5% of referrals actually received an eye exam***
- ***Identification of referral-warranted diabetic retinopathy and other ophthalmic conditions is not enough***



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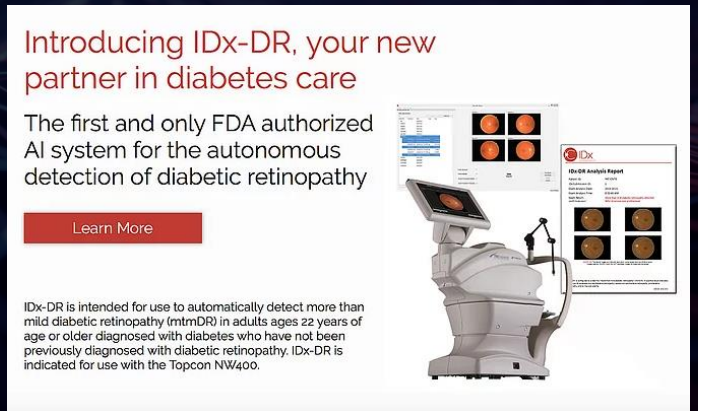
What's now?

- IDx - DR
  - FDA approved in 2018 for AI recognition of DR (including CSME) in a primary care setting
  - ***Sensitivity = 87.4%***
  - ***Specificity = 89.5%***

Validation of automated screening for referable diabetic retinopathy with the IDx-DR device in the Hoorn Diabetes Care System.
Acta ophthalmologica (2018) 96(1):63-68

Diagnostic accuracy of a device for the automated detection of diabetic retinopathy in a primary care setting.
Diabetes care (2019) 42(4):651-656



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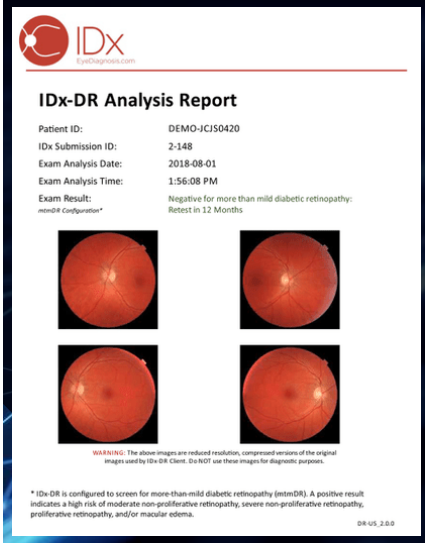
What's now?


IDx

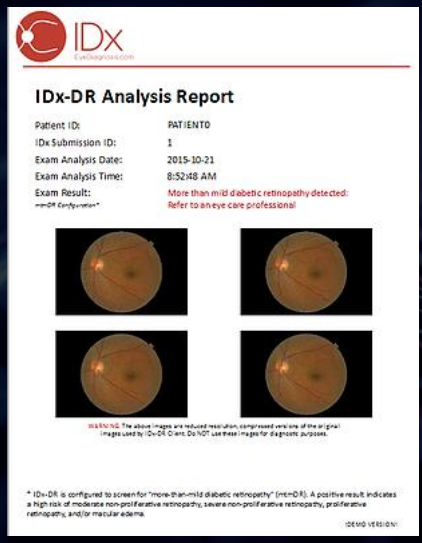
IDx-DR Analysis Report

Patient ID: DEMO-JCJS0420
IDx Submission ID: 2-148
Exam Analysis Date: 2018-08-01
Exam Analysis Time: 1:56:08 PM
Exam Result: Negative for more than mild diabetic retinopathy: Retest in 12 Months

WARNING: The above images are reduced resolution, compressed versions of the original images used by IDx-DR Client. Do NOT use these images for diagnostic purposes.

* IDx-DR is configured to screen for more-than-mild diabetic retinopathy (mtmDR). A positive result indicates a high risk of moderate non-proliferative retinopathy, severe non-proliferative retinopathy, proliferative retinopathy, and/or macular edema.

DR-US_2.0.0


IDx

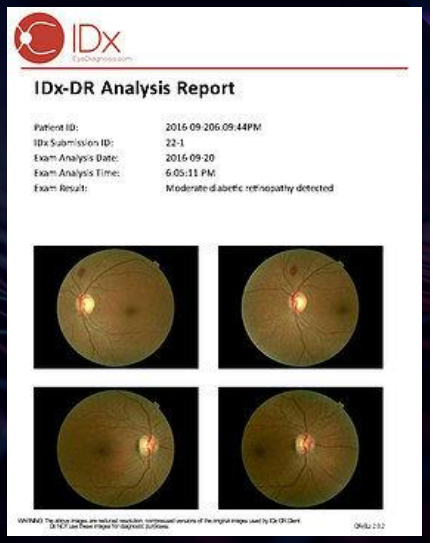
IDx-DR Analysis Report

Patient ID: PATIENT0
IDx Submission ID: 1
Exam Analysis Date: 2015-10-21
Exam Analysis Time: 8:52:48 AM
Exam Result: More than mild diabetic retinopathy detected: Refer to an eye care professional

WARNING: The above images are reduced resolution, compressed versions of the original images used by IDx-DR Client. Do NOT use these images for diagnostic purposes.

* IDx-DR is configured to screen for "more-than-mild diabetic retinopathy" (mtmDR). A positive result indicates a high risk of moderate non-proliferative retinopathy, severe non-proliferative retinopathy, proliferative retinopathy, and/or macular edema.

IDEMO VERSION


IDx

IDx-DR Analysis Report

Patient ID: 2016-09-206:09:44PM
IDx Submission ID: 22-1
Exam Analysis Date: 2016-09-20
Exam Analysis Time: 6:05:11 PM
Exam Result: Moderate diabetic retinopathy detected

WARNING: The above images are reduced resolution, compressed versions of the original images used by IDx-DR Client. DO NOT use these images for diagnostic purposes.

OKAU 2.0.2

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What's now?

Comparison of the handheld RETeval ERG system with a routine ERG system in healthy adults and in pediatric patients

Eye (2022) *35*(8):2180-2189

Methods

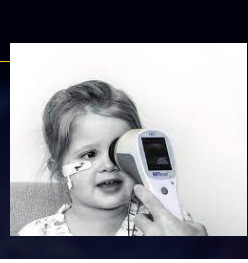
- Cone and rod ERGs were recorded using a standard photic stimulator and the RETeval device using ***skin electrodes, without mydriasis and under dark / light conditions*** in 44 healthy adult subjects and 37 pediatric patients

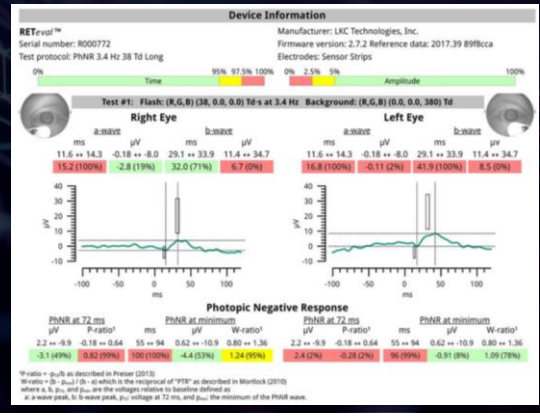
Results

- ***Lack of absolute agreement in the measurements between the two devices, highlighting the need for device-specific reference data***
- Pediatric group showed high level of diagnostic agreement between both systems
  - ***RETeval***
    - ***Sensitivity = 1.0***
    - ***Specificity = 0.91***

Conclusions

- ***ERGs are similar between the two methodologies***
- ***RETeval device is useful tool for assessing pediatric retinal function***





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Takeaways…

- **Putnam's Clinical Practice Guidelines**
  - **AMD**
  - **Catquest-9SF**
  - **Corneal Arcus and Cataract Grading**
  - **Corneal Ectasia**
  - **CQ and HCQ Screening Guidelines**
  - **DR + DR Follow-up Schedule**
  - **MCI**
  - **mTBI + BIVSS + Morgan's Norms**
  - **Ocular Trauma + Patient Intake Form**
  - **Pediatric Myopia Progression**
  - **Primary Brain Tumors**
  - **POAG**
  - **Sudden Onset Diplopia**
  - **Sudden Vision Loss**
  - **Thyroid Eye Disease**
  - **Uveitis + Bayesian Probability**

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Takeaways…

Putnam Preferred Practice Pattern – DR Worksheet

- **History**
  - Duration of DM diagnosis
  - Past glycemic control (*FBS* and *HbA1C*)
  - Medications
  - MHx (Obesity / renal disease / *HTN* / *dyslipidemia* / neuropathy)
  - OcHx (Trauma / Eye disease / Surgery or Injections)
- Laboratory testing
  - Fasting glucose (<110 mg/dL) and A1c (<6%)
  - Lipid panel (HDL/*LDL* + *total cholesterol* + triglycerides)
- B/P measured 3X
  - Mean Arterial Pressure (MAP) = [systolic + (2*diastolic)]/3
  - Mean Ophthalmic Perfusion Pressure = [(0.67*MAP) - IOP]
    - Difference between diurnal and nocturnal MAP is nocturnal hypotension
- BCVA
  - ETDRS
  - Pelli-Robson or PV 5%
- CCT Threshold
- Baseline Imaging
  - Full color fundus
    - (+/-) CSME - Retinal thickening within 500 µm of macular center
      - Hard exudates within 500 µm of macular center
      - Retinal thickening >1DD with any portion within 1DD of the macular center
    - (+/-) Signs of NPDR
    - (+/-) Center-involved
    - (+/-) ONH neovascularization
    - (+/-) Vitreous / pre-retinal hemorrhage
  - FAF (ultra-wide-field, if possible)
  - OCT 5-line Raster
    - Identification of changes foveal thinning of inner retinal layers
  - OCTA
    - Create baseline vascular appearance
    - Identify early neovascularization (deep plexus / choriocapillaris / Bruch's / intraretinal)
- Oral Supplementation
- Oral Supplementation
  - Lutein and Zeaxanthin and meso-zeaxanthin
    - MacuHealth **[10/2/10]** / Nature's Plus Ultra Lutein **[20/2/0]**
  - Ω-3 1000mg (DHA 650mg + EPA 350mg)
  - *Trans*-resveratrol 500mg QD
  - Curcumin 500-1000mg QD

Diabetic Retinopathy (Management Recommendations)

Management Recommendations for Patients with Diabetes

Severity of Retinopathy	Presence of Macular Edema	Follow-up (Months)	Panretinal Photocoagulation (Scatter) Laser	Focal and/or Grid Laser*	Intravitreal Anti-VEGF Therapy
Normal or minimal NPDR	No	12	No	No	No
Mild NPDR	No	12	No	No	No
	ME	4–6	No	No	No
	CSME†	1*	No	Sometimes	Sometimes
Moderate NPDR	No	6–12	No	No	No
	ME	3–6	No	No	No
	CSME†	1*	No	Sometimes	Sometimes
Severe NPDR	No	4	Sometimes	No	No
	ME	2–4	Sometimes	No	No
	CSME†	1*	Sometimes	Sometimes	Sometimes
Non-high-risk PDR	No	4	Sometimes	No	No
	ME	4	Sometimes	No	No
	CSME†	1*	Sometimes	Sometimes	Sometimes
High-risk PDR	No	4	Recommended	No	Considered
	ME	4	Recommended	Sometimes	Usually
	CSME†	1*	Recommended	Sometimes	Usually

Anti-VEGF = anti-vascular endothelial growth factor; CSME = clinically significant macular edema; ME = non-clinically significant macular edema; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy

* Adjunctive treatments that may be considered include intravitreal corticosteroids or anti-VEGF agents (off-label use, except aflibercept and ranibizumab). Data from the Diabetic Retinopathy Clinical Research Network in 2011 demonstrated that, at two years of follow-up, intravitreal ranibizumab with prompt or deferred laser resulted in greater visual acuity gain and intravitreal triamcinolone acetonide plus laser also resulted in greater visual gain in pseudophakic eyes compared with laser alone. Individuals receiving the intravitreal injections of anti-VEGF agents may be re-examined as early as one month following injection.

† Exceptions include hypertension or fluid retention associated with heart failure, renal failure, pregnancy, or any other causes that may aggravate macular edema. Deferral of photocoagulation for a brief period of medical treatment may be considered in these cases. Also, deferral of CSME treatment is an option when the center of the macula is not involved, visual acuity is excellent, close follow-up is possible, and the patient understands the risks.

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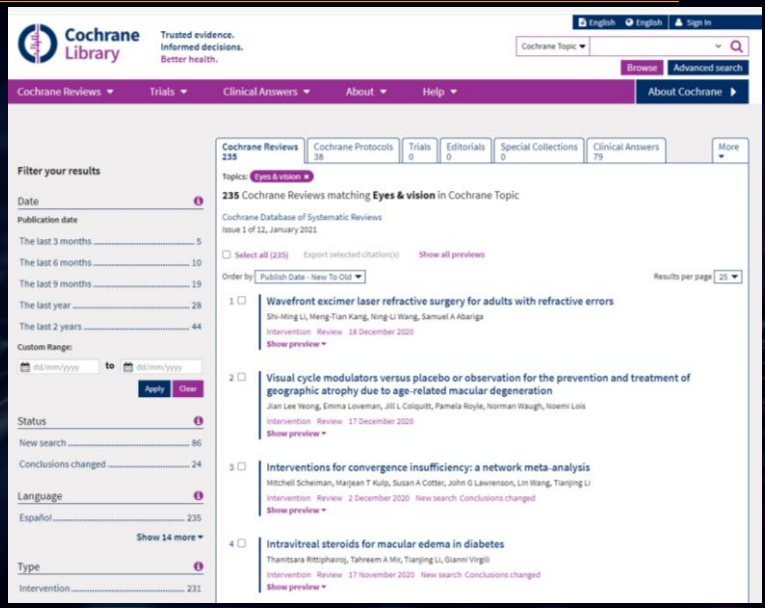
https://www.cochrane.org/evidence



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Wrap-Up

- **Preventive medicine and systemic disease diagnosis and management of vasculopathy, neurodegeneration, autoimmune and collagen vascular disease includes comprehensive eye exams, ancillary testing and high-resolution imaging**
  - ***This is what optometry does***
- **Mitigation of systemic *microvascular insults*, *inflammation* and *oxidative stress* have direct benefits in both retinal and systemic health and function**
- **Smartphone-based apps have a force multiplying effect**
  - ***No replacement for a comprehensive exam but accurate, repeatable screening devices allow for population-level use***
- **AI and Deep Learning algorithms are here to stay**

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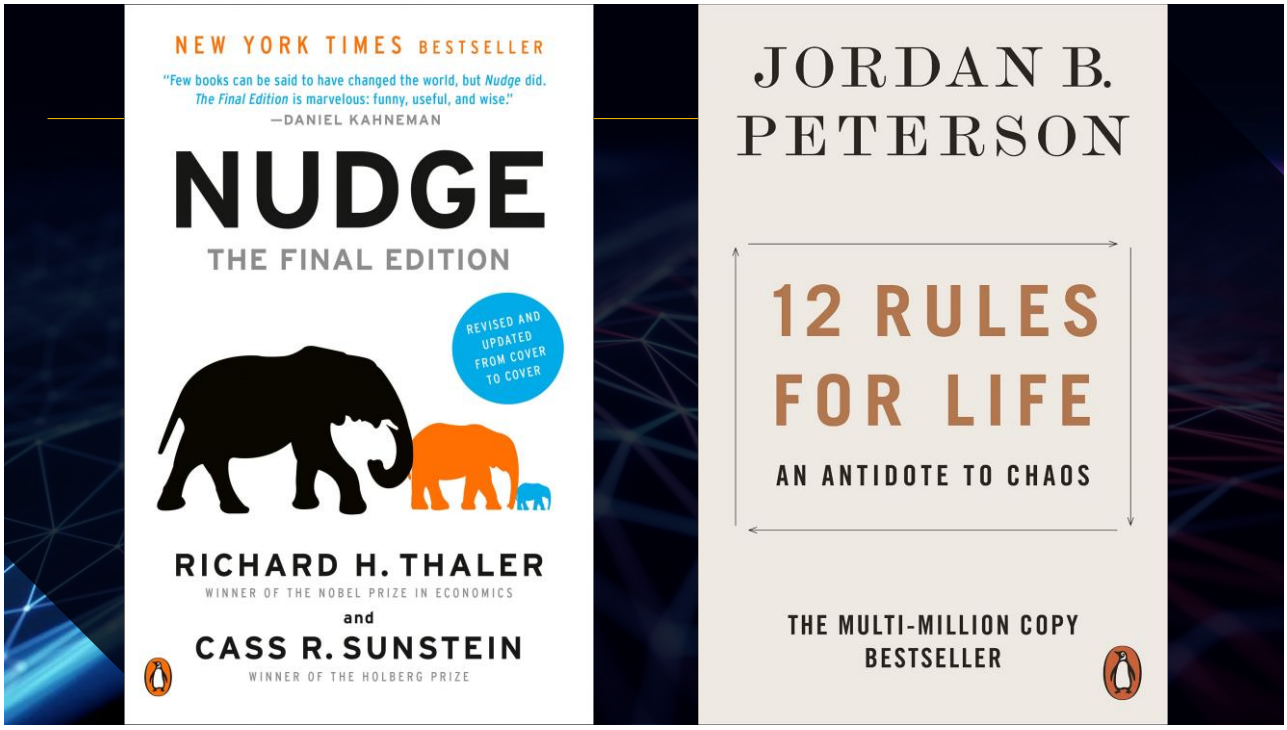
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Questions?
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