Subclinical Retinopathy *(and more!)* Diagnosis and Management

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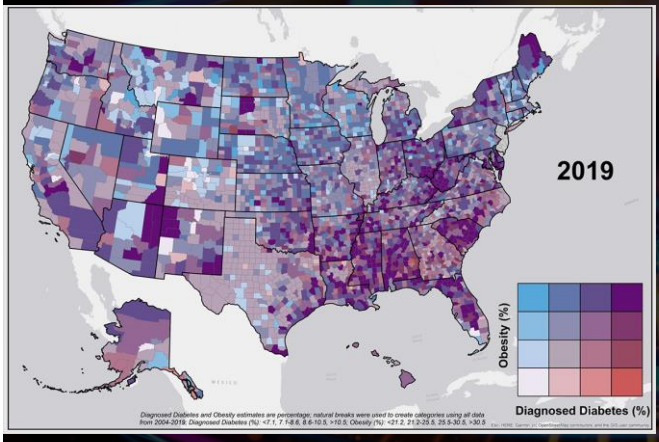
Clinical Retinopathy *Prevalence*



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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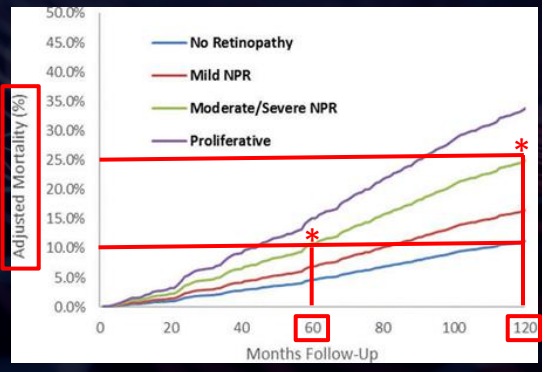
Clinical Retinopathy
Pathogenesis

Retinopathy is Associated With Stroke, Dementia and Mortality
Stroke (2021) 52 (Suppl_1) A8-A8

Methods
- NHNES data from 2005 to 2008 linked to mortality through 2015

Results
- 5,543 participants with gradable retinal imaging,
  - 696 had retinopathy
  - 289 had stroke
  - 597 had dementia
- Age-associated ***stroke risk (adj OR 2.39)*** and ***dementia risk (adj OR 1.68)***
- Over 10-years, dose-dependent relationship b/t retinopathy severity and all-cause mortality
  - ***Adjusted HR:***
    - ***1.0 (None)***
    - ***1.5 (Mild NPR)***
    - ***2.4 (Moderate/Severe NPR)***
    - ***3.4 (Proliferative DR)***



Conclusions
- Participants with retinopathy have:
  - ***2.4X increase in stroke risk***
  - ***1.7X increase in dementia risk***
  - ***Severe retinopathy confers a higher risk of death (adjusted for age and vascular risk factors)***
  - ***Retina may serve as a tissue biomarker for cerebrovascular and neurodegenerative diseases***

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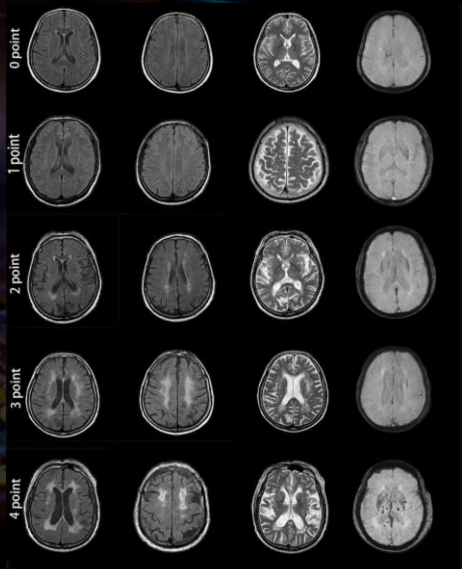
Clinical Retinopathy
Pathogenesis – Microvascular insults

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
- 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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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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Systemic Diagnosis and Mangement

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

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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

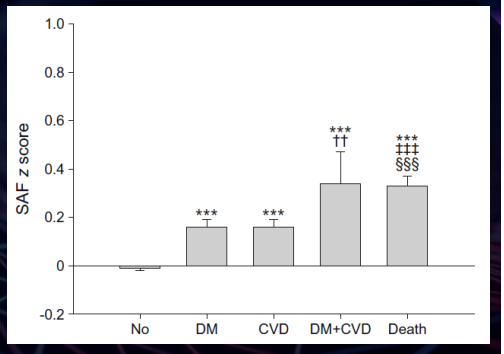
- 72,880 participants ***without*** DM or CVD underwent baseline skin AF values
- Participants were diagnosed by a fasting blood glucose ≥126mg/dL or HbA1c ≥ 6.5%
- Participants were diagnosed as having incident CVD
  - MI / coronary interventions / CVA / TIA / vascular surgery

Results

- Median follow-up of 4 years
  - 1056 participants (1.4%) developed DMII
  - 1258 individuals (1.7%) were diagnosed with CVD
  - 928 (1.3%) 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

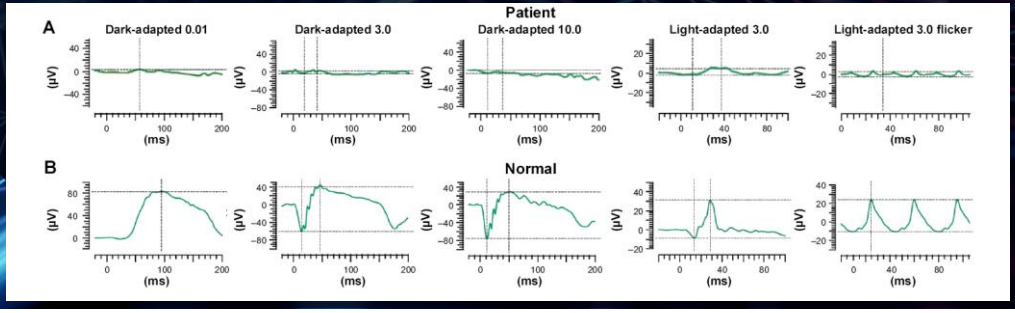
Screening for DR using new mydriasis-free, full-field flicker ERG recording

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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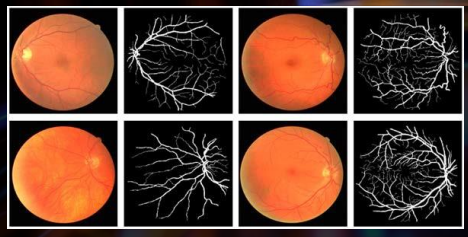
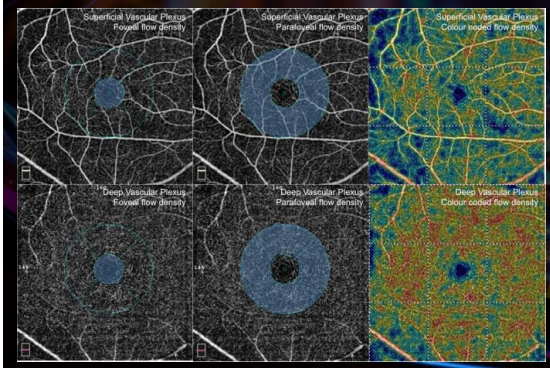
Vasculopathies
Hypertension





- 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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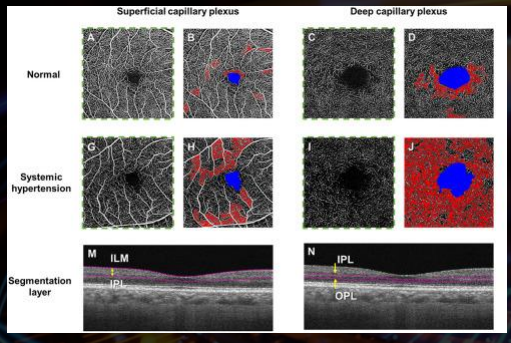
Vasculopathies
Hypertension



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
- 9 studies analyzed vessel density at the superficial capillary plexus (SCP)
- 7 analyzed vessel density at the deep capillary plexus (DCP)
- 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 significantly lower SCP and DCP 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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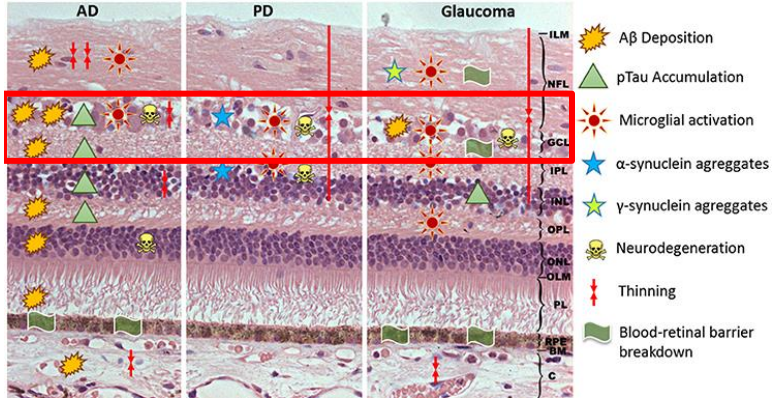
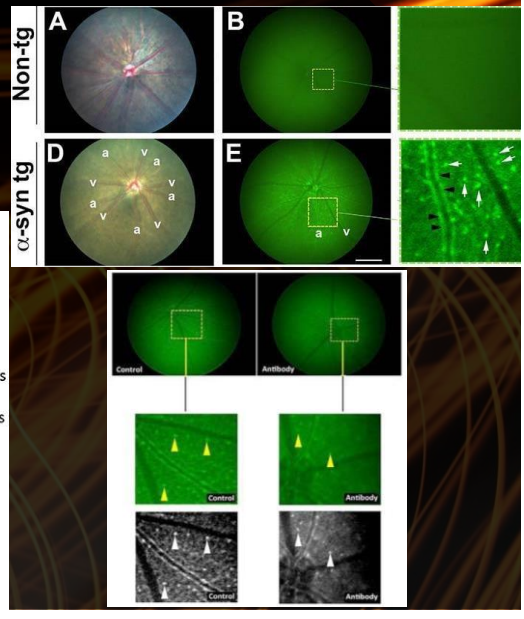
Neurodegenerative disease

Parkinson's Disease and Lewy Body 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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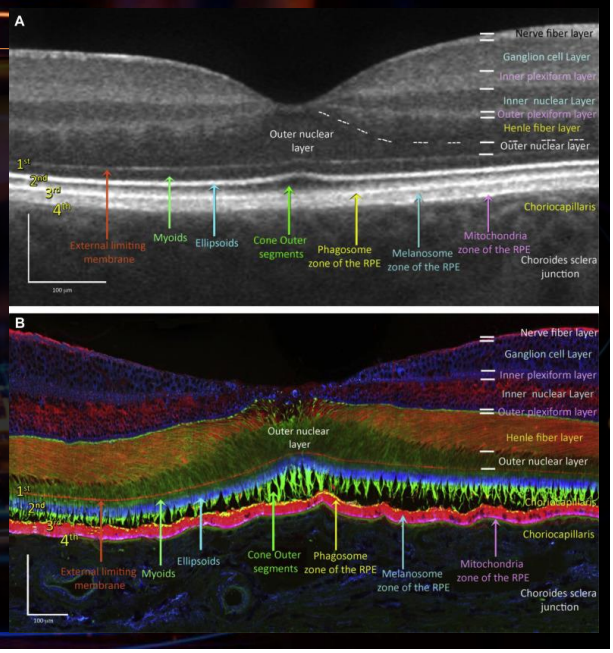
Clinical Retinal Imaging
Parkinson's disease (PD)

Central retina thickness measured with SD-OCT in Parkinson's disease: Meta-analysis
Medicine (2023) 102(40):e35354

Methods
- Searched PubMed and the Excerpta Medica databases to identify studies comparing macular thickness between patients with PD and healthy controls

Results
- 32 studies with a cross-sectional design including 2118 PD patients and 2338 controls
- Identified significant thickness differences between PD patients and controls
  - ***GC-IPL (MD –0.41)***
  - ***Macular GCC (MD –0.33)***

Discussion
- ***Results corroborate increased prevalence of changes in SD-OCT measures in individuals with PD highlighting the efficacy of macular thickness as biomarker for PD***



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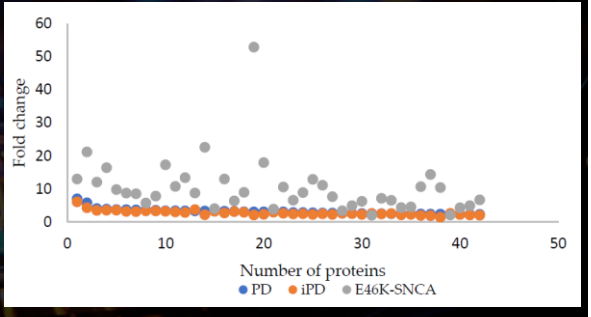
Neurodegenerative disease
Parkinson's Disease

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, lactoferrin and MMP9 were measured

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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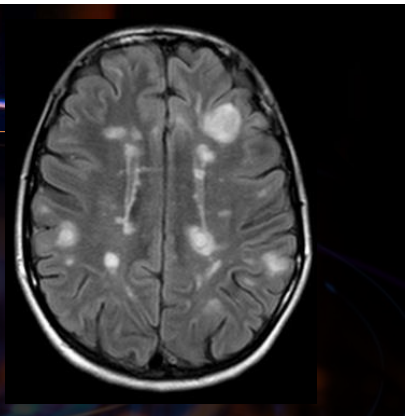
Neurodegenerative disease
Multiple Sclerosis



- Autoimmune disease represented by axon demyelination, disruption of inflammatory homeostasis and neuronal death affecting genetically susceptible individuals with ***mean onset 20-40 yo***
  - ***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

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis
Science 2022 (375) 6578:296-301

- Tested hypothesis that MS is caused by EBV in a cohort of ***10 million*** young adults on active duty in the US military
  - ***955*** diagnosed with MS during their service
- ***Risk of MS increased 32X after infection with EBV***
  - ***NOT increased after other viral infection with including the similarly transmitted CMV***
  - ***Nf-L*** serum levels increased ***only*** after EBV seroconversion
    - ***Findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause***

RESEARCH

REPORT

MULTIPLE SCLEROSIS

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis

Kjetil Bjornevik[1†], Marianna Cortese[2†], Brian C. Healy[3,4], Jens Kuhle[5], Michael J. Mina[6,7,8], Yumei Leng[9], Stephen J. Elledge[9], David W. Mechaber[10], Ann J. Ascherio[2,11‡], Kassandra L. Munger[2‡], Alberto Ascherio[2,11‡‡]

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system of unknown etiology. We tested the hypothesis that MS is caused by Epstein-Barr virus (EBV) in a cohort comprising more than 10 million young adults on active duty in the US military, 955 of whom were diagnosed with MS during their period of service. Risk of MS increased 32-fold after infection with EBV but was not increased after infection with other viruses, including the similarly transmitted cytomegalovirus. Serum levels of neurofilament light chain, a biomarker of neuroaxonal degeneration, increased only after EBV seroconversion. These findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause of MS.

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system (CNS) of unknown etiology. The demyelination in the brain and spinal cord is an immune-mediated process (1) possibly triggered by a viral infection (2). Among the putative causal agents, the top candidate is Epstein-Barr virus (EBV) (3). EBV is a human herpesvirus that after infection persists in latent form in B lymphocytes throughout the life of the host (3). A causal role of EBV is supported by the increased MS risk after infectious mononucleosis (4), elevated serum antibody titers against EBV nuclear antigens (EBNAs) (5), and by the presence of EBV in MS demyelinated lesions reported in some (6–8), but not all (9), pathological studies. Evidence of causality, however, remains inconclusive.

Causality implies that some individuals who developed MS after EBV infection would not have developed MS if they had not been infected with EBV. Ruling out a randomized trial, the gold standard to study this counterfactual occurrence is an "experiment of nature," a longitudinal investigation of MS incidence in a cohort of EBV-negative individuals, some of whom will be infected with EBV during the follow-up and some who will not. The ubiquitous nature of EBV, which infects ~95% of adults, and the fact that MS is a relatively rare disease, has until now impeded such an investigation. Over the course of a 20-year collaboration with the US military, we have identified cases of MS in a cohort composed of active-duty US military personnel between 1993 and 2013, a racially diverse population of >10 million individuals. Active-duty members are screened for HIV at the start of military service and biennially thereafter, and residual serum from these tests (~82 million serum samples) is archived in the Department of Defense Serum Repository (DoDSR) (10). We used samples stored in the DoDSR to determine EBV status at time of first sample and the relation between EBV infection and MS onset during the period of active duty. In a preliminary study, we found that 5.3% of individuals were EBV-negative at the time of first sample (11), corresponding to hundreds of thousands of EBV-negative young adults at risk of EBV infection and MS.

We documented 955 incident MS cases among active-duty military personnel (including 35 cases from our preliminary study [11]). For each MS case, we identified up to three serum samples collected before the date of MS onset (the first available, the last collected before disease onset, and one in between). Cases were matched to two randomly selected individuals without MS of the same age, sex, race/ethnicity, branch of military service, and date of collection of blood samples who were on active military duty when the case was diagnosed (Fig. 1A and fig. S1). There were 801 MS cases and 1566 control sets with samples available to assess EBV infection status. Most of the individuals in our study were <20 years of age at the time of their first blood collection (Fig. 1B), and those who developed MS had symptom onset a median of 10 years after time of first sample (Fig. 1C).

Only one of the 801 MS cases occurred in an individual who was EBV-negative in the last sample, which was collected at a median of 1 year before MS onset [hazard ratio (HR) for MS comparing EBV-positive versus EBV-negative = 265; 95% confidence interval (CI): 3.7 to 19,160; $P = 0.001$, conditional logistic regression]. At baseline, 35 MS cases and 107 controls were EBV-negative. All but one of these 35 EBV-negative MS cases became infected with EBV during the follow-up, and all seroconverted before the onset of MS (fig. S3). The median time from the first EBV-positive sample to MS onset was 5 years (range: 0 to 19 years), and the median time from estimated EBV seroconversion, defined as the midpoint between the last seronegative sample and the first seropositive sample, to MS onset was 7.5 years (range: 2 to 21 years). The high seroconversion rate among individuals who developed MS during follow-up (97%) contrasts with the 0% rate of seroconversion observed among individuals who did not develop MS (Fig. 2A), a rate consistent with previous reports among EBV-negative young adults (12). The HR for MS comparing EBV seroconversion versus persistent EBV seronegativity was 32.4 (95% CI: 4.3 to 245.3, $P < 0.001$) (Fig. 2C).

Behavioral, environmental, or personal characteristics may correlate with a protein position to both infection and MS. To assess this possibility, we measured antibodies against cytomegalovirus (CMV), a herpesvirus that, like EBV, is transmitted through the saliva. CMV displays socioeconomic and racial/ethnic disparities in age at infection in the US population (13) similar to those of EBV (14), thus constituting an ideal negative control (15). Among those who were CMV-negative at baseline, seroconversion for CMV occurred at a similar rate in those who later developed MS and those who did not (Fig. 2B). MS risk was lower among CMV-positive

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‡These authors contributed equally to this work.

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Herpesvirus affecting humans

- ***HSV 1/2***
- ***VZV***
- ***CMV***
- ***EBV***
- **Herpesvirus 6 (A/B)**
- **Herpesvirus 7**
- ***Herpesvirus 8***
  - ***Kaposi's sarcoma***

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Neurodegenerative disease

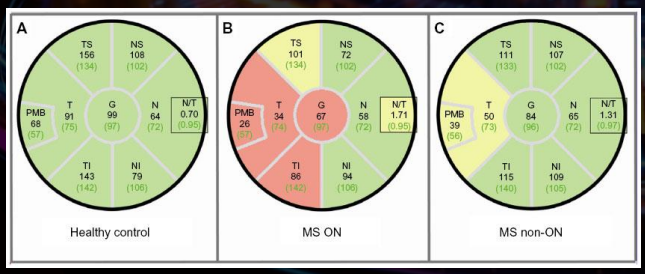
Multiple Sclerosis

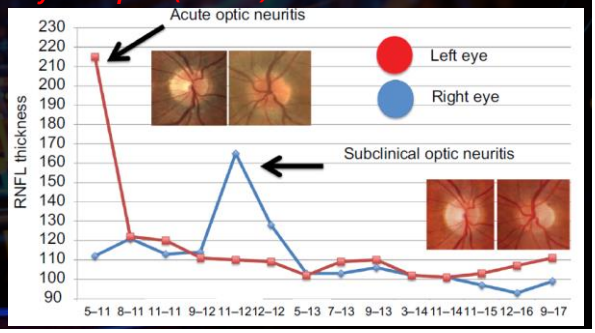
Retinal asymmetry in multiple sclerosis

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 (NMOSD)***





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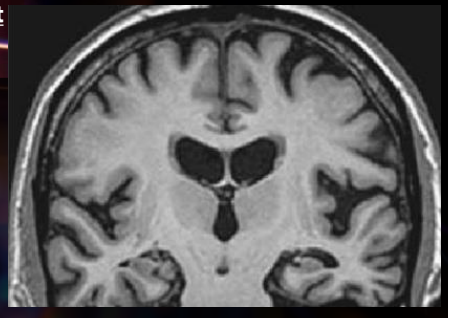
Neurodegenerative disease

Alzheimer's disease (AD)

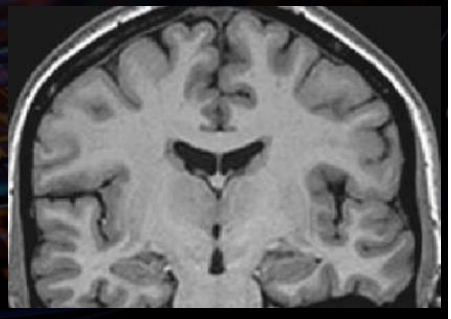
- AD is characterized by an insidious onset of cognitive decline beginning with deficits in episodic memory:
  - forgetting recent personal and family events
  - losing items around the house
  - repetitive questioning
- As the disease progresses, other deficits gradually arise including:
  - Aphasia **(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**

AD subject



Control



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Neurodegenerative disease
Alzheimer's disease (AD)

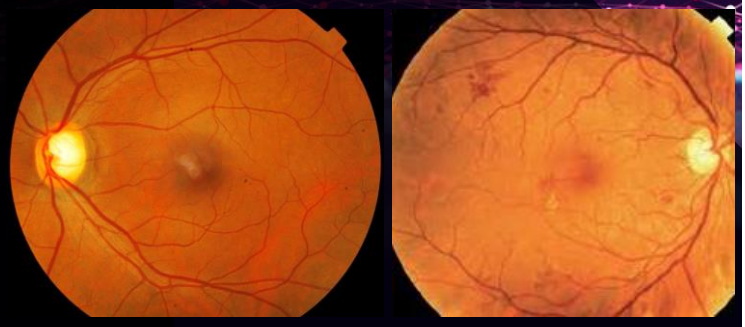
Associations between recent and established ophthalmic conditions and risk of AD
Alzheimer's and Dementia (2019) 15:34-41

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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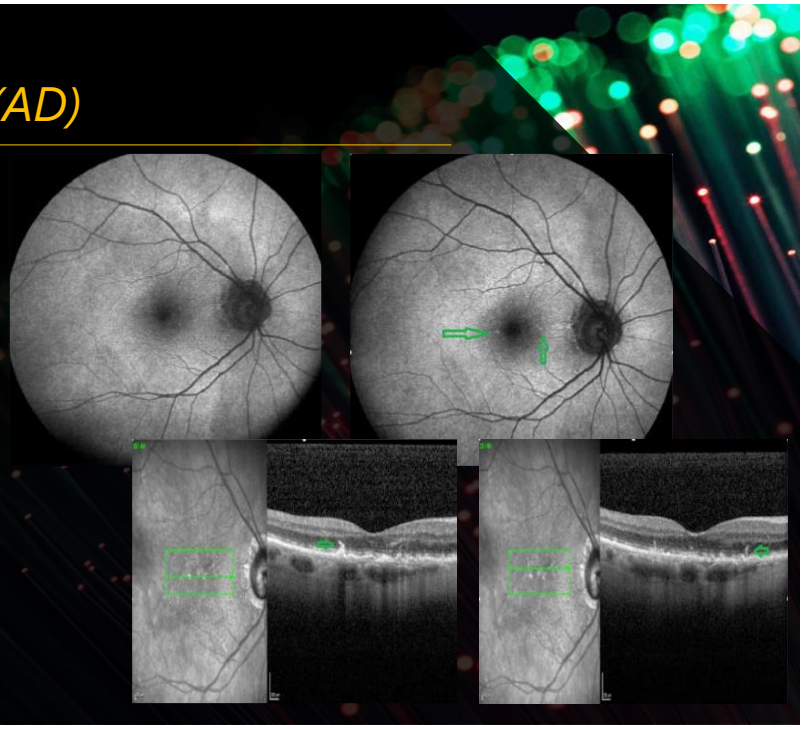
Neurodegenerative disease
Alzheimer's disease (AD)

Retinal amyloid pathology and proof-of-concept imaging trial in Alzheimer's disease
JCI Insights (2017) 2(16)

- Curcumin (derived from turmeric) is a lipophilic polyphenol and fluorophore with high affinity to A_β
- A_β in AMD Lesions isolated in patient diagnosed with Alzheimer's Disease in 4 separate studies since 2017
- High bioavailability, proprietary blend used in conjunction with cSLO:
  - ***100% sensitivity***
  - ***81% specificity***
- ***Retinal A_β load was strongly correlated with brain amyloid plaque burden confirmed through PET imaging***



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Neurodegenerative disease

Alzheimer's disease (AD)

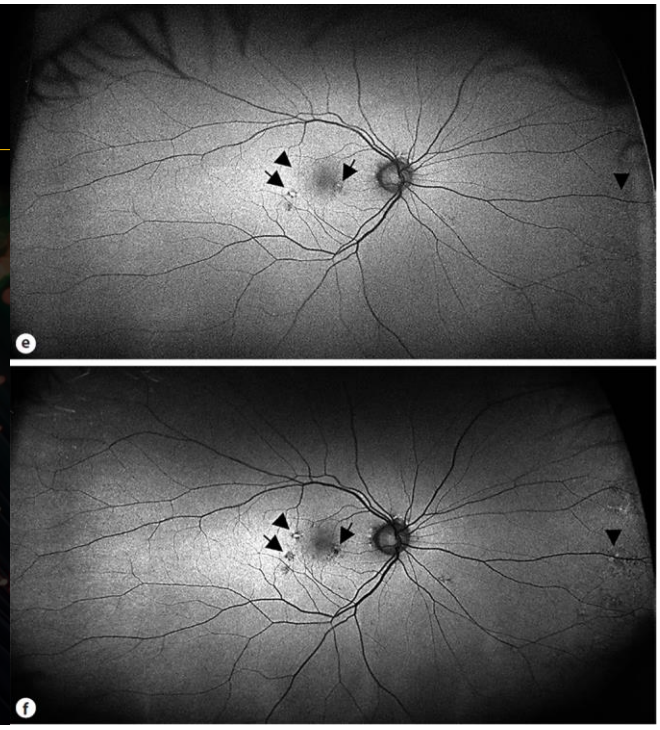
Peripheral Retinal Imaging Biomarkers for Alzheimer's Disease: A Pilot Study
Ophthalmic Research (2018) 24.5

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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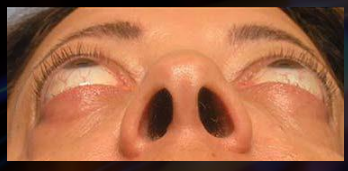
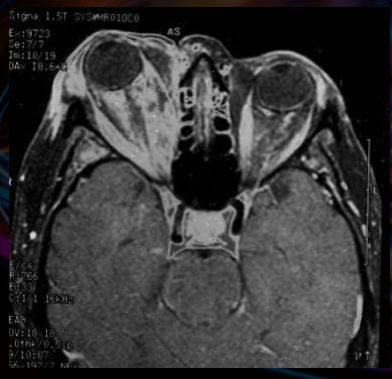
Autoimmune disease

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 (associated with IBD)***
  - Addison's disease (hypocortisolism)

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Autoimmune disease

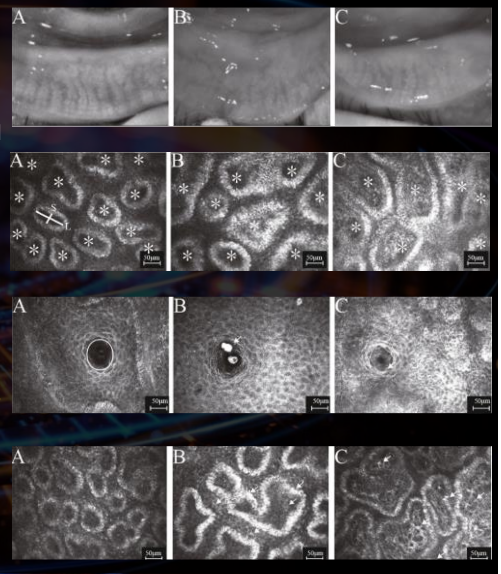
Grave's disease –> Thyroid Eye Disease

***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
- Complete ophthalmic examination was performed including external eye, ocular surface and MGs including *in vivo* confocal ophthalmoscopy

Results
- 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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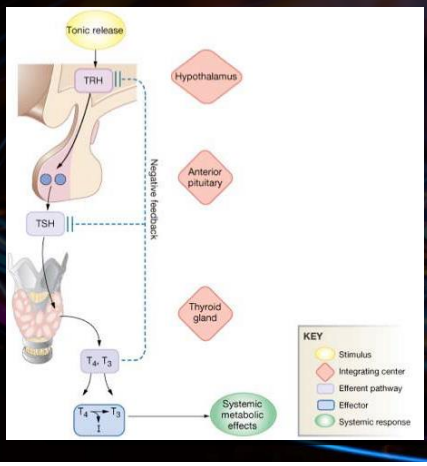
Autoimmune disease

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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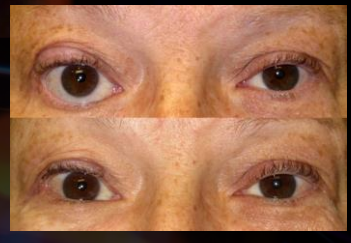
Autoimmune disease

Grave's disease –> Thyroid Eye Disease



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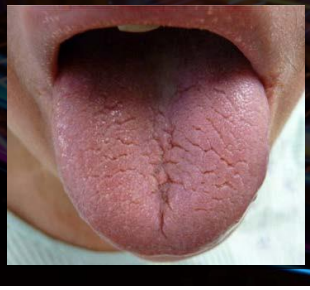
Autoimmune disease
Sjogren's disease



- ***2nd most common chronic autoimmune rheumatic disease***
  - Associated with a high burden of illness.
- Common clinical manifestations include xerostomia and KCS 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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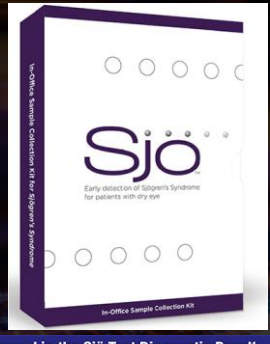
Autoimmune disease
Sjogren's disease

Early detection of Sjogren's syndrome: sensitivity and specificity of Sjo Diagnostic Test
Invest Ophthal Vis Sci (2016) 57:5681

Methods
- Traditional antibody markers
  - SSA, SSB, ANA and RF
- Novel biomarkers
  - Salivary protein-1 [SP1]
  - Carbonic anhydrase-6 [CA6]
  - Parotid secretory protein [PSP]
- Serum samples using the Sjö panel assessed from 267 confirmed SS patients 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 POAG patients and 179 controls were included
- Overall prevalence of AiD
  - ***17% in POAG group vs. 10% in 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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Autoimmune disease

Prevalence of Autoimmune Disease in AMD

Propensity-Matched Analysis of AMD Risk with Systemic Immune-Mediated Inflammatory Disease

Ophthal Retina (2024) S2468-6530(24)00058-7

Methods

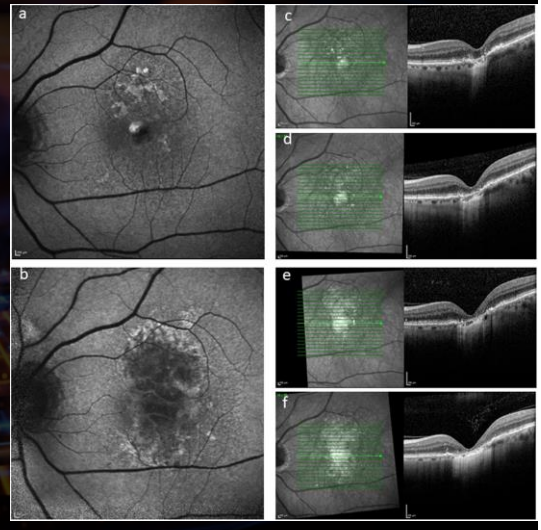
- National database (2006–2023), using ICD-10 codes to select for IMIDs
- Risk was calculated for IMIDs and compared between AMD and control patients

Results

- AMD (n=217) and controls (n=197) had mean age of 75 ± 10 years
  - ***IMID (RR 1.50)***
    - ***RA (RR 1.40)***
    - ***SLE (RR 1.73)***
    - ***Crohn's disease (RR 1.42)***
    - ***UC (RR 1.45)***
    - ***Psoriasis (RR 1.48)***
    - ***Vasculitis (RR 1.48)***
    - ***Scleroderma (RR 1.65)***
    - ***Sarcoidosis (RR 1.42)***

Conclusions

- Results suggest ***increased risk of developing AMD in patients with RA, SLE, Crohn's disease, ulcerative colitis, psoriasis, vasculitis, scleroderma, and sarcoidosis compared with patients with no IMIDs***



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Systemic Diagnosis and Mangement

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

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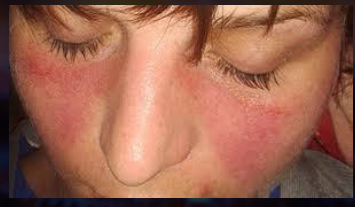
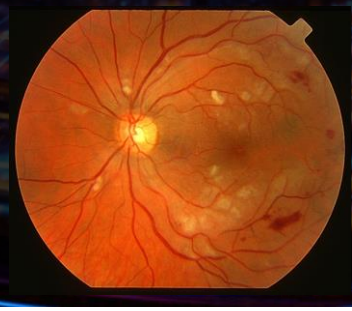
Collagen Vascular Disease

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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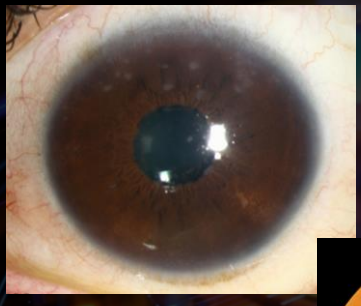
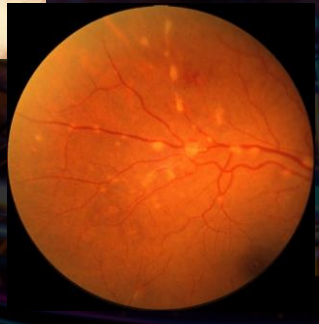
Collagen Vascular Disease
Sarcoidosis





- 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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Development and validation of Bayesian network for differential diagnosis of anterior uveitis

Eye (2016) 30(6): 865-872

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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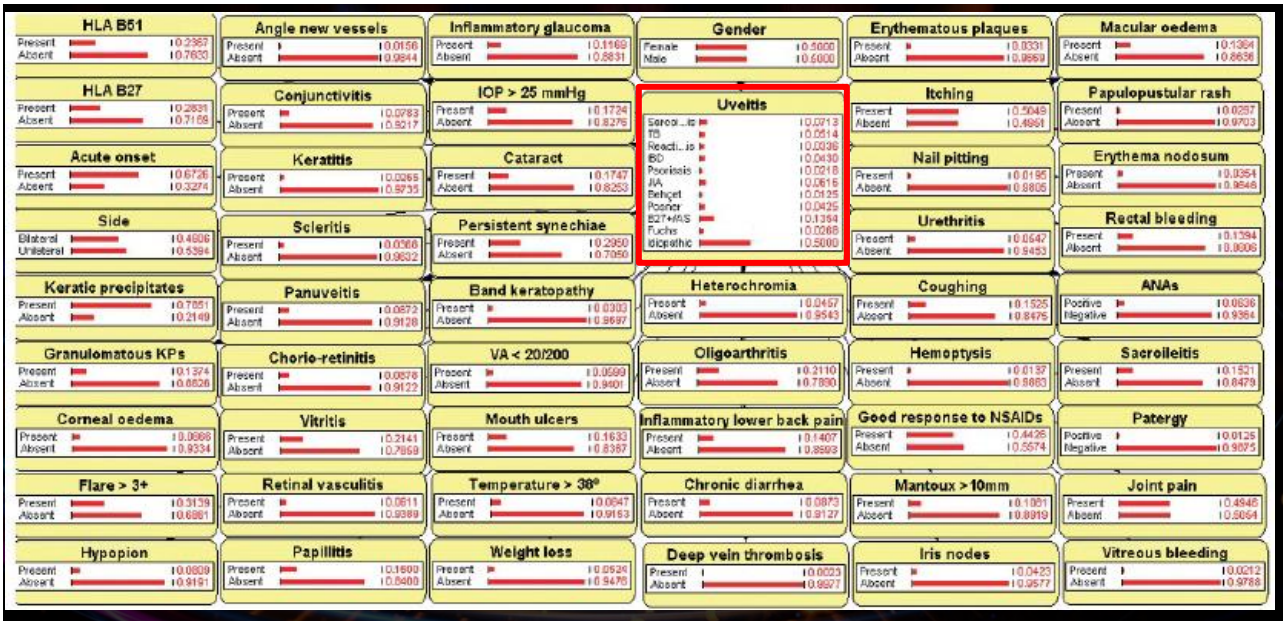

Bayesian inference mode using only population averages and zero clinical data

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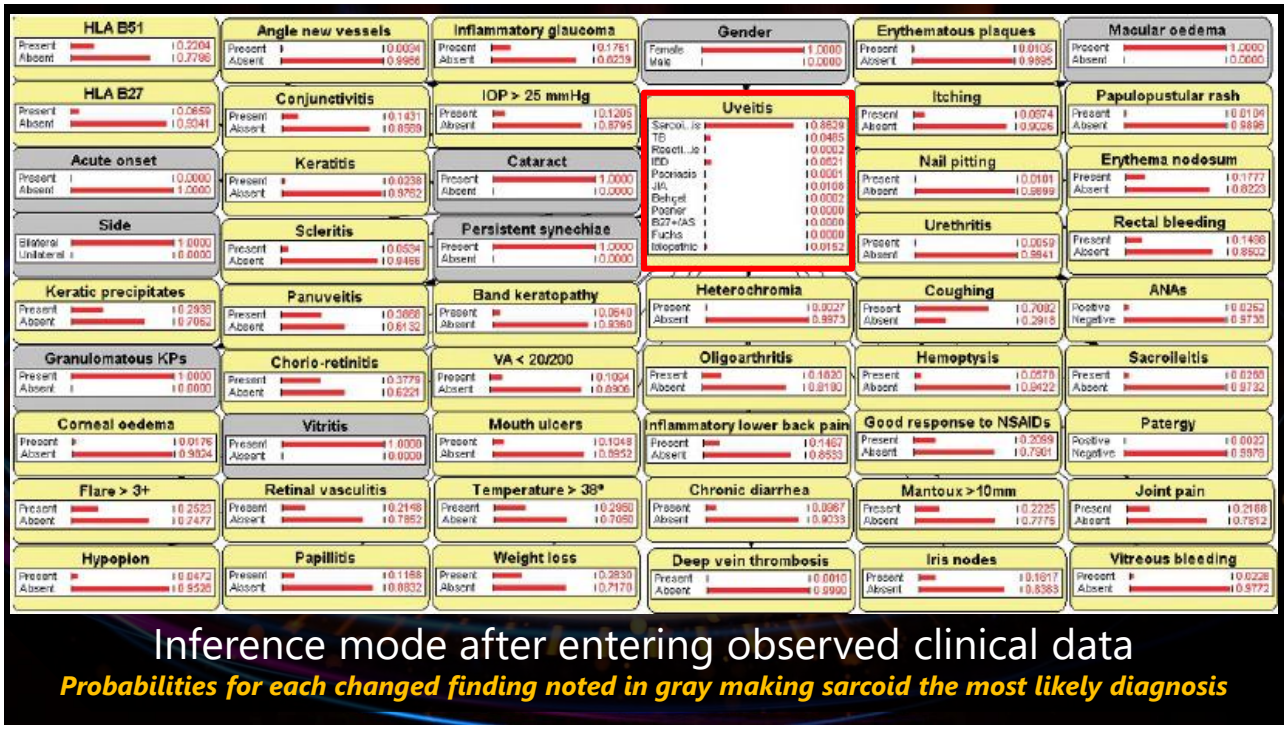

Inference mode after entering observed clinical data

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

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What does this mean clinically?

25 Total

Uveitis Laboratory Work Up: Making Smart Choices

Understanding Bayesian statistics and Implications

Disease X has a 0.100 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) / (0.99*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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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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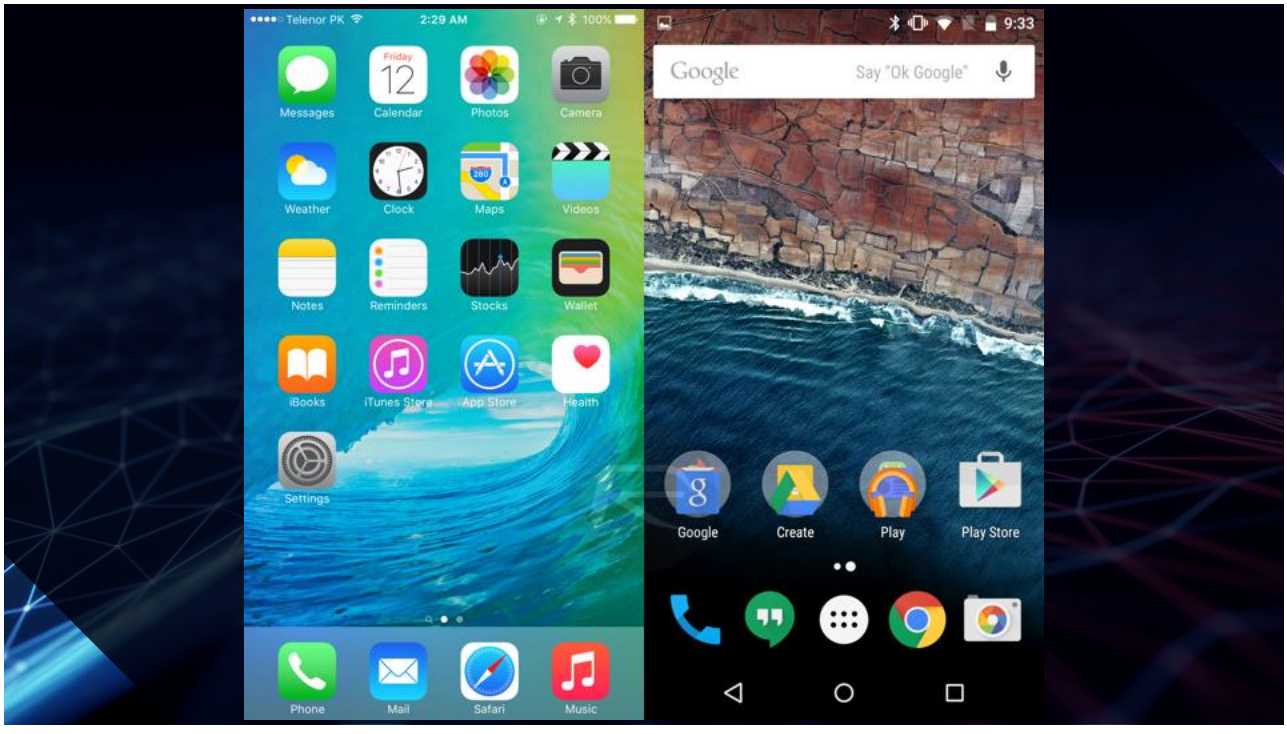

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Preventative Medicine + Systemic Disease Smartphone Applications

- *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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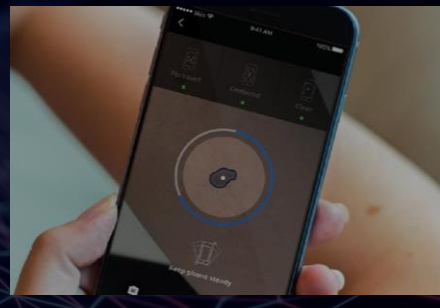
Clinical Systemic Disease Management

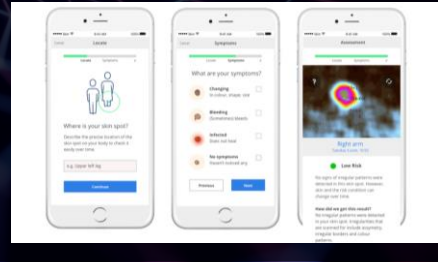
Smart Phone Applications – Periocular Melanoma

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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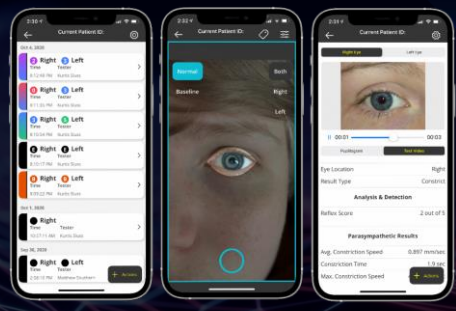
Clinical Systemic Disease Management

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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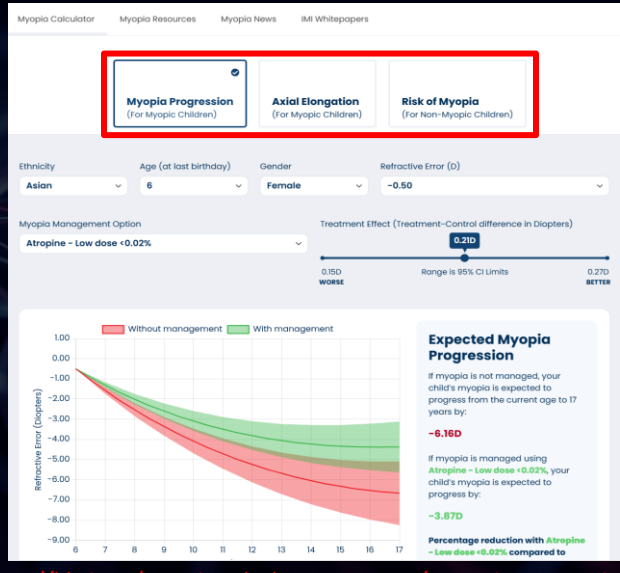
Clinical Systemic Disease Management

Smart Phone Applications – Pediatric Myopic Progression

Myopia: Should We Treat It Like a Disease? The research is mounting…

Rev Optom (2020) 157(10):32-38

- **Selection Criteria**
  - Ethnicity
  - Age
  - Refractive error
  - Management Options
    - 9 Treatments
- 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
  - ***Macular degeneration***
  - ***Cataracts***
  - ***Glaucoma***



https://bhvi.org/myopia-calculator-resources/#myopia-progression

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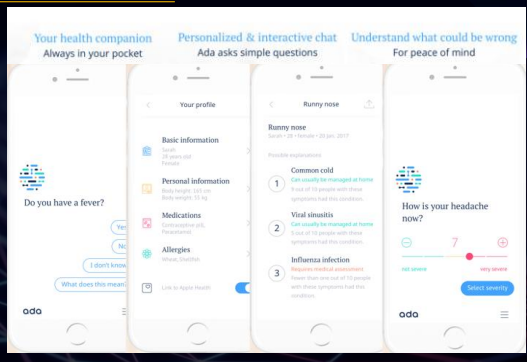
Clinical Systemic Disease Management

Smart Phone Applications – Doc in a Box

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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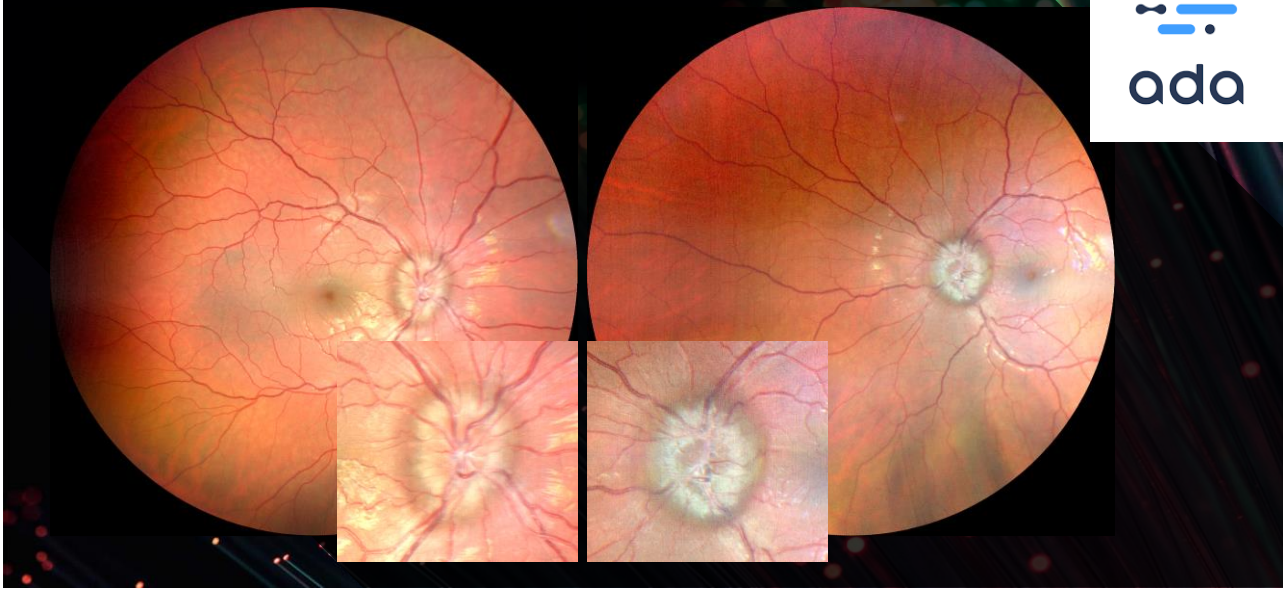
Clinical Systemic Disease Management

Smart Phone Applications – Case Report



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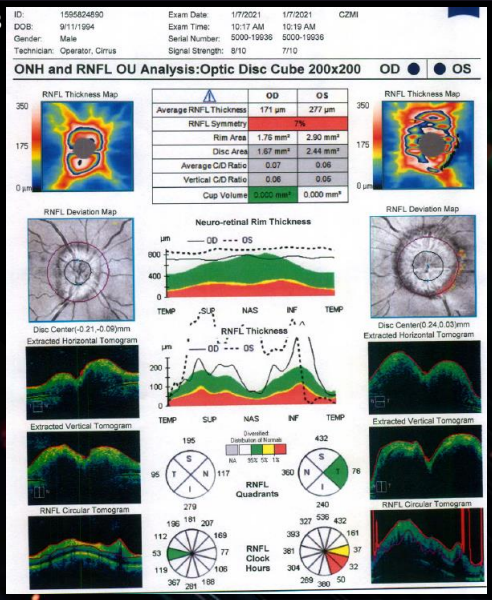
Clinical Systemic Disease Management

Smart Phone Applications – Case Report

7Jan2023



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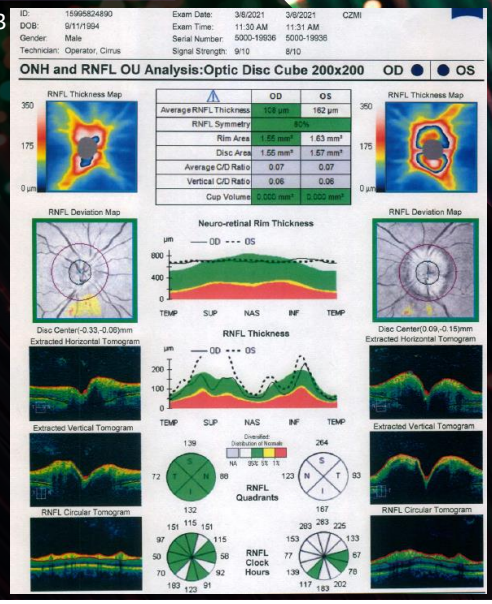

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Opportunity and Limitations

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

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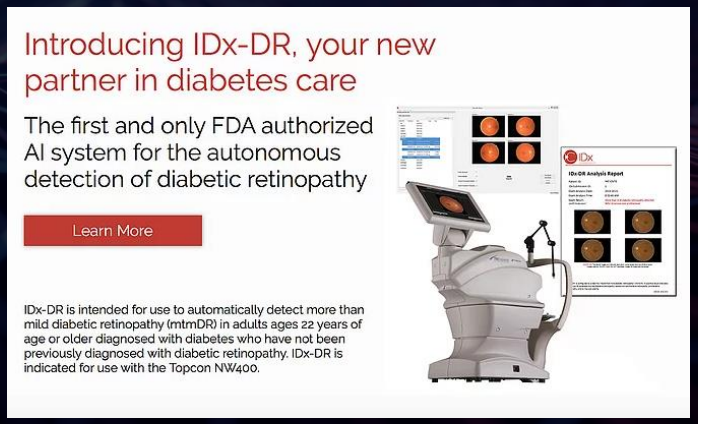
What's now?

- 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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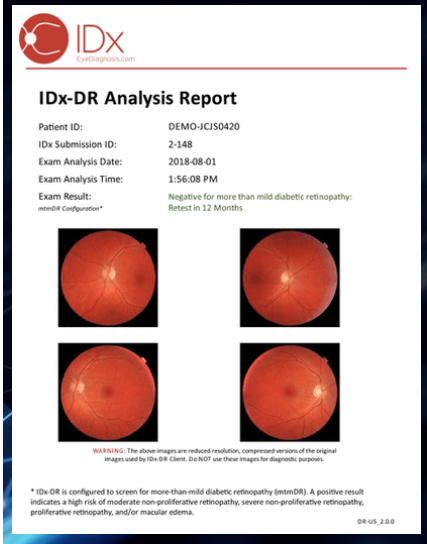
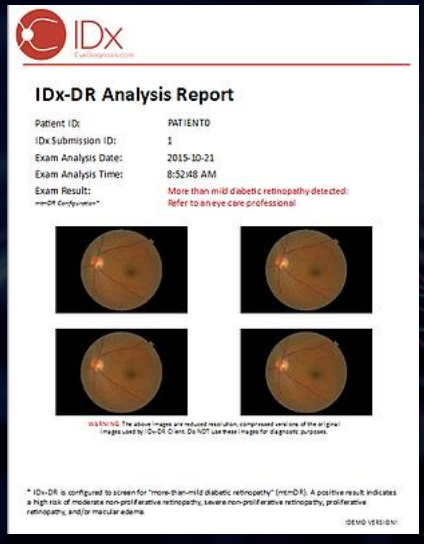
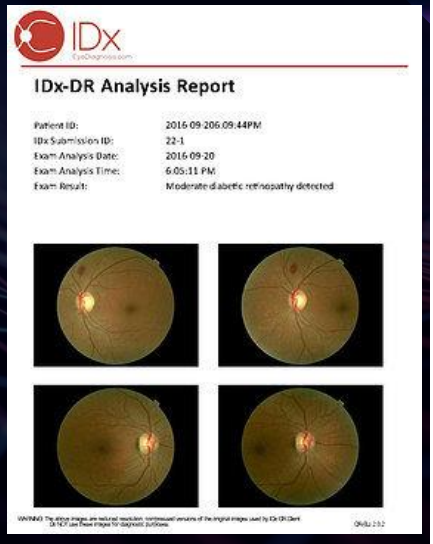
What's now?







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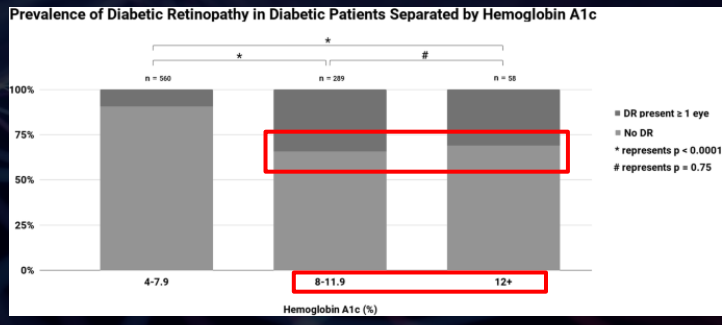
What's now?

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

Methods:
- 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
  - 52% triggered 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 received an eye exam***
- ***Identification of referral-warranted diabetic retinopathy and other ophthalmic conditions is not enough***



~35% of patients with Hb A1C>8 showed DR

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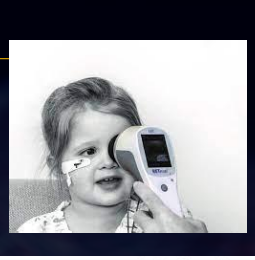
What's now?

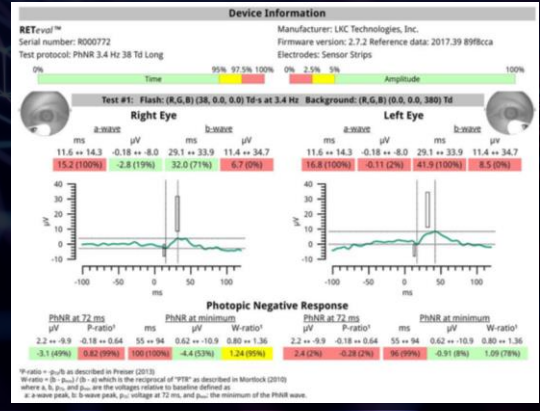
Comparison of the handheld RETeval ERG system with a routine ERG system in healthy adults and in pediatric patients
Eye (2022) *35*(8):2180-2189

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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Clinical Pearls

Preferred Practice Patterns

Putnam's Clinical Practice Guideline – POAG Worksheet

- Age (OR = 2.2X per decade)
- Ethnicity (Black or Hispanic = 2X)
- FHx (OR = 2X)
  - 1st or 2nd degree relative
  - Age of onset
- Systemic Review of concurrent inflammatory conditions
  - Collagen vascular disease (RA / SLE / sarcoid)
  - Vascular disease (DM / HTN / dyslipidemia) [OR = 1.5X]
- Laboratory testing
  - 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 (OR = 1.5X per mm)
  - ETDRS
  - Pelli-Robson or PV 5%
- Ocular Response Analyzer
  - Corneal hysteresis (CH) and compensated IOP (IOPcc)
- Central Corneal Thickness (OR = 1.3X per 40µm)
- Repeated IOP measures (OR = 1.2X per mmHg)
  - GAT vs. rebound IOP (iCare)
- OHTS + EMGT calculators
  - *CAVEAT: Requires IOP of 24-32 in 1 eye and IOP of 21-32 the other*
- Baseline Imaging
  - OCT macular GCC
    - Inferior, temporal loss or superior, temporal loss
    - ~50% of RGC located w/n 4.5mm of foveal center
    - [1] Focal GCC thinning, [2] Age and [3] CCT most predictive = HR: 3.1
      - IOP and VF were *NOT* predictive in multivariate model
  - OCT RNFL
    - Confirmatory loss associated with macular GCC
  - OCTA
    - Create baseline vascular appearance
    - Identify early loss of perfusion (deep plexus / choriocapillaris / Bruch's / intraretinal)
  - 24-2HVF vs 10-2HVF
    - 6 deg vs 2 deg test point spacing
    - *MUST HAVE AT LEAST 1 REPEATABLE, CONFIRMATIORY TEST*

Mean Ocular Perfusion Pressure

- 50 - 60 mmHg
- <50mmHg = OAG risk

Table 2. Summary of Epidemiologic Studies Linking Diastolic Perfusion Pressure and Glaucoma[1-5]

Study	Design	Participants	Glaucoma Risk From Low DPP vs Normal DPP
Baltimore Eye Survey	Cross-sectional	Non-Hispanic Whites and African Americans	6-fold
Egna-Neumarkt Study	Cross-sectional	Non-Hispanic Whites	2.5-fold
Proyecto VER	Cross-sectional	Hispanics	4-fold
Los Angeles Latino Eye Study	Cross-sectional	Latinos/Hispanics	1.9-fold
Barbados Eye Study	Longitudinal	Afro-Caribbeans	3.2-fold (4 years)

Table 3. Patient Subgroups In Which to Consider the Value of Assessing Ocular Perfusion Pressure

- Normal-tension glaucoma
- Eyes with optic disc hemorrhage
- Patients with progression at low IOP
- History of low BP, multiple systemic antihypertensives, symptoms of orthostasis
- Patients with nocturnal hypotension

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Clinical Pearls

Preferred Practice Patterns

TABLE 7 CONSENSUS-BASED GUIDELINES FOR FOLLOW-UP GLAUCOMA STATUS

Target IOP Achieved	Progression of Damage	Duration of Control (mos)	Approximate Follow-up Interval (mos)*
Yes	No	≤6	6
Yes	No	>6	6–12
Yes	Yes	NA	1–2
No	Yes	NA	1–2
No	No	NA	3–6

Target IOP = ~25% reduction

**Std Dev of GAT = 2-3 mmHg*

- *Mild OAG 15-17 mmHg*
- *Moderate OAG 12-15 mmHg*
- *Severe OAG 10-12 mmHg*

Mean RNFL Thickness

- Healthy = 94 ± 8µm (Cirrus) vs. 103 ± 10µm (Spectralis)
- Suspect = 87 ± 10µm (Cirrus) vs. 92 ± 10µm (Spectralis)
- Glaucoma = 70 ± 10µm (Cirrus) vs. 73 ±11µm (Spectralis)

Suspected glaucomatous damage (RNFL)

- Difference >9µm in average RNFL thickness asymmetry OD v. OS
- Decrease >5 µm in average RNFL thickness
- Decrease >7µm in sector of RNFL thickness

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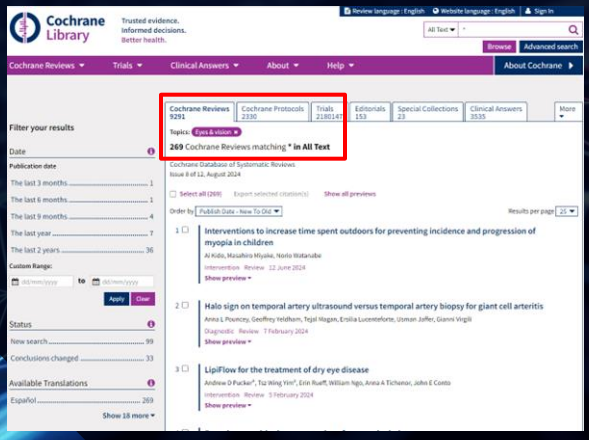
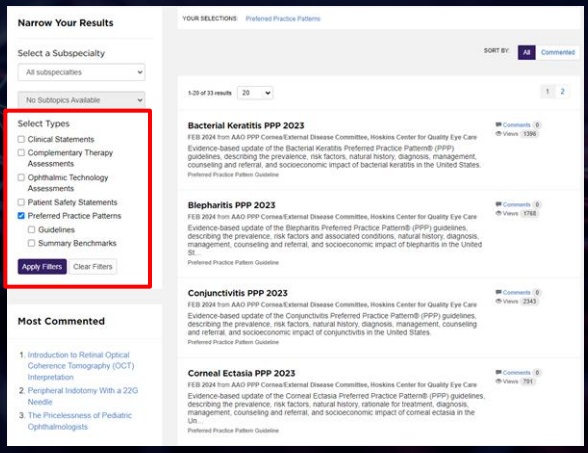
Takeaways…

https://www.cochranelibrary.com/cdsr/reviews



https://www.aao.org/preferred-practice-patterns



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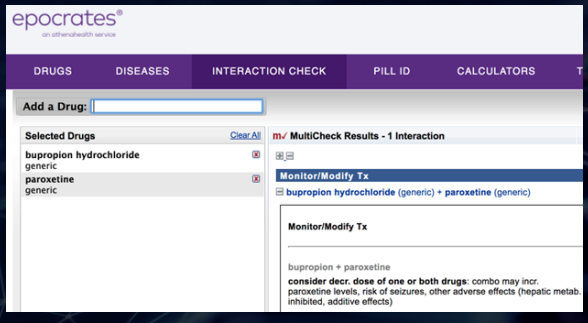
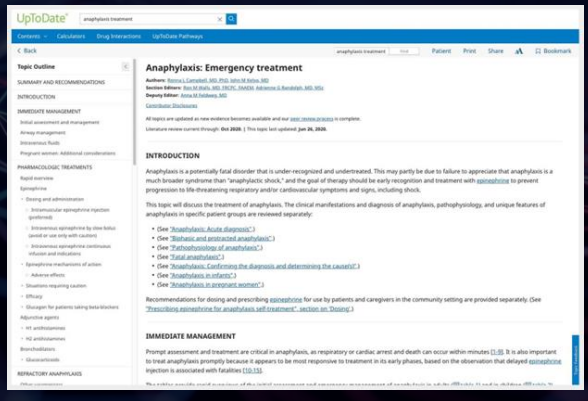
Takeaways…

https://www.epocrates.com/



https://www.uptodate.com/contents/search



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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
  - *Google search: "I-XRAY"*

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Clinical Pearls

Low-Cost Imaging Modalities

- Retinal Imaging
- Anterior Segment Imaging

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Low-Cost Imaging Modalities

Technology-Enabled Diagnosis

oDocs VisoScope 20D CAD Files

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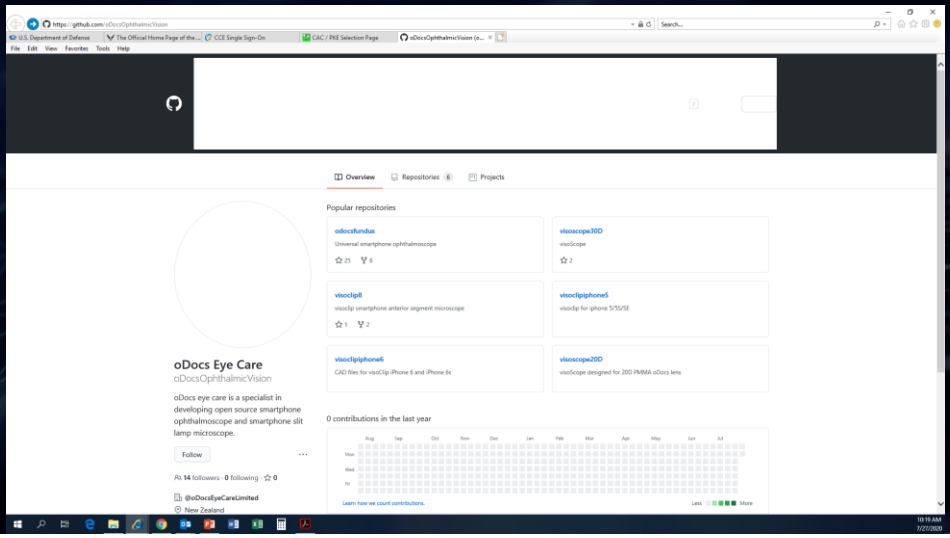
Low-Cost Imaging Modalities

Technology-Enabled Diagnosis

https://odocseyecare.shop/collections/all



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Low-Cost Imaging Modalities

Technology-Enabled Diagnosis

Slit Lamp iPhone Adapter CAD Files

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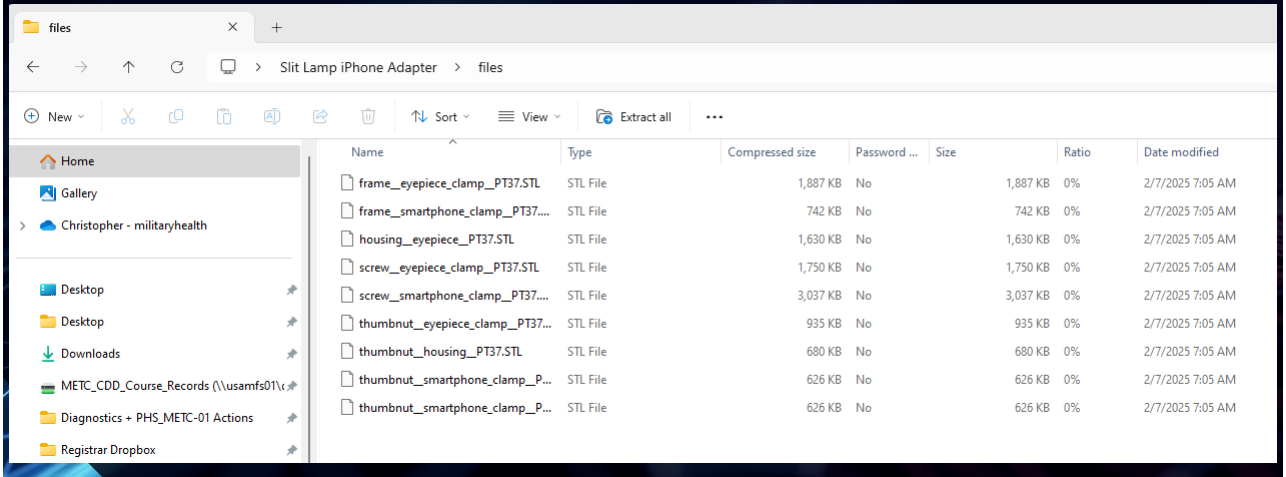
Low-Cost Imaging Modalities

Technology-Enabled Diagnosis



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Questions?
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