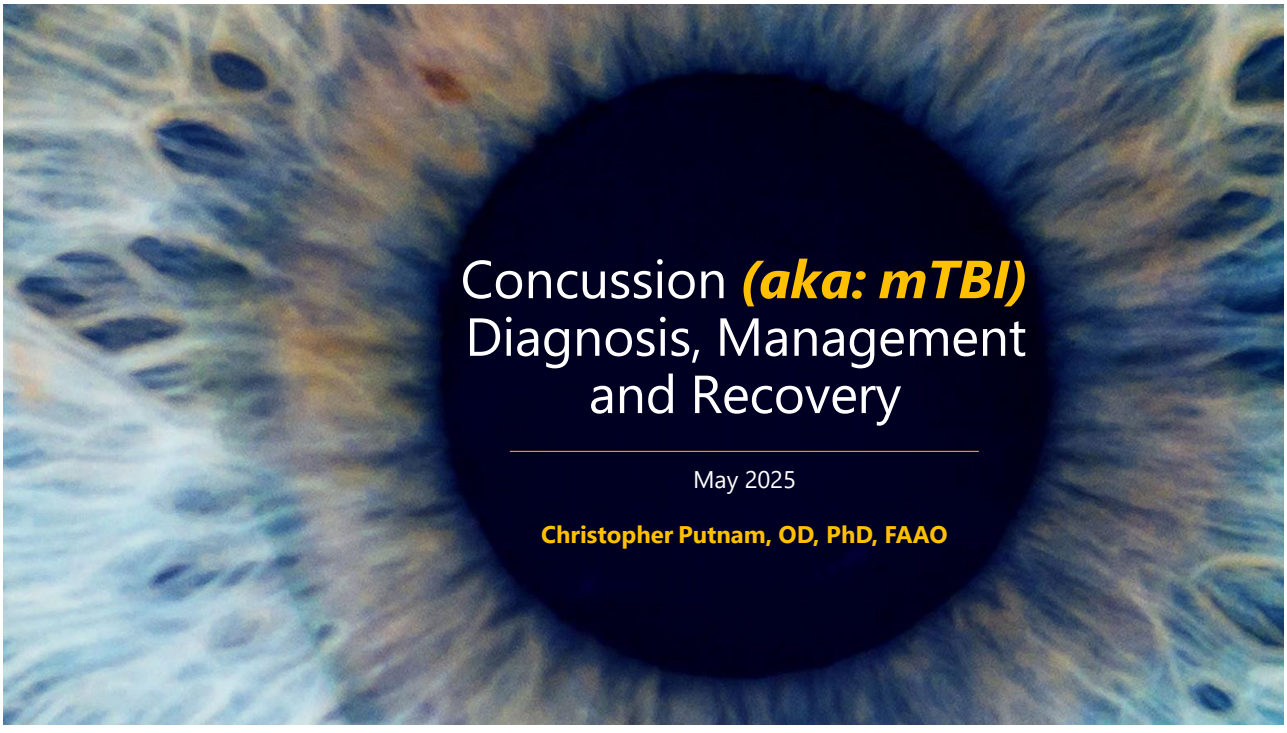
Concussion (aka: mTBI)
Diagnosis, Management
and Recovery
May 2025
Christopher Putnam, OD, PhD, FAAO

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South Dakota
State University
Pacific
University
Oregon
DEPARTMENT OF THE AIR FORCE
UNITED STATES OF AMERICA
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UNIVERSITY of
HOUSTON
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UMSL Optometry
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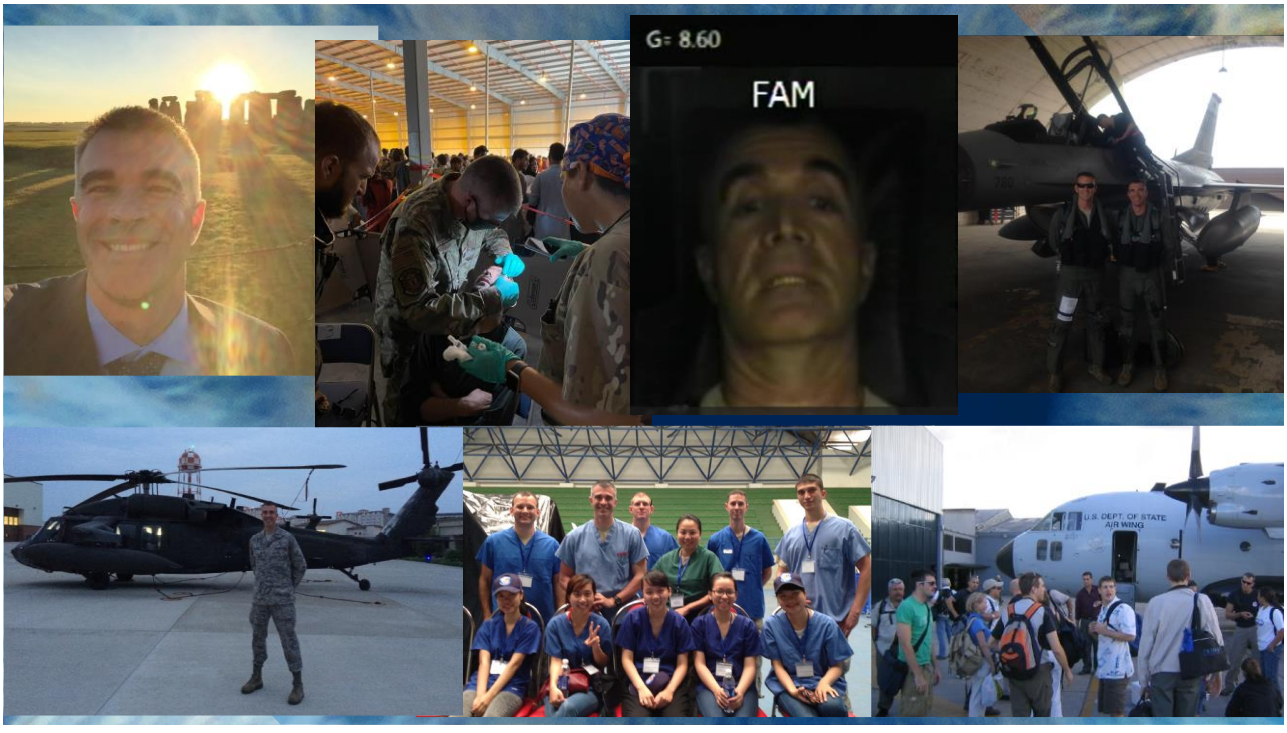

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Clinical Concussion Management

Concussion (mTBI) Happens….

8

Clinical Concussion Management

....over and over again

9

Clinical Concussion Management

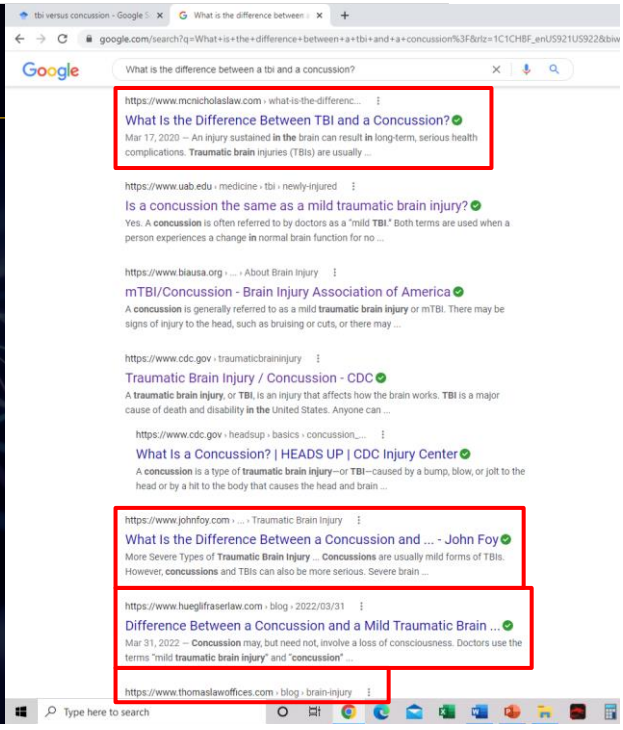
Misconceptions

Google results for:

- ***What is the difference between a mTBI and a concussion?***

Within first 12 hits:

- ***4 law firms***
- **3 advertisements for programs, diets and supplements**
- **2 health centers**
- **1 medical page written by HCP**
- ***Brain Injury of America PR page****
- **CDC**



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Clinical Concussion Management
Misconceptions

Misconceptions about TBI among U.S. Army behavioral health professionals
Rehab Psychology (2015) 60(4): *344-352*

Table 2
Percentage of Accurate Responses on New mTBI Items

Questionnaire items	% Correct
1. The effects of mTBI tend to be longer lasting and slower to recover than concussion. (False)	62%
2. mTBI typically causes permanent brain damage and poor functional outcome. (False)	72%
3. Delayed symptom onset after mTBI is common. (False)	34%
4. Early education of patients can reduce the number and frequency of postconcussion symptoms. (True)	82%
5. Longstanding symptoms of mTBI may more likely be attributable to noninjury variables (e.g., depression, chronic pain) than to the patient's head injury. (True)	67%
6. Most research suggests mTBI from IED blasts have worse cognitive outcome and recovery than blunt trauma alone. (False)	60%
7. Most people recover from mTBI in: (Selected 1 to 3 weeks o 1 to 3 months.	53%
8. What percentage of individuals who experience a mTBI can be expected to achieve a full recovery? (Selected an answer above 90%)	28%

Note. $N = 181$ respondents. Among those who provided full demographic information were psychologists ($n = 63$), psychiatrists ($n = 17$), social workers ($n = 44$), and psychiatric nurse practitioners ($n = 27$).

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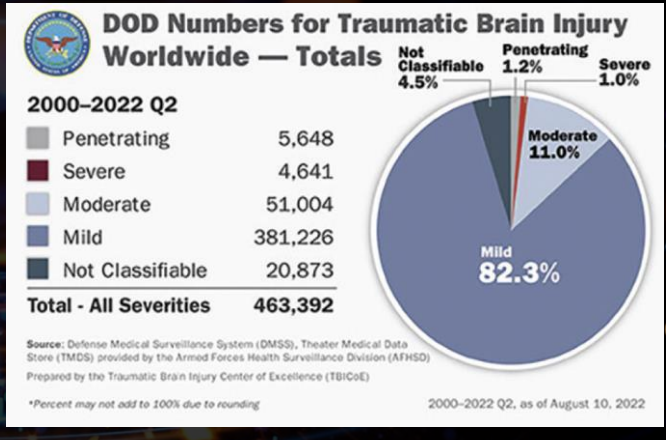
Clinical Concussion Management
Demographics

Annual Incidence
- U.S. estimates ~225 per 100,000 individuals
  - ***~1.5 million people suffer a mTBI***
  - ~500,000 are hospitalized for TBI
  - ~270,000 experience moderate or severe TBI
  - ~60,000 result in cases of epilepsy
  - ~50,000 people die from head injury
  - ~80,000 results in chronic disability

Age
- Highest risk: Children ages <5yo
  Adolescents 15-25yo ***(Injury)***
  Adults > 75yo

Race
- No racial predilection to traumatic brain injury.

Gender
- ***Males 2X more likely with a 4X risk of fatal head injury***
  Males also account for 65% of adolescent head trauma



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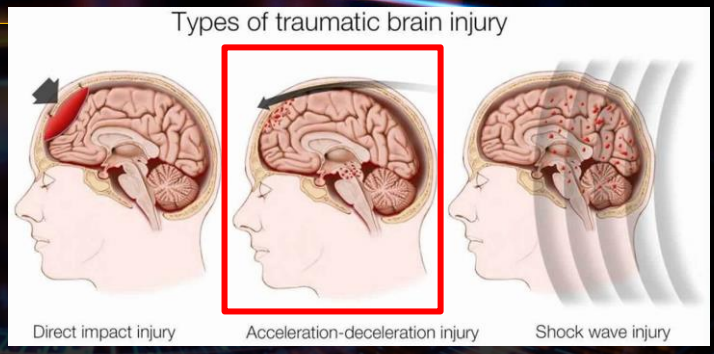
Clinical Concussion Management

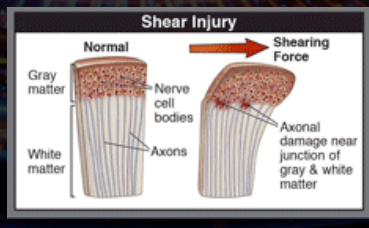
Types of Injury

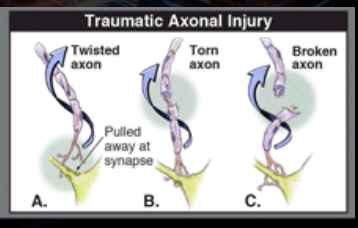
1) Biomechanical
60-165g range
**1g of force = 9.8N*

2) Anatomical
Axonal shearing/stretching

3) Physiological
Sub-cellular
Electrochemical







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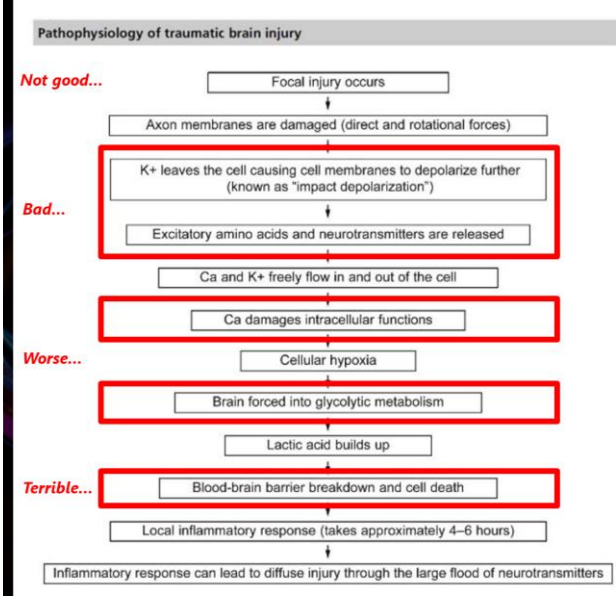
Clinical Concussion Management

Concussion / mTBI Secondary Insult



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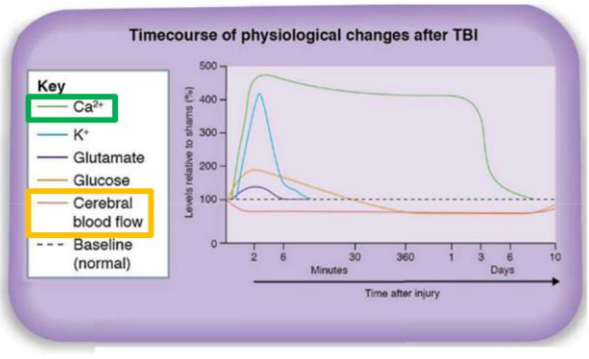

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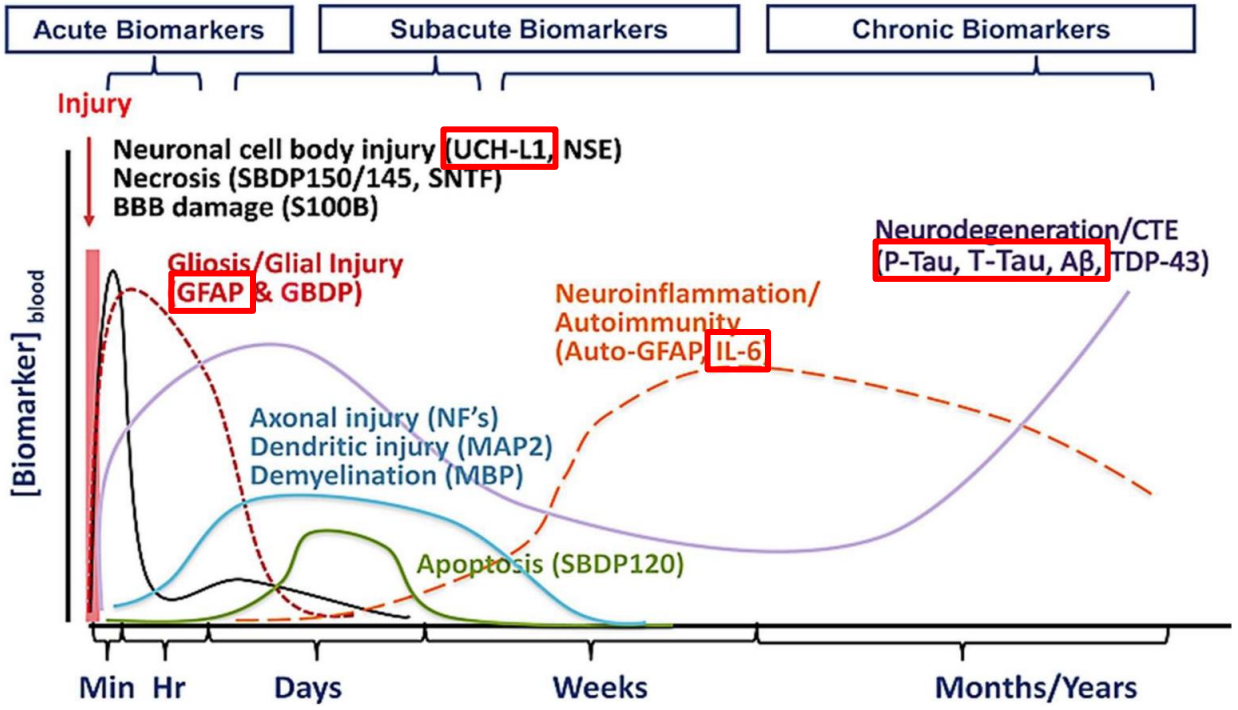

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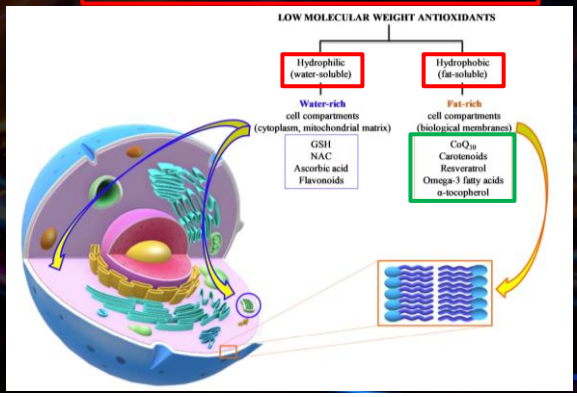
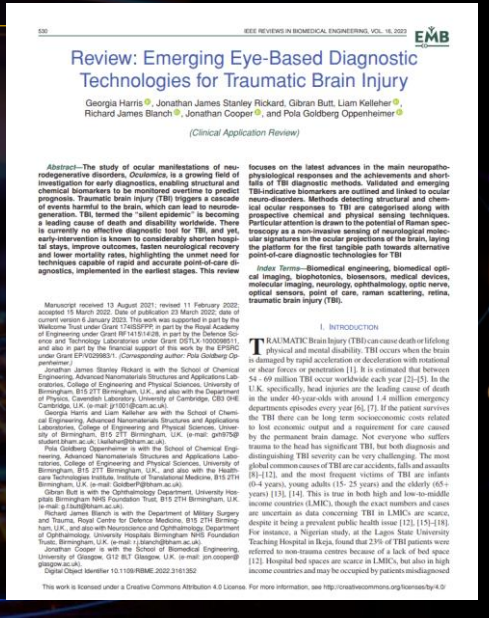
Clinical Concussion Management

Concussion / mTBI Secondary Insult

- Ca^{2+} dysregulation
  - Increased excitatory NT release
    - Glucose dysmetabolism
      - Mitochondrial dysfunction
        - Free radical / ROS overproduction
          - Lipid peroxidation





IEEE REVIEWS IN BIOMEDICAL ENGINEERING, VOL. 16, 2023

Review: Emerging Eye-Based Diagnostic Technologies for Traumatic Brain Injury

Georgia Harris, Jonathan James Stanley Rickard, Gibran Butt, Liam Kelleher, Richard James Blanch, Jonathan Cooper, and Pola Goldberg Oppenheimer

(Clinical Application Review)

Abstract—The study of ocular manifestations of neurodegenerative disorders, *Oculomics*, is a growing field of investigation for early diagnostics, enabling structural and chemical biomarkers to be monitored overtime to predict prognosis. Traumatic brain injury (TBI) triggers a cascade of events harmful to the brain, which can lead to neurodegeneration. TBI, termed the "silent epidemic" is becoming a leading cause of death and disability worldwide. There is currently no effective diagnostic tool for TBI, and yet, early-intervention is known to considerably shorten hospital stays, improve outcomes, fasten neurological recovery and lower mortality rates, highlighting the unmet need for techniques capable of rapid and accurate point-of-care diagnostics, implemented in the earliest stages. This review focuses on the latest advances in the main neuropathophysiological responses and the achievements and shortfalls of TBI diagnostic methods. Validated and emerging TBI-indicative biomarkers are outlined and linked to ocular neuro-disorders. Methods detecting structural and chemical ocular responses to TBI are categorised along with prospective chemical and physical sensing techniques. Particular attention is drawn to the potential of Raman spectroscopy as a non-invasive sensing of neurological molecular signatures in the ocular projections of the brain, laying the platform for the first tangible path towards alternative point-of-care diagnostic technologies for TBI

Index Terms—Biomedical engineering, biomedical optical imaging, biophotonics, biosensors, medical devices, molecular imaging, neurology, ophthalmology, optic nerve, optical sensors, point of care, raman scattering, retina, traumatic brain injury (TBI).

I. Introduction

TRAUMATIC Brain Injury (TBI) can cause death or lifelong physical and mental disability. TBI occurs when the brain is damaged by rapid acceleration or deceleration with rotational or shear forces or penetration [1]. It is estimated that between 54 - 69 million TBI occur worldwide each year [2]–[5]. In the U.K. specifically, head injuries are the leading cause of death in the under 40-year-olds with around 1.4 million emergency departments episodes every year [6], [7]. If the patient survives the TBI there can be long term socioeconomic costs related to lost economic output and a requirement for care caused by the permanent brain damage. Not everyone who suffers trauma to the head has significant TBI, but both diagnosis and distinguishing TBI severity can be very challenging. The most global common causes of TBI are car accidents, falls and assaults [8]–[12], and the most frequent victims of TBI are infants (0-4 years), young adults (15- 25 years) and the elderly (65+ years) [13], [14]. This is true in both high and low-to-middle income countries (LMIC), though the exact numbers and cases are uncertain as data concerning TBI in LMICs are scarce, despite it being a prevalent public health issue [12], [15]–[18]. For instance, a Nigerian study, at the Lagos State University Teaching Hospital in Ikeja, found that 23% of TBI patients were referred to non-trauma centres because of a lack of bed space [12]. Hospital bed spaces are scarce in LMICs, but also in high income countries and may be occupied by patients misdiagnosed

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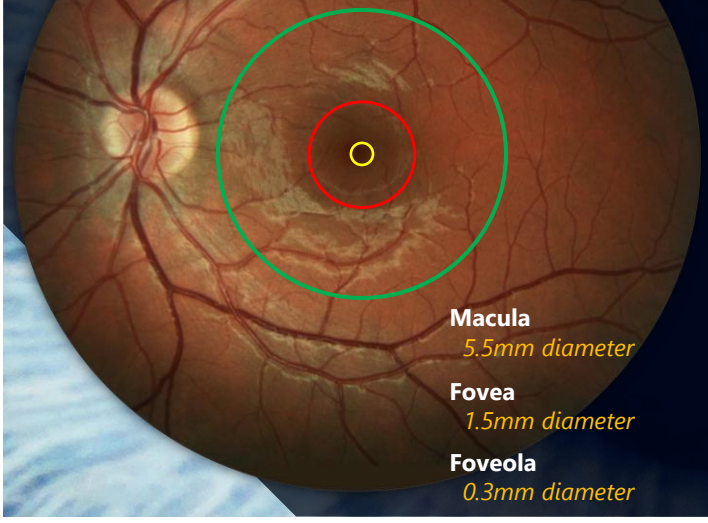
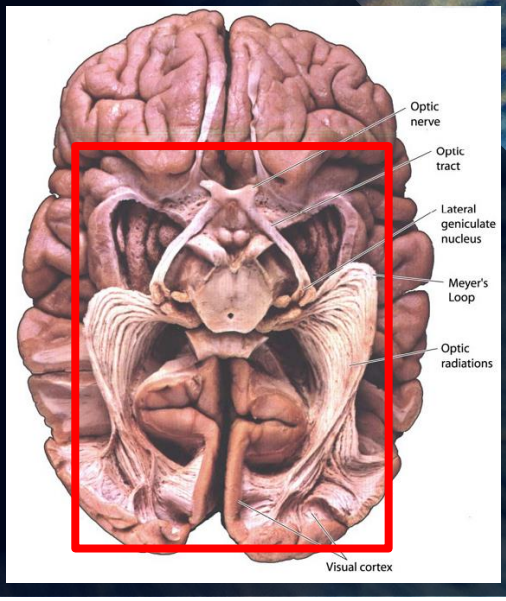
Clinical Concussion Management

Concussion / mTBI Secondary Insult - The "Why…"

- **Visual pathway up to retrobulbar space is immersed in CSF**
  - ***By extension: GC-IPL + RNFL***





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Clinical Measurement Point of Care

- **Glasgow Coma Scale**
  - **iStat Alinity**
  - **Quanterix**
- **Sport Concussion Assessment Tool (SCAT-6)**
- **Military Acute Concussion Evaluation (MACE 2)**

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Clinical Concussion Management

Point of Care – Glasgow Coma Scale (GCS)

Classification	Admission Glasgow Coma Scale and clinical characteristics
Mild	GCS 13–15
Category 0	GCS 15, No LOC, no PTA, No risk factors
Category 1	GCS=15, LOC <30 min, PTA <1 h, No risk factors
Category 2	GCS=15 and risk factors present
Category 3	GCS=13–14, LOC <30 min, PTA <1 h, with or without risk factors
Moderate	GCS=9–12
Severe	GCS <8
Critical	GCS 3–4, unreactive pupils and absent/decorticate motor reactions (GCS motor scale 1 or 2)

Debate b/t 13 v. 14

* Risk Factors of intracranial lesions in patients with minor head injury

1- Loss of consciousness
2- Post traumatic amnesia
3- Seizure
4- Headache
5- Vomiting
6- Skull fracture (basilar or cranial vault)
7- Focal neurological deficit (FND)
8- Coagulopathy or taking anticoagulant
9- Age > 60 years

Glasgow Coma Scale (GCS)

	Eyes	Voice	Motor
1	No eye opening	No speech	No movement
2	Eyes to painful stimulus	Incoherent speech	Extending Decerebrate
3	Opens eyes to voice	Inappropriate words	Flexing Decorticate
4	Spontaneously opens eyes	Confused	Withdraws from painful stimulus
5		Oriented	Localises to painful stimulus
6			Obeys commands

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Clinical Measurement

Point of Care – Serum Testing

iStat Alinity

FDA-approved (2021) for acute traumatic intracranial injury (TII) on CT following mTBI

- glial fibrillary acidic protein (GFAP)
- ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1)

Sensitivity = 0.958
Specificity = 0.404
NPV = 0.993 (Patient truly ***DOES NOT*** have TII)
PPV = 0.098 (Patient truly **DOES** have TII)

Quanterix

FDA-approved (2018) for mTBI and concussions in adults

- ***Neurofilament light (NF-L)***
- Tau
- Glial fibrillary acidic protein (GFAP)
- Ubiquitin carboxyl-terminal hydrolase L1 (UCH-L1)

Presence of CT intracranial lesions with 97.5% accuracy
Absence of CT intracranial lesions 99.6% accuracy

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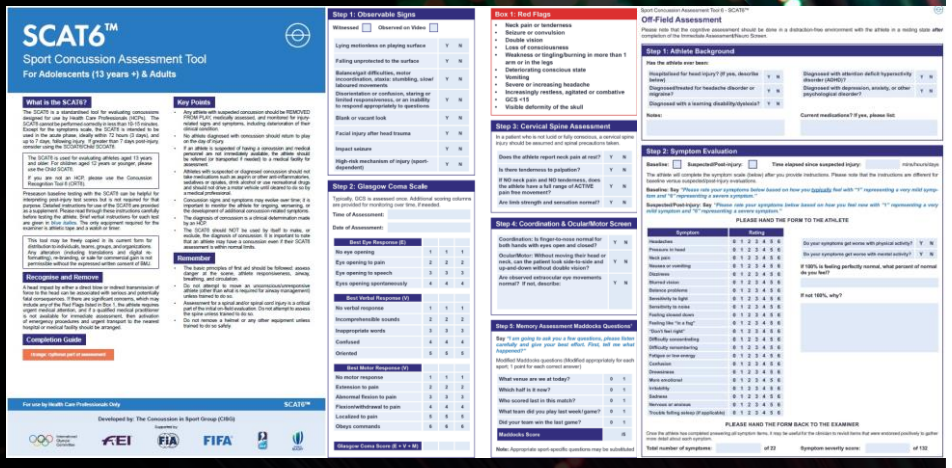
Clinical Measurement

Point of Care – Sports Concussion Assessment Tool 6 (SCAT-6)

- **Red Flags**
  - Neck pain
  - Diplopia
  - Paresthesia
  - HA
  - Seizure
  - LOC
  - Vomiting
  - Agitation
- **GCS**
- **Observable Signs**
- **Cognitive Screening**
- **Neurological Screening**



https://completeconcussions.com/wp-content/uploads/2023/06/SCAT6.pdf

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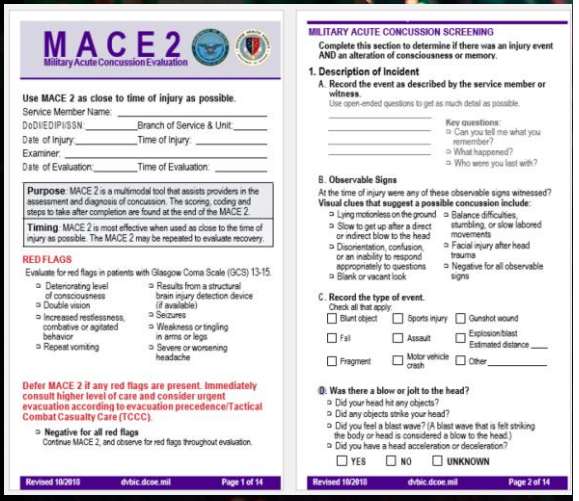
Clinical Measurement

Point of Care – Military Acute Concussion Evaluation (MACE 2)

- **Concussion Screening**
  - Description of the injury event and
  - Screening questions about LOC, AOC and PTA
- **Cognitive Exam**
  - Assigns scores for orientation, immediate memory, concentration and delayed recall. The
  - Scores are totaled out of 30 possible points
- **Neurological Exam**
  - Pupil response to light, speech fluency and word finding, grip strength and pronator drift and balance.
- **Symptom Screening**
  - Headache, dizziness, memory problems, balance problems, nausea/vomiting, difficulty concentrating, irritability, visual disturbances tinnitus and concussion history in the past 12 months.

Integrated VOMS…. MORE ON THIS LATER



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Clinical Measurement Screening Tools

- ***Brain Injury Vision Symptom Survey (BIVSS)***
- **Post-Trauma Vision Symptoms (PTVS)**
- **Standard Assessment of Concussion (SAC)**
- **Post-Concussion Symptom Scale (PCSS)**
- **Mini-Mental State Exam (MMSE)**
- **Montreal Cognitive Assessment (MoCA)**

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Clinical Measurement

Screening Tools - Binocular Injury Vision Symptom Survey (BIVSS)

BIVSS sensitivity

- ***82% for correctly predicting TBI***
  - *True Positive*
- ***91% for correctly predicting controls***
  - *Correct Rejection*
- ***TBI patients were significantly more symptomatic than controls (>1SD)***

BIVSS CHECKLIST (Brain Injury Vision Symptom Survey)

Patient Name: Today's date: _____

My brain injury was: ____ years ago My age is: ____ years today's date: _____

☐ I have had a medical diagnosis of brain injury (check box if true) Cause of injury: _____

☐ I sustained a brain injury without medical diagnosis (check box if true)

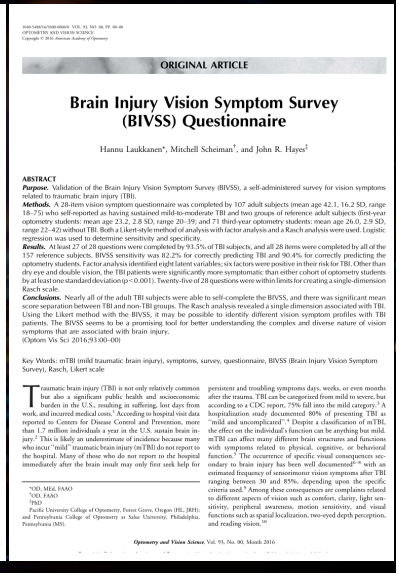
☐ I have NOT ever sustained a brain injury (check box if true)

Please check the most appropriate box, or circle the item number that best matches your observations. All information will be held in confidence. Thank you for your help!

SYMPTOM CHECKLIST *Circle a number below:*

Please rate each behavior. How often does each behavior occur? (circle a number)	Never	Seldom	Occasionally	Frequently	Always
EYESIGHT CLARITY					
Distance vision blurred and not clear -- even with lenses	0	1	2	3	4
Near vision blurred and not clear -- even with lenses	0	1	2	3	4
Clarity of vision changes or fluctuates during the day	0	1	2	3	4
Poor night vision / can't see well to drive at night	0	1	2	3	4
VISUAL COMFORT					
Eye discomfort / sore eyes / eyestrain	0	1	2	3	4
Headaches or dizziness after using eyes	0	1	2	3	4
Eye fatigue / very tired after using eyes all day	0	1	2	3	4
Feel "pulling" around the eyes	0	1	2	3	4
DOUBLING					
Double vision -- especially when tired	0	1	2	3	4
Have to close or cover one eye to see clearly	0	1	2	3	4
Print moves in and out of focus when reading	0	1	2	3	4
LIGHT SENSITIVITY					
Normal indoor lighting is uncomfortable -- too much glare	0	1	2	3	4
Outdoor light too bright -- have to use sunglasses	0	1	2	3	4
Indoors fluorescent lighting is bothersome or annoying	0	1	2	3	4
DRY EYES					
Eyes feel "dry" and sting	0	1	2	3	4
"Stare" into space without blinking	0	1	2	3	4
Have to rub the eyes a lot	0	1	2	3	4
DEPTH PERCEPTION					
Clumsiness / misjudge where objects really are	0	1	2	3	4
Lack of confidence walking / missing steps / stumbling	0	1	2	3	4
Poor handwriting (spacing, size, legibility)	0	1	2	3	4
PERIPHERAL VISION					
Side vision distorted / objects move or change position	0	1	2	3	4
What looks straight ahead--isn't always straight ahead	0	1	2	3	4
Avoid crowds / can't tolerate "visually-busy" places	0	1	2	3	4
READING					
Short attention span / easily distracted when reading	0	1	2	3	4
Difficulty / slowness with reading and writing	0	1	2	3	4
Poor reading comprehension / can't remember what was read	0	1	2	3	4
Confusion of words / skip words during reading	0	1	2	3	4
Lose place / have to use finger not to lose place when reading	0	1	2	3	4

BIVSS_28 item clinical use_20014 (Hanna Laukkanen) Predictive score: = 31 **total score for all 28-items: _____**



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OPTOMETRY AND VISION SCIENCE
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ORIGINAL ARTICLE

Brain Injury Vision Symptom Survey (BIVSS) Questionnaire

Hannu Laukkanen*, Mitchell Scheiman†, and John R. Hayes‡

ABSTRACT

Purpose. Validation of the Brain Injury Vision Symptom Survey (BIVSS), a self-administered survey for vision symptoms related to traumatic brain injury (TBI).

Methods. A 28-item vision symptom questionnaire was completed by 107 adult subjects (mean age 42.1, 16.2 SD, range 18–75) who self-reported as having sustained mild-to-moderate TBI and two groups of reference adult subjects (first-year optometry students: mean age 23.2, 2.8 SD, range 20–39; and 71 third-year optometry students: mean age 26.0, 2.9 SD, range 22–42) without TBI. Both a Likert-style method of analysis with factor analysis and a Rasch analysis were used. Logistic regression was used to determine sensitivity and specificity.

Results. At least 27 of 28 questions were completed by 93.5% of TBI subjects, and all 28 items were completed by all of the 157 reference subjects. BIVSS sensitivity was 82.2% for correctly predicting TBI and 90.4% for correctly predicting the optometry students. Factor analysis identified eight latent variables; six factors were positive in their risk for TBI. Other than dry eye and double vision, the TBI patients were significantly more symptomatic than either cohort of optometry students by at least one standard deviation ($p < 0.001$). Twenty-five of 28 questions were within limits for creating a single-dimension Rasch scale.

Conclusions. Nearly all of the adult TBI subjects were able to self-complete the BIVSS, and there was significant mean score separation between TBI and non-TBI groups. The Rasch analysis revealed a single dimension associated with TBI. Using the Likert method with the BIVSS, it may be possible to identify different vision symptom profiles with TBI patients. The BIVSS seems to be a promising tool for better understanding the complex and diverse nature of vision symptoms that are associated with brain injury.

(Optom Vis Sci 2016;93:00–00)

Key Words: mTBI (mild traumatic brain injury), symptoms, survey, questionnaire, BIVSS (Brain Injury Vision Symptom Survey), Rasch, Likert scale

Traumatic brain injury (TBI) is not only relatively common but also a significant public health and socioeconomic burden in the U.S., resulting in suffering, lost days from work, and incurred medical costs.[1] According to hospital visit data reported to Centers for Disease Control and Prevention, more than 1.7 million individuals a year in the U.S. sustain brain injury.[2] This is likely an underestimate of incidence because many who incur "mild" traumatic brain injury (mTBI) do not report to the hospital. Many of those who do not report to the hospital immediately after the brain insult may only first seek help for persistent and troubling symptoms days, weeks, or even months after the trauma. TBI can be categorized from mild to severe, but according to a CDC report, 75% fall into the mild category.[2] A hospitalization study documented 80% of presenting TBI as "mild and uncomplicated".[3] Despite a classification of mTBI, the effect on the individual's function can be anything but mild. mTBI can affect many different brain structures and functions with symptoms related to physical, cognitive, or behavioral function.[4] The occurrence of specific visual consequences secondary to brain injury has been well documented[5–9] with an estimated frequency of sensorimotor vision symptoms after TBI ranging between 30 and 85%, depending upon the specific criteria used.[5] Among these consequences are complaints related to different aspects of vision such as comfort, clarity, light sensitivity, peripheral awareness, motion sensitivity, and visual functions such as spatial localization, two-eyed depth perception, and reading vision.[10]

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Clinical Measurement Entrance Skills

- Sensorimotor
  - Pursuit / Saccades
  - Vergences / Accommodation
- OMAT
- VOMS
- DEM vs. King-Devick

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Clinical Concussion Management

Sensorimotor Exam "Big 3"

Task	Expected Values
Best-corrected visual acuity	20/20 OD, OS
Eye Alignment	Orthophoria at distance and low exophoria at near
Versions	Full range of motion in muscle-isolating gazes
Vergences	>15 prism diopters crossing in and >8 uncrossing
Vergence Facility	15 cycles per minute or more crossing and uncrossing
Near-point of convergence (x3)	5 cm on 1st try; 5 cm on 3rd try
MEM	0 to +0.75 Diopters
Accommodative amplitudes	12.5 diopters, OD, OS / (15 – age/4)
Stereoacuity (Global or Local)	<100" of arc
Negative/positive relative accommodation	+2.50/-2.50 D
Eye tracking- DEM	Horizontal and vertical percentiles eye and the ratio b/t the two
Confrontational visual field- HVF	Full in each eye
Pupil testing	PERRL (-) APD defect; NPi index of 3.6 or greater (0-5 scale)
Intraocular pressure	10 – 22 mm Hg in each eye
Retina	Intact, no detachments or tears, Well-perfused ON w/distinct margins
OCT	Symmetric RNFL falling w/n expected population norms

Pursuits
Saccades

+/- 2D Facilities

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Clinical Measurement

Entrance Skills – OculoMotor Assessment Tool (OMAT)

OculoMotor Assessment Tool (OMAT) Test Procedure and Normative Data

Optom Vis Sci (2021) 98(6): 636–643

Methods

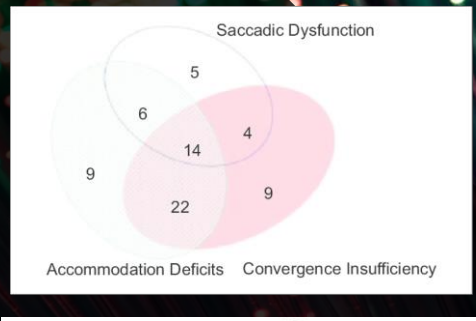
- Healthy participants (n=376) with (-) self-reported history of concussions were recruited to perform the following 3 tasks for 60 seconds each: horizontal saccades, vertical saccades and vergence jumps

Results

- Statistical difference was observed in the number of eye movements for all three tasks between the initial and latter 30-seconds
  - ***Horizontal saccades [70±15 vs. 63±13]***
  - ***Vertical saccades [68±14 vs. 63±13]***
  - ***Vergence jumps [43±11 vs. 39±10]***
- ***No significant sex-related differences were identified in the number or change in eye movements between the initial and latter 30-seconds***

Conclusions

- Results establish ***normative database for various eye movements*** to compare patient populations who have binocular endurance dysfunctions potentially due to mTBI



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Clinical Measurement

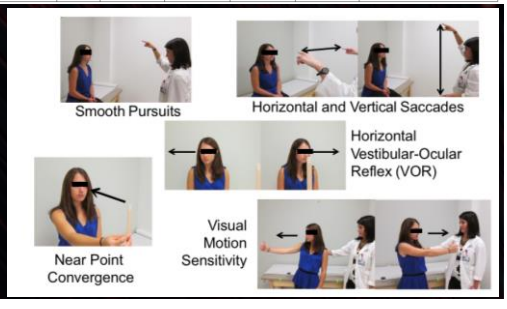
Entrance Skills – Vestibular Ocular Motor Screening (VOMS)

- Smooth pursuits
- Saccades
  - Horizontal
  - Vertical
- Near point of convergence
- Vestibular-Ocular Reflex (requires metronome)
  - Horizontal (180 bpm)
  - Vertical (180 bpm)
- Visual motion sensitivity (50 bpm)
- **FOR YOUR CONSIDERATION….**
  - **Head Impulse Test (HIT)**
  - **Dynamic VA @ 2Hz**

https://health.mil/Reference-Center/Publications/2020/07/31/Vestibular-Ocular-Motor-Screening-VOMS

Vestibular/Ocular-Motor Screening (VOMS) for Concussion

Vestibular/Ocular Motor Test:	Not Tested	Headache 0-10	Dizziness 0-10	Nausea 0-10	Fogginess 0-10	Comments
BASELINE SYMPTOMS:	N/A					
Smooth Pursuits						
Saccades – Horizontal						
Saccades – Vertical						
Convergence (Near Point)						(Near Point in cm): Measure 1: _____ Measure 2: _____ Measure 3: _____
VOR – Horizontal						
VOR – Vertical						
Visual Motion Sensitivity Test						



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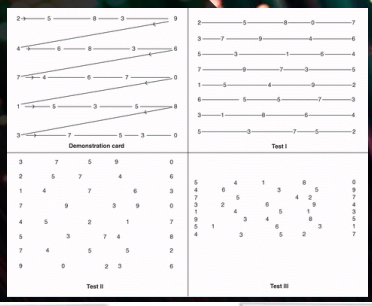
Clinical Measurement
Entrance Skills – DEM and King-Devick

In adolescents (age 9-19) with concussions, does King-Devick Test provide more efficient screening tool compared to traditional screening tools including ImPACT, SAC and SCAT5?
J Neuro Sci (2019) 398:91-97

Results
- 3 articles found KD test gave similar results to ImPACT test and visual symptoms on the PCSS
- 2 articles looked at the VOMS test and noted that vertical and horizontal vestibular ocular reflex are most useful to diagnose and manage adolescent concussions.



Discussion
- All analyzed the efficiency of screening tools such as ***VOMS, PCSS, KD, SCAT5, ImPACT, and NPC***
- ***All five of the studies provided similar results that oculomotor function is vital to concussion diagnosis in adolescents***
- KD test is an effective screening tool but is not a complete neurologic assessment
  - ***KD must be used concurrently with a clinical evaluation for appropriate diagnosis***

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Clinical Measurement
Clinical Testing

- **Automated Neuropsychological Assessment (ANAM)**
- **Immediate Post-Concussion Assessment Tool (ImPACT_v6)**
- **Computerized Cognitive Assessment Tool (CCAT)**
- **RightEye**
- **EyeBOX**
- ***neuroFit One***
- **ADA (AI Application)**

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Clinical Measurement

Clinical Testing – Automated Neuropsychological Assessment (ANAM)

Comparing composite scores for the ANAM4 TBI-MIL for research in mTBI

Arch Clin Neuropsych (2020) *35*:56-69

Method

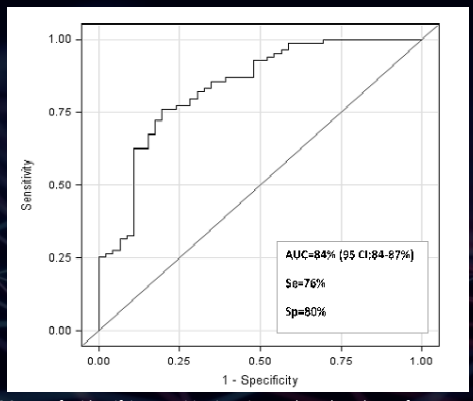
- Male service members with mTBI (n=56) or (-) TBI history (n=733) completed eight ANAM4 TBI-MIL tests.
- Throughput scores used to calculate 8 composite scores
  - Overall test battery mean (OTBM)
  - Global deficit score (GDS)
  - Neuropsychological deficit score-weighted (NDS-W)
  - Low score composite (LSC)

Results

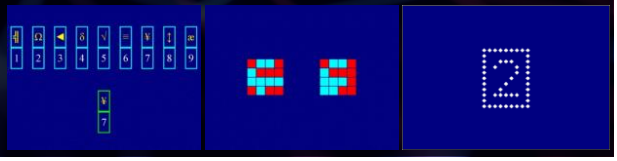
- OTBM and ACS were normally distributed. Other composites had skewed, zero-inflated distributions (62.9% had GDS = 0)
- ***All composites differed significantly between participants with and without mTBI with deficit scores***

Conclusions

- ***ANAM4 TBI-MIL has no well-validated composite score***
- Deficit scores showed larger group differences than the OTBM, but similar AUC values with highly correlated deficit scores



ROC curve for identifying cognitive impairment based on the performance of ANAM best model using subtests selected by step-down multivariate analysis



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Clinical Measurement

Clinical Testing – ImPACT (v4) and CCAT

Sensitivity and Specificity of Computer-Based Neurocognitive Tests in Sport-Related Concussion: NCAA-DoD CARE Consortium

Sports Med (2021) 51:351-365

Methods

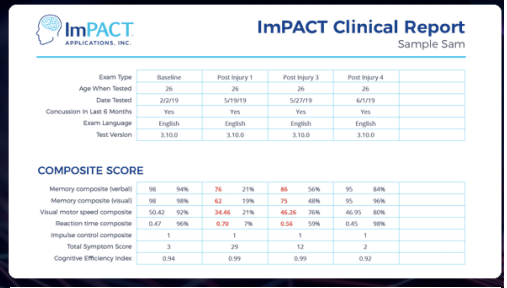
- Collegiate athletes and non-varsity cadets from the NCAA-DoD CARE
- Consortium divided into two groups [concussed (n=1414) & healthy (n=8305)
- Normative Change method and the Reliable Change Index (RCI) method were used to determine if the change scores were significant.

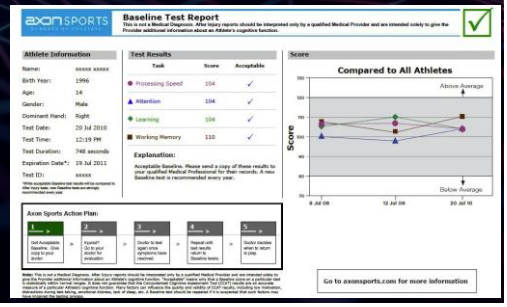
Results

- CCAT performed best when using a 75%-confidence interval and 2 NCF (sensitivity = 0.513, specificity = 0.715)
- ImPACT performed best with an 87.5%-confidence interval and 1 NCF (sensitivity = 0.626, specificity = 0.559)

Conclusion

- ***Overall low sensitivity and specificity results provide evidence for multi-dimensional assessment for concussion diagnosis including:***
  - ***Symptom evaluation***
  - ***Postural control assessment***
  - ***Neuropsychological status***





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Clinical Measurement

Clinical Testing – RightEye (Bernell)

Smooth Pursuit Eye Movements as a Biomarker for Mild Concussion within 7-Days of Injury

Brain Injury (2021) 35(14):1682-1689

Methods

- 91 concussed adolescents and 140 controls performed computerized test of circular, horizontal and vertical tracking task using Right Eye eye tracker
- Oculomotor tracking was assessed by computing the rate of fixation, saccades and smooth pursuits made while performing the tasks

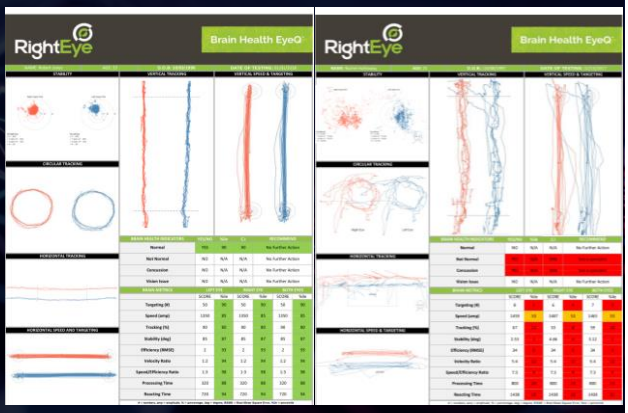
Results

- Predictive visual tracking task was able to differentiate the TBI group from the non-TBI group
- ***TBI group showed significant difference in:***
  - ***Fixation, saccades and SPEM percentages for circular tracking movement***
  - ***Fixation and smooth pursuits for horizontal and vertical tracking***

Conclusions

- ***Predictive visual tracking able to differentiate deficits in oculomotor functions in individuals with and without mTBI***

Control **mTBI**



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Clinical Measurement

Clinical Testing – EyeBox (Oculogica)

Eye tracking for classification of concussion in adults and pediatrics

Frontiers in Neurology (2022) *13*:2686

Methods

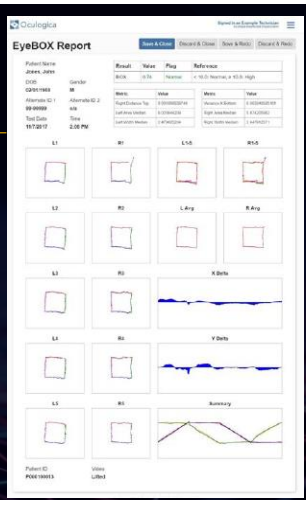
- Potentially concussed subjects recruited in ED and concussion clinic settings prospectively underwent eye tracking and a subset of the SCAT-3 at 6 sites
- Results of an eye tracking-based classifier model were then validated against a pre-specified algorithm with a cutoff for concussed vs. non-concussed

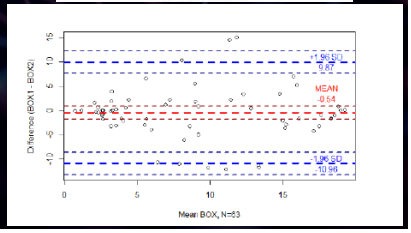
Results

- When concussion defined by SCAT3 subsets, sensitivity (81%) and specificity (66%) of eye tracking algorithm had AUC was 0.718
- ***Misclassification rate (n=282) was 32%***

Conclusion

- ***Pre-specified algorithm and cutoff for diagnosis of concussion vs. non-concussion has sensitivity and specificity useful as baseline-free aid in concussion diagnosis***
- ***Eye tracking has potential to serve as objective "gold-standard" for detection of neurophysiologic disruption due to brain injury***





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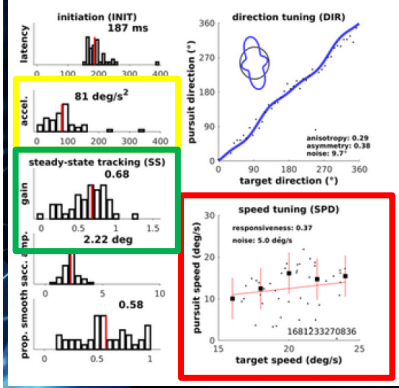
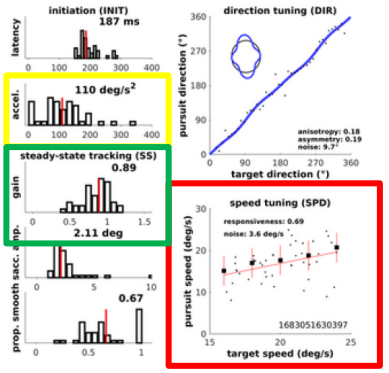
Clinical Measurement
Clinical Testing – neuroFit One

Detailed neuroFit One Results

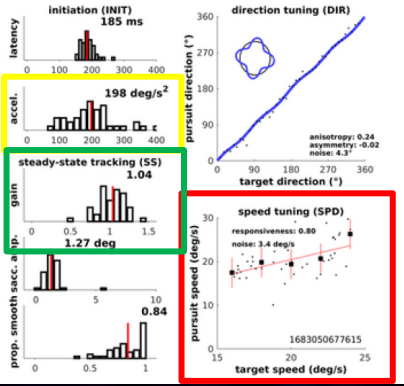
SOF Veteran with TBI & PTSD
nFit -1.06



Median JIFX Active Duty Participant
nFit 0.02



Active Duty Pilot
nFit 1.44



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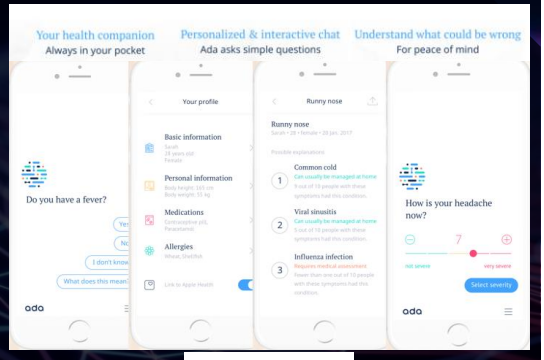
Clinical Measurement
Clinical Testing – AI Software

How accurate are digital symptom assessment apps for suggesting conditions and urgency advice: Clinical vignettes comparison to GPs
BMJ Open (2020) 10:e040269

Methods
- For 8 apps and 7 general practitioners: 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 but nature of iterative improvements to software offers scalable improvements to care***



ada

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Clinical Measurement

Clinical Testing – Where does automated testing leave us?

Utility of VOMS, SCAT5, and ImPACT Baseline Evaluations for Acute Concussion Identification in Collegiate Athletes: NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium

Am J Sports Med (2022) 50(4):1106-1119

Methods

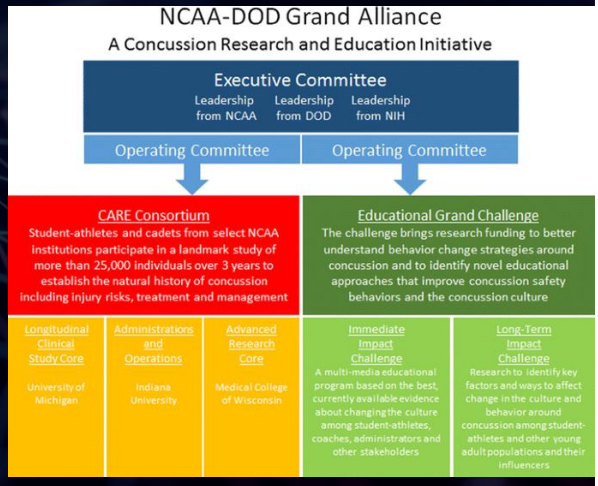
- Preseason and postinjury VOMS, SCAT3, ImPACT PCSS and ImPACT composite scores were analyzed for 3958 preseason and 496 acute collegiate athlete evaluations in NCAA-DoD CARE Consortium.

Results

- ***Effect sizes were large and overall predictive utilities were clinically useful for postinjury VOMS Total, SCAT5 Symptom Evaluation total score and ImPACT PCSS total score***
- ***Effect sizes were small and predictive utilities were poor for Standardized Assessment of Concussion and all ImPACT composites***

Conclusion

- ***VOMS Total and symptom severity (SCAT5, ImPACT) total scores had large effect sizes and clinically useful AUCs for identifying acute concussion***
- ***However, all tools demonstrated high within-patient test-retest variability resulting in poor reliability***
  - ***Incorporating baseline assessments did not significantly increase diagnostic yield for acute concussion***



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Clinical Measurement

Baseline Imaging

- IR Pupillometry
- SD-OCT
  - RNFL
  - GCC

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Clinical Measurement

Baseline Imaging – IR Pupillometry

Accommodative and pupillary dysfunctions in concussion and mTBI : Review

J Neurorehab (2022) 50(3):261-278

Methods

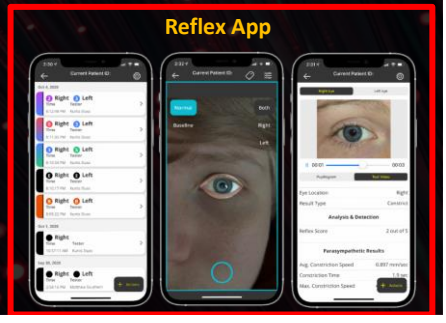
- PubMed, Google Scholar, and Semantic Scholar databases were searched for accommodation, pupil, VT, vision rehabilitation and acute/chronic mTBI

Results

- ***Most static and dynamic pupil response parameters were typically reduced, slowed, delayed, and/or more variable***
- ***Most of the abnormal accommodative parameters could be significantly improved with vision therapy***

Conclusions

- ***Most response parameters were abnormal and directly related to visual symptoms***
- ***For accommodation, improvements following vision therapy suggests presence of considerable visual system plasticity, even in older adults with chronic brain injury***
- ***VALIDATED STUDIES....***



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Clinical Measurement

Baseline Imaging - RNFL + Mac GCC

Investigating possible retinal biomarkers of head trauma in Olympic boxers using SD-OCT

Eye and Brain (2018) 10: 101-110

Methods

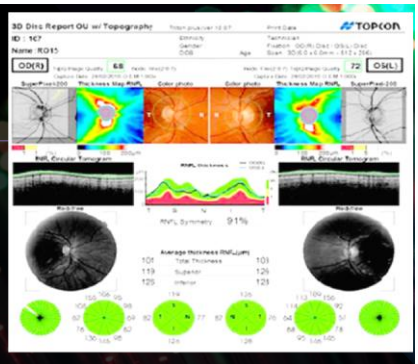
- Macular GCC and RNFL thickness was measured using SD-OCT OCT 18 months apart in 16 Olympic boxers ***aged 20-33***
- Healthy controls without past or present history of concussion were screened to provide comparison of cross-sectional. longitudinal data

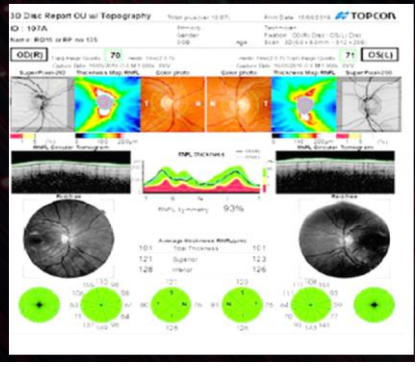
Results

- Baseline macula and RNFL measures were thinner in boxers vs. healthy controls
- ***Cross-sectional results showed thinner macula sectors and RNFL quadrants in Olympic boxers compared to controls***

Conclusion

- ***Significant change to macula and RNFL densities, occurring over an 18-month interval is an unexpected finding in otherwise heathy elite athletes***
- ***SD-OCT may prove clinically useful retinal biomarker of neuropathologic change after mild traumatic brain injury and/or repeat head blows***





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Clinical Management

- NCAA CARE Consortium
  - Return to Play / Return to Learn
- Ophthalmic Lenses
- Nutraceuticals

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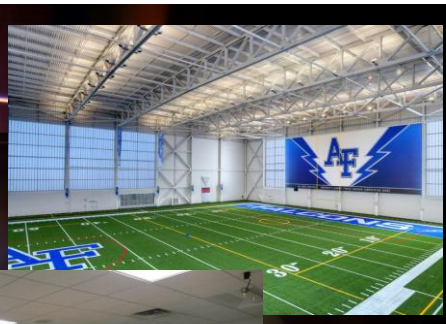
Clinical Concussion Management

USAFA Concussion Clinic Model



Originated in 2012 with following goals:

- Creation of single source rehabilitation for athletes and Cadets with suspected or confirmed mTBI/concussion
- Return to athletic competition
- Reduce academic impact

Multidisciplinary medical team

Sports Medicine → **Optometry** → Human Performance Lab → Sports Medicine → Return to competition

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Clinical Concussion Management

mTBI/Concussion Visual Symptoms

Vergence dysfunction in mTBI review
Ophthal Physiol Opt (2019) 31: 456–468

- Reading problems (~80%)
- ***Vergences***
- ***Versions*** ***"Big 3"***
- ***Accommodation***
- Other symptoms
  - Strabismus
  - CN palsy
  - Nystagmus

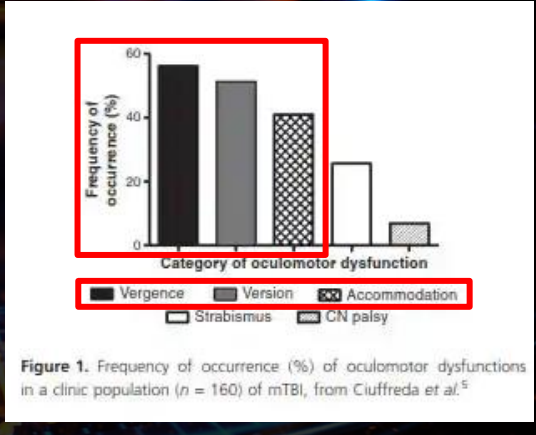

Figure 1. Frequency of occurrence (%) of oculomotor dysfunctions in a clinic population (n = 160) of mTBI, from Ciuffreda *et al.*[5]

Return to Play Protocol

- 5-6 step process
  - Increasing neurocognitive integration (hours of schoolwork)
  - Increasing physical activities (light to moderate activities)

http://www.themichelicenter.com/concussionrtpblog/

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Clinical Concussion Management

Retinal Carotenoid + Ω-3 Fatty Acids

Dietary Supplements in Health Promotion

Published by CRC Press in 2015

Lutein and Zeaxanthin are found throughout retina and brain and *may be uniquely suited to affecting processes initiated by concussive events including inflammatory stress.* Secondary injury be immediately following impact in closed head injuries and is likely a contributor to neuronal dysfunction and loss.

Inflammation is an acute and chronic response to concussive head injury (Cederberg etal., 2010).

- Lutein has been shown to decrease the expression of COX-2 and reduce nNOS in a dose-dependent manner

- Lutein and zeaxanthin also stabilize cell membranes along with Ω-3 FAs reducing neuronal signaling disruption

12 Possible Benefits of Lutein and Zeaxanthin for Visual Symptoms of Mild Traumatic Brain Injury

Emily R. Bovier and Billy R. Hammond, Jr.

CONTENTS

12.1 OVERVIEW

Most of the reported cases of traumatic brain injury (TBI) in the United States are classified as a concussion or a mild traumatic brain injury (MTBI). This approximation (75% of the annual 1.7 million cases; Paul et al., 2010) is likely underestimated since epidemiological reports do not include cases assessed outside of hospital settings, such as data from the military, or incidents that go untreated. MTBI is becoming a major public health problem, not only with respect to the general population, but also for specific groups of individuals such as athletes and military personnel. The growing concern regarding consequences of MTBI is evident in the recent media attention given to athletes and soldiers suffering from deficits associated with concussive events. According to U.S. Military Casualty Statistics from the 2010 Congressional Research Service Report for Congress, the incidence of MTBI between 2000 and 2010 was 137,328 cases (out of 178,876 total TBI cases).

Typically, when the quality of life of patients with TBI is considered, attention is given to patients with more severe forms of TBI or to secondary symptoms related

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Clinical Concussion Management

Retinal Carotenoids + Ω-3 Fatty Acids

REVIEW

ω-3 Fatty Acid Supplementation as a Potential Therapeutic Aid for the Recovery from Mild Traumatic Brain Injury/Concussion[1,2]

Erin Cernkovich Barrett, Michael I. McBurney, and Eric D. Ciappio*
DSM Nutritional Products, Parsippany, NJ

Advances in Nutrition An International Review Journal

ABSTRACT

Mild Traumatic Brain Injury/Concussion

antioxidants MDPI

Review

Antioxidant Therapies in Traumatic Brain Injury

Valentina Di Pietro [1,2,3], Kamal M. Yakoub [1,2], Giuseppe Caruso [4], Giacomo Lazzarino [5], Stefano Signoretti [6], Aron K. Barbey [3], Barbara Tavazzi [7,8,*], Giuseppe Lazzarino [9,*], Antonio Belli [1,2,*] and Angela Maria Amorini [9]

1 Neurotrauma and Ophthalmology Research Group, Institute of Inflammation and Aging, University of Birmingham, Birmingham B15 2TT, UK
2 NIHR Surgical Reconstruction and Microbiology Research Centre, University Hospitals Birmingham NHS Foundation Trust, Birmingham B15 2TT, UK
3 The Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana Champaign, Champaign, IL 61801, USA
4 Department of Laboratories, Oasi Research Institute – IRCCS, Via Conte Ruggero 73, 94018 Troina (EN), Italy
5 UniCamillus, Saint Camillus International University of Health Sciences, Via di Sant'Alessandro 8, 00131 Rome, Italy
6 UOC Neurochirurgia, ASL Roma2, S. Eugenio Hospital, Piazzale dell'Umanesimo 10, 00144 Rome, Italy
7 Institute of Biochemistry and Clinical Biochemistry, Catholic University of Rome, Largo F. Vito 1, 00168 Rome, Italy

J Neurosurg 121:42–54, 2014
©AANS, 2014

Amelioration of oxidative stress and protection against early brain injury by astaxanthin after experimental subarachnoid hemorrhage

Laboratory investigation

Xiang-Sheng Zhang, M.D.,[1] Xin Zhang, M.D., Ph.D.,[1,2] Meng-Liang Zhou, M.D., Ph.D.,[1] Xiao-Ming Zhou, M.D.,[1] Ning Li, M.D.,[1] Wei Li, M.D.,[1] Zi-Xiang Cong, M.D.,[1] Qing Sun, M.D.,[1] Zong Zhuang, M.D.,[1] Chun-Xi Wang, M.D.,[1] and Ji-Xin Shi, M.D., Ph.D.[1]

[1]Department of Neurosurgery, Jinling Hospital, School of Medicine, Second Military Medical University, Shanghai, China; and [2]Department of Neurosurgery, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu Province, China

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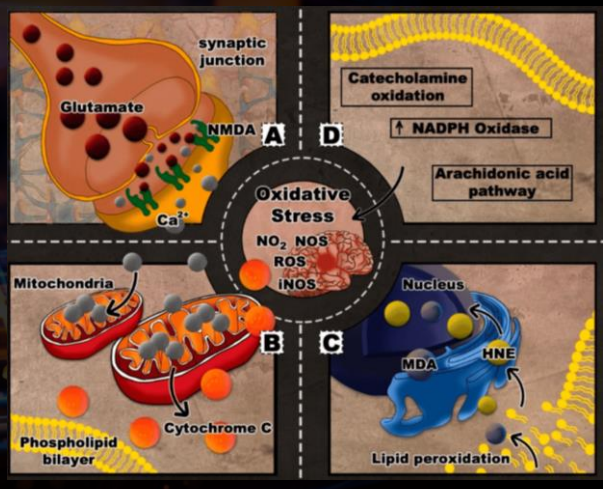
Clinical Concussion Management

Targeted Therapeutic Interventions

Oxidative stress and mitochondrial dysfunction following traumatic brain injury: From mechanistic view to targeted therapeutic opportunities
Fundamental & Clinical Pharmacology (2022) 36(4):612-662

Abstract

- TBI pathology results from primary insult followed by multi-mechanistic biochemical process termed secondary brain injury
  - ***Currently no pharmacological agents for definitive treatment of patients with TBI***
- Peer-review suggests oxidative stress and mitochondrial dysfunction are key mediators of the secondary injury cascade in TBI pathology
  - ***Oxidative damage results in the structural and functional impairments of cellular and subcellular components resulting in free radical formation and cellular apoptosis***
  - Clinical studies evaluating mitochondria-targeted therapies such as antioxidants and compounds with pleiotropic effects after TBI are promising



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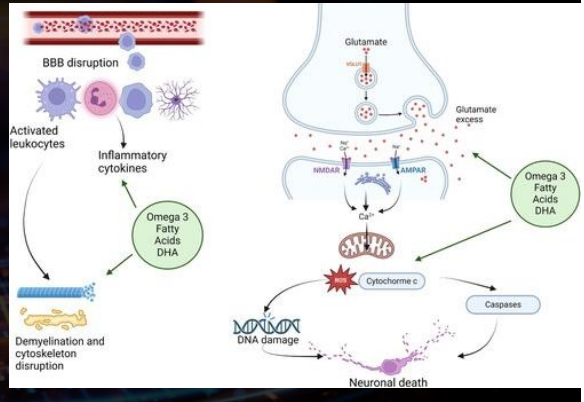
Clinical Concussion Management

Targeted Therapeutic Interventions

Nutraceutical Management Improves Outcomes Following Concussion
Optom Advisor (November 2024)

- Eye care professionals have treated oculomotor dysfunction and provided neurorehabilitative care for patients following a concussion for some time, but optometrists can allow these individuals further protection still with nutraceutical management and supplementation.
- Eye care clinicians are well-equipped to not only manage the visual sequelae resulting from a mild traumatic brain injury (mTBI), but accelerate recovery, reduce long-term symptoms and possibly reduce overall cost burdens

- **Omega-3 (DHA + EPA) – 1000 mg BID**
- **Carotenoids (lutein, *meso*-zeaxanthin, zeaxanthin) – 20 mg QD**
- **BCAA (leucine, isoleucine, valine) – 45g QD**
- **Creatine – 4000 mg QID**
- **Riboflavin (B2) – 400 mg QD**
- **Magnesium (Mg) – 400mg QD to BID***
- **Choline (CDP-choline or citicoline) – 1000mg QD**



Magnesium L-threonate
VS.
Magnesium citrate

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Clinical Concussion Management

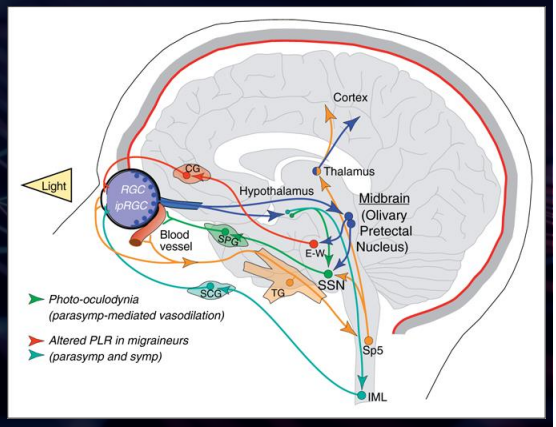
Recovery and Expectation Management

Photophobia Associated with Traumatic Brain Injury: Systematic Review and meta-analysis
OVS (2021) 98(8):891-900

Results
- 75 eligible publications identified the prevalence of photophobia at ~30% at 1 week after the injury. Prevalence decreased to 19% between 1-wk and 1-mo after TBI and to 14% between 1-3 mos after the injury.
- ***At 3 months: Photophobia leveled off to a near plateau***
- ***At 3-6 months: Photophobia increased in 18%***
- ***At 6-12 months: Photophobia decreased in 15%***

Conclusions
- ***Photophobia is frequent complaint after TBI and largely resolves for most individuals within 3 months after the injury***
- ***For some patients, photophobia can last up to 12 months and possibly longer***

NEEDED:
- ***Objective quantification / measure of photophobia***
- ***Validated photophobia questionnaire***



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Clinical Concussion Management

Recovery and Expectation Management

Colored Glasses to Mitigate Photophobia Symptoms Post-Concussion Brain Injury
J Athl Train (2017) 52(8):725–729

Results
- Assessed 51 post-concussion patients for visual symptoms including photophobia and photosensitivity
  - ***39 patients reported visual symptoms***
  - ***76% complained of photophobia***
- Using OTS glasses of 1 or more colors, symptoms were relieved in 85% of patients reporting photophobia. Colors that provided the most relief were blue, green, red, and purple. No adverse events were reported.

Color	Frequency (Percentage)[a]
Blue	15 (45)
Green	10 (30)
Red	9 (27)
Purple	9 (27)
Magenta	4 (12)
Indigo	4 (12)
Violet	3 (9)
Aqua	3 (9)
Orange	2 (6)
Rose	2 (6)
Pink	2 (6)

Hmmm… is it λ-dependent or PLT-dependent?

Conclusions
- ***Empirical assessment of frequency-specific photophobia is easy to perform***
- ***Traditional penlight is used to elicit photophobia and then the colored glasses are tested for optimal relief***
- ***More work is needed to identify the best colors and methods of mitigating frequency-specific photophobia (NEXT SLIDE…)***

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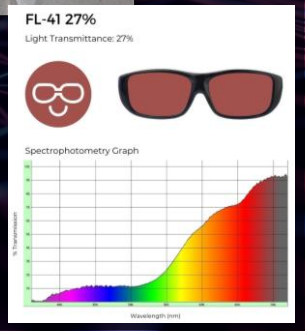
Clinical Concussion Management

Recovery and Expectation Management – FL-41

fMRI evidence that precision ophthalmic tints reduce cortical hyperactivation in migraine
Cephalalgia (2011) *31*(8):925-936.



FL41 Tint

- Developed in UK in the 1980s for fluorescent light sensitivity
- Transmission minimum is 480nm
- λ plays a role in discomfort severity in migraines
  - Short (blue) and long (red) wavelengths can be uncomfortable for migraine patients
    - 480 nm is particularly triggering in migraine patients
    - ***Retinal carotenoid peak absorption = 460nm***

****Correlation between the ipRGC action spectrum and the transmission minimum of FL-41 is probably not a coincidence....***

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Clinical Concussion Management

Resources

- AOA's resources (aoa.org/VR)
- College of Optometrists in Vision Development (covd.org)
- **Neuro-Optometric Rehabilitation Association (noravisionrehab.org)**
- American Academy of Optometry (aaopt.org)
- Optometric Extension Program Foundation (oepf.org)

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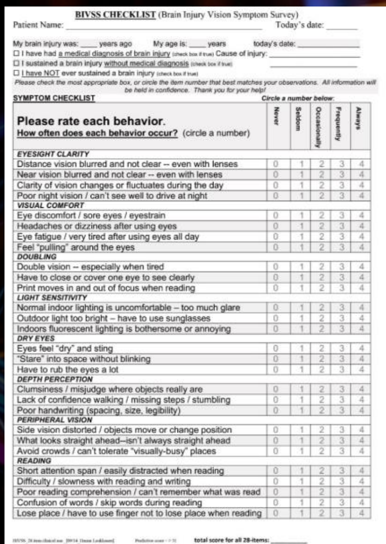
Clinical Concussion Management
Take Home Points

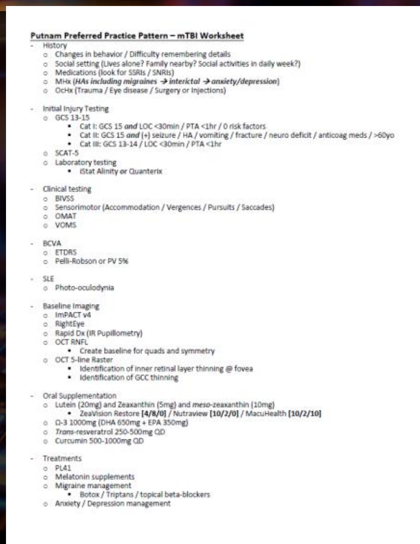

BIVSS CHECKLIST (Brain Injury Vision Symptom Survey)
Patient Name: ______ Today's date: ______

My brain injury was: ____ years ago My age is: ____ years today's date: ______
☐ I have had a medical diagnosis of brain injury (check box if true) Cause of injury: ______
☐ I sustained a brain injury without medical diagnosis (check box if true)
☐ I have NOT ever sustained a brain injury (check box if true)
Please check the most appropriate box, or circle the item number that best matches your observations. All information will be held in confidence. Thank you for your help!

SYMPTOM CHECKLIST — *Circle a number below:*

Please rate each behavior. How often does each behavior occur? (circle a number)	Never	Seldom	Occasionally	Frequently	Always
EYESIGHT CLARITY					
Distance vision blurred and not clear -- even with lenses	0	1	2	3	4
Near vision blurred and not clear -- even with lenses	0	1	2	3	4
Clarity of vision changes or fluctuates during the day	0	1	2	3	4
Poor night vision / can't see well to drive at night	0	1	2	3	4
VISUAL COMFORT					
Eye discomfort / sore eyes / eyestrain	0	1	2	3	4
Headaches or dizziness after using eyes	0	1	2	3	4
Eye fatigue / very tired after using eyes all day	0	1	2	3	4
Feel "pulling" around the eyes	0	1	2	3	4
DOUBLING					
Double vision -- especially when tired	0	1	2	3	4
Have to close or cover one eye to see clearly	0	1	2	3	4
Print moves in and out of focus when reading	0	1	2	3	4
LIGHT SENSITIVITY					
Normal indoor lighting is uncomfortable – too much glare	0	1	2	3	4
Outdoor light too bright – have to use sunglasses	0	1	2	3	4
Indoors fluorescent lighting is bothersome or annoying	0	1	2	3	4
DRY EYES					
Eyes feel "dry" and sting	0	1	2	3	4
"Stare" into space without blinking	0	1	2	3	4
Have to rub the eyes a lot	0	1	2	3	4
DEPTH PERCEPTION					
Clumsiness / misjudge where objects really are	0	1	2	3	4
Lack of confidence walking / missing steps / stumbling	0	1	2	3	4
Poor handwriting (spacing, size, legibility)	0	1	2	3	4
PERIPHERAL VISION					
Side vision distorted / objects move or change position	0	1	2	3	4
What looks straight ahead--isn't always straight ahead	0	1	2	3	4
Avoid crowds / can't tolerate "visually-busy" places	0	1	2	3	4
READING					
Short attention span / easily distracted when reading	0	1	2	3	4
Difficulty / slowness with reading and writing	0	1	2	3	4
Poor reading comprehension / can't remember what was read	0	1	2	3	4
Confusion of words / skip words during reading	0	1	2	3	4
Lose place / have to use finger not to lose place when reading	0	1	2	3	4

total score for all 28-items: ______


Putnam Preferred Practice Pattern – mTBI Worksheet

- History
  - Changes in behavior / Difficulty remembering details
  - Social setting (Lives alone? Family nearby? Social activities in daily week?)
  - Medications (look for SSRIs / SNRIs)
  - MHx (*HAs including migraines → interictal → anxiety/depression*)
  - OcHx (Trauma / Eye disease / Surgery or Injections)
- Initial Injury Testing
  - GCS 13-15
    - Cat I: GCS 15 *and* LOC <30min / PTA <1hr / 0 risk factors
    - Cat II: GCS 15 *and* (+) seizure / HA / vomiting / fracture / neuro deficit / anticoag meds / >60yo
    - Cat III: GCS 13-14 / LOC <30min / PTA <1hr
  - SCAT-5
  - Laboratory testing
    - iStat Alinity *or* Quanterix
- Clinical testing
  - BIVSS
  - Sensorimotor (Accommodation / Vergences / Pursuits / Saccades)
  - OMAT
  - VOMS
- BCVA
  - ETDRS
  - Pelli-Robson or PV 5%
- SLE
  - Photo-oculodynia
- Baseline Imaging
  - ImPACT v4
  - RightEye
  - Rapid Dx (IR Pupillometry)
  - OCT RNFL
    - Create baseline for quads and symmetry
  - OCT 5-line Raster
    - Identification of inner retinal layer thinning @ fovea
    - Identification of GCC thinning
- Oral Supplementation
  - Lutein (20mg) and Zeaxanthin (5mg) and *meso*-zeaxanthin (10mg)
    - ZeaVision Restore **[4/8/0]** / Nutraview **[10/2/0]** / MacuHealth **[10/2/10]**
  - Ω-3 1000mg (DHA 650mg + EPA 350mg)
  - *Trans*-resveratrol 250-500mg QD
  - Curcumin 500-1000mg QD
- Treatments
  - PL41
  - Melatonin supplements
  - Migraine management
    - Botox / Triptans / topical beta-blockers
  - Anxiety / Depression management

https://www.aan.com/practice/sports-concussion-toolkit/

Highly Effective Treatment in mTBI
Expectation Management
- Patient "WILL" Improve
- Address Cognitive Bias of Overestimation and Somatization
- Adequate Rest + Sleep Hygiene
  - Maximize Restorative Sleep
- Moderate Exercise
- Good Nutrition
- Risk Management
  - Proper PPE
  - Avoidance of high-risk activities
  - Avoidance of drugs and alcohol

If vestibular component suspected…
- *VOMS*
- *Head Impulse Test*
- *Dynamic VA*

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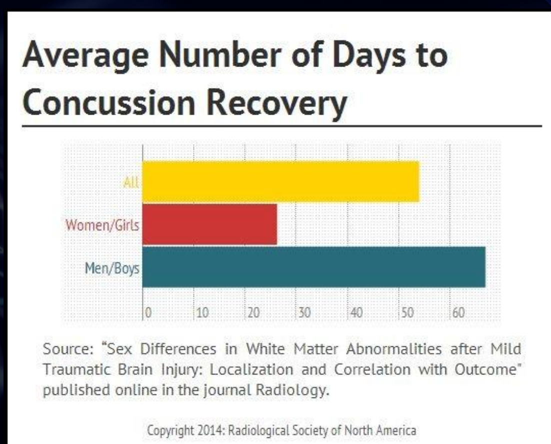
Clinical Concussion Management
Take Home Points

Recovery Timetable for *Uncomplicated mTBI*
- 21% recovered within 24 hours (rapid)
- 85% recovered within 7 days (gradual)
- 97% recovered within 30 days (prolonged)

- No differences between any injured and control subjects at ***90 days***.

- Data From NCAA Concussion Study (McCrea et al. 2019)

- ***CONSIDER ETIOLOGY OF PROLONGED SYMPTOMS***
  - *Severity was greater than initially assessed*
  - *Concurrent medical and/or psychosocial conditions*
  - *H/O unreported or subclinical concussions*
  - *APOE risk allele*
  - ***Supplementation strategy + VT may positively influence recovery***



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Role of Retinal Imaging in Neurodegenerative Disorders

March 2025

Christopher Putnam, OD, PhD, FAAO

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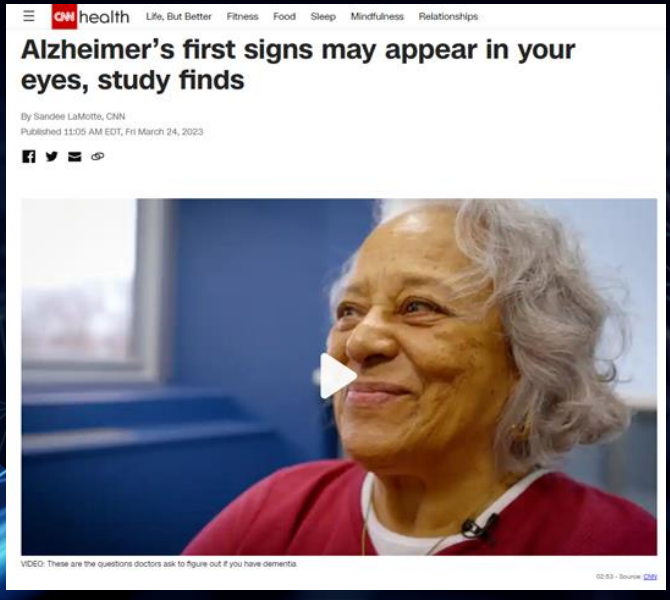
Retinal Imaging in Neurodegenerative Disorders

Alzheimer's Disease – CNN in March 2023



Retinal pathological features and proteome signatures of Alzheimer's disease
Acta Neuropathologica (2023) 145:409-438

- Retinal and brain tissue samples over 14 years from 86 human donors with Alzheimer's disease (AD) and mild cognitive impairment (MCI)
- Retinal correspondence of structural effects with brain and cognitive effects in AD
  - Entorhinal and temporal cortex
- ***Microglial cells declined by 80% in those with cognitive issues***
  - Responsible for repair and maintenance including clearing β-amyloid from the brain and retina.

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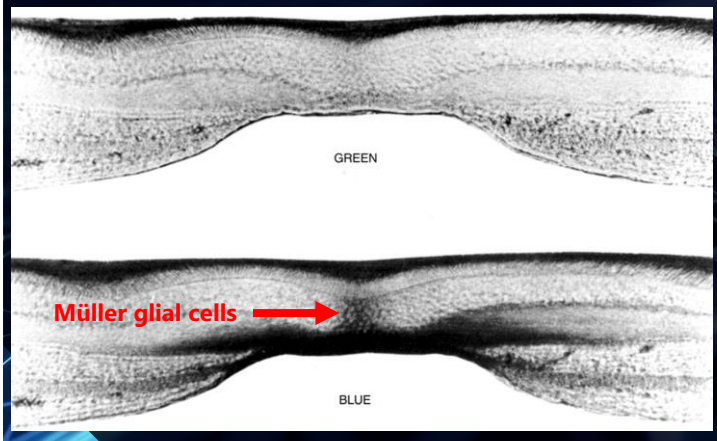
Retinal Imaging in Neurodegenerative Disorders

Alzheimer's Disease – CNN in March 2023



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Clinical Retinopathy

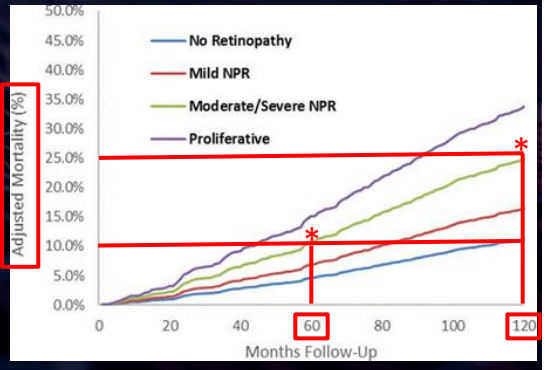
Pathogenesis

Retinopathy is Associated With Stroke, Dementia and Mortality

Stroke (2021) 52 (Suppl_1) A8-A8

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

Results
- 5,543 participants aged ≥18 years with gradable retinal imaging, 696 had retinopathy, 289 had stroke, and 597 had dementia
- Mean subject age was associated with ***higher risk of stroke (adj OR 2.39)*** and ***dementia (adj OR 1.68)***
- Over a median duration of 10 years, there was a dose-dependent relationship between severity of retinopathy 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:
  - ***2X 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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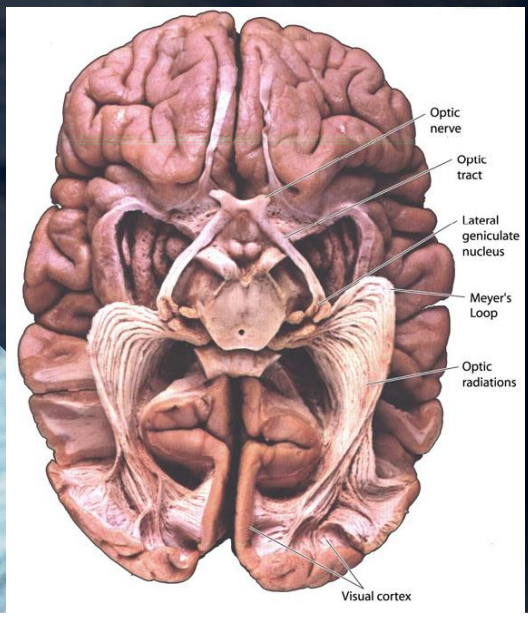
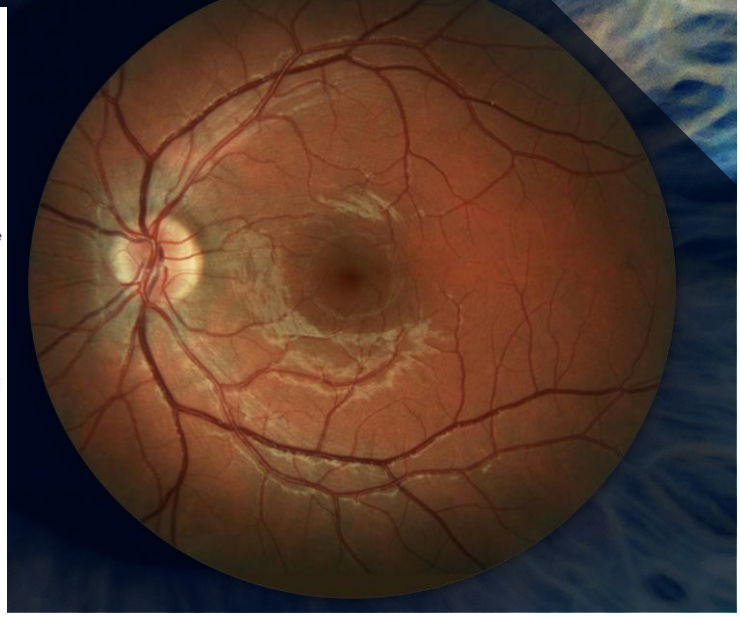
Neural anatomy is retinal anatomy…





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Clinical Retinal Imaging

- Adaptive Optics
- Macular Pigment Optical Density
- Red-Free Imaging
- ***Optical Coherence Tomography + Angiography***
- ***Fundus Autofluorescence***

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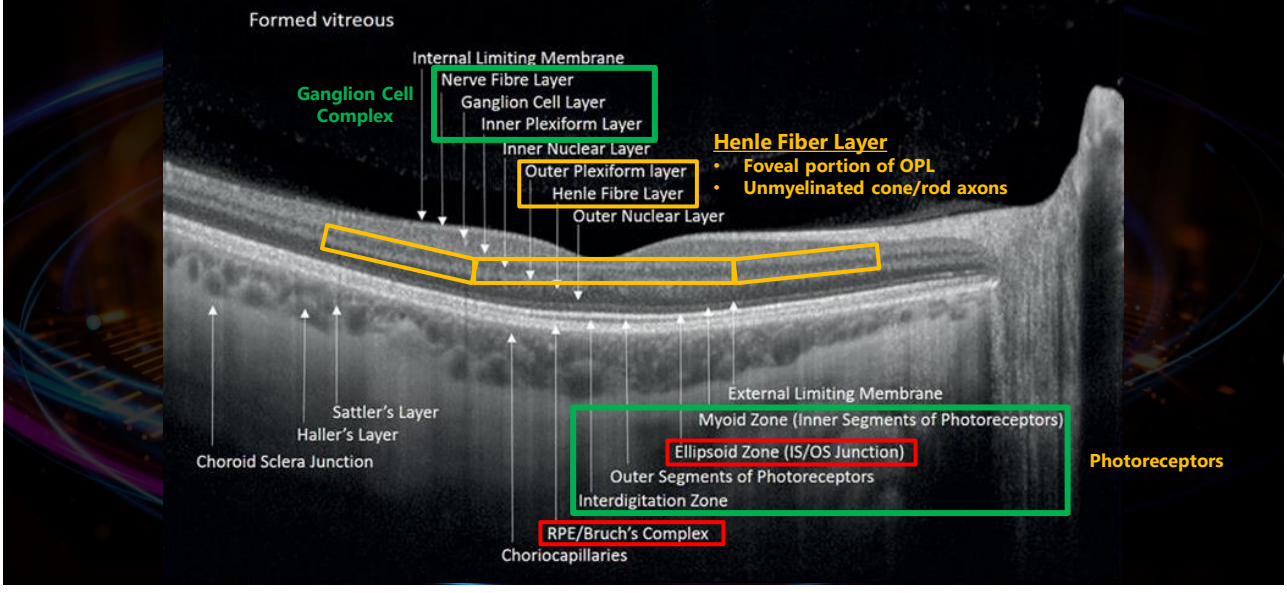
Clinical Retinal Imaging
Optical Coherence Tomography



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Clinical Retinal Imaging
Optical Coherence Tomography

Table 1. OCT Devices the Authors Have Used to Analyze Progression

	Cirrus HD-OCT (Carl Zeiss Meditec)	Spectralis OCT (Heidelberg Engineering)	RTVue-100 (Optovue)
Axial resolution	5 µm	7 µm	5 µm
Scanning speed	27,000 A-scans/sec	40,000 A-scans/sec	26,000 A-scans/sec
Manufacturer signal index (MSI) recommended threshold	Signal strength = 6 or 7 (max=10)	Quality = 15 (max=40)	Signal strength index = 39 (max=100)
RNFL scanning protocol	6x6 mm² cube centered on optic disc; RNFL thickness generated from 3.46-mm diameter circle	3.45 mm circle scan centered on optic disc	Radial and circular scans centered on optic disc; RNFL thickness generated from a 3.45-mm diameter circle
RNFL thickness map	OD	OD	OS
Normative database and reporting			
Macular scanning protocol	6-mm² grid measures the macular GCIPL thickness with an elliptical annulus around the fovea	30° x 25° volumetric scan of 8x8-mm² grid oriented on foveal-BMO axis	7-mm² area of macula, with center shifted 0.75 mm temporally
Retinal layers measured in the macula	GCIPL measures ganglion cell layer and inner plexiform layer	Full thickness macula	GCC measures RNFL, ganglion cell layer and inner plexiform layer
Macular thickness map	OS	OS	OD

Abbreviations: RNFL= retinal nerve fiber layer thickness; GCIPL= ganglion cell inner plexiform layer; GCC= ganglion cell complex.

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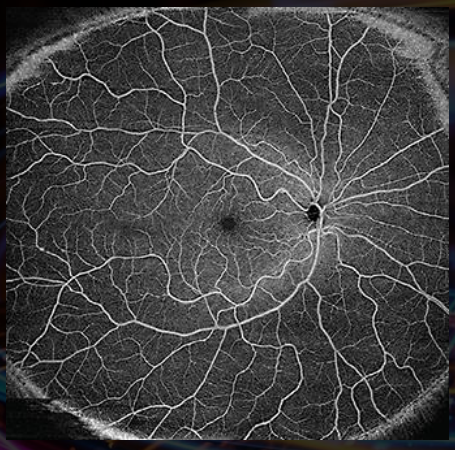
Clinical Retinal Imaging

Optical Coherence Tomography Angiography



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Clinical Retinal Imaging

Optical Coherence Tomography Angiography

Model (Manufacturer)	Cirrus HD-OCT 5000 (Carl Zeiss Meditec)[1]	Plex Elite (Carl Zeiss Meditec)[1]	3D OCT-1 Maestro2 (Topcon)[2]	Triton (Topcon)[2]	Spectralis 2nd and 3rd Generation (Heidelberg)[3]	Spectralis OCT-A (Heidelberg)[3]	iVue80 Optovue (VIsionix)[4]	Optovue Avanti with Angiovue (Visionix)[4]
SD-OCT or SS-OCT?	SD-OCT	SS-OCT	SD-OCT	SS-OCT	SD-OCT	SD-OCT***	SD-OCT	SD-OCT
Scanning Speed (A-scans per second)	27,000-68,000*	100,000-200,000	50,000	100,000	85,000**	85,000	80,000	70,000
Axial Resolution (µm in tissue)	5	6.3	6	8	Optical: 7 Digital: 3.9	3.9	5	5
Imaging Modes	SD-OCT, cSLO	SS-OCT, OCT-A, LSO, CCD camera	SD-OCT widefield, color fundus, red-free fundus, IR fundus, enhanced IR fundus and external eye photography	SS-OCT, color fundus, red-free fundus, IR fundus	SD-OCT, cSLO	OCT-A	SD-OCT wide-field	SD-OCT widefield, OCT-A, enhanced-depth imaging
SD-OCT Normative Database: *Number of subjects*	284 RNFL study 282 macula, ganglion cell, ONH study		399		201 (RNFL thickness)		480	
SD-OCT Normative Database: *Ethnicity*	43% Caucasian 24% Asian 18% African American 12% Hispanic 1% Indian 2% Mixed ethnicity		59% Caucasian 20% African American 18% Hispanic/Latino 3% Other		European descent		47% Caucasian 19% Asian 10% African 15% Hispanics 8% Indian 1% Other	

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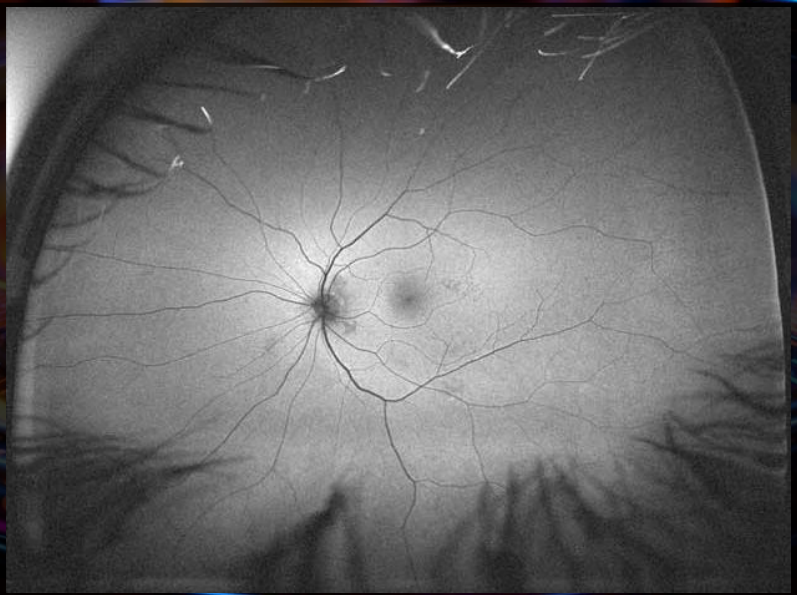
Clinical Retinal Imaging

Fundus Autofluorescence (Ultra-widefield)



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Neurodegenerative Disorders

- Huntington's Disease
- Vascular dementia
  - Cortical Infarction
- Frontotemporal dementia
- Multiple Sclerosis
- Parkinson's Disease
  - Lewy Body Dementia
- ***Alzheimer's Disease***
- ***Chronic Traumatic Encephalopathy***
  - ***mTBI relationship…***

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Dementia

An umbrella term used to describe a collection of brain diseases and their symptoms, which include: memory loss, impaired judgment, personality changes, and an inability to perform daily activities.

Alzheimer's Disease

Prevalence
60-70% of dementia cases

Characterized by
Amyloid plaques and beta tangles.

Symptoms include
Impairments in memory, language, and visuospatial skills.

Vascular Dementia

Prevalence
10-20% of dementia cases

Characterized by
Disease or injury to the blood vessels leading to the brain.

Symptoms include
Impaired motor skills and judgement.

Frontotemporal Dementia

Prevalence
10% of dementia cases

Characterized by
Deterioration of frontal and temporal lobes of the brain.

Symptoms include
Personality changes and issues with language.

Lewy Body Dementia

Prevalence
5% of dementia cases

Characterized by
Lewy body protein deposits on nerve cells.

Symptoms include
Hallucinations, disordered sleep, impaired thinking and motor skills.

Other Dementias

Prevalence
5% of dementia cases

Dementias related to
- Parkinson's disease
- Huntington's disease
- HIV
- Crutzfeldt-Jakob disease
- Korsakoff syndrome

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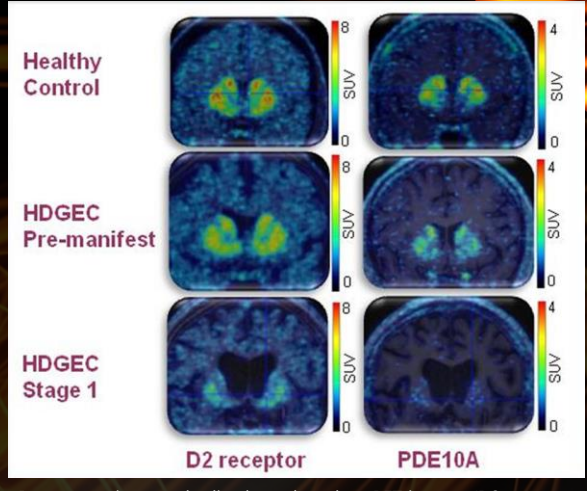
Clinical Retinal Imaging

Huntington's disease (HD)

- Rare neurodegenerative disorder characterized by
  - Chorea
  - Behavioral and psychiatric disturbances
  - ***Cognitive decline with mean onset 30-50 years***
- AD inheritance with a genetic HTT mutation elongation with longer repeats translating to earlier onset
- Diagnosis is based on clinical signs/symptoms in an individual with a parent with known HD and is ***confirmed by DNA determination***
- Management is typically multidisciplinary
  - Symptom mitigation with an aim of improving quality of life



Representative standardized uptake values PET images (D2 receptors and PDE10A enzyme) depicting coronal brain section at the level of ***basal ganglia*** at different stages of the disease overlaid on top of individual MRI image

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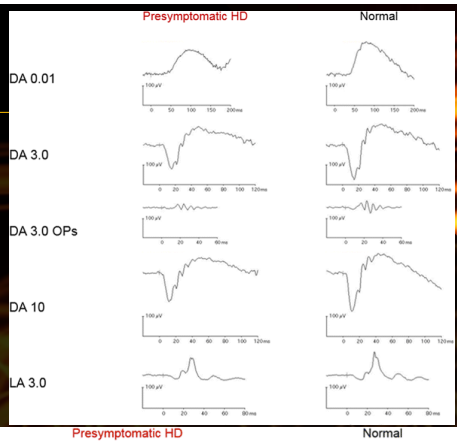
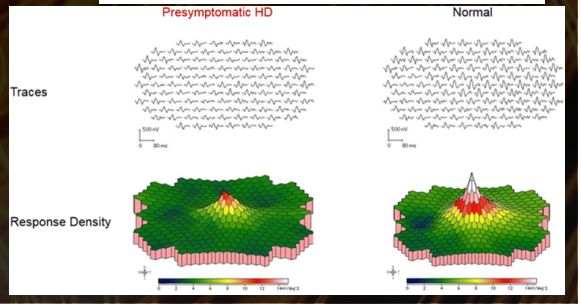
Clinical Retinal Imaging
Huntington's disease (HD)

- Average RNFL and macular SD-OCT scans found no significant difference between HD and healthy individuals although…
  - ***HD demonstrates reduction in temporal RNFL thickness compared to healthy controls***
  - ***Disease duration negatively correlates with both RNFL thickness and macular volume***
- ffERG and mfERG show early retinal dysfunction in a ***pre-symptomatic*** HD patients
  - ***ffERG amplitudes were subnormal for the dark-adapted measures and oscillatory potentials (Enter RETeval…)***
  - ***mfERGs revealed functional abnormalities of the central retina with attenuated P1 amplitudes***





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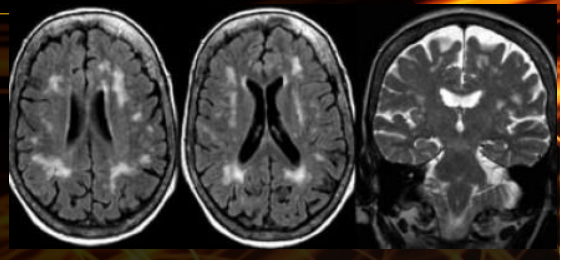
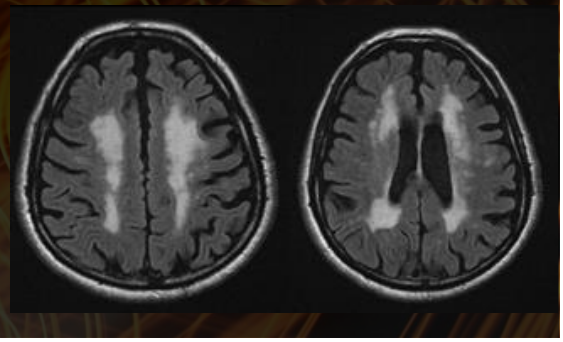
Clinical Retinal Imaging
Vascular dementia (VaD)

- Recognized as the 2nd most common cause of dementia
- Mechanistic relationship between vascular and degenerative pathology is elusive:
  - ***Uncertainties in diagnostic criteria***
  - ***Inexact relationship between cerebrovascular pathology and cognitive impairment***
- Cognitive changes are highly variable and dependent on neural substrates affected by the vascular pathology
- ***MMSE relatively insensitive to characteristic VaD deficits***
  - ***Developed for AD detection***

    MoCA and Vascular Dementia Assessment Scale (VADAS-cog)
    - More sensitive to variable deficits found in a VaD population such as executive function, attention, memory, language and praxis





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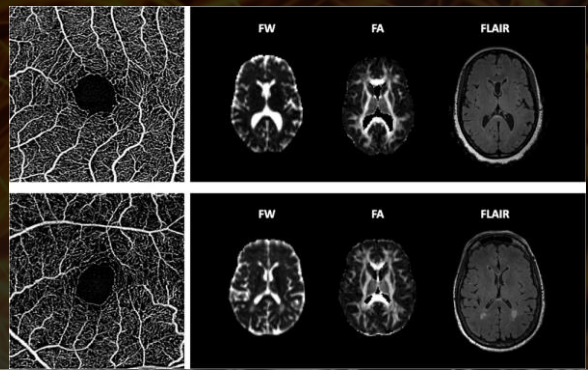
Clinical Retinal Imaging
Vascular dementia (VaD)

- Retinal vascular changes reflect the cerebral microvasculature
- Retinal vascular changes in stroke including cerebral small vessel disease offer clues to the specific pathophysiologic which play an important role in the development and progression of neurologic diseases
- ***Changes in the retinal vasculature may also act as biomarkers of the effectiveness of new therapies and reflect treatment response***
  - ***Clinical Pearl***
    - ***Strong relationship with PVD, CHF and CVD***
    - ***Critical Case Hx and ROS + Medications***

Retinal perfusion is linked to cognition and brain MRI biomarkers
Alzheimer's and Dementia (2023)

Results
- ***Lower retinal capillary perfusion is associated with worse information processing, fluid cognition and MRI biomarkers of cerebral small vessel disease***
  - ***However.. NOT related to crystallized cognition***



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Clinical Retinal Imaging
Frontotemporal dementia (FTD)

- Frontotemporal dementias are a heterogeneous group of neurodegenerative disorders characterized by marked impairments in behavior, personality, language and motor function
- 3rd most common neurodegenerative disorder affecting persons aged ≤65
- ***~40% = Apathy, disinhibition and social withdrawal***
- ***~40% = Prominent language impairments***
- ***~20% = Muscle atrophy, apraxia and progressive supranuclear palsy (PSP)***
- Pathologic manifestations
  - Frontotemporal lobar degeneration accompanied by astrocytosis, microgliosis and ***tau protein deposition***

*****One of the greatest current challenges is to identify markers for prodromal disease stages allowing earlier initiation of disease-modifying therapies***

Table 1 Current Biomarkers in FTD

Biomarker	Method of analysis	Advantages	Limitations
Imaging biomarkers			
Gray matter atrophy	Volumetric T1-weighted MRI	• Noninvasive • Ability to apply various different processing techniques • Discrimination between FTD and AD, as well as between some FTD subtypes	• Less sensitive to detecting changes in subcortical structures • Inconsistent results and correlation with time course of disease • Difficult to stratify FTD spectrum with structural imaging alone
White matter integrity loss	DTI	• Noninvasive • Can easily reflect changes in microstructures • Can detect white matter changes that precede gray matter changes in FTD • Sensitive differentiation of FTD from other types of dementia and control subjects	• Varying distribution patterns and rates of neurodegeneration observed among different individuals
Brain metabolism	FDG-PET	• Early visualization of alterations in brain metabolism that may precede gray matter atrophy • May reveal abnormalities in presymptomatic stage of FTD	• Expensive, not covered by many insurers • Requires prolonged positioning that is increasingly difficult in patients with advanced dementia or concurrent motor dysfunction
Fluid biomarkers			
NfL	CSF	• Strong correlation with disease severity, progression, survival, and cerebral atrophy	• Increased in several other neurodegenerative diseases • Must be combined with other disease-specific biomarkers • Equally elevated in FTD subtypes
Progranulin	Blood sample	• Discriminates between *GRN* mutation carriers and noncarriers with high sensitivity remains constant over disease	• Should be combined with CSF sample due to varying regulation • Does not reflect extent of neurodegeneration
Genetic biomarkers			
C9orf72, MAPT,* and *GRN	Blood sample	• Direct correlation between clinical manifestations and molecular mechanisms of pathology • Can potentially identify presymptomatic/prodromal carriers • Provides a basis for targeted therapies (i.e., ASOs)	• Genetic testing is generally restricted to patients with suggestive family history • Pleiotropic effects and incomplete penetrance further complicate identification of at-risk individuals • Availability limited to specialized clinical/research settings

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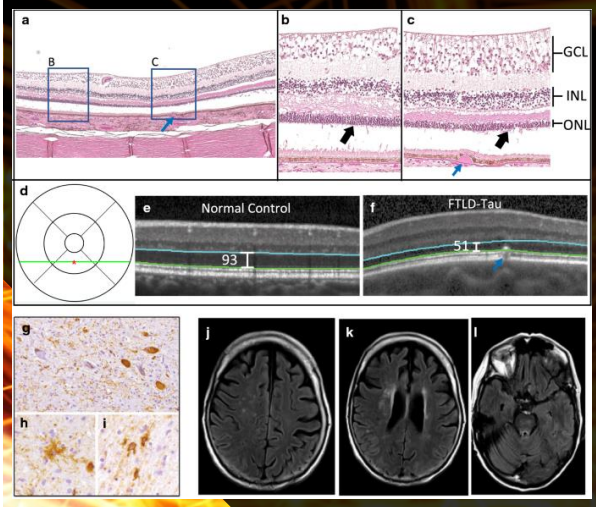
Clinical Retinal Imaging
Frontotemporal dementia (FTD)



Outer Retina Thinning Distinguishes Frontotemporal Degeneration from Alzheimer's Disease
IOVS (2019) 60:2296

Results

46 eyes from 27 FTD patients and 20 eyes from 10 AD patients were included. FTD patients compared to AD patients had a thinner outer retina, a thinner ONL but a thicker OPL

Conclusions

- ***Outer retina thinning detected by SD-OCT may distinguish FTD from AD***
  - Thicker outer plexiform layer in FTD patients may be from bipolar and horizontal cell dendrite sprouting as ONL thins
- ***No difference in RNFL and GCL thicknesses was seen between FTD and AD***
- ***Specific dementia brain pathologies may be associated with specific retinal abnormalities***

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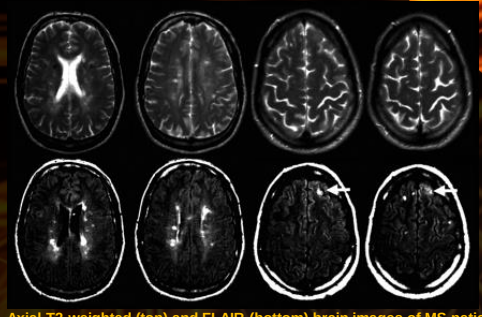
Clinical Retinal Imaging
Multiple Sclerosis (MS)

- Progressive neurological disorder characterized by inflammatory and degenerative components that affect genetically susceptible individuals with ***mean onset 20-40 years old***
- Autoimmune disease represented by axon demyelination, disruption of inflammatory homeostasis and neuronal death suggesting that ***cerebral pathology may mirror ocular manifestations***
  - Disease progression governed by the slow, subclinical injury accumulation of neuroaxonal structures
- Etiology remains unclear* with no definitive cure
  - MS cases 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*****



Axial T2-weighted (top) and FLAIR (bottom) brain images of MS patient illustrating the increased sensitivity of FLAIR for lesion detection. Due to CSF nullification, FLAIR shows lesions with more clarity than T2-weighted images

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Clinical Retinal Imaging
Multiple Sclerosis (MS)

Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis
Science (2022) 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***

Herpesvirus affecting humans

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


RESEARCH
REPORT
MULTIPLE SCLEROSIS
Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis
Kjetil Bjornevik, Marianna Cortese, Brian C. Healy, Jens Kuhle, Michael J. Mina, Yumei Leng, Stephen J. Elledge, David W. Niebuhr, Ann I. Scher, Kassandra L. Munger, Alberto Ascherio
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.

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Clinical Retinal Imaging
Multiple Sclerosis (MS)

Ocular Manifestations of Multiple Sclerosis: Population-Based Study
J Neuro-Ophthal (2024) 10:1097

Methods
- Retrospective, population-based study examining patients with confirmed MS based on neuroimaging, CSF studies and serum studies

Results
- Of the 116 patients with MS
  - ***66% were female with median age of onset 36 years***
  - ***53% had MS-related neuro-ophthalmic manifestations***
  - ***28% had visual symptoms as presenting MS symptom***
    - ***Optic neuritis = 37%***
      - ***Unilateral = 93%***
      - ***<20/200 = 16%***
    - ***Internuclear ophthalmoplegia = 16%***
    - ***Nystagmus = 13%***

MS-Related Visual Conditions	n	%
Total patients with MS-associated eye conditions	61	53
Optic neuritis	43	37
Optic neuritis at MS presentation	26	22
Unilateral	40	93*
Bilateral	2	5*
Internuclear ophthalmoplegia	19	16
Nystagmus	15	13
Gaze-evoked	12	10
Pendular torsional	2	2
Upbeat	1	1
Saccadic intrusion	3	3
Cranial nerve 6 palsy	2	2
Skew deviation	3	2
Abnormal smooth pursuit	1	1
Retrochiasmal lesion	1	1

Conclusions
- Population-based frequency of MS-related ocular disease demonstrates high frequency of ocular manifestations at disease onset and during the disease course

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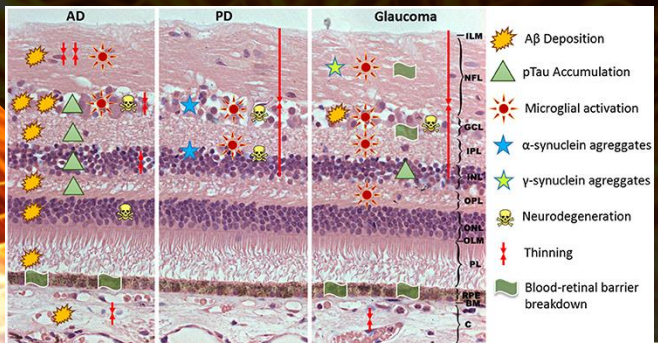
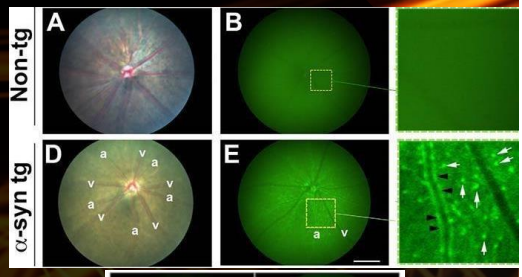
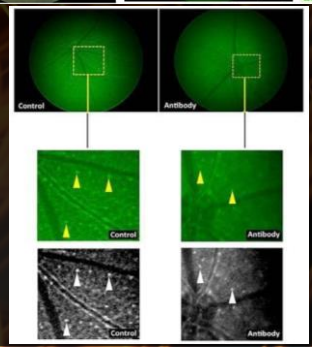
Clinical Retinal Imaging

Parkinson's disease (PD)

- 4th most common neurodegenerative disorder affecting 2–3% of the population ≥65 years of age
- 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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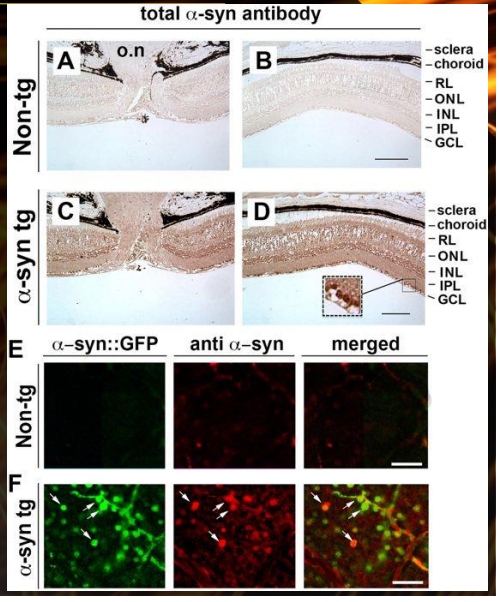
Clinical Retinal Imaging

Lewy Body Dementia (LBD)

- Similar in form to Parkinson's disease characterized by Lewy bodies consisting mainly of CNS α-synuclein affecting:
  - Cerebral cortex (processing, perception and language)
  - Limbic cortex (emotion and behavior)
  - Hippocampus (memory)
  - Midbrain and basal ganglia (movement)
  - Brain stem (circadian entrainment and alertness)
- Primary distinction from Parkinson's is time to between of cognitive and movement disorder
  - **LBD**
    - Cognitive symptoms develop ***<12*** months after movement symptoms (parkinsonism)
  - **Parkinson's Disease**
    - Cognitive symptoms develop ***>12*** months after movement symptoms
- ***Post-mortem prevalence 3X higher than clinical prevalence***
  - Recent meta-analysis of the clinical diagnostic criteria found that ~20% of DLB diagnoses were incorrect

****Use of imaging biomarkers as diagnostic criteria may bridge the gap between clinical and pathological prevalence rates***



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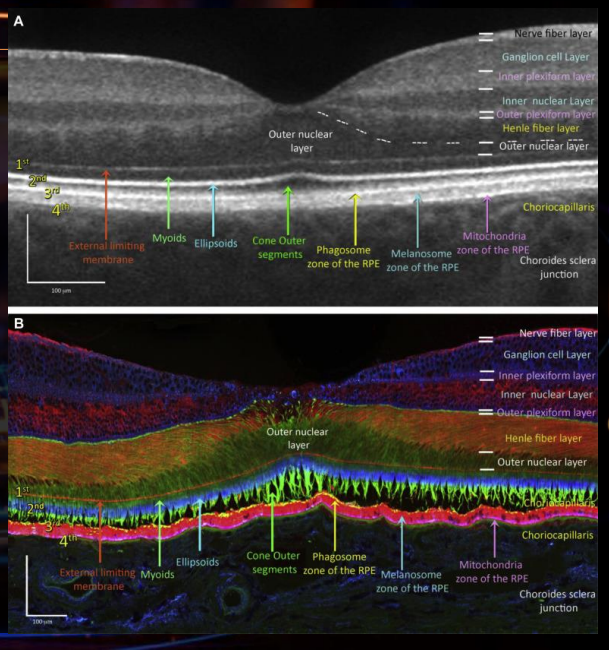
Clinical Retinal Imaging
Parkinson's disease (PD)

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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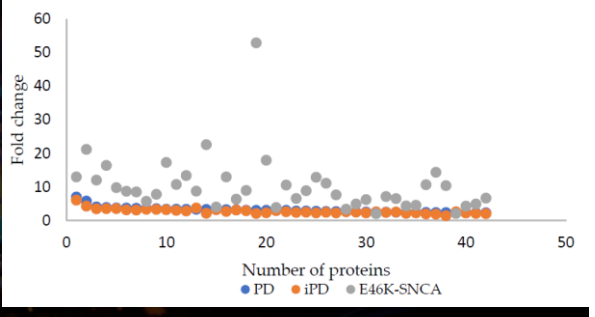
Clinical Retinal Imaging
Parkinson's disease (PD)

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
- Oligomeric α-synuclein, α-synuclein, lactoferrin and MMP9 were measured

Results
- ***Total α-synuclein decreased significantly in PD patients***
- ***Oligomeric α-synuclein increased significantly in PD patients***
- ***Neither MMP9 nor 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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Alzheimer's Disease
and Cognitive Impairment

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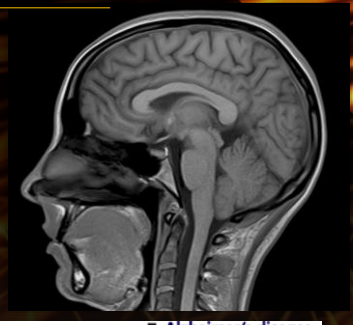
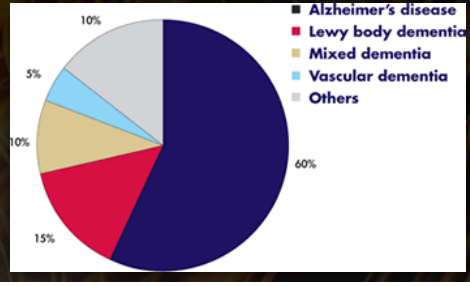
Clinical Retinal Imaging
Alzheimer's disease (AD)

- Most common form of dementia affecting ~50M individuals worldwide
  - Accounts for ***~65% of all case of dementia*** in elderly population
  - ***Detection confounded by age-related cognitive decline overlap***
- Hallmark of extracellular plaques comprised of A_β and intraneuronal neurofibrillary tangles of hyperphosphorylated tau protein
  - End-stage AD demonstrates widespread atrophy similar to other end-stage dementias
  - ***A_β accumulation predates clinical symptoms by 15-20 years***
  - ***A_β imaging has demonstrated preclinical diagnostic diagnosis criterion***





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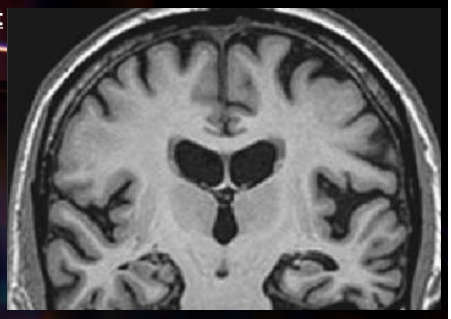
Clinical Retinal Imaging

Alzheimer's disease (AD)

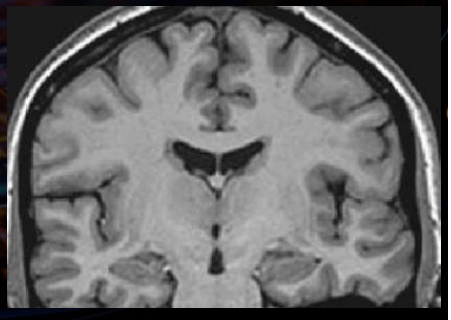
- AD is characterized by an insidious onset of cognitive decline beginning with deficits in episodic memory:
  - forgetting recent personal and family events
  - losing items around the house
  - repetitive questioning
- As the disease progresses, other deficits gradually arise including:
  - Aphasia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

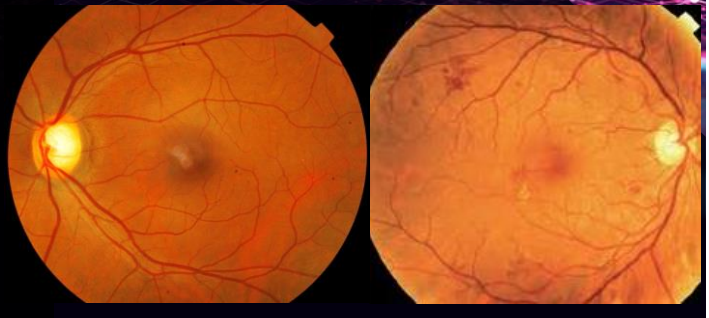
Alzheimer's disease (AD)

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 dementia risk



Shared characteristics:

1) Progressive neurodegeneration
2) Chronic microvascular insults
3) Protracted oxidative stress

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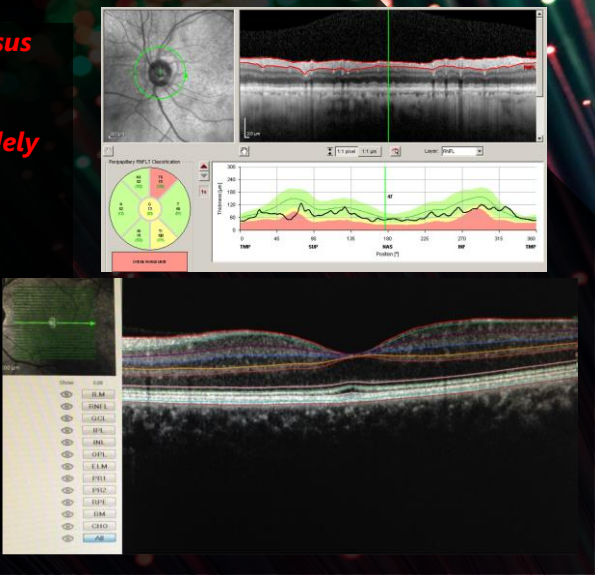
Generalized Retinal Findings
of Alzheimer's and Cognitive Impairment

- ***RNFL thickness is measurably thinner in AD versus healthy, age-matched controls***
- ***Decreased macular ganglion cell complex (GCC) volume along with retinal drusen have been widely observed***
- Clinical utility of these findings is limited by:
  - Lack of specificity
    - RNFL decrease also found in:
      - Glaucoma
      - Lewy body dementia
      - Parkinson's disease
      - Huntington's disease
      - Multiple sclerosis
      - Vascular dementia
      - Alzheimer's disease
- ***Lack of correlation with disease severity***



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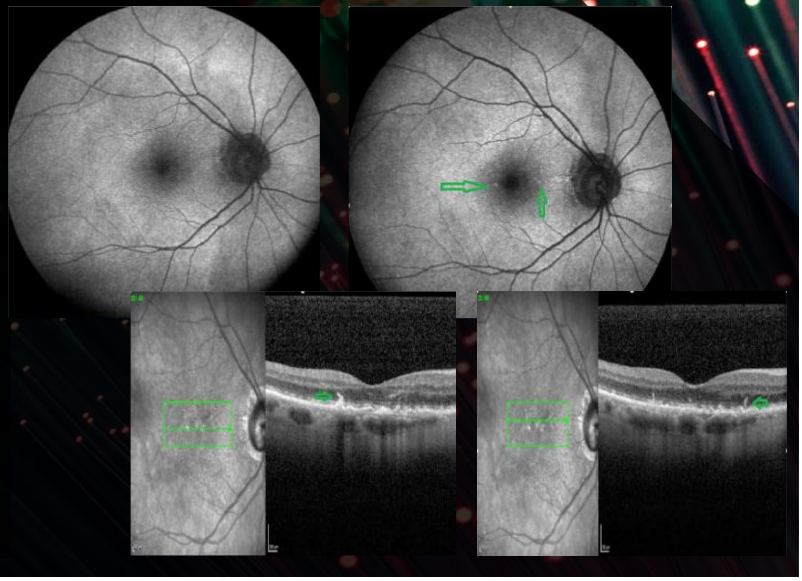
Clinical Retinal Imaging
Alzheimer's disease (AD)

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

- Curcumin is a lipophilic polyphenol and a fluorophore with a high affinity to A_β
- ***A_β in drusen 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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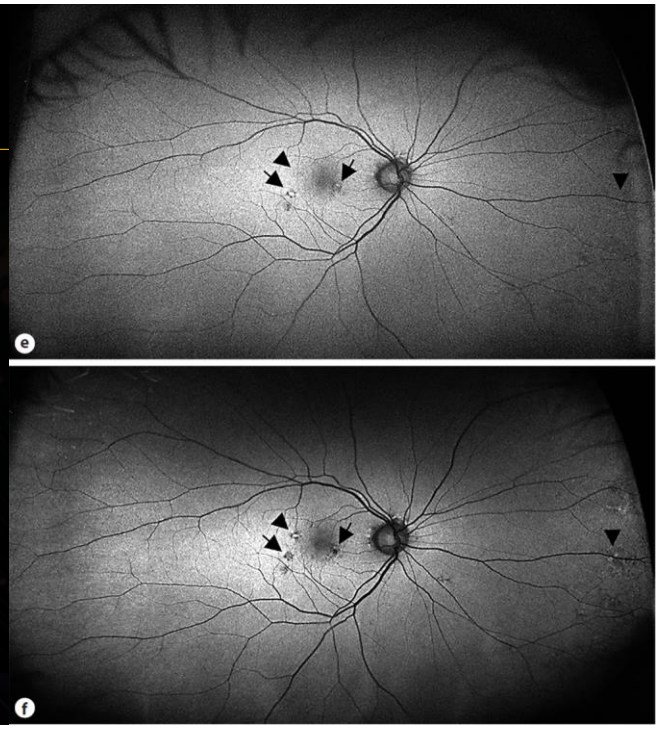
Clinical Retinal Imaging
Alzheimer's disease (AD)

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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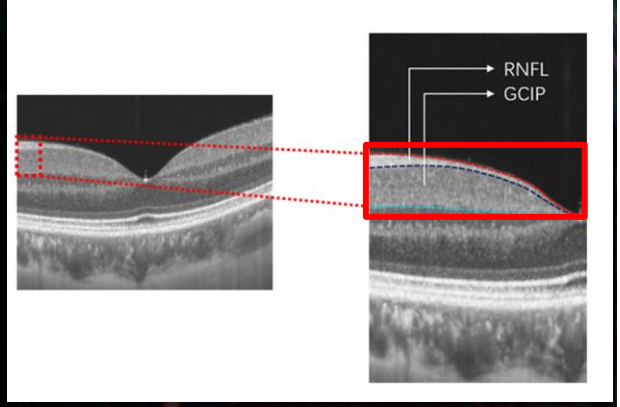
Clinical Retinal Imaging
Alzheimer's disease (AD)

Retinal GC-IPL, white matter hyperintensities and their interaction with cognition in older adults
Front Aging Neuroscience Research (2023) 15:124085

Methods
- Participants underwent neuropsych battery, structural 3T MRI and OCT imaging
- Cerebral small vessel disease (CSVD) markers
  - Cerebral microbleeds (CMB)
  - White matter hyperintensities (WMH)
  - Enlarged perivascular spaces (EPVS)
- RNFL and macular GC-IPL

Results
- Older adults with cognitive impairment showed
  - ***Lower RNFL + Lower macular GC-IPL thickness + Lower hippocampal volume correlated with MoCA***
  - ***GC-IPL thickness, total WMHI and PWMH correlated with hippocampal volume in older adults after adjusting for covariates***

Conclusion
- ***Both GC-IPL thinning and higher WMH burden are associated with hippocampal volume and older adults with both pathologies are more susceptible to subclinical cognitive decline***



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Hypothesized Role of Retinal Carotenoids in Neurodegeneration

- Optical Hypothesis
- Protection Hypothesis
- Neural Hypothesis
  - Efficiency component
  - Cognitive component

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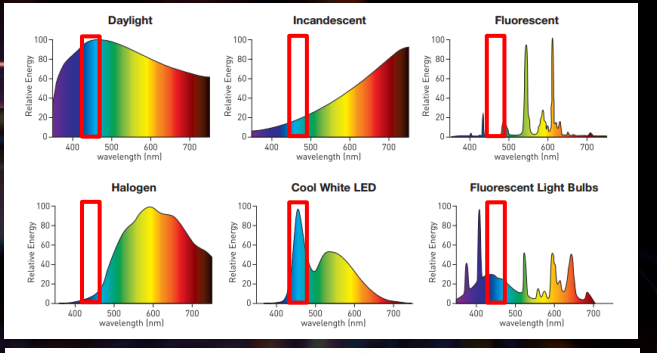
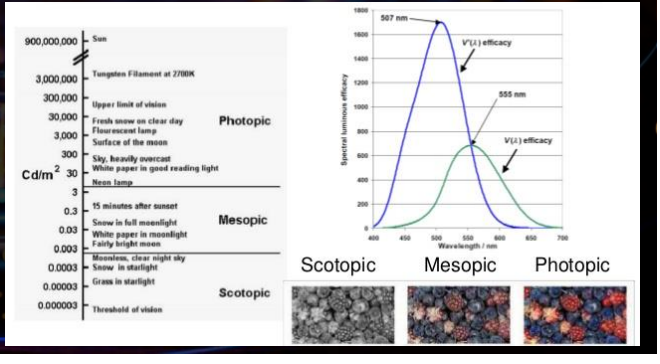
Retinal Carotenoids

Optical Hypothesis

- Acuity Hypothesis
  - ***Reduction in chromatic aberrations***
    - ***2.3D reduction to 1.1D***
  - ***Improved temporal vision (CFF)***
- Glare Hypothesis
  - ***Reduction of photo-oculodynia***
  - Improved luminance edge detection
- Visibility Hypothesis
  - Improved resolution and color sensitivity
  - Extension of cone function at mesopic levels





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Retinal Carotenoids
Optical Hypotheses

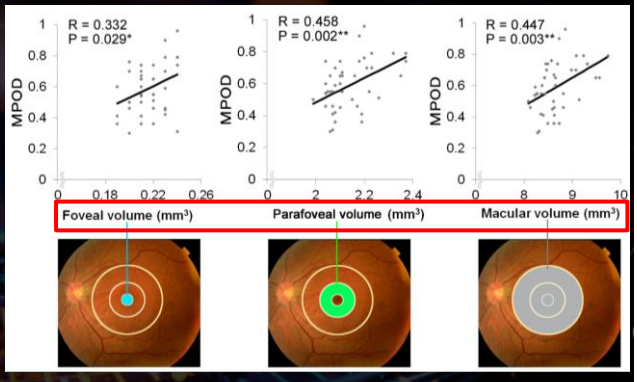
Association between MPOD and visual function outcomes: systematic review and meta-analysis

Eye (2021) 35(6):1620-1628

METHODS
- MEDLINE®, Cochrane and PubMed databases were searched for correlations of MPOD and visual function in adults with healthy eyes at all timepoints and all designs

RESULTS
- Meta-analysis of 22 publications, MPOD was found to be significantly correlated with:
- ***Foveal CS with a spatial frequency of 7, 11 and 21 cpd***
- ***Foveal photostress recovery at 10 cpd and 16% contrast***
- ***Foveal glare disability at 460 nm***

CONCLUSIONS
- Identified link between MPOD and visual function
  1) ***Photostress recovery***
  2) ***Glare disability***
  3) ***Contrast sensitivity***



- ***No statistically significant change in MPOD among studies <5mg/d of total L / MZ / Z***
- ***Pooled mean MPOD increase was 0.11 units among studies ≥20mg/d of total L / MZ / Z***

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Retinal Carotenoids
Optical Hypothesis

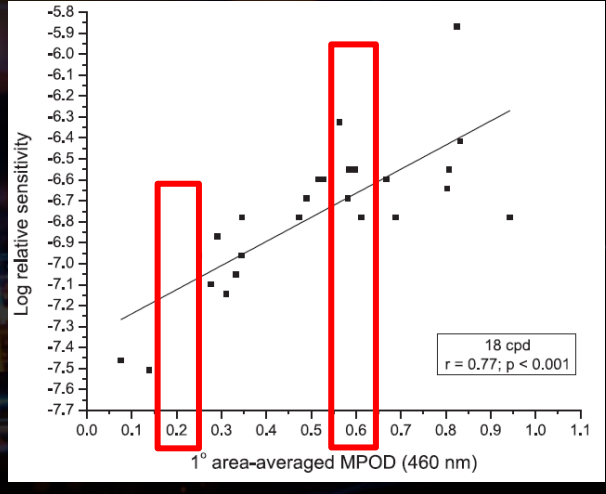
UPDATE: FDA de novo approval Nov2024 of PBM
- **Valeda (LumiThera)**

Macular Pigment and Visual Performance in Low-Light Conditions

IOVS (2015) 56:2459-2468

Dark Adaptation Kinetics
- ***Significant relationships were found between retinal carotenoids and time required to detect mesopic-level targets***
  - Higher retinal carotenoids were associated with shorter adaptation time
- ***As contrast decreases, benefit of greater retinal carotenoids increases***
- ***Retinal carotenoid levels was also significantly associated with absolute dark-adapted threshold***
- ***Subjects ranged in age from 22 to 50yo***
  - ***No age effects were observed***

Dark Adaptation



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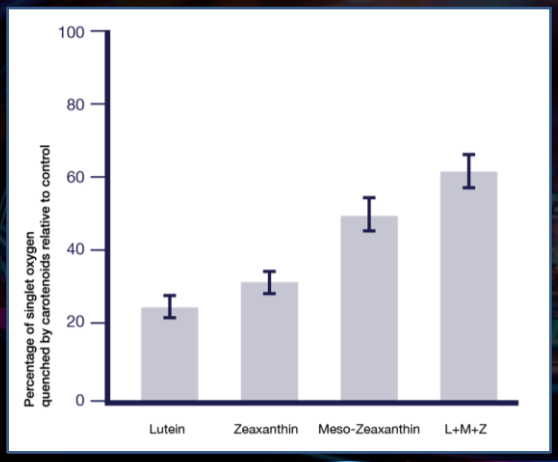
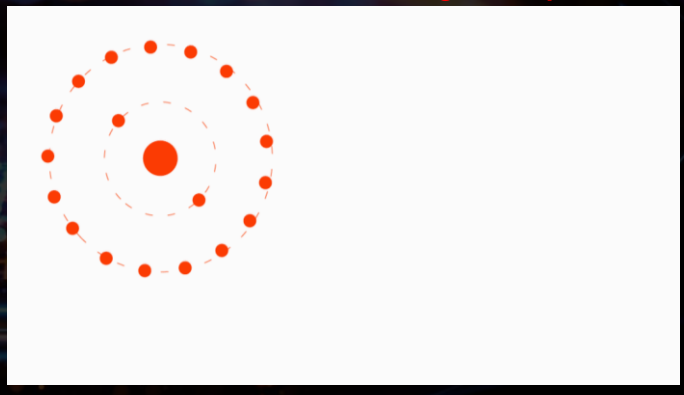
Retinal Carotenoids
Protection Hypothesis

Studies singlet oxygen scavenging mechanism of human macular pigment
Arch Biochem Biophys (2010) doi:10.1016/j.abb.2010.07.024



L / MZ / Z are NOT consumed during REDOX process



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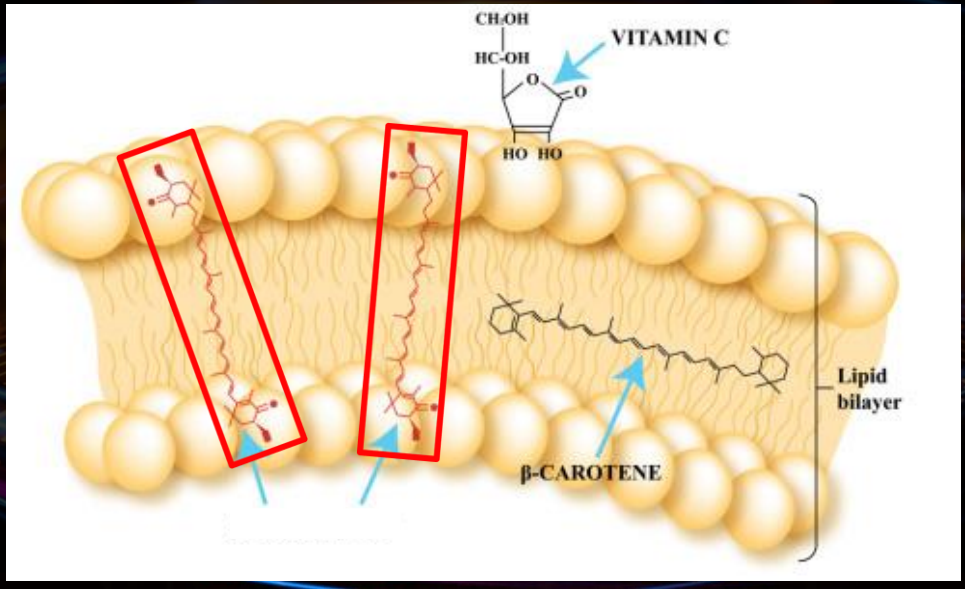
Retinal Carotenoids
Protection Hypothesis



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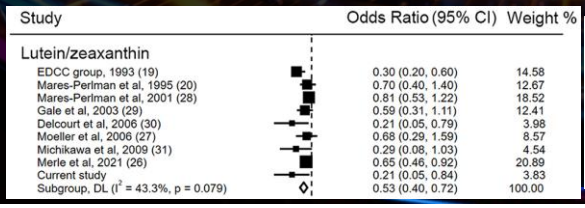
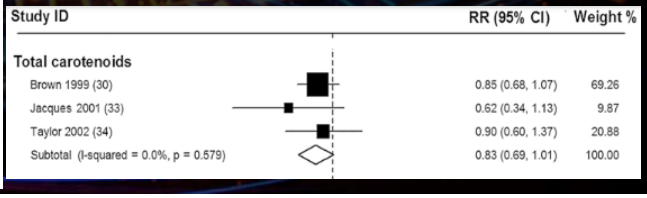
Retinal Carotenoids
Protection Hypothesis

Identified an inverse association between AMD findings and retinal L and Z
- *Eye* (2019) 32(5):992-1004

Putative protective role of L and Z in diabetic retinopathy
- *Br J Ophthal* (2018) 101(5):551-55

Long-term outcomes of adding L/Z and Ω-3 fatty acids to AREDS supplements on AMD progression: AREDS2 report 28
- *JAMA Ophthal* (2022)140(7):692-698





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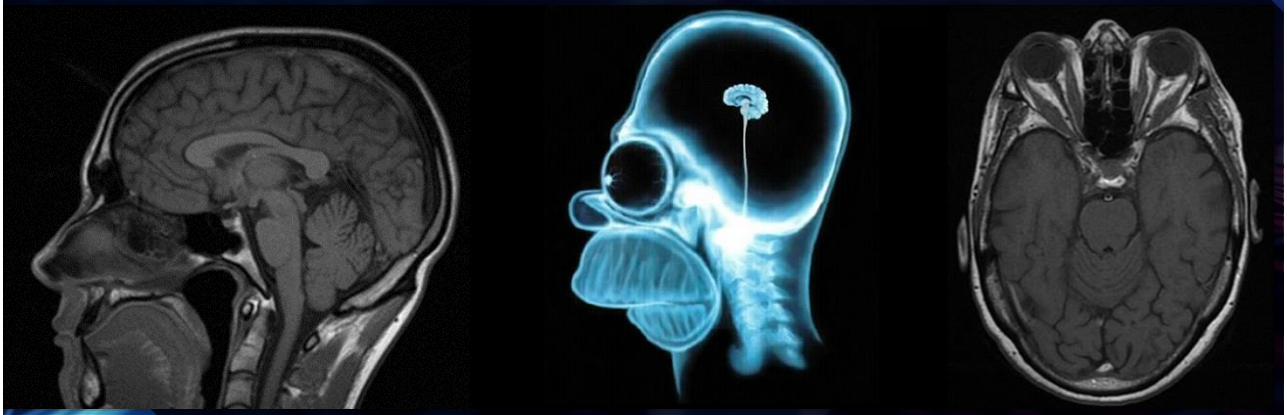
Retinal Carotenoids
Proxy for cortical levels?

(HINT: Yes)



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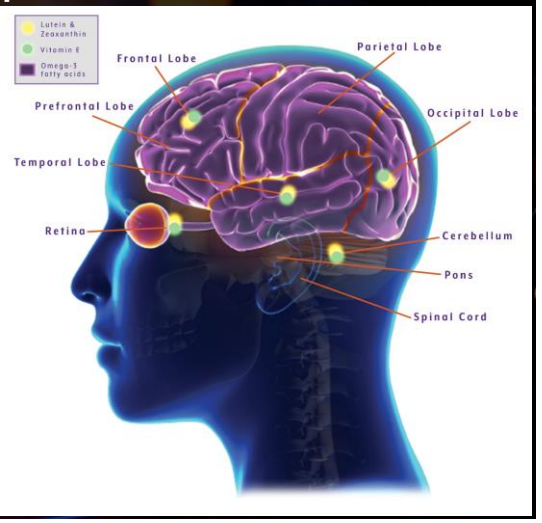
Retinal Carotenoids
Neurocognitive Hypothesis

Supplemental retinal carotenoids enhance memory in healthy individuals with low levels of macular pigment in a randomized, double-blind, placebo-controlled clinical trial

J Alzheimer's Disease (2018) 61(3): 947-961

- 12 month, double-blind, placebo-controlled trial
- Mean age of 45±12 included 91 participants
- 45 subjects consumed ***10mg L / 10mg MZ / 2mg Z***
  - 46 subjects consumed placebo
- Cognitive skills tested
  - ***Verbal and visual learning***
  - ***Immediate and delayed memory***
  - ***Executive function***
  - ***Verbal fluency***
- Following 12-month supplementation:
  - Active group showed statistically significant improvements in associated learning and reduction of errors in verbal and visual learning + with concomitant MPOD and serum level increase
- ***Demonstrated memory enhancing effect of daily carotenoid supplementation in individuals with low MP at baseline***



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Retinal Carotenoids
Neurocognitive Hypothesis

Relationship of L and Z Levels to Neurocognitive Functioning: fMRI Study of Older Adults

J Int Neuropsych Soc (2018) *23*(1):11-22

Table 2. Relationship of lutein and zeaxanthin to brain activation during encoding ($N = 43$)

Region	*x*	*y*	*z*	Extent	Z-Score	Effect Size (*r*)
MPOD						
L insular cortex	−40	10	−14	99	3.03	0.45
L insular cortex	−42	0	−10	*	2.94	0.44
R middle temporal gyrus	62	−58	2	10	2.75	0.41
L cerebellum	−10	−76	−22	11	2.52	0.38
L supramarginal gyrus	−64	−34	26	3	2.44	0.37
Serum						
L lateral occipital cortex	−24	−74	38	45	2.96	0.44
L postcentral gyrus	−20	−44	66	31	2.90	0.43
L parietal operculum cortex	−48	−30	24	39	2.90	0.43
L precentral gyrus	−58	0	32	5	2.76	0.41
R lateral occipital cortex	36	−68	50	17	2.60	0.39
R lateral occipital cortex	26	−78	28	7	2.48	0.37

Note. The above table includes brain activity that was significantly and negatively associated with lutein and zeaxanthin levels during encoding of word pairs.
MPOD = macular pigment optical density. *x*, *y*, and *z* coordinates are in MNI space (mm). L = left and R = right.
* = cluster overlap with preceding row.

Table 3. Relationship of lutein and zeaxanthin to brain activation during recall ($N = 43$)

Region	*x*	*y*	*z*	Extent	Z-Score	Effect size (*r*)
MPOD						
L inferior frontal gyrus	−42	8	24	48	3.10	0.46
L cerebellum	−10	−74	−22	24	2.96	0.44
L occipital pole	−12	−102	−2	9	2.78	0.41
L planum polare	−46	−4	−6	8	2.56	0.38
L insular cortex	−38	−4	−12	15	2.53	0.38
R middle frontal gyrus	46	34	18	7	2.47	0.37
R occipital pole	16	−96	12	2	2.40	0.36
Serum						
L central opercular cortex	−48	−4	10	21	3.36	0.49
R lateral occipital cortex	22	−68	58	9	2.56	0.38
L central opercular cortex	−58	2	2	7	2.48	0.37
L superior parietal lobule	−38	−42	60	4	2.45	0.37

Note. The above table includes brain activity that was significantly and negatively associated with lutein and zeaxanthin levels during retrieval of word pairs. *x*, *y*, and *z* coordinates are in MNI space (mm).
MPOD = macular pigment optical density. L = left and R = right.

Insular cortex
- perception
- self-awareness
- ***cognitive functioning***
- interpersonal experience

Middle temporal gyrus
- ***facial recognition***
- word meaning assessment while reading

Supramarginal gyrus
- ***language perception and processing***

Cerebellum
- motor control and ***learning***

Inferior frontal gyrus
- ***Language comprehension and production***

Occipital pole
- ***Visual processing***

Middle frontal gyrus
- ***Attention and executive functions***

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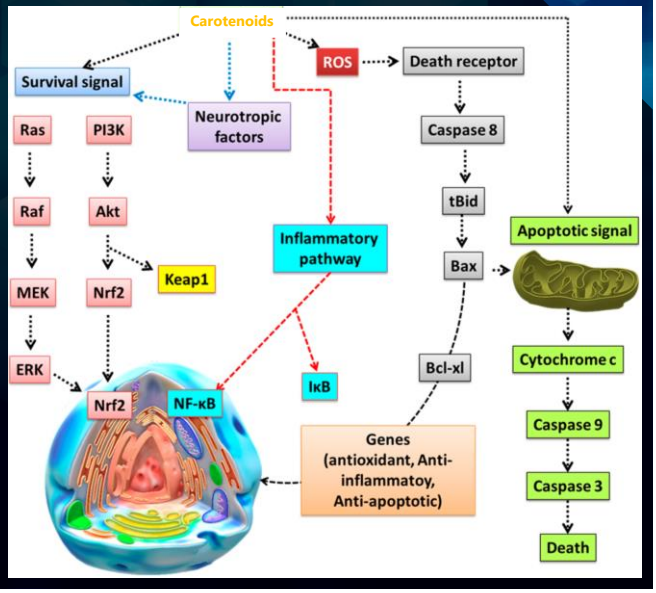
Retinal Carotenoids
Neurocognitive Hypothesis

Macular pigment, visual function and macular disease among subjects with Alzheimer's disease: an exploratory study
Journal of Alzheimer's Disease (2018) 42(4):1191-1202
- ***AD patients have significantly lower macular pigment, lower L/Z serum concentrations and higher prevalence of AMD compared to controls***

Relationships between macular pigment optical density and cognitive function in unimpaired and mildly cognitively impaired older adults
Neurobiology of aging (2019) 35(7):1695-1699
- ***Macular pigment was broadly related to cognition including MMSE, visual-spatial abilities, language, attention and neuropsychological status***

Double-blind, placebo-controlled study on the effects of lutein and zeaxanthin on neural processing speed and efficiency
PLoS One (2016) 9(9)
- ***Supplementation with L/Z (~0.09 OD) produced significant increases in CFF thresholds and visual motor reaction time compared to placebo***



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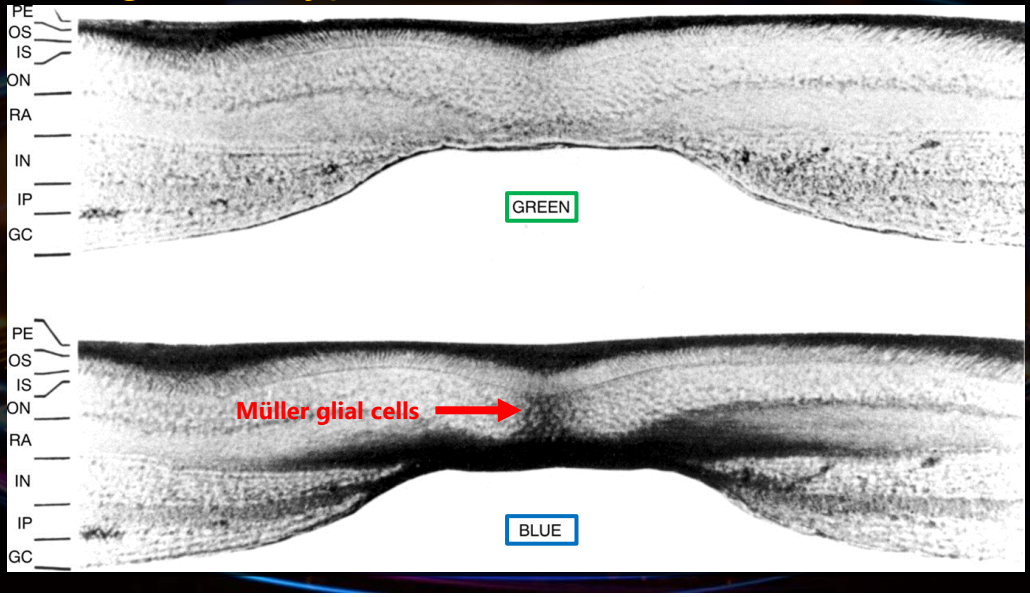
Retinal Carotenoids
Neurocognitive Hypothesis



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What's now?

1. Aβ accumulation is an established biomarker of Alzheimer's disease development and typically precedes clinical cognitive decline by 15-20 years
2. ***FAF imaging with curcumin provides the ability to detect Aβ-containing drusen in a high-resolution, non-invasive method capable of population-level screening***
3. ***Inner retinal OCT (GCL-IPL) thickness is significantly correlated with both serum Nf-L (axonal damage) and cortical regions associated with cognition***
4. Clinical trials of existing AD treatments indicate that early, modest reduction in Aβ accumulation can substantially alter the long-term disease course
   - **** Lecanemab-irmb (Leqembi)***
   - **** Aducanumab (Aduhelm) – Discontinued by Biogen in 2024***
   - **** Donanemab-azbt (Kisunla)***
5. ***L / MZ / Z have been positively correlated in objective measures of neurocognitive performance (fMRI) as well as MMSE performance, visual-spatial abilities, language, attention and neuropsychological status***

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What's now?

Research studies reported at AAIC 2020 suggest:

- History of at least one flu vaccination was associated with a ***17% reduction*** in Alzheimer's incidence
  - More frequent flu vaccinations were associated with an ***additional 13% reduction*** in Alzheimer's incidence
- Vaccination against pneumonia between ***ages 65 and 75*** demonstrated ***40% reduction*** depending on genetic risk
- ***Individuals with dementia have a 6X mortality risk after infections than those without dementia***

alzheimer's association

AAIC 20

CONTACT: Alzheimer's Association Media Line, 312.335.4078, media@alz.org
AAIC 2020 Press Office, aaicmedia@alz.org

FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2020

FLU, PNEUMONIA VACCINATIONS TIED TO LOWER RISK OF ALZHEIMER'S DEMENTIA

CHICAGO, JULY 27, 2020 — Flu (influenza) and pneumonia vaccinations are associated with reduced risk of Alzheimer's disease, according to new research reported at the Alzheimer's Association International Conference® (AAIC®) 2020.

Three research studies reported at AAIC 2020 suggest:

- At least one flu vaccination was associated with a 17% reduction in Alzheimer's incidence. More frequent flu vaccination was associated with another 13% reduction in Alzheimer's incidence.
- Vaccination against pneumonia between ages 65 and 75 reduced Alzheimer's risk by up to 40% depending on individual genes.
- Individuals with dementia have a higher risk of dying (6-fold) after infections than those without dementia (3-fold).

"With the COVID-19 pandemic, vaccines are at the forefront of public health discussions. It is important to explore their benefit in not only protecting against viral or bacterial infection but also improving long-term health outcomes," said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer.

"It may turn out to be as simple as if you're taking care of your health in this way — getting vaccinated — you're also taking care of yourself in other ways, and these things add up to lower risk of Alzheimer's and other dementias," Carrillo said. "This research, while early, calls for further studies in large, diverse clinical trials to inform whether vaccinations as a public health strategy decrease our risk for developing dementia as we age."

Seasonal Flu Vaccine May Reduce Incidence of Alzheimer's Dementia
Previous research has suggested vaccinations may have a protective factor against cognitive decline, but there have been no large, comprehensive studies focused on the influenza (flu) vaccine and Alzheimer's disease risk, specifically. To address this gap, Albert Amran, a medical student at McGovern Medical School at The University of Texas Health Science Center at Houston, and team, investigated a large American health record dataset (n=9,066).

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What's now?

Antihypertensive medications and risk for incident dementia and Alzheimer's disease: meta-analysis of prospective cohort studies

Lancet Neurol (2020) *19*(1):61-70

Methods

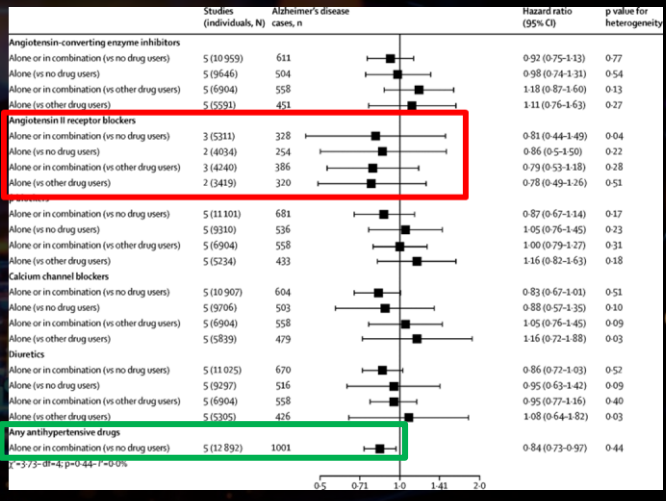
- Meta-analysis included 2000 participants, dementia events over 5 years, measured B/P and verified use of AHMs
- Assessed the association of incident dementia and clinical AD with use of 5 AHM classes, within strata of baseline high ***(≥140/90 mmHg)*** ***vs.*** normal ***(<140/90 mmHg)***

Results

- 3728 dementia cases and 1741 AD diagnoses across cohorts of 7-22 years were analyzed. Those using any AHM had reduced risk for developing dementia ***(HR: 0.88)*** and AD ***(HR: 0.84)*** compared with those not using AHM

Interpretation

- ***Among patients with HTN, use of any AHM with efficacy to lower blood pressure may reduce dementia risk***



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What's now?

Association between cataract extraction and development of dementia

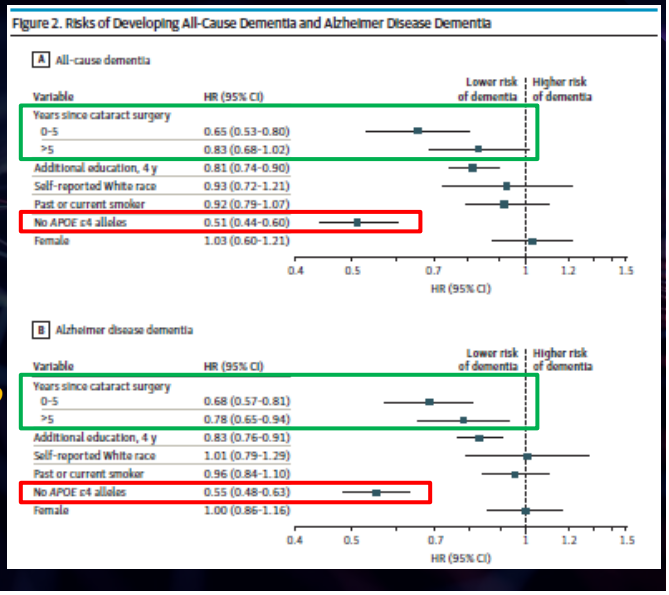
JAMA Internal Medicine (2022) 182(2):134-141

RESULTS

- 3038 participants aged 74±6 years
- Based on 23,554 person-years of follow-up, cataract extraction was associated with significantly reduced risk ***(HR: 0.71)*** of dementia after controlling for risks and stratifying by apoE genotype, sex, and age group at cataract diagnosis
- ***Similar results were found with development of AD***

CONCLUSIONS

- ***Cataract extraction was significantly associated with lower risk of dementia development***



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What's now?

Predictive validity of a Brain Care Score for dementia and stroke: UK Biobank cohort data

Front Neuro (2023) 10:3389

Methods

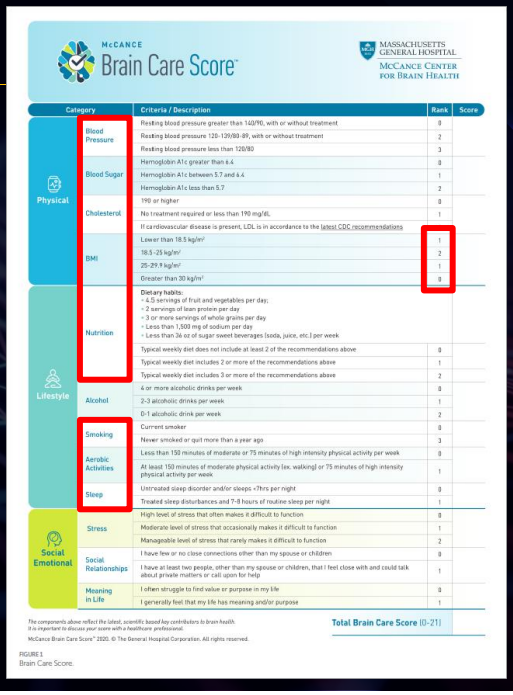
- BCS was derived from the United Kingdom Biobank (UKB) baseline evaluation for participants aged 40–69 years
- Associations of BCS and risk of subsequent incident dementia and stroke were adjusted for sex assigned at birth and stratified by age groups at baseline

Results

- BCS was derived for 398,990 participants (mean age: 57) over 12 years
  - 5,354 incident cases of dementia
  - 7,259 incident cases of stroke
- ***Five (5) point higher BCS at baseline associated with:***
  - ***<50: 59% lower risk of dementia / 48% lower stroke risk***
  - ***50-59: 32% lower risk of dementia / 52% lower stroke risk***
  - ***>59: 8% lower risk of dementia / 33% lower stroke risk***

Discussion

- ***BCS has clinically relevant and statistically significant associations with dementia and stroke risk in ~400,000 UK residents***



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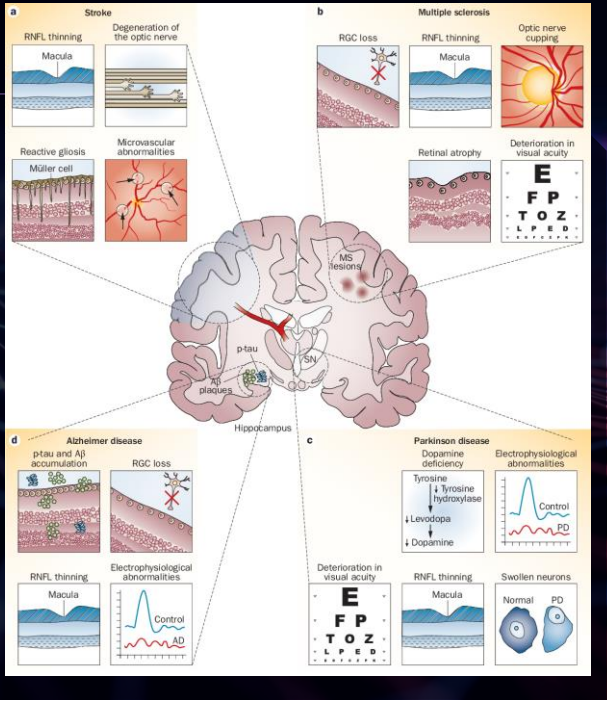
What's now?

- **Vascular dementia**
  - RNFL thinning
  - Microvascular abnormalities
- **Multiple sclerosis**
  - RGC loss
  - Retinal atrophy
- **Alzheimer's disease**
  - Amyloid β and p-tau accumulation
  - ***ERG abnormalities***
- **Parkinson's disease**
  - RNFL thinning
  - ***ERG abnormalities***



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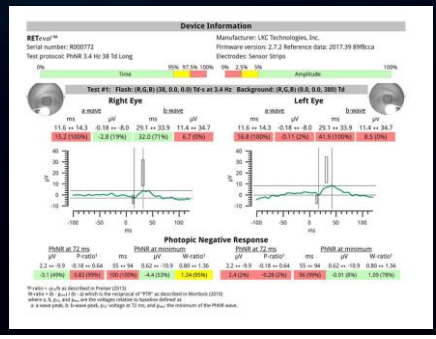
What's next?

Enhancing Risk Assessment in Patients with DR by Combining Measures of Retinal Function (RETeval) and Structure

Trans Vis Sci Tech (2020) 9(9): 40

Methods

- 279 diabetic patients who participated in an earlier cross-sectional study
  - Baseline RETeval ERG and fundus photographs were obtained
  - ETDRS-DR severity ≥ level 53 (ETDRS-DR+)
  - Clinically significant macular edema (VTDR+)
- ***Positive finding corresponded to RETeval DR Score >23.5 (RETeval+).***



Results

For patients with VTDR+:

- ***Incidence of intervention was 19%, 31%, and 53% at 1, 2 and 3yrs of follow-up***
  - **RETeval (+): *Intervention incidence increased to 34%, 54% and 74%***
  - **RETeval (−): *Intervention incidence decreased to 3%, 4% and 29%***

Conclusions

- ***Prediction of subsequent intervention was best when combining structural and functional information***

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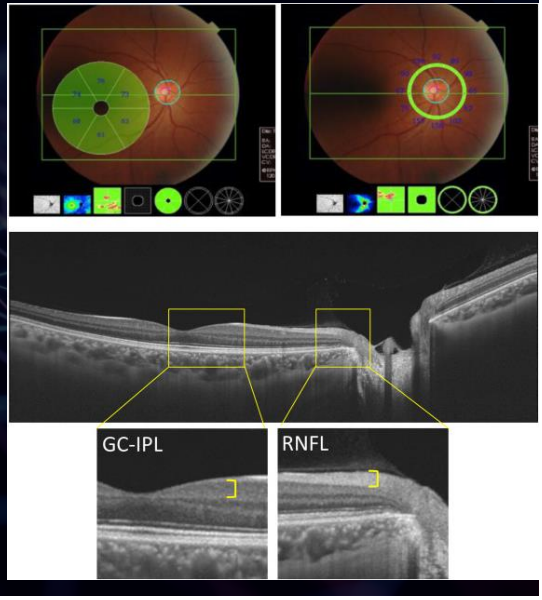
What's next?

Association of Inner Retinal Thickness with Prevalent Dementia and Brain Atrophy in a General Older Population

Ophthal Sci (2022) 2(2)



Methods

- Thicknesses of the inner retinal layers (GC-IPL and RNFL) were measured by SS-OCT. Associations of GC-IPL and RNFL thickness with each brain regional volume were analyzed using multiple regression analysis

Results

- 61 participants (5.7%) were diagnosed with dementia
- ***Presence of dementia associated with lower GC-IPL thickness***
  - ***No significant association was observed with RNFL thickness***
- ***Lower GC-IPL thickness was significantly associated with***
  - ***Lower volume cognitive regions***
    - ***Hippocampus, amygdala, entorhinal and parahippocampal gyrus***
  - ***Lower volume visual regions***
    - ***Cuneus, lingual gyrus and thalamus***

Conclusions

- ***Measurement of GC-IPL thickness by SS-OCT might be useful for identifying high-risk individuals with dementia***

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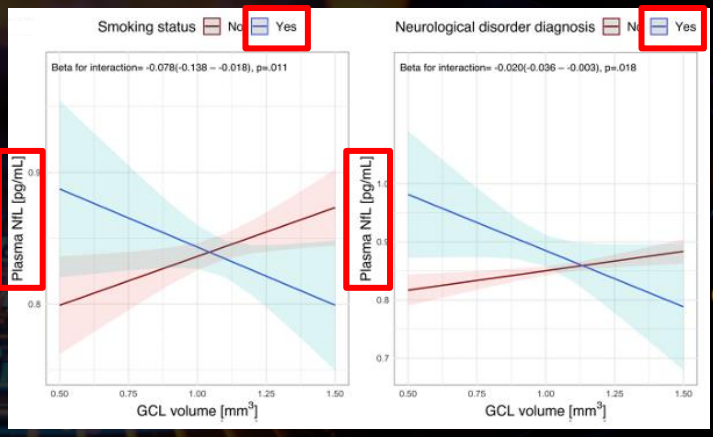
What's next?

NfL and retinal layer determinants and association: Population-based study

Clin Trans Neuro (2022) 9(4):564-569

Abstract

- Retinal atrophy measured through OCT and plasma NfL levels are biomarkers markers of neurodegeneration, but their relationship is not well-defined
- 4369 participants had measured plasma NfL levels and macular GCC along with presence of risk factors for neurodegeneration
  - Age / Smoking / FHx neurological disorders
- ***Plasma NfL levels were associated with inner retinal atrophy and outer retinal thickening***
- ***Findings indicate that inner retinal atrophy can reflect neuroaxonal damage mirrored by rising plasma NfL levels***



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What's next?

APOE-ε4 Genotype is Associated with Elevated Post-Concussion Symptoms in Military Veterans with a Remote History of Mild Traumatic Brain Injury

Arch Clin Neurpsych (2019) 34:706-712

Methods

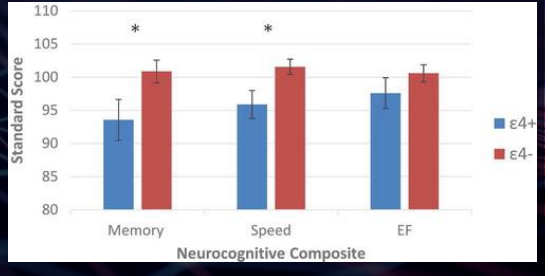
- Participants (n=77) were administered neuropsychiatric measures 5 years following most recent mTBI and provided DNA sample for APOE genotyping
- Subjects were divided into two groups based on their ε4 status
  - ***n = 14 APOE-ε4 (+)***
  - ***n = 63 APOE-ε4 (-)***

Results

- ANCOVAs showed significant main effect of ε4 genotype on NSI total score and somatic symptom cluster after adjusting for PTSD symptoms and mTBI history
  - ***APOE-ε4 (+) subjects displayed significantly greater symptoms than 63 APOE-ε4 (-) subjects***

Conclusions

- ***Findings suggest that genetic risk may help to explain the poorer long-term outcomes often observed in this population***



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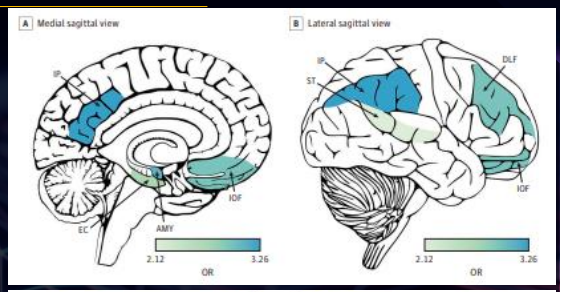
What's next?

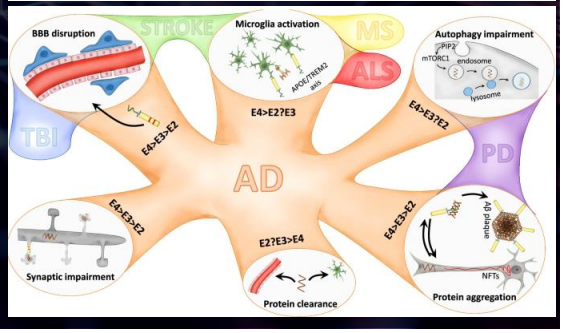
Association of APOE Genotypes and Chronic Traumatic Encephalopathy
JAMA Neurol (2022) 79(8):

Design
- Cross-sectional genetic association study analyzed brain donors from Veterans Affairs–Boston University–Concussion Legacy Foundation Brain Bank
- All donors had exposure to repetitive head impact from contact sports or military service

Results
- 364 consecutive brain donors (294 individuals with CTE and 70 controls)
- Among donors older than 65 years:
  - ***APOEε4 status significantly associated with CTE (OR 2.34)***
  - ***Non-significant association (p=0.08) between APOEε4 status and dementia (OR 2.64)***
- Significant associations were observed for p-tau burden in the ***frontal and parietal cortices, amygdala and entorhinal cortex*** (OR 2.45-3.26)
- ***No associations were observed for APOEε2 status***

Conclusions
- ***APOEε4 may confer increased risk for CTE-related neuropathological and clinical outcomes among older individuals with RHI exposure***





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Final Thoughts….

- **Concussion patients may benefit from evidence-based nutraceuticals and supplements**
  - ***Prevention AND Treatment***
- Non-resolving, uncomplicated concussion symptoms over 6 months requires further inspection
  - Original injury more severe than diagnoses
  - Underlying psychosocial or medical conditions
- High-risk cognitive impairment patients may benefit from evidence-based nutraceuticals and supplements
  - ***Primary care optometry is well-suited to identify early, subclinical ocular changes associated with increased risk of dementia***

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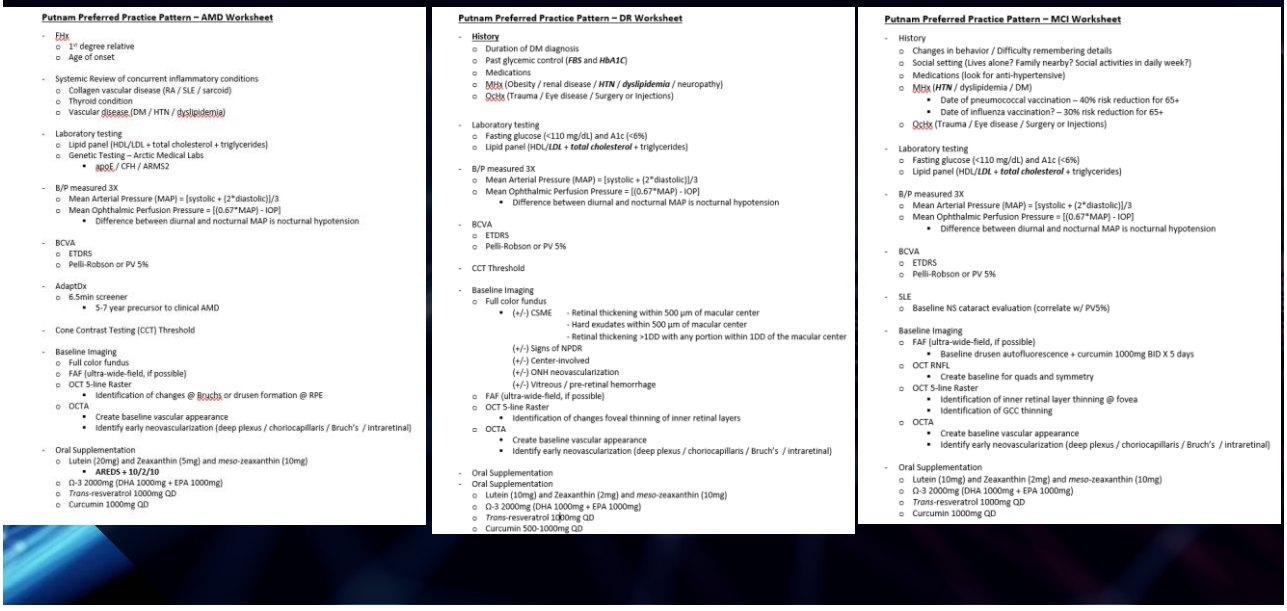
Final Thoughts….



Putnam Preferred Practice Pattern – AMD Worksheet

- FHx
  - 1st degree relative
  - Age of onset
- Systemic Review of concurrent inflammatory conditions
  - Collagen vascular disease (RA / SLE / sarcoid)
  - Thyroid condition
  - Vascular disease (DM / HTN / dyslipidemia)
- Laboratory testing
  - Lipid panel (HDL/LDL + total cholesterol + triglycerides)
  - Genetic Testing – Arctic Medical Labs
    - apoE / CFH / ARMS2
- 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%
- AdaptDx
  - 6.5min screener
    - 5-7 year precursor to clinical AMD
- Cone Contrast Testing (CCT) Threshold
- Baseline Imaging
  - Full color fundus
  - FAF (ultra-wide-field, if possible)
  - OCT 5-line Raster
    - Identification of changes @ Bruchs or drusen formation @ RPE
  - OCTA
    - Create baseline vascular appearance
    - Identify early neovascularization (deep plexus / choriocapillaris / Bruch's / intraretinal)
- Oral Supplementation
  - Lutein (20mg) and Zeaxanthin (5mg) and *meso*-zeaxanthin (10mg)
    - **AREDS + 10/2/10**
  - Ω-3 2000mg (DHA 1000mg + EPA 1000mg)
  - *Trans*-resveratrol 1000mg QD
  - Curcumin 1000mg QD

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 (10mg) and Zeaxanthin (2mg) and *meso*-zeaxanthin (10mg)
  - Ω-3 2000mg (DHA 1000mg + EPA 1000mg)
  - *Trans*-resveratrol 1000mg QD
  - Curcumin 500-1000mg QD

Putnam Preferred Practice Pattern – MCI Worksheet

- History
  - Changes in behavior / Difficulty remembering details
  - Social setting (Lives alone? Family nearby? Social activities in daily week?)
  - Medications (look for anti-hypertensive)
  - MHx (***HTN*** / dyslipidemia / DM)
    - Date of pneumococcal vaccination – 40% risk reduction for 65+
    - Date of influenza vaccination? – 30% risk reduction for 65+
  - 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%
- SLE
  - Baseline NS cataract evaluation (correlate w/ PV5%)
- Baseline Imaging
  - FAF (ultra-wide-field, if possible)
    - Baseline drusen autofluorescence + curcumin 1000mg BID X 5 days
  - OCT RNFL
    - Create baseline for quads and symmetry
  - OCT 5-line Raster
    - Identification of inner retinal layer thinning @ fovea
    - Identification of GCC thinning
  - OCTA
    - Create baseline vascular appearance
    - Identify early neovascularization (deep plexus / choriocapillaris / Bruch's / intraretinal)
- Oral Supplementation
  - Lutein (10mg) and Zeaxanthin (2mg) and *meso*-zeaxanthin (10mg)
  - Ω-3 2000mg (DHA 1000mg + EPA 1000mg)
  - *Trans*-resveratrol 1000mg QD
  - Curcumin 1000mg QD

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