Concussion *(aka: mTBI)* Diagnosis, Management and Recovery

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Financial Disclosures

- None

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Clinical Concussion Management

mTBI Happens….

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Clinical Concussion Management

….over and over again

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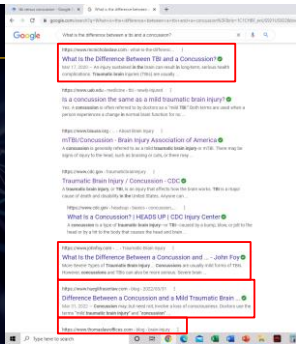
Clinical Concussion Management

Misconceptions

Google results for:
What is the difference between a TBI 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

Method/Design:
Active duty U.S. Army psychologists, psychiatrists, social workers, and psychiatric nurses from locations across the DoD and behavioral health professionals from a major military hospital (n=181) were surveyed on 27 common misconceptions about TBI

Results
Mean percentages for the subcomponents of the questionnaire suggested that responses were generally accurate for general information about brain damage (84%) but less accurate for unconsciousness (46%), amnesia or memory loss (53%) and recovery items (65%)
- ***Total percent correct was 51% on the mTBI items***
- ***Sizable portion viewing mTBI as being associated with lengthier recovery and poorer outcome than what has been indicated by recent research***

Conclusion/Implications
- ***Misconceptions about mTBI are prevalent among behavioral health providers***
- ***Health care professionals may not be receiving accurate information about TBI recovery***

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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 or 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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DEMOGRAPHICS

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

Age
Highest risk: Children ages 5-9 to nine and adults >80

Race
No racial predilection to traumatic brain injury.

Gender
Males 2X more likely and have a 4X risk of fatal head injury

Males also account for 65% of adolescent head trauma

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Clinical Concussion Management
Demographics

mTBI in the United States: Demographics, brain imaging procedures, healthcare utilization and costs
Brain Inj (2019) 9:1151-1157

Methods
Data from the OptumHealth Care Solutions claims database

Results
Total of 80,004 patients with mTBI were included:
- ***60% were under 26 years and 64% were male.***
- mTBI was most frequently diagnosed in an ED for all age groups, ***except patients aged 11-17 years (outpatient)***
- 47% received neuroimaging: ***98% received CT.***
- Mean follow-up health-care costs were $13,564 ± $41,071

Conclusions
Substantial healthcare resource utilization / costs associated with mTBI diagnosis during 12-month period

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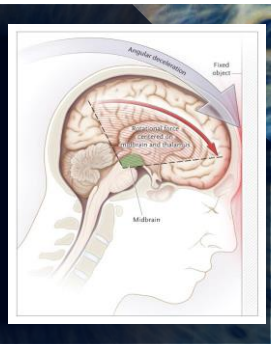
ETIOLOGY

Causal mechanisms

1) Biomechanical
80-100g of force
(60-165g range)

2) Anatomical

3) Physiological
Sub-cellular
Electrochemical



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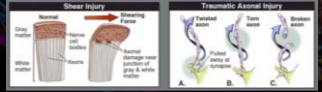
Clinical Concussion Management
Types of Injury



Initial Clinical Symptom Presentation

Somatic	Cognitive	Affective	Sleep
Headache	Confusion	Emotional lability	Trouble falling asleep
Dizziness	Anterograde amnesia	Irritability	Sleeping more than usual
Balance disruption	Retrograde amnesia	Fatigue	Excessive drowsiness
Nausea/Vomiting	Loss of consciousness	Anxiety	Sleeping less than usual
Visual disturbances (photophobia, blurry/ double vision)	Disorientation	Sadness	
Phonophobia	Feeling mentally "foggy"		
	Vacant stare		
	Inability to focus		
	Delayed verbal and motor responses		
	Slurred/incoherent speech		

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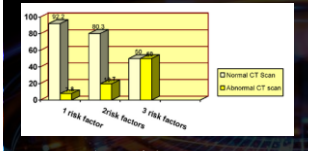
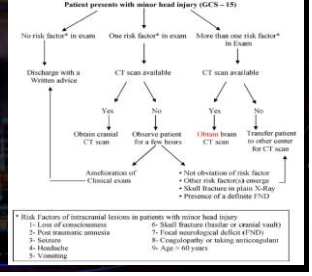
Clinical Concussion Management
Initial Presentation or Time of Injury



ED presentation population
- n=682
- 6.7% had subdural hematoma, subarachnoid hematoma or pneumocephalus
- ***<1% required neurosurgery***

Aguilar-Shea et al., (2019)



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Assessment and Diagnosis

Clinical Interview
- LOC or AOC (dazed/confused)
- What is the last thing you remember? What is the first thing you remember?
- Sensory, motor, balance, seizure, speech
- Nausea, emesis, headache, dizziness, phono/photophobia
- Irritability, mood, anxiety, sleep
- Previous head injuries
- Hx of medication use

Initial Injury Testing
- GCS
  - iStat / Quanterix
- SCAT-5
- MACE

Clinical Cognitive Screening
- BIVSS
- MMSE
- MoCA

Clinical Sensorimotor
- OMAT
- VOMS

Clinical Testing
- ImPACT v4
- RightEye

Baseline Imaging
- Rapid Dx
- SD-OCT

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Clinical Measurement Point of Care

- Glasgow Coma Scale
  - iStat Alinity
  - Quanterix
- Sport Concussion Assessment Tool (SCAT-5)
- 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)

* 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) requiring 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 5 (SCAT-5)

- **Red Flags**
  - Neck pain / diplopia / paresthesia
  - HA / seizure / LOC / vomiting / agitation
- **GCS**
- **Observable Signs**
- **Cognitive Screening**
- **Neurological Screening**

https://scat5.cattonline.com/

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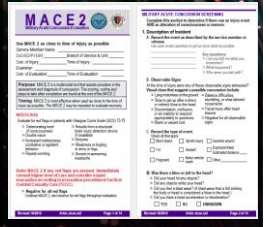
Clinical Measurement
Point of Care – Military Acute Concussion Evaluation (MACE 2)

- **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***



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Clinical Measurement
Screening Tools

- Brain Injury Vision Symptom Survey (BIVSS)
- Post-Trauma Vision Symptoms (PTVS)
- Mini-Mental State Exam (MMSE)
- Montreal Cognitive Assessment (MoCA)

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Clinical Measurement

Screening Tools - Binocular Injury Vision Symptom Survey (BIVSS)

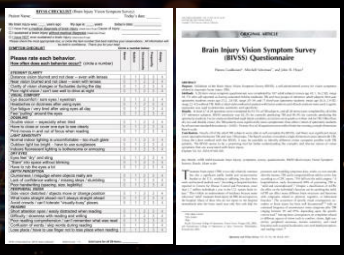
Results

- At least 27 of 28 questions were completed by 94% of TBI subjects
- All 28 items were completed by the 157 reference subjects

BIVSS sensitivity:

- ***82% for correctly predicting TBI***
  - ***True Positive***
- ***91% for correctly predicting the controls***
  - ***Correct Rejection***

- ***TBI patients were significantly more symptomatic than control cohort by at least 1 SD***



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Clinical Measurement

Screening Tools – Post-Trauma Vision Symptoms (PTVS)

- Post-Trauma Vision Symptoms (PTVS)
  - 4 Section / 40 question survey

****Unable to find any peer-reviewed validation studies***

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Clinical Measurement

Screening Tools – MMSE vs. MoCA

Differences in cognitive profiles between traumatic brain injury and stroke: Comparison of the MoCA and MMSE

J Trauma (2016) 19(5): 271-274.

Methods

1230 patients were evaluated, including TBI group (*n*=103) and stroke group (*n*=127).

Results

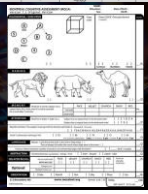
- ***MoCA (+) rates in TBI group = 94% and stroke group = 87%***
- ***MMSE (+) rates in TBI group = 70% and stroke group = 57%***

- ***TBI group:***
  - ***87% patients with normal MMSE had abnormal MoCA***
- ***Stroke group:***
  - ***70% patients with normal MMSE had abnormal MoCA***

Conclusion

In screening post-TBI cognitive impairment, MoCA tends to be more sensitive than MMSE.

Variables	Controls (n=403) Number (%)	Controls (n=403) Cognitive score (mean ± SD)	Cases (n=400) Number (%)	Cases (n=400) Cognitive score (mean ± SD)	P value*
MMSE score (0-30)					
Normal (>24)	55 (87.30%)	27.60±1.88	3 (5%)	25.33±0.57	<0.05
Mild cognitive impairment (21-24)	6 (9.52%)	23.66±0.51	25 (41.55%)	22.56±0.96	<0.05
Moderate cognitive impairment (10-20)	2 (3.17%)	19.50±0.70	32 (53.33%)	17.78 ± 1.86	<0.05
Severe cognitive impairment (< 10)	-	-	-	-	-
P value*		<0.05		<0.05	
MOCA score (0-30)					
Normal (≥ 26)	19 (30.15%)	28.00±1.10			
Mild cognitive impairment (<26)	44 (69.85%)	22.54±2.10	60 (100%)	21.65±1.86	<0.05
P value*		<0.05			



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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

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

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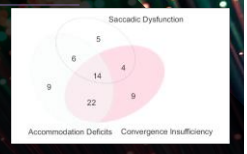
Clinical Measurement
Entrance Skills – OculoMotor Assessment Tool (OMAT)

OculoMotor Assessment Tool (OMAT) Test Procedure and Normative Data
Optom Vis Sci (2021) 98(6): 636–643

Methods
Healthy participants (n=376) with no prior self-reported history of concussions were recruited to perform the following three tasks for 60 seconds each: horizontal saccades, vertical saccades and vergence jumps

Results
Statistical difference was observed between the initial and latter 30-seconds
- ***Horizontal saccades [70±15 / 63±13]***
- ***Vertical saccades [68±14; 63±13]***
- ***Vergence jumps [43±11; 39±10])***

Conclusions
Established ***normative database for various eye movements*** to compare different patient populations who have binocular endurance dysfunctions potentially due to traumatic brain injury



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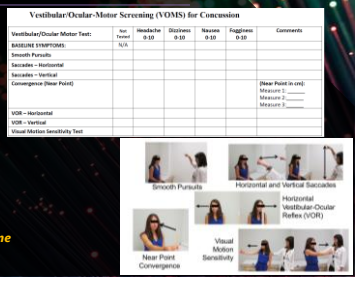
Clinical Measurement
Entrance Skills – Vestibular Ocular Motor Screening (VOMS)

- Smooth pursuits
- Saccades
  - Horizontal
  - Vertical
- Near point of convergence
- Vestibular-Ocular Reflex
  - Horizontal
  - Vertical
- Visual motion sensitivity

*****requires tape measure and metronome***



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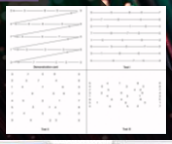
Clinical Measurement
Entrance Skills – DEM and King-Devick

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

Results
KD test gave similar results to visual motor speed and reaction time of the ImPACT test and visual symptoms on the PCSS. Two 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 of the studies were cross-sectional cohort studies with one having a retrospective design. 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 must be used concurrently with a clinicdt evaluation for appropriate diagnosis***



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Clinical Measurement
Clinical Testing

- **Automated Neuropsychological Assessment (ANAM)**
- **ImPACT Tool**
- **Computerized Cognitive Assessment Tool (CCAT)**
- **RightEye**
- **EyeBOX**
- **AI Software - ADA**

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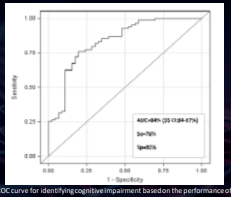
Clinical Measurement
Clinical Testing – Automated Neuropsychological Assessment (ANAM)

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 no self-reported TBI history (n=733) completed eight ANAM4 TBI-MIL tests. Throughput scores were used to calculate 8 composite scores

Results
The OTBM and ACS were normally distributed. Other composites had skewed, zero-inflated distributions ***(63% had GDS = 0)*** All composites differed significantly between participants with and without mTBI with deficit scores showing the largest effect sizes

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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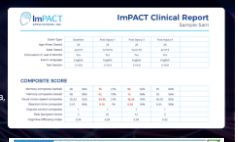
Clinical Measurement
Clinical Testing – ImPACT (v4) and CCAT

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 were divided into two testing groups [concussed (n=1414) and healthy (n=8305)]. Normative Change method, using published normative data, and the Reliable Change Index (RCI) method were used to determine if the change scores were significant.

Results
- ImPACT performed best using 87.5%-confidence interval and 1 components failed (sensitivity = 0.583, specificity = 0.625).
- CCAT performed best when using 75%-confidence interval and 2 components failed (sensitivity = 0.513, specificity = 0.715).

Conclusion
Overall low sensitivity and specificity results provide evidence for the use of a multi-dimensional assessment for concussion diagnosis including symptom evaluation, postural control assessment, neuropsychological status and other functional assessments



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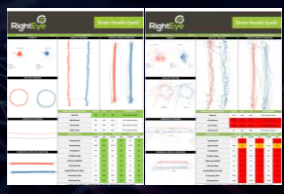
Clinical Measurement
Clinical Testing – RightEye (Bernell)

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 visually healthy, age-matched controls performed a 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

- ***TBI group showed a significant differences in:***
  - ***Fixation, saccades percentages for circular tracking movement***
  - ***Fixation and smooth pursuits for horizontal and vertical tracking***

Conclusions

- ***Predictive visual tracking was able to differentiate deficits in oculomotor functions in individuals with and without concussion***
- ***Eye tracking technology may serve as a quick objective tool to detect and monitor neural deficits due to TBI***

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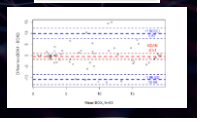
Clinical Measurement
Clinical Testing – EyeBox (Oculogica)

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-5 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 is defined by SCAT-5 subsets, the eye tracking algorithm had a sensitivity of 80% and specificity of 66% and AUC of 0.718 and a misclassification rate of 31.6%.

Conclusion

Algorithm for diagnosis of concussion vs. non-concussion may be useful as a baseline-free aid in diagnosis of concussion.

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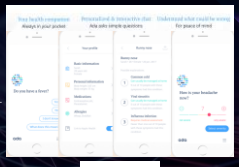
Clinical Measurement
Clinical Testing – AI Software

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

BMJ Open (2020) 10:e040269



Intervention/comparator

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***
  - GPs: 82%
  - ***Ada: 71%***
- ***Safe urgency advice***
  - GPs: 97%
  - ***Ada: 97%***

Conclusions

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

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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: Findings From the NCAA-DoD Concussion Assessment, Research and Education (CARE) Consortium

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

Methods

Preseason and postinjury VOMS, SCAT5, ImPACT Post-Concussion Symptom Scale (PCSS), and ImPACT composite scores were analyzed for 3958 preseason and 496 acute (≤48 hours) collegiate athlete evaluations in the NCAA-DoD CARE Consortium.

Results

Effect sizes were large, and overall predictive utilities were clinically useful for postinjury VOMS Total, SCAT5 Symptom Evaluation total severity score and the ImPACT PCSS total severity score.

Conclusion

- ***VOMS, SCAT5 and 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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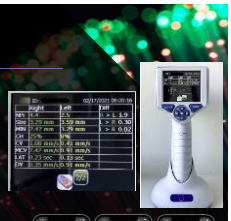
Clinical Measurement
Baseline Imaging – IR Pupillometry

Accommodative and pupillary dysfunctions in concussion and mTBI : Review

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

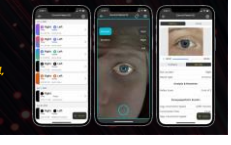


Methods

PubMed, Google Scholar, and Semantic Scholar databases were searched from 1980–2020, using key words of accommodation, pupil, vision therapy, vision rehabilitation, and objective testing, for peer-reviewed papers, as well as related textbooks in the area, in those with concussion / mTBI.

Results

For both systems, most static and dynamic response parameters were typically reduced, slowed, delayed and/or variable. Most of the abnormal accommodative parameters could be significantly improved with vision therapy



Conclusions

- ***Most response pupillary and accommodative parameters were abnormal, which could explain visual symptoms and related problems.***
- ***Improvements following therapy suggest the presence of considerable visual system plasticity, even in older adults with chronic brain injury.***

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Clinical Measurement

Baseline Imaging – RNFL and Macular 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 OCT in UK Olympic boxers attending two mandatory eye screening programs, 18 months apart. Healthy controls without past or present history of concussion were also screened to provide cross-sectional comparison

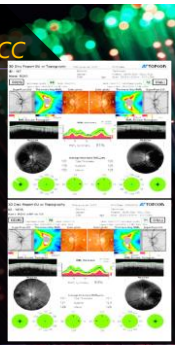
Results

16 Olympic boxers aged 20–33 years and 20 healthy, matched controls were recruited.

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***
- ***Baseline macula and RNFL measures were thinner than healthy controls***
- ***OCT may prove clinically useful as a candidate retinal biomarker of mTBI***



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Clinical Management

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

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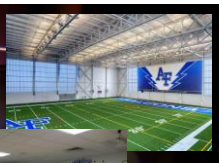
Clinical Concussion Management

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 (2011) 31: 456–468

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

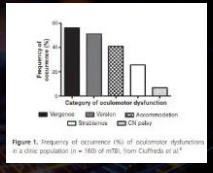

Figure 1. Frequency of occurrence (%) of oculomotor dysfunctions in a clinic population (n = 160) of mTBI, from Ciuffreda et al.[4]

Return to Play exercise 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

Macular Pigment + Ω-3 Fatty Acids

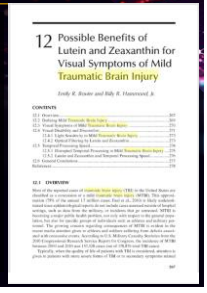
Dietary Supplements in Health Promotion

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***



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Clinical Concussion Management

Macular Pigment + Ω-3 Fatty Acids

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

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

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Clinical Concussion Management

Recovery and Expectation Management

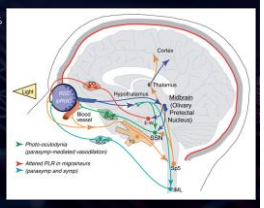
Photophobia Associated with Traumatic Brain Injury: Systematic Review and meta-analysis
OVS (2021) 98(8):891-900

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 neared plateau***
- ***At 3-6 months: Photophobia increased in 18%***
- ***At 6-12 months: Photophobia decreased in 15%***

Conclusions
- ***Photophobia is a 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***

Needs
- ***Objective quantification / measure of photophobia***
- ***Validated photophobia questionnaire and having specific photophobia ICD-10 code for improved data gathering and analysis***



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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)*
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)

* Multiple colors often provided relief. Yellow provided no relief.

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***

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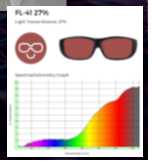
Clinical Concussion Management

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



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

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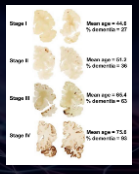
Clinical Concussion Management

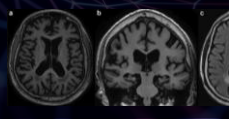
What's Next? – Chronic Traumatic Encephalopathy

Neuroimaging Biomarkers of Chronic Traumatic Encephalopathy: Targets for the Academic Memory Disorders Clinic
Neurotherpeutics (2021) 18:772-791

Abstract
CTE is a neurodegenerative disease associated with exposure to repetitive head impacts, such as those from contact sports.

- Pathognomonic lesion for CTE is the ***perivascular accumulation of hyper-phosphorylated tau*** in neurons and cell bodies
- Optimal tau PET radiotracer with high affinity for the ***3R/4R neurofibrillary tangles*** is lacking
- ***Amyloid PET scans have tended to be negative***
- Structural and functional imaging show ***frontotemporal and medial temporal lobe neurodegeneration***





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Clinical Concussion Management

Take Home Points

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

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

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Clinical Concussion Management

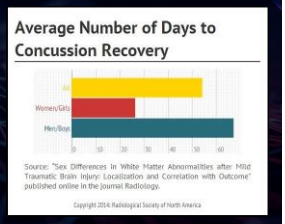
Take Home Points

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).



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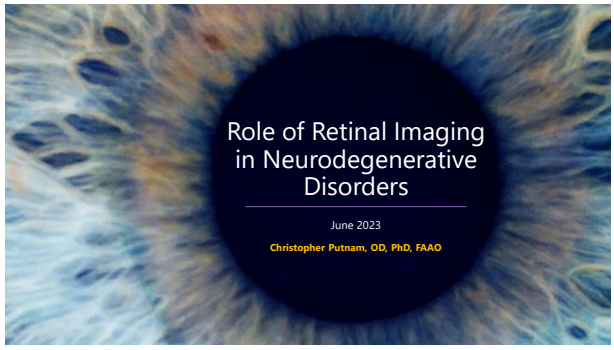

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Clinical Retinopathy

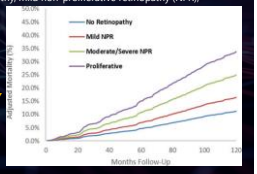
Pathogenesis

Retinopathy is Associated With Stroke, Dementia and Mortality

Stroke (2021) 52 (Suppl_1) A8-A8

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

Results:
Of 5,543 participants aged ≥18 years with gradable retinal imaging, 696 had retinopathy, 289 had stroke, and 597 had dementia. Subject mean age was 56.3±11.7 years. Retinopathy was associated with higher risk of stroke (OR=2.39) and dementia (OR: 1.68). ***Over a median duration of 10 years, there was a dose-dependent relationship between retinopathy severity and all-cause mortality (HR=1.0 / 1.5 / 2.4 / 3.4)***



Conclusions:
Participants with retinopathy have:

- ***2.4X increase in stroke risk***
- ***1.7X increase in dementia risk***

Severe retinopathy confers a higher risk of death (adjusted for age and vascular risk factors)

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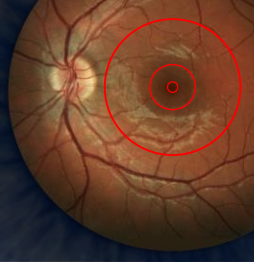
RETINAL ANATOMY

Macula
5.5mm diameter

Fovea
1.5mm diameter

Foveola
0.3mm diameter



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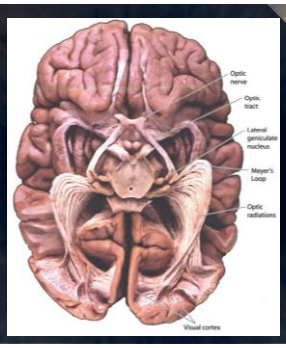
NEURAL ANATOMY



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Clinical Retinal Imaging

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

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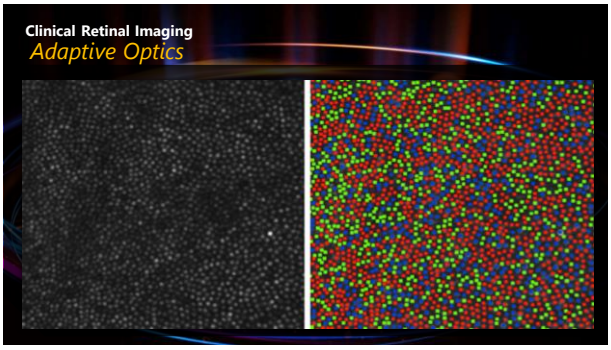

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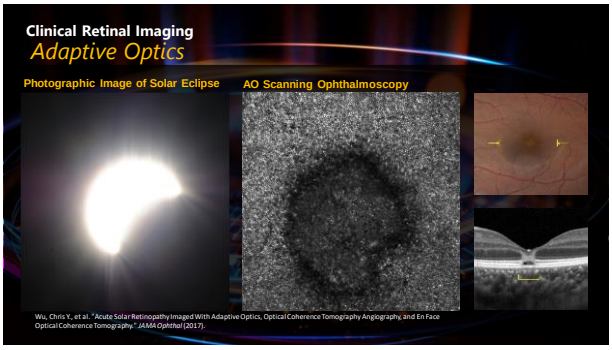

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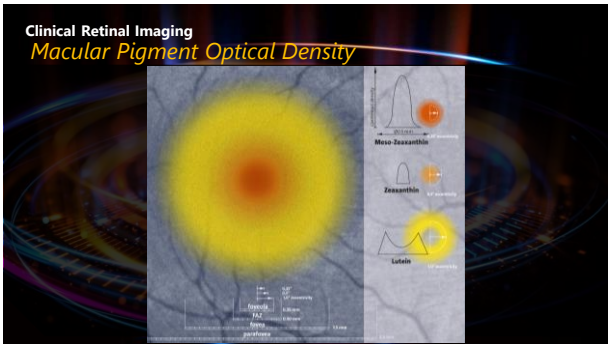

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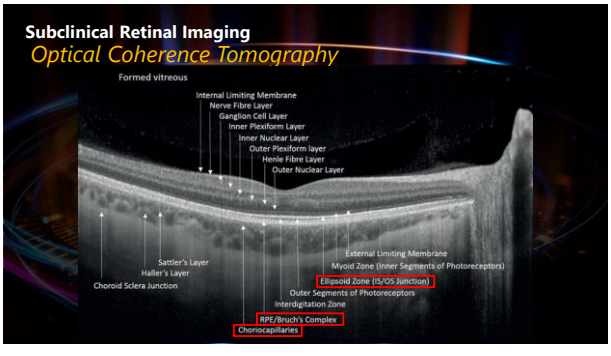

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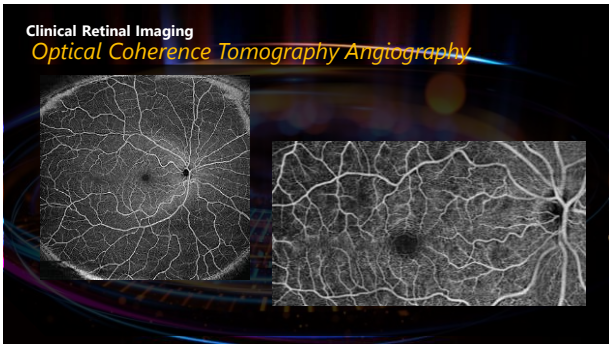

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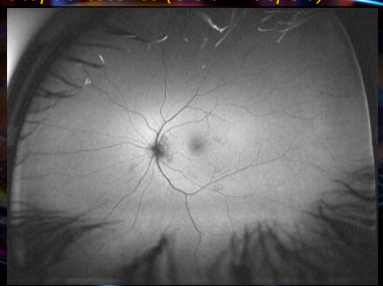
Clinical Retinal Imaging

Fundus Autofluorescence (Ultra-widefield)



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Neurodegenerative Disorders

- Huntington's Disease
- Vascular dementia
  - Cortical Infarction
- Frontotemporal dementia
- Multiple Sclerosis
- Parkinson's Disease
  - Dementia with Lewy Bodies
- ***Alzheimer's Disease***
- Chronic Traumatic Encephalopathy

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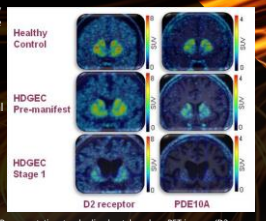
Clinical Retinal Imaging

Huntington's disease (HD)

- Rare neurodegenerative disorder of the CNS characterized by chorea, behavioral and psychiatric disturbances and cognitive decline with a mean onset at 30-50 years of age
- Follows an 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 and focused on 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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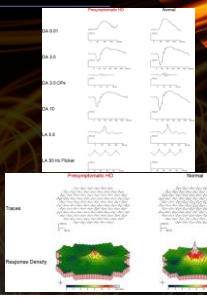
Clinical Retinal Imaging

Huntington's disease (HD)

- SD-OCT scans of the macula and RNFL found no difference in average RNFL between HD and healthy individuals although
  - HD subjects demonstrated significant reduction in temporal RNFL thickness compared to healthy controls
  - Disease duration negatively ***correlates with both RNFL thickness and macular volume***
- ERG and mfERG detected early retinal dysfunction in a presymptomatic patient with HD
  - ***Full-field ERG amplitudes were subnormal in both eyes for the dark-adapted measures and oscillatory potentials (RETeval?)***
  - mfERGs revealed functional anomalies of the central retina with attenuated P1 amplitudes for both eyes although mfERG P1 peak times were normal at all eccentricities



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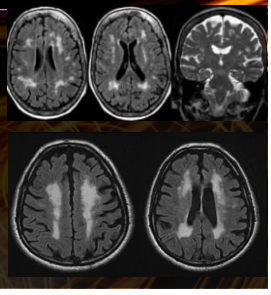
Clinical Retinal Imaging

Vascular dementia (VaD)

- Recognized as the 3rd most common cause of dementia after AD and LBD
  - ~15% of dementia cases
- Though there is an established relationship between vascular and degenerative pathology, the mechanistic link is elusive:
  - ***Uncertainties in diagnostic criteria***
  - ***Inexact relationship between cerebrovascular pathology and cognitive impairment***
  - ***Lack of identifiable tractable treatment targets***
- ***Cognitive changes are highly variable and dependent on the particular neural substrates affected by the vascular pathology***
- MMSE has proven relatively insensitive to characteristic VaD deficits
- MoCA and vascular dementia assessment scale (VADAS-cog)
  - More sensitive to the highly variable deficits found in a VaD population such as executive function, attention, memory, language and praxis



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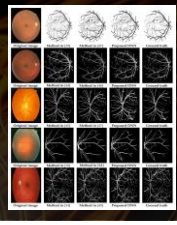
Clinical Retinal Imaging

Vascular dementia (VaD)

- Retinal vascular changes 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

Aiding the diagnosis of diabetic and hypertensive retinopathy using artificial intelligence-based semantic segmentation
J Clinical medicine (2019) *8*(9):1446.



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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
- 2nd most common neurodegenerative disorder affecting persons aged ≤ 65
- ***~40% demonstrate apathy, disinhibition and social withdrawal***
- ***~40% demonstrate prominent language impairments,***
- ***~20% exhibit muscle atrophy, apraxia and eye movement abnormalities progressive supranuclear palsy (PSP)***
- Pathologic manifestations involve selective frontotemporal lobar degeneration accompanied by astrocytosis, microgliosis, and the deposition of tau proteins

*****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 • Can easily apply various different processing techniques • Discrimination between FTD and AD, as well as between some FTD subtypes	• Less sensitive to detecting changes in presymptomatic stages • Inconsistent results and correlation with time course of disease • Limited specificity for FTD spectrum with structural imaging alone
White-matter integrity loss	DTI	• Noninvasive • Can easily reflect changes in microstructure • Can detect white matter changes that precede gray matter changes in FTD • Can discriminate between FTD from other types of dementia and control subjects	• Varying distribution patterns and rate of neurodegeneration observed among different individuals
Brain metabolism	FDG-PET	• Early visualization of alterations in brain metabolism that may precede gray matter atrophy • Can detect functional abnormalities in presymptomatic stage of FTD	• Expensive, not covered by many insurers • Requires prolonged positioning that is increasingly difficult in patients with behavioral dementia or concurrent motor dysfunction
Fluid biomarkers			
$A\beta_{42}$	CSF	• Strong correlation with disease severity, progression, survival, and cerebral atrophy	• Increased in several other neurodegenerative disorders • 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 low specificity • Does not reflect extent of neurodegeneration
Genetic biomarkers			
C9orf72, *MAPT*, and *GRN*	Blood sample	• Direct correlation between clinical manifestations and molecular mechanisms of disease • Can potentially identify presymptomatic/preclinical carriers • Provide a clear basis for targeted therapies (i.e., ASOs)	• Genetic testing is generally restricted to patients with suggestive family history • Incomplete penetrance and variable penetrance further complicate identification of at-risk individuals • Testing is generally limited to specialized clinical research settings

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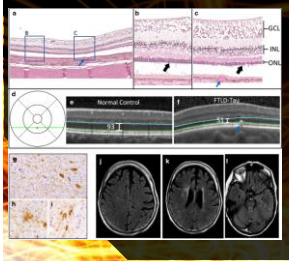
Clinical Retinal Imaging

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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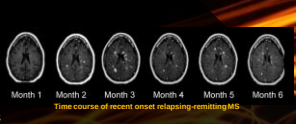
Clinical Retinal Imaging

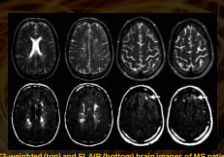
Multiple Sclerosis (MS)

- Progressive neurological disorder characterized by inflammatory and degenerative components that affect genetically susceptible individuals with a mean age of 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*****



Time course of recent onset relapsing-remitting MS



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 both periventricular and cortical–juxtacortical 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 (375) 6578:296-301

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 32X after infection with EBV but ***was not increased after infection with other viruses, including the similarly transmitted CMV***

Serum levels of ***NfLC*** increased only after EBV seroconversion

- Findings cannot be explained by any known risk factor for MS and suggest EBV as the leading cause

REPORT

MULTIPLE SCLEROSIS

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

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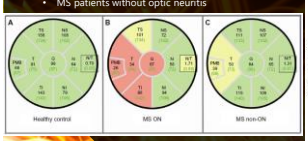
Clinical Retinal Imaging

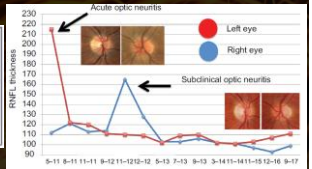
Multiple Sclerosis (MS)

Retinal imaging with OCT: Biomarker in MS?

Eye and Brain (2018) 8:701-706

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





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Clinical Retinal Imaging

Multiple Sclerosis (MS)

Retinal asymmetry in multiple sclerosis

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

Abstract

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

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

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

mGCIPL	Cut-off	References	Specificity	Sensitivity	PPV	NPV
IEPD	10 %	Pezold et al., 2014	99.4	2.7	0.990	0.01
IEPD	4 %	Conic et al., 2017	82.8	51.7	0.6	99.9
IEAD	4 µm	Holen-Rønnop et al., 2019	86.8	43.5	0.7	99.9

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

Table 5 Subgroup analysis multiple sclerosis compared to NMSOD

mGCIPL	Cut-off	References	Specificity	Sensitivity	PPV	NPV
IEPD	10 %	Pezold et al., 2014	2.7	100	29.2	100
IEPD	4 %	Conic et al., 2017	72.8	51.7	82.6	37.7
IEAD	4 µm	Holen-Rønnop et al., 2019	76.3	43.5	33.3	82.1

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

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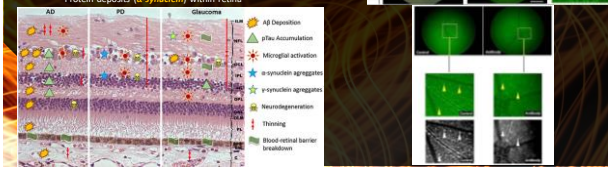
Clinical Retinal Imaging
Parkinson's disease (PD)

- 2nd 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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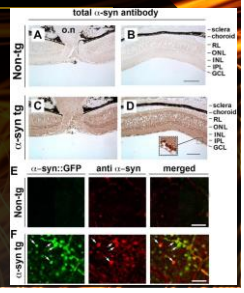
Clinical Retinal Imaging
Dementia with Lewy bodies (LBD)

- 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
  - **DLB -** 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 in the diagnostic criteria may help bridge the gap between clinical and pathological prevalence rates*****



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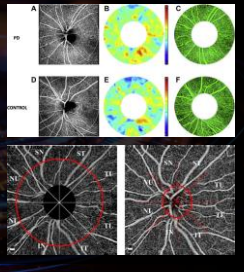
Clinical Retinal Imaging
Parkinson's disease (PD)

Identifying peripapillary radial capillary plexus alterations in Parkinson's disease using OCTA
Ophth Retina (2021) 6(1):29-36

Methods
Participants underwent OCT) imaging using the Zeiss Cirrus HD-5000 AngioPlex. Capillary perfusion density (CPD) and capillary flux index (CFI) were assessed using a 4.5x4.5 mm peripapillary scan, and RNFL thickness was assessed using a 200x200 µm optic nerve cube OCT scan

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

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



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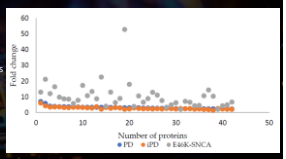
Clinical Retinal Imaging
Parkinson's disease (PD)

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. α-synuclein and MMP9 were measured using a human magnetic luminex assay kit while lactoferrin was measured using a human lactoferrin ELISA kit. Oligomeric α-synuclein was measured using a human α-synuclein oligo ELISA kit.

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

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



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Alzheimer's Disease
and Cognitive Impairment

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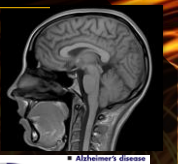
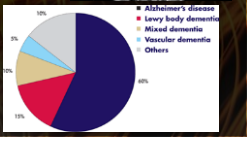
Clinical Retinal Imaging
Alzheimer's disease (AD)

- 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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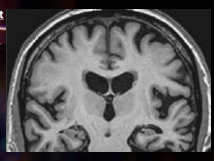
Clinical Retinal Imaging

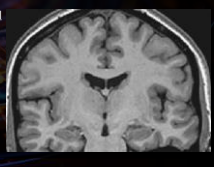
Alzheimer's disease (AD)

AD subject



- 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
  - apraxia
  - agnosia
  - visuospatial difficulties
  - executive dysfunction
- Clinical diagnosis is made using McKhann (1984) criteria:
  - definite AD (established by postmortem or biopsy),
  - probable AD
  - possible AD (other cognitive syndromes equally likely)

Control



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

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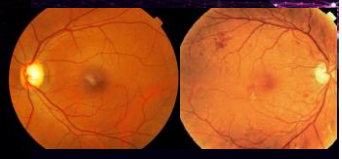
Clinical Retinal Imaging

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 AD risk

Shared characteristics:

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

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Clinical Retinal Findings *related to Alzheimer's and Cognitive Impairment*

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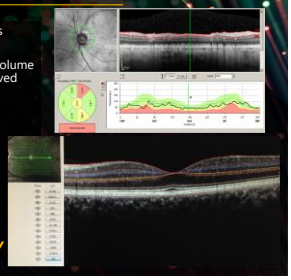
Generalized Retinal Findings *of Alzheimer's and Cognitive Impairment*

- 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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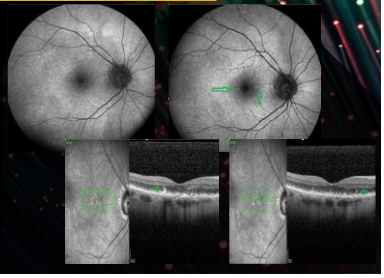
Clinical Retinal Imaging

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 fluorophore with a high affinity to Aβ
- Aβ in AMD Lesions isolated in patient diagnosed with Alzheimer's Disease in 4 separate studies since 2017
- High bioavailability, proprietary blend used in conjunction with cSLO:
  - ***100% sensitivity***
  - ***81% specificity***
- ***Retinal Aβ 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

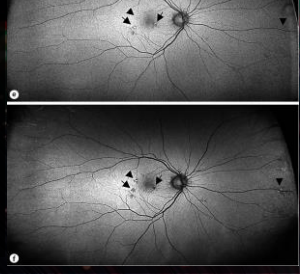
Ophthalmic Research (2018) 24.5

Results:

- Baseline analysis showed a significantly higher prevalence of peripheral hard drusen in AD subjects (25%) vs. 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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Oral Supplementation Related to Neural Function and Cognitive Performance

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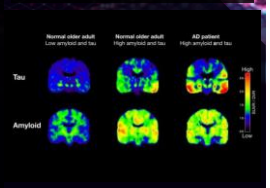
Oral Supplementation

Neural Function and Cognitive Performance

- Medical food approach improved cognitive biomarkers ***without clear effects in AD and MCI***
- Antioxidant-rich food supplementations improved specific cognitive outcomes in MCI and mild-to-moderate dementia but ***only in small samples***
- Supplementation with Ω-3 PUFAs ***improved specific cognitive domains and cognitive-related biomarkers*** in MCI and AD.
- Antioxidant vitamin and trace element improved only cognitive-related outcomes and biomarkers ***without effect on cognition in AD and MCI***
- High-dose B vitamin supplementation in AD and MCI improved cognitive outcomes but ***only in the subjects with a high baseline plasma Ω-3 PUFAs***

Nutritional interventions in patients with Alzheimer's disease and other later-life cognitive disorders
J Gerontology and Geriatrics (2018) 66:101-118



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Hypothesized Roles Macular Pigment

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

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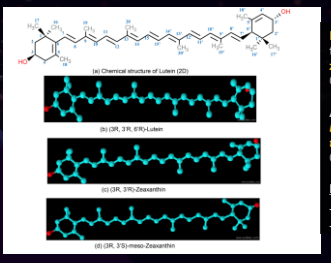
Lutein & Zeaxanthin: Macular Pigment



Macular pigment is the collective name for the isomeric carotenoids **lutein** and **zeaxanthin** and **meso-zeaxanthin**
(Bone et al., 1997)

Accumulated within the sensory retina at ***levels 1000X higher than found in serum to the exclusion of all other carotenoids***
(Landrum et al., 1997)

Primary Metabolites:
3'-oxolutein
3'-epilutein

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Lutein & Zeaxanthin Related to Neural Function and Cognitive Performance: fMRI Study (2018)

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	−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.

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

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

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

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

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Lutein & Zeaxanthin Related to Neural Function and Cognitive Performance: fMRI Study (2018)

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.

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

Occipital pole
- ***Visual processing***

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

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Macular Pigment
Neurocognitive Hypothesis

Macular pigment, visual function and macular disease among subjects with Alzheimer's disease: an exploratory study
Journal of Alzheimer's Disease (2014) 42(4):1191-1202

- CONCLUSIONS: ***AD patients have significantly lower MP, 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 (2014) 35(7):1695-1699

- CONCLUSIONS: ***MPOD 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 (2014) 9(9)

- CONCLUSIONS: Significant correlations found between MP and CFF thresholds and visual motor performance ***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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Macular Pigment Optical Density:
Proxy for cortical levels?

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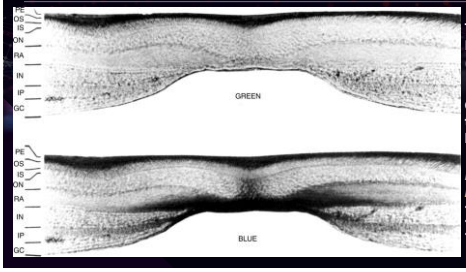
Take Home Points:
Clinical Macular Pigmentation supplementation



Target a 4:1 L:Z ratio *(L ≥20mg)*

Generic brands tend to have lower bioequivalencies

Health status matters
- **BMI**
- **Smoking**
- ***Diet****

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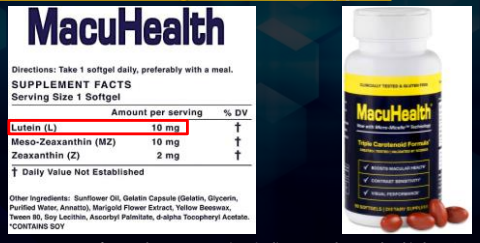
Take Home Points:
Clinical Macular Pigmentation supplementation



Assessment of L, Z and MZ concentrations in dietary supplements by chiral HPLC
Eur Food Res Tech (2016) 242:599-608

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What's now?

1. Aβ accumulation is an established biomarker of AD development and typically precedes clinical cognitive decline by 15-20 years
2. FAF imaging with curcumin has the provides the ability to detect drusen containing Aβ in a high-resolution, non-invasive method capable of population-level screening.
3. Clinical trials of existing AD treatments indicate that early, modest reduction in Aβ accumulation can substantially alter the long-term disease course.
   ***Aducanumab (Biogen submitted FDA application in 2020)**
   ***Donanemab clinical trial data available now**
4. L and Z are 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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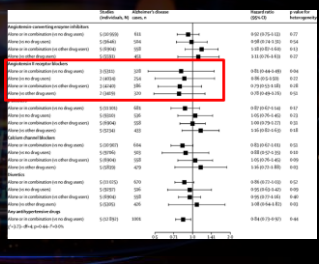
What's now?

Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of prospective cohort studies
Lancet Neurol (2020) 19(1);61-70

Methods
Meta-analysis included more than 2000 participants, dementia events over 5 years, measured blood pressure 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 (SBP ≥140 mm Hg or DBP ≥90 mm Hg) and normal (SBP <140 mm Hg and DBP <90 mm Hg) blood pressure

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 people with hypertension, use of any AHM with efficacy to lower blood pressure may reduce the risk for dementia.



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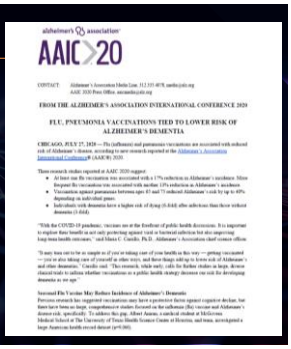
What's now?

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 2020

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.

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What's now? *(Update May 2023)*

Donanemab in Early Alzheimer's Disease
N Engl J Med (2021) 384:1691-1704

RESULTS
131 were assigned to receive donanemab and 126 to receive placebo. The baseline iADRS score was 106 in both groups. The

- ***Change from baseline in the iADRS score at 76 weeks was −6.86 with donanemab and −10.06 with placebo***
- ***Most secondary outcomes showed no substantial difference.***
- ***At 76 weeks, the reductions in the amyloid plaque level and the global tau load was greater with donanemab than with placebo***

CONCLUSIONS
In early AD, donanemab resulted in a better composite score for cognition and ADL than placebo at 76 weeks

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What's now?

Methods
Participants from the Health and Retirement Study (n=12,030) reported on their loneliness, social isolation, and assessed on clinical, behavioral, and genetic risk factors. Cognitive status was assessed at baseline and every 2 years over a ***10-year follow-up***

Results
Loneliness was associated with a 40% increased risk of dementia

- ***Association held controlling for social isolation and clinical, behavioral, and genetic risk factors***
- ***Association was similar across gender, race, ethnicity, education and genetic risk.***

Discussion

- Loneliness is associated with increased risk of dementia
  - Modifiable factor that can reduce dementia risk.


GERONTOLOGICAL SOCIETY OF AMERICA

Original Research Report

Loneliness and Risk of Dementia

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Abstract

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What's now?

Association between cataract extraction and development of dementia
JAMA Internal Medicine. (2021)

RESULTS
3038 participants were included aged 74.4 (6.2) years; 1800 women and 1238 men. Based on 23,554 person-years of follow-up, cataract extraction was associated with significantly reduced risk ***(HR=0.71)*** of dementia compared with participants without surgery after controlling for years of education, self-reported race and smoking history and stratifying by apolipoprotein E genotype, sex, and age group at cataract diagnosis.

- ***Similar results were found with the development of AD.***

CONCLUSIONS AND RELEVANCE
Cataract extraction was significantly associated with lower risk of dementia development

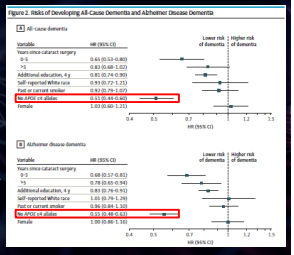
Figure 2. Risks of Developing All-Cause Dementia and Alzheimer Disease Dementia

A All-cause dementia

Variable	HR (95% CI)
Years since cataract surgery	
0-5	0.65 (0.53-0.80)
>5	0.83 (0.68-1.02)
Additional education, 4 y	0.81 (0.74-0.90)
Self-reported White race	0.93 (0.72-1.21)
Past or current smoker	0.92 (0.79-1.07)
No APOE ε4 alleles	0.51 (0.44-0.60)
Female	1.03 (0.90-1.21)

B Alzheimer disease dementia

Variable	HR (95% CI)
Years since cataract surgery	
0-5	0.68 (0.57-0.81)
>5	0.78 (0.65-0.94)
Additional education, 4 y	0.83 (0.74-0.91)
Self-reported White race	1.01 (0.79-1.29)
Past or current smoker	0.96 (0.84-1.10)
No APOE ε4 alleles	0.51 (0.45-0.61)
Female	1.00 (0.86-1.16)

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What's now?

Mechanisms Associated with Type 2 Diabetes as a Risk Factor for Alzheimer-Related Pathology
Mol Neurobio (2019) 56:5815-5834

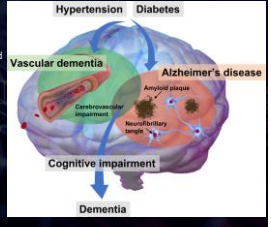
Abstract
Current evidence suggests dementia and pathology in AD are both dependent and independent of amyloid processing and can be induced by multiple 'hits' on vital neuronal functions.

- ***T2D poses the most important risk factor for developing AD after aging and dysfunctional neuronal signaling is a major contributor in both diseases.***

Classic signs of T2D (hyperglycemia and insulin dysfunction) resulted in modest, stable deficit in spatial recognition memory, with very little long-term modification of proteins in the hippocampus.

Amyloid beta 42 (Aβ42) induced a more severe, but short-lasting deficits in memory and deregulation of proteins.

- ***Interaction of Aβ with the T2D phenotype exacerbated and prolonged the memory deficits and induced more severe aberrant regulation of proteins associated with autophagy, inflammation and glucose uptake***



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What's next?

Retinal imaging in Alzheimer's & neurodegenerative diseases
Alzheimer's & Dementia (2020)

- SD-OCT in detection of retinal structural changes
- Imaging of amyloid β and other proteinopathies
- Retinal vascular imaging through OCTA
- Retinal imaging of neuroinflammation and metabolism
- Next generation imaging
  - Fluorescent lifetime imaging ophthalmoscopy (FLIO)
  - Detection of apoptotic retinal ganglion cells (DARC)


Alzheimer's & Dementia

REVIEW ARTICLE

Retinal imaging in Alzheimer's and neurodegenerative diseases

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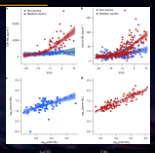
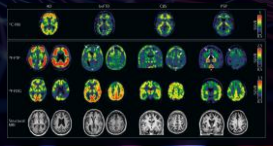
What's next?

Diagnostic and prognostic value of serum Nf-L and p-Tau in frontotemporal lobar degeneration (FTD)
J Neurol Neurosurg Psychiatry (2020)



Methods
Retrospective study of 417 participants were analyzed for serum NfL and p-Tau181 concentrations. Diagnostic values of serum biomarkers in the differential diagnosis between FTLD, AD and healthy aging acting as markers of disease severity

Results
- ***Significantly higher levels of serum Nfl in patients with FTD syndromes, compared with healthy controls, and lower levels of p-Tau181 compared with patients with AD***
- ***Serum NfL concentrations showed a high accuracy in discriminating between FTD and healthy controls***
- ***Serum p-Tau181 showed high accuracy in differentiating FTD from AD***
- ***Serum NfL levels correlated with cognitive function, disease severity and best predictors of survival probability.***



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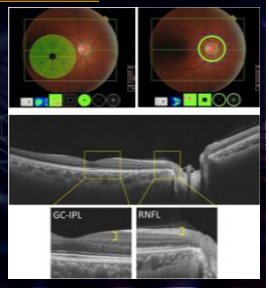
What's next?

Association of Inner Retinal Thickness with Prevalent Dementia and Brain Atrophy in a General Older Population
Ophthal Sci (2022) 2(2)



Methods
The thicknesses of the inner retinal layers (GC-IPL and RNFL) were measured by SS-OCT. The 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 significantly increased with lower GC-IPL thickness, but no significant association was observed with RNFL thickness.***
- ***Lower GC-IPL thickness was significantly associated with lower volume of hippocampus, amygdala, entorhinal area, and parahippocampal gyrus (cognitive regions) and cuneus, lingual gyrus, and thalamus (visual regions).***

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

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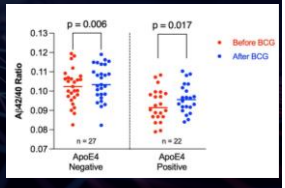
What's next?

Evaluation of BCG Vaccination and Plasma Amyloid: A Prospective, Pilot Study with Implications for Alzheimer's Disease
Microorganisms (2022) 10(2):424-431

Bacillus Calmette–Guérin (BCG) vaccine has been used for 100 years to prevent tuberculosis. Not all countries, including the United States, adopted the initial World Health Organization recommendation to use BCG. Recent population studies demonstrate lower prevalence of Alzheimer's disease (AD) in countries with high BCG coverage.

Follow-up plasma amyloid testing 9 months after vaccination revealed a reduction in the APS in all the risk groups: low risk group, intermediate risk group and the high-risk group. Greater benefit was seen in younger participants and those with the highest risk.

- Both the favorable direction of change after BCG as well as the utility of the APS (as a surrogate AD biomarker) may prompt a definitive large-scale multicenter investigation of BCG and AD risk as determined by plasma amyloid peptide ratios and APS



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Questions?

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