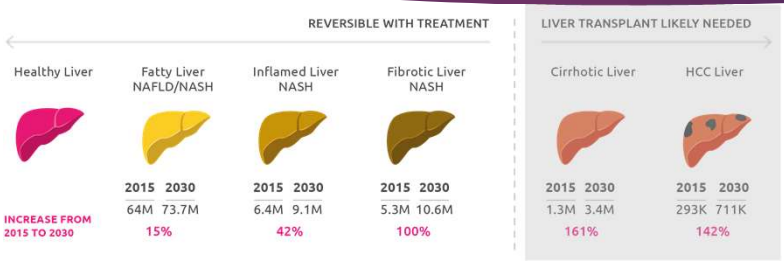

Innovative Radiology:
New MRI Technology to Assist in Complex Diagnoses
CARLOS DUNCKER, MD, PHD, FACNM


CONSULTANT FOR
PERSPECTUM DIAGNOSTICS
Disclosures



USA Liver disease is on the rise

USA Liver disease is on the rise

Over 64 million people are projected to have NAFLD, with annual medical costs of about $103 billion

For perspective, Hepatitis C affects 3.2M Americans[1]

Canbay A, *et al.* (2018); EASL Abstract PS-057

David Bernstein
Chief, Hepatology
Northwell Health, New York

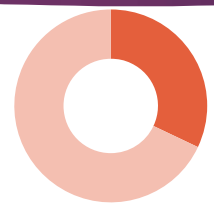
"We only see them once they've been found.

Something had to be done to identify them to see the specialist, but most of them never see the specialist.

There's a large population out there with undiagnosed disease, it's important to identify it so you can screen for complications that occur."

Dallas Fort-Worth

6.8 MILLION



32% OBESITY PREVALENCE RATE

>2.1M JUST IN DFW

Health Official: San Antonio's High Obesity Rate 'Not a Factory Defect'

ROSEANNA GARZA | MAY 10, 2018

IN 2014, THE SAN ANTONIO METROPOLITAN HEALTH DISTRICT REPORTED THAT **71%** OF ADULTS IN BEXAR COUNTY WERE OVERWEIGHT OR OBESE.

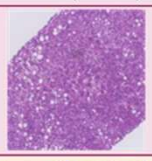
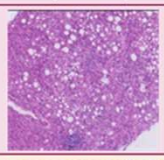
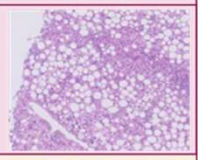
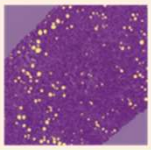
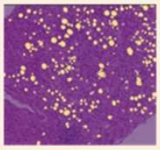
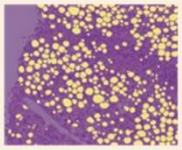
NAFLD/NASH The scale, challenge and opportunity

- Prevalence is massive and rising
- Medically serious condition
- Time bomb: Soon to become the № 1 cause of liver transplantation
- Who needs intervention?
- Non-invasive screening
- Monitoring impact of lifestyle change

Liver Biopsy: The Gold Standard?

Method	Invasive biopsy needle
Sample size	16 gauge needle, 30mm length
Risk of complications	1.8-5.3%[1]
Mortality rate	0.01-0.2%[2]
Quantification	Subjective
Sampling location	Affecting fibrosis staging up to 50% of the time[3,4,5]
Repeatability before/after treatment	Unknown
Sample size	Variable (1/50,000th of liver)[8]
Cost	$2,000-$7,000[9] + Pain meds, ER, US, work day(s)
Inter-reader variability	50% disagreement even among NASH experts[6,7]

1. Kim et al., 2008. 2. Kalambokis et al., 2007 3. Morisaka et al., 2018 4. Poniachichik et al. 1996
5. Regev et al. 2002 6. Ratziu et al., 2005 7. Bedosa et al, 2003 8. Standish et al., 2006. 9. health.costhelper.com/biopsy.html

	Brunt steatosis grade	1 (5%-33%)	2 (33%-66%)	3 (>66%)
	H&E: Proportion of hepatocytes containing fat			
Quantitative Pathology	Fat detection: Percentage of fat that makes up the overall tissue area			
	*Fat fraction % (of tissue proportion)	Fat fraction 5%	Fat fraction 8%	Fat fraction 27%

Steatosis

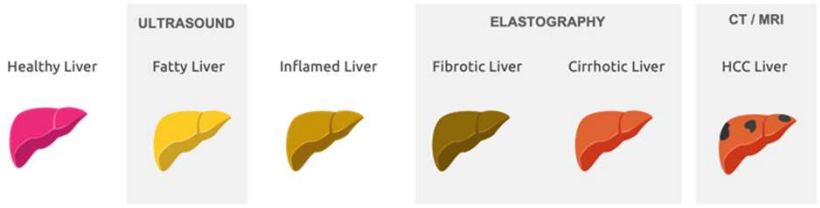
Quantitative (Digital) Pathology

Beyond Liver Biopsy

Imaging Technology Biomarkers in Liver Disease

Abdominal US
Elastography (Transient, Shear wave, MRE)
PDFF, CAP, ^{1}H-MRS
Iron

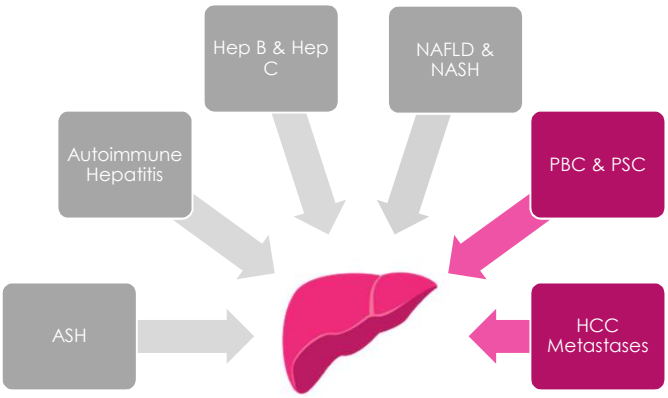
Doing the work with the tools we have



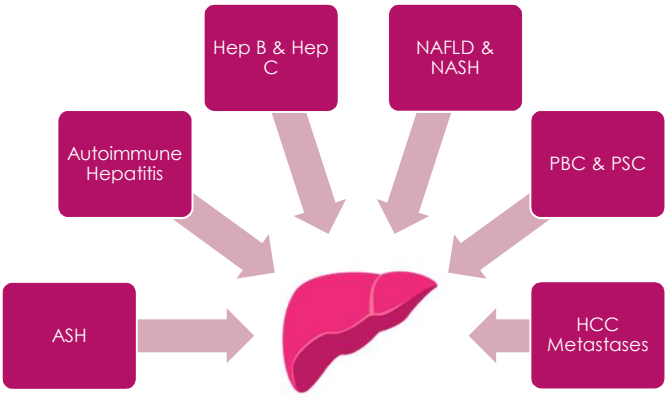
Assessment of Liver Disease

Diagnostic gap with current imaging modalities

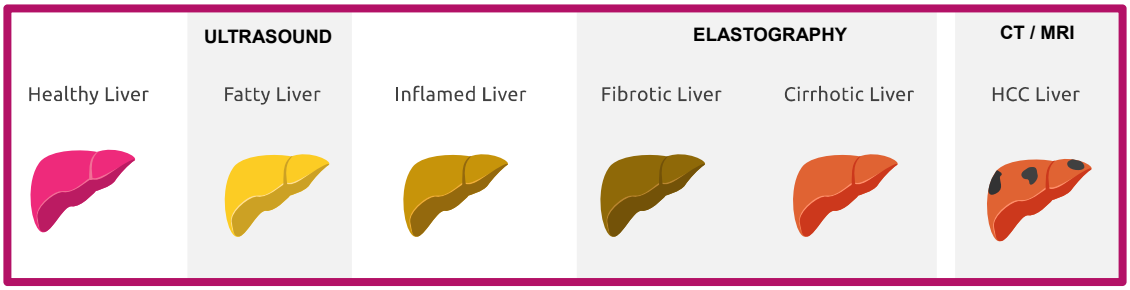
Current role of MRI in routine diagnosis



Vision: **A One-Stop-Shop, 15 min, no contrast**



A One-Stop-Shop Multiparametric MRI



ASSESSING A WIDE VARIETY OF LIVER DISORDERS
Not only NAFLD

MP-MRI Assessment of Liver Disease:

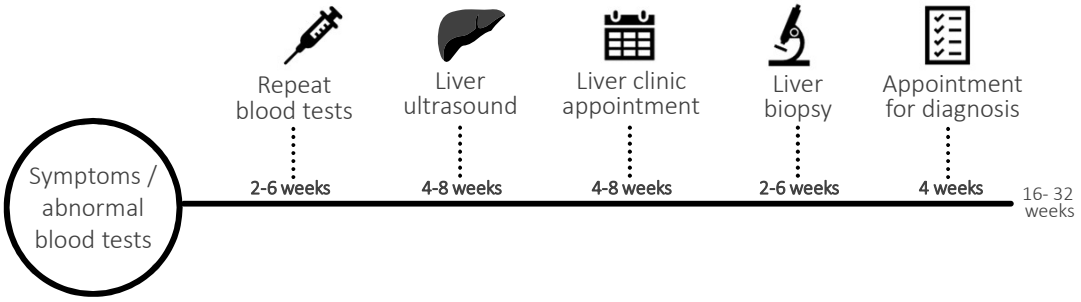
Scientific/medical requirements

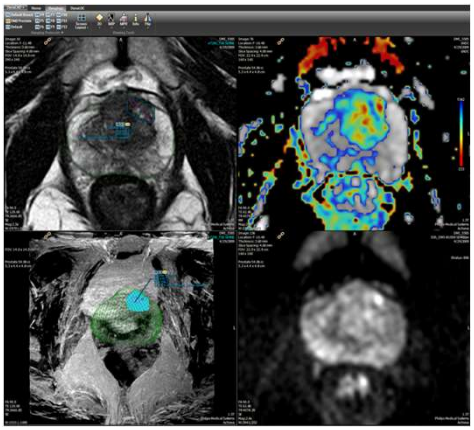
- Measure fibrosis, inflammation, ballooning, steatosis, iron
- Representative of a large liver volume
- High diagnostic accuracy
- Highly reproducible
- Measures change accurately
- Predicts prognosis
- Large-scale multicentre validation
- No IV contrast
- Patient-friendly
- No risk

Logistic requirements

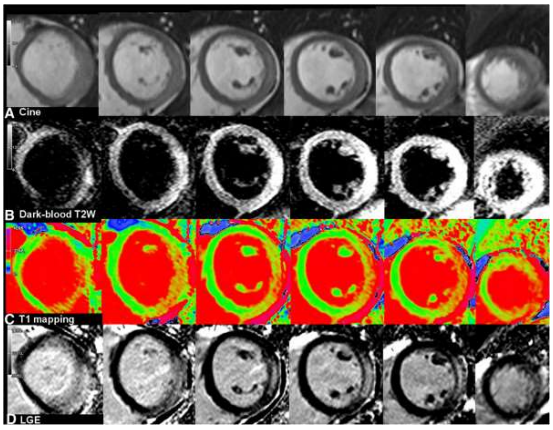
- Fast
- Affordable
- Widely available
- Standardized across scanners
- Regulatory cleared – FDA, CE

Current diagnostic pathway



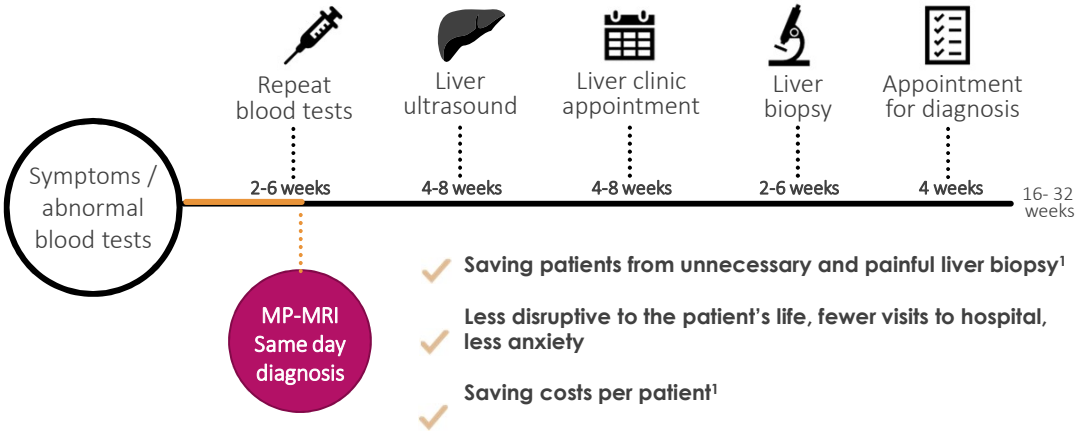


https://prostatemri.radnet.com/our-program/multiparametric-mri



https://www.researchgate.net/figure/Whole-heart-multiparametric-cardiovascular-magnetic-resonance-CMR-tissue_fig1_262567500

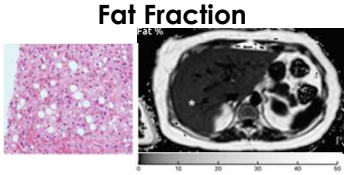
Transforming Clinical Care



- **Saving patients from unnecessary and painful liver biopsy[1]**
- **Less disruptive to the patient's life, fewer visits to hospital, less anxiety**
- **Saving costs per patient[1]**

MP-MRI: Liver Tissue Characterization

Fat Fraction

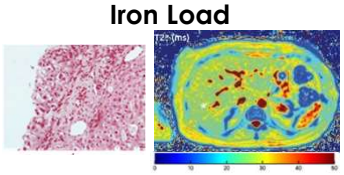


MRI-PDFF

Chemical shift-based method for water-fat separation

Shown to correspond to histological measures of ***steatosis***†

Iron Load

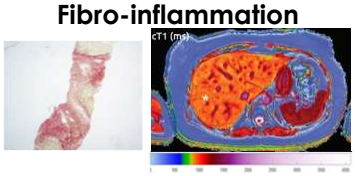


T2* map

MR relaxation time

Shown to decrease with increased ***hepatic iron overload***‡

Fibro-inflammation



Corrected T1

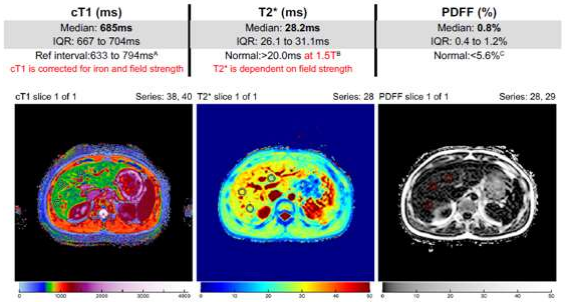
Free-water content in tissue

Shown to increase in ***inflammation and fibrosis, when corrected for hepatic iron***

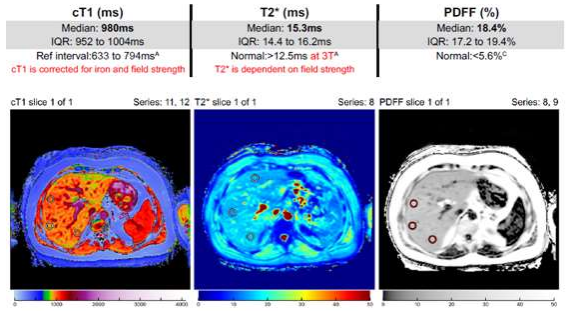
†Idilman et al., 2013; Reeder et al., 2017 ‡ Wood et al., 2005; Hoad et al., 2015. • Banerjee et al, 2014; Pavlides et al, 2015; Pavlides et al., 2016

Single scan, highly reproducible, quantifying all components of NASH

Healthy Patient



Diseased Patient



MP-MRI for Longitudinal Assessment

cT1 has Best-In-Class Repeatability

	CoV (%)
Liver*MultiScan*™ cT1 (ms)	**3.1 %**
MRE (kPa)	11 %
FibroScan (kPa)	40 %

Harrison et al, 2018 PLOS One

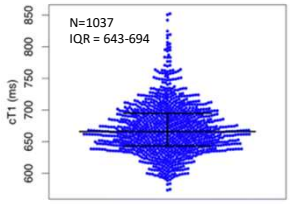
cT1 Normal Values

>1000 Subjects, UK Biobank Population Health Study

Abdominal Radiology
January 2019, Volume 44, Issue 1, pp 72–84

Reference range of liver corrected T1 values in a population at low risk for fatty liver disease—a UK Biobank sub-study, with an appendix of interesting cases

A. Mojtahed, C. J. Kelly, A. H. Herlihy, S. Kin, H. R. Wilman, A. McKay, M. Kelly, M. Milanesi, S. Neubauer, E. L. Thomas, J. D. Bell, R. Banerjee, M. Harisinghani

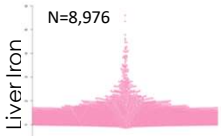


•https://doi.org/10.1371/journal.pone.0209340

Measurement of liver iron by magnetic resonance imaging in the UK Biobank population

Andy McKay, Henry R. Wilman, Andrea Dennis, Matt Kelly, Michael L. Gyngell, Stefan Neubauer, Jimmy D. Bell, Rajarshi Banerjee, E. Louise Thomas

30% of patients with NAFLD have iron overload *(Valenti et al. 2003)*



Elevated iron 4.9% in general population

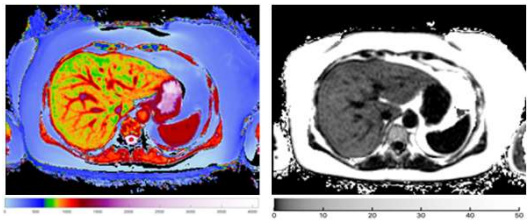
Liver Biopsy vs MP-MRI of the Liver

	Biopsy	MP-MRI
Method	Invasive Biopsy needle	Non-invasive MRI scan, no contrast needed
Risk of complications	16 gauge needle, 40mm length	None
Mortality rate	1.8-5.3%	None
Quantification	0.01-0.2%	Objective
Sampling location	Subjective	Standardized[1]
Inter-reader Variability	Affecting fibrosis staging up to 50% of the time	Excellent intra/Inter-reader variability[2]
Repeatability before/after treatment	50% disagreement even among NASH experts	Standardized
Sample Size	Variable (1/50,000th of liver)	Multiple liver slices – whole liver can be sampled

1. Ratziu et al., 2005 *2. LMSv2 FDA Submission., 2017*

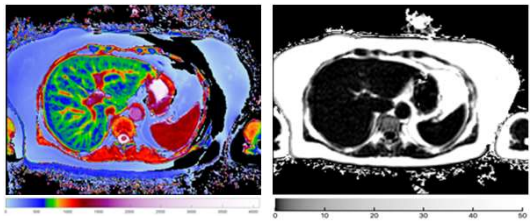
Case Study: NAFLD

57 y/o female overweight patient with chronic fatigue and fibromyalgia on low-calorie diet



MONTH 0

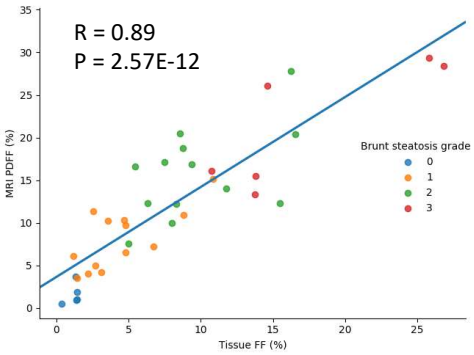
PDFF (Fat): 16.5% (*normal range: <5.6%*)
T2* (Iron): 14.5ms (*normal range: >12.5ms*)
cT1 (Fibroinflammation): 878.4ms (*reference range:* 633-794ms)



MONTH 6

PDFF: 2.4%
T2*: 16.2ms
cT1: 738.3ms

Metrics that are sensitive to small changes in steatosis



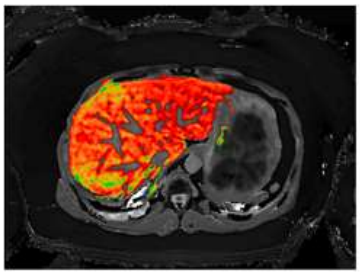
Tissue fat fraction (Digital Pathology) vs MRI PDFF

Courtesy Dr. Ben Irving, Prof. Michael Brady, Perspectum Diagnostics

Case Study: NASH

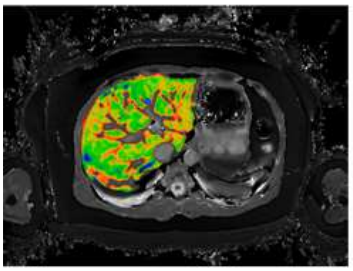
Patient before and after lifestyle modification intervention

NASH Patient – August 2017
(Pre-lifestyle intervention)



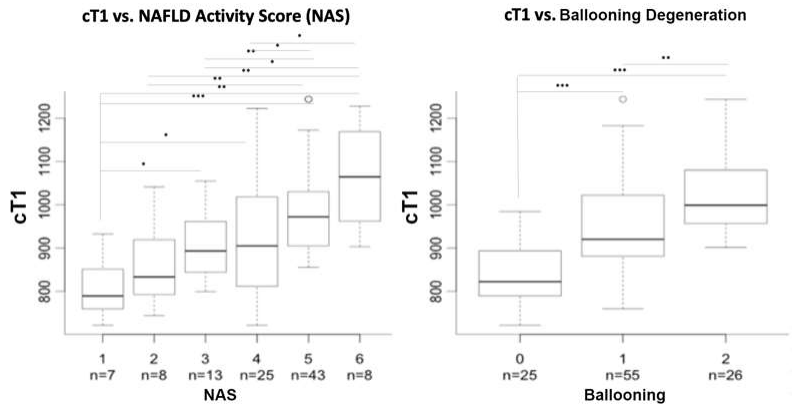
cT1: 1045ms
Reference range: 633-794ms

NASH Patient – October 2017
(Post-lifestyle intervention)



cT1: 855ms
Reference range: 633-794ms

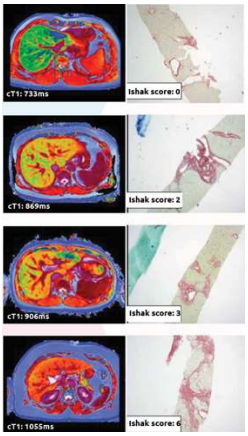
Pooled analysis from 106 biopsy-confirmed NAFLD patients from two studies in 3 UK hospitals

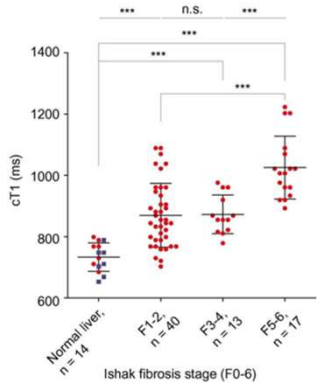


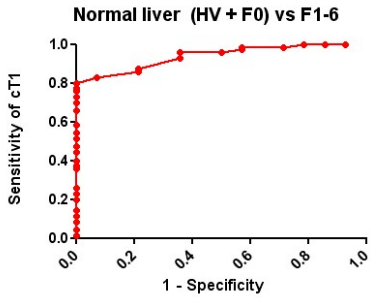
Wilman et al. (2017). J Hepatol 6(S1):242-243

cT1 to Stage Chronic Liver Disease

cT1 correlates with fibrosis in liver clinic patients







AUROC is 0·94 (95% CI 0·89 – 0·99) to detect **any disease** in a general population (viral hepatitis n=31, FLD n=31, other n=17); **sensitivity 86%, specificity 93% .**

The first non-invasive test to clearly identify even early fibrosis

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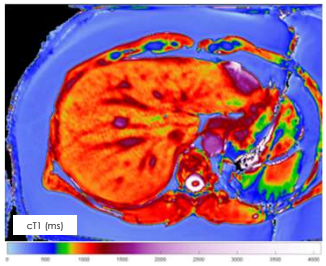
Banerjee et al. (2014) J Hepatol 60(1): 69–77

Case Study: NAFLD

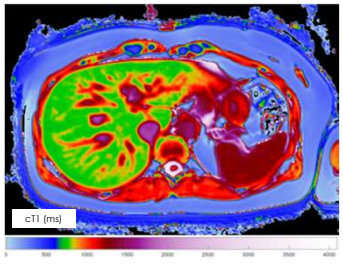
44 y/o obese female patient following bariatric surgery



Pre-operative: March 2011

PDFF: 20.4%
cT1: 996.1ms

- BMI = 34.3: **Liver biopsy showed 90% of hepatocytes had lipid inclusions, inflammation, Ishak score = 3 (Metavir 2), pericellular fibrosis.**



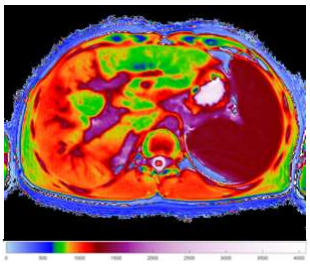
Post-operative: March 2012

PDFF: 1.7%
cT1: 783.5ms

- BMI = 24.4: **No clinical indication to support a follow-up biopsy.**

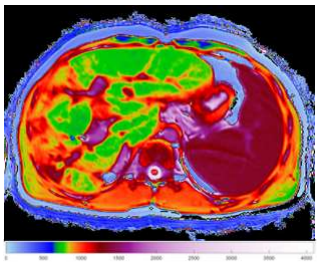
Case Study: PSC/AIH Overlap

22 y/o male, with PSC and AIH overlap syndrome; liver transplant initially planned based on biopsy; underwent steroid treatment following Liver*MultiScan*



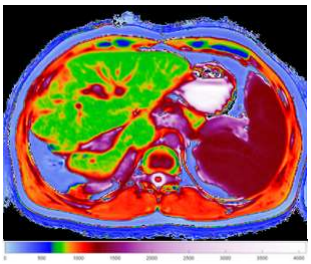
Pre-treatment: February 2012

cT1 Median: 960 ms
cT1 IQR: 193 ms



Post-treatment: October 2012

cT1 Median: 846 ms
cT1 IQR: 141 ms



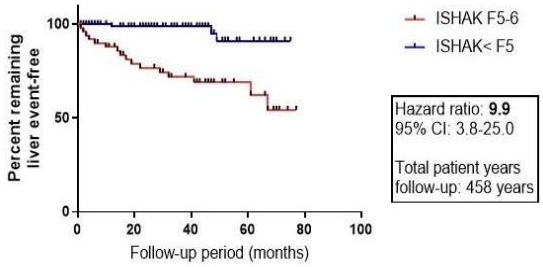
Post-treatment: October 2013

cT1 Median: 824 ms
cT1 IQR: 62 ms

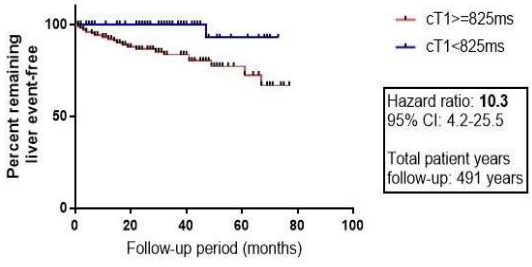
cT1 and biopsy correlate with clinical outcomes

A prognostic biomarker in CLD patients from varying etiologies

Kaplan-Meier curve for liver-related event free survival with patients stratified according to ISHAK score
(n=150, median follow-up period: 35 months)



Kaplan-Meier curve for liver-related event free survival with patients stratified according to cT1
(n=166, median follow-up period: 35 months)

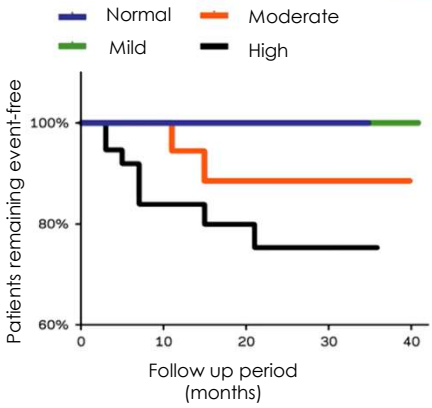


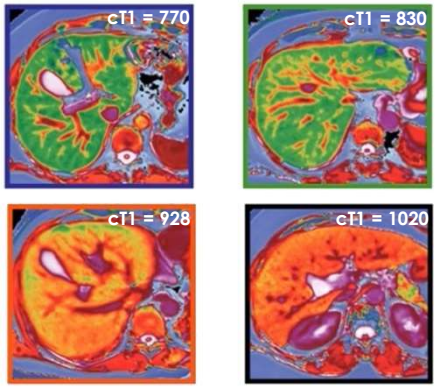
cT1 is a prognostic tool for the clinician.
Neither liver iron nor fat alone predicted clinical outcomes.

Jayaswal et al. AASLD, 2018.

Prospectively, cT1 Predicts Clinical Outcomes

100% NPV to rule out liver related outcomes





Events: Ascites (4), Encephalopathy (3), Liver-related death (2), HCC (1)

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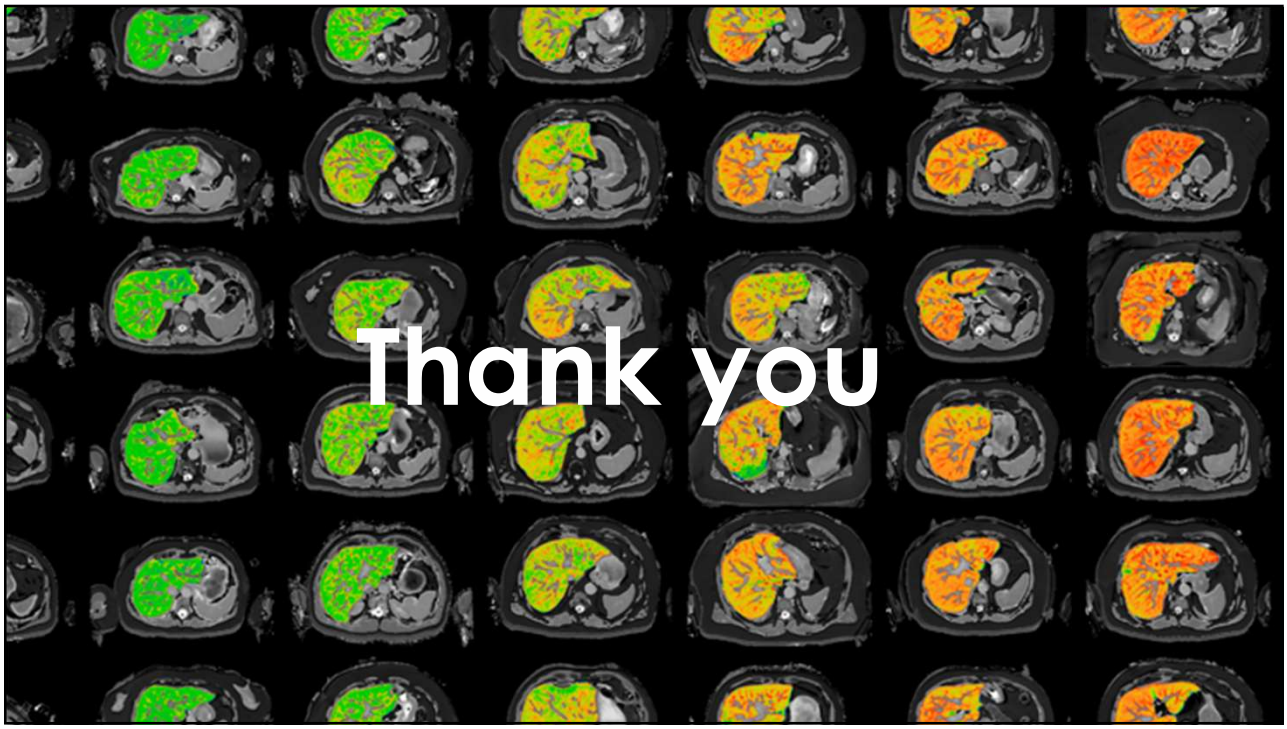
Adapted from Pavlides et al. (2016) J Hepatol. 64(2):308–315

MP-MRI holds the key to addressing a looming epidemic

- Identification of patients at risk
- Staging of disease
- Prognostic information
- Non-invasive monitoring of liver health



AMERICAN RADIOLOGY ASSOCIATES
Your Health Is Our Vision

Quantitative MRI Imaging for Memory Loss

BEN WHITE, MD
AMERICAN RADIOLOGY ASSOCIATES, NEURORADIOLOGY DIVISION
ADJUNCT ASSISTANT PROFESSOR, TEXAS A&M UNIVERSITY COLLEGE OF MEDICINE

Full credit to my colleague Joe Parkey, MD for creating the initial version of this talk

Causes of Memory Loss

- Normal aging
- Medications
- Alcohol
- Depression
- Anxiety
- Sleep Problems
- Alzheimer's disease
- Other Neurodegenerative (ND) Disorders

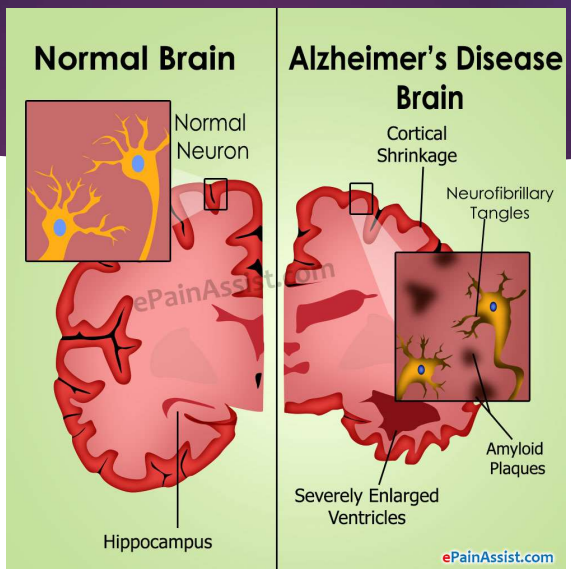
Causes of Memory Loss

- Normal aging
- Medications
- Alcohol
- Depression
- Anxiety
- Sleep Problems

Brain Atrophy: (Generally) Mild

- Alzheimer's disease
- Other ND Disorders

Brain Atrophy: Excessive



Most Common Types of Dementia

MR findings in Dementia

	AD	VaD	FTLD	Lewi*
Hippocampal atrophy	+++	++	++	-
Temporal atrophy	++	+	+++	-
Frontal atrophy	-	+	+++	-
Parietal atrophy	++	+	-	-
Lacunes	-	+++	-	-
WML's	-	+++	-	-
Strategic infarcts	-	+++	-	-

http://www.radiologyassistant.nl/en/p43dbf6d16f98d/dementia-role-of-mri.html

Percentage of Dementia Patients

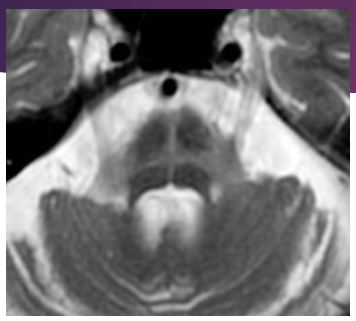
- Alzheimer's disease (50% to 70% of patients)
- Vascular dementia (25%)
- Dementia with Lewy Bodies (20-25%)
- Frontotemporal dementia(s) (10-20%)

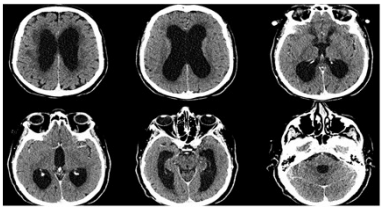
- NPH
- Parkinson's dementia
- MS, HIV
- Rarer:
  - CJD, PSP, MSA, CBD, HD, WKS

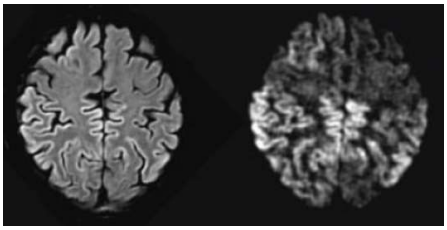
Role of Imaging in Dementia

- Lesion & reversibility detection
- Qualitative MRI
  - Subjective, unreliable
  - Can sometimes detect reversible/treatable cases as well as some dementia etiologies
  - Poor at differentiating senescent changes from AD
- Nuclear Medicine
  - FDG PET, Amyloid PET, DATscan
    - Limited availability
    - $$$$
    - Insurance

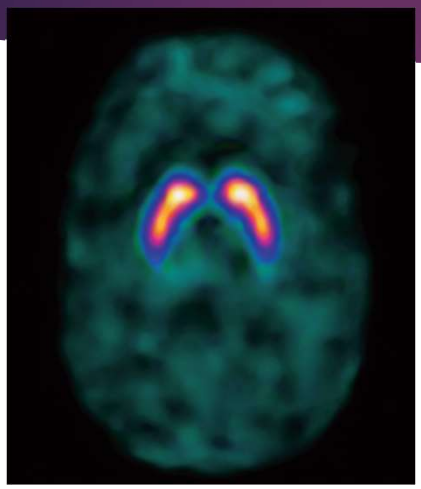
Some pathologies

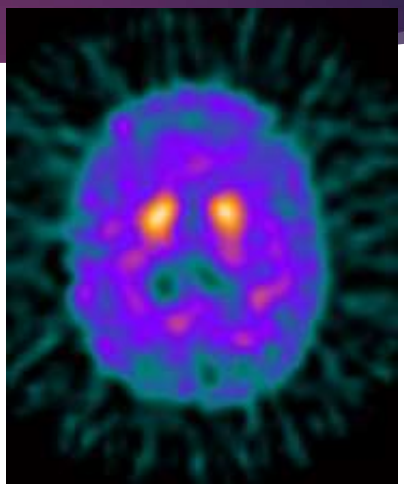






DAT Scans (I-123 Ioflupane)

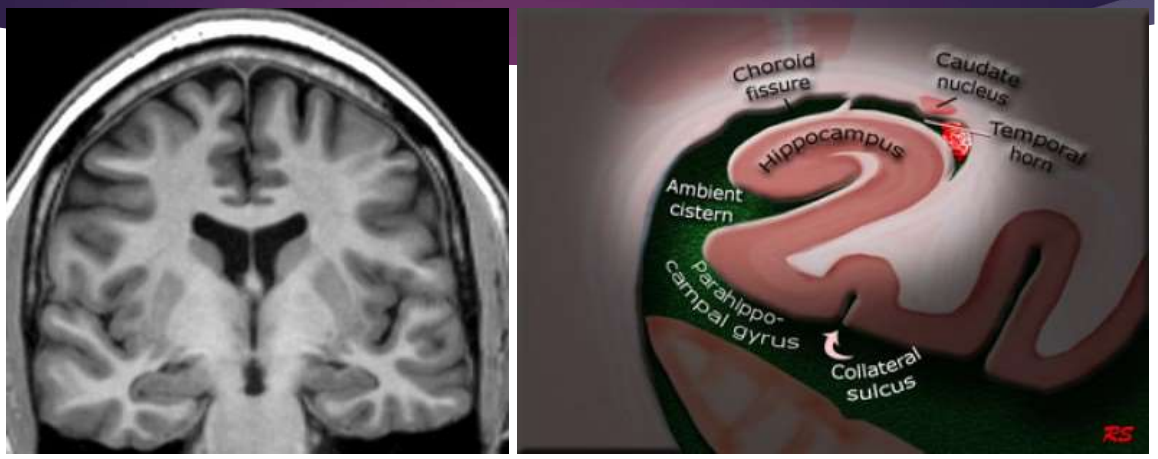




Aging versus Alzheimer's?

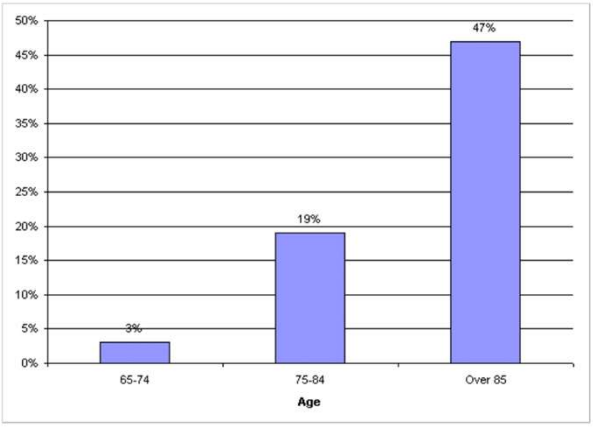
BUT…

Anatomy: Hippocampus



http://www.radiologyassistant.nl/en/p43dbf6d16f98d/dementia-role-of-mri.html

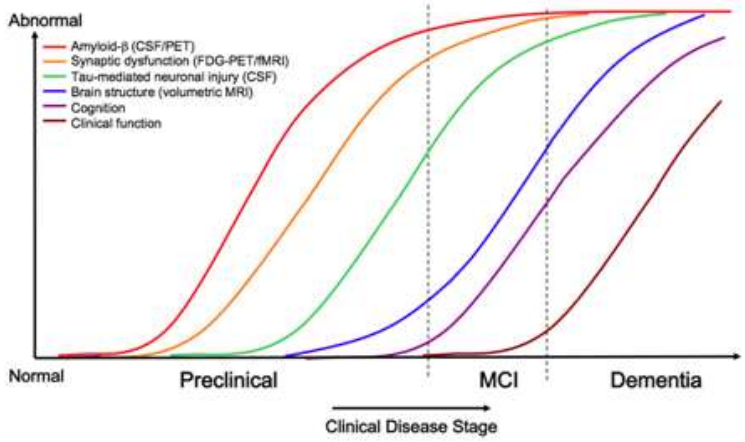
Alzheimer's disease by age



AD becomes more common and atrophy are both more common with age

Alzheimers.net (2015).

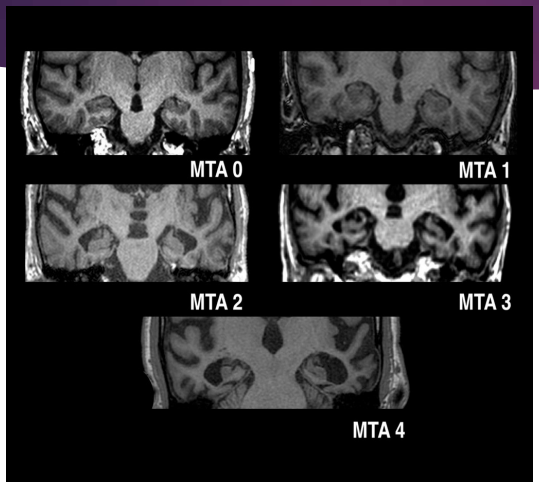
Progression of AD



And can we find it earlier in a reliable way that may help guide treatment?

Jack et al. Hypothetical model of dynamic biomarkers. Lacet Neurol. Jan 2010

Qualitative MRI: Mesial Temporal Atrophy Visual Scoring



Based on:

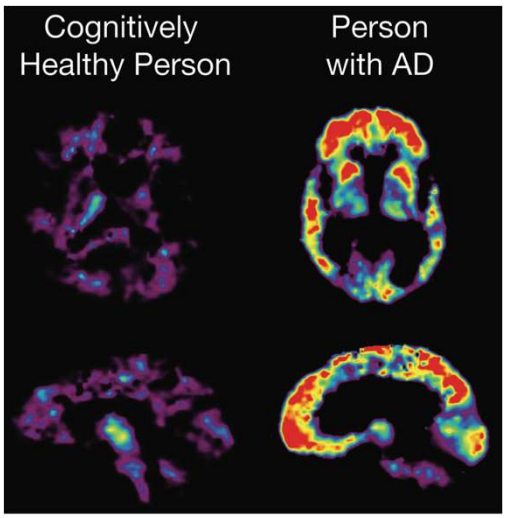
- width of the choroid fissure
- width of the temporal horn of the lateral ventricle
- height of the hippocampus

<75 years: >= 2 is abnormal

>=75 year: >=3 is abnormal

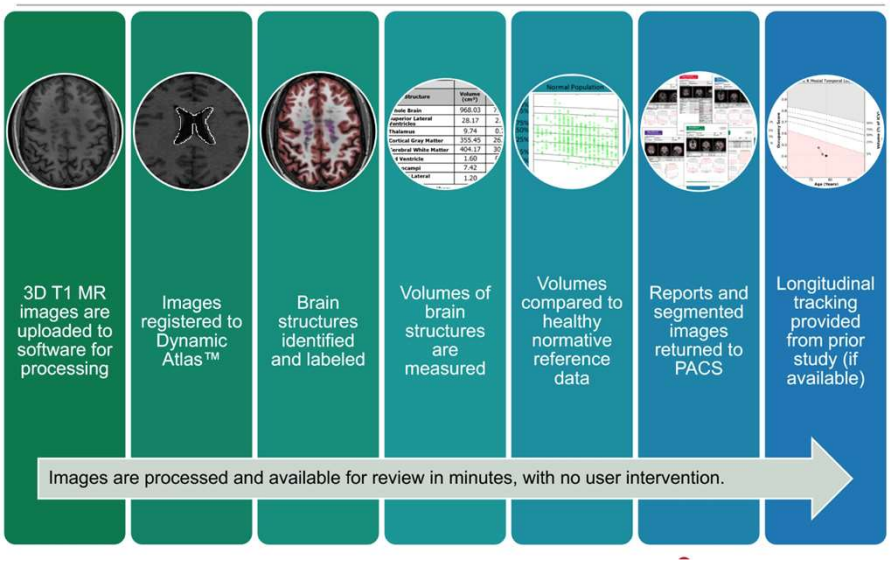
Dr Bruno Di Muzio, Radiopaedia.org, rID: 42027

Amyloid PET Imaging



Super expensive, one trick pony

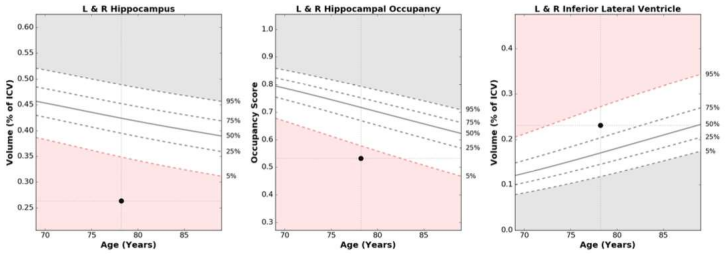
How NeuroQuant Works



MORPHOMETRY RESULTS

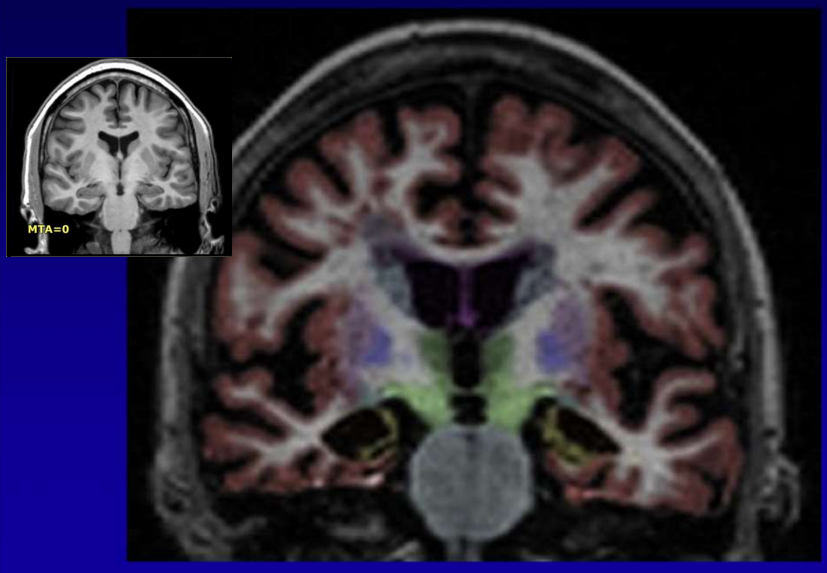
Hippocampal Occupancy Score (HOC)		0.53	
Brain Structure	**Volume (cm³)**	**% of ICV (5%-95% Normative Percentile)**	**Normative Percentile**
Hippocampi	3.86	0.26 (0.35 - 0.49)	1
Superior Lateral Ventricles	41.89	2.86 (1.52 - 4.64)	64
Inferior Lateral Ventricles	3.38	0.23 (0.12 - 0.27)	87

AGE-MATCHED REFERENCE CHARTS



Translating to Clinical Practice

Case: 06/08/2010



Translating to Clinical Practice
Case: 06/08/2010

Entry Date
6/8/2010

Result Narrative

HISTORY:
Alzheimer's disease, volumetric.

COMPARISON STUDIES:
None.

PULSE SEQUENCES:
MR imaging was performed on a 1.5 Tesla superconducting magnet using T2, FLAIR, T1, gradient-echo, and diffusion weighted pulse sequences.

FINDINGS:
Brain volume is normal for age. Ventricles are normal in size and position. The cerebral hemispheres, deep nuclei, brain stem, and cerebellum are normally formed. There are several high T2/FLAIR signal intensities seen in the periventricular and deep white matter as well as the pons, most consistent with microvascular ischemic/hypertensive changes. There is no evidence of acute infarct. No old hemorrhage seen. There is a small amount fluid seen within the right temporomandibular joint, likely degenerative change. Status post right cataract surgery.

IMPRESSION:
Microvascular ischemic/hypertensive changes.

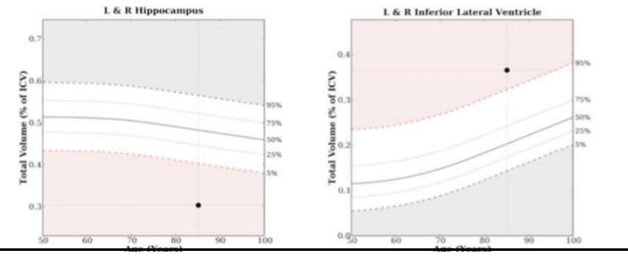
I have reviewed the image(s) and agree with the resident's interpretation..

Translating to Clinical Practice
Case: 06/08/2010

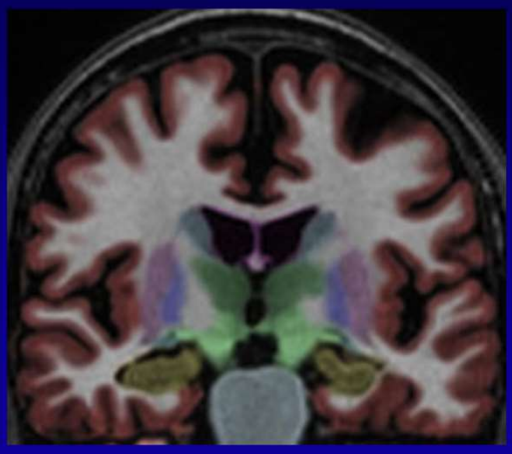
MORPHOMETRY RESULTS

Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	4.24	0.30 (0.40-0.57)	< 1
Lateral Ventricles	45.77	3.28 (1.57-4.65)	70.97
Inferior Lateral Ventricles	5.11	0.37 (0.14-0.32)	98.71

AGE-MATCHED REFERENCE CHARTS*



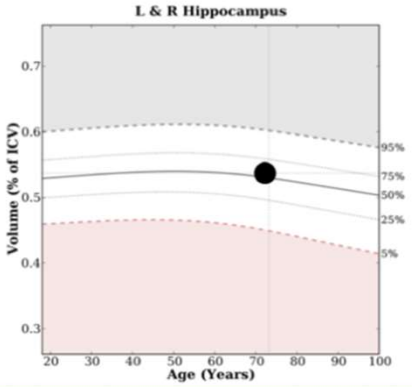
Memory loss

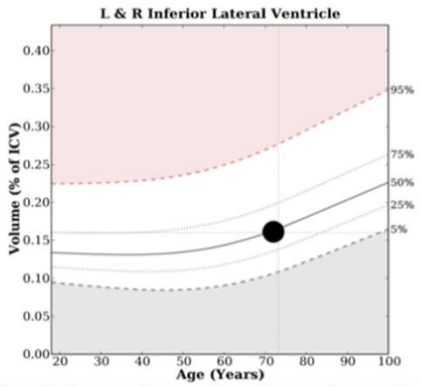


Interpretation Examples

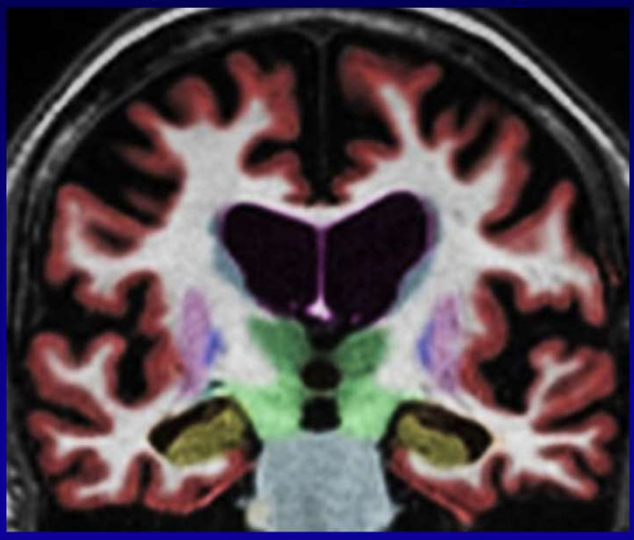
Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	8.64	0.54 (0.45-0.60)	56
Lateral Ventricles	33.32	2.07 (0.98-3.65)	55
Inferior Lateral Ventricles	2.57	0.16 (0.11-0.28)	45

AGE-MATCHED REFERENCE CHARTS*





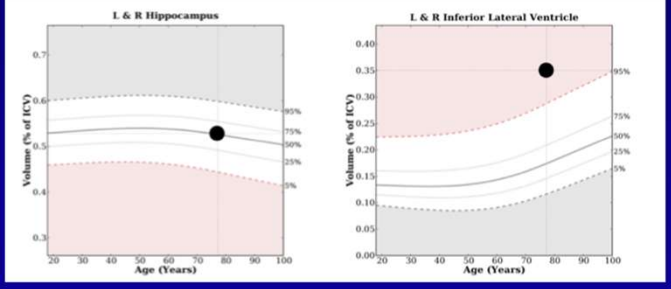
Interpretation Examples



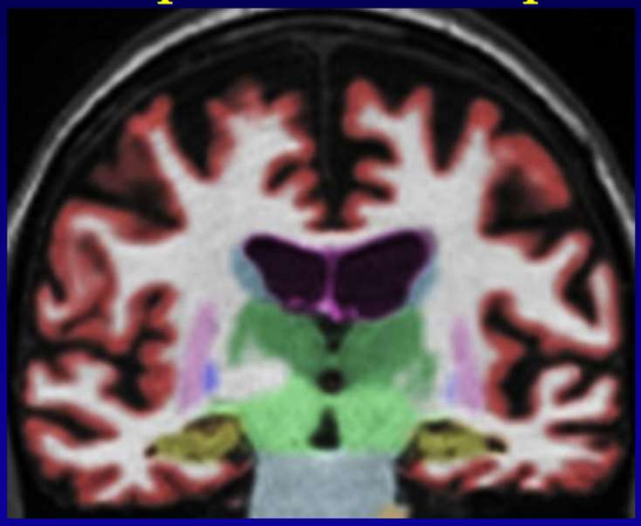
Interpretation Examples

Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	7.81	0.53 (0.44-0.60)	52
Lateral Ventricles	60.13	4.07 (1.15-3.90)	> 99
Inferior Lateral Ventricles	5.18	0.35 (0.12-0.29)	> 99

AGE-MATCHED REFERENCE CHARTS*



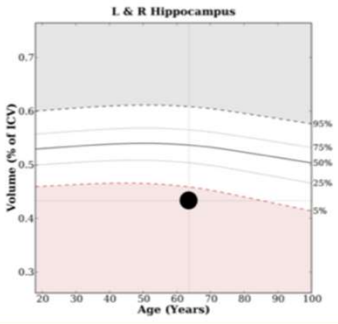
Interpretation Examples

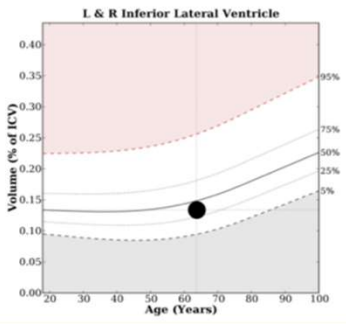


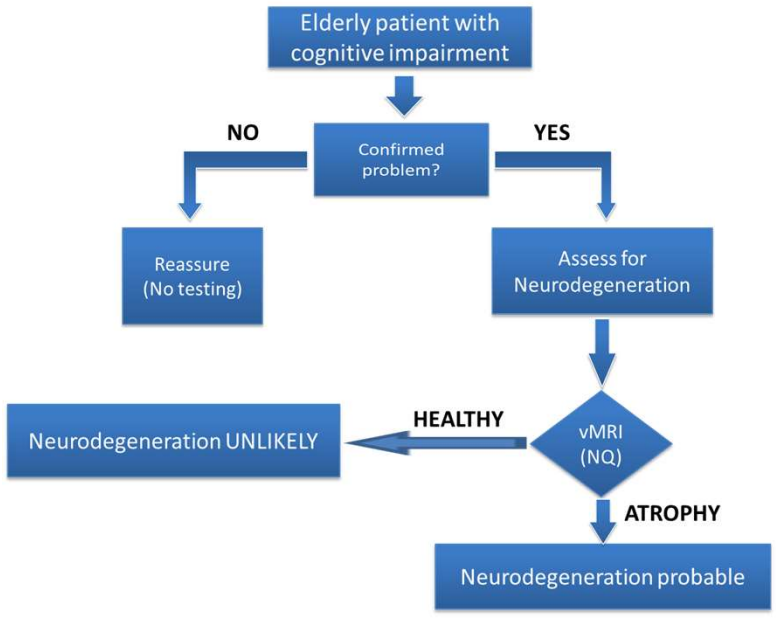
Interpretation Examples

Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	7.33	0.43 (0.46-0.61)	< 1
Lateral Ventricles	36.70	2.17 (0.62-3.11)	76
Inferior Lateral Ventricles	2.26	0.13 (0.09-0.26)	36

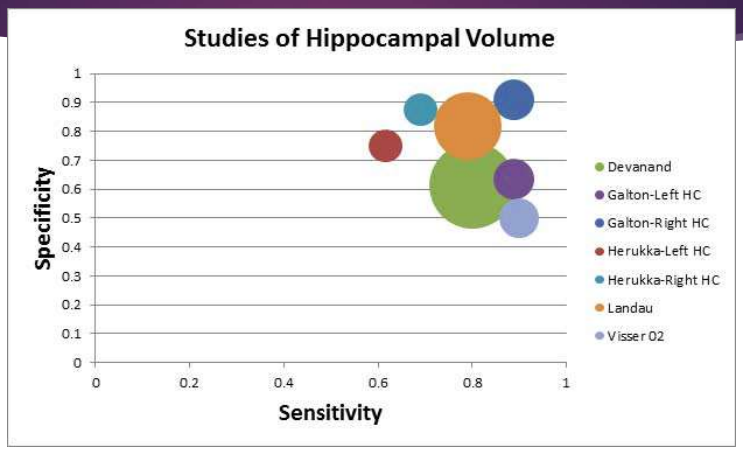
AGE-MATCHED REFERENCE CHARTS*







Statistics of NeuroQuant



Example Centers Using Neuroquant

- Johns Hopkins Medical Institution
- Cleveland Clinic
- Yale Hospital
- Duke University MC Center
- UCSD
- UC Irvine
- Cedars-Sinai Medical Center
- Hoag Memorial Hospital
- Vanderbilt University Medical Center
- George Washington University Medical Center
- Medical University of South Carolina
- University of Kansas School of Medicine
- Emory University Hospital
- University of Virginia Medical Center
- University of Washington Medical Center
- University of Louisville Medical Center
- Virginia Mason Medical Center, Seattle WA
- University of Texas Southwestern Medical Center

Prediction of MCI outcome

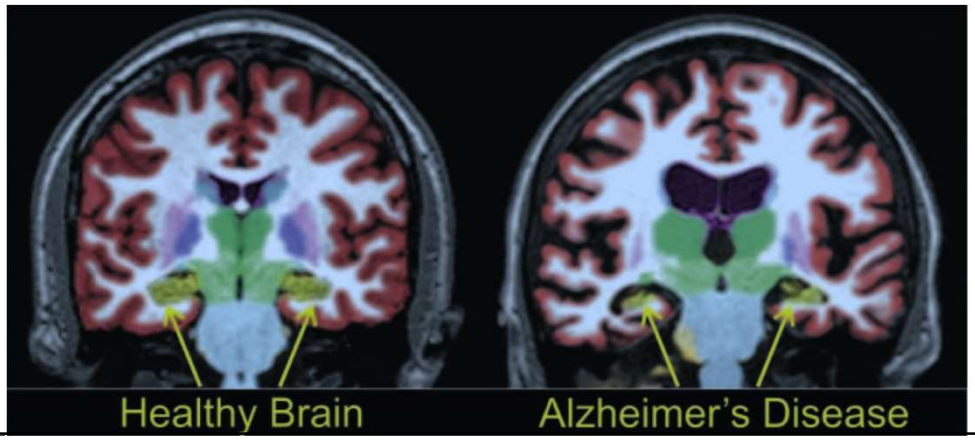
- The hazard ratio is greater than any other biomarker, including CSF amyloid or Tau with a 4X risk of converting to dementia in the next 3 years if you satisfy the vMRI cutoff
- 29X risk of converting if you satisfy both the vMRI cutoff and the AVLT (Auditory Verbal Learning Test) memory test cutoff

NeuroQuant in Dementia Conclusions:

- Provides direct supportive evidence of tissue damage and pathology in neurodegenerative disease
- "Informs, rather than determines, diagnosis."
- Data directly available to clinician and helps shape overall clinical impression.
  - Trigger additional workup for curable etiologies when data are not suggestive of neurodegeneration
  - Accurate and early diagnosis guides clinical decisions
  - Education and management for the patient, caregiver, and family
- Quantitative assessment of asymmetry and change over time.

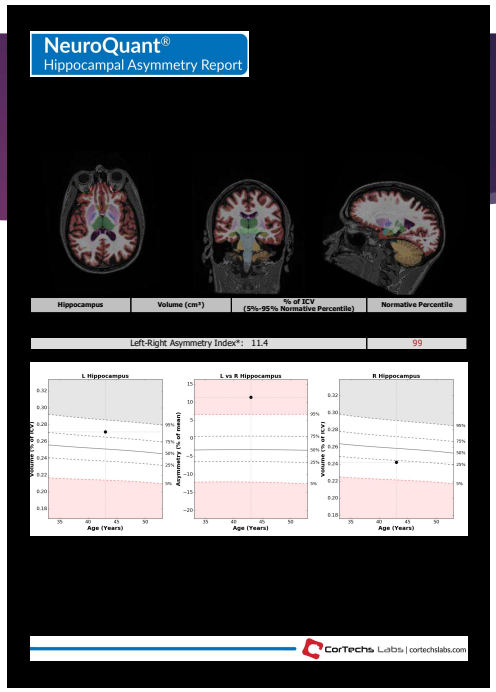
Conclusion

- Quantitative structural imaging
  - Trigger/justify additional workup
  - Tissue damage
  - Accurate and early diagnosis of ND



Several other use cases

Example:
Hippocampal Asymmetry for epilepsy evaluation



Comprehensive Clinical Assessments

Five volumetric reports provide analysis for a broad range of brain structures and clinical indications

Color					
Report	Age Related Atrophy	Hippocampal Volume Asymmetry	Multi Structure Atrophy	Triage Brain Atrophy	Brain Development
Clinical Indication	▪ Age associated neurodegenerative conditions ▪ Alzheimer's disease ▪ Frontotemporal dementia ▪ Dementia with Lewy bodies ▪ Hippocampal sclerosis	▪ Temporal lobe epilepsy ▪ Unilateral degenerative conditions	▪ Multiple Sclerosis ▪ Age associated neurodegenerative conditions	▪ Age associated neurodegenerative conditions ▪ Wide assessment of atrophy in brain regions and structures	▪ Brain development in children ages 3 and up

Questions?

THANK YOU