



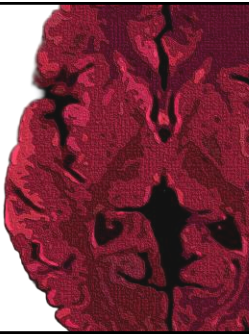
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Neuroimaging in Alzheimer's Disease and Related Dementias

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Department of Radiology

Thank you to Drs. Asthana, Johnson, Carlsson, Bendlin, Rowley...



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DISCLOSURES

No conflict of interest to disclose.

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EDUCATIONAL OBJECTIVES

- ☐ Contextualize the recent shift in Alzheimer's disease therapeutics and how this impacts imaging
- ☐ Master the imaging-based patient diagnosis and selection criteria
- ☐ Review both standard and up-and-coming ADRD imaging methods
- ☐ Interpret imaging biomarkers of therapeutic response
- ☐ Detect, classify, and grade amyloid-related imaging abnormalities

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INTRODUCTION

Alzheimer's disease has entered a new era – and so have radiologists.

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ALZHEIMER'S DISEASE (AD) AT SCALE

Irreversible and progressive neurodegenerative disorder

- Continuum in the clinical manifestations with multiple stages
- Symptoms include cognitive decline, memory loss, and behavioral changes
- Sixth cause of death in the US with mortality within 5-12 after symptom onset

Most common cause of dementia

- 55 million people living with dementia worldwide – 60 to 70% due to AD
- About 1 in 9 individuals over 65 diagnosed with AD
- Overall prevalence expected to triple by 2050 due to aging population

High societal and economic impacts

- Total costs expected to increase from \$360 billion to \$1 trillion in 2050



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PATHOLOGICAL HALLMARKS

A β PROTEINOPATHY

- **Amyloid-beta (A β)** is a polypeptide that aggregates into extracellular plaques
- The pathological mechanism involves increased production and impaired clearance
- A β accumulation begins two decades before cognitive impairment, defining prodromal AD

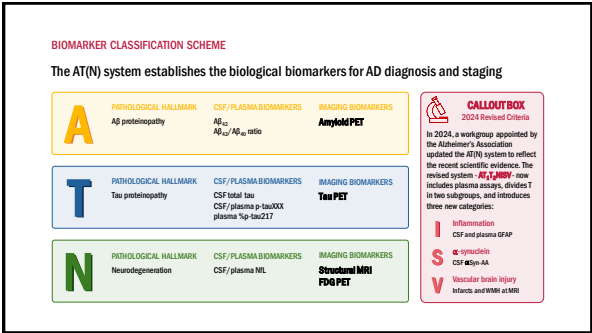
TAU PROTEINOPATHY

- **Hyperphosphorylated tau proteins** accumulate into neurofibrillary tangles (NFTs)
- NFTs accumulate inside the neurons and cause neurodegeneration via several pathways
- Tau accumulation follows a stereotypical spatial pattern defined by Braak stages

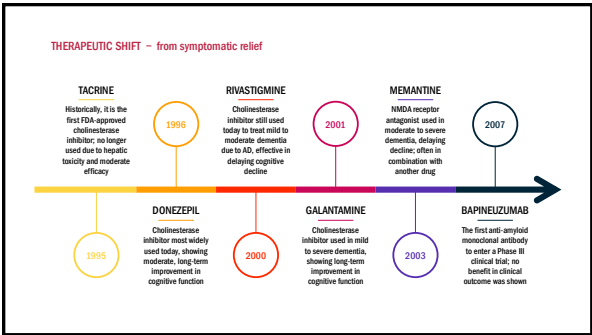
NEURODEGENERATION

- **Neurodegeneration** is directly correlated with hyperphosphorylated tau burden
- A β also plays a role in neurodegeneration through oxidative stress and microglial activation
- Pathological changes includes synaptic dysfunction, neuronal death, and inflammation

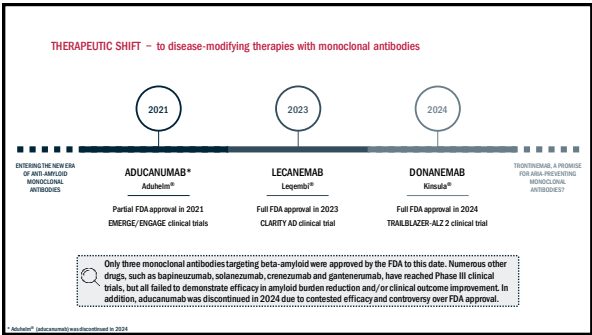
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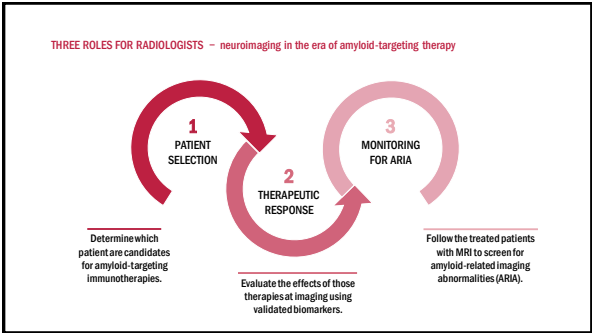
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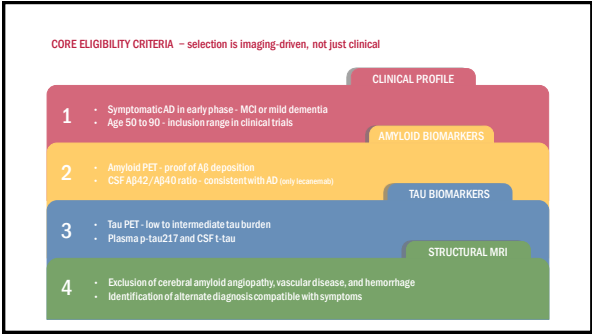


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PATIENT SELECTION

Who should receive treatment?

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CLINICAL PROFILE

Where Selection Begins

→ Only patients who are early on the disease continuum are eligible

Early clinical stage of AD (as defined by the NIA-AA core clinical criteria)

- Diagnosis of MCI or mild dementia
- Subjective and slowly progressive decline in memory

Age 50 to 90 years old (inclusion range varies between clinical trials)

Composite measures for cognitive performance

ADUCANUMAB	LECANEMAB	DONANEMAB
MMSE24-30 Global CDR 0.5 RBANS GMI <85	MMSE22-30 Global CDR 0.5 to 1.0 CDR Memory Test <2.0 MMSE-AMS <150 below age-adjusted mean	MMSE20-28

*Alphabet soup defined at the end of this exhibit

Non-amnesic variants of AD

Beyond the typical amnesic syndrome observed in AD and characterized by impairment of episodic memory, about 30% of AD patients present clinically with a non-amnesic variant of AD.

Those include posterior-predominant cortical atrophy (occipital deficits), logopenic variant of primary progressive aphasia (speech impairment), corticobasal syndrome (movement disorder), dysexecutive AD, and behavioral variant of AD.

Clinical trials on anti-amyloid therapies enrolled predominantly participants with the amnesic variant of AD. This led to an underrepresentation of non-amnesic variants of AD, creating a gap in knowledge on the benefits and risks of monoclonal antibodies for these patients.

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AMYLOID BIOMARKERS

Confirming the Target

→ Evidence of A β plaque deposition is a requirement for treatment

Amyloid PET

- Measurement of amyloid plaque burden
- Correlation with longitudinal cognitive decline
- A β -negativity on PET reduces the likelihood of AD
- Plaque burden higher in amnesic variant of AD

What radiotracers do we use?

- ¹¹C-Pittsburgh Compound B – known as PIB
→ Short half-life (~20 min), on-site cyclotron required
- ¹⁸F-based tracers – florbetapir, flutemetamol and florbetaben
→ Longer half-life, transport between sites possible

A β positivity outside of AD

Positivity for A β on amyloid PET scans is also observed outside of the diagnosis of AD.

In cognitively unimpaired older adults, high rates of A β positivity are observed. By the ninth decade, more than 40% of individuals without cognitive decline are A β + on amyloid PET.

Other neurodegenerative disorders may be associated with amyloid positivity as well. For instance, α -synucleinopathies show amyloid positivity rates up to 56%.

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AMYLOID BIOMARKERS

Confirming the Target

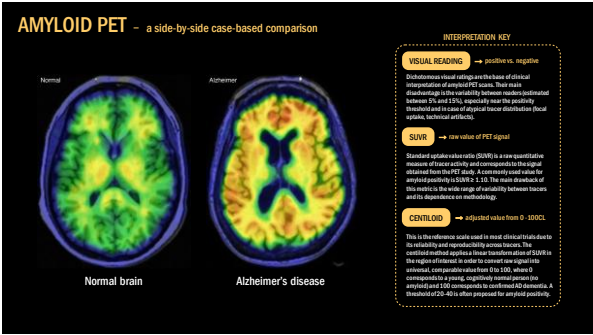
→ What does A β plaque deposition mean in a cognitively normal person?

Amyloid PET

- May indicate that individuals with greater cognitive or neuronal reserve may tolerate substantial A β burden without overt impairment until much later in life
- There is additional evidence that the clinical course of non-demented older individuals is affected by their A β status, with a higher rate of memory decline in amyloid-positive individuals
- Amyloid deposition can precede the clinical onset of dementia by 15–20 years
 - Positivity in the cognitively unimpaired seems to correspond to a preclinical phase of AD

POTENTIAL PREDICTOR This supports the potential inclusion of A β into predictive models of disease progression

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TAU BIOMARKERS

Scaling the Downstream Neuropathological Changes

→ **Tau burden could be an important biomarker for individualized treatment**

Tau PET (only used as inclusion criteria in donanemab clinical trial)

- Burden and spatial distribution of tau proteins
- Role in adjusting the therapeutic window to downstream neuropathology
- Greater benefit from treatment in patients with low-to-intermediate tau burden
- Not a strict eligibility criteria, but good predictor of clinical response to treatment
- Limited accessibility and uncertain reimbursement status

What radiotracers do we use?

- ¹⁸F-flortaucipir → Excellent selectivity for AD tau pathology versus non-AD tauopathies
- New-generation tracers (such as ¹⁸F-MK-6240) → Less off-target binding, greater dynamic range of signal

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TAU BIOMARKERS

Scaling the Downstream Neuropathological Changes

→ **Tau PET signal and distribution pattern correlates with neuropathology**

Braak stages – defined at autopsy

- Spatiotemporal patterns of NFTs distribution
- More dynamic AD stage marker than Aβ
- Braak stage ↔ tau burden ↔ disease severity
 - Braak stages I and II – Mostly asymptomatic
 - Braak stages III and IV – Mild cognitive impairment
 - Braak stages V and VI – Dementia

Correlation between Braak stages and tau PET signal

Tau PET is more sensitive to later Braak stages (V and VI) and less sensitive to earlier Braak stages (I through IV). Hence, the absence of tau tracer binding does not exclude clinically relevant earlier stage of tau pathology.

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TAU BIOMARKERS

Scaling the Downstream Neuropathological Changes

→ Tau PET signal and distribution pattern correlates with neuropathology

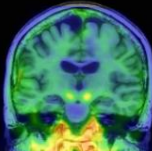
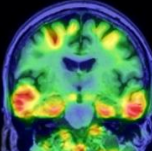
What is the impact of Tau positivity?

- There also seems to be an interaction between A β and tau pathologies
- PET studies showed a more substantial cognitive decline in a subgroup with evidence of A β and tau positivity
 - Because this risk was present in middle-aged adults in the preclinical phase of AD, *these findings suggest a potential role for tau imaging in the risk stratification of individuals within the amyloid-positive group*

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TAU PET

a side-by-side case-based comparison

Normal brain

Alzheimer's disease

INTERPRETATION KEY

VISUAL READING

The FDA approval of ¹⁸F flutemetamol is restricted to a binary visual interpretation (A β positive versus non-A β positive) only. More recently, efforts have been made to develop a refined visual interpretation that includes spatial extent of tau in addition to magnitude of tau signal. This more nuanced approach aims to better capture disease stage and predict cognitive decline (see BOLD stages).

QUANTIFICATION TOOLS

Quantitative measurement are used in research but have not yet been validated, with large gaps between SUVr readings and visual ratings. The Centiloid framework established a common metric, validated across tau tracers by quantifying binding magnitude within a standard reference mask. The inferior cerebellar cortex is generally used as a reference region for intensity normalization, as it shows the least involvement in tau spread.

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STRUCTURAL MRI

Screening for Risk

→ MRI is the safety filter that determines ineligibility and risk for complications

MRI-based exclusion criteria

T2WI/T2 FLAIR - Advanced small vessel disease - Severe WMH burden (grade Fazekas 3) - More than 2 lacunar infarcts - Prior large ischemic stroke	T2* GRE / SWI - Cerebral amyloid angiopathy (CAA) - More than 4 microbleeds - Any superficial siderosis - Prior intracranial macrohemorrhage
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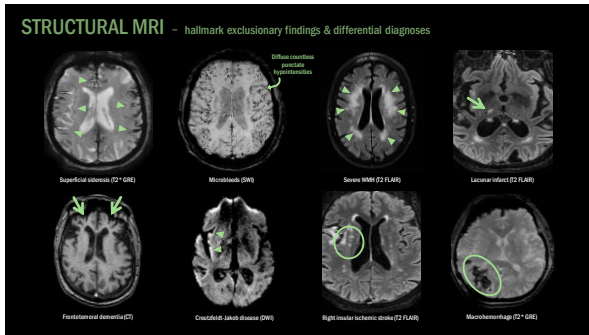
+ Baseline volumetric parameters

- Measurement of baseline whole brain, ventricular and hippocampal volumes

+ Rule out a potential alternate diagnosis

- Other neurodegenerative disease, space-occupying lesion, or other structural abnormalities

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Practical Role of Imaging in Dementia

Neuroimaging in the Clinical Diagnosis of Dementia: Observations from a Memory Disorders Clinic
Paul R. Borghesani, MD, PhD,† Sharme M. DeMers, MD,* Virek Manchanda, MD,‡
 Sumit Pruthi, MD,‡ David H. Lewis, MD,‡ and Soo Borison, MD*†*

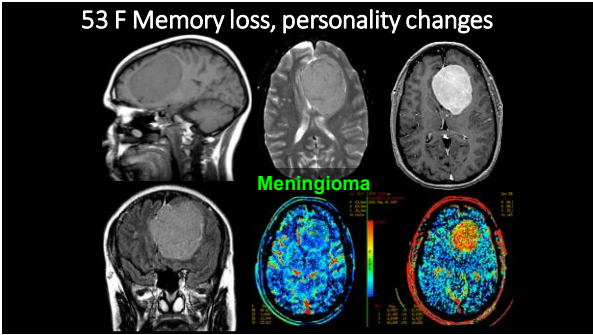
CONCLUSION: Overall, neuroimaging confirmed, clarified, or contradicted the initial clinical diagnosis in more than 80% of patients, whereas fewer than 20% had abnormal/not diagnostic patterns. Imaging suggested a complex dementia etiology in 21% of cases clinically thought to be caused by a single process, whereas 46% of complex clinical differential diagnoses appeared to reflect a single causal pattern. Further work is needed to determine whether refinement of clinical diagnoses using specialized neuroimaging improves clinical decision-making and patient outcomes. J Am Geriatr Soc 58:1453–1458, 2010.

Borghesani. J Am Geriatr Soc 58:1453–1458, 2010

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53 F Memory loss, personality changes

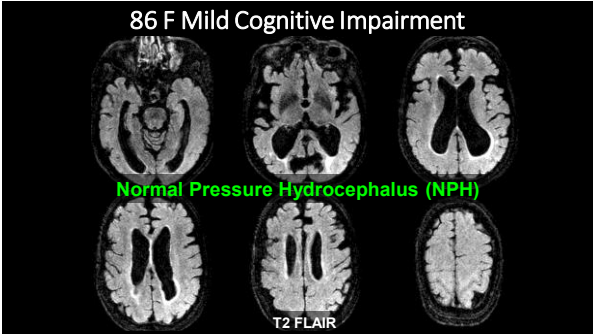
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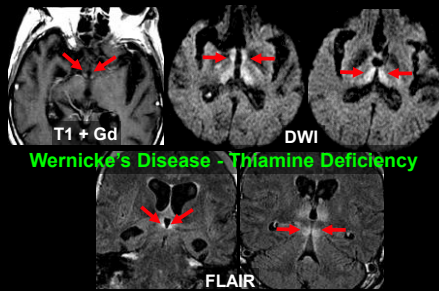


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73 M with memory loss

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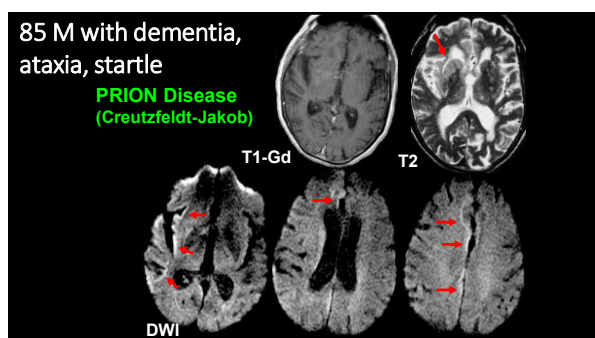
73 M with memory loss



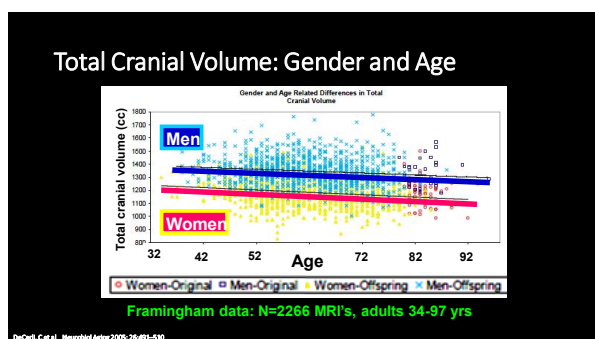
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85 M with dementia,
ataxia, startle

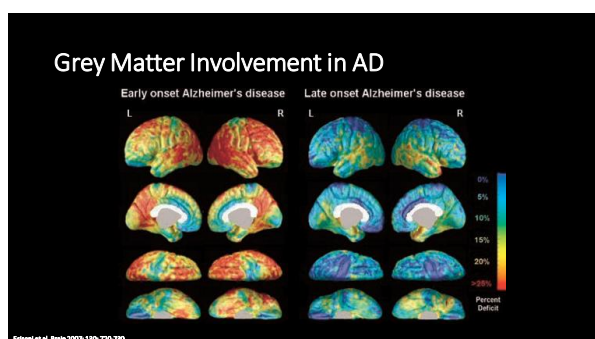
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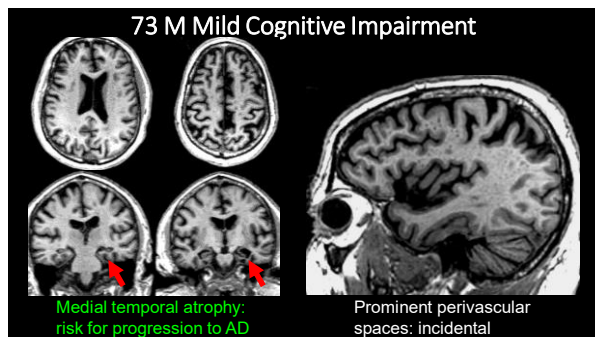
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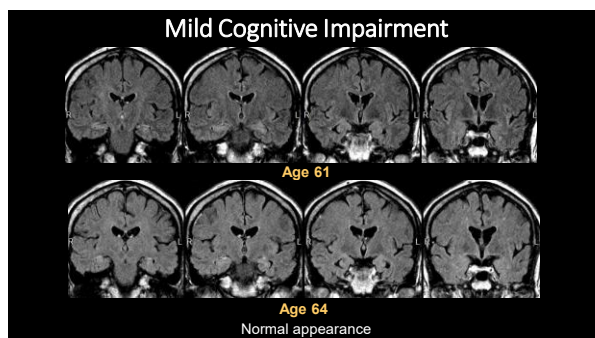
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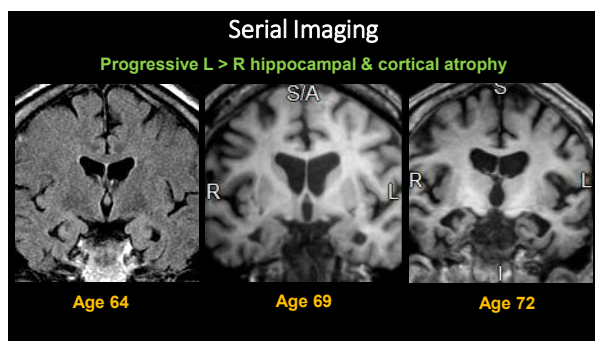
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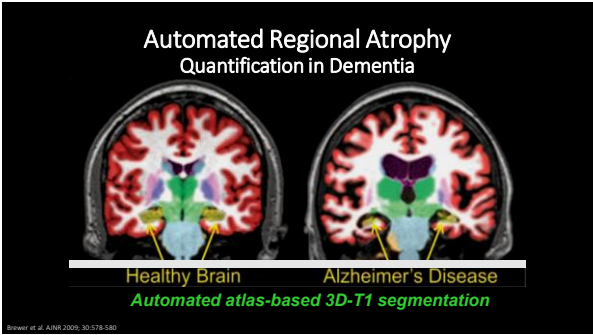
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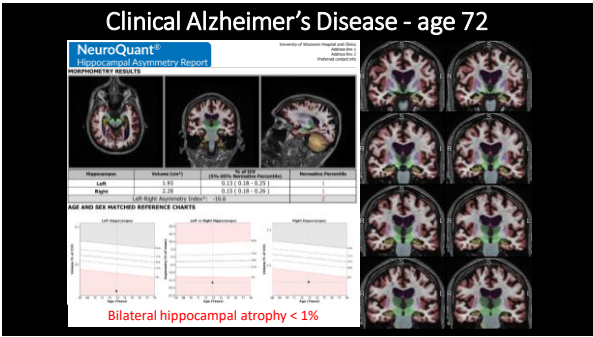
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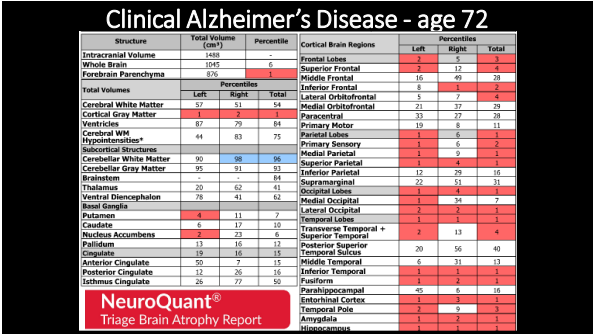
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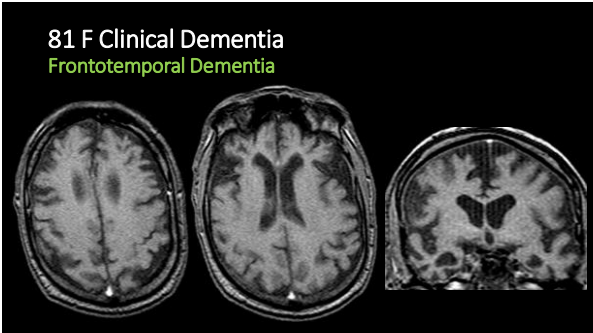
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STRUCTURAL MRI
Screening for Risk

→ MRI is the safety filter that determines ineligibility and risk for complications

MRI-based exclusion criteria

T2WI/T2 FLAIR	T2* GRE/SWI
Advanced small vessel disease - Severe WMH burden (grade Fazekas 3) - More than 2 lacunar infarcts Prior large ischemic stroke	Cerebral amyloid angiopathy (CAA) - More than 4 microbleeds - Any superficial siderosis Prior intracranial macrohemorrhage

+ **Baseline volumetric parameters**

- Measurement of baseline whole brain, ventricular and hippocampal volumes

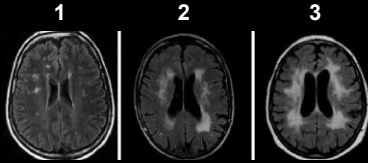
+ **Rule out a potential alternate diagnosis**

- Other neurodegenerative disease, space-occupying lesion, or other structural abnormalities

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White Matter Grading Scale
Fazekas

1 2 3

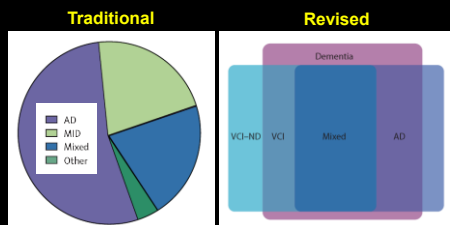


Periventricular white matter (PVWM)
0 = absent
1 = "caps" or pencil-thin lining
2 = smooth "halo"
3 = irregular periventricular signal extending into the deep white matter

Deep white matter (DWM)
0 = absent
1 = punctate foci
2 = beginning confluence
3 = large confluent areas

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Contribution of Vascular Disease to Dementia



Moorhouse, P. *Lancet Neurol* 2008; 7: 346-55

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White Matter Hyperintensity Risk Factors: Stroke Risk Profile

Stroke Risk Profile Predicts White Matter Hyperintensity Volume The Framingham Study

Tom Jernsekalath, MD, Philip A. Wolf, MD, Alexa Beiser, PhD, Joseph Massaro, PhD,
Jadva Seshadri, MD, Ralph B. D'Agostino, PhD, Charles DeCarli, MD

Background and Purpose—Previous studies of cardiovascular risk factors and white matter hyperintensity (WMH) on brain MRI have been limited by the failure to exclude symptomatic cerebrovascular disease and dementia or by the use of semiquantitative rather than quantitative methods to measure WMH volume (WMHV). We examined the relationship between Framingham Stroke Risk Profile (FSRP) and WMHV measured quantitatively as a stroke and dementia-free subset of the Framingham Offspring Cohort.

Methods—Brain MRI was performed in 1414 members of the Framingham Offspring Cohort. Pixel-based quantitative measures of WMHV corrected for head size were obtained using a semiautomated algorithm. WMHV was not normally distributed and therefore was log-transformed (LWMHV). The FSRP and its component risk factors assessed a mean of 7.5 years before MRI were related to both continuous measures of LWMHV and to the presence of large volumes of LWMHV (LWMHV-large). All analyses were adjusted for age and sex.

Results—FSRP was strongly associated with LWMHV and LWMHV-large. Age, smoking, history of cardiovascular disease, hypertension, and left ventricular hypertrophy by electrocardiogram were all significantly related to LWMHV or LWMHV-large.

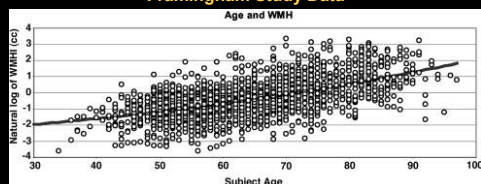
Conclusions—FSRP and several cardiovascular risk factors were related to both WMHV measured continuously and to a categorical designation of large volumes of WMH. These findings provide strong evidence of a vascular basis for WMH. (*Stroke*. 2004;35:1857-1863.)

Jernsekalath et al. *Stroke* 2004; 35:1857-1863

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WMH volume versus age

Framingham Study Data

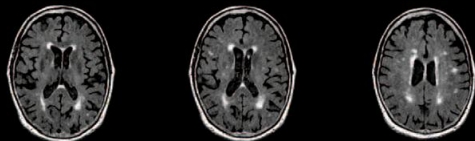


N=1330, stroke-free and dementia-free

Agawad et al. *Stroke* 2004;35:1605-1613

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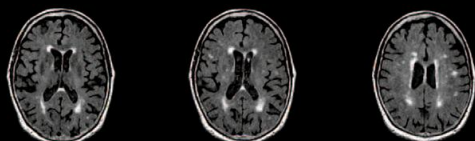
Are all WMHs the same?



- Deep white matter/subcortical: chronic small vessel ischemic
- Periventricular: relates to a combination of demyelination, ependymitis granularis, and subependymal gliosis, less closely tied with ischemia

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Are all WMHs the same?

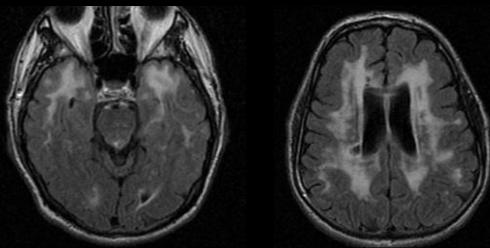


- Multiple types of pathology are bright on T2
 - Ischemia / gliosis
 - Damage to small blood vessel walls
 - Breaches of the barrier between the cerebrospinal fluid and the brain
 - Loss and deformation of the myelin sheath

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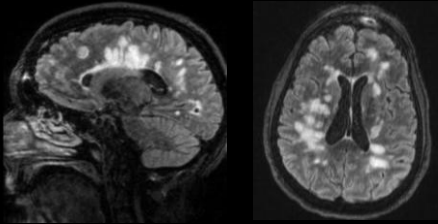
CADASIL Syndrome:

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy



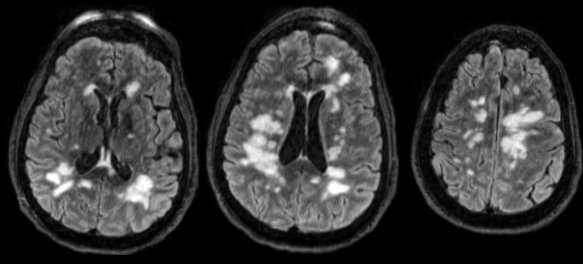
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Multiple Sclerosis



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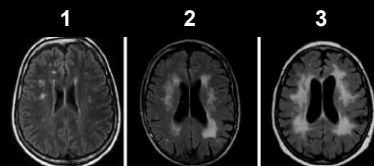
Levamisole Toxicity



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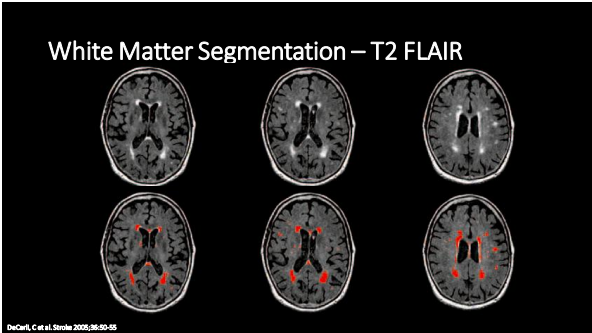
White Matter Grading Scale

Fazekas



- Periventricular white matter (PVWM)
- 0 = absent
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 - 2 = beginning confluence
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White Matter Grading Scales: Useful???
LADIS Leukoaraiosis And DISability Study
618 independently living elderly

WMH assessment vs	Disability
Fazekas	Depression
Scheltens	Gait
ARWMC	Incontinence
Volume	Memory

- Volumes more sensitive than visual scales
- No correlation # lesions, lesion type
- Scales: ceiling effects, not discriminant

Van Swieten et al. Stroke 2006;37:604-610

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STRUCTURAL MRI
 Screening for Risk

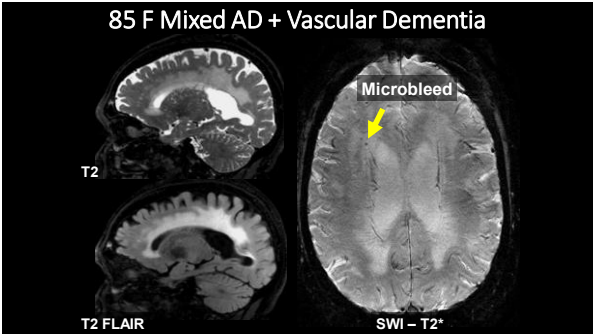
→ MRI is the safety filter that determines ineligibility and risk for complications

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- + Baseline volumetric parameters
 • Measurement of baseline whole brain, ventricular and hippocampal volumes
- + Rule out a potential alternate diagnosis
 • Other neurodegenerative disease, space-occupying lesion, or other structural abnormalities

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Cerebral Amyloid Angiopathy

Epidemiology

- Important cause of ischemia and hemorrhage in the elderly
- Age Dependent
 - 2%: ages 65-74
 - 8%: ages 75-84
 - 12%: ages >85
- CAA incidence of 80-90% in Alzheimer's Disease

MRI Findings

- Leukoencephalopathy
- Small cortical infarcts
- Lobar/subarachnoid hemorrhage
- Superficial siderosis
- Microbleeds

GRE-T2*

SWI

Hawden et al. Ann N Y Acad Sci 2007; 1124: 316

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Amyloid β Angiitis – T1 CUBE Black Blood MRI + C

Inflammatory Amyloid Angiopathy

Leptomeningeal enhancement

Arterial wall enhancement

Pararenchymal enhancement

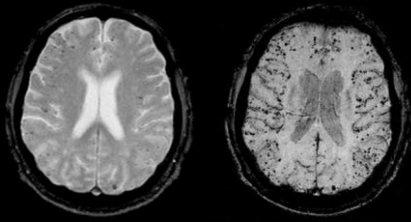
Vasogenic edema

Extensive Microhemorrhages

Autoimmune response to vascular amyloid β deposits

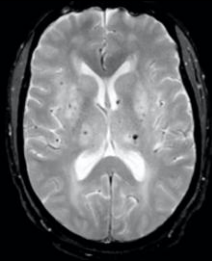
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Cerebral Amyloid Angiopathy



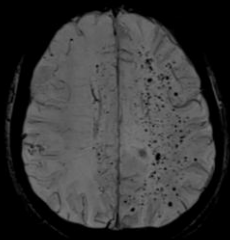
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Hypertensive Microhemorrhages

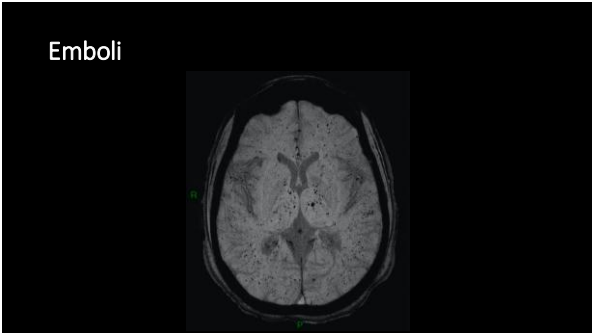


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Iatrogenic Microhemorrhages



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FDG PET

When the Diagnosis is Unclear

→ Brain metabolism is not an eligibility criteria, but can be useful

Measurement of glucose metabolism

- Marker of regional neuronal function and activity

Typical FDG PET imaging pattern in AD

- May confirm diagnosis in borderline cases

Differential with other neurodegenerative diseases

- Also identifies changes related to normal aging

Marginal role in patient selection

- Not required by FDA for lecanemab and donanemab

FDG PET in AD - What regions are involved?

POSTERIOR CINGULATE
Most specific and earliest region, with 88% of AD patients showing hypometabolism in this region.

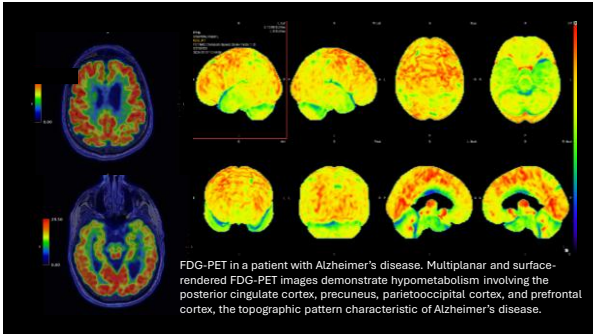
PRECORPUS
Hypometabolism in 71% of cases of AD, typically detectable before structural changes such as atrophy occur.

ENTORHINAL CORTEX
71% of AD patients - less specific than posterior cingulate, but great sensitivity (93.8% against frontotemporal dementia).

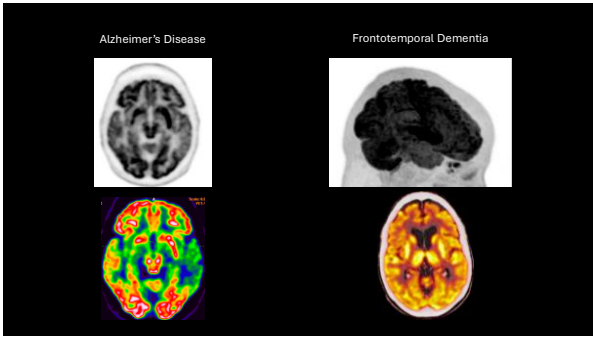
Medial temporal lobe (hippocampus)
Involved early, with hypometabolism preceding structural changes by years - predicts conversion from MCI to dementia.

FRONTAL ASSOCIATION CORTEX
Involved later in the disease - relative sparing of FDG PET may help differentiate from behavioral frontotemporal dementia.

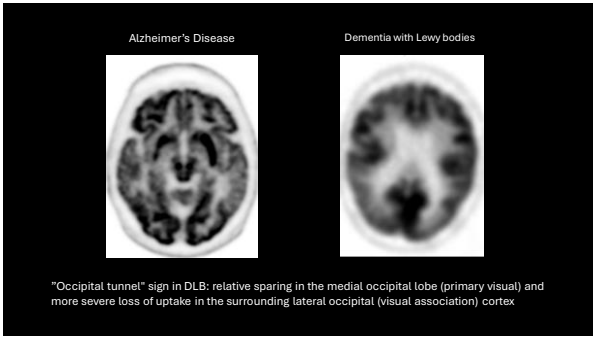
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PERFUSION IMAGING

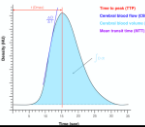
When the Diagnosis is Unclear

→ Perfusion is not an eligibility criteria, but can be useful

Imaging the passage of fluid through the circulatory system

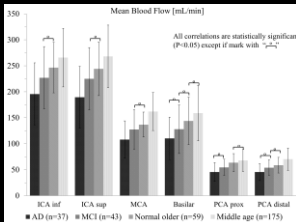
Usually referring to the delivery of blood to a capillary bed in tissue

- Usually referring to the delivery of blood to a capillary bed in tissue
- Some techniques use contrast



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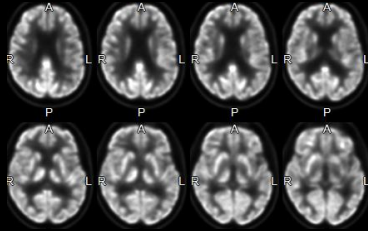
Cerebral blood flow



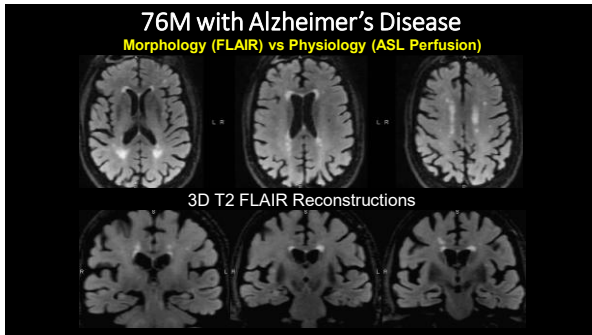
AD patients have decreased blood flow

68

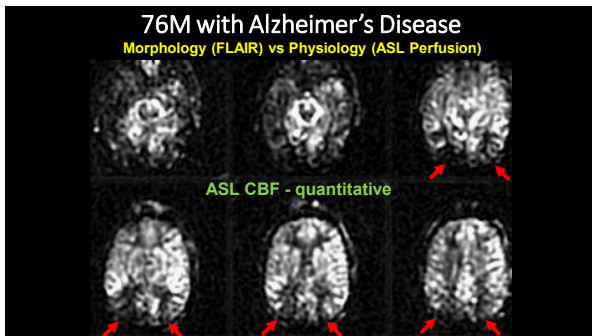
Arterial Spin Labeling



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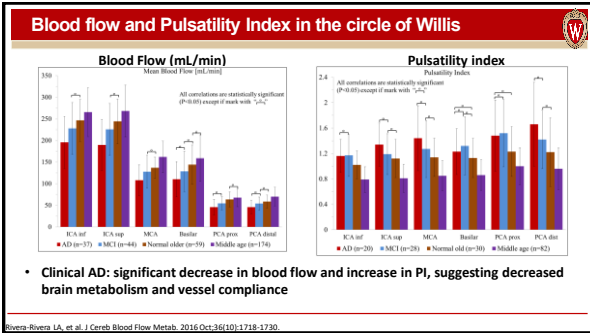
4D FLOW MRI
Research Topics

→ Flow measures are not an eligibility criteria, but can be useful

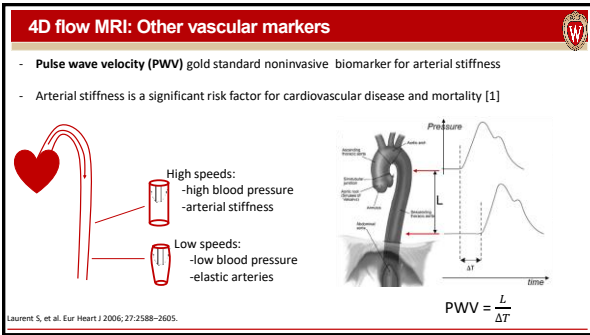
Phase contrast MRI method with a blood flow vector and temporal component

- Enables both volumetric angiographic and quantitative assessment of blood flow velocities in a single acquisition
- Wall shear stress, pulsatility, pressure gradients, vessel area measurements

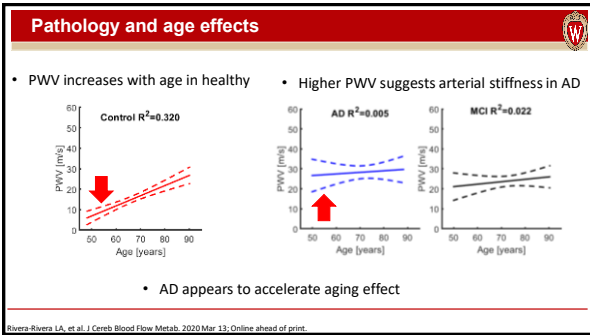
72



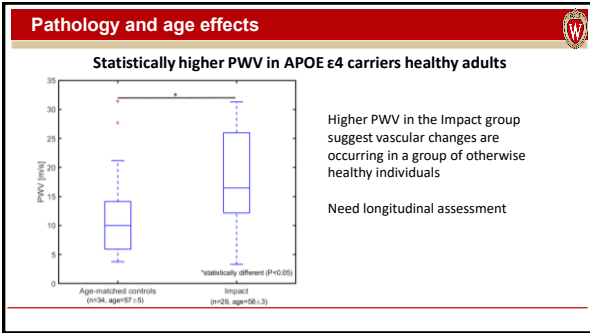
73



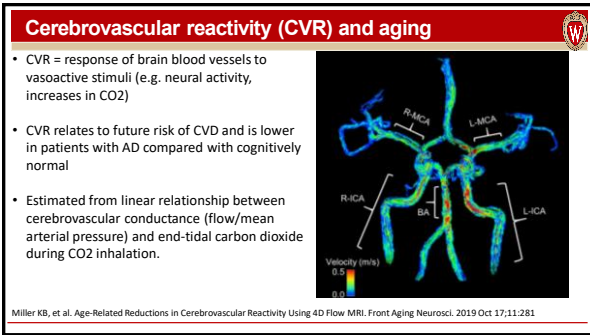
74



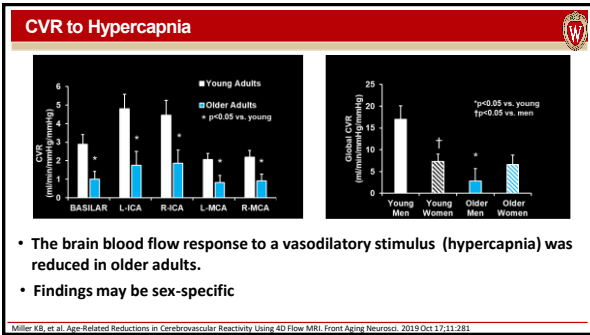
75



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78

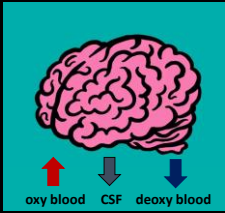
Assessment of other brain compartments

Multiple compartments (e.g. 4D flow probes arteries, ignores tissue)

arterial pressure (fast velocities)
↓
tissue (small displacements)
↓
CSF (slow velocities)

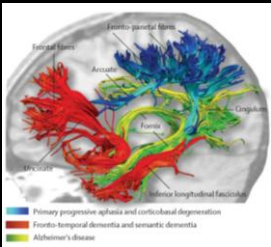
Need for multi-scale characterization

- Intracranial PWV
- Strain mapping
- Intracranial pressure



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DTI Tractography in Degenerative Disorders



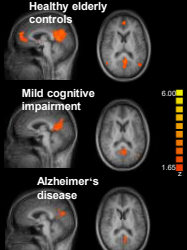
Mod from Catani by Ciccarelli, Lancet Neurol 2008; 7:715-727

80

fMRI Resting Connectivity - Lost with AD

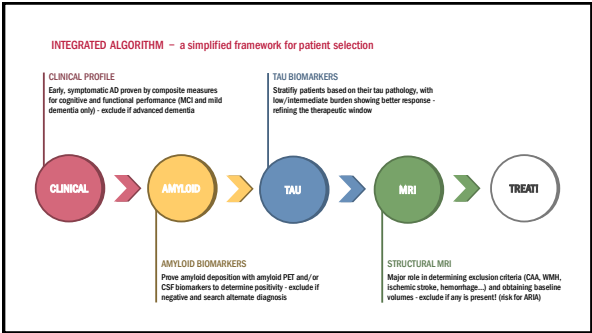
ICA group comparison (voxel-wise)

Healthy elderly controls
Mild cognitive impairment
Alzheimer's disease



Courtesy of Dr. Walter Koch, Munich, Germany

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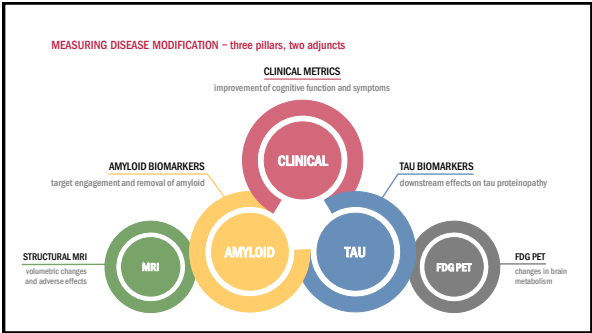


83

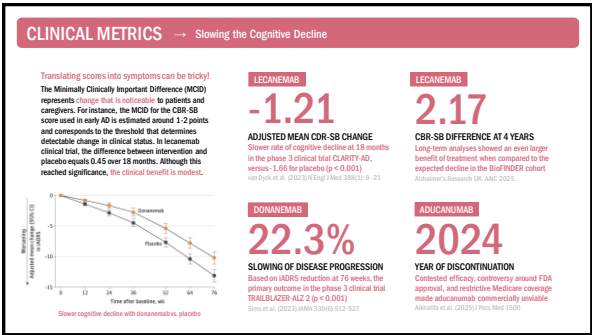
THERAPEUTIC RESPONSE

Is the treatment working?

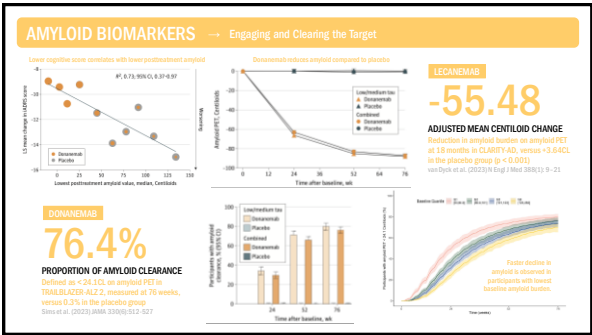
84



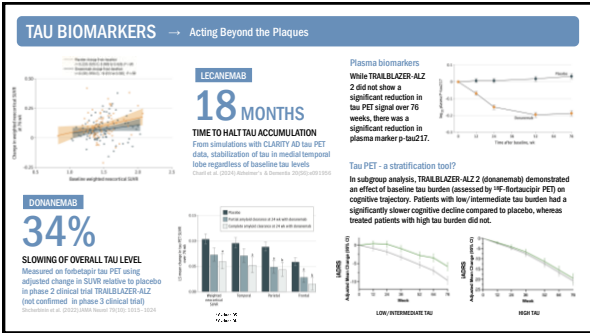
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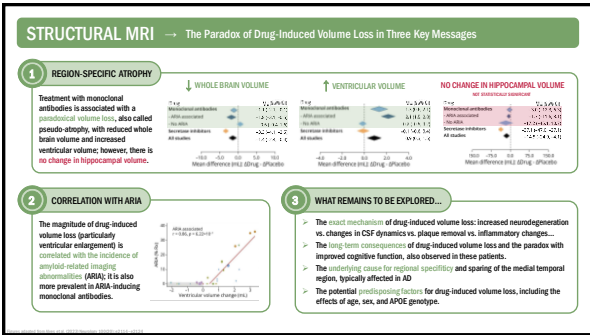
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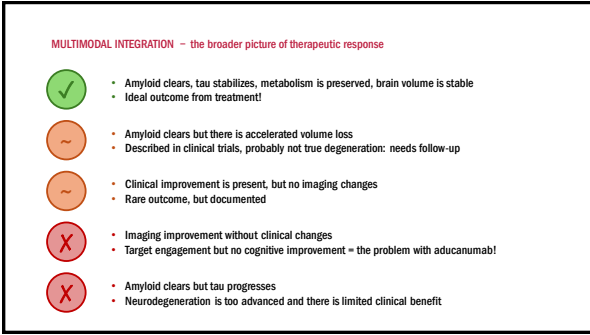
87



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MONITORING FOR ARIA

Is the brain tolerating treatment?

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AMYLOID-RELATED IMAGING ABNORMALITIES – better known as ARIA

Class-specific adverse events of amyloid-targeting monoclonal antibodies

MRI-defined entity first described in 2009 - with bapineuzumab

Two different forms exist – may occur concurrently

ARIA-E

ARIA with edema

ARIA-H

ARIA with hemorrhage

Clinical manifestations

THE MOST FREQUENT	FREQUENT	OCCASIONAL	RARE
Asymptomatic!	Headache Confusion Dizziness Nausea/vomiting Neuropsychiatric symptoms	Fatigue Visual disturbance Gait disturbance	Encephalopathy Focal neurological deficit Seizures Coma Death

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FACTS & FIGURES

ARIA-E Incidence Rates

ADJUNCTIVE

35.0%

versus 2.0% for placebo
(EMERGE high-dose)

LECAEMUS

12.6%

versus 1.7% for placebo
(CLARITY H2)

DOMANISUM

24.0%

versus 2.1% for placebo
(TRAILBLAZER ALZ 2)

ARIA-H Incidence Rates

ADJUNCTIVE

20%

versus 7.0% for placebo
(EMERGE high-dose)

LECAEMUS

17.3%

versus 9.0% for placebo
(CLARITY H2)

DOMANISUM

31.4%

versus 13.6% for placebo
(TRAILBLAZER ALZ 2)

92%

ARIA-E detected within the first 6 months of treatment
(CLARITY H2 (documented))

9.1%

isolated forms of ARIA-H
(CLARITY H2 (documented) + CLARITY H2 (documented))

4 MONTHS

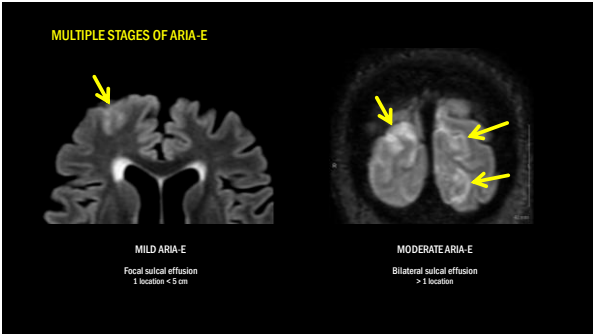
80% of cases of ARIA-E are resolved
(CLARITY H2 (documented))

COGNITION

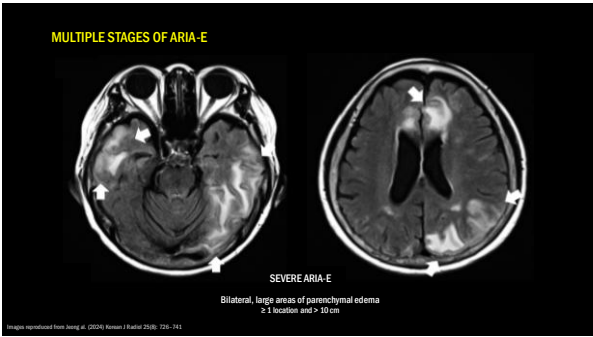
ARIA does not affect cognitive outcomes
(CLARITY H2 (documented))

Figure 1. Number of subjects to first Serious Amyloid-Related Imaging Abnormalities (ARIA) (Event 3) in Documented Treated Participants
Adapted from Zimmer et al. (2023) JAMA Neurol. ARIA-E and ARIA-H were assessed using a modified NIA-AA ARIA definition.

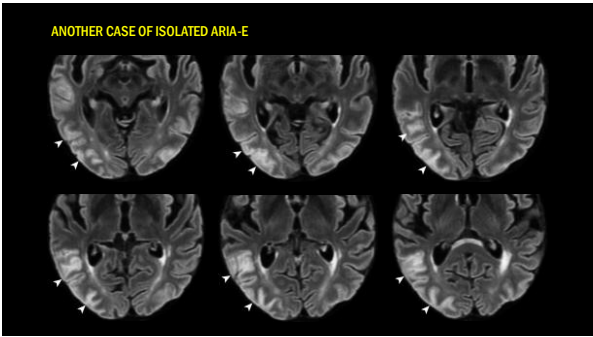
93



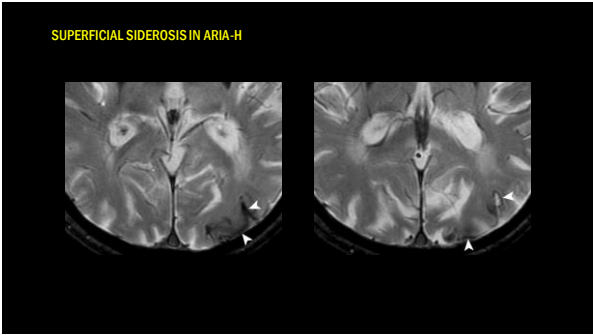
98



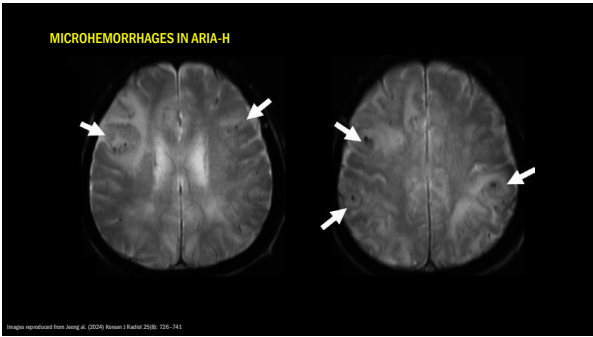
99



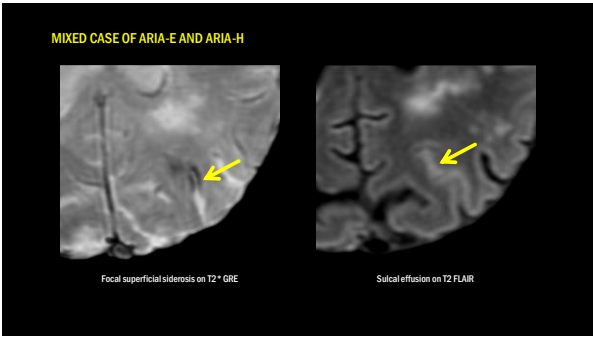
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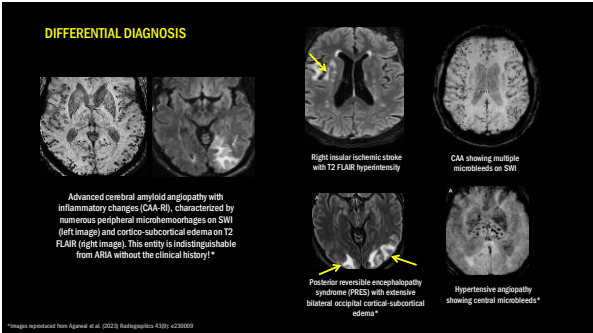
101



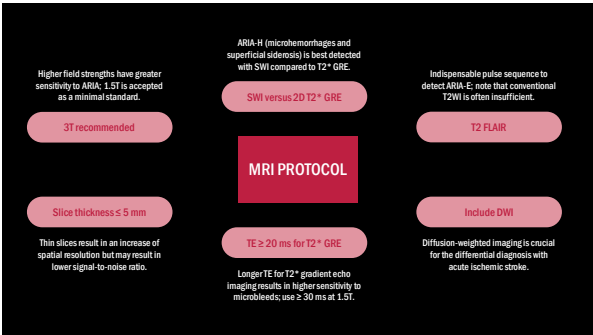
102



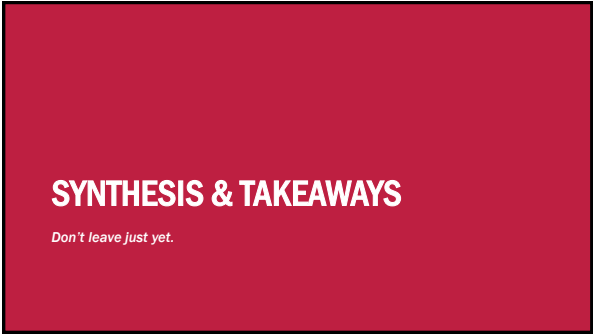
103



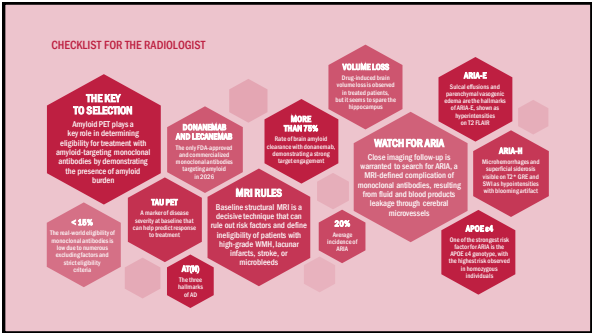
104



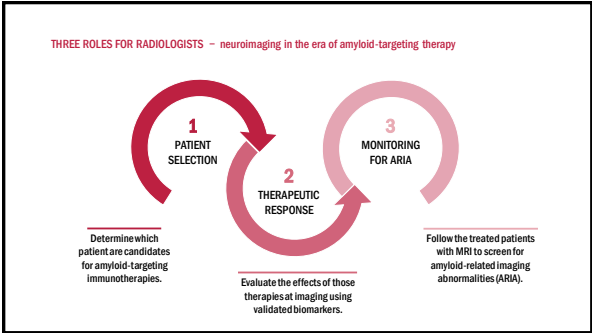
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REFERENCES & MORE

The papers behind the slides. And more.

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THE READING LIST YOU ACTUALLY WANT – and the key to the alphabet soup



<https://bit.ly/4mDQZvk>

THANK YOU!

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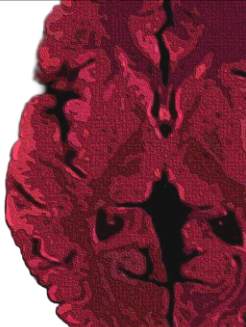
WISCONSIN
UNIVERSITY OF WISCONSIN-MADISON

**Neuroimaging in Alzheimer's
Disease and Related
Dementias**

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University of Wisconsin-Madison, School of Public Health and Medicine
Department of Radiology

Thank you to Drs. Asthana, Johnson, Carlsson, Bendlin, Rowley...



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