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An expanded role for neuroimaging in the evaluation of memory impairment

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Abstract

Alzheimer's disease (AD) affects millions of people worldwide. The neuropathologic process underlying AD begins years, if not decades, before the onset of memory decline. Recent advances in neuroimaging suggest that it is now possible to detect AD-associated neuropathological changes well before dementia onset. Here, we evaluate the role of recently developed *in vivo* biomarkers in the clinical evaluation of AD. We discuss how assessment strategies might incorporate neuroimaging markers to better inform patients, families and clinicians when memory impairment prompts a search for diagnosis and management options.

AD pathobiology

Since their first description by Alois Alzheimer in 1907, [3] amyloid-containing plaques and tau-associated neurofibrillary tangles (NFTs) have remained the two hallmark pathological lesions of AD. Senile and neuritic plaques are composed of amyloid-beta (Aβ), a 38–43 amino acid peptide that derives from the much larger cell membrane-associated amyloid precursor protein and gradually accumulates over time in the extracellular spaces of the brain. [4] Within plaques, Aβ is present in aggregated/insoluble forms such as fibrils and soluble forms such as oligomers. [5] In animal models, Aβ initiates downstream loss of dendrites and synapses [5] and functional disruption of neuronal networks.[6] Genetic evidence indicates that APOE ε4, the most important known genetic risk factor for late onset AD, accelerates the onset of Aβ deposition into plaques and decreases the transport of Aβ across the blood brain barrier. [7] Furthermore, a recently discovered mutation in Aβ-precursor protein protects against AD [8] providing additional evidence regarding the central role of Aβ

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in AD pathogenesis. However, neocortical Aβ plaques are present not only in cognitively impaired patients but also in cognitively normal older adults. [9] Poor correlations between Aβ deposition and memory decline, [10] together with the observation that immunotherapy-induced Aβ plaque removal may not prevent neurodegeneration, [11] suggest that additional entities besides Aβ are required for AD-associated degeneration.

Neurofibrillary tangles, primarily found in neuronal cell bodies, are composed of the hyperphosphorylated, aggregated form of the microtubule binding protein, tau. Unlike Aβ plaques, tau-associated NFTs strongly correlate with clinical severity [10] and follow a defined temporal topographic pattern in which medial temporal lobe regions underlying memory function are affected in the earliest stages of the disease. [12] Recent work in animal models [13,14] and humans [15,16] points to a synergistic relationship between Aβ and tau whereby Aβ-associated neurodegeneration occurs only in the presence of tau. Intriguingly, evidence from animal models indicates that reducing tau levels rescues mice from premature mortality and memory deficits without altering Aβ levels or plaque burden. [13] These findings, along with other biochemical and experimental evidence, support a two-stage disease process in which Aβ deposition initiates the neurodegenerative cascade (including tau hyperphosphorylation and aggregation), which in turn becomes increasingly independent of the initiating Aβ. [17]

Imaging and fluid biomarkers for assessing Alzheimer's pathology

Neuropathological findings indicate that Aβ accumulation and tau pathology begin years or even decades before the onset of clinical symptoms. [18] Neuroimaging and cerebrospinal fluid (CSF) markers can detect the earliest pathologic changes associated with AD enabling identification of clinically normal individuals in the pre-symptomatic or pre-clinical stage of AD. [19] In the sections below, we review the most extensively validated *in vivo* biomarkers of amyloid pathology and AD-related neurodegeneration. For simplicity, we do not review the putative markers of synaptic injury, such as FDG-PET or functional MRI, which may prove useful in distinguishing between certain neurodegenerative disorders.

Volumetric structural MRI

Structural MRI is a convenient first imaging modality for assessing AD neurodegeneration because current practice guidelines include its use during the routine evaluation of patients with cognitive complaints, primarily to exclude structural abnormalities such as infarction, brain tumors or hydrocephalus. [20] Brain atrophy on structural MRI reflects the loss of dendrites, synapses, and neurons. [21] Though atrophy is not specific to AD, there is a strong association between the severity of atrophy and cognitive decline along the aging continuum and the degree of atrophy correlates with Braak pathologic staging at autopsy. [21] Importantly, the topographic distribution of MRI-based atrophy in AD maps well onto the distribution of NFT pathology, with the entorhinal cortex and hippocampus demonstrating the largest magnitude of gray matter loss in patients with a high tau burden. [22]

A number of methodologies, ranging from whole brain or voxel-based techniques to region of interest-based methods, have been proposed to quantitatively evaluate brain atrophy on MRI. Within the last decade, the routine acquisition of high-quality 3D T1-weighted images

and rapid advances in image analysis algorithms have led to the availability of volumetric MRI-based software tools (vMRI) capable of automatically subdividing the brain into neuroanatomic regions and quantifying tissue loss within each region for a single individual. [23–25] Fully automated quantitative vMRI-based neuroanatomic assessments can detect AD-associated volume loss, predict disease progression, and be used as an outcome measure in therapeutic trials. [26,27] Recently, the FDA has approved one such vMRI technology [28] that can assist in the clinical work-up of memory decline (Figure 1). In Table 2, we review recent (from 2009–2012) prospective studies using vMRI methods to predict clinical progression from MCI to AD.

However, structural MRI has limitations. vMRI does not directly evaluate Aβ and tau but rather provides an indirect assessment of neurodegeneration that occurs downstream from molecular pathology. Another limitation is that though certain patterns of volume loss are characteristic of different diseases (e.g. entorhinal cortex atrophy in AD), the finding of medial temporal lobe atrophy by itself is nonspecific and can also be seen in other neurologic and psychiatric disorders. Therefore, vMRI of medial temporal lobe structures, in isolation, cannot distinguish AD from hippocampal sclerosis or other neurodegenerative diseases such as frontotemporal dementia (FTD). Moreover, neuropathologic evidence demonstrates the presence of uncommon AD subtypes that spare the medial temporal lobes, especially in younger patients. [29] Despite these weaknesses, given its capability for precise anatomic description with high reliability, analysis of MRI data across a wide range of scanner types/manufacturers and the ability to efficiently generate normative databases from multi-center data, vMRI will undoubtedly play a significant role in decision-making during the clinical evaluation of dementia. The optimal diagnostic and prognostic value of vMRI will be obtained when combined with clinical/cognitive testing and other markers including CSF and imaging measures of Alzheimer's pathology.

Molecular imaging and fluid biomarkers of Aβ deposition

Within the last decade, a number of PET-based radiotracers have been developed to noninvasively assess for the presence of Aβ, of which the most extensively examined is ^{11}C-labelled [*N*-methyl]-2-(4′-methylaminophenyl)-6-hydroxybenzothiazole (Pittsburgh Compound-B, PIB). Studies using transgenic mouse models and human brain sections indicate that PIB selectively binds to the fibrillar form of Aβ in neuritic plaques and cerebral amyloid angiopathy. [30,31] *In vivo*, ante-mortem PIB retention strongly correlates with *in vitro*, post-mortem measures of fibrillar Aβ pathology in autopsy-confirmed AD but does not associate with NFTs, Lewy bodies or other protein aggregates. [32,33] In humans, the overall pattern of increased PIB retention mirrors the distribution of fibrillar Aβ plaques found at autopsy and involves the prefrontal, parietal, and lateral temporal cortices. [34] A recent review suggests that the overwhelming majority of AD patients and cognitively impaired individuals who progress to AD are amyloid 'positive'. [35] Furthermore, approximately 24% of cognitively normal older adults greater than 60 years of age also show increased cerebral PIB retention and the prevalence of amyloid positivity is closely related to age and APOE ε4 carrier status. [35] Together, these findings raise the possibility that amyloid imaging may yield positive results long before the appearance of cognitive symptoms, which, as discussed below, has both positive and negative consequences.

As either an alternative or adjunct to amyloid PET imaging, CSF sampling can also detect Aβ pathology. Though the majority of Aβ is produced in the brain and secreted into the extracellular spaces of the brain, a fraction of central nervous system-produced Aβ diffuses into the CSF and is present in modest concentrations (approximately 10–15 ng/mL). [36] CSF assessments measure the monomeric form of Aβ. Low CSF Aβ levels strongly correlate with increased PIB binding, intracranial plaque deposition and total Aβ load, demonstrating the value of these CSF measurements as a marker of fibrillar Aβ pathology. [36] However, an important clinical consideration with CSF sampling is the need for lumbar puncture, an uncomfortable procedure that carries a small risk of morbidity.

Imaging evaluation strategy for MCI and AD

Clinical assessment of the elderly patient with a memory complaint usually begins with a mental status evaluation to objectively confirm the presence of the cognitive deficit. If the degree of cognitive decline is greater than expected for healthy aging and further information is needed to guide management, the determination of whether a neurodegenerative process underlies the cognitive complaint can help determine which further diagnostic method to use. Above and beyond excluding other conditions to explain cognitive deficits (e.g. brain tumor, traumatic brain injury, infarctions, chronic hemorrhage, hydrocephalus, or encephalitis) structural MRI using vMRI techniques at this stage can be useful to document objective evidence of atrophy. As illustrated in Figure 2, vMRI can assist in supporting or contradicting a putative clinical diagnosis while providing an informative assessment of disease risk. The presence of reduced hippocampal volume provides support to the clinical impression that a neurodegenerative process contributes to the cognitive deficit but does not exclude the possibility of a congenitally small hippocampus or hippocampal damage from a prior insult. Importantly, low hippocampal volumes do not specify whether the underlying etiology is due to AD or other diseases such as frontotemporal dementia (FTD), dementia with Lewy bodies, or hippocampal sclerosis (Figure 2). Nevertheless, once a neurodegenerative etiology is supported through clinical and radiological evaluation, distinguishing among neurodegenerative disorders may benefit from supplemental testing for amyloid. This would likely be reserved for cases where additional tailoring of education or management is required and may be limited, as the more clinically relevant distinction is between benign or curable etiologies versus those with a near-term dire prognosis (Figure 2). It is important to note that in light of prior [11] and recent [37] clinical trials evidence that removing Aβ plaques using immunotherapeutic methods may not halt the neurodegenerative process, amyloid testing to confirm Alzheimer's as the underlying etiology may prove most useful when therapies preventing downstream neurodegeneration become clinically available (Figure 2).

Challenges remain regarding the clinical application of vMRI in the patient with cognitive impairment. The difficulty in establishing normative ranges across a broad population of patients is a significant obstacle, but one that can be overcome by the availability of large databases of images in cognitively normal elders and subjects with both MCI and AD enrolled in multi-site, multi-national initiatives such as the Alzheimer's Disease Neuroimaging Initiative (ADNI) in North America and the AddNeuroMed Consortium in Europe (see Table 2). Because atrophy is not diagnostic of AD neuropathologically and

because the hippocampus is affected by a broad array of disorders, the diagnosis of AD cannot rely on simple 'cut points' or 'thresholds' in hippocampal volume [38, 39] derived from studies of progression to AD dementia. Furthermore, the degree of abnormality, along with other radiological features, including *ex-vacuo* dilatation of adjacent temporal horn and qualitative assessment of sulcal widening and cortical volume loss, will inform the impression of presence or absence of neurodegeneration. Importantly, the diagnosis of AD cannot be established by imaging alone; radiologic input serves to *inform*, rather than establish, an overall clinical impression.

Recommendations to use medial temporal atrophy on structural MRI among cognitively impaired individuals have already been proposed by an international AD working group[40] and vMRI is one of the biomarkers recently incorporated into revised diagnostic criteria for AD, which noted that such biomarkers could serve "as optional clinical tools for use where available and when deemed appropriate by the clinician." [41] Consistent with these recently revised diagnostic guidelines for AD [41] and MCI [42], by supporting the presence or absence of neurodegeneration, vMRI-based methods can also inform the likelihood of whether a patient with clinically confirmed memory loss will progress to dementia. The absence of vMRI-based brain atrophy diminishes the likelihood of neurodegeneration and increases the likelihood that a non-neurodegenerative, and potentially treatable, cause underlies the memory complaint. It is important to note that normal brain volumes for age, though not excluding the possibility of future neurodegeneration, can also be helpful for guiding clinical management while providing a more accurate predictive prognosis. Normal hippocampal volumes confer a better near-term prognosis and can foster increased efforts towards finding a treatable cause for the memory impairment while providing needed, albeit cautious, reassurance to the patient and caregivers who will be anxious about being given a dire prognosis.

Amyloid biomarkers in MCI and AD

The ability to specifically assess fibrillar Aβ pathology *in vivo* has generated considerable clinical excitement. Recently, the FDA has approved the fluorine-based amyloid tracer [F-18]florbetapir (Amyvid, Eli Lilly Inc) for use in patients being evaluated for AD and other causes of cognitive decline (Figure 3). Furthermore, commercial CSF Aβ assays with established normative ranges for amyloid status are now clinically available (http://www.athenadiagnostics.com). However, as noted by the FDA, though a negative florbetapir (amyloid) scan is inconsistent with a neuropathological diagnosis of AD at the time of image acquisition, a positive florbetapir scan does not establish a diagnosis of AD. [43] Furthermore, elevated deposition of amyloid may occur in other neurological conditions and is often present in healthy elders with normal cognition. Recently, it has become increasingly evident that Aβ oligomers (e.g. dimers, trimers, tetramers and higher oligomers), rather than fibrillar Aβ plaques, represent the principal synaptotoxic form of amyloid that initiate the neurodegenerative process underlying AD. Insoluble Aβ fibrils, though serving as a reservoir for the neurotoxic oligomers, might themselves be relatively inactive. [44] Importantly, neither CSF analytes nor amyloid imaging can detect the oligomeric form of Aβ. [36] Similarly, in cognitively normal older individuals, though some studies have found a relationship between Aβ plaque deposition and neurodegeneration, [45,46] recent studies

suggest that tau and other 'downstream' markers of neuronal injury modulate the effect of Aβ on cognitive decline and brain atrophy. [15–16, 47] In addition, recent clinical trials using monoclonal antibodies (solanezumab and bapineuzumab) that target Aβ and promote its clearance from the brain demonstrate minimal effect on disease trajectory modification in patients with mild or moderate AD: solanezumab showed marginal improvement in cognitive and functional decline and bapineuzumab, though affecting fibrillar Aβ and tau levels, did not modify the disease trajectory. [37] Taken collectively, this indicates that Aβ deposition precedes neurodegeneration and in the absence of cognitive decline or brain atrophy, represents an elevated risk state in much the same fashion that hypercholesterolemia serves as a risk factor for heart disease in the absence of myocardial damage. Just as cholesterol levels would not be used to diagnose a myocardial infarction in the setting of chest pain, detecting amyloid deposition may be less valuable than markers of neuronal damage when determining the cause of ongoing memory impairment. Nevertheless, it is hoped that a future contribution of Aβ testing, from diagnostic and therapeutic perspectives, may be among cognitively normal adults *before* the onset of neurodegeneration.

Role of biomarkers in guiding clinical management

Biomarker testing can help inform near-term prognosis by providing an objective assessment as to whether neurodegeneration is likely to be present. Whereas cognitive testing validates the patient or caregiver complaint that initiated the clinical visit, vMRI provides an orthogonal measure that is less overlapping with the patient complaint thereby guarding against circularity in concluding that the cognitive problem is due to Alzheimer's. The presence of brain atrophy on vMRI, together with documented memory impairment confirmed by cognitive testing, suggests a prognosis of near-term decline and can prompt a discussion on evaluating the risk/benefit ratio for considering aggressive disease management versus symptomatic care (Figure 2). For patients and family members, these findings can help initiate a dialogue on future planning including determining the need for residential and driving support, involvement of a geriatric case manager, and financial decisions.

Evaluation with amyloid testing can prove useful once a neurodegenerative etiology for cognitive decline has been established, especially in younger patients and in patients presenting with complaints atypical for AD. An amyloid test may be helpful for making a more informative dementia diagnosis (e.g. AD vs. FTD) in these patients, and can help guide the selection of medications for symptomatic management. As with vMRI, amyloid testing may also be of benefit to refine and tailor expectations while providing additional education to patients and caregivers.

The absence of brain atrophy on vMRI confers a better near-term prognosis and can provide cautious, but increased, optimism to physicians, patients and caregivers. While not excluding the possibility of future neurodegeneration, normal brain volumes can guide clinical management by prompting the physician to intensify efforts towards detecting a treatable cause for the patient's memory impairment (Figure 2). Such physician optimism is not lost on patients and may serve as needed reassurance to those patients with an

inappropriately debilitating fear about progressing to dementia. Importantly, the intensified physician effort on behalf of patients whose complaints and cognitive impairments are incongruous with vMRI findings may lead to an improved likelihood of successful treatment and subsequent return of patients to normal cognitive function.

Potential pitfalls with biomarker testing

In addition to valid concerns of added expense (see Table 1b), it is our opinion that biomarker assessment of patients without objective evidence of memory impairment could cause potential harm. For example, given the high frequency of non-specific memory complaints in the general population and the high prevalence of amyloid positivity among the cognitively normal population, there is a significant chance that a patient's memory complaint is unrelated to intra-cranial Aβ deposition. A finding of elevated amyloid or low hippocampal volume might lead to inappropriate attribution of memory complaints to AD, circumventing a thorough workup for other potentially treatable causes while exacerbating the debilitating worry that initially brought the patient to the clinic. Even in those patients where memory impairment is clinically confirmed, elevated amyloid does not assure that the cause of the impairment is AD. Amyloid positivity, in patients with objective memory decline, might lead to an overly simplistic attribution of memory complaints to AD and incomplete evaluations for modifiable causes of cognitive impairment. Finally, a negative amyloid test is not necessarily a result to be celebrated since other neurodegenerative disorders should remain under consideration.

Future Directions – Preclinical AD

Currently, there are no effective treatments that delay the onset or halt the progression from MCI to AD. There is increasing recognition that early intervention before the onset of neurodegeneration or clinical symptoms may represent the most effective treatment against AD [19] and a number of secondary prevention trials in preclinical older individuals are currently underway. We believe that a screening strategy for assessing dementia risk in cognitively normal adults could be useful if a meaningful therapy with minimal side effects becomes clinically available. Biomarker testing in asymptomatic patients is inherently controversial and we therefore note that this evaluation strategy, though not currently applicable, *may become relevant when/if meaningful preventative interventions are available*.

Genetic, biochemical, and imaging evidence indicates that fibrillar Aβ pathology begins at least 15 years before the onset of clinical symptoms. [48] Increasing levels of Aβ oligomers that progressively lead to plaque deposition are likely present at an even earlier age. [49] These observations suggest that screening for the presence of amyloid should start in cognitively normal older adults (greater than 60 years of age), similar to the current screening strategies for hypercholesterolemia or common cancers such as breast, colon or prostate carcinoma. Though CSF concentrations of Aβ may become aberrant before amyloid imaging, [48] additional factors such as the need for assessing therapeutic response over time, clinical availability, and patient comfort should also be considered when determining whether to use fluid or imaging markers for amyloid status screening.

In cognitively normal older adults, a negative amyloid test indicates a significantly lower risk of developing AD. Since increased amyloid tracer uptake can also be seen with other conditions, such as cerebral amyloid angiopathy, [32] a positive amyloid test could be further evaluated using cognitive testing and possibly, vMRI. Positive amyloid status along with the presence of progressive medial temporal lobe atrophy would suggest that the patient has entered the neurodegenerative phase of the disease process, which would change the risk/benefit calculation in considering more aggressive, less benign medications that may become available. Although neuropathology remains the only way to definitively diagnose AD, available fluid and imaging markers supplement the physician toolbox for managing and educating patients and families worried about AD. As disease-modifying therapies are developed, this physician toolbox will likely evolve to further address the need for improved predictive prognosis and disease management in preclinical AD.

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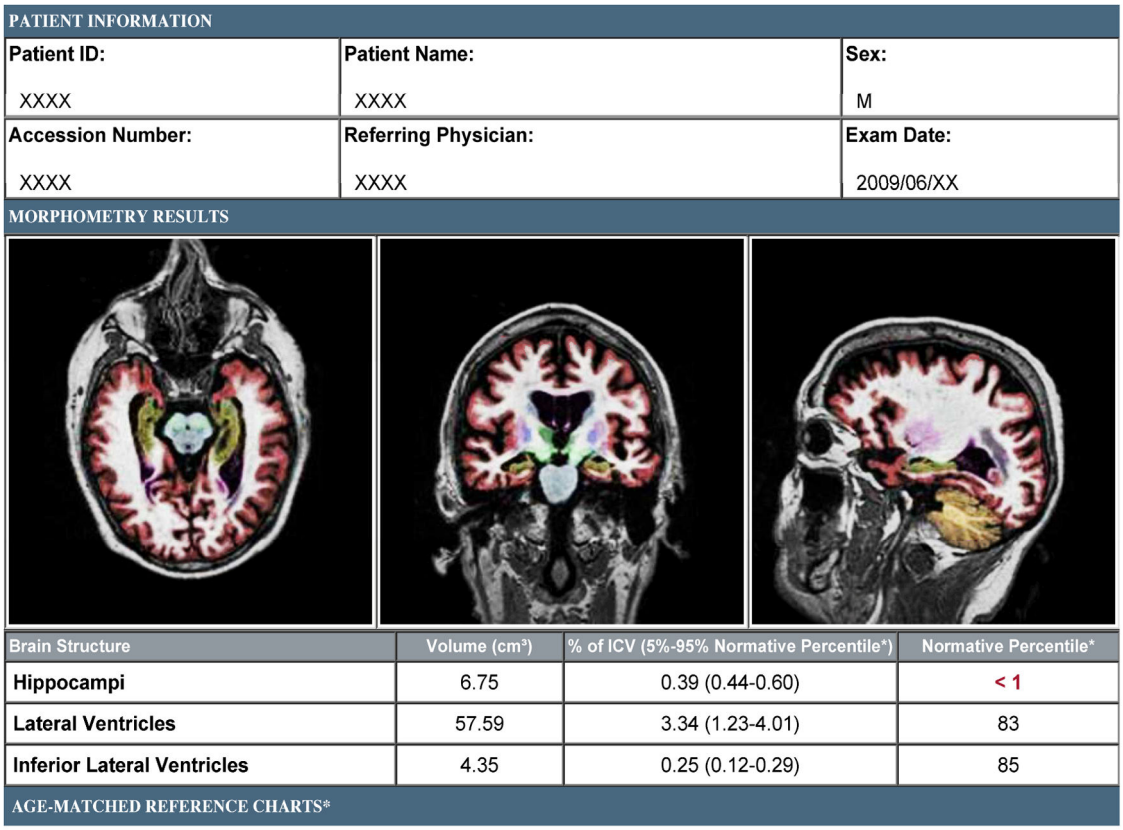
CLINICAL PERSPECTIVE

Late onset Alzheimer's disease (AD) is the most common form of dementia with an estimated prevalence of 30 million people worldwide, a number that is expected to quadruple in 40 years. With increasing awareness that symptoms develop over many years, there is a growing need to identify non-demented older individuals at risk for AD. Mild cognitive impairment (MCI) represents a transitional state between normal aging and dementia. Clinical features of amnestic MCI are presented in Table 1a and reviewed in references 1 and 2. In this piece, we focus on recent advances in biomarker development for the predictive prognosis of MCI and suggest that a neuroimaging-based evaluation strategy can help guide clinical management decisions in older individuals with memory impairment.



PATIENT INFORMATION

Patient ID:	Patient Name:	Sex:
XXXX	XXXX	M
Accession Number:	**Referring Physician:**	**Exam Date:**
XXXX	XXXX	2009/06/XX

MORPHOMETRY RESULTS

Brain Structure	Volume (cm³)	% of ICV (5%-95% Normative Percentile*)	Normative Percentile*
Hippocampi	6.75	0.39 (0.44-0.60)	< 1
Lateral Ventricles	57.59	3.34 (1.23-4.01)	83
Inferior Lateral Ventricles	4.35	0.25 (0.12-0.29)	85

AGE-MATCHED REFERENCE CHARTS*

Figure 1.

Brain MRI evaluation of a patient with amnestic MCI using a volumetric technique (NeuroQuant™, http://www.cortechslabs.com). The top panel illustrates subcortical regions, such as the hippocampus (shown in dark yellow), automatically classified on axial, coronal, and sagittal T1-weighted MRI images. The middle and bottom panel demonstrate volumes and normative percentiles for the hippocampus and ventricles. Analyses of the baseline MRI scan demonstrated hippocampal volumes that were at the < 1 normative percentile, lending objective support to an impression of medial temporal lobe atrophy. At the time of

volumetric assessment, the patient's Mini-Mental Status Exam (MMSE) was 29/30 yet memory impairment was suggested by more detailed neuropsychological testing. Three years later, his MMSE was 22/30 and he had clinically progressed to dementia with high biomarker probability of AD, as supported by evidence of neuronal injury on structural MRI and elevated amyloid on a florbetapir scan (see Figure 3).

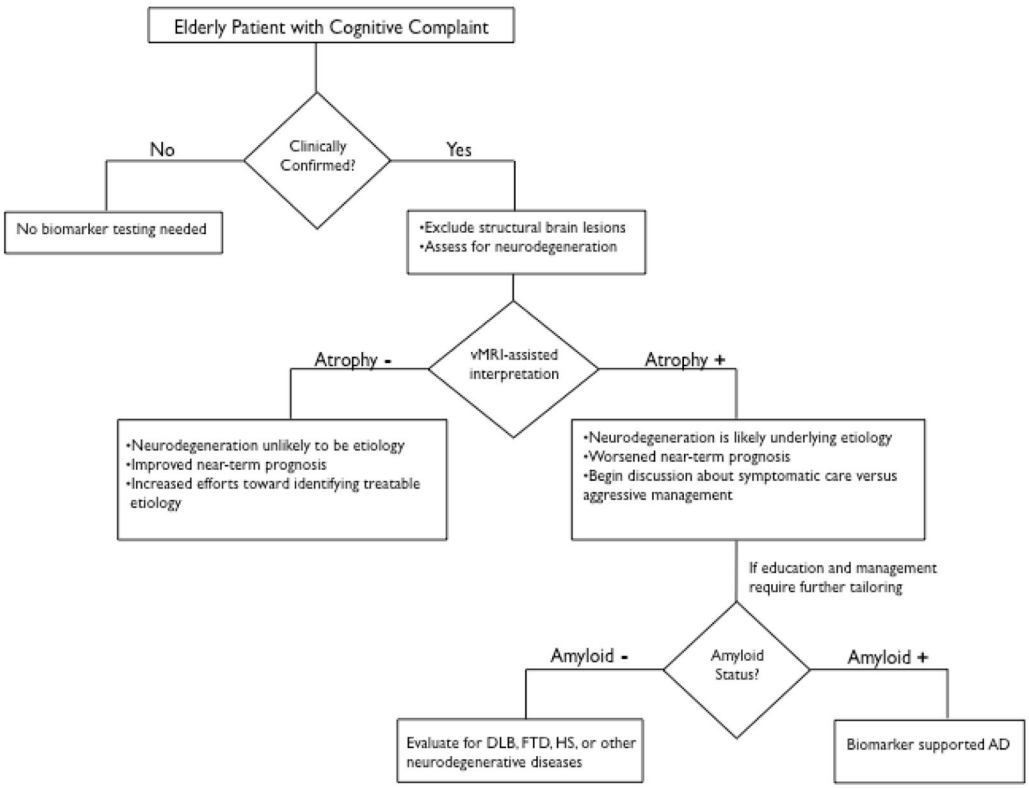


Figure 2.

Recommended decision tree for evaluating the elderly patient with a cognitive complaint. DLB = Dementia with Lewy bodies, FTD = frontotemporal dementia, HS = Hippocampal sclerosis, vMRI = automated volumetric MRI. Figure adapted from reference 63.

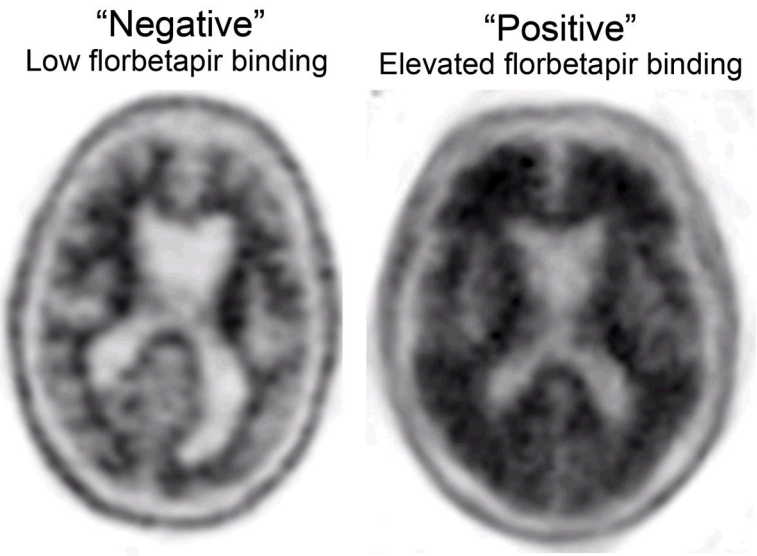


Figure 3.

Assessing amyloid deposition using florbetapir (Amyvid™, http://www.amyvid.com). The axial PET image on the left shows normal preserved gray-white contrast with the cortical radioactivity less than the adjacent white matter (amyloid 'negative' scan). The axial PET image on the right demonstrates areas of decreased gray-white contrast with increased cortical radioactivity that is comparable to the radioactivity in the adjacent white matter (amyloid 'positive' scan). The florbetapir scan on the right was acquired on an MCI individual who clinically progressed to dementia with high biomarker probability of AD, as supported by this amyloid positive scan and evidence of neuronal injury on structural MRI (see Figure 1).

Table 1

(a) Clinical features and **(b)** disease progression markers in amnestic MCI individuals.

Table 1a

Clinical Characteristics	
Memory Impairment	Episodic memory dysfunction
Non-memory Cognitive Impairment	Executive dysfunction, apraxia, aphasia, and/or visuospatial dysfunction maybe present in amnestic MCI multi-domain
Functional Impairment	No change in ability to perform activities of daily living
Behavioral Impairment	Depression and anxiety maybe present
Annual Rate of Progression to Dementia	Variable (range 3%–15%) [1]

Table 1b

Markers of Disease Progression	Characteristics	Procedure(s)#	Approximate Cost (in US dollars)%
Structural Neuroimaging with vMRI	Medial temporal lobe and/or neocortical atrophy, white matter abnormalities may also be present	**a.** Non-contrast MRI Brain CPT 70551 **b.** 3D Quantitative Segmental Volume Reporting and Assessment $^{\Psi}$ CPT 76377	**a.** 437.20 ($365.75^{T}+71.45^{P}$) **b.** 82.68 ($44.57^{T}+38.11^{P}$)
FDG-PET	Temporoparietal hypometabolism	Brain Imaging (PET) Metabolic Evaluation CPT 78608	1266.40 ($1041.99^{T}+150^{L}+74.41^{P}$)
Amyloid Imaging	Increased uptake in frontal, parietal, and/or temporal regions	PET Imaging Limited Area CPT 78811	2721.83 ($1041.99^{T}+1600^{L}+79.84^{P}$)
CSF Amyloid CSF Tau (total tau)	Decreased Increased	**a.** CSF lumbar puncture CPT 62270 **b.** CSF Analysis and Interpretation * CPT 83520	**a.** 242.58 ($78.93^{F}+163.65^{P}$) **b.** 1080
APOE ε4 carrier status	Dose-dependent effect (risk of AD: ε4/ε4 > ε3/ε4 > ε3/ε3 > ε3/ε2 > ε2/ε2)	**a.** Buccal Swab or Routine Venipuncture CPT 36415 **b.** ApoE Genotype Analysis & Interpretation $^{\Phi}$ CPT 81401	**a.** 3 **b.** 500

#Determined using data from the Centers for Medicare and Medicaid Services (www.cms.gov) For informational purposes only. Selected CPT code may vary.

%Determined, when possible, using National Payment Amount data from the Centers for Medicare and Medicaid Services (www.cms.gov) For informational purposes only. Payment amount varies by location.

$^{\Psi}$Using NeuroQuant® (http://www.cortechs.net/products/neuroquant.php)

*Using the ADmark® Phospho-Tau/Total-Tau/Ab42 CSF Analysis & Interpretation (Symptomatic) test (http://www.athenadiagnostics.com/content/test-catalog/find-test/service-detail/q/id/311)

$^{\Phi}$Using the ADmark® ApoE Genotype Analysis & Interpretation (Symptomatic) (http://www.athenadiagnostics.com/content/test-catalog/find-test/service-detail/q/id/35)

T Approximate Technical Charge

P Approximate Professional Charge

F Approximate Facility Price

L Approximate Ligand Price

Table 2

Studies in non-demented older individuals evaluating the ability of automated, volumetric MRI (vMRI) studies for predicting the risk of progressing to AD. Given the vast number of studies evaluating the ability of MRI measures to predict progression from MCI to AD, we focused on prospective studies using automated or semi-automated MRI methods and provide representative examples. We assessed the levels of evidence using the AHA/ASA guidelines. [50] ADNI = a multi-site, multi-center cohort from North America, AddNeuroMed = a multi-site, multi-center cohort from Europe.

Study	Participants	Source of Participants	Study Quality Level	vMRI Method	Results	Limitations
Bakkour et al., 2009[51]	49 cognitively impaired older adults	Memory disorders clinic from the US	B[#]	Baseline regional gray matter thickness	Predicted AD progression with 85% sensitivity and 65% specificity	Hippocampus and ventricles not assessed
Costafreda et al., 2011[52]	103 MCI patients	AddNeuroMed Consortium	B	Hippocampal shape analysis	Predicted AD progression at 1 year with 77% sensitivity and 80% specificity	Clinical applicability to population based cohort not assessed
Den Heijer et al., 2010[53]	518 older adults	Population based cohort from the Netherlands	B	Hippocampal volume	Baseline (mean HR = 2.2) and longitudinal (mean HR = 1.6) hippocampal volumes associated with higher dementia risk	Manual correction of brain regions was necessary in a subset of cases
Desikan et al., 2009[54]	129 cognitively impaired older adults	Population based cohort primarily from East Boston	B	Baseline regional gray matter volumes	Combination of entorhinal cortex (HR = 0.60) and inferior parietal lobule (HR = 0.62) best predicted time to AD progression	Manual correction of brain regions was necessary in a subset of cases
Heister et al., 2011[55]	192 MCI patients	ADNI	B	Fully-automated baseline hippocampal occupancy score	Predicted time to AD progression (HR = 3.9)	Clinical applicability to population based cohort not assessed
Jack et al., 2010[56]	218 MCI patients	ADNI	B	Baseline hippocampal volume with high (75th percentile) and low (25th percentile) amyloid deposition	Predicted time to AD progression (HR = 2.6)	Clinical applicability to population based cohort not assessed
Kovacevic et al., 2009[57]	269 MCI patients	ADNI	B	Fully-automated baseline volumes of medial temporal lobe	Smaller brain associated with longitudinal decline in MMSE and CDR-SB	Clinical applicability to population based cohort not assessed
Sluimer et al., 2009[58]	44 MCI patients	Memory disorders clinic from the Netherlands	C	Longitudinal atrophy rates of six brain regions	Medial temporal lobe atrophy best predicted (HR = 15.8) time to AD progression	Very limited populations examined
Vemuri et al., 2009[59]	192 MCI patients	ADNI	B	Structural abnormality index score (STAND)	Predicted time to AD progression (HR = 2.6, 75th versus 25th percentile)	Unclear clinical applicability of vMRI method
Westman et al., 2011[60]	101 MCI patients	AddNeuroMed Consortium	B	Hippocampal volume and gray matter thickness	Correctly classified 74% of MCI patients who progressed to AD at one year	Clinical applicability to population based cohort not assessed

[#] vMRI method presented here further validated on the ADNI cohort and population based cohorts from North America [61,62]