ALZHEIMER DISEASE DIAGNOSIS USING BIOMARKERS

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The populations of developed countries, (e.g. United States (US)), are undergoing relentless aging, a trend that developing countries are now starting to experience.[1] In the US alone, the percent of older adults in the general population will increase from 13% in 2010 to over 20% by 2040.[2] Not only are there many more older adults but also they also are living longer as the average life expectancy in the US is 81 years for women and 76 years for men.[3] As the American society continues to grey, advancing age remains the greatest risk factor for developing a dementia, in particular Alzheimer disease (AD). Every 66 seconds an individual in the US is diagnosed with AD with more than 5 million American currently living with this disease. The annual costs worldwide for AD is now more than US $604 billion, which represents 1% of the world's aggregate gross domestic product (GDP). If Alzheimer's disease were a country, it would have the 18th largest GDP in the world. Costs for dementia care in the US are expected to continue to rise and will exceed $1.1 trillion by 2030.[4] Currently, more than 15 million caregivers provide an estimated 18.1 billion hours of unpaid care and has led to a significant strain on the economy.

The precise sequence of steps that leads to many neurodegenerative disorders often remains unknown. The brain has high metabolic demands, accounting for up to 20 percent of the body's total haul yet is only 2 % of the total weight. Even at rest significant metabolic requirements are needed for "housekeeping" or maintaining neuronal general health. Over time, it has been speculated that "wear and tear" of aging ultimately leads to bioenergetic failure and reduced capacity of neurons to function properly. Certain hubs of the brain may be more susceptible to disease. With aging, neuronal health may be compromised and may lead to increased vulnerability to neurodegenerative disorders- especially. AD.[5]

AD is the 6th leading cause of death in the US and is the only disorder among the leading causes of death for which there is no truly effective therapy.[6] The pathophysiological processes of AD results in the neurodegeneration and loss of synaptic function, beginning with higher order association cerebral cortical areas that subserve cognitive functions. These changes are gradual and take years to develop. AD has two major stages: 1) preclinical 2) Clinical. The preclinical phase is often difficult to diagnose and new methods are actively being pursued. Clinical presentation of the illness is marked by the gradual onset of deficits in memory, reasoning, insight, attention, and language. These symptomatic deficits impair the ability of the affected individual to perform accustomed activities at their normal level (e.g., job responsibilities, operating a motor vehicle, managing finances, operating appliances). Clinical diagnosis of early-stage symptomatic AD rests on the determination that a person has experienced the gradual onset of progressive intra-individual decline in two or more cognitive domains (almost always including memory) that is sufficient to impair usual function. The affected person may still be performing usual activities but not at his/her previous level and may subsequently progress to overt clinical impairment. As the disease progresses the cognitive impairment worsens and activities eventually are relinquished. In the final stages the ability to perform even basic functions (dressing, grooming, toileting, feeding) is lost and the person is totally dependent. The disorder is universally fatal; the course from symptomatic onset to death generally is 7-10 years.[7]

The current clinical diagnosis of AD is syndromic.[8] Capturing the history (typically from a collateral source such as family member or friend) of progressive cognitive and functional loss can be time-consuming and sometimes is inexact. AD frequently occurs with other comorbid disorders, such as stroke or parkinsonism, that may also contribute to the cognitive impairment and complicate the diagnosis.[9,10] Atypical presentations of AD occur[11] and non-AD dementing disorders may mimic AD.[12] Dementia screening tools (e.g., Mini Mental State Examination;[13] Montreal Cognitive Assessment[14]) that provide a "snapshot" of an individual's cognitive status at a point in time do not assess intra-individual decline and thus may result in false positive and false negative findings.[15] The Ascertain Dementia 8-item questionnaire (AD8) is an informant-based screening tool (another is the Informant Questionnaire on Cognitive Decline in the Elderly or IQCODE[16]) that, using the individual's previously attained abilities as the control, assesses functional change due to cognitive loss and thus captures intra-individual decline. The AD8 (Table 1) takes 2-3 minutes to complete by a collateral source, does not require pencil or paper, and has a positive predictive value of 87% for detecting even early-stage AD when two or more of the 8

questions are answered "yes" [17]. The AD8 primarily focuses on changes caused by memory and/or thinking difficulties. If dementia is suspected using the AD8, then a full evaluation is warranted. However, the current clinical diagnostic process can be still be in in accurate when performed by experienced clinicians at Alzheimer Disease Centers (17%).[18] Primary care physicians may have greater inaccuracy rates and indeed may fail to recognize dementia in >50% of affected patients.[19] The Affordable Care Act has now mandated annual wellness visits with cognitive screening to be performed. These changes may lead to greater necessity to identify individuals that may be at risk for developing AD [20-24].

Table 1. AD8: 8-item Informant Interview to Differentiate Aging and Dementia

Report only a change caused by memory and thinking difficulties:
1. Is there repetition of questions, stories, or statements?
2. Are appointments forgotten?
3. Is there poor judgment (e.g., buys inappropriate items, poor driving decisions)?
4. Is there difficulty with financial affairs (e.g., paying bills, balancing checkbook)?
5. Is there difficulty in learning or operating appliances (e.g., television remote control, microwave oven)?
6. Is the correct month or year forgotten?
7. Is there decreased interest in hobbies and usual activities?
8. Is there overall a problem with thinking and/or memory?

Over the past 10-15 years significant advances have been made in diagnostic testing for AD [21-25]. Biomarkers for detection of early changes in AD have rapidly expanded and are now being utilized to diagnose individuals in the preclinical stage. The amyloid-beta (Aβ) and tau proteins, when dysregulated, are the major neuropathological hallmarks of AD, Aβ plaque deposition in the cerebral cortical parenchyma and intraneuronal neurofibrillary tangles [26, 27]. Molecular biomarkers of Aβ and tau now are available with cerebrospinal fluid (CSF) assays, wherein the AD is often characterized by reduced CSF $A\beta_{42}$ and elevated CSF tau/p-tau,[28] or with increased cerebral retention of amyloid tracers, which have high affinity for Aβ in plaques, as detected by positron emission tomography (PET).[29] The US Food and Drug Administration has approved the [^{18}F] amyloid tracers florabetapir (Amyvid®) in 2012, flutemetamol (Vizamyl®) in 2013, and florbetaben (Neuraceq®) in 2014 for the evaluation of persons with progressive cognitive impairment. Tau tracers for PET imaging in AD also are being evaluated in research settings.[30] "Downstream" markers (i.e., reflecting the consequences of the molecular pathology of AD) include reduced temporoparietal cerebral metabolism as demonstrated by FDG-PET or cerebral volume loss (e.g., hippocampal atrophy; cortical thinning) as shown by structural magnetic resonance imaging (MRI).[31] Efforts continue to develop blood-based biomarkers for AD[32-34] . Currently, changes in blood based measures may be small and uncertainty remains as to how candidate blood markers reflect what is occurring within the central nervous system.

Routine incorporation of AD biomarkers into the clinical diagnostic process for AD must await standardization and validation (sensitivity and specificity) in practice settings.[35] There also are unresolved issues regarding the costs, reimbursement, and variable access to these potential tests in the community. In addition, problems still exist with regards to lack of standardization for many biomarkers. Importantly, the clinical utility of biomarkers must be demonstrated; absent this demonstration, third party payers, including the Centers for Medicare and Medicaid Services (CMS), do not currently reimburse amyloid PET imaging. The Imaging Dementia-Evidence for Amyloid Scanning (IDEAS) study, supported in part by CMS and led by the Alzheimer's Association, the American College of Radiology, and the American College of Radiology Imaging Network, began in 2016 to learn whether amyloid

PET imaging in a general clinical setting can benefit the diagnosis and care of AD in persons whose cognitive symptoms do not allow a definitive diagnosis by standard clinical methods.[36] More information about the IDEAS study and participating sites can be found at www.ideas-study.org.

Biomarkers ideally could move the diagnosis of AD from the current syndromic "black box" to an etiological diagnosis based on molecular pathology. Already, quantitative structural magnetic resonance imaging of the brain has become commonly accepted in the clinical assessment of suspected AD and can be easily performed on existing scans if the correct sequences are ordered .[37] Ongoing global standardization and harmonization efforts aim to permit generalized application of CSF biomarkers for the routine clinical diagnosis of AD.[38] Currently, results are often sent to certain reference labs for validation.

Clinical trials are now actively using biomarkers to potentially evaluate the efficacy of therapy. Anti-Aβ experimental therapies now incorporate either elevated retention of an amyloid tracer on PET scan or decreased levels of CSF $A\beta_{42}$ as part of their inclusion criteria. These next generation clinical trials are trying to identify the correct population of individuals that are at greatest risk for progressing to AD and would be most sensitive to pathological change. The promise of AD biomarkers also is highlighted by their inclusion in recent sets of clinical diagnostic criteria for AD. One set of criteria from an International Working Group (IWG)[39] requires biomarker evidence for the diagnosis of AD. The other set of criteria from working groups established by the National Institute on Aging (NIA) and the Alzheimer Association (AA)[40] suggest that biomarkers could be used to support a clinical diagnosis of AD but are not required (currently only within research criteria). The IWG and NIA-AA criteria are compared in Table 2, and a proposal to harmonize these two sets of criteria is shown in Table 3.

Table 2. Comparison of IWG Criteria and NIA-AA Criteria for Clinical Diagnosis of AD

Similarities

- Incorporate biomarkers for AD into the diagnostic process
- Move toward an etiologic diagnosis for MCI
  - "Prodromal AD" (IWG)
  - "MCI due to AD" (NIA-AA)

Differences

IWG	NIA-AA
"AD" refers only to the clinical stage	"AD" refers to the pathologic process, whether asymptomatic or symptomatic
Requires objective memory impairment (but not intra-individual decline)	Intra-individual decline and impairment (subjective and/or objective) in memory or non-memory domains
Abnormal biomarker required for diagnosis	Abnormal biomarkers support diagnosis but not required

Table 3. Key Recommendations to Harmonize Clinical Diagnostic Criteria for AD

Concept	"Alzheimer disease" refers to the brain disorder regardless of clinical status
Terminology	"Symptomatic AD" refers to the clinically expressed disorder, from very mild (encompassing "MCI due to AD" and "prodromal AD") to severe dementia
Biomarkers	On the successful completion of standardization efforts, the incorporation of molecular and degeneration biomarkers into the clinical diagnostic algorithm should be revisited but until then their role should be to help characterize atypical presentations to support clinical diagnoses
Memory	Amnestic presentations are the "typical" clinical phenotype for AD, but the diagnosis can also be made with non-amnestic presentations (especially with biomarker support)

The NIA-AA working groups also use *in vivo* biomarkers to characterize preclinical AD,[41] where the molecular pathology of AD is present prior to the appearance of symptoms. Increasing evidence indicates that cognitively normal older adults who are AD molecular biomarker-positive are at notably increased risk of developing symptomatic AD.[42-47] The use of biomarkers to identify preclinical AD thus now makes secondary prevention trials possible and is being actively investigated in individuals with genetic mutations that lead to AD (e.g. Dominantly inherited Alzheimer's Network (DIAN).[48]

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