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Sensitivity and Specificity of Diagnostic Accuracy in Alzheimer's Disease: A Synthesis of Existing Evidence

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Abstract

Purpose of the Study: This report synthesizes existing evidence to compare the accuracy of various Alzheimer's disease (AD) diagnostic approaches. **Design and Methods:** Meta-analyses and reviews of diagnostic accuracy of AD were identified through a search of the PubMed and Cochrane Library databases using the keyword combinations of "sensitivity specificity Alzheimer's disease diagnosis" and "accuracy of Alzheimer's disease diagnosis." **Results:** From 507 abstracts initially identified, 41 systematic reviews or meta-analyses were selected. Cerebrospinal fluid-tau demonstrated variable sensitivity (range 73.3%-100%) and specificity (range 70.0%-92.4%) in diagnosing AD when compared to neuropathological verification of clinical criteria for AD. Various positron emission tomography approaches showed a similar range of sensitivity (range 80.0%-100%) and specificity (range 62.0%-90%) as diagnostic protocols. **Implications:** Issues that remain in the study of AD diagnosis include the need to determine the comparative effectiveness of diagnostic approaches. Variations in study quality make empirically derived conclusions about the diagnostic accuracy of existing approaches tenuous.

Keywords

sensitivity, specificity, clinical, dementia, meta-analysis, systematic review

Introduction

Federal recognition to increase the understanding of and treatment modalities for Alzheimer's disease (AD) continues.[1] A cornerstone of any study of AD, whether it involves prevention, treatment, or another objective, is accurate diagnosis.[2] Emerging diagnostic techniques (such as neuroimaging or biomarkers) could serve as more accurate supplements to symptom-specific clinical approaches.[3] This report reviews and synthesizes existing evidence to determine the accuracy of various diagnostic techniques. In particular, we sought to determine whether neuroimaging tools or biomarkers are of similar or greater accuracy when compared to recommended clinical diagnostic criteria.

Current and Emerging Approaches to AD Diagnosis

The Alzheimer's association (initially called the Alzheimer's Disease and Related Disorders Association [ADRDA]), along with the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), established widely accepted clinical criteria for the diagnosis of AD.[4] These NINCDS-ADRDA clinical criteria were first created in 1984 and have evolved into more recent recommendations.[5,6] Core to these criteria are the presence of dementia symptoms that are assessed via comprehensive neuropsychological tests (eg, memory, language, perception, attention, constructive abilities, orientation, problem solving, and functional deficiencies). Similar domains are apparent in the *Diagnostic and Statistical Manual*'s Alzheimer's criteria.[7] Newly proposed criteria now provide a framework for what the Alzheimer's research community would consider a gold standard in clinical AD diagnosis—a documented presence of symptoms that are consistent with the clinical syndrome of dementia along with biomarker evidence for the pathology of AD.[8] Biomarkers are now recommended for inclusion in routine procedures for specific indications, with

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exclusions in place for other indications (see http://www.alz.org/research/funding/amyloid_imaging_task_force.asp).

With the integration of biomarkers to provide some indication of pathological decline, routine diagnostic practice may shift from the current or traditional understanding that AD is reflected in the presence of dementia symptoms (eg, memory impairment and cognitive decline) to an understanding of AD as a pathological disease that takes hold years before the appearance of clinical symptoms.[9]

To this end, considerable research has focused on biomarkers that serve as proxies for the neuropathological decline that occurs concurrently in the AD-afflicted brain in order to supplement symptom-reliant clinical criteria. For example, changes in cerebrospinal fluid (CSF) are potentially indicative of neurological disruptions in the brain.[10] Using lumbar punctures, clinicians and researchers have examined whether elevated concentrations of total tau proteins (T-tau), the 42 amino acid form of amyloid beta ($A\beta_{1\text{-}42}$), and phosphorylated tau protein (P-tau) in CSF serve as precursors to or parallel the neuropathological decline occurring in the AD-afflicted brain.[10]

Another approach to diagnosing AD is the use of neuroimaging, which can provide visual displays to examine changes in the size of, structure of, or activity in the brain (eg, cerebral atrophy and decreased uptake of glucose). Identifying these potential abnormalities in the brain can reflect AD or exclude other causes of dementia symptoms (eg, tumors). In AD, cells cannot take up glucose as well as during normal neurological function and one type of radiopharmaceutical, 18F-fluorodeoxyglucose (FDG), "can compete with glucose for absorption and metabolism"[11] in the brain.[12,13] FDG positron emission tomography (FDG-PET) can identify regions of the brain where FDG uptake is impaired. Another form of neuroimaging that can be used to diagnose AD is single-photon emission computed tomography (SPECT); unlike PET, SPECT scanning relies on photon-emitting isotopes instead of radioisotopes. In addition, SPECT imaging is used to assess regional blood flow, as reduction in oxygen use or blood flow is apparent in regions of the AD brain.[14] Computerized tomography uses a noninvasive scanning procedure that combines a number of X-ray pictures to generate a 2-dimensional brain image. Magnetic resonance imaging (MRI) relies on radio waves and magnetic fields to generate both 2- and 3-dimensional images of the brain.[15]

Electroencephalography (EEG) has also received attention for its potential to clinically diagnose AD. EEG is able to examine neuronal activity of the cerebral cortex. EEG has been utilized to examine the brain function in dementia, cognitive aging, and various neurological disorders.[14,16]

Purpose and Scope

This report synthesizes and compares the sensitivity and specificity of AD diagnostic protocols. Sensitivity is defined as the percentage of patients correctly classified as having AD according to a "gold standard" criterion (which may vary by study), whereas specificity is the percentage of patients correctly classified as not having AD. Earlier consensus guidelines suggest that an accurate diagnostic procedure in AD is one that has a sensitivity and specificity greater than 80%,[17] although in light of diagnostic protocols for other diseases this could be considered a fairly low threshold.[18]

The original scope of this review was to identify all single studies of AD diagnostic accuracy in order to conduct a systematic review or meta-analysis. However, our initial review revealed that a considerable number of reviews and meta-analyses of specific AD diagnostic procedures already exist, leading us to turn our focus to synthesizing this existing evidence. Specifically, our synthesis aimed to identify and compare the findings of systematic reviews, meta-analyses, or guidelines that examine diagnostic accuracy in AD.[19] Our synthesis question was as follows: "What is the accuracy of available Alzheimer's disease diagnostic procedures, and how does diagnostic accuracy vary across procedures?"

Methods

Identification of Evidence

The first author identified published studies through a search of the PubMed and Cochrane Library databases. The systematic review search query as well as the single study or narrow diagnosis filter was used on PubMed to identify systematic reviews or meta-analyses of diagnostic accuracy of AD. The key word combinations of "sensitivity specificity Alzheimer's disease diagnosis" and "accuracy of Alzheimer's disease diagnosis" were included. A supplemental search on Google.com was also conducted using these keyword combinations. The following inclusion criteria were applied to all abstracts: (1) the study was a meta-analysis or systematic review and (2) the study reported information related to the accuracy of AD diagnosis. The first author screened all abstracts for inclusion. The database search took place in January 2012. Following the abstract screening process, the first author retrieved all included reports. A hand search of reference sections of each included report was then conducted to identify additional systematic reviews or meta-analyses of interest.

Data Extraction and Synthesis

The following information was abstracted: (1) basic review characteristics, including whether the study was a meta-analysis and sample size (either number of individuals included or number of studies considered); (2) type of diagnostic procedures evaluated; and (3) results pertaining to the sensitivity and specificity of the diagnostic procedure. Following these extraction procedures, the eligibility criteria of initially selected reviews or meta-analyses were reconsidered. Final results were then categorized and cross-tabulated according to each type of diagnostic approach. Clinical criteria (which relied on earlier NINCDS-ADRDA/*Diagnostic and Statistical Manual of Mental Disorders* [DSM] criteria), CSF methods, PET, SPECT, MRI, and EEG were the focus of this synthesis, although as noted in Table 1 several other diagnostic protocols (eg,

Table 1. Characteristics of Synthesized Evidence (Meta-Analyses or Systematic Reviews).

Author, Year	Meta-Analysis	Diagnostic Test	Study Sample	Neuropathological Verification Included/discussed
American College of Medical Genetics/American Society of Human Genetics Working Group, 1995[20]		ApoE4		
Allan et al, 2010[21]		Tau, $A\beta_{1-42}$, MRI, SPECT, clinical criteria		X
Andreasen and Blennow, 2005[22]		Tau, $A\beta_{1-42}$		
Andreasen et al, 2003[23]		Tau, $A\beta_{1-42}$		
Bailey, 2007[24]		Tau, $A\beta_{1-42}$		
Bancher et al, 1998[25]		Biomarkers		
Blennow and Hampel, 2003[10]		Biomarkers	60 studies, 3900 persons with AD, 2200 controls	
Bloudek et al, 2011[3]	x	Tau, $A\beta_{1-42,}$ FDG-PET, SPECT, MRI	119 studies	
Cedazo-Minguez and Winblad, 2010[12]		PET		
Deisenhammer et al, 2009[26]		Tau, $A\beta_{1-42}$		
Dewan and Gupta, 1992[27]		Clinical diagnosis, SPECT		x
Dougall et al, 2004[28]		SPECT	48 studies, N = 3973	x
Dubois et al, 2007[6]		MRI, P-tau, T-tau, $A\beta_{1-42,}$ FDG-PET, SPECT	69 studies, 3900 persons with AD, 2170 controls	x
Durand-Martel et al, 2010[13]		FDG-PET	47 studies, N = 268	x
Formichi et al, 2006[29]		Tau, $A\beta_{1-42}$	N = 5992	
Guidelines.gov (EFNS, 2007; SIGN, 2006)[a]		Clinical diagnosis		x
Holtzman, 2011[30]		CSF biomarkers		
Jacova et al, 2007[31]		Neuropsychological testing		
Jagust, 2004[32]		PET, SPECT		
Jelic and Kowalski, 2009[16]		EEG	46 studies	
Jelic and Wahlund, 2007[33]		MRI, PET, EET		
Jellinger, 2010[34]		Biomarkers, clinical diagnosis		x
Kantarci and Jack, 2003[35]		Neuroimaging		x
Knopman et al, 2001[4]		Clinical, neuroimaging, biomarkers		x
Mitchell, 2009[36]	x	MMSE	34 studies, N = 26 109	
Mitchell, 2009[b,37]	x	Tau		
Mitchell and Brindle, 2003[38]		Tau, $A\beta_{1-42,}$ ApoE4, clinical diagnosis	5 studies, N = 1287	x
Patwardhan et al, 2004[39]	x	FDG-PET	15 studies	
Pupi et al, 2005[40]		PET		
Silverman et al, 1999[41]		MRI, SPECT, PET		x
Sjogren et al, 2003[42]		Tau, $A\beta_{1-42}$		
Small and Leiter, 1998[43]		Neuroimaging[b]		
Sonnen et al, 2008[44]		PET		
Sunderland et al, 2003[45]	x	$A\beta_{1-42}$	N = 4624	

(continued)

Table 1. (continued)

Author, Year	Meta-Analysis	Diagnostic Test	Study Sample	Neuropathological Verification Included/discussed
Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group, 1998[17]		Tau, $A\beta_{1\text{-}42}$, ApoE4		
Wahlund et al, 2005[46]		MRI	36 studies	
Waldemar, 1995[47]		SPECT		
Wiltfang et al, 2005[48]		Biomarkers		
Yuan et al, 2009[15]	x	FDG-PET, SPECT, MRI	24 studies, N = 1112	
Zakzanis, 1998[49]	x	Neuropsychological testing, MRI, PET, SPECT	27 studies, N = 1278	

Abbreviations: MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; PET, positron emission tomography; CSF, cerebrospinal fluid; MMSE, Mini-Mental State Examination; AD, Alzheimer's disease; FDG, 18F-fluorodeoxyglucose; EEG, electroencephalography; ApoE4, apolipoprotein E4; $A\beta_{1\text{-}42}$, 42 amino acid form of amyloid; P-tau, phosphorylated tau protein; T-tau, total tau protein.

[a] See http://guidelines.gov/syntheses/synthesis.aspx?id=16413&search=dementia.

[b] No sensitivity or specificity data reported.

neuropsychological testing and combination of biomarkers) were considered in a handful of reviews.

Results

Report Identification

From a total of 507 abstracts, 157 reports were retrieved by the first author. The primary reasons for limiting the number of reports from 507 to 157 were that (1) most of the abstracts initially identified did not focus on diagnostic accuracy of AD but on other topics; (2) there was a lack of information reported on the diagnostic accuracy of AD; and/or (3) the article focused on diagnostic accuracy for other disorders. After the first author screened these 157 reports, 36 reviews were considered for further synthesis. The principal reason for limiting these 157 reports to 36 was that the other 119 reports were single studies and not systematic reviews or meta-analyses of AD diagnostic accuracy. As noted previously, the original scope of this review was to identify all single studies of AD diagnostic accuracy, but the large number of meta-analyses and reviews that already existed led us to adopt the evidence-based synthesis approach reported here. Reviewing the bibliographies (via a manual search of the reference sections) of these included articles resulted in the identification of an additional 5 reviews or meta-analyses. Thus, 41 systematic reviews or meta-analyses served as the focus of this evidence-based synthesis.

Study Characteristics

The 41 reports included 7 meta-analyses and 34 reviews. A wide range of studies and participants (5-119 studies reviewed; 1112-26 109 patients pooled) were considered, although many reviews did not indicate the number of studies or participants included (see Table 1). In all, 12 of the reports examined the accuracy of CSF-tau criteria; 12 considered PET (5 focused on FDG-PET); 9 examined CSF-$A\beta_{1\text{-}42}$; 7 examined SPECT; 9 examined the diagnostic accuracy of existing clinical criteria; 6 considered MRI; and 2 examined EEG or other diagnostic techniques. Another 11 reports examined combinations of techniques and their diagnostic value.

Most of the reviews included did not specify whether the criterion measure of AD (eg, the "gold standard") was neuropathological verification (often considered the definitive method to reach an AD diagnosis),[6] in vivo clinical criteria, or a combination of both. As shown in Table 1, only 9 reviews or meta-analyses differentiated or even discussed their results according to neuropathological or in vivo AD diagnosis.

Accuracy of AD Diagnostic Procedures

Table 2 shows the results of the evidence-based synthesis of AD diagnostic procedures. The reported sensitivity (range 53.0%-100%) and specificity (range 55%-99%) of clinical diagnostic criteria were highly variable across systematic reviews. T-tau and P-tau demonstrated a sensitivity that ranged from 73.3% to 86% and a specificity that ranged from 70.0% to 92.4% in diagnosing AD. Another CSF compound, CSF-$A\beta_{1\text{-}42}$, yielded large sensitivity (range 85.0%-100%) and specificity (range 63.0%-90.8%) ranges. Various PET approaches indicated variable sensitivity (range 80.0%-100%) and specificity (range 62.0%-90%). Other techniques showed somewhat less, but nonetheless variable, accuracy in diagnosing AD including SPECT (range 63.0%-100%; range 65.0%-100%) and MRI (range 72.8%-85%; range 69.0%-89.0%). Two reviews examined EEG with wide-ranging results (range 19.0%-98%; range 63.0%-100%).

Diagnostic combinations were considered, and variation in accuracy was apparent in these findings as well (sensitivity range 36.0%-100%; specificity range 50.0%-100.0%). The most common combinations considered included various CSF biomarkers, including T-tau and P-tau (sensitivity = 81%; specificity = 91%),[21] T-tau, P-tau, and $A\beta_{1\text{-}42}$ (sensitivity 85%-90%; no specificity reported),[22] and T-tau and $A\beta_{1\text{-}42}$ (sensitivity = 36-100%; specificity = 50%-92%).[3,4,17,26,29,30,38,48] Combinations of neuroimaging techniques were also examined, including PET and SPECT (sensitivity = 85%-90%; specificity = 85%-90%).[32]

We further examined the findings of accuracy for those reviews or meta-analyses that reported neuropathological verification as the gold standard of AD diagnosis.[4,6,13,38,27,41] The sensitivity of clinical criteria (NINCDS-ADRDA) ranged from 76% to 93%, and the specificity ranged from 55% to 91%. For FDG-PET scans, sensitivity ranged from 84% to 93%, and specificity ranged from 58% to 74%.

While not an explicit focus of our review, our systematic search did yield several studies that compared the ability of diagnostic protocols to differentiate AD from other dementia subtypes. A recent meta-analysis[50] compared tau concentrations in controls, those with AD, and individuals with Lewy Body dementia, frontotemporal lobar degeneration, vascular dementia, and Creutzfeldt-Jacob disease. When compared to controls, tau and phosphorylated tau concentrations were only moderately or slightly elevated in dementia subtypes. The ability of tau and P-tau concentrations to differentiate the various dementia subtypes with AD ranged considerably (sensitivity 73%-91% and specificity of 74%-98%), leading the authors to conclude that insufficient diagnostic accuracy exists to differentiate dementia subtypes from controls or those with AD.[50] Similar findings were apparent in Knopman and colleagues' systematic review of AD diagnostic approaches at the time.[4] In their meta-analysis, Bloudek and colleagues found that FDG-PET appeared most effective in discriminating AD from those with other dementias (sensitivity = 92%; specificity = 78%), with CSF-P-tau and SPECT approaches showing less accuracy (sensitivity = 78%; specificity = 77%; sensitivity = 79%; specificity = 81%, respectively).[3]

Several diagnostic combinations were also examined for their accuracy in predicting the transition from mild cognitive impairment (MCI) to AD. Combining CSF biomarkers (tau, P-tau, and $A\beta_{1\text{-}42}$) showed considerable sensitivity (range 83%-90%) and specificity (range 64%-100%) in predicting this transition.[12,21,30] A meta-analysis by Yuan et al found that FDG-PET appeared more accurate in predicting conversion of MCI to AD

Table 2. Synthesized Sensitivity and Specificity Estimates for Diagnostic Accuracy of Alzheimer's Disease: Clinical, CSF, PET, SPECT, and MRI.

	Clinical[a]		CSF		PET		SPECT		MRI	
Author, Year	SN, %	SP, %	SN, %	SP, %	SN, %	SP, %	SN, %	SP, %	SN, %	SP, %
Allan et al, 2010[21]			86[b]	89[b]			63	93		
Andreasen and Blennow, 2005[22]			>80[b]	>80[b]						
			82[c]	88[c]						
Andreasen et al, 2003[23]			86[b]	91[b]						
			82[c]	88[c]						
			86[d]	91[d]						
Bailey, 2007[24]			85-90[b]	85-90[b]						
			82[c]	88[c]						
Blennow and Hampel, 2003[10]			86[b]	90[b]						
			81[c]	90[c]						
			80[d]	92[d]						
Bloudek et al, 2011[3]			80[b]	82[b]	90[e]	89[e]	90	85	83	89
			82[c]	90[c]						
			80[d]	83[d]						
Cedazo-Minguez and Winblad, 2010[12]					94	73-78				
Dewan and Gupta, 1992[27]	88%	91%					86	96		
Dougall et al, 2004[28]							68-100	65-91		
Dubois et al, 2007[6]			86[b]	90[b]	88-95	62-74	65-80	65-93	>85	>85
			81[c]	90[c]						
			80[d]	92[d]						
Durand-Martel et al, 2010[13]	76%	58%			84[e]	74[e]				
					92.9	78.6				
Formichi et al, 2006[29]			84.6[b]	89.8[b]						
			80.8[c]	89.1[c]						
EFNS, 2007	81%	70%								
SIGN, 2006		≤80%								
Jacova et al, 2007[31]	53-80%	67-99%								
Jagust, 2004[32]					93	76				
Jelic and Wahlund, 2007[33]					≥80[f]	≥80[f]			≥80	≥80
Knopman et al, 2001[4]	81%	70%	78-92[b]	81-83[b]	93	63	77-89	43-94		
			80-97[c]	86-95[c]						
Mitchell, 2009b[37]			77.6[d]	87.9[d]						
Mitchell and Brindle, 2003[38]	93%	55%	80[d]	84[d]						
Patwardhan et al, 2004[39]					86	86				
Pupi et al, 2005[40]					93	73				
Silverman et al, 1999[41]					93	74	78	71	79-83	69-85
Sjogren et al, 2003[42]			86.1[b]	90.8[b]						
			81.6[d]	88.4[d]						
Sonnen et al, 2008[44]					100	90				
Sunderland et al, 2003[45]			92[b]	89[b]						

(continued)

Table 2. (continued)

	Clinical[a]		CSF		PET		SPECT		MRI	
Author, Year	SN, %	SP, %	SN, %	SP, %	SN, %	SP, %	SN, %	SP, %	SN, %	SP, %
Ronald and Nancy Reagan Research Institute of the Alzheimer's Association and the National Institute on Aging Working Group, 1998[17]			100[b] 82[c]	63[b] 70[c]						
Wahlund et al, 2005[46]									>80	>80
Waldemar, 1995[47]							90-100	85-100		
Wiltfang et al, 2005[48]			78-85[b] 44-94[d]	81-84[b] 90-100[d]						
Yuan et al, 2009[15] (conversion from MCI to AD)					88.8[e]	84.9[e]	83.8	70.4	72.8	81.0
Zakzanis, 1998[49]					95	71				

Abbreviations: MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; PET, positron emission tomography; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; AD, Alzheimer's disease; FDG, 18F-fluorodeoxyglucose; ADRDA, Alzheimer's Disease and Related Disorders Association; DSM-III-R, *Diagnostic and Statistical Manual of Mental Disorders* (Third Edition Revised); $A\beta_{1\text{-}42}$, 42 amino acid form of amyloid; P-tau, phosphorylated tau protein; T-tau, total tau protein; SN, sensitivity; SP, specificity.

[a] Includes NINCA-ADRDA, *DSM-III-R*, or similar clinical assessments of dementia symptoms.

[b] Aβ1-42.

[c] T-tau.

[d] P-tau

[e] FDG-PET.

[f] Perfusion, dopamine, and glucose tested.

(sensitivity = 88.8%; specificity = 84.9%) when compared to other imaging techniques such as SPECT (sensitivity = 83.8%; specificity = 70.4%) or MRI (sensitivity = 72.8%; specificity = 81.0%).[15]

Discussion

The findings of recent meta-analyses emphasize that CSF-tau and $A\beta_{1\text{-}42}$ assays show some promise as supplements to clinical criteria relying on earlier NINCDS-ADRDA or *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition [*DSM-IV*]) guidelines.[6,36] Along with CSF protocols, FDG-PET has potential as an adjunct to clinical criteria. The FDG-PET has also demonstrated slightly more accuracy when compared to other diagnostic approaches; for example, FDG-PET appeared superior to SPECT when diagnosing AD.[4] In addition, a recent meta-analysis suggests that FDG-PET offers diagnostic value that is superior to CSF-tau and SPECT.[3] While both CSF and FDG-PET show potential as diagnostic tools in AD, the few comparative studies available seem to imply that FDG-PET is a more accurate supplement to clinical diagnosis of AD at this time.[15] However, direct comparisons between various biomarkers and their efficacy within single studies or reviews are not common.

Combining multiple CSF assays or markers and/or neuroimaging approaches appears to enhance the accuracy of AD diagnosis.[12,21] In addition, reviews in the late 1990s and early 2000s concluded that high levels of CSF T-tau and lower CSF levels of $A\beta_{1\text{-}42}$ in the earlier stages of AD demonstrated their ability to diagnose the disease sooner than was possible at the time,[17,42] and CSF biomarkers are still under consideration for use in routine diagnostic practice (see http://alz.org/research/science/earlier_alzheimers_diagnosis.asp). A recent meta-analysis emphasize the value of FDG-PET in predicting conversion from MCI to AD when compared to SPECT or structural MRI techniques.[15]

Various limitations are important to note when considering the conclusions of this summary of evidence. While cross-referencing did occur, it is possible that additional reviews and systematic analyses were missed and thus not considered in this evidence-based synthesis. As mentioned earlier, recent guideline recommendations have begun to emphasize identification of neuropathological decline through various biomarkers as part of standard or routine AD diagnostic protocols.[8,51] For this reason, the ''clinical criteria'' utilized in many reviews and meta-analyses rely on earlier, symptom-specific guidelines that do not match these evolving criteria. Systematic reviews or meta-analyses that separated their findings based on interdisciplinary assessments in addition to NINCDS-ADRDA or DSM-IV guidelines were also unavailable for this evidence-based synthesis. The reviews included tended to focus on individuals across all stages of dementia, with an emphasis on those in the moderate to severe stages. The focus on already synthesized evidence may have also screened out recent individual studies that could have added important information;[52,53] for example, other PET imaging mechanisms are available such as Pittsburgh Compound B (PiB-PET) or Florbetapir F 18 tracers that can image amyloid plaques in PET scans. One meta-analysis that was completed and published after this synthesis was concluded (February 2012)[54] found that among 7 (N = 270 patients) studies, FDG-PET had a pooled sensitivity of 78.7% and a specificity of 74.0% in predicting conversion from MCI to AD. In 6 (N = 222 patients) studies, PiB-PET had a higher sensitivity (93.5%) but a lower specificity (56.2%) in predicting the conversion of MCI to AD. As the diagnostic value of these emerging PET imaging tracers appear quite high in some single studies (sensitivity and specificity estimates in the 90% ranges for Florbetapir F 18),[53] considering these diagnostic tools in subsequent meta-analyses would help to advance clinical understanding of their utility in AD diagnosis.

The extensive ranges of sensitivity and specificity reported for various diagnostic protocols are due in part to heterogeneous study quality and definitions of AD. Many reviews did not report length of follow-up in their analyses, include various study characteristics to examine variation across reports, or consider whether results diverged across pathological verification or in vivo AD diagnosis when analyzing accuracy.[6] The latter is particularly problematic. Only a handful of the reviews included here differentiated or presented results that used pathological verification of AD as a criterion against which to test the sensitivity and specificity of various diagnostic procedures (see Table 1). Sensitivity and specificity results are similarly diverse, as summarized previously. The majority of reviews and meta-analyses combined single studies that used clinical guidelines (NINCDS-ADRDA or DSM-IV) and/or pathological verification as gold standards for AD diagnosis when reporting results. Reasons for this included maximizing study samples for meta-analytic purposes.[40] However, this is a potentially critical limitation as in many patients, sensitivity of in vivo clinical diagnosis may be high but specificity is lower. This trend of high sensitivity at the expense of specificity has emerged in recent analyses of the accuracy of clinical diagnosis of AD in the National Institute on Aging Alzheimer's Disease Centers in the United States.[55] Interpreting the diagnostic accuracy of many of the procedures presented here is therefore challenging; where possible, future reviews should differentiate the standard of AD diagnosis when presenting results. Given that AD is represented as a diverse set of clinical conditions, the search for an accurate diagnosis of the disease is further complicated. Alternatively, the use of pathological diagnosis as a gold standard is challenging since a proportion of older persons that fulfill predetermined criteria for AD (which themselves have been subjected to recent revision)[56] do not present with clinical symptoms while alive.[55] In addition, AD often co-occurs with other comorbid dementias that can complicate the accuracy of AD diagnosis.

Our results align with the findings from a recent meta-analysis on the diagnostic accuracy of biomarkers to predict conversion to AD diagnosis.[52] Of the 142 longitudinal studies focusing on biomarkers of interest, there was extensive variation across studies in (1) how outcomes were reported; (2) selection biases and appropriate blinding; (3) missingness in data points; and (4) the varying intervals between when a diagnostic test is

performed and when follow-up assessments are conducted. In general, the evidence base of biomarker diagnostic accuracy according to Noel-Storr et al[52] is small, and conclusions of accuracy as well as study quality is heterogeneous. If there is a clear recommendation that emerges from this work as well as our evidence-based synthesis, it is the need to adhere to established reporting standards of diagnostic accuracy recommended in the Standards for Reporting of Diagnostic Accuracy and Quality Assessment of Diagnostic Accuracy Studies checklist (the STARD Statement; see http://www.stard-statement.org/).[57] The STARD checklist provides 25 items designed to ensure quality reporting of diagnostic accuracy, and it appears that many studies of biomarkers or other AD diagnostic protocols do not follow these rigorous standards.[52] For the field of AD diagnostic accuracy to evolve and yield more consistent findings to guide clinical practice, the STARD reporting guidelines should be followed.

In order to facilitate clinical decision making, more comparativeness effectiveness research across emerging diagnostic techniques is also required. The available evidence appears equivocal; for example, using pathological verification as the criterion of AD diagnosis, we found that brain SPECT was less sensitive and more specific for AD diagnosis than established clinical criteria.[32,28] Other reviews found that combining clinical criteria with CSF biomarkers and imaging data or FDG-PET resulted in more accurate prediction of AD than if clinical criteria alone were utilized.[6,13,17,34] Existing scientific and clinical gaps make it difficult to determine, however, whether the use of CSF, FDG-PET, or similar tools truly adds value to recommended clinical criteria.[4] Moreover, the invasive nature of some biomarker techniques, such as the lumbar puncture used for CSF protocols, may raise a number of other issues for patients and their families (eg, ranging from headaches or other side effects to the troubling historical legacy of spinal tap procedures for African Americans; see http://www.cdc.gov/tuskegee/index.html). It is imperative that researchers and clinicians continue to critically appraise not only the accuracy of emerging diagnostic techniques in AD but also their perceived benefits for persons with AD and their families throughout the disease trajectory.

Declaration of Conflicting Interests

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