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REVIEW

Increasing Precision of Clinical Diagnosis of Alzheimer's Disease Using a Combined Algorithm Incorporating Clinical and Novel Biomarker Data

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ABSTRACT

Establishing the in vivo diagnosis of Alzheimer's disease (AD) or other dementias relies on clinical criteria; however, the accuracy of these criteria can be limited. The diagnostic accuracy is 77% for a clinical diagnosis of AD, even among experts. We performed a review through PubMed of articles related to specific diagnostic modalities, including *APOE* genotyping, cerebrospinal fluid (CSF) testing, fludeoxyglucose F 18 positron emission tomography (PET), amyloid PET, tau PET, computed tomography (CT), single-photon emission CT, magnetic resonance imaging (MRI), and B12 and thyroid-stimulating hormone screening, to determine the specificity and sensitivity of each test used in the clinical diagnosis of AD. We added a novel immunomagnetic reduction assay that provides ultrasensitivity for analyzing the levels of plasma tau and beta amyloid 42 ($A\beta_{42}$). The sensitivity and specificity of the current diagnostic approach (structural CT or MRI with screening labs) remain low for clinical detection of AD and are primarily used to exclude other conditions. Because of limited diagnostic capabilities, physicians do not feel comfortable or skilled in rendering a clinical diagnosis of AD. Compounding this problem is the fact that inexpensive, minimally invasive diagnostic tests do not yet exist. Biomarkers (obtained through CSF testing or PET imaging), which are not routinely incorporated in clinical practice, correlate well with pathologic changes. While PET is particularly costly and difficult to assess, CSF measures of tau and beta amyloid are not costly, and these tests may be worthwhile when the tiered approach proposed here warrants further testing. There is a need for developing bloodborne biomarkers that can aid in the clinical diagnosis of AD. Here we present a streamlined questionnaire-enriched, biomarker-enriched approach that is more cost-effective than the current diagnosis of exclusion and is designed to increase clinical confidence for a diagnosis of dementia due to AD.

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INTRODUCTION

The original criteria described by the working group formed by the National Institute of

Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) (referred to as the NINCDS-ADRDA criteria) [1] set forth tiers of probability for confidence in a diagnosis of Alzheimer's disease (AD). The highest tier was "definite AD", which was autopsy confirmed. The next tier was "probable AD", which presented as a progressive amnestic disorder with dementia that affected two areas of cognition and functional impairment without other causes identified. "Possible AD" was described as a progressive amnestic syndrome that could have other contributors to the cognitive impairment (e.g., stroke, epilepsy).

These definitions stayed constant for almost 3 decades. In 2011, the National Institute on Aging–Alzheimer's Association (NIA-AA) working group met to review and update the diagnostic criteria (Table 1). The first principle is that, to have AD, one must have dementia [2]. The updated definition of dementia is cognitive impairment that interferes with the ability to function at work or at usual activities that is associated with a decline from a previous level of functioning and that is not caused by delirium or a psychiatric disorder [2]. Features discovered on history and examination should include the involvement of at least two cognitive domains, such as memory, reasoning and judgment, visuospatial, language, personality, behavior, and comportment. According to the 2011 NIA-AA guidelines, the diagnosis of AD requires that certain core criteria be met [2, 3]: report of cognitive concern by patient, caregiver, or clinician; gradual onset over months to years; evidence of longitudinal cognitive decline; differential diagnosis that rules out vascular, traumatic, and medical causes of cognitive decline; and objective evidence of impairment in two or more cognitive domains and inability to function at work or usual activities. Like the older NINCDS-ADRDA criteria, the tiers of probability included "proven AD", "probable AD", and "possible AD". In this schema, proven AD is that which is confirmed by widely accepted neuropathology criteria at autopsy or after biopsy. Probable AD refers to evidence of amnestic predominant dementia that has an insidious onset, history of progressive worsening, and no evidence of cardiovascular

Table 1 Diagnostic guidelines for Alzheimer's disease from the National Institute on Aging–Alzheimer's Association Adapted from McKhann et al. [2]

Disease state	Definition
Dementia core criteria	Cognitive or behavioral symptoms that interfere with the ability to function at work or at usual activities, represent a decline from previous levels of functioning, and are not explained by delirium or major psychiatric disorder
	The cognitive or behavioral impairment involves a minimum of two of the following domains: impaired ability to acquire and remember new information, impaired reasoning and handling of complex tasks, impaired visuospatial abilities, impaired language functions, and changes in personality or behavior or comportment
Probable Alzheimer's dementia	Meets criteria for dementia, in addition to insidious gradual onset, history of worsening cognition by report or observation, or initial and most prominent cognitive deficits in either amnestic (impaired learning or recent recall) or non-amnestic (language, visuospatial, or executive dysfunction)
Possible Alzheimer's dementia	Above criteria with:
	Atypical course (sudden onset, insufficient historical detail, or objective progressive decline) or etiologically mixed presentation (meets all core clinical criteria, but has evidence of cerebrovascular disease, features of dementia with Lewy bodies, or evidence of another neurologic or non-neurologic disease or medication that could affect cognition)
Proven Alzheimer's dementia	Patient meets the clinical and cognitive criteria for AD dementia, and the neuropathologic examination demonstrates the presence of the AD pathology

disease, dementia with Lewy bodies, frontotemporal dementia, or aphasia. Possible AD refers to amnestic predominant dementia that has an atypical course or an etiologically mixed presentation, such as possible comorbidities that could contribute to the dementia presentation.

The NIA-AA working group reviewed biomarker evidence to support a clinical diagnosis of AD. They defined AD pathophysiology as either (1) beta amyloid (Aβ) seen on cerebrospinal fluid (CSF) testing or amyloid positron emission tomography (PET) or (2) neuronal injury as documented by demonstration of tau on CSF testing, fludeoxyglucose F 18 (^{18}F-FDG) PET, or evidence of atrophy on structural magnetic resonance imaging (MRI). They concluded that probable AD with evidence of AD pathophysiology strengthened the probability of AD as the pathology but left this criterion as informative but not essential. In contrast, the International Working Group (IWG) [4] described the specific clinical phenotype (typical AD) as episodic memory impairment that occurred gradually and progressively and was reported by the patient or informant as having persisted for more than 6 months; in addition, the patient must display objective evidence of an amnestic syndrome of the hippocampal type based on significantly impaired performance on an episodic memory test. In contrast to the report of the NIA-AA working group, the IWG did consider biomarker evidence as not only supportive but as also essential. They defined in vivo evidence of Alzheimer's pathology as one of the following: decreased $A\beta_{1-42}$, together with increased total tau (T-tau) or phospho-tau (P-tau) in the CSF; increased tracer retention on amyloid PET; or AD autosomal dominant mutation present in *PSEN1*, *PSEN2*, or *APP*.

The consequence of guidelines that fail to incorporate biomarker evidence of support is that biomarker evidence is not routinely used in clinical practice. Historically, the diagnosis of AD has been approached by excluding other health conditions. In other words, the diagnosis of AD has been and continues to be a diagnosis of exclusion.

INACCURACY OF DIAGNOSIS OF ALZHEIMER'S DISEASE IN CLINICAL PRACTICE

The timely diagnosis of AD is an unmet need in clinical practice. Physicians are reluctant to make a diagnosis of dementia and, more specifically, a diagnosis of dementia caused by AD. The consequence of this reluctance is that diagnosis is delayed by an average of 2–3 years after symptom onset [5, 6]. In addition, one study evaluating the clinical diagnosis found that up to 50% of patients with any form of dementia are not formally diagnosed during life [7].

Not only is there a delay in diagnosis, but there is also evidence that a diagnosis of AD can often be quite inaccurate. Twenty-five percent of patients clinically diagnosed with probable AD during their lifetime did not have evidence of AD at autopsy [8]. In a clinical imaging/pathology series of 57 individuals clinically diagnosed with AD, 13 (23%) had no ($n = 7$) or sparse ($n = 6$) Aβ plaques at autopsy. Twelve of these individuals were diagnosed neuropathologically with a dementia disease other than AD, most frequently caused by aggregation of tau. Thus, diagnostic accuracy is 77% for a clinical diagnosis of AD, even among the experts. In another study, florbetaben PET was consistent with histopathologic results in all 12 patients for whom standard uptake value ratios (SUVRs) were available [9].

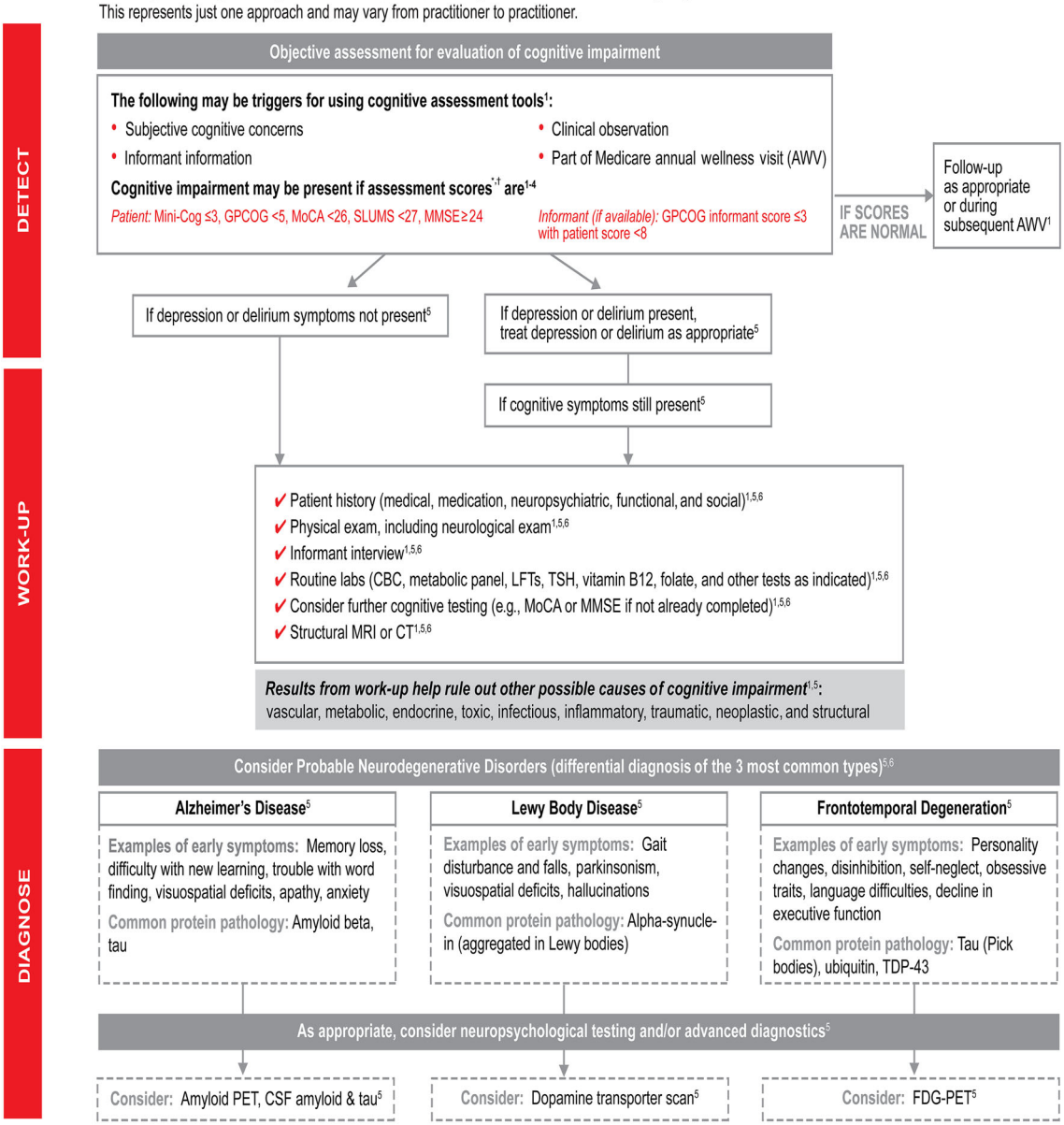
These data show that it is imperative that the clinical diagnosis be improved without a commensurate increase in cost. Thus, the diagnosis of AD dementia must transition from a diagnosis of exclusion to a diagnosis of inclusion. A solution might include a tiered approach with the incorporation of questionnaires and biomarkers. A representative outline of current practice is shown in Fig. 1.

A NEW TIERED APPROACH TO DIAGNOSING ALZHEIMER'S DISEASE

A new tiered approach to diagnosing AD could allow a more accurate diagnosis with lower cost

Using a Stepwise Approach to Diagnose Alzheimer's Disease

An example of a diagnostic algorithm to assess, detect, and diagnose Alzheimer's disease in your practice.
This represents just one approach and may vary from practitioner to practitioner.



Please note: The above is not all-inclusive and expresses only some of the more widely recognized tools for cognitive assessment. For additional diagnostic resources, please visit: Alz.org and Actonalz.org. *No one tool is recognized as the best brief assessment to determine if a full dementia evaluation is needed. Cut-off scores may vary by reference as well as the education level of the patient. †A cut point of <3 on the Mini-Cog has been validated for classifying subjects as "probably impaired," but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of ≤3 is recommended as it may indicate a need for further evaluation of cognitive status.[7,8]

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◀**Fig. 1** A proposed stepwise approach to assessing a patient for dementia. It incorporates details that include the traditional diagnosis of exclusion while preparing the reader for the possibility of incorporating advanced biomarkers. *CBC* complete blood count, *CSF* cerebrospinal fluid, *CT* computed tomography, *FDG-PET* fludeoxyglucose F 18 positron emission tomography, *GPCOG* General Practitioner Assessment of Cognition, *LFTs* liver function tests, *Mini-Cog* Mini-Cognitive Assessment Instrument, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *SLUMS* Saint Louis University Mental Status, *TDP-43* TAR DNA-binding protein 43, *TSH* thyroid-stimulating hormone. Copyright Eli Lilly and Co., all rights reserved. Used with permission

and higher sensitivity. Herein, a revised approach to the current diagnostic algorithm is proposed. The rationale for each step is explained. This article is based on previously conducted studies and does not involve any new studies of human or animal subjects performed by any of the authors.

Step 1: Structured Questionnaires

Informant-based questionnaires could be incorporated into the diagnostic process. These questionnaires could be used routinely in both clinical and research settings to differentiate between individuals with amnestic mild cognitive impairment (MCI) and AD from individuals who are cognitively normal [10, 11]. The Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) and the Ascertain Dementia 8-Item Informant Questionnaire (AD8) have demonstrated good diagnostic accuracy for AD and have been found to correlate well with other conventional cognitive screening tests, such as the Mini-Mental State Examination (MMSE) [12, 13].

The Alzheimer's Questionnaire (AQ) is a 21-item, informant-based assessment designed for ease of use in the clinical setting that has demonstrated high sensitivity and specificity for both amnestic MCI and AD [14, 15]. The concurrent validity of the AQ with other established measures of cognition was demonstrated by Malek-Ahmadi et al. [16], who found that the AQ correlates strongly with the Clinical Dementia Rating Sum of Boxes and correlates moderately with the MMSE and Montreal Cognitive Assessment (MoCA).

The AD8 is also a screening interview. It is a brief, sensitive screening measure that reliably differentiates between individuals with and without dementia. The AD8 comprises eight yes/no questions asked of an informant to rate change by querying memory, orientation, judgment, and function [12], and it takes approximately 2–3 min for the informant to complete. The AD8 has a sensitivity of 84% and specificity of 80% as well as excellent ability to discriminate between non-demented older adults and those with mild dementia (92%) regardless of the cause of impairment. The sensitivity and specificity of AD8 were determined in a 2006 study involving 255 patient-informant dyads, and these data were subsequently compared with the independently derived Clinical Dementia Rating and with patients' performance on neuropsychologic tests [12]. Like the AQ, the AD8 is highly correlated with the Clinical Dementia Rating and neuropsychologic testing.

The IQCODE was developed as a way of measuring cognitive decline from a premorbid level using informant reports. Each item is rated on a 5-point scale from 1, meaning "much better", to 5, meaning "much worse", and the ratings are averaged over the 16 items to give a score ranging from 1 to 5, with 3 representing no change on any item. In clinical situations, a screening cutoff of 3.44+ on the Short IQCODE is a reasonable compromise for balancing sensitivity and specificity.

The informant-based questionnaires as a group have high sensitivity, specificity, and area under the curve (AUC) in differentiating normal controls from AD patients. The sensitivity and specificity of the AD8 are 85% and 86%, respectively, with an AUC of 0.83 [12]. The sensitivity and specificity of the IQCODE are 79% and 82%, respectively, with an AUC of 0.85 [13]. The sensitivity and specificity of the AQ are 99% and 96%, respectively, with an AUC of 0.99. All of these questionnaires are simple to administer, informant-based, and not

time-consuming. More importantly, they allow structure for the primary care physician or specialist to capture incident cognitive decline.

For the purposes of specificity, additional questions to detect dementia with Lewy bodies (e.g., the Lewy Body Composite Risk Score [LBCRS]) [17] and frontotemporal dementia [18] could be added without significant increases in the burden of time.

Step 2: Aggregate Risk Analysis

Epidemiologic studies have shown that a variety of health conditions increase the risk for AD dementia. The patient's medical history is gathered at the time of the consultation to ascertain whether medical conditions such as diabetes, hypertension, hypercholesterolemia, head injury, or cardiovascular disease are present. During the past decade, models have been proposed to quantify individual risk for developing AD on the basis of a patient's individual demographics. These models incorporate age, family history, health conditions, and other factors to estimate risk (Table 2). On the basis of aggregate risk scoring, a score of less than 5 is low risk, 5-12 is moderate risk, and 12 and above is high risk [19, 20]. Doing an aggregate risk analysis during the consultation enriches the probability of AD if the score is high.

Table 2 Aggregate risk scoring for risk factors for Alzheimer's disease Adapted from Kivipelto et al. [19] and Norton et al. [20]

Risk factor	Odds ratio
A first-degree relative with AD	3.0
History of head injury with LOC	2.0
Age >65 years	1.0
Age >75 years	4.0
Age >85 years	16.0
Education <7 years	3.6
Female sex	1.5
Systolic BP >140 mmHg	2.2
BMI >30 kg/m^2	2.3
Cholesterol >6.5 mmol/l	1.9
APOE ε4 positivity	4.0
History of stroke	2.4
History of myocardial infarction	2.5
Untreated type 2 diabetes mellitus	2.0
Low physical activity (sedentary)	1.7
Continuation of smoking	2.3

BMI body mass index, *BP* blood pressure, *LOC* loss of consciousness

Step 3: Bedside Cognitive Screening

A variety of brief cognitive tests were developed for assessing general cognitive function. The use of the AD8 in conjunction with a brief assessment, such as assessing the patient's ability to remember a word list, could improve clinicians' ability to detect dementia in the primary care setting to 97% for dementia and 91% for MCI [12]. Below are a few of the more commonly used and easier to administer measures. Several diagnostic tests are now available for use in primary care as alternatives to the MMSE.

Mini-Mental State Examination (MMSE)

The MMSE is a copyrighted test that has frequently been used for the initial assessment of cognitive impairment. The MMSE has increasing sensitivity as the decline of the score over time is taken into account [21]. It is quick and easy to administer and can track the overall progression of cognitive decline, but it is not considered to be a good test for the definitive diagnosis of AD [22].

Mini-Cognitive Assessment Instrument (Mini-Cog)

The Mini-Cog combines an uncued three-item recall test with a clock-drawing test that serves as a recall distractor [23]. The Mini-Cog and the MMSE have similar sensitivity (76% vs. 79%, respectively) and specificity (89% vs. 88%, respectively) for dementia. The shortness of the Mini-Cog is a distinct advantage when the goal is to improve recognition of cognitive impairment in primary care [23].

Short Blessed Test (SBT)

The SBT is easily administered by a nonphysician and has been shown to discriminate among mild, moderate, and severe cognitive deficits [24, 25]. It consists of the items in the Blessed Orientation-Memory-Concentration Test, includes three orientation questions (month, year, and time of day), counting from 20 to 1, saying the months backward, and recalling a five-item name and address memory phrase [24]. The SBT is quite sensitive to early cognitive changes due to AD.

Saint Louis University Mental Status (SLUMS)

The SLUMS is a 30-point, 11-item, clinician-administered screening questionnaire that tests for attention, numeric calculation, immediate and delayed recall, animal naming, digit span, clock drawing, figure recognition/size differentiation, and immediate recall of facts from a paragraph [26]. In particular, the clock drawing test is designed to assess impairment in executive function. Due to copyright issues, the Veterans Administration has stopping using the MMSE, and they and others now use the SLUMS instead.

Montreal Cognitive Assessment (MoCA)

The MoCA is a brief cognitive screening tool with a high sensitivity and specificity for detecting MCI in patients who perform within the normal range of the MMSE [27]. The limitation of the MoCA may be its more complex interpretation, and it requires training to be administered properly.

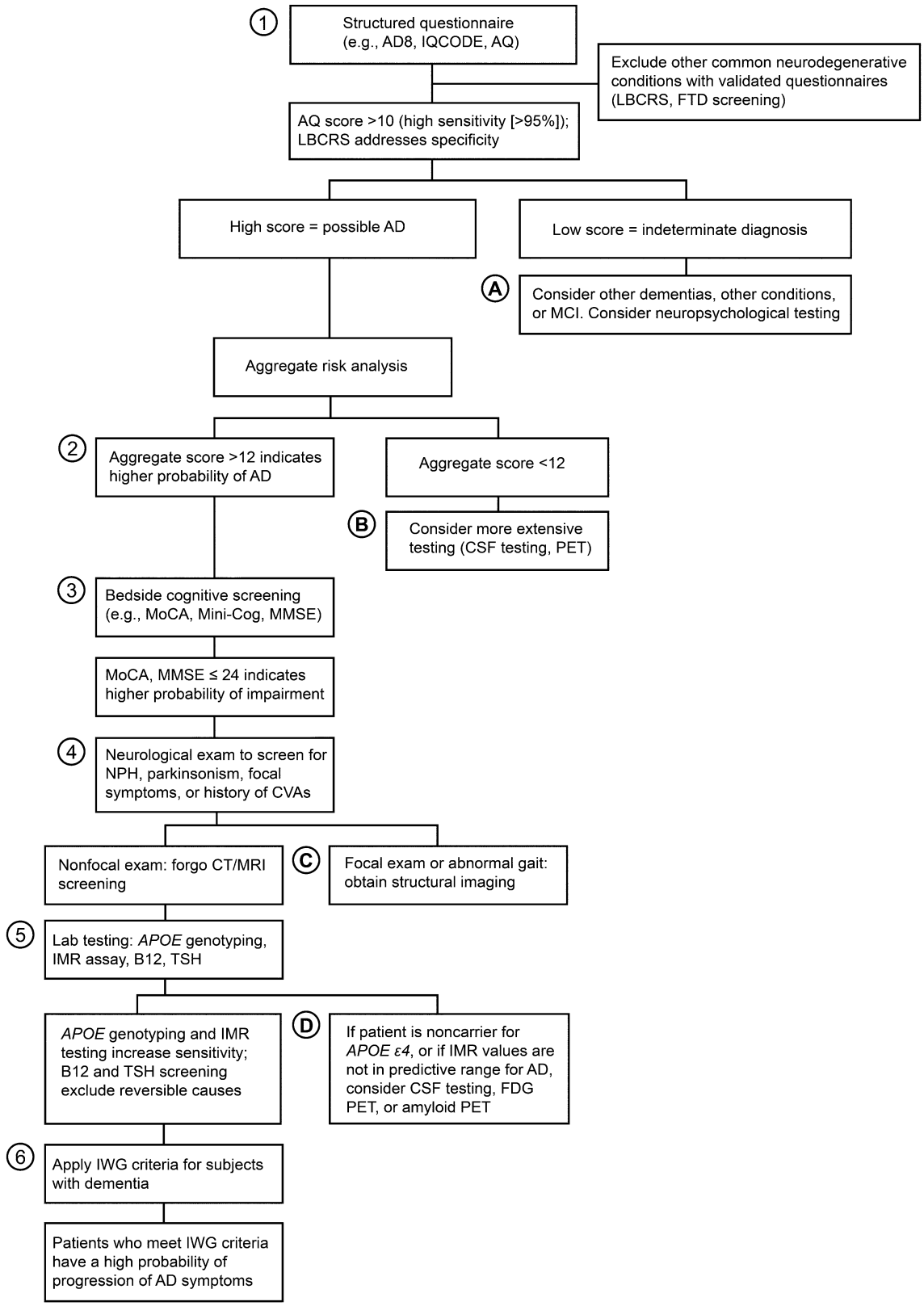
Step 4: Physical and Neurologic Examination

The potential for reversible dementias is commonly pursued in the diagnostic consideration but the yield is quite low. In one meta-analysis, conditions requiring neuroimaging made up only 2.2% of cases with reversible cause seen in less than 10% of total cases. In fact, the meta-analysis found that only 0.6% of dementia cases actually reversed partially or fully [28].

A comprehensive physical and neurologic examination can detect incident focality (e.g., hemiparesis, asymmetry of tone or reflexes, hemi-sensory changes) and gait abnormalities. This examination can be used to detect cerebrovascular disease, mass lesions, parkinsonism, or communicating hydrocephalus [29]. Patients who show no salient neurologic abnormalities on examination have a lower probability that imaging studies will find an abnormality that needs intervention.

Though controversial and counter to conventional practice, we recommend that in the absence of abnormal neurologic findings on examination, structural imaging should not be obtained. The current practice guideline is to incorporate structural imaging as part of the diagnostic evaluation for AD [2, 3] to exclude other conditions. This practice comes from the previous American Academy of Neurology guidelines. In a class II study, 5% of patients had a clinically significant structural lesion (i.e., a potentially treatable lesion) but no features in their history or examination that would have predicted the lesion. Thus, the recommendation is to include CT or MRI in the patient's initial evaluation to avoid missing any treatable conditions [30]. However, this percentage means the number needed to treat (NNT) is 1 in 20. At an estimated cost of $1000 per scan, that is $20,000 per identified treatable condition.

The obvious question is, "Does obtaining structural imaging add value?" In one study, data from MRI did not significantly improve discrimination performance in predicting all causes of dementia beyond that of a model that incorporated demographic, cognitive, health, lifestyle, physical function, and genetic data. In other words, clinical information might be just as good as structural imaging [31]. Another study found that CT impacted the diagnosis only 12% of the time and treatment 11% of the time [32]. Other recommendations include that structural imaging is useful only with the following caveats, as recommended by Wollman and Prohovnik: "we suggest that neuroimaging should be considered: (1) when clinical expertise is insufficient; (2) as a complement to specific likelihood ratios; and (3) in specific types of patients, for whom clinical evaluation is inappropriate or inadequate" [33]. Efforts are underway to develop algorithms to enhance the


1
Structured questionnaire (e.g., AD8, IQCODE, AQ)
Exclude other common neurodegenerative conditions with validated questionnaires (LBCRS, FTD screening)
AQ score >10 (high sensitivity [>95%]); LBCRS addresses specificity
High score = possible AD
Low score = indeterminate diagnosis
A
Consider other dementias, other conditions, or MCI. Consider neuropsychological testing
Aggregate risk analysis
2
Aggregate score >12 indicates higher probability of AD
Aggregate score <12
B
Consider more extensive testing (CSF testing, PET)
3
Bedside cognitive screening (e.g., MoCA, Mini-Cog, MMSE)
MoCA, MMSE ≤ 24 indicates higher probability of impairment
4
Neurological exam to screen for NPH, parkinsonism, focal symptoms, or history of CVAs
Nonfocal exam: forgo CT/MRI screening
C
Focal exam or abnormal gait: obtain structural imaging
5
Lab testing: APOE genotyping, IMR assay, B12, TSH
APOE genotyping and IMR testing increase sensitivity; B12 and TSH screening exclude reversible causes
D
If patient is noncarrier for APOE ε4, or if IMR values are not in predictive range for AD, consider CSF testing, FDG PET, or amyloid PET
6
Apply IWG criteria for subjects with dementia
Patients who meet IWG criteria have a high probability of progression of AD symptoms

◀**Fig. 2** New conceptual framework for assessment of dementia due to Alzheimer's disease (AD). The primary diagnostic steps (tier 1) are indicated by the *circled numbers*. The supplemental diagnostic steps (tier 2) are indicated by the *circled letters*. The net cost per patient associated with tier 1 is less than $1200 USD. The sensitivity of tier 1 diagnosis is >90%; the specificity is yet to be determined. Because CT and MRI have a very low probability of supplying meaningful information, we advocate forgoing these studies in most patients. However, if normal pressure hydrocephalus (NPH), parkinsonism, focal symptoms, or a history of cerebrovascular accidents (CVAs) are present, these imaging studies are warranted. *AD8* Ascertain Dementia 8-Item Informant Questionnaire, *AQ* Alzheimer's Questionnaire, *CSF* cerebrospinal fluid, *CT* computed tomography, *FDG* fludeoxyglucose F 18, *FTD* frontotemporal dementia, *IMR* immunomagnetic reduction, *IQCODE* Informant Questionnaire on Cognitive Decline in the Elderly, *IWG* International Working Group, *LBCRS* Lewy Body Composite Risk Score, *MCI* mild cognitive impairment, *Mini-Cog* Mini-Cognitive Assessment Instrument, *MMSE* Mini-Mental State Examination, *MoCA* Montreal Cognitive Assessment, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *TSH* thyroid-stimulating hormone. Used with permission from Barrow Neurological Institute

utility of structural imaging in clinical practice and to increase the sensitivity for detection and differentiation of dementia [34, 35]. Until such time as these technologies mature, our recommendation is to obtain structural imaging only when abnormal neurologic findings are found on examination for the purposes of an initial dementia evaluation. This position statement does not exclude the utility of structural imaging in the tiered approach. If there is any evidence of abnormality on neurologic examination that is referable to the central nervous system, then structural imaging is warranted.

Step 5: Laboratory Screening Tests Combined with Advanced Bloodborne Biomarkers

Like structural imaging, screening for deficiencies in B_{12} and thyroid stimulating hormone are low-cost, high-yield tests for identifying reversible causes of dementia [2, 36]. However, they are insufficient for detecting AD, because they are only used to exclude other conditions.

To move from a diagnosis of exclusion to a diagnosis of inclusion, one must consider including apolipoprotein E (*APOE*) genotyping. Also controversial, the rationale for doing so is as follows. The lifetime risk for developing AD for a patient who is homozygotic for the *APOE ε4* is 91%, and the lifetime risk for a patient who is heterozygotic for *APOE ε4* is 47% [37]. *APOE ε4* carrier status is highly predictive of AD; an *APOE ε4* carrier who is symptomatic has a 94–97% chance of having AD [38]. In one study, the clinical diagnosis of AD improved from 55% to 84% when *APOE ε4* carrier status was added to the model [39]. In addition, 50% of MCI subjects who are *APOE ε4* carriers progress to AD dementia in 3 years compared to 20% of non-*APOE ε4* carriers [40]. MCI subjects (amnestic subtype) who are *APOE ε4* carriers convert to AD >99% of the time [40]. *APOE ε4* carriers are 26 times more likely to progress in cognitive decline. In addition, the presence of the *APOE ε4* allele predicts AD pathology on PET imaging [41].

APOE genotyping could be added to disease-associated biomarkers to improve diagnostic yield. Disease-associated biochemical markers are present in the blood; however, the measurable amounts are only 10% of those present in the CSF. As a result, the sensitivity and accuracy of the technology used for measuring the levels of these disease-associated proteins in the blood are critical, in addition to other issues that also affect CSF biomarker measurements [42–45]. Recent advances in technology have improved the sensitivity and accuracy of the measurement of these disease biochemicals in the blood. Among these technologies, the immunomagnetic reduction (IMR) technology stands out in its ability to measure three important AD pathology-associated proteins ($A\beta_{40}$, $A\beta_{42}$, and tau) [46]. Due to the unique principles on which this technology is based, IMR assays show ultrasensitivity in the detection of low amounts of the proteins in the non-blood-cell fraction of blood samples, plasma, collected from subjects diagnosed with preclinical AD and clinical AD dementia

[47–50]. In a pilot study, the main objective was to assess the $A\beta_{40}$, $A\beta_{42}$, and tau levels measured by the ultrasensitive IMR assays in plasma samples. When two cohorts were combined with a cutoff value of 382.68 $(pg/ml)^2$, the product of $A\beta_2$ and tau achieved 92% accuracy with a sensitivity of 96% and a specificity of 90% [46]. Although these new technologies have not yet been directly correlated with neuropathologic findings, there have been studies that attempt to correlate CSF levels and pathology. A 2008 study by Chiu et al. evaluated the combination of an abnormally low $A\beta_2$ level in the CSF and an abnormally high tau level in the CSF and found that this combination predicted the presence of AD pathologic features with a sensitivity of 91.6%, a specificity of 85.7%, and an overall accuracy of 90.2% [48].

Step 6: Apply IWG Criteria in the Clinical Diagnosis of AD

As mentioned in the introduction, IWG [4] incorporates biomarker data into the clinical diagnosis. Biomarker evidence of AD increases the probability that a patient has AD. By the IWG-2 criteria, Kaplan-Meier survival probability estimates of progressing to AD dementia exceed 90% in 5 years, suggesting positive biomarker evidence enriches the probability of progression [4]. However, the question of which specific biomarker is most predictive remains unanswered.

DISCUSSION

In this article, we propose a new algorithm for detecting dementia associated with AD. The rationale behind this algorithm is that the historical medical evaluation of dementia due to AD is inaccurate 25% of the time, that the diagnosis of AD has been, but should no longer be, a diagnosis of exclusion, that physicians do not feel confident in making a diagnosis of AD dementia, and that there is often a delay in diagnosis of 2–3 years [5, 6]. Technology is becoming available that greatly improves the diagnostic accuracy of AD. We present a novel algorithm that incorporates a structured history, an aggregate risk assessment, a cognitive screening measure, a through neurologic examination, and incorporation of biomarkers such as *APOE* and IMR assay. The use of this algorithm could improve the accuracy of a diagnosis of dementia due to AD to >90% without escalation of costs. This novel algorithm is summarized in Fig. 2. The algorithm must be assessed for efficacy but has the potential for accurately diagnosing a significant percentage of patients with AD, which could increase physician confidence. The resulting reduction in the time to diagnose patients might reduce the total morbidity. This outcome will certainly be the case with the advent and introduction of the disease-modifying therapies that are currently being developed.

A tiered approach allows additional tests to be added as needed. If there is focality on the examination (parkinsonism, gait abnormality, spasticity, or hemiparesis), then structural imaging could be added. If the subject is a non-*APOE ε4* carrier, then amyloid PET or CSF testing for AD biomarkers could be attained. If the aggregate risk is low, then a more biomarker-intense approach could be taken. In short, this tiered system allows for flexibility. Since most AD dementia patients are likely to be *APOE ε4* positive or are likely to have high screening scores for risk and impairment, in most cases, additional testing might not be necessary. Future research should include validation of the updated algorithm and determination of outcomes.

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