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Review Article

Appropriate use criteria for lumbar puncture and cerebrospinal fluid testing in the diagnosis of Alzheimer's disease

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Abstract

Introduction: The Alzheimer's Association convened a multidisciplinary workgroup to develop appropriate use criteria to guide the safe and optimal use of the lumbar puncture procedure and cerebrospinal fluid (CSF) testing for Alzheimer's disease pathology detection in the diagnostic process.
Methods: The workgroup, experienced in the ethical use of lumbar puncture and CSF analysis, developed key research questions to guide the systematic review of the evidence and developed clinical indications commonly encountered in clinical practice based on key patient groups in whom the use of lumbar puncture and CSF may be considered as part of the diagnostic process. Based on their expertise and interpretation of the evidence from systematic review, members rated each indication as appropriate or inappropriate.
Results: The workgroup finalized 14 indications, rating 6 appropriate and 8 inappropriate.
Discussion: In anticipation of the emergence of more reliable CSF analysis platforms, the manuscript offers important guidance to health-care practitioners and suggestions for implementation and future research.

Keywords: Alzheimer's disease pathology; Amyloid PET; AUC; CSF Aβ-42, diagnostic utilities; Modified Delphi; p-tau181; t-tau, LP; MCI; PICOTS (population, interventions, comparisons, outcomes, timing, and settings) framework; SCD

1. Introduction and scope

Mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia are prevalent syndromes with multiple pathologies responsible for the clinical presentation in the patient. Traditionally, clinicians have diagnosed AD dementia using primarily clinical criteria [1]. However, due to the positive correlation of cerebrospinal fluid (CSF) biomarkers with pathology, their use provides an opportunity to diagnose AD with higher degrees of sensitivity and specificity earlier in the disease course, as compared with clinical diagnosis alone. The definition of AD by its underlying

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pathological processes that are documented in vivo by biomarkers or by postmortem examination is a hallmark of the NIA-AA Research Framework [2], and a key principle underlying the application of CSF biomarkers to AD diagnosis in this document.

Currently, CSF biomarker testing has the status of an *in vitro* diagnostic test in some European countries and is used in routine clinical practice. Considerable advances in the detection of AD pathology through the improved reliability of CSF biomarkers and cross-platform interpretation of CSF testing for amyloid and tau proteins increase the likelihood of its broad clinical use internationally, including in the United States, where it is typically assigned to the research realm [3–5].

A group of experts (workgroup) convened by the Alzheimer's Association developed these appropriate use criteria (AUC) to assist health-care practitioners with the information necessary on the appropriate and inappropriate use of lumbar puncture (LP) and, thus, optimize patient safety and care. The workgroup's efforts to build on the AUC for amyloid positron emission technology (PET) [6] and CSF recommendations recently published [7,8]. These criteria are intended to support clinicians in consistently identifying appropriate patient populations for LP and CSF testing, while considering the cost-effective use of limited health-care resources. Thus, we hope that these AUC will be an important resource for policymakers and third-party payers in making preauthorization and coverage decisions.

It is noteworthy that these AUC do not provide recommendations for the research use of CSF biomarker testing for AD nor rule out conditions other than AD dementia or MCI-AD as possible causes of cognitive decline.

In developing these criteria, the workgroup evaluated the appropriateness of a wide range of clinical indications based on a systematic review of the current evidence, the experience of its members with CSF testing, and ethical standards for patient care.

While recommendations regarding the use of specific analytes were outside the scope of the workgroup's charge, when discussing the diagnostic value of biomarkers, the document focuses on CSF amyloid (*A*) β42 (sometimes normalized to a related peptide $A\beta$40), t-tau and p-tau181.

In presenting these criteria, we acknowledge the limitations of currently available medical interventions for AD, as researchers work toward developing disease-modifying treatments. However, an early and accurate diagnosis forms the foundation of excellent medical care. CSF confirmation of AD pathology may bring a myriad of benefits to patients and their families: (1) education, advanced care planning, and clinical care early in the disease process, including treatment with AD medications to treat symptoms, as appropriate; (2) necessary time to prepare for adjustments to work responsibilities, safe driving conditions, and financial planning; and (3) opportunities to enroll as participants in clinical trials aimed at delaying the disease and hopefully providing benefits to other patients and families if successful.

2. Background

2.1. Overview of the neuropathology underlying MCI and AD

At the microscopic level, the primary neuropathological features of AD include neuritic plaques and neuronal, especially synaptic, degeneration, together with other features, including cerebral amyloid angiopathy, neurofibrillary tangles, and neuropil threads [9,10]. Plaques are rounded lesions in the neuropil, primarily composed of aggregated β-amyloid (Aβ). The form ending at position 42 (Aβ42) is more prone to aggregation than shorter isoforms, of which Aβ40 is the most abundant [11,12]. Plaques exist as diffuse and neuritic plaques; the latter variant consists of a central core of amyloid fibrils surrounded by dystrophic neurites (processes filled with fibrillary tau protein), reactive astrocytes, and microglia [13]. Tangles are detected in the neuronal cytoplasm, in the form of paired helical filaments, primarily composed of hyperphosphorylated tau protein [14]. Intraneuronal accumulation of abnormally phosphorylated tau is believed to precede tangle formation in AD [15], with tau pathology spreading in a relatively consistent way from the brainstem to the transentorhinal region, hippocampal formation, and the neocortex [15,16].

The percentage of individuals who are cognitively unimpaired at death harboring plaques and tangles in their brains increases with age, particularly after the age of 65 years [17–21]. At the same time, it has long been known that the severity of neuropathological changes (density of plaques and tangles) varies considerably between patients with AD, and the severity of the pathology overlaps with the amounts of plaques and tangles found in cognitively unimpaired older adult patients [17,20,22,23]. The neuropathological features of amnestic MCI are intermediate between the neurofibrillary changes of aging and the pathologic features of early AD dementia, including the presence of mixed pathologies [24–26]. In addition to plaques and tangles, varying degrees of α-synuclein, TDP-43, cerebrovascular, and other pathologies such as hippocampal sclerosis and microinfarcts are often seen in these patients across the AD continuum [27,28]. Thus, the frequent occurrence of AD pathology in cognitively unimpaired older adult patients, as well as the presence of non-AD pathologies, complicates proper clinical stratification of patients with cognitive disturbances based on purely clinical grounds. This should be considered in clinical studies evaluating the diagnostic performance of biomarkers.

2.2. Use of CSF testing in the context of other available diagnostic tools

Recommendations for the appropriate use of CSF must be made in the context of the many other diagnostic tools in use. First, the patient's history obtained from an informant who knows the patient well is paramount and focuses on changes

in the patient's memory, thinking, behavior, and function over time [29]. It is important to assess common, treatable causes of cognitive complaints such as sedating medications, mood disorders, and sleep disorders. A neurological examination may reveal signs of non-AD causes of dementia. Objective neurobehavioral tests are helpful in documenting the type and severity of cognitive impairment but are not by themselves diagnostic. Routine blood test including blood counts, blood chemistries, vitamin B12 level, and thyroid-stimulating hormone level are typically recommended to rule out other causes of or contributors to cognitive impairment [30]. Either a noncontrast head computed tomography scan or brain magnetic resonance imaging is usually performed to assess for cerebrovascular disease and brain atrophy.

If, after completion of this evaluation, the clinician still has significant uncertainty as to the etiology of the cognitive impairment, certain advanced diagnostic procedures can be helpful in narrowing the differential diagnosis. In some cases, fluorodeoxyglucose PET may be helpful in distinguishing between frontotemporal dementia (FTD) and AD dementia [31,32]. Amyloid PET is used to determine whether significant quantities of neuritic plaques are present in the brain, which may support the diagnosis of AD dementia or essentially rule out AD as the etiology of a cognitive complaint [33]. CSF testing is widely used throughout clinical neurology to diagnose numerous pathologies, ranging from neuroinflammatory conditions to infectious diseases. In contrast to amyloid PET, CSF studies can evaluate for many potential diagnoses, which is particularly helpful in complex and atypical cases where the differential diagnosis list can be long.

This AUC recommends the use of CSF biomarker testing for six clinical indications deemed as appropriate (see below). However, the decision to use CSF testing is also based on the clinical judgment of the provider and by the patient's individual situation. Where diagnostic confidence of the physician is high, the use of advanced biomarker testing may not be needed.

3. Methods

3.1. Overview of AUC development process

The Alzheimer's Association convened an international expert workgroup in February 2017 to begin the development of these AUC, with Avalere Health providing technical and editorial assistance to manage the development process. The workgroup participated in teleconference meetings on a biweekly basis until December 2017.

In alignment with the Institute of Medicine's Clinical Practice Guidelines We Can Trust recommendations on group composition, the association strived to establish a multidisciplinary workgroup comprising a variety of clinicians and other professionals with relevant expertise [34]. Each member had published extensively on topics related to the key considerations around the use of LP, such as dementia research, clinical practice and ethics, and biomarker test validation and clinical utilities. The members included four neurologists, one neuroethicist, one laboratory medicine physician, and a pathology and laboratory medicine biomarker researcher (list of member names provided in Supplementary Appendix A). Five of the members were American, and two were European (Spanish and Swedish).

The workgroup developed the clinical indications shown in the Table 1 in Section 6 through a confidential and formalized process adapted from one recommended by RAND and University of California, Los Angeles [35].

3.2. Scope and key research questions

The process began with the workgroup defining the scope and parameters of the AUC and developing key research

Table 1
Clinical indications for appropriate use of LP and cerebrospinal fluid testing in the diagnosis of AD

No.	Indication	Ratings
1	Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no SCD or expressed concern about developing AD	Inappropriate
2	Cognitively unimpaired patient based on objective testing, but considered by patient, family informant, and/or clinician to be at risk for AD based on family history	Inappropriate
3	Patients with SCD (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD	Appropriate
4	Patients with SCD (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD	Inappropriate
5	MCI that is persistent, progressing, and unexplained	Appropriate
6	Patients with symptoms that suggest possible AD	Appropriate
7	MCI or dementia with an onset at an early age (<65)	Appropriate
8	Meeting core clinical criteria for probable AD with typical age of onset	Appropriate
9	Symptoms of REM sleep behavior disorder	Inappropriate
10	Patients whose dominant symptom is a change in behavior (e.g., Capgras Syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression) and where AD diagnosis is being considered	Appropriate
11	Use to determine disease severity in patients having already received a diagnosis of AD	Inappropriate
12	Individuals who are apolipoprotein *E* (*APOE*) *ε4* carriers with no cognitive impairment	Inappropriate
13	Use of LP in lieu of genotyping for suspected ADAD mutation carriers	Inappropriate
14	ADAD mutation carriers, with or without symptoms	Inappropriate

Abbreviations: AD, Alzheimer's disease; LP, lumbar puncture; REM, rapid eye movement; SCD, subjective cognitive decline; ADAD, autosomal dominant Alzheimer's disease; MCI, mild cognitive impairment.

questions to guide a systematic review of the available evidence on LP and CSF using the PICOTS (population, interventions, comparisons, outcomes, timing, and settings) framework [36] (Supplementary Appendix C).

The workgroup then developed a list of 14 clinical indications that are encountered in clinical practice based on key patient groups in whom the use of LP and CSF may be considered as part of the diagnostic process.

3.3. Systematic evidence review approach and findings

In a parallel effort, the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University (OHSU) conducted the systematic review. The primary purpose of the review was to summarize and assess the strength of evidence for the safety, diagnostic accuracy, and effect on patient outcomes of LP and CSF in diagnosing AD and MCI, in cases posed in the key research questions listed in Supplementary Appendix C.

Searches for the review were conducted using Ovid MEDLINE® without revisions (1996 to April 2017) and supplemented with review of reference lists of relevant articles and systematic reviews.

The database search resulted in 2147 potentially relevant articles. After reviewing abstracts and titles, 448 articles were selected for full-text review, of which 75 studies and 4 systematic reviews were determined to meet inclusion criteria.

Two OHSU Evidence-based Practice Center staff reviewers independently assessed the quality of each study for inclusion. The strength of overall evidence was graded as high, moderate, low, or very low using the GRADE method (based on the quality of evidence, consistency, directness, precision, and reporting bias). In conjunction, the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) method was used for systematic reviews, the U.S. Preventive Services Task Force criteria were applied to randomized trials and cohort studies, and select criteria from QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies-2) were used for diagnostic accuracy studies [37–40].

Studies captured in the review were grouped into the following categories: (1) studies in which CSF biomarkers were evaluated in comparison with a reference standard, including autopsy neuropathological evaluation or amyloid PET imaging; (2) studies of selected patients who were initially seen at a clinic without an initial diagnosis, underwent a rigorous clinical workup, and had an expert clinical diagnosis as the reference standard against which CSF results were compared; and (3) systematic reviews and meta-analyses of these and other studies, for example, case-control studies.

3.4. Limitations of the review and the inclusion of excluded studies

In evaluating the results of the findings, the workgroup considered one possible source of bias: most studies on diagnostic accuracy reviewed compared CSF biomarker accuracy to the reference standard of clinical diagnosis instead of the more objective reference standards of amyloid PET or neuropathology. Yet, it is noteworthy that newer studies (the majority of which did not meet the study inclusion criteria) to a greater extent are able to capture the value of biomarkers by using these more objective reference standards in evaluating the diagnostic utilities of CSF Aβ42, t-tau, and p-tau. It should also be pointed out that amyloid PET has shown to have false negatives in autopsy studies [41].

In light of this limitation, the workgroup included additional studies as part of the evidence base for rating the clinical indications and developing this guidance document, as shown in Supplementary Appendix E.

3.5. Discussion of the evidence

Key Question 1: What are the reported adverse effects of LP procedure for individuals undergoing evaluation for suspected AD? What are the differences in patient subgroups?

CSF can be collected safely and reliably via LP [42]. The procedure's safety for CSF collection, which has been documented in more than 7000 patients with suspected AD in 10 studies (see Supplementary Appendix F), [43–52] is consistent with its safety record in a wide array of neurologic disorders, which include documentation of more than 30,000 patients [42,53]. Recognition of patient- and LP-related risk factors is a key to maximizing patient safety. To minimize patient risk, it is important to evaluate the patient for potential contraindications, including use of medications that could interfere with coagulation, recent seizures, some disorders of blood clotting, intracranial lesions, impaired consciousness, and papilledema [42].

Additional best practices that the workgroup recommends in ensuring LP safety include the following: (1) the use of an atraumatic narrow bore needle (associated with less risk for post-LP headache [PLPH]), (2) avoidance of repeated attempts in difficult LP cases to reduce risk for lower back pain, and (3) avoidance of collecting more than 30 mL of CSF (the threshold for PLPH risk) [42,45,50,53,54]. Finally, fear of the procedure has been shown to be an independent risk factor that can be influenced by the attitude of the clinical staff and can be decreased by providing sensitive, matter-of-fact, verbal communication about the procedure to the individual by clinicians familiar and comfortable with LP [42,45].

Key Question 2: In persons experiencing cognitive impairment, what is the diagnostic accuracy of LP and CSF in reporting CSF amyloid (Aβ42) and tau levels (t-tau, p-tau) or ratios of analytes as indicators of AD pathology presence or absence?

In the evaluation of the diagnostic accuracy for an index test, that is, the ability to discriminate between patients with and without the target condition, it is crucial to use an accurate reference standard. Accuracy measures of the test

depend on the trueness of the reference standard or how well the reference standard can identify or rule out the target condition. For many conditions, an accurate reference is not available, in which case the evaluation has to depend on expert clinical diagnosis or consensus clinical diagnosis.

For AD, the accuracy of a diagnosis based on purely clinical criteria is suboptimal, with sensitivity and specificity figures around 80% and 70%, respectively, in patients followed clinically for several years at expert research centers [30]. These figures are probably substantially lower in patients in early disease stages. The reason for this is manifold, including that clinical symptoms often are vague or uncharacteristic, and overlap with those seen in other neurodegenerative disorders. In addition, the severity of plaques and tangles load overlaps with that found in cognitively unimpaired older adult patients [17,22]. Moreover, a substantial proportion of older adult patients with clinical AD has multiple pathologies, with variable severities of other proteinopathies (TDP-43 and α-synuclein), as well as cerebrovascular disease, except for plaques and tangles [27,28].

As the pathology progresses, increased numbers of neurons are affected in characteristic patterns and precede by 10–20 years or more the clinical expression of AD dementia [55,56]. These pathologic changes are reflected by decreased concentration of Aβ42 and increased p-tau CSF concentration that reflect increased amyloid plaque deposition and increased tangle density, respectively [57–60]. Increased CSF t-Tau concentration reflects the increase, intensity, and spread of neuronal injury and neurodegeneration [60–62].

For AD diagnostics, amyloid PET ligands have been developed to assess brain amyloid status [6]. Amyloid PET is an US Food and Drug Administration– and European Medicines Agency–approved technique to identify or rule out brain amyloidosis, based on validation against autopsy studies [6,63–67]. It may, therefore, be an ideal reference standard for assessing the accuracy of the CSF biomarker Aβ42, as well as the Aβ42/Aβ40 ratio. Because Aβ neuritic plaques are one of the defining pathological features of AD, assessing the accuracy of these CSF biomarkers to identify or rule out brain amyloid deposition which is evaluated by amyloid PET may also be used as a proxy for their diagnostic accuracy for detection of AD. When amyloid PET is the reference standard for detection of brain neuritic plaque burden in assessments of the diagnostic accuracy of CSF AD biomarkers, instead of clinical diagnosis alone, there is an improved diagnostic accuracy for this aspect of AD neuropathobiologic changes, with pooled values for sensitivity and specificity of 90% and 84%, respectively [68]. Studies have shown a concordance of between 85%–95% for CSF Aβ42, alone or combined with t-tau or p-tau, and amyloid PET [58,69–73]. For more detailed discussion of the characteristics of Aβ42 and the tau proteins in their respective hallmark AD neuropathologic misfolded states can be found [59–62].

Therefore, we present the diagnostic accuracy (sensitivity, specificity, and binary discrimination power) expressed as the highest receiver operating characteristic (ROC) area under the curve value for all studies comparing the CSF biomarkers with amyloid PET and autopsy diagnosis (Supplementary Appendix E). In total, 18 publications were identified by the workgroup that presented sensitivity and specificity figures for 3697 individuals, using amyloid PET as the standard for neuritic plaque burden assessment.

Four studies were based on the same consecutive memory clinic outpatient cohort but were all included in the table because different analytical techniques for measurement of the CSF biomarkers were used (Supplementary Appendix E). These studies showed a mean sensitivity of 87.6% for CSF Aβ42 to identify, and a mean specificity of 86.2% to exclude brain amyloidosis, with a ROC area under the curve value of 0.90. The corresponding figures for the CSF Aβ42/Aβ40 ratio was a sensitivity of 96.0%, a specificity of 91.3%, and a ROC area under the curve value of 0.96.

Thirteen studies were case-control, multi-center, and other cohort studies (Supplementary Appendix E), showing a mean sensitivity of 93.2% for CSF Aβ42 to identify, and a mean specificity of 84.5% to exclude brain amyloidosis, with a ROC area under the curve of 0.933. The corresponding figures for the CSF Aβ42/Aβ40 ratio were a sensitivity of 96.0%, a specificity of 88.0%, and a ROC area under the curve of 0.936.

There were seven studies evaluating the ratios between t-tau or p-tau and Aβ42 in CSF (Supplementary Appendix E). These studies showed mean sensitivities of 91.1%–92.1% to identify brain amyloidosis, mean specificities of 86.3%–89.8% to exclude brain amyloidosis, and ROC area under the curve of 0.95–0.96, for the CSF t-Tau/Aβ42 and p-tau/Aβ42 ratios. Further studies are required to determine the relative merits of the ratios t-Tau/Aβ42 and p-tau/Aβ42 compared with the Aβ42/Aβ40 ratio in detection of plaque burden and for prediction of cognitive, memory, and functional decline at all stages of AD.

Potential reasons for misclassifications may include technical variability for both CSF analyses and amyloid PET assessments, especially close to the cutoffs; amyloid PET and CSF Aβ42 partly reflect different aspects of brain amyloidosis (e.g., fibrillary vs. soluble monomeric and oligomeric forms); the use of different PET ligands and protocols; and different analytical techniques for CSF measurements across studies. Nevertheless, the CSF biomarkers showed high accuracy to identify or rule out brain amyloidosis in studies using amyloid PET as the reference standard, figures being higher than those obtained when using clinical diagnosis alone as the reference standard.

Autopsy diagnosis is generally regarded as the "gold standard" for diagnosis of AD but is not as widely available as

amyloid PET. Only available on death, it is not necessarily contemporaneous with the CSF sample time, thus is less often available for use as a reference standard. Diagnostic accuracy results for five studies that included 764 subjects, which compared the CSF biomarkers with neuropathology, are summarized in the table in Supplementary Appendix E, following the amyloid PET studies. The overall mean sensitivity value for either Aβ42 alone or in various combinations with either t-Tau or p-tau is 90.0%, specificity of 84.0%, and a ROC area under the curve value of 0.92. In all of these studies, the AD diagnoses were based on neuropathology, but in most cases, the determination of normal was based on clinical evaluation, thus likely reducing the accuracy for controls. This limitation is likely responsible for the somewhat lower specificity (exclusion of AD pathology) value of 84% because the brains of approximately 20%–40% of cognitively normal older adult patients have AD pathology [74–76] and therefore the specificity estimation is likely to be falsely low. Thus, these studies show, as also demonstrated using amyloid PET as the reference standard, the improved diagnostic performance of the CSF biomarkers using neuropathology as the reference standard compared with clinical diagnosis alone.

Key Question 3: In persons with little or no cognitive impairment, what is the diagnostic accuracy (sensitivity, specificity) of LP and CSF in assessing CSF amyloid (Aβ42,) and tau levels (t-tau, p-tau) or ratios of analytes as indicators of AD presence or absence?

The accuracy for detection of AD neuropathology in persons with little or no cognitive impairment is comparable with that described previously in Key Question 2, albeit in a smaller number of study subjects. Two studies evaluated the diagnostic accuracy of CSF biomarkers in cognitively unimpaired individuals for the presence of AD neuropathology using amyloid PET imaging as the standard of truth [77,78]. The studies included 158 individuals with a mean Mini–Mental State Examination score of 29, 30 of whom were amyloid PET negative, and 128 were amyloid PET positive. The sensitivity and specificity values for CSF Aβ42 or the ratios Aβ42/Aβ40 and t-Tau/Aβ42 or p-tau/Aβ42 in these two study groups fell within the range of the values, described previously in Key Question 2, found in the 18 reported studies that compared CSF AD biomarker results to amyloid PET as the measure of amyloid plaque burden or to neuropathologic evidence for AD in a mixture of cognitively normal, MCI, and AD individuals (see Supplementary Appendix E).

Key Question 4: What is the accuracy of CSF amyloid (Aβ42) and tau levels (t-Tau, p-Tau) or ratios of analytes for predicting progression from MCI to AD? Does the literature report rates of progression from MCI to AD (in individuals with MCI who are found to have amyloid and tau levels in high risk of AD ranges)?

When MCI is associated with AD pathology based on positive CSF AD biomarkers, the risk of progression to a clinical diagnosis of AD dementia is higher than when CSF Aβ42 and tau biomarkers are normal. Conversely, individuals whose CSF Aβ42 and tau biomarkers are nonpathologic have a high likelihood of remaining free from AD dementia over the time of observation, up to 10 years thus far [79–81].

The wide range of specificity values across studies that document the predictive performance of these CSF biomarkers likely occurs due to differences across studies in the longitudinal observation time period, with specificities generally improving with increased longitudinal observation time, anywhere from 1 to 10 + years from the time of MCI diagnosis to the time limit for the study [47,75,79–81]. Other key factors such as patient age at the time of diagnosis and disease heterogeneity are likely to impact rates of progression in an individual patient [82]. Prolonged follow-up studies for at least five years, and ideally longer, are needed to provide robust estimates of the value of biomarkers in clinical practice, and for research studies such as clinical trials. There may be value in providing estimates of the risk of progression to a clinical diagnosis of dementia within three years of a clinical diagnosis of MCI [81].

Pathological CSF AD biomarker results in MCI patients have been shown to predict progression to a clinical diagnosis of AD dementia within a broad time window of 5 to 10 years. Thus, the predictive performance of CSF Aβ42 and tau biomarkers for cognitive decline in preclinical AD and MCI patients over a more narrowly defined period of time such as 2-3 years is of growing interest for potential use clinically and in research studies such as treatment trials [83–85]. Further studies will be required to establish universal cut points that can be applicable for prediction of risk for cognitive decline within a 2- to 3-year period and to test for the comparative performance characteristics for single biomarker tests versus combinations such as the ratios t-tau/Aβ42 or Aβ42/Aβ40.

Key Question 5: What are the effects of CSF testing for suspected AD on both clinical outcomes (diagnosis) and intermediate outcomes (e.g., management with medications)?

With respect to the question on the effects of CSF testing for suspected AD on patient outcomes, this is clearly an area lacking in studies because there were no study reports on the effects of CSF testing on clinical outcomes or the use of medications. Five studies [86–90] reported on change in diagnosis and confidence in diagnosis using CSF biomarkers in 1819 individuals whose age ranged from 51 to 74 years (Supplementary Appendix G). The incidence of change in diagnosis resulting from CSF testing ranged from 7% to 27%, with the majority being a change from MCI or non-AD to a diagnosis of AD. There were 8.5% [88] and 10.3% [90] changed diagnoses from AD to non-AD or MCI in the two studies that reported this information. Confidence in diagnosis or change in confidence in diagnosis was reported in two studies; one used patient vignettes, and the other involved physician responses following receipt of CSF Aβ42, t-Tau, or p-tau181 results for their patients [87,88]. In the study that used patient vignettes, the

clinician participants were significantly more confident in diagnoses with AD-consistent CSF values compared with those that were borderline or normal CSF values [87]. In the other study, 32% of physicians were more confident in their diagnoses following receipt of CSF Aβ42, t-Tau, or p-tau181 results, with the greatest increase in confidence reported for the AD-diagnosed patients (from 51% to 73%). Further studies across more diverse patient populations will be required to more fully document the impact of CSF AD biomarker test results on diagnostic decision-making and to test for the effects on patient outcomes.

4. Rating of clinical indications

Using the evidence summary, their clinical experience and expertise, as well as their knowledge of research outside of the scope of the evidence review, the workgroup employed a three-step, modified Delphi approach (consisting of an online survey and two rounds of in-person scoring) to reach consensus ratings for each of the clinical indications. Workgroup members were asked to assess the benefits and risks to patients of using LP and CSF in diagnosis in rating each indication. In each of the three rounds, members were asked to assign to each indication a rating within ranges of appropriate, uncertain, or inappropriate for use of LP for diagnosis of MCI or AD. A 9–1 rating scale was used in each of the three rounds of voting. The rating scale ranged from:

Score of 7 to 9, Appropriate:

- 9 = Highly confident that the indication is appropriate
- 8 = Moderately confident that the indication is appropriate
- 7 = Only somewhat confident that the indication is appropriate

Score of 4 to 6, Uncertain:

- 6 = Uncertain, but possibility that appropriate
- 5 = Uncertain
- 4 = Uncertain, but possibility that inappropriate

Score of 1 to 3, Inappropriate:

- 3 = Only somewhat confident that the indication is inappropriate
- 2 = Moderately confident that indication is inappropriate
- 1 = Highly confident that the indication is inappropriate

After each round of voting, results were tabulated displaying ratings given for each indication and reported to the workgroup. When an indication received all seven workgroup members' ratings in a single category of appropriate, uncertain, or inappropriate, that indication was considered to have reached consensus rating and was removed from the next round of voting. When voting for an indication resulted in only a single vote falling into a category, then that vote was considered as an outlier and was removed from the ratings.

The first round of voting was an anonymous online survey, in which each member was asked to assign a single rating to each indication and also enter a rationale for that rating. Workgroup members were then brought together for a daylong forum to complete the Delphi process with a second and a third round of voting. The in-person forum began with a presentation of the first-round survey rating results and rationales. After extensive discussion, a second round written vote was collected and tabulated. The results were reported to the workgroup for further discussion. A third round, in-person vote was then taken. In this final round, the workgroup reached consensus on each indication, with all members rating the remaining indications as falling with the same category of appropriate, uncertain, or inappropriate.

5. Definitions

The following terms are used in these AUC:

AD refers to a progressive brain disease that is neuropathologically characterized by amyloid plaques, neurofibrillary tangles, and neuronal damage [91]. AD brain pathology accumulates over many years and eventually leads to cognitive decline. AD has three clinical stages: preclinical (cognitively unimpaired or only subtle or subjective cognitive decline [SCD]), prodromal (characterized by MCI), and dementia (characterized by cognitive and functional impairment) [29,92,93].

Autosomal dominant Alzheimer's disease (ADAD) is AD with an autosomal dominant pattern of inheritance that is caused by mutations in one of three different genes: amyloid precursor protein (*APP*), presenilin 1 (*PSEN1*), or presenilin 2 (*PSEN2*) [56]. In most but not all cases, ADAD has an early age of onset, before 65 years [94].

Dementia refers to the clinical syndrome of a decline in memory or thinking that is severe enough to significantly impair function in an individual's usual daily activities. There is a broad spectrum of dementia severity, and there are many causes of dementia, including AD [29].

A dementia expert/specialist is a physician who is experienced in the assessment and diagnosis of dementia. Dementia experts must be skilled in applying the published, standardized clinical criteria for SCD, MCI, and AD. Expertise is typically acquired through formal training and clinical experience in neurology, psychiatry, and geriatric medicine; however, not all physicians in these disciplines are dementia experts [6].

SCD is defined as a self-experienced persistent decline in cognitive capacity in comparison with a previously normal status, not related to an acute event. Individuals experiencing SCD achieve normal performance on standardized neuropsychological measures [95,96].

MCI is defined by cognitive decline as observed by the patient, informant, or physician; mild deficits on formal

cognitive testing in one or more cognitive domains; and generally preserved functional abilities [97].

Probable AD dementia is diagnosed when a patient with dementia has experienced an insidious onset and slow progression of cognitive decline in episodic memory and at least one other cognitive domain with impairment of activities of daily living, and other potential etiologies for dementia have been ruled out [29].

Possible AD dementia is diagnosed when individuals with dementia experience cognitive decline in episodic memory and at least one other cognitive domain with impairment of activities of daily living, but either (1) have a sudden onset of impairment, or there is insufficient history to document cognitive decline or (2) have an etiologically mixed presentation because of evidence of cerebrovascular disease, features of dementia with Lewy bodies, or some other cognitively impairing condition [29].

6. Appropriate use criteria

See Table 1 for appropriate use criteria.

7. Discussion of individual indications

7.1. Preamble

The indications discussed below are general guidelines for when CSF testing might be appropriate, which may be modified by the patient's specific clinical situation and/or the provider's clinical judgment. For example, the age of the patient influences decision-making in several ways. Among the oldest old, questions about the ease and feasibility of performing a LP may arise. The prevalence of amyloid positivity increases with age, and multiple brain pathology is a common finding among older patients. Therefore, interpreting a positive CSF amyloid biomarker as indicating AD is not straightforward. Even the presence of both low Aβ42 and high tau or p-tau in an older adult may be ambiguous because CSF tau may increase with age; nevertheless, CSF biomarkers do retain diagnostic value among older adult patients [98].

Co-pathology and comorbid conditions are an important consideration in using and interpreting CSF biomarkers. For example, in a patient with Alzheimer's pathology and comorbid cerebrovascular or Lewy body pathology, or factors such as medications or medical conditions that may impair cognition, deciding how much of the clinical picture may be due to AD and how much can be explained by other conditions requires clinical judgment beyond simply obtaining a CSF biomarker test.

In the appropriate use of any biomarker test, such as CSF Alzheimer's biomarkers, the clinician should consider the pre-test probability and the likely prevalence of disease. For example, if the pre-test probability of Alzheimer's is high, adding a CSF biomarker test with high sensitivity and specificity will not necessarily add much to the clinical judgment.

While the workgroup did not propose an algorithm to determine at what stage of the diagnostic evaluation CSF biomarkers would be appropriate for use, nor consider their use in comparison with other diagnostic tests or biomarkers, in general, they agreed that a detailed clinical and cognitive evaluation should precede the use of CSF biomarkers for each indication. In other words, there should be an initial clinical diagnosis or differential diagnosis, followed by a determination of how CSF biomarkers might contribute to the diagnosis and to clinical decision-making.

7.2. Clinical indications

Indication 1 (inappropriate): Cognitively unimpaired and within normal range functioning for age as established by objective testing; no conditions suggesting high risk and no subjective cognitive decline or expressed concern about developing Alzheimer's disease.

This indication refers to the use of CSF biomarker testing in a patient who lacks significant risk factors for Alzheimer's disease, and in addition, neither the patient nor an informant reports concerns about memory or cognitive changes, and the clinical evaluation has included cognitive testing that is normal.

A percentage [10–25%] of asymptomatic people may have positive CSF biomarkers for AD, and this increases with age, particularly after 60 years [99,100]. However, it is unclear whether positive CSF biomarkers can accurately predict, if or when an individual will develop MCI or AD dementia. Therefore, CSF biomarker testing of patients who are at low risk and have normal cognition is not likely to provide a useful prognostic readout and will not assist medical decision-making.

Testing of asymptomatic individuals with CSF biomarkers may be performed in a research setting, such as screening for a prevention clinical trial, but it is not recommended as part of clinical care. This recommendation for research use is also consistent with the AUC for amyloid PET.

Indication 2 (inappropriate): Cognitively unimpaired patient based on objective testing, but considered by patient, family informant, and/or clinician to be at risk for AD based on family history.

This indication refers to patients with a clinical history and cognitive assessment that are not consistent with symptomatic AD, but who are concerned about their risk for AD because of a family history of late onset AD. The rationale is similar to that discussed for Indication 1 previously. Although a positive family history may increase the lifetime risk for AD [101], the extent of increased risk for an individual is uncertain. Testing would not assist in medical decision-making.

Indication 3 (appropriate): Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are considered to be at increased risk for AD.

SCD occurs when a patient's cognitive abilities decline as assessed by the patient, a family member, or a physician, but the patient's performance on objective cognitive testing remains within the normal range. Clinical methods to operationalize SCD have been proposed [95,102]. The presence of SCD increases the risk of future cognitive decline and dementia [103], and it is also related to greater levels of neocortical Aβ-amyloid burden [104] and has been associated with AD imaging features such as lower volumes of the hippocampus [105,106], and other AD signature areas [107]. Because SCD is a complex syndrome that may be caused by multiple etiologies besides AD pathology, including other neurological or medical conditions, drug use, or psychological factors, the SCD-initiative has proposed a set of specific SCD features, under the name of SCD-plus, which are associated with an increased likelihood to be an expression of the preclinical stage of AD [95,102] and are associated with future cognitive decline [108]. The following features are associated with increased risk in an individual with SCD: persistent decline in memory rather than other cognitive domains; onset in the last 5 years; age at onset >60 years; concerns (worries) associated with SCD; feeling of worse performance than others of the same age group and confirmation of cognitive decline by an informant and presence of the apolipoprotein *(APOE)ε4* genotype.

For patients with SCD, the decision to perform CSF biomarker testing should be individualized, with the strongest support for testing arising when the patient, informant, and clinician all are concerned that the patient has experienced cognitive decline. In addition, CSF testing may be helpful in this group when positive AD biomarkers might influence life decisions or negative AD biomarkers would lead to further testing for alternative etiologies. Cognitive tests are not perfectly accurate, and some patients, especially highly educated individuals, may score within the normal range for the population despite having experienced significant cognitive decline.

In some studies, people with SCD have a higher risk of progressing to significant memory loss or AD, especially those who meet criteria for SCD-plus [96]. The workgroup members recognize that there is limited evidence related to CSF biomarkers in SCD. However, studies have shown an increased rate of CSF biomarkers consistent with AD pathology in SCD [109–111]. The workgroup strongly suggests that clinicians only offer testing in this population when consistent with patient goals and after a full discussion of potential biomarker test outcomes.

Indication 4 (inappropriate): Patients with subjective cognitive decline (cognitively unimpaired based on objective testing) who are not considered to be at increased risk for AD.

This indication refers to patients with subjective cognitive decline (SCD) who have been evaluated and found by a clinician to be at low risk for AD. The workgroup recognizes that studies of SCD did not always rate the clinician's suspicion for AD. Nevertheless, there is evidence that SCD with a low index of suspicion for AD (e.g., limited or no concerns by an informant and by the clinician) is less likely to progress to cognitive decline, MCI, or AD over time [95]. Therefore, if the clinician has low suspicion for AD, the likelihood of positive AD biomarkers is low. Thus, CSF biomarker testing would be unlikely to help in clinical decision making, regardless of the results.

Indication 5 (appropriate): Mild cognitive impairment that is persistent, progressing, and unexplained.

MCI is a syndrome defined by cognitive decline, generally preserved functional abilities, and mild deficits on formal cognitive testing in one or more cognitive domains [97,112]. The workgroup acknowledges that CSF biomarkers would be most helpful in patients with MCI when symptoms are persistent and a clinical and medical workup has failed to provide a clear explanation for the MCI symptoms. Many studies have shown that MCI is associated with an increased risk of progression to dementia [113] and that different subtypes of MCI may have different risks; for example, amnestic MCI may have a higher risk of progression to AD than nonamnestic MCI [114].

The rate of AD in MCI is approximately 50%, with a 54% diagnosis rate in one large autopsy study [26]. There is strong and consistent evidence that MCI is associated with an increased risk of an AD profile of CSF biomarkers [98,111,115] and that an AD CSF biomarker profile is associated with an increased risk of progression to dementia [47,116]. Therefore, the presence of an AD biomarker profile in MCI suggests that the symptoms are caused by AD pathology, whereas normal or non-AD levels of CSF biomarkers make AD unlikely as the cause of the cognitive decline. CSF biomarkers can thus help to stratify patients with MCI to allow therapy or interventions to be initiated appropriately and to enable better prognostication. The workgroup feels that in most cases of MCI, CSF biomarkers would be appropriate, unless some other etiology was being strongly considered.

Indication 6 (appropriate): Patients with symptoms that suggest possible AD.

Possible AD has been defined in research criteria as a designation that includes atypical AD or mixed pathology (AD plus another etiology of dementia). Atypical clinical presentations such as primary progressive aphasia (PPA—particularly logopenic variant)—and posterior cortical atrophy (PCA) [29] are most often but not always associated with AD pathology. Many studies have shown that CSF biomarkers indicate an AD profile in most cases of logopenic PPA and PCA [117–119]. CSF biomarkers can therefore provide information to help to confirm or exclude AD in atypical presentations. Mixed pathology (e.g., AD plus

vascular cognitive impairment or AD plus Lewy body dementia) is often found in dementia in older individuals. The question of whether AD is contributing to dementia may be uncertain after a thorough clinical evaluation that may include structural brain imaging. The presence of an AD profile of CSF biomarkers increases the likelihood that AD is indeed contributing, while normal CSF biomarkers suggest a cause other than AD.

Indication 7 (appropriate): MCI or dementia with an onset at an early age (<65).

MCI is less common in younger age groups but still carries a risk of progression to dementia. Few studies have evaluated MCI in younger individuals, but many studies have included subjects with MCI who are younger than 65 years [98]. In these studies, CSF biomarkers have comparable sensitivity and specificity for AD. Even with the smaller evidence base for younger patients, the workgroup felt that CSF biomarkers may be used to evaluate whether AD pathology underlies cognitive symptoms regardless of the age at onset.

Although the onset of dementia before age 65 is relatively uncommon, it is often associated with atypical presentations of AD and neurodegenerative disorders such as FTD. Brain pathology in younger patients is more likely to consist of a single etiology rather than mixed pathology.

Many studies of CSF biomarkers have considered patients with younger onset of dementia, and the ability of CSF biomarkers to distinguish between AD dementia and FTD has been demonstrated in clinical and autopsy series [118,120]. In patients below age 65, many other disorders besides AD may cause dementia. AD biomarkers may increase confidence in an AD diagnosis in younger patients when there is diagnostic uncertainty. The workgroup felt that if the clinical presentation was that of typical AD with younger age at onset, CSF biomarkers might not add much more confidence to the clinician's diagnosis.

Indication 8 (appropriate): Meeting core clinical criteria for probable Alzheimer's disease with typical age of onset.

Probable AD dementia is diagnosed when a patient with dementia has experienced the insidious onset and slow progression of cognitive decline in episodic memory, and at least one other cognitive domain and other potential etiologies have been ruled out [29]. The clinical diagnosis of probable AD dementia is associated with a neuropathological diagnosis of AD in 70%–90% of cases [26,121,122]. Neurological disorders that cause similar clinical syndromes account for most misdiagnoses and include hippocampal sclerosis, dementia with Lewy bodies, and FTD [122,123].

Given the significant rate of AD misdiagnosis, the workgroup felt that it would be appropriate to obtain CSF biomarkers in some cases of probable AD with a typical age of onset at age 65 years and older. Clinical judgment should play a major role in determining appropriateness. For example, if the clinician was less certain about the diagnosis of probable AD or considering other etiologies, CSF biomarkers may be useful. In addition, if the patient is basing major life decisions on their diagnosis (e.g., retiring or moving), confirmation of the clinical diagnosis with CSF biomarkers may ensure that the patient is making these decisions with the most complete information. These concerns can similarly influence the decision to obtain CSF biomarkers in younger onset clinically typical AD. However, if the clinician has high confidence in the diagnosis of probable AD, there are no other major diagnostic considerations, and the patient is unlikely to make major life changes based on their diagnosis, then CSF biomarkers may not be helpful.

Indication 9 (inappropriate): Symptoms of REM sleep behavior disorder.

REM sleep behavior disorder (RBD), in isolation, is a strong predictor of the eventual development of an α-synuclein-related disorder such as Parkinson's disease, Lewy body dementia, or multiple system atrophy [124]. The connection, if any, between RBD and AD is less clear. Therefore, the workgroup thought that AD CSF biomarkers are not relevant to diagnostic decision-making in RBD.

Indication 10 (appropriate): Patients whose dominant symptom is a change in behavior (e.g., Capgras syndrome, paranoid delusions, unexplained delirium, combative symptoms, and depression) and where Alzheimer's disease diagnosis is being considered.

In some patients, neuropsychiatric symptoms may be the earliest and most prominent symptom of dementia [125]. Especially, in cases where an older patient has no prior history of psychiatric illness, clinicians may suspect that a neurodegenerative illness, including AD, may be the etiology of these neuropsychiatric symptoms. Some patients with atypical presentations of AD may have paranoid delusions or more complex delusions such as Capgras syndrome early in the course [126]. If the neuropsychiatric symptoms do not have an obvious explanation and AD is a diagnostic consideration, the workgroup agreed that CSF biomarkers would be appropriate.

Delirium in older adult patients often has a medical explanation, such as infection, medical illness, or metabolic upset. In situations without a clear medical cause, clinicians may be concerned that the patient has underlying AD. For example, postoperative cognitive decline may be related to underlying AD pathology [127]. As part of a workup for persistent, unexplained delirium, CSF biomarkers may be considered.

Indication 11 (inappropriate): Use to determine disease severity in patients having already received a diagnosis of Alzheimer's disease.

Clinical methods are used to stage and follow progression in patients with AD dementia. There is no evidence that CSF biomarkers can reliably stage AD dementia. Therefore, the workgroup did not think the use of CSF biomarkers for staging dementia was appropriate.

Indication 12 (inappropriate): Individuals who are APOEε4 carriers with no cognitive impairment.

The *APOEε4* allele is the most common genetic risk factor for late onset AD. The workgroup discussed this as a potential indication because it is possible for people to find out, whether deliberately through a testing service or as part of a general genetic screen, whether they are *APOEε4* carriers or not. Although carrying an *APOEε4* allele is associated with an increased lifetime risk of developing AD dementia, it is only one of many risk factors and is not a reliable indicator of whether an individual will develop AD dementia [128,129]. Therefore, the workgroup thought that merely carrying an *APOEε4* allele was not adequate justification for CSF biomarker testing. CSF biomarkers could be used in a research setting, for example, a clinical trial, in *APOEε4* carriers to help to determine whether preclinical AD pathology might be present or not.

Indication 13 (inappropriate): Use of LP in lieu of genotyping for suspected autosomal dominant mutation carriers.

In patients with a family history of ADAD, genetic testing is highly accurate in determining whether an individual is an ADAD mutation carrier. CSF biomarkers may be normal in mutation carriers before amyloid deposition [130] and therefore CSF biomarkers are not reliable indicators of whether an individual is a mutation carrier. The workgroup agreed that it was inappropriate to perform CSF biomarker testing to determine ADAD mutation status.

Indication 14 (inappropriate): Autosomal dominant mutation carriers, with or without symptoms.

Early in the disease, levels of CSF biomarkers are different in ADAD as compared with late onset AD [56], which may make interpretation of CSF biomarkers in ADAD patients complex. In addition, because CSF biomarkers change many years before the onset of dementia, abnormal CSF biomarkers in an ADAD mutation carrier may not be reliable in determining whether cognitive changes are related to AD brain pathology or another cause. Therefore, the workgroup does not recommend testing CSF biomarkers in known ADAD mutation carriers for clinical purposes at this time, although use for research purposes is supported by the workgroup.

8. Implementation of these AUC

The discussion of the appropriateness or inappropriateness of these indications is intended to assist dementia experts on decisions regarding testing, and primary care and other providers in determining when to refer to a dementia expert for more specialized testing. The workgroup described six clinical indications where CSF biomarker testing is believed to be appropriate. These recommendations are largely consistent with those proposed by the AUC for PET-amyloid imaging. Similar to the AUC for amyloid imaging, the workgroup recommends that CSF biomarker testing is appropriate for patients with progressive and unexplained MCI, patients with possible AD where comorbidities frequently make the diagnosis uncertain, and in cases with early onset (<65) of MCI and dementia. In addition, we adopt the recommendation that CSF biomarker testing should be conducted by dementia experts.

We also describe three appropriate indications that differ from the Appropriate use criteria for amyloid PET: (1) patients meeting core clinical criteria for probable AD with typical age of onset; (2) individuals experiencing SCD but who score within the normal range on cognitive testing and who are considered to be at increased risk of AD; and (3) patients whose dominant symptom is a change in behavior and where an AD diagnosis is being considered [6].

To evaluate whether patients with SCD are at increased risk of AD, we recommend taking into account the SCD plus features defined by the SCD-I as being highly related to preclinical AD [96]. Some of the SCD plus features have been associated with an increased risk of AD dementia [104,131–135]. Other factors not currently recognized as SCD plus features, such as family history with an age of disease onset before 75, may also be associated with higher AD risk. We acknowledge that the field is rapidly evolving and therefore some of these criteria may need to be revisited in the future.

A dementia expert is a provider with specialized training and experience in the diagnosis and treatment of dementia who devotes more than 25% of their practice to dementia care. While there may be future circumstances where the potential professional users of CSF biomarkers could be broadened, the workgroup believes restricting use to dementia experts will help ensure accurate and appropriate clinical use of the CSF biomarkers.

When conducting CSF biomarker testing, the workgroup found that best practices would generally mean that the dementia expert would also: (1) determine whether CSF testing for AD biomarkers is appropriate for patients who meet the AUC criteria; (2) educate the patient and family about the benefits and risks of testing, and assess their motivation and psychological readiness to learn more about their risk of AD; (3) ensure the procedure is performed with reliable assays following established guidelines; and (4) integrate the results into the evaluation and treatment plan in an in-person meeting with the patient and family.

In determining whether testing is appropriate, the workgroup emphasizes the critical role of a careful history (including from an informant) and clinical examination before offering testing. Although CSF biomarker testing can provide important information about the presence or absence of AD pathology, it "does not substitute for a careful history and examination." The history and examination provide a foundational understanding of whether a patient's clinical status establishes appropriateness for biomarker testing and are "required to understand the clinical context to incorporate the test results into clinical decision-making." Dementia experts will select the most appropriate biomarker testing based on availability, contribution to diagnosis and treatment, cost, tolerability, and patient preference. For many clinicians, the decision may be based on whether to offer CSF biomarker testing or amyloid PET. Amyloid

PET and CSF amyloid are both sensitive and specific markers of cerebral amyloidosis with a high rate of concordance [58,69–73]. Although CSF testing also includes measures of tau (total tau and phosphorylated tau), an important dimension of AD pathology, the workgroup does not wish to suggest a particular pathway in this AUC in the absence of comparative studies between Amyloid PET and CSF AD biomarkers. The workgroup acknowledges that at present, there are no AD CSF biomarker tests that are approved by the Food and Drug Administration in the United States, and therefore, these tests are not commonly used in the clinic at present. In Europe, CSF biomarker tests are more frequently used, but the indications for prescription and also principles for reimbursement by health insurance vary across European countries [136].

Implementation of biomarkers as proposed in these AUCs will include consent and disclosure practices. Informed consent for CSF biomarker testing should include a careful discussion regarding the potential results and impact of these results on clinical and nonclinical decisions. The clinicians should verify cognitive capacity and, if needed, identify appropriate surrogate decision makers. The workgroup suggests that consent conversations reflect potential value and benefit of testing tailored to the patient's circumstance (age, syndrome, goals). This will be particularly important for patients who present with MCI, subjective cognitive impairment, or subtle cognitive decline. These populations may face unique discrimination and stigma risks given a younger age and a higher likelihood of being employed at the time of diagnosis.

Similar precautions are suggested during the disclosure of biomarker results. The following are helpful practices to ensure best utility of the CSF biomarker results: in-person disclosure, when possible, and verification by the clinician that the patient and family want to receive the results; verification that the patient and family understand the goals of the test and what a potential result means; and disclosure of CSF biomarker in language that is understandable to the patient and family. Following disclosure, the patient and family should have an opportunity to ask questions for clarification, and the clinicians should verify that the patient and family have an accurate understanding of the results. This conversation may also address next steps for clinical care. Subsequently, the workgroup suggests providing an opportunity for follow-up via telephone and access to social workers and other care management professionals, as helpful.

9. Further research questions

The field of AD biomarkers and of CSF testing continues to evolve, and new study data are accumulating in multiple key areas, including improved standardization of preanalytical practices and new analytical platforms, both of which will further improve on center to center reproducibility and implementation of common cut points for these biomarkers. The continuation of large-scale longitudinal studies using the more optimal test platforms and preanalytical protocols can help to improve on the predictive performance of the CSF AD biomarkers for cognitive decline and disease progression in prodromal and preclinical AD patients, and support further studies on best practices for disclosure of CSF biomarker data. Further studies of new biomarkers are warranted to determine possible enhancements to individualize patient disease characterization and progression prediction given the presence of co-pathologies in many patients with AD.

The workgroup identified a number of areas where more research is needed:

1. Studies of the "next generation" of CSF biomarker assays that have less variability and greater interlaboratory comparability, together with a large set of comparisons against pathological standards such as amyloid PET imaging and autopsy brain examination [137], will yield more precise estimates of the sensitivity and specificity of CSF biomarkers, as well as more consistent cut-off points and definitions of gray zones around them. Efforts to optimize and control preanalytical factors related to collection and processing of CSF, and standardizing analytical factors involved in assay measurement are well underway [138]. One question that will need further data is whether measuring a ratio of CSF Aβ42/40 yields better diagnostic performance than measuring Aβ42 alone. Another question is how to characterize neurodegeneration using CSF biomarkers, and whether neurodegeneration in the absence of positive amyloid biomarkers predicts progression in persons with MCI [139].
2. The investigation of candidate AD biomarkers is a very active field of research to determine the added value on top of the diagnostic utilities of CSF Aβ42, t-Tau, and p-tau181. This is especially of interest for more refined prediction of disease progression, and also important to help deepen our understanding of the intricacies of AD disease progression throughout the several-decades-long continuum involving amyloidosis, tauopathy, and neurodegeneration [140]. Thus, investigators are studying new AD biomarkers that are believed to reflect at least one neuropathologic pathway involved in AD progression, including synapse degeneration and loss, glial activity and inflammation, synucleinopathy, and TDP-43 pathology.
3. Long-term follow-up of persons with different clinical diagnoses and positive or negative CSF biomarkers for Aβ42, t-Tau, and p-tau are needed, including the possibility of eventual autopsy validation. Comparisons against reference standards such as amyloid PET imaging and neuropathologic brain examination will yield more precise estimates of the sensitivity and

specificity of CSF biomarkers, as well as more consistent cut-off points. In particular, obtaining more data on biomarkers in the oldest old will be important. Also, further studies of elderly people with SCD are needed to clarify the predictive value of CSF biomarkers. Recent studies have suggested that subtle neuropsychiatric symptoms such as irritability or sleep upset may be associated with an increased risk of developing MCI [141,142], however, there are currently no published data to determine whether CSF testing would be of additional value in candidates with such mild symptoms. Further studies of the longitudinal trajectories of CSF AD biomarkers in ADAD patients are warranted to further characterize the detailed time courses of these biomarkers.

4. These data will enable studies of the added value of CSF biomarkers in clinical decision-making, analogous to the way in which amyloid PET imaging is being evaluated in the Imaging Dementia—Evidence for Amyloid Scanning Study [143]. The overarching questions include whether obtaining the test alters the diagnostic impression; medical decision-making, subsequently; and health-care costs [143]. Studies have begun to look at some of these questions [87,144], but much more work is needed to document the potential impact of CSF AD biomarker testing on clinical outcomes in patients across the spectrum of AD. Comparisons between amyloid PET and CSF AD biomarkers fold into this framework.
5. The acceptability of LP in diverse settings and for different indications recommended in these criteria should be studied further to provide an idea of how the entire process of decision-making about obtaining CSF biomarker tests, interpreting and disclosing them, and using the information for medical decision-making works in practice. Especially valuable will be such studies conducted in community settings.
6. In the future, more data will be needed on people who are cognitively normal with elevated amyloid, to estimate risks of future cognitive decline as prevention trials for AD are considered. These studies will need to be complemented by research on how to disclose results and evidence of the risk of developing dementia.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.jalz.2018.07.220.

RESEARCH IN CONTEXT

1. Systematic review: The Workgroup developed key research questions using the PICOTS framework to guide a systematic review of the clinical literature on LP and CSF testing, conducted by the Evidence-based Practice Center at Oregon Health & Science University.
2. Interpretation: Applying their interpretation of the evidence with their clinical expertise and appreciation of individual patient factors, the Workgroup developed 14 clinical indications to guide healthcare practitioners in determining when LP and CSF analysis should and should not be used to confirm or rule out AD pathology in the diagnostic process.
3. Future directions: The AUC manuscript offers guidance on implementation and suggests areas for future research. Examples of the latter include: (a) improved standardization of pre-analytical practices using new analytical platforms, large-scale patient populations and amyloid PET imaging or autopsy brain examination as reference standard, (b) evidence generation on cognitively normal individuals with elevated amyloid, (c) research on best practices for disclosure of CSF biomarker data.

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