AMERICAN ACADEMY OF NEUROLOGY

PRACTICE PARAMETER: DIAGNOSIS OF DEMENTIA (AN EVIDENCE-BASED REVIEW)

Report of the Quality Standards Subcommittee of the American Academy of Neurology

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Article abstract—*Objective*: To update the 1994 practice parameter for the diagnosis of dementia in the elderly. *Background:* The AAN previously published a practice parameter on dementia in 1994. New research and clinical developments warrant an update of some aspects of diagnosis. *Methods:* Studies published in English from 1985 through 1999 were identified that addressed four questions: 1) Are the current criteria for the diagnosis of dementia reliable? 2) Are the current diagnostic criteria able to establish a diagnosis for the prevalent dementias in the elderly? 3) Do laboratory tests improve the accuracy of the clinical diagnosis of dementing illness? 4) What comorbidities should be evaluated in elderly patients undergoing an initial assessment for dementia? *Recommendations:* Based on evidence in the literature, the following recommendations are made. 1) The DSM-III-R definition of dementia is reliable and should be used (Guideline). 2) The National Institute of Neurologic, Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) or the *Diagnostic and Statistical Manual*, 3rd edition, revised (DSM-IIIR) diagnostic criteria for AD and clinical criteria for Creutzfeldt–Jakob disease (CJD) have sufficient reliability and validity and should be used (Guideline). Diagnostic criteria for vascular dementia, dementia with Lewy bodies, and frontotemporal dementia may be of use in clinical practice (Option) but have imperfect reliability and validity. 3) Structural neuroimaging with either a noncontrast CT or MR scan in the initial evaluation of patients with dementia is appropriate. Because of insufficient data on validity, no other imaging procedure is recommended (Guideline). There are currently no genetic markers recommended for routine diagnostic purposes (Guideline). The CSF 14-3-3 protein is useful for confirming or rejecting the diagnosis of CJD (Guideline). 4) Screening for depression, B_{12} deficiency, and hypothyroidism should be performed (Guideline). Screening for syphilis in patients with dementia is not justified unless clinical suspicion for neurosyphilis is present (Guideline). *Conclusions:* Diagnostic criteria for dementia have improved since the 1994 practice parameter. Further research is needed to improve clinical definitions of dementia and its subtypes, as well as to determine the utility of various instruments of neuroimaging, biomarkers, and genetic testing in increasing diagnostic accuracy.

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Introduction. *Mission statement.* The Quality Standards Subcommittee of the American Academy of Neurology (AAN) is charged with developing practice parameters for physicians. This evidence-based review addresses major issues in the diagnosis of dementia.

Background and justification. Dementia is a common disorder in the elderly, involving as many as 10% of those over 65 years of age. The AAN previously published a practice parameter on dementia in 1994,[1] and since that time many new clinical and research developments have occurred. The purpose of the current practice parameter is to highlight and to update major areas of current interest and investigation in the diagnosis of dementia in the elderly. It is not intended to serve as a comprehensive review of the differential diagnosis of dementia.

The appointment of authors for this guideline was done in cooperation with the Alzheimer's Association and overlaps significantly with the membership of the Medical and Scientific Advisory Council and the Board of Directors of the association. The Alzheimer's Association agrees with the content of this paper in all important regards.

This guideline has been endorsed by the American Association of Neuroscience Nurses and the American Geriatrics Society.

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Clinical question statement. The Diagnosis of Dementia Committee reviewed the issues, problems, and challenges related to the diagnosis of dementia. Based on work that has been published since 1994, the Committee formulated four questions to be addressed in the practice parameter:

1. Are the current criteria for the diagnosis of dementia reliable?
2. Are current diagnostic criteria sufficiently accurate to establish a diagnosis for the prevalent dementias in the elderly?
3. Do laboratory tests improve the accuracy of the clinical diagnosis of dementing illness?
4. What comorbidities should be evaluated in elderly patients undergoing an initial assessment for dementia?

Process. *Panel selection.* A group of clinicians from various disciplines with extensive experience in diagnosing and caring for patients with dementia was assembled. The group was charged with focusing on the diagnosis of dementia. Committee members disclosed any real or potential conflicts of interest. Other work groups formulated practice parameters on the detection of dementia[1] and the management of dementia.[2]

Literature review process. A literature search was conducted using MEDLINE, Excerpta Medica, and BIOSIS. The search included articles published from January 1985 through November 1999. The search strategy sought only studies published in English and studies on human disease. The principal search term was dementia. Other terms entered into the search included neuroimaging, diagnostic techniques, diagnostic imaging, biologic markers, CSF, diagnostic errors, differential diagnosis, and neuropsychologic tests. The original search yielded 1,175 articles of which approximately 300 articles were identified as relevant to our search questions. For articles on AD, we included only those based on more than 25 patients. For the less common dementias there was no minimal sample size. An additional 300 articles not identified by the literature search strategy, including ones published after the initial search was conducted, were submitted by committee members or obtained from bibliographies of articles identified in the search.

Each article was classified based on the quality of evidence (Class I through IV, table 1). After review of the evidence, recommendations were drafted, reviewed by all committee members, and identified as a Practice Standard, Guideline, or Option (table 2). When appropriate, data on specificity, sensitivity, and other numerical measures of diagnostic precision were extracted from the articles and placed in tables. Final inclusion of articles in this Practice Parameter was based on consensus of the Committee that they were relevant and informative in consideration of the four questions.

In addition to the review and final approval by the Quality Standards Subcommittee and the Practice Committee of the AAN, this Practice Parameter was reviewed by AAN members who had identified themselves as interested reviewers, by the Geriatric and Behavioral Neurology Sections of the AAN, by representatives of the American Geriatrics Society, and by representatives of the Alzheimer's Association.

Analysis of the evidence. *Are the current criteria for the diagnosis of dementia reliable?* The diagnostic formulations of dementia that are the most widely used in North America are based on definitions contained in the National Institute of Neurologic, Communicative Disorders and Stroke–AD and Related Disorders Association (NINCDS-ADRDA) Work Group,[2] the *Diagnostic and Statistical Manual*, 3rd edition, revised (DSM-IIIR),[3] and the *Diagnostic and Statistical Manual*, 4th edition (DSM-IV).[4] The DSM-IIIR states:

> The essential feature of Dementia is impairment in short- and long-term memory, associated with impairment in abstract thinking, impaired judgment, other disturbances of higher cortical function, or personality change. The disturbance is severe enough to interfere significantly with work or usual social activities or relationships with others. The diagnosis of Dementia is not made if these symptoms occur. . .in Delirium. . .[3]

The DSM-IIIR definition of dementia has good to very good reliability (kappa's ranging from 0.5 to 0.9).[5-7] The closely related NINCDS-ADRDA and DSM-IV definitions of dementia have not been subjected to assessment of reliability.

Practice recommendations.

The DSM-IIIR definition of dementia, which is identical to the DSM-IV definition, is reliable and should be used routinely (Guideline).

Are current diagnostic criteria able to establish a diagnosis for the prevalent dementias?

Alzheimer's disease. The reliability of the diagnosis of AD is moderate (generalized kappa's in the 0.51 to 0.73 range) in Class II studies.[8-10] When standardized clinical diagnostic criteria are used, interrater reliability[6] and consistency of diagnosis between the initial visit and 1-year follow-up is high (95% in Forette[11]).

There are 13 studies, 3 Class I[12-14] and 10 Class II,[9,15-22] that have addressed the diagnostic accuracy of the clinical diagnosis of AD using neuropathologic confirmation as the "gold standard." Both the DSM-IIIR "Dementia of the Alzheimer type" (DAT) and the NINCDS-ADRDA "probable" AD definitions achieved either good sensitivity (average across cited studies = 81%, range 49 to 100%) for AD at the expense of specificity (average across cited studies = 70%, range 47 to 100%) or vice versa in the majority of the cited studies. A diagnosis of "possible" AD achieved very high

Table 1 *Classification of evidence*

Class	Description
I	Evidence provided by a well designed prospective study in a broad spectrum of persons with the suspected condition, using a "gold standard" for case definition, in which test is applied in a blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.
II	Evidence provided by a well designed prospective study of a narrow spectrum of persons with the suspected condition, or a well designed retrospective study of a broad spectrum of persons with an established condition (by "gold standard") compared with a broad spectrum of controls, in which test is applied in blinded evaluation, and enabling the assessment of appropriate tests of diagnostic accuracy.
III	Evidence provided by a retrospective study in which either persons with the established condition or controls are of a narrow spectrum, and in which test is applied in a blinded evaluation.
IV	Any design in which test is not applied in blinded evaluation OR evidence provided by expert opinion alone or in descriptive case series (without controls).

Table 2 *Definitions for practice recommendations based on classification of evidence*

Recommendation	Description
Standard	Principle for patient management that reflects a high degree of clinical certainty (usually this requires Class I evidence that directly addresses the clinical question, or overwhelming Class II evidence when circumstances preclude randomized clinical trials).
Guideline	Recommendation for patient management that reflects moderate clinical certainty (usually this requires Class II evidence or a strong consensus of Class III evidence).
Practice Option	Strategy for patient management for which the clinical utility is uncertain (inconclusive or conflicting evidence or opinion).
Practice Advisory	Practice recommendation for emerging and/or newly approved therapies or technologies based on evidence from at least one Class I study. The evidence may demonstrate only a modest statistical effect or limited (partial) clinical response, or significant cost-benefit questions may exist. Substantial (or potential) disagreement among practitioners or between payers and practitioners may exist.

sensitivity (average across 4 studies = 93%, range 85 to 96%) but at the price of specificity (average across 4 studies = 48%, range 32 to 61%),[13,14,17,22] reflecting the many features that non-AD dementias share with AD.

Vascular dementia (VAD). Four criteria for vascular dementia that are currently used include the State of California AD Diagnostic and Treatment Centers criteria (the "California" criteria),[23] the National Institute of Neurologic Disorders and Stroke and the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria,[24] the Hachinski Ischemic Score (HIS) as modified by Rosen,[25,26] and those found in DSM-IV.[4] In studies that compared clinical diagnoses and neuropathologic findings, the NINDS-AIREN and the California criteria (as well as DSM-IIIR) had very low sensitivity but higher specificity. Only one Class I study[12] reported the sensitivity (43%) and specificity (95%) of a published criteria, NINDS-AIREN, for VAD. Four Class II studies with patient samples drawn from referral cohorts[15-17,27,28] reported sensitivity and specificity of the diagnosis of vascular dementia with any criteria. With one exception, their results had the same diagnostic accuracy as the population-based studies, with low sensitivity (average across 5 studies = 50%, range 20 to 89%) but higher specificity (average across 5 studies = 87%, range 64 to 98%) for the HIS, DSM-IIIR, NINDS-AIREN, or California clinical criteria. A retrospective (Class II) study[27] in which the HIS showed better sensitivity and specificity (both 89%) was the one analysis of six in which the diagnosis of vascular dementia appeared both sensitive and specific.

Recent neuropathologic analyses[12,14] offer a perspective on the difficulty in correctly diagnosing cerebrovascular pathology in dementia. Rather than considering vascular dementia as simply present or absent, these studies distinguished between "some or any" vascular lesions versus "pure" vascular pathology, i.e., the circumstance in which vascular pathology was both sufficient to account for cognitive symptoms and unaccompanied by other pathology. Some vascular pathology exists in 29 to 41% of dementia cases coming to autopsy in population-based cohorts, even though pure vascular pathology accounted for dementia in only 9 to 10%.[12,14] The Hachinski Ischemic Score, while lacking neuroimaging criteria, may be more suitable for identifying the majority of dementia patients with vascular dementia, i.e., those with at least some cerebrovascular pathology,[27] because of the low sensitivity of the NINDS-AIREN and California criteria.[12,15-17,28]

Dementia with Lewy bodies (DLB). DLB has been defined clinically by the presence of dementia, gait/balance disorder, prominent hallucinations and delusions, sensitivity to traditional antipsychotics, and fluctuations in alertness.[29] Two Class II studies evaluated the interrater reliability of the diagnosis of DLB based on the Consortium for DLB diagnostic criteria[29] and found it to be relatively low.[10,30]

One Class I study[12] investigated the diagnostic accuracy of DLB criteria against neuropathologic findings and found that sensitivity was low (22%) but specificity (100%) was high. Five Class II studies also showed low sensitivities (average across 5 studies = 58%, range 34 to 75%) but higher specificities (average across 5 studies = 87%, range 71 to 94%) for the diagnostic criteria of Consortium for DLB.[10,30-33] In a prospective clinical study based on a DLB case registry with neuropathologically confirmed cases, hallucinations, depression, delusions, and delusional misidentification were all significantly higher in patients with DLB than AD.[34] However, all of these features occurred in patients with AD

as well. The presence of visual hallucinations and delusional misidentification as early symptoms showed sensitivities and specificities of >50% but <75%. In another study, the clinical diagnosis of DLB was confirmed in only 5 of 10 cases at postmortem examination.[35] The lack of specificity of the DLB clinical diagnosis appeared attributable to an equivalent amount of spontaneous extrapyramidal disturbance between the five cases with DLB at autopsy and the five without DLB at autopsy (four with AD, one with progressive supranuclear palsy).[35]

Prominent deficits in attention, profound deficits in visuo-constructional skills, and relative sparing of memory are the neuropsychologic features of DLB.[36,37] However, neuropsychologic tests do not reliably differentiate DLB from either AD or VAD.[37] Similarly, even though patients with DLB show less temporal lobe atrophy on MRI than do patients with AD[38] and more hypoperfusion in the occipital lobes,[39] neuroimaging has not proven successful in differentiating DLB from AD.

Frontotemporal dementia (FTD). FTD is less common than AD, VAD, or DLB,[14,17,40] particularly in very elderly dementia cohorts. An autopsy-based Class II study (using retrospective clinical diagnoses determined from review of medical records) showed that most patients with FTD fulfill diagnostic criteria for AD.[41] In contrast, a Class II study without autopsy confirmation[42] found that the Lund-Manchester criteria[43] (an earlier version of the Consensus diagnostic criteria for FTD[44]) differentiated 100% of FTD and AD patients. Early loss of personal awareness, early loss of social awareness, hyperorality, and stereotyped, perseverative behavior were somewhat sensitive (63 to 73%) and highly specific (97 to 100%) for differentiating the two conditions.[42]

Neuropsychologic test profiles of patients with FTD typically reveal deficits on frontal systems tasks, including verbal fluency, abstraction, and executive function.[45] Using discriminant analysis, one study found that the FAS word fluency test was the instrument that best differentiated FTD from AD.[46] Although it has been suggested that tests of constructional ability differ significantly between FTD and AD,[43] this is not always the case.[46] Some patients with AD demonstrate substantial executive deficits;[47] hence neither the clinical nor neuropsychologic profile of the frontotemporal syndrome is specific for FTD. There are no clinical features that are useful for establishing either the histologic subtype of FTD or linkage to tau mutations.

Prion diseases. Until recently, diagnosis of Creutzfeldt–Jakob disease (CJD) disease rested on clinical symptoms, the characteristic electroencephalographic pattern of periodic sharp wave complexes and the pathologic examination of brain tissue. The diagnostic criteria for CJD were tested in a prospective, Class I study[48] in which 188 autopsy-confirmed cases (97%) were identified of 193 cases diagnosed with "probable" CJD based on criteria of Masters et al.[49] In this same cohort, among 54 cases diagnosed with "possible" CJD, the diagnosis was confirmed in 44 (81%). Only 2 pathologically diagnosed CJD cases were found among 111 patients who had been given other clinical diagnoses. Brown et al.[50] proposed a simplified diagnostic scheme that has not been subjected to prospective study but is very similar to that used by Poser et al.[48]

Conclusions. The criteria of probable AD has good sensitivity for neuropathologic AD but less optimal specificity. The clinical phenotypes embodied in the diagnostic criteria for VAD, DLB, and FTD do not map precisely onto neuropathologic phenotypes. Although there are strong clinical-pathologic relationships for these disorders in the majority of patients, there are many patients with atypical or nonspecific clinical presentations. The clinical phenotype of CJD is more tightly linked to its expected CJD pathology.

Practice recommendations.

- The NINCDS-ADRDA for the diagnosis of probable AD or DSM-IIIR criteria for DAT should be routinely used (Guideline).
- The Hachinski Ischemic Index criteria may be of use in the diagnosis of cerebrovascular disease in dementia (Option).
- The Consortium for DLB diagnostic criteria may be of use in clinical practice (Option).
- The Consensus diagnostic criteria for FTD may be of use in clinical practice (Option).
- Clinical criteria for CJD should be used in rapidly progressive dementia syndromes (Guideline).

Do laboratory tests improve the accuracy of clinical diagnosis of dementing illness?

Structural neuroimaging for differential diagnosis. Since the previous practice parameter on dementia,[1] one additional Class II study[51] has addressed structural imaging in the diagnostic evaluation of patients with dementia. The study[51] found that 5% of patients had a clinically significant structural lesion but no features in the history or examination that would have predicted the lesions. Other Class II studies that have examined the decision to order a brain imaging study on clinical history and examination alone have shown imperfect precision, although specificity and sensitivity may be approximately 90%.[52,53] Given the goal of minimal undetected structural lesions, the data supports the use of a neuroimaging examination—either a noncontrast CT or MR scan—under most circumstances at the time of the initial dementia assessment to identify pathology such as brain neoplasms or subdural hematomas. A third condition, normal pressure hydrocephalus, which might be detected by CT or MR and might be responsive to treatment is very rare.[54]

Quantitative imaging to diagnose AD. Only one prospective (Class I) study of quantitative computed tomographic imaging was found that used autopsy-confirmed diagnosis as the diagnostic standard.[55] Among 86 autopsied cases, a minimum width of the medial temporal lobe falling below the 5th percentile was 95% sensitive but only 40% specific for AD.

Several Class II studies without neuropathologic confirmation of the diagnosis have reported the utility of medial temporal lobe atrophy, particularly hippocampal or entorhinal atrophy, for the clinical diagnosis of AD.[56,57] In differentiating clinically diagnosed AD (NINCDS-ADRDA criteria) from elderly normal controls, the sensitivity of various medial temporal atrophy measures on CT[58] or MRI[59-62] ranged from 77 to 92%, with specificities ranging from 49 to 95%. Automated volumetric techniques with MRI were most reliable but are currently labor-intensive and not widely available. There are no studies that have determined the added value of measurements of hippocampal or entorhinal volume once a clinical diagnosis of AD has been made. The range of estimates suggests that measurement of hippocampal atrophy by MRI may not be useful in clinical practice because of its low precision.

Combining medial temporal measures with other potentially informative markers, such as functional neuroimaging[58] or apolipoprotein E genotyping, may improve diagnostic accuracy.[63] Determination of the rate of change of hippocampal atrophy[64] may also be of value diagnostically but is unlikely to be of use in clinical practice. Prediction of subsequent AD in individuals without dementia has also been attempted with MRI of the hippocampus and entorhinal cortex,[65,66] but that is beyond the scope of this parameter.

Functional neuroimaging. SPECT and AD. Based on Class II studies, the sensitivity of SPECT was lower than that of the clinical diagnosis.[58,67] In a single prospective study, when specificity was set at 89% overall sensitivity was 43%.[67] Sensitivity increased as the severity of dementia worsened, but the pretest probability of AD also became higher.[68,69] The added value of SPECT was greatest for a positive test among patients with mild dementia in whom there was substantial doubt about the diagnosis of AD (e.g., prior probability between 30 and 50%).[68] In this situation, a positive SPECT would have increased the posttest probability of AD by 30%, whereas a negative test result would have increased the likelihood of no AD by only 10%. Higher sensitivity (77 to 86%) and specificity (90 to 94%) have been reported using automated and quantitative methods for SPECT analysis.[70,71]

To assess the value of SPECT in the differential diagnosis of dementia, we identified two SPECT studies (Class I) with autopsy-confirmed diagnoses in a large number of subjects.[55,72] For the differentiation of AD versus non-AD dementia, hypoperfusion in the temporal–parietal lobe(s) was reported to be 86 to 95% sensitive and 42 to 73% specific. Although encouraging, these figures are not consistently better than those obtained by diagnosis with established clinical criteria.

PET and AD. The largest series of dementia cases who underwent PET scans and also had autopsy confirmation was reported in a Class II study[73] that included 22 patients with various types of dementia (64% AD). In this study, visual interpretations of PET scans, which have high interrater reliability,[74] yielded a sensitivity of 93% and a specificity of 63%.

A direct comparison (Class II) of FDG-PET and HMPAO-SPECT in their ability to differentiate AD from vascular dementia indicated higher diagnostic accuracy for PET regardless of dementia severity.[75] Using receiver–operator characteristic curves, SPECT diagnostic accuracy was 62.9% for Mini-Mental State Examination (MMSE) score >20 and 81.2% for MMSE score <20. For PET, diagnostic accuracy was 87.2% for MMSE score >20 and 100% for MMSE score <20. Other Class II studies confirmed a lower sensitivity for high-resolution SPECT compared with PET.[76] FDG-PET appears superior to MRI measures of hippocampal atrophy because changes in cerebral glucose metabolism antedate the onset of memory decline whereas the MRI hippocampal changes do not.[77]

PET scanning appears to have promise for use as an adjunct to clinical diagnosis, but further prospective studies with PET are needed to establish the value that it brings to diagnosis over and above a competent clinical diagnosis.

SPECT, PET, and FTD. SPECT and PET may be helpful in distinguishing FTD from AD. Many patients with FTD show hypoperfusion of anterior cerebral cortex with relative sparing of posterior cortex with SPECT[78-80] and PET.[81] In these four Class II studies, the highly selected study participant pool makes it difficult to generalize on the reported specificities and sensitivities. In patients with cognitive or behavioral deficits suggestive of FTD, no studies addressed what additional value a SPECT or PET scan provides.

Genetic biomarkers. No studies have addressed the value of genetic counseling for patients with dementia or their families when autosomal dominant disease is suspected. Because the genetics of dementing illnesses is a very young field, expertise in genetic counseling for the dementias of the elderly is likely to be found only in specialized dementia research centers. Advances in the identification of genetic markers for AD and other dementias have raised awareness of the familial nature of the dementias, even when autosomal dominant transmission is not evident.

AD and genetic risks. In a large neuropathologically confirmed cohort of patients with dementia, the use of apolipoprotein E4 slightly increased the positive predictive value of the AD diagnosis (Class II).[18] These authors showed that relative to the neuropathologic diagnosis of AD, the sensitivity of the clinical diagnosis of AD was 92%, whereas sensitivity of having at least one APOE E4 allele was only 65%. However, in patients with clinical diagnoses of AD, the addition of APOE testing increased the positive predictive value (using the prevalence of AD in this dementia autopsy series) of a diagnosis of AD by approximately 4% (from 90 to 94%) if an APOE E4 allele was present. In patients with a

clinical diagnosis of non-AD, the absence of an APOE E4 allele increased the negative predictive value by 8% (from 64 to 72%).

FTD and genetic risks. A relatively high prevalence of tau mutations was found in a Dutch population (17.8% of all FTD cases and 40.3% of all familial FTD cases).[82] In contrast, no tau mutations were found in a large U.S. clinical non-AD dementia sample.[83] The yield of diagnostic and prognostic information from screening of sporadic cases of suspected FTD for the known mutations of the tau gene is likely to be very low.

DLB and genetic risks. There are no clinically relevant associations between any genetic markers and DLB.

CJD and genetic risks. Although familial CJD has been linked to a number of different mutations in the prion gene,[84] and a polymorphism at one codon has been shown to be more common in sporadic CJD,[85,86] there is no evidence currently that genetic analysis of the prion gene is of value in the diagnosis of suspected CJD.

CSF markers. Since the publication of the previous practice parameter, we encountered no new published studies that addressed the issue of routine versus selective CSF analysis in the evaluation of a patient with dementia. However, since 1994, there has been intense interest in developing markers related to the neuropathology of AD in CSF.

CSF ß-amyloid$_{1-42}$. Reduced levels of ß-amyloid$_{1-42}$ in CSF of patients with AD compared with normal elderly controls have been observed repeatedly in Class II and III studies.[87-90] Using post-hoc cut-points, moderate sensitivities (78 to 92%) and specificities (81 to 83%) have been achieved in distinguishing patients with AD from normal elderly controls.[87-89] It is unclear whether CSF levels of ß-amyloid$_{1-42}$ retain diagnostic usefulness in patients with very mild AD.[91]

CSF tau. CSF tau level was shown to be significantly elevated in patients with AD compared with normal controls in Class II and III studies.[92-95] CSF tau distinguished AD from normal controls with 80 to 97% sensitivity and 86 to 95% specificity. However, elevated CSF tau level has also been detected in patients with other neurodegenerative diseases.[92] CSF tau levels may be useful in supporting a diagnosis of AD early in the course of dementia.[93,95] Although sensitivity and specificity of CSF tau measurements appear very good, there are no studies that determine the benefits of CSF tau over a good clinical diagnosis.

CSF ß-amyloid$_{1-42}$ and tau. The diagnostic yield may be improved by the simultaneous measurement of CSF ß-amyloid$_{1-42}$ and tau. In Class II and III studies, sensitivities of 85% and specificities of 87% have been reported.[88-90] Additional studies are needed to establish the value that the combined use of these markers brings to diagnosis over and above a competent clinical diagnosis.

CSF AD7C-NTP. Although specificities of 89 and 94% have been cited for CSF AD7C protein in early AD and possible or probable AD versus demented controls, patient selection and characterization in the studies[96-98] lacked scientific rigor. A recent Class II study with better methodology[99] showed that CSF AD7C-NTP had a specificity of 87% and a sensitivity of 70%.

CSF 14-3-3 protein and neuron-specific enolase. An immunoassay for the detection of the 14-3-3 protein in CSF has been described[100] that had a specificity of 99% and a sensitivity of 96% for the diagnosis of CJD among patients with dementia who had not had a stroke within one month of testing. A large German national surveillance study (Class I) of CJD also reported a sensitivity of 94%, specificity of 93%, and positive predictive value of 95% for 14-3-3 CSF assay.[101] In this same population, the CSF 14-3-3 protein assay was superior to EEG or MR in identifying cases of CJD.[48] However, other acute neurologic conditions such as stroke, viral encephalitis, and paraneoplastic neurologic disorders can provide false positive results.[100-103] A negative 14-3-3 immunoassay does not rule out CJD.[104] The additional use of neuron-specific enolase does not appear to substantially improve diagnostic accuracy.[105]

Other biomarkers. No other biomarkers that had been extensively studied and had promising detection abilities for AD or other dementias were uncovered in the literature search.

Conclusions. The CSF 14-3-3 protein assay is useful for confirming the diagnosis of CJD. In contrast, no laboratory tests have yet emerged that are appropriate for routine use in the clinical evaluation of patients with suspected AD. Several promising avenues—genotyping, imaging and biomarkers—are being pursued, but proof that a laboratory test has value is arduous. Ultimately, the putative diagnostic test must be administered to a representative sample of patients with dementia who eventually have pathologic confirmation of their diagnoses. A valuable test will be one that increases diagnostic accuracy over and above a competent clinical diagnosis.

Practice recommendations.

- Structural neuroimaging with either a noncontrast CT or MR scan in the routine initial evaluation of patients with dementia is appropriate (Guideline).
- Linear or volumetric MR or CT measurement strategies for the diagnosis of AD and are not recommended for routine use at this time (Guideline).
- For patients with suspected dementia, SPECT cannot be recommended for routine use in either initial or differential diagnosis as it has not demonstrated superiority to clinical criteria (Guideline).
- PET imaging is not recommended for routine use in the diagnostic evaluation of dementia at this time (Guideline).

- Genetic testing of patients with suspected DLB and CJD is not recommended (Guideline).
- Routine use of APOE genotyping in patients with suspected AD is not recommended at this time (Guideline).
- There are no other genetic markers recommended for routine use in the diagnosis of AD (Guideline).
- Testing for tau mutations or AD gene mutations is not recommended for routine evaluation in patients with FTD at this time (Guideline).
- There are no CSF or other biomarkers recommended for routine use in determining the diagnosis of AD at this time (Guideline).
- The CSF 14-3-3 protein is recommended for confirming or rejecting the diagnosis of CJD in clinically appropriate circumstances (Guideline).

What comorbidities should be screened for in elderly patients undergoing an initial assessment for dementia? The prior Practice parameter[1] recommended a number of laboratory tests (including complete blood count, serum electrolytes, glucose, blood urea nitrogen/creatinine, folate, B_{12}, thyroid function, and syphilis serology) as routine assessment in patients undergoing assessment for dementia. Since that time, no studies were identified that evaluated these recommendations. However, since 1994, several studies have been published that specifically addressed the diagnostic value of vitamin B_{12} levels, thyroid function analysis, and syphilis screening. No studies were identified that addressed the utility of such tests as 24-hour urine collection for heavy metals or serum toxicology screens.

Depression. Prospective studies show that individuals with depression and coexistent cognitive impairment are highly likely to have an underlying dementia on longitudinal follow-up.[106-111] In one of the studies,[110] nearly 12% of patients with dementia were also depressed. Validated instruments for screening for depression exist, such as the Geriatric Depression Scale, short form,[112] the Centers for Epidemiologic Studies Depression scale,[113] and the Hamilton Depression Scale.[114]

Vitamin B_{12}. Vitamin B_{12} deficiency is common in the elderly.[115] Reports of improvement in cognitively impaired individuals with B_{12} deficiency are equivocal.[116-119] Patients with B_{12} deficiency have had slightly lower cognitive performance than nondeficient subjects,[120] but low vitamin B_{12} levels in nondemented subjects carried no risk for the subsequent development of dementia.[121] The number of patients with dementia caused by B_{12} deficiency states has been very small in prevalence studies[122] or meta-analyses of clinic samples.[123,124] Diagnostic algorithms for refined diagnoses of vitamin B_{12} deficiencies have been published.[125]

Thyroid functions. Hypothyroidism is common in the elderly.[126-128] Nondemented patients with hypothyroidism had lower mental status test scores, word fluency, visuospatial abilities, and learning than euthyroid controls,[129] but two other studies[128,130] found no relationship between TSH and cognitive function. The vast majority of patients with clinically significant hypothyroidism in these studies[128-130] lacked dementia. On the other hand, elevated TSH levels carried an increased risk for dementia in a population-based study.[131] In dementia prevalence studies[122] and clinic sample meta-analyses,[123,132] there were only a very small number of patients with dementia attributable to hypothyroidism, which was either partially or completely reversed with treatment of hypothyroidism.

Other common metabolic abnormalities possibly associated with dementia. Other metabolic disturbances are also sometimes included in the differential diagnosis of dementia. In the series of Clarfield[123] and Weytingh,[124] hypoparathyroidism and hepatic encephalopathy were mentioned as illnesses that with treatment resulted in complete resolution of dementia.

Tests for syphilis. There are only a few areas in the United States, mainly in the southern tier of the country and in some regions of the Midwest, with high numbers of syphilis cases.[133] Thirty-one U.S. counties account for 50% of all reported cases of primary and secondary syphilis.[133] Within the last 20 years, there have been no reported cases of tertiary syphilis in any of the incidence[134-138] or prevalence[122,135,139-145] studies conducted in North America. Except in these high-incidence regions, screening for the disorder in patients with dementia without an increased pretest probability would appear to be ill-supported because positive serum Venereal Disease Research Laboratory, rapid plasma reagin, and fluorescent treponemal antibody tests are nonspecific.[146,147]

Conclusions. Depression, B_{12} deficiency, and hypothyroidism are comorbidities that are likely to appear in the elderly and in patients with suspected dementia in particular. Although treatment of these disorders may not completely reverse cognitive dysfunction, they should be recognized and treated. No new evidence has appeared since 1994 to support or refute the recommendation to perform "routine" blood tests in patients being evaluated for dementia.

Practice recommendations.

- Depression is a common, treatable comorbidity in patients with dementia and should be screened for (Guideline).
- B_{12} deficiency is common in the elderly, and B_{12} levels should be included in routine assessments of the elderly (Guideline).
- Because of its frequency, hypothyroidism should be screened for in elderly patients (Guideline).

- Unless the patient has some specific risk factor or evidence of prior syphilitic infection, or resides in one of the few areas in the United States with high numbers of syphilis cases, screening for the disorder in patients with dementia is not justified (Guideline).

Recommendations for future research. Although the DSM-IIIR definitions of dementia are reliable, clarification of the cognitive domains of dementia in the definitions would allow diseases such as some forms of VAD, as well as DLB and FTD, to be better integrated. Memory disorders are not necessarily part of the initial presentation of these disorders. Therefore, memory disorder should not be a required part of the definition of dementia. In addition, the definitions of the specific, common diseases that cause dementia—AD, VAD, DLB, and FTD—should be refined to minimize incompatibilities and confusing overlap between categories. Explicit recognition of the pathologic overlap of AD, VAD, and DLB in the diagnostic criteria might lead to a more realistic approach to clinical diagnosis. Further work must be done to improve the precision of the diagnoses of VAD and DLB in particular. The diagnosis of mild cognitive impairment (see Practice Parameter on Early Detection of Dementia) also should be integrated with the definition of dementia as well as the definitions of specific diseases. As we move into an era of earlier recognition of cognitive impairment, clarification of the distinctions between no cognitive impairment, mild cognitive impairment, and early dementia is needed.

Biomarkers for AD and other dementias are critically needed, and the validation of these markers will require cross-sectional studies and longitudinal, population-based studies with diagnosis confirmation at autopsy. If a goal of therapy for patients with dementia is to intervene before the disease has diminished cognitive function, imaging techniques or biomarkers must be capable of detecting AD pathology in asymptomatic individuals. The same consideration applies to DLB and FTD pathology. Even if a biomarker does not substantially enhance diagnostic precision in symptomatic patients, a biomarker with high sensitivity and specificity for a particular dementing disorder in symptomatic patients is one that could be of use in presymptomatic detection. The genomic identification of specific dementias and risk of their development offer prospects for future research.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use specific procedures. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific patient care decisions are the prerogative of the patient and the physician caring for the patient, based on all the circumstances involved.

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Appendix
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