Protocol for proposed practice guideline project: Etiologic Diagnosis of Dementia

Proposal of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology

Authors (alphabetical order—final order to be determined later in the guideline development process)

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Approved by the Guideline Development, Dissemination, and Implementation Subcommittee on March 8, 2018. All comments submitted during the 30-day public comment period in which this protocol is posted will be reviewed and addressed by the development panel members. Although all comments will be considered, development panel members will not specifically respond to individual comments online.

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This practice guideline protocol was developed with financial support from the American Academy of Neurology. Authors who serve as AAN subcommittee members (GSD, NL, SP, ARG, KS) or methodologists (MJA), or who are AAN staff members, were reimbursed by the AAN for expenses related to travel to subcommittee meetings where drafts of manuscripts were reviewed.
Disclosures

M.J. Armstrong: receives AAN travel reimbursement for GDDI subcommittee meetings; serves on the Level of Evidence editorial board for Neurology (but is not compensated financially) and serves as an evidence-based medicine methodologist for the AAN.

L. Baudendistel reports no disclosures.

M. Baudendistel reports no disclosures.

M. Carrillo serves on advisory boards without any compensation for the Alzheimer’s Association Medical & Scientific Advisory Council, Health Research Alliance - Board of Directors, NeuGRID EU Board of Advisors, and the Genworth Financial Medical Advisory Council.

G.S. Day receives AAN travel reimbursement for GDDI subcommittee meetings and for the North Carolina Neurological Society Annual Meeting (Feb 2016), sponsored by the AAN; receives research support as in-kind gift of radiotracer from Avid Radiopharmaceuticals (a wholly-owned subsidiary of Eli Lilly); applied to imaging research in patients with Alzheimer disease and CJD; has received research support from the American Brain Foundation/AAN Clinical Research Training Fellowship and the Weston Brain Institute’s Eugene M Johnson Junior Weston Brain Fellowship; holds more than $10,000 in stock in ANI Pharmaceuticals (not related to dementia treatment or diagnosis); has received honoraria for serving as an AAN Annual Meeting Faculty (April 2016, 2017, 2018) from the AAN and for speaking at the North Carolina Neurological Society Annual Meeting (Feb 2016); provides ad hoc review, editing of
material, reference literature for online educational and reference library Dynamed (content related to diagnosis and management of dementia); and has performed case review and provided comment for a case pertaining to diagnosis and management of a patient with Wernicke encephalopathy

A. Holden receives travel reimbursement from the Alzheimer’s Association to Alzheimer Association meetings.

N. Licking receives AAN travel reimbursement for GDDI subcommittee meetings

J. Graff-Radford received travel reimbursement from AAN for amyloid imaging guideline panel in-person meeting and for conference subcommittee meetings; orders imaging tests for diagnosis of dementia, but does not interpret test results.

W.T. Hu serves on scientific advisory boards for patient advocacy group, US Dementia Action Alliance (uncompensated); has received reimbursement for travel for presenting on clinical trials and use of biomarkers at Eli Lilly conference (2 trips to Indianapolis) and Hoffman LaRoche (1 visit to Basel Switzerland); serves on an editorial advisory board for Alzheimer’s and Dementia: Diagnosis, Assessment, and Disease Monitoring; holds a patent on using the ratio of phosphorylated tau to total tau to diagnose one form of frontotemporal degeneration (US 9,618,522 B2: Diagnostic testing in dementia and methods related thereto); serves as a consultant to AARP as part of the Global Council on Brain Health; receives honoraria from the Alzheimer’s Association for community presentations; performs diagnostic lumbar punctures for young onset
dementia and mild cognitive impairment as less than 10% of his clinical effort; receives research support from Avid Pharmaceuticals for a study as a PI comparing CSF biomarkers with cerebral amyloid PET imaging; for an autopsy-based study as a site PI of tau PET imaging; and grant funding from the National Institute on Aging (R01, R21, K23, P50) for study as a PI and from the National Institute of Environmental Health (P30).

S. Potrebic receives AAN travel reimbursement for GDDI subcommittee meetings, RITE work group and Registry Committee.

A. Rae-Grant receives AAN travel reimbursement for tGDDI subcommittee meetings, has edited *The Comprehensive Review in Clinical Neurology* with Wolters-Kluwer and *Multiple Sclerosis and Related Disorders: Diagnosis, Medical Management, and Rehabilitation* with DEMOS and received royalties from these textbooks; and is an external editor for Dynamed, an online textbook of medicine.

D. Salmon has received funding for travel to Boston University to consult for NIA grant and to a BrightFocus Grant Review Meeting on 2/24/2017, from Takeda Pharmaceutical to consult on clinical trial for Dementia with Lewy Bodies on 6/6/2017, and from the Shanghai Institute of Mental Health to travel to a meeting in Shanghai, China on 9/20/2017; serves currently as a consultant to Takeda Pharmaceutical on clinical trial for Dementia with Lewy Bodies since 9/20/2016 (no remuneration received yet, but potential for approx. $5000); receives research support for serving as a co-investigator on several NIH grants, and as a co-investigator for a State of California Grant on Alzheimer’s Disease.
K. Sullivan receives AAN travel reimbursement for GDDI subcommittee meetings; has received financial or material support or compensation from the Georgia Governor's Office of Highway Safety.

D.F. Tang-Wai has received honoraria for speaking as a lecturer at the Canadian Conference on Dementia and Geriatric Refresher Day at the University of Western Ontario; serves as Clinician investigator member of Krembil Research Institute of Neurology, Medicine, University of Toronto; receives non-financial research support for serving as a co-investigator for the following studies: Toronto Dementia Research Alliance Clinical Research Platform, sponsored by Brain Canada; Seeing What They See, sponsored by the Economic and Social Research Council (ESRC) and the National Institute for Health Research (NIHR); Towards a better understanding of the language impairment and neural basis of primary progressive aphasia: A longitudinal study, sponsored by the Canadian Institutes of Health Research, and for serving as a collaborator on Validation of ocular measures as potential biomarkers for early detection of brain amyloid and neurodegeneration, sponsored by Brain Canada MIRI Grant & W Garfield Weston Foundation.

**Description of AAN Document Types**

This protocol is the planning document for one of four AAN document types: focused systematic review, comprehensive systematic review, practice advisory (based on a systematic review), or practice guideline (based on a comprehensive systematic review). The term *guideline* is the general term that refers to all AAN evidence-based documents, with the exception of case
definitions. Because it is for planning purposes only, this protocol document is not a substitute for the complete guideline.

Abbreviations:

AD: Alzheimer disease; AD dementia: dementia due to Alzheimer disease changes in the brain;
LBD: Lewy body disease; DLB: dementia with Lewy bodies (dementia due to LBD); FTLD:
frontotemporal lobar degeneration; bvFTD: behavioral variant frontotemporal dementia
(dementia due to FTLD); VCID: vascular cognitive impairment and dementia; MRI: magnetic resonance imaging; PET: positron emission topography (a specialized brain scan); CSF:
cerebrospinal fluid

GUIDELINE PROJECT PROTOCOL

Guideline project development plan
This proposed project will be developed in accordance with the processes described in the 2017 edition of the AAN clinical practice guideline development process manual.¹ The developers of this Guideline project intend to develop a practice guideline based on a systematic review. This protocol will be posted for public comment. Patient representatives are included on the panel.

Guideline project timeline
Following is the tentative timeline for development of this practice guideline based on a systematic review:
• **Panel formation:** August 2017

• **Drafting of protocol:** December 2017

• **Approval of protocol by the AAN Guideline Development, Dissemination, and Implementation Subcommittee (GDDI):** January 2018 (tentative)

• **Protocol posted for public comment:** March 2018

• **Literature search:** April 2018 (tentative)

• **Panel review of abstracts:** April 2018 to May 2018 (tentative)

• **Review of full articles, data extraction, and development of evidence tables:** June 2018 to September 2018 (tentative)

• **Develop recommendations based on systematic review and other pillars (principles, strong related evidence from other conditions, inferences):** November 2018 to April 2019 (tentative)

• **Submit draft guideline to AAN GDDI for review and approval for public comment:** April 2019 (tentative)

• **Post guideline for public comment:** June 2019 (tentative)

• **Submit to AAN GDDI for review and approval of final document (Neurology will do preliminary review concurrently; when approved by GDDI, the AAN Practice Committee also will review):** August 2019 (tentative)

• **Submission to Neurology:** October 2019 (tentative)

**Composition of the development panel**

In August 2017, the AAN GDDI recruited a multidisciplinary panel consisting of 10 AAN members and 4 patient representatives to develop this Guideline project protocol. The panel
included 7 content experts (GSD, MJA, JG, WTH, ARG, DS, DTW), a methodology expert (MJA), 5 AAN GDDI members (GSD, NL, SP, ARG, KS), and 3 patient advocates/representatives (LB, MB, AH). Subsequently, an additional patient representative and content expert from the Alzheimer’s Association (MCC) was added to the panel; this panel member did not assist with development of the clinical questions, but did review the protocol.

All panel members were required to submit online conflict of interest (COI) disclosure forms and their curriculum vitae copies. The panel leadership, consisting of the co-lead developers (GSD, NL), AAN GDDI leadership and AAN staff persons, reviewed the COI disclosure forms and CVs for financial and intellectual COI. These documents were screened specifically to exclude both those individuals with a clear financial conflict and those whose profession and intellectual bias would diminish the credibility of the review in the eyes of the intended users. In accordance with AAN policy, the co-lead developers (GSD, NL) have no COI relevant to the development of this Guideline. One of the development panel members was determined to have COI, but the COI was judged to be not significant enough to preclude this developer from authorship (WTH). The developer determined to have COI (WTH) will not be permitted to review or rate the evidence. This individual will be consulted in an advisory capacity to help with the validation of the key questions, the scope of the literature search, and the identification of seminal articles to validate the literature search. The panel member with COI will be allowed to participate in the recommendation development process. The co-lead developers recommended the final panel membership to the AAN GDDI leadership, who reviewed the list of members and the panel leaders’ COI forms, and provided final approval. This panel will be solely responsible for the final decisions about the design, analysis, and reporting of the proposed systematic review and
proposed subsequent practice guideline which will then be submitted for approval to the AAN GDDI.

Introduction to proposed practice guideline project topic

This protocol describes the planned approach for an upcoming AAN evidence-based guideline discussing the diagnosis of specific causes (i.e., etiologies) of dementia. In keeping with the AAN’s approach to public comment, the protocol was written in terms aimed at promoting feedback on the proposed plan from most individuals—whether medical professionals or lay public.

Dementia (also called major neurocognitive disorder in medical terminology) is a general term used to describe diseases or disorders resulting in memory and thinking problems that are severe enough to interfere with daily life. In older adults, dementia is most often caused by brain diseases, which lead to the progressive loss of brain cells and increasing disability. To qualify for a diagnosis of dementia, memory and thinking problems must represent a decline from one’s prior level of functioning, and cannot be explained by delirium (confusion often relating to infection, or another active medical issue) or another psychiatric disorder. The earliest symptoms of dementia are often subtle: daily tasks may take more time to complete or become more difficult; a person may have more trouble multitasking, or problems may arise when a person’s routine is changed. As dementia progresses, declines in daily function become more obvious, eventually compromising performance of basic activities of daily living (e.g. dressing, bathing, eating), and resulting in increased disability and reliance on others.

Prior American Academy of Neurology (AAN) guidelines focused on establishing the clinical criteria and testing necessary to detect dementia in the elderly. Although it is important...
to identify patients with “dementia”, it is equally important to determine the cause (i.e., etiology) of dementia, as different causes may associate with different risk factors and outcomes, and may require different approaches to evaluation, patient and caregiver counselling, and treatment—components critical to delivery of the best possible care for patients with dementia.6,7 Importantly, patients and caregivers consistently indicate that they want to know the specific cause(s) of their dementia.8-10 The emphasis on determining the cause of dementia is expected to increase even more as effective treatments for specific causes of dementia become available.11 The most common types of dementia in older adults include Alzheimer disease (AD) dementia (most often due to AD neuropathologic change), dementia with Lewy bodies (DLB; most often due to cortical Lewy body disease [LBD]), behavioral variant frontotemporal dementia (bvFTD; most often due to frontotemporal lobar degeneration [FTLD]), and vascular cognitive impairment and dementia (VCID; most often due to arterial or venous cerebrovascular disease), and dementia due to combinations of the above diseases. Validated criteria are available to help clinicians recognize the symptoms, signs and findings on testing that associate with a diagnosis of AD dementia,2 DLB,12 bvFTD13 and VCID.14 The types of dementia are determined by clinicians after obtaining a thorough history and completing a physical examination. Tests of memory and thinking may also be used to assess how memory and thinking change across time (for example, screening tests such as the Mini-Cog, Montreal Cognitive Assessment, or the Mini-Mental State Examination, or more extensive neuropsychological testing), and to help make a diagnosis. Additional tests may be ordered to ensure that dementia is not better explained by another cause, including blood tests measuring vitamin B12 and thyroid hormone levels, and brain imaging.4 However, even with a comprehensive approach, the clinical findings arising from various causes of dementia (e.g., AD,
LBD, FTLD and cerebrovascular disease) may overlap, be misinterpreted, or be altogether missed on history and examination. As a result, the most common causes of dementia are all-too-often under-recognized or misdiagnosed, compromising the delivery of optimal care and research.\(^7\)

There is a clear need to determine the clinical tools and widely available diagnostic tests that can be used to accurately diagnose the most common causes of dementia (that is, AD, LBD, FTLD, cerebrovascular disease). The proposed guideline will consider which symptoms, signs and commonly available tests are most useful for this purpose. This guideline will also consider the prevalence of potentially modifiable diseases or disorders that are likely to worsen dementia severity or affect the quality of life of patients living with dementia: specifically, possible dementia risk factors cited in prior AAN dementia diagnosis guidelines (thyroid dysfunction, and vitamin B12 deficiency),\(^4\) mid- (hypertension, obesity, hearing loss) and late-life risk factors (smoking, depression, physical inactivity, social isolation and diabetes) identified in the recently published Lancet Commissions study,\(^15\) and related disorders likely to influence dementia risk (sleep disruptions due to obstructive sleep apnea, excessive alcohol consumption or other causes\(^{16,17}\)). This knowledge will help clinicians to prioritize screening for these disorders in patients with dementia. The hope is that early diagnosis and management of potentially modifiable diseases or disorders will improve care and outcomes in patients with dementia.

**Rationale for this practice guideline**

The AAN practice guideline on the diagnosis of dementia was published in 1994\(^5\) and updated in 2001.\(^4\) These guidelines continue to be highly accessed and cited, emphasizing the relevance of this topic to clinical practice and research. In the years since the last guideline update was
published, there has been tremendous increase in public awareness concerning the frequency, costs, and negative consequences (that is, morbidity and mortality) associated with the most common causes of dementia. Increasing concern has fueled remarkable advances in research concerning the causes and mechanisms of dementia, leading to advances in clinical and research diagnostic criteria, biomarker development and application, and interventions. The purpose of this practice guideline is to systematically assess all high-quality studies that inform the etiologic diagnoses of dementia (that is, the cause(s) of dementia) in patients ≥40 years-of-age, with a focus on identifying the clinical features (i.e., features determined on history and physical examination) and results of commonly-available diagnostic tests that identify patients with common causes of dementia (i.e., AD, LBD, FTLD, cerebrovascular disease).

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1 A biomarker is defined by the National Institutes of Health as “A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition. Also called molecular marker and signature molecule.”

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Clinical questions

The systematic review for this practice guideline will address three questions. These questions are presented below in three different formats:

<table>
<thead>
<tr>
<th>Question #</th>
<th>Question</th>
<th>PICOT format</th>
<th>Plain-language format</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>In patients $\geq 40$ years-of-age with dementia, which clinical features, when present, predict the etiologic cause of dementia, and should, therefore, be considered at the time of diagnosis?</td>
<td>P: In patients $\geq 40$ years-of-age with dementia I: which clinical features, when present C: as opposed to when absent O: predict the etiologic cause of dementia?</td>
<td>In people over 40 years-old who have dementia, what issues (e.g. problems in daily life, findings on the physical exam) can help clinicians figure out the cause of dementia?</td>
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<tr>
<td>2</td>
<td>In patients $\geq 40$ years-of-age with dementia, which widely available diagnostic tests can be used to predict the etiologic cause of dementia, and should, therefore, be considered at the time of diagnosis?</td>
<td>P: In patients $\geq 40$ years-of-age with dementia I: which widely available diagnostic tests, when &quot;positive&quot;/&quot;abnormal&quot; C: as opposed to when &quot;negative&quot;/&quot;normal&quot; O: can accurately predict the etiologic cause of dementia?</td>
<td>In people over 40 years-old who have dementia, what widely available tests can help clinicians figure out the cause of dementia?</td>
</tr>
<tr>
<td>3</td>
<td>In patients $\geq 40$ years-of-age with dementia, what is the prevalence of potentially modifiable diseases or disorders that may worsen dementia severity or quality of life of patients living with dementia (specifically thyroid dysfunction, vitamin B12 deficiency, and sleep disruption due to obstructive sleep apnea or other causes; mid-life hypertension, obesity and hearing loss; and late-life smoking, excessive alcohol consumption,</td>
<td>P: In patients $\geq 40$ years-of-age with dementia I: what is the prevalence of potentially modifiable diseases or disorders that may worsen dementia severity or quality of life of patients living with dementia (specifically thyroid dysfunction, vitamin B12 deficiency, and sleep disruption due to obstructive sleep apnea or other causes; mid-life hypertension, obesity and hearing loss; and late-life smoking, excessive alcohol consumption,</td>
<td>In people over 40 years-old who have dementia, how common are problems that may make it harder to live with dementia (specifically low/high thyroid hormone, low vitamin B12, sleep disruption (due to problems breathing or other causes); mid-life high blood pressure, obesity and hearing loss; and late-life cigarette smoking, excessive alcohol consumption, depression, physical inactivity, social isolation and diabetes)?</td>
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depression, physical inactivity, social isolation and diabetes)?

<table>
<thead>
<tr>
<th>Question # with type*</th>
<th>Population</th>
<th>Intervention</th>
<th>Co-intervention</th>
<th>Outcome</th>
<th>Study design</th>
</tr>
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<tbody>
<tr>
<td>1 Diagnostic</td>
<td>Patients ≥40 y with dementia</td>
<td>Clinical features(^a) present</td>
<td>Clinical features(^a) absent</td>
<td>Etiologic diagnosis of dementia</td>
<td>Observational (prospective/retrospective, cross-sectional); gold standard = pathology-confirmed diagnoses</td>
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| "Will include features across the following categories:  
1. Demographics (e.g., age, sex, race, education)  
2. History (e.g., past medical history, social history, family history, medical use, symptom(s) at onset, current symptoms)  
3. Physical examination findings (e.g., blood pressure, BMI, findings on general examination, findings on neurological examination)  
Performance on bedside measures of cognitive function (e.g., MMSE, MoCA, other)" | | | | | |
<p>| 2 Diagnostic          | Patients ≥40 y with dementia | Widely available(^b) diagnostic test positive/abnormal | Widely available(^b) diagnostic test negative/normal | Etiologic diagnosis of dementia | Observational (prospective/retrospective, cross-sectional); gold standard = pathology-confirmed diagnoses |
|                       |            |              |                 |         |              |
| &quot;Widely available&quot; includes tests that are accessible within the continental United States through direct (clinical) referral to a tertiary care center or commercial provider. &quot;Less widely available&quot; includes tests that are not yet approved for use in clinical populations (i.e., research only).&quot; | | | | | |</p>
<table>
<thead>
<tr>
<th>3a Frequency</th>
<th>Patients ≥40 y with dementia</th>
<th>Number of patients with potentially modifiable(^c) comorbidity</th>
<th>Number of patients without potentially modifiable(^c) comorbidity absent</th>
<th>Class I and II observational population studies (population-based prospective, retrospective, or cross-sectional studies)</th>
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\(^c\) Potentially modifiable comorbidities will include thyroid dysfunction, vitamin B12 deficiency, and sleep disruption due to obstructive sleep apnea or other causes; mid-life hypertension, obesity and hearing loss; and late-life smoking, depression, physical inactivity, social isolation and diabetes.

1 *Question type refers to one of the following: screening, diagnostic, therapeutic, prognostic, natural history, and frequency.*
Rationale for Clinical Questions

We have prioritized questions that are relevant to the evaluation of patients diagnosed with dementia. The answers to these questions are expected to 1) define the clinical features (symptoms and signs) and widely accessible diagnostic tests that identify patients with common causes of dementia; and, 2) identify potentially modifiable medical problems (comorbidities) that are common in patients with dementia and may worsen dementia severity or the quality of life of patients living with dementia. Evidence-based recommendations derived from these questions will have immediate implications for improving the clinical assessment, diagnostic evaluation, and treatment of patients with the most common causes of dementia.

This guideline will not address screening for dementia or mild cognitive impairment in the general population (considered elsewhere\textsuperscript{26,27}), nor will it reconsider the validity of published criteria for the diagnosis of dementia.\textsuperscript{2,3} Additionally, whereas prior practice guidelines on the diagnosis of dementia included evidence specific to patients with rapidly progressive dementia,\textsuperscript{4} the current guideline will focus on the causes (etiologic diagnoses) of more typical, gradually progressive dementing illnesses. Practice guidelines specific to the diagnosis of rapidly progressive dementia are important and necessary, but are beyond the scope of this guideline.

Types of participants

We will use definitions of dementia specified in individual articles, provided they conform to generally accepted definitions of dementia.\textsuperscript{2,3} We will include studies of participants with a clinical diagnosis of dementia at all stages. We acknowledge that definitions of very mild dementia and mild cognitive impairment may overlap.\textsuperscript{27,28} We will plan to include studies that include patients with very mild severity dementia, provided the diagnostic criteria establishes the
presence of cognitive impairment, which results in a meaningful impact on daily life. This
guideline will focus on patients with the most common causes of dementia (i.e., AD, LBD,
FTLD, cerebrovascular disease). This guideline will not include patients with less common
causes of dementia, or those in whom dementia develops as a complication of a longstanding
neurologic disease or process (e.g., multiple sclerosis, idiopathic Parkinson disease, Creutzfeldt-Jakob disease, HIV/AIDS). While the clinical questions in this guideline are different than those
in the 2001 guideline, the literature search will include studies published since the release of the
2001 guideline update. This decision reflects the development panel’s intent to more accurately
reflect present day approaches to the clinical assessment and diagnostic evaluation of patients
with dementia, and the application of modern diagnostic criteria.

**Types of “intervention”**

For question 1, we will review studies that address whether certain pieces of readily available
information (clinical features) can help clinicians determine the type of dementia present. In
particular, we plan to look at 1) demographics (e.g., age, sex, race, education), 2) history (e.g.,
past medical history, social history, family history, medication use, symptom(s) at onset, current
symptoms), 3) physical examination findings (e.g., blood pressure, BMI, findings on general
examination, findings on neurological examination), and 4) performance on cognitive testing that
can be performed in the clinician’s office (e.g., MMSE, MoCA, other).

For question 2, we will review studies reporting on the usefulness of tests for the diagnosis of
dementia that are FDA-approved for use in dementia diagnosis, and widely available throughout
the United States (directly accessible, or widely accessible via referral to tertiary care centers or commercial providers). These tests will include (but need not be limited to) commercially-available blood tests, genetic tests, EEG, structural neuroimaging, polysomnography (sleep studies), FDA-approved nuclear imaging studies (including FDG-PET, SPECT, amyloid PET and dopamine transporter imaging), and CSF biomarkers. Amyloid PET imaging is currently the topic of an in-process guideline. Widely available tests will not be excluded, even if most insurers do not presently reimburse them.

Finally, for question 3, we will review studies that address the frequency with which other potentially treatable medical conditions (comorbidities) are encountered in patients with dementia. This question will focus on diseases or disorders deemed likely to negatively affect dementia severity or the quality of life of patients living with dementia, including thyroid dysfunction, vitamin B12 deficiency, and sleep disruption due to obstructive sleep apnea or other causes; mid-life hypertension, obesity and hearing loss; and late-life smoking, excessive alcohol consumption, depression, physical inactivity, social isolation and diabetes. The hope is that early diagnosis and management of common comorbidities may improve the care of patients with dementia.

**Comparison group**

The comparison group for questions 1 and 2 will include patients with a diagnosis of dementia who *do not* have the “intervention” of interest. By way of example, for studies assessing the strength of association between a clinical symptom or sign (e.g., short-term memory loss) and a
specific cause of dementia (e.g., AD dementia), the comparison group may include patients with
dementia who do not have short-term memory loss.

Types of outcome measures
To determine the actual cause of dementia, the guideline will preferentially use an autopsy
diagnosis (histopathological examination of brain tissue establishing the etiology of dementia),
recognizing that this is the most reliable way to determine the cause of dementia. When autopsy
diagnosis is not available, we will consider diagnoses made using testing thought to be highly
predictive of the cause of dementia as an alternate outcome (e.g., disease-specific biomarkers);
such studies will be interpreted in light of the results of guideline question 2, considering the
accuracy of such tests.

Research Approach

<table>
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<tr>
<th>Study aim</th>
<th>Include</th>
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<tr>
<td>Screening</td>
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<td>Diagnostic accuracy</td>
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<td>Prognostic accuracy</td>
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<td>Impact on quality of life</td>
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<tr>
<th>Definition of condition being studied</th>
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<tr>
<td>AD: Neuropathologic or biomarker diagnosis, according to established criteria (will specify criteria used by each study)</td>
<td>AD: Neuropathologic or biomarker diagnosis, according to established criteria (will specify criteria used by each study)</td>
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<td>LBD: Neuropathologic or biomarker diagnosis according to formal criteria (will specify criteria used by each study)</td>
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<td>FTLD: Neuropathologic or biomarker diagnosis according to formal criteria</td>
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<td>Cerebrovascular disease:</td>
<td>Parkinson’s disease dementia</td>
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**Population**

<table>
<thead>
<tr>
<th>1. People with dementia</th>
<th>1. Studies including only patients with MCI or subjective cognitive impairment</th>
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<tbody>
<tr>
<td>2. Studies including ≥20 participants</td>
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</table>
2. Animal/non-human studies
3. Studies including <20 participants (Question 3 will consider only population-based studies)

| **Special sub-populations to be considered** | Sex (male vs female) | N/A |
| Race/ethnicity | Various age ranges | N/A |
| - Early-onset (40-64.9 years) | - Late-onset (65-89.9 years) | - Oldest old (≥90 years) |

| Setting | Population-based | N/A |
| Clinic-based | Subspecialty clinic-based |

| “Intervention” [The “I” of the PICO questions – may be a test, a prognostic factor, a treatment, etc. depending on question being asked] | See PICO questions above | N/A |

| Comparison | See PICO questions above | N/A |
| Outcomes of interest | See PICO questions above | N/A |
| Timing of outcome assessment (if relevant) | As reported by included studies | N/A |

| Study design | Randomized controlled trial | Animal studies |
| Cohort study | Review (except for ref list) |
| Case-control study | Meta-analysis |
| Cross-sectional studies | Case report |
| | Letters to the editor |
| | Study protocols |
| | Opinion pieces, editorials |

| Publication language | All | N/A |

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2. **Consideration of patient preferences**

We will include information on patient preferences regarding the etiologic diagnosis of dementia through several methods. We will include two panel members with lived experience with dementia on our panel as well as two advocates associated with the Alzheimer’s Association.

These individuals will represent patient views and preferences throughout the entire guideline.
development process. Three of the four patient representatives were involved in the development of the draft guideline questions and protocol, and all will be involved in assessing the face validity of the systematic review and developing recommendations. Additionally, we performed a literature search using the MESH terms “patient preference” and “dementia” prior to finalizing the PICO questions. This resulted in 58 abstracts, of which seven were deemed particularly relevant. The results of these seven articles supports the importance of identifying dementia and disclosing the diagnosis.\textsuperscript{9,29-34} No article described patient preferences or suggested PICO questions that are not currently included in the protocol. These articles will be used to inform patient preferences during recommendation development. At that time, an updated literature search for patient preferences relating to the diagnosis of dementia will be performed. Finally, we will seek comment at both the protocol and guideline stage from advocacy groups representing the most common causes of dementia, and from the general public.

**Considerations for Special Populations and Multiple Morbidities**

There is increasing evidence that age, sex and race/ethnicity may influence the relationship between clinical findings and dementia etiologies, risk factors for dementia, the sensitivity and specificity of diagnostic testing, and the response to therapeutic interventions. AAN guidelines now specifically identify special populations for whom recommendations might possibly be different. There may or may not be available evidence for these special populations, but the literature search will specifically look for evidence for efficacy in these populations in addition to general populations of patients with dementia. Specific to age, evidence will be stratified where possible and considered separately across patients falling within three pre-specified age groups: 1) patients with early-onset dementia, including individuals with symptomatic onset $<65$
years; 2) patients with late-onset dementia, including individuals with symptomatic onset beyond 65 years; and, 3) the “oldest-old”, including individuals with symptomatic onset in the 10th decade of life or later. Patients with dementia beginning prior to the age of 40 will be excluded, arguing that the causes and contributors to dementia in this age group are sufficiently unique to warrant separate consideration. Our proposed questions will also specifically consider the effect of additional patient-specific factors on the etiologic diagnosis of dementia (e.g., family history, personal genetic history, comorbid health issues).

Literature search strategy

Inclusion and exclusion criteria

Inclusion Criteria:

- General:
  - Human studies
  - Date: 2001 to present
  - Languages: all languages
  - Study types: RCTs, prospective cohort studies, retrospective cohort studies (including case-control studies) with autopsy confirmed diagnoses, population-based epidemiological studies

- Population:
  - Patients age ≥40 years
  - People with all stages of dementia (e.g., very mild, mild, moderate, severe)
  - Studies with ≥20 patients

- Outcomes: clinical-pathologic correlation (etiologic diagnosis)
Exclusion Criteria:

- **General:**
  - Animal studies
  - Study types: retrospective cohort studies (including case-control series) without autopsy confirmed diagnoses, case studies, reviews, meta-analyses

- **Population**
  - Patients age <40 years
  - Rapidly progressive dementia
  - Studies with <20 patients

- **Outcomes:** those not listed above

**Terms and databases to be used in the literature search**

**Databases:** Medline, Embase, ClinicalTrials.gov

**Keywords**

- **a) Key Text words and Index words for the condition or closely related conditions, if appropriate (linked by the word "OR"):**
  - Dementia (all stages, including very mild, mild, moderate, severe)
  - Cognitive impairment (not mild cognitive impairment), Alzheimer disease, Alzheimer disease dementia, Alzheimer dementia
  - Lewy body disease (LBD)
  - Frontotemporal lobar dementia (FTLD), Behavioral variant frontotemporal dementia (dementia due to FTLD, aka by FTD)
  - Cerebrovascular disease AND dementia
  - Dementia with Lewy bodies (dementia due to LBD, aka DLB)
  - Mixed vasular dementia
  - Vascular cognitive impairment and dementia (VCID)

- **b) Key text words for identification of special populations and relevant comorbidities (linked by the word "OR"):**
No additional keywords will be used. Studies on special populations will be captured with the listed condition and intervention keywords, and evidence on the defined special populations will be stratified for analysis.

c) **Key Text words and Index words for the intervention (linked by the word "OR"):**

**Question 2**

- Blood tests
- Genetic tests
- EEG
- Structural neuroimaging (brain MRI, CT)
- Polysomnography (sleep studies)
- FDA-approved nuclear imaging studies (including FDG-PET, SPECT, amyloid PET dopamine transporter imaging
- CSF biomarker

**Question 3**

- Mood disorders
- Hypertension
- Diabetes
- Dyslipidemia
- Tobacco and alcohol use
- Sensory changes [hearing and vision loss]
- Sedentary lifestyle
- Obstructive sleep apnea
- Endocrine dysfunction
- Nutritional/vitamin deficiency

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may emerge between the time information is developed and when it is published or read); 3) addresses only the question(s) specifically identified; 4) does not mandate any particular course of medical care; and 5) is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. AAN provides this information on an “as is” basis, and makes no warranty, expressed or implied, regarding the information. AAN specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. AAN assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information or for any errors or omissions.

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The AAN’s Conflict of Interest Policy is available at https://www.aan.com/AAN-Resources/Details/about-the-aan/relationships-and-conflicts-of-interest-policy/. All AAN guideline authors must meet the stipulations outlined in the policy in order to participate on a guideline development panel. This policy is further described in the 2017 AAN Clinical Practice Guideline Development Manual, available at AAN.com/Guidelines/Home/Development.
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