

PERSPECTIVE

Alzheimer's Association clinical practice guideline for the Diagnostic Evaluation, Testing, Counseling, and Disclosure of Suspected Alzheimer's Disease and Related Disorders (DETeCD-ADRD): Executive summary of recommendations for primary care

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Abstract

US clinical practice guidelines for the diagnostic evaluation of cognitive impairment due to Alzheimer's disease (AD) or AD and related dementias (ADRD) are decades old and aimed at specialists. This evidence-based guideline was developed to empower all—including primary care—clinicians to implement a structured approach for evaluating a patient with symptoms that may represent clinical AD/ADRD. Through a modified-Delphi approach and guideline-development process (7374 publications were reviewed; 133 met inclusion criteria) an expert workgroup developed recommendations as steps in a patient-centered evaluation process. This summary focuses

Alireza Atri and Bradford C. Dickerson contributed equally to this study.

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on recommendations, appropriate for any practice setting, forming core elements of a high-quality, evidence-supported evaluation process aimed at characterizing, diagnosing, and disclosing the patient's cognitive functional status, cognitive-behavioral syndrome, and likely underlying brain disease so that optimal care plans to maximize patient/care partner dyad quality of life can be developed; a companion article summarizes specialist recommendations. If clinicians use this guideline and health-care systems provide adequate resources, outcomes should improve in most patients in most practice settings.

KEYWORDS

Alzheimer's disease, cerebrospinal fluid, dementia, diagnosis, frontotemporal dementia, Lewy body dementia, magnetic resonance imaging, mild cognitive impairment, molecular biomarkers, positron emission tomography, vascular cognitive impairment

Highlights

- US clinical practice guidelines for the diagnostic evaluation of cognitive impairment due to Alzheimer's disease (AD) or AD and related dementias (ADRD) are decades old and aimed at specialists.
- This evidence-based guideline was developed to empower all—including primary care—clinicians to implement a structured approach for evaluating a patient with symptoms that may represent clinical AD/ADRD.
- This summary focuses on recommendations, appropriate for any practice setting, forming core elements of a high-quality, evidence-supported evaluation process aimed at characterizing, diagnosing, and disclosing the patient's cognitive functional status, cognitive-behavioral syndrome, and likely underlying brain disease so that optimal care plans to maximize patient/care partner dyad quality of life can be developed; a companion article summarizes specialist recommendations.
- If clinicians use this guideline and health-care systems provide adequate resources, outcomes should improve in most patients in most practice settings.

1 | INTRODUCTION

A major global health challenge is the timely detection, accurate diagnosis, appropriate disclosure, and proper management of mild cognitive impairment (MCI) or dementia due to Alzheimer's disease (AD) or Alzheimer's disease related dementias (ADRD), which include frontotemporal lobar degeneration (FTLD), Lewy body disease (LBD), vascular contributions to cognitive impairment and dementia (VCID), mixed etiology dementias, and others. By mid-century, the number of Americans living with dementia will more than double from 5.8 to 13.8 million,¹ leading to an explosion of the already exorbitant individual and societal costs and burden.^{2,3}

All too often, cognitive and behavioral symptoms due to AD/ADRD are undiagnosed, undisclosed, or misattributed.^{2,4-11} A minority of primary care providers (PCPs) report feeling highly confident in making a diagnosis of AD or ADRD,¹² 39% of PCPs report "never or only sometimes" being comfortable making a dementia diagnosis,² and many PCPs say they lack the tools to care for patients with cognitive prob-

lems and rely on specialists (although recognizing the challenges of accessing specialists in many settings).¹ In 50% of individuals with US billing records indicating dementia due to AD or ADRD, the patient or care partner report not being informed of the diagnosis⁴—even though the vast majority want to know their diagnosis—^{4,13-15} despite evidence supporting individually and societally meaningful medical and psychosocial benefits of timely diagnosis.^{3,4,15-22} As a result of delayed diagnosis and disclosure, patients and families experience distressing, costly, and potentially harmful delays in receiving appropriate care.^{4,17} Barriers to timely and accurate diagnosis and appropriate disclosure of MCI or dementia due to AD/ADRD are multifactorial, but many could be mitigated by the establishment—followed by effective dissemination and implementation—of evidence-supported clinical practice guidelines for the diagnostic evaluation of suspected MCI or dementia in primary as well as specialty care settings.

To address these gaps, the Alzheimer's Association convened a Diagnostic Evaluation, Testing, Counseling, and Disclosure Clinical Practice Guideline Workgroup (the DETeCD-ADRD CPG Workgroup).

Our emphasis is on good clinical practice for the process of evaluating a patient presenting with an illness (i.e., symptoms, obtained through history, and signs, obtained through examination) that may represent the clinical manifestations of common brain diseases, especially AD and ADRD—in some cases with exacerbating medical conditions or factors. While this guideline applies to a patient with any severity of cognitive or behavioral impairment, it does not consider individuals who do not have symptoms; therefore, it does not address the topic of screening in asymptomatic people.^{23–28} This DETeCD-ADRD CPG seeks to empower all clinicians, including those in primary, specialty, or subspecialty care, to implement a structured yet individualized patient-centered approach to diagnostic evaluation that includes clear communication with the patient and an informant or care partner(s). The guideline also empowers patients and families to expect that symptoms concerning for AD or ADRD should be appropriately evaluated and disclosed, and that the health-care system should provide necessary resources for best practices. The purpose of the patient-centered evaluation process is to provide timely, accurate, and compassionate diagnosis, disclosure, and counseling regarding stage of functional impairment (cognitive functional status), the constellation of symptoms and signs of the illness (cognitive-behavioral syndrome), and the likely underlying disease(s) and conditions that are contributing to it—ultimately to ensure that all potential medical and psychosocial issues are considered so that a care plan can be developed to optimize goals, function, and quality of life for the patient and family.^{29–31}

This executive summary distills the core elements of a high-quality, evidence-supported, patient-centered evaluation and disclosure process that are appropriate for primary care and any other practice setting. A companion article summarizes recommendations for specialists (Dickerson BC, et al.).³²

2 | METHODS

The Alzheimer's Association convened a multi-disciplinary DETeCD-ADRD CPG expert workgroup composed of 10 voting members from primary care, specialty and subspecialty care, long-term and palliative care, health economics, and bioethics, and retained a team from Avalere Health with expertise in developing clinical appropriate use criteria and practice guidelines. Staff from the Alzheimer's Association and Avalere teams supported the DETeCD-ADRD CPG workgroup in developing the guideline through a formalized process modeled after that described in the American Academy of Neurology Clinical Practice Guideline Process Manual,³³ the American College of Cardiology Foundation/American Heart Association Task Force on Clinical Practice Guidelines,³⁴ and the Institute of Medicine's *Clinical Practice Guidelines We Can Trust*,³⁵ ensuring that the process was transparent, that conflict of interest was managed appropriately, that the workgroup was composed of multidisciplinary experts who were engaged in all steps of the process, and that the DETeCD-ADRD CPG Recommendations and Report underwent external peer review by a group including a patient advocate (all in accordance with best practices described in the Institute of Medicine's *Clinical Practice Guidelines We*

Can Trust). Details of the DETeCD-ADRD CPG developmental process and methods, summarized briefly here, can be found in [supporting information](#).

The process included a systematic review of the published evidence focused on the diagnosis of MCI and dementia likely due to AD based on six PICOTS (patient population/intervention/comparator/outcome/timing/setting) framework questions formulated by the workgroup and was conducted and independently graded by the Pacific Northwest Evidence-based Practice Center at Oregon Health & Science University. Of the initially identified 7374 potentially relevant articles, abstracts, and titles, 1908 articles underwent full-text review, and 133 primary studies or systematic reviews met criteria for inclusion and assessment by the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) method. In aiming to place the evidence into a realistic clinical context, the workgroup also considered non-evidence-based clinical experience-informed factors including deductive inferences from accepted clinical principles;³⁶ the relative value of the benefit compared to the risk of harm and burden of the action; the availability of the resources to perform the action; the cost of the action; and the availability of potentially effective alternative approaches, consistent with best practices in guideline development.^{33–35,37,38}

The workgroup attempted to phrase each recommendation as a practical action that is considered one of a series of steps in the evaluation and disclosure process. Recommendations 1 through 11 were purposefully written (and re-written several times after several rounds of modified-Delphi discussions and voting by the workgroup) so that they could be assigned the highest strength of recommendation. That is, the benefit of performing the recommended action, as part of the goal-oriented and dynamic evaluation and disclosure process delineated in Figures 1 and 2, outweighs the potential harm and burden in the majority of circumstances. In so doing, the workgroup sought to describe the fundamental principles and steps of the process of a patient-centered evaluation that should usually be performed from start to finish.

For each recommendation, a series of bullet points describing the rationale and considerations for implementation were written, followed by a narrative citing evidence for the recommendation, considerations for how to operationalize the action(s) represented by that recommendation, and specific situations that may be exceptions. The DETeCD-ADRD CPG Report was then circulated to a panel of external reviewers for peer review. Based on feedback from the external reviewers, and developments in the field (particularly related to advances in and accessibility of cerebrospinal fluid [CSF] and positron emission tomography [PET] biomarkers in the United States from 2020–2023), the 19 DETeCD-ADRD CPG Recommendations underwent several revisions and the final 19 DETeCD-ADRD CPG Recommendations (Box 1) achieved unanimous consensus for adoption on October 25, 2023. The DETeCD-ADRD CPG Report was revised accordingly, point-by-point responses to reviews were documented, and the final DETeCD-ADRD CPG Comprehensive Report was unanimously approved by workgroup members, and is available online (<https://www.alz.org/clinicalguidelines>).

CORE ELEMENTS OF EVALUATION OF PATIENT WITH SUSPECTED COGNITIVE IMPAIRMENT

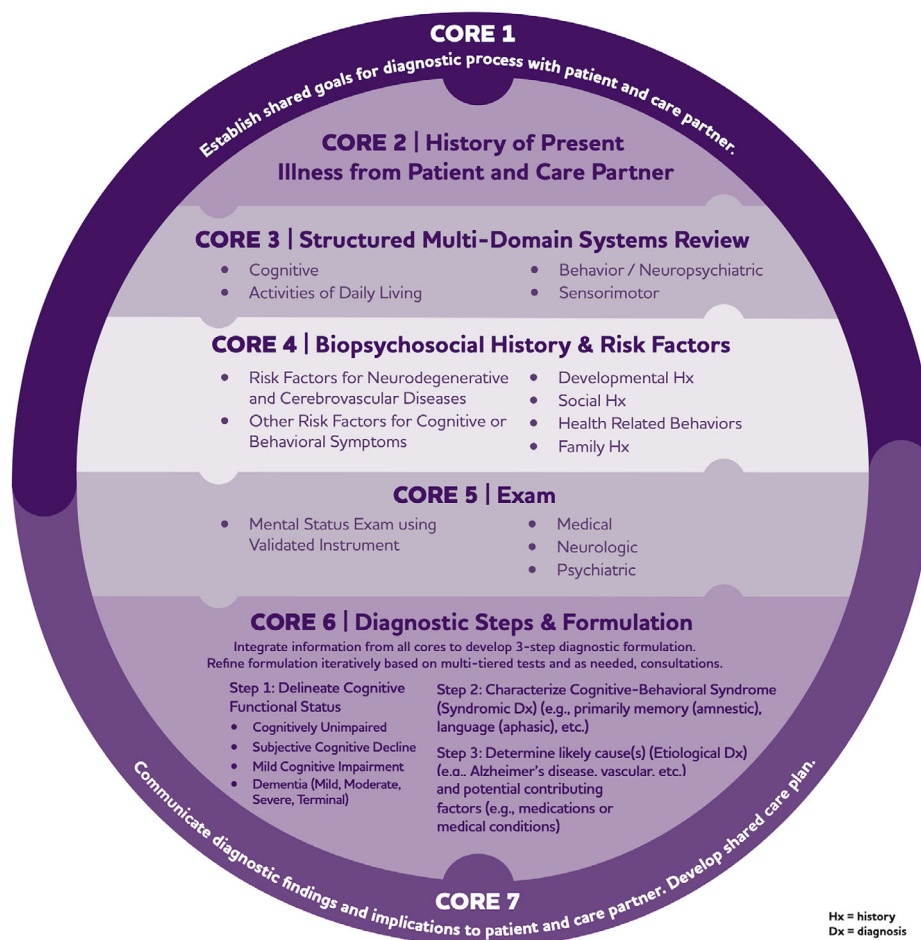


FIGURE 1 For patients who may be exhibiting symptoms and/or signs of cognitive impairment due to AD or ADRD, the three steps of the diagnostic formulation may be accomplished by following a process of seven core elements. AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias, Dx, diagnosis; Hx, history.

2.1 | Framework of the DETeCD-ADRD guideline

Recognizing that diagnostic and staging criteria for diseases in this field (i.e., AD and ADRD) will evolve, the workgroup focused the scope of this practical and clinically focused guideline on the principles of a patient-centered diagnostic evaluation and disclosure process in any practice setting. The workgroup considered a major goal of the diagnostic evaluation process to be the development of a three-step diagnostic formulation. The first step is to delineate the cognitive functional status (i.e., the overall level of impairment). Regardless of the specific symptoms, a patient with dementia requires a different level of support and management from that of a patient with MCI. The second step is to characterize the patient's cognitive-behavioral syndrome. The particular cognitive-behavioral syndrome recognized by the clinician provides important information about the likely underlying cause(s) and potential contributing factors, and therefore may play a critical role in guiding diagnostic decision making. Also, the specific cognitive-behavioral syndrome communicates the needs of the patient to other professionals and to patients and families who are knowledgeable about these syn-

dromes. By characterizing the full array of cognitive and behavioral symptoms, the clinician establishes the foundation for personalized symptom-based care and management. Finally, the third step is for the clinician to generate and narrow the differential diagnosis of the brain disease(s) or disorder that is the likely cause(s) of the patient's cognitive-behavioral syndrome, recognizing the importance of differentiating AD from ADRD or other diseases, disorders (e.g., mood disorders), conditions (e.g., sleep apnea), and factors (e.g., effects of medications or alcohol) that may cause or contribute to cognitive or behavioral symptoms. Although some segments of the field have evolved to clarify the importance of separating the clinical syndrome from the likely etiology, many diagnostic criteria still consider these conditions clinicopathologic entities; that is, to meet clinical diagnostic criteria, a patient is usually required to exhibit a particular clinical syndrome(s) and some diagnostic test abnormalities supportive of particular neuropathologic changes. The guideline also emphasizes the importance of identifying accompanying factors or conditions that may exacerbate symptoms, which may or may not be possible to ameliorate with medical or behavioral treatments; and of promoting brain-healthy behaviors (see Box 2).

EVALUATION OF PATIENT WITH SUSPECTED COGNITIVE IMPAIRMENT

Primary Care Setting

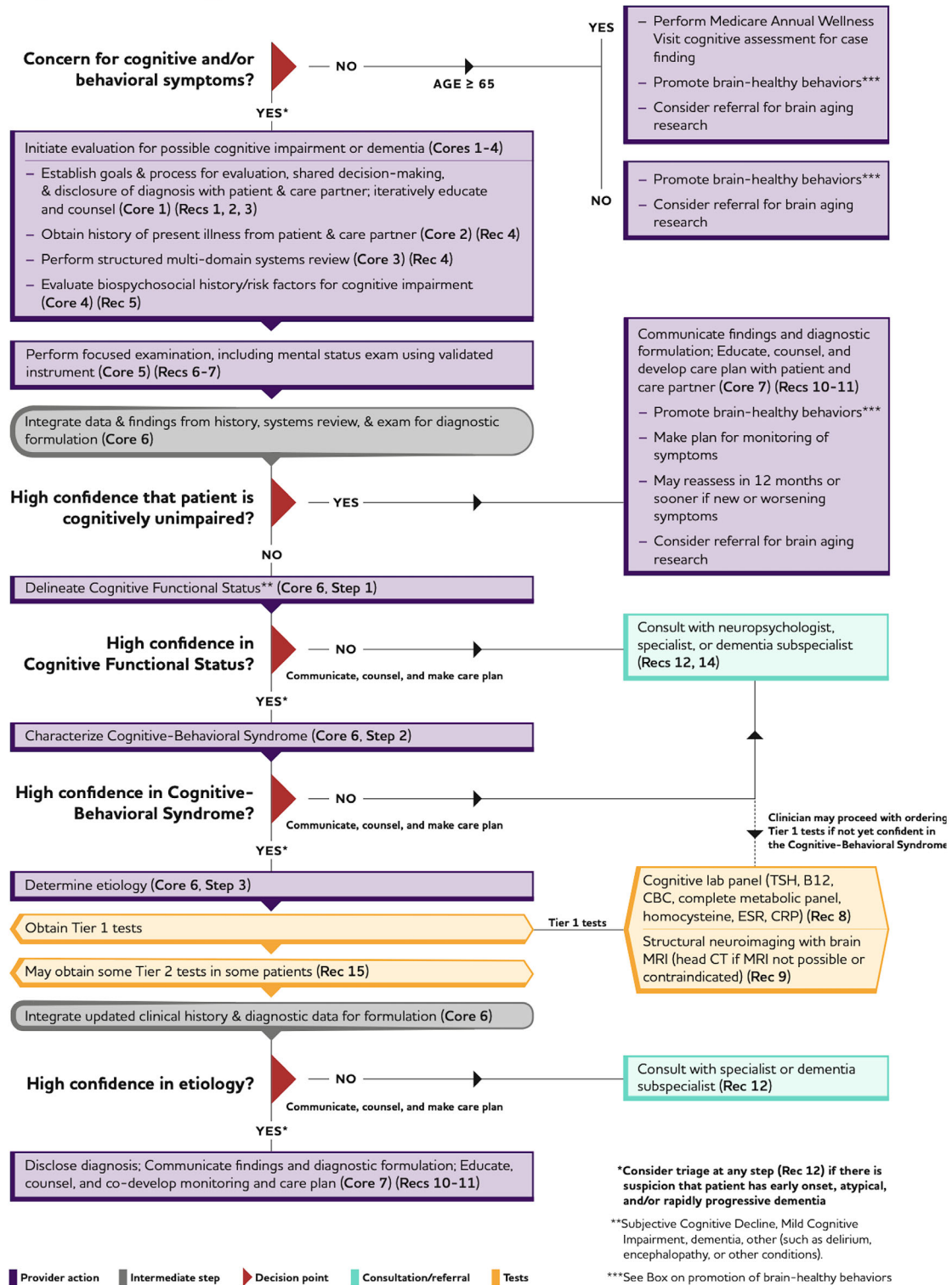


FIGURE 2 In a primary care setting, this diagram shows the implementation of the seven core elements of the diagnostic evaluation process, illustrating how each clinical practice recommendation fits into the typical workflow, using the first tier of assessments and diagnostic tests. Ultimately, the goal is to evaluate a person with cognitive and/or behavioral symptoms to determine whether they have cognitive impairment and if so its impact on daily function (cognitive functional status), the cognitive-behavioral syndrome, and the likely etiology (-ies) of the impairment. This diagnostic formulation should then be disclosed clearly and compassionately, and a treatment plan can then be initiated. CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

BOX 1: DETeCD-ADRD Recommendations

RECOMMENDATION 1: For patients who self-report or whose care partner or clinician report cognitive, behavioral, or functional changes, the clinician should initiate a multi-tiered evaluation focused on the problem (Strength of Recommendation A).

Rationale

- The timely evaluation of an individual with cognitive or behavioral symptoms concerning for MCI or dementia represents best medical practice.

Considerations for Implementation

- Any middle-aged or older patient who self-reports—or whose spouse, family, or other informant (or clinician) reports concern regarding symptoms of cognitive, behavioral, or functional decline—should undergo an evaluation to determine whether they might have a cognitive-behavioral syndrome arising as a result of a specific neuropathology. A clinician should not assume “normality” or ascribe cognitive or behavioral symptoms to “normal aging” without an appropriate evaluation, which would constitute suboptimal care.
- The evaluation process for possible cognitive or behavioral impairment can be initiated and in most cases completed at any of a variety of clinical practice settings: primary care, specialty care, or dementia subspecialty care. The practitioner’s proficiency with this patient population and the profile of the individual patient should guide the evaluation process.
- The evaluation begins with a history from not only the patient but also—importantly—from someone who knows the patient well (an informant).

RECOMMENDATION 2: The clinician should use patient-centered communication to develop a partnership with the patient or with patient and a care partner to (1) establish shared goals for the evaluation process and (2) assess capacity (understanding and appreciation) to engage in the goal-setting process for the evaluation (Strength of Recommendation A).

Rationale

- Competent, hence ethical, medicine relies on a clinician and patient freely and openly exchanging facts as a foundation to allow a patient to exercise her or his autonomy.
- Clinicians caring for patients with cognitive-behavioral syndromes may face unique challenges arising from impairments that may be present in a patient’s awareness of the illness (anosognosia) or understanding and appreciation of medical facts and the ability to use this information to make decisions about medical care or other important activities (capacity).
- Impairments in awareness and capacity can impact the evaluation process, including the ability to provide accurate information and to fully participate in the goal-setting process.
- Impairments in awareness and capacity that may be present at the outset or that will arise sooner or later in all patients with dementia due to AD or ADRD dictate the need to engage a care partner in the communication of the diagnosis, usually from the beginning.

Considerations for Implementation

- The clinician should establish a critical triadic clinician-patient-informant/care partner relationship during the evaluation and disclosure process. This relationship seeks to build a strong foundation to establish shared goals, obtain information necessary for an accurate diagnosis, effectively communicate an appropriate explanation of the illness being faced, and help formulate and implement a robust plan of care.
- Throughout the process, the clinician should develop a dialogue with the patient and care partner that uses patient-centered communication to collaboratively set goals and to adjust them, when necessary, as the process unfolds.
- Throughout the process, the clinician should assess informational and educational needs, capacity, and the impact of the evaluation and disclosure process on the patient and care partner, providing structured information and educational resources, while tailoring the communication of this information to the individuals; the clinician’s assessment of awareness and capacity should guide the timing and content of the information shared with the patient and their care partner.

RECOMMENDATION 3: The evaluation process should use tiers of assessments and tests based on individual presentation, risk factors, and profile to establish a diagnostic formulation, including (1) the overall level of impairment, (2) the cognitive-behavioral syndrome, and (3) the likely cause(s) and contributing factors (Strength of Recommendation A).

Rationale

- A structured yet personalized diagnostic evaluation of cognitive or behavioral symptoms—with hierarchical use of tiers of assessments and tests tailored to the patient—balances effectiveness and efficiency.
- This structured yet individualized approach ensures that essential information is collected in all cases while allowing leeway for clinical judgment regarding need for further assessments, tests, or consultative input.
- Ultimately, the clinician will integrate available data to arrive at a confident diagnosis based on established clinical criteria (Tables 1–4), or to exclude such diagnoses.

- The first step of this three-step approach to diagnostic formulation is fundamentally important: for the clinician to delineate the patient's cognitive functional status—the overall level of functional independence or dependence related to their cognitive or behavioral condition (i.e., cognitively unimpaired; subjective cognitive decline; mild cognitive impairment; mild, moderate, severe, or terminal dementia; Table 1). This determination has important implications for the evaluation process and care planning.
- The second step in diagnostic formulation is to characterize the specific clinical profile of the patient's cognitive-behavioral syndrome (i.e., "syndromic diagnosis"; Tables 2–4), because this places the patient in an epidemiologic context of prior probabilities of specific disease processes that can cause the syndrome (Tables 2–4)—influencing next steps in the diagnostic approach—and also heavily impacts symptom management and care planning.
- Although each cognitive-behavioral syndrome is probabilistically more associated with specific neurodegenerative pathologic changes and diseases than others—most clinical syndromes can be caused by more than one type of pathology or disease—the probability/likelihood of a particular syndrome being due to a specific disease is also a function of individual patient demographics, characteristics, and dementia risk factors (e.g., age, developmental and educational history, family history, cerebrovascular risk factors).
- The third step in diagnostic formulation is to establish the most likely brain disease (or condition) causing the clinical syndrome (i.e., "etiological diagnosis"; Tables 2–4); and to delineate any other conditions or factors that may be contributing to the illness.

Considerations for Implementation

- A structured and individualized approach, detailed in Recommendations 4 to 9, should be used to first attempt to delineate, characterize, and establish the status, syndrome, and likely cause(s) of the illness, which in many patients will be sufficient to allow a highly confident diagnosis to be made. Some patients may require more specialized assessments and tests.
- For a majority of individuals with a typical presentation of dementia due to AD, a first tier of clinical assessments, laboratory tests, and neuroimaging (Figure 2) should be sufficient for the clinician to achieve high probabilistic diagnostic confidence.
- For each individual, the clinician must then decide if sufficient data exist to make a probabilistically confident etiological diagnosis, with reference to established clinical diagnostic criteria (Tables 1–4), or if additional tests or referrals are needed to achieve the desired level of confidence in the diagnosis. Molecular biomarker confirmation may be desired for a variety of reasons.
- To establish each of the three steps of the diagnostic formulation, in some cases, multiple tiers of assessments or diagnostic testing may need to be pursued, depending on the complexity of the patient, the proficiency of the clinician, and the availability of resources.
- Clinicians should consider that there is substantial variability between patients in the clinical manifestations of cognitive impairment or dementia arising from AD/ADRD which may relate to factors associated with the disease itself, other comorbid conditions, or patient-specific vulnerability or resilience factors.
- While clinicians should weigh that with increasing age, there is greater likelihood that a patient's cognitive or behavioral symptoms may result from multiple neurodegenerative brain diseases or comorbidities, a primary driver(s) or cause(s) of the symptoms—a specific primary etiologic diagnosis—that is most likely, should be established and communicated.

RECOMMENDATION 4: During history taking for a patient being evaluated for cognitive or behavioral symptoms, the clinician should obtain reliable information involving an informant regarding changes in (1) cognition, (2) activities of daily living (ADLs and instrumental ADLs [IADLs]), (3) mood and other neuropsychiatric symptoms, and (4) sensory and motor function. Use of structured instruments for assessing each of these domains is helpful (Strength of Recommendation A).

Rationale

- The history of present illness (HPI) is the cornerstone of the approach to medical diagnosis. In the evaluation of a patient when a diagnosis of AD or another dementia syndrome is a consideration, the goal of the HPI is to provide a narrative account of the patient's principal cognitive and behavioral symptoms and their impact on their daily function, and community.
- Careful characterization of symptoms of concern, exploration of plausible relationships between symptoms and pertinent events, and a comprehensive survey of all major domains (cognition, daily function, behavior/neuropsychiatric, sensorimotor) using a structured approach is important for sensitive detection and accurate delineation of potentially clinically relevant changes and syndromes. A structured comprehensive approach is critical because patients and care partners often do not possess the knowledge or vocabulary to represent changes; may not recognize, or may under-report, misclassify, or misattribute symptoms; and, without a structured approach, busy or distracted clinicians may not inquire about all relevant domains.

Considerations for Implementation

- To obtain the HPI, the clinician should integrate information from an interview with the patient and an informant (care partner) to: (a) characterize the nature of the symptoms about which there is concern; (b) establish the time course of the symptoms (i.e., sequential order of onset, frequency, tempo, and nature of change over time); (c) explore plausible relationships between events and the presenting symptoms (and any potential triggers or contextual features); (d) evaluate impact of symptoms on the patient's function in activities of daily living, interpersonal relationships, personal and public health and safety, and the need for care partner support.

- In due course, a structured survey of all major domains of cognition, mood/behavior, and sensorimotor function should be performed to try to identify relevant symptoms not volunteered by the patient or informant during the HPI.

RECOMMENDATION 5: During history taking for a patient being evaluated for cognitive or behavioral symptoms, the clinician should obtain reliable information about individualized risk factors for cognitive decline (Strength of Recommendation A).

Rationale

- Each person has his or her own individual profile of risk factors—some of which are potentially modifiable (Box 2)—for the underlying brain diseases associated with dementia.
- Each person has a profile of resilience and risk factors that can modify the likelihood, types, and trajectory of cognitive, behavioral, and functional changes associated with neuropathological changes. These factors can also impact the reporting of symptoms and performance on cognitive tests and must be considered uniquely for each individual and informant.
- In older people, cognitive and behavioral symptoms may arise from a combination of several factors, including one or multiple types of neuropathological changes (e.g., AD neuropathologic change with or without Vascular Ischemic Brain Injury or LBD) or contributing conditions (e.g., obstructive sleep apnea, use of medications that may impair cognition, mood disorder, high alcohol consumption).
- Some conditions that contribute to cognitive impairment are, to varying amounts, modifiable during the life course.

Considerations for Implementation

- During the evaluation process, the clinician should systematically obtain knowledge regarding the patient's risk factors for neurodegenerative, cerebrovascular, and other diseases or conditions that may cause brain dysfunction.
- During the evaluation process, the clinician should obtain information about the patient's reserve and vulnerability profile with regard to cognitive and behavioral function.
- The clinician should integrate this information regarding risk factors into the diagnostic evaluation process to: (a) contextualize symptoms and test performance against the patient's risk profile; (b) estimate the likelihood that the patient's symptoms may be due to potential effects of one or more diseases, conditions, or other factors, some of which may require specific diagnostic testing and may be more responsive to intervention than others; (c) incorporate the patient's risk factor profile into the overall care plan by educating and counseling the patient and care partner regarding modifiable risk factors and likely non-modifiable processes, developing a plan that includes treatments of specific diseases and conditions, and identifying strategies to mitigate the effects of modifiable risk factors, while promoting brain healthy lifestyles (Box 2).

RECOMMENDATION 6: In a patient being evaluated for cognitive or behavioral symptoms, the clinician should perform an examination of cognition, mood, and behavior (mental status exam), and a dementia-focused neurologic examination, aiming to diagnose the cognitive-behavioral syndrome (Strength of Recommendation A).

Rationale and Considerations for Implementation

- If a clinician ascertains a history of symptoms of changes in memory, thinking, reasoning, language, attention, perception, or behavior, a structured examination should be performed that includes a dementia-focused mental status examination and an elemental neurologic examination.
- In addition to the history discussed in Recommendation 5, the examination enables the clinician to characterize the cognitive-behavioral syndrome if one is present and generate hypotheses about the differential diagnosis of the possible etiology (-ies).
- The examination may identify signs of neurologic or psychiatric impairment that suggest an atypical cognitive-behavioral syndrome, such as one with prominent sensorimotor, language, perceptual, or behavioral components, which may warrant referral to a specialist.

RECOMMENDATION 7: In a patient being evaluated for cognitive or behavioral symptoms, clinicians should use validated tools to assess cognition (Strength of Recommendation A).

Rationale and Considerations for Implementation

- While there is no single cognitive assessment instrument that fits all circumstances, the use of a validated instrument to detect cognitive impairment is an invaluable step in the evaluation process for the identification of potentially clinically significant cognitive impairment.
- The interpretation of an individual's cognitive test score profile (not simply whether performance is below or above a cut-off score) facilitates accurate detection and diagnosis of the cognitive functional status and cognitive-behavioral syndrome.
- The patient's performance on a validated brief cognitive test should not be interpreted in isolation but should be carefully integrated with patient's overall risk profile (Recommendation 6), history of presenting illness (Recommendation 5), and other physical or medical examination and diagnostic findings.
- It is possible that when a concern exists, a validated brief cognitive test may not be sufficiently informative or may not capture mild but clinically significant impairments (e.g., in individuals with extremes of age, education, and intelligence, or in those with complex medical or demographic considerations including language and culture); in such situations a clinician should strongly consider referral to a neuropsychologist or specialist.

RECOMMENDATION 8: Laboratory tests in the evaluation of cognitive or behavioral symptoms should be multi-tiered and individualized to the patient's medical risks and profile. Clinicians should obtain routine Tier 1 laboratory studies in all patients (Strength of Recommendation A).

Rationale

- A multi-tiered approach to the selection of laboratory diagnostic tests in a patient with cognitive or behavioral impairment should balance individualized risk factors and medical conditions the patient is known to have or is suspected of having.
- A routine laboratory panel as first-line diagnostic testing (in conjunction with structural neuroimaging, see Recommendation 9) aids in the recognition and treatment of common comorbid conditions that rarely cause but may often contribute to cognitive or behavioral symptoms.
- Routine first-line laboratory testing in patients suspected of having AD/ADRD is nearly universally recommended by specialty society practice parameters, and non-US health authority guidelines, but lack consistency regarding which tests should be included.

Considerations for Implementation

- In all, or almost all, patients with suspected cognitive or behavioral symptoms, the clinician should obtain a basic set of Tier 1 laboratory tests ("cognitive lab panel"; Table 5) that includes complete blood count (CBC) with differential; complete metabolic (e.g., Chem-20) panel with renal and hepatic panels, electrolytes, glucose, calcium, magnesium, and phosphate; thyroid-stimulating hormone (TSH); vitamin B12 level; homocysteine level; C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR).

RECOMMENDATION 9: In a patient being evaluated for a cognitive-behavioral syndrome, the clinician should obtain structural brain imaging to aid in establishing the cause(s). If magnetic resonance imaging (MRI) is not available or is contraindicated, computed tomography (CT) should be obtained (Strength of Recommendation A).

Rationale

- Structural brain imaging is useful to exclude non-AD/ADRD-related conditions and for diagnostic inclusion of changes related to AD/ADRD.
- Structural brain imaging may show evidence of regional brain atrophy consistent with AD or another neurodegenerative disease. Absence of such changes does not exclude presence of underlying AD/ADRD pathological changes.
- The regional atrophy pattern on structural brain imaging is often probabilistically associated with a type of neurodegenerative pathologic change, although not specific for only that type of pathologic change.
- Some patients who present with gradually progressive cognitive or behavioral symptoms have a brain tumor or other lesion (e.g., infarct, neuroinflammatory, infectious) that can be readily identified using structural brain imaging.
- Structural brain imaging, particularly MRI, is often very helpful for determining the potential contribution of VCID, including cerebral amyloid angiopathy.

Considerations for Implementation

- As part of Tier 1 testing for etiological diagnosis, structural brain imaging should be obtained in almost all patients. When available, brain MRI without contrast provides standard of care for individuals that do not have an absolute or relative contraindication—a head CT should be considered in others.
- An individualized risk-benefit calculus, based on goals, circumstances, and clinical status, should also guide the type and timing of brain imaging. For example, without highly compelling clinical reasons, obtaining neuroimaging in a bed-bound and non-communicative individual with longstanding and very severe dementia should be avoided.
- The interpretation of structural brain imaging must also take into consideration the patient's age, because aging itself can be associated with relatively minimal/mild and diffuse cerebral atrophy, leukoaraiosis (white matter changes, better detected on T2 and fluid-attenuated inversion recovery MRI sequences), or isolated microhemorrhage (better detected on gradient echo/susceptibility weighted imaging MRI sequences), and indication for the scan (e.g., when a cognitive symptom or disorder is being evaluated), because patterns and extent of atrophy, leukoaraiosis, and microhemorrhage are associated with AD/ADRD and VCID. Cerebral atrophy, leukoaraiosis, or microhemorrhage should not be routinely interpreted as "age related" in a patient with cognitive or behavioral symptoms, particularly if not obviously minimal/very mild and diffuse; instead, in such cases, the extent and pattern should be clearly delineated and clinical correlation should be advised.
- The interpretation of structural brain imaging is often facilitated through a dialogue between the clinicians involved in evaluating the patient and the radiologist who is interpreting the scan.

RECOMMENDATION 10: Throughout the evaluation process, the clinician should establish a dialogue with the patient and care partner about the understanding (knowledge of facts) and appreciation (recognition that facts apply to the person) of the presence and severity of the cognitive-behavioral syndrome. The patient and care partner's understanding and appreciation of the syndrome guide education, diagnostic disclosure, and methods for communicating and documenting diagnostic findings (Strength of Recommendation A).

Rationale

- Competent, ethical medicine relies on a doctor and patient freely and openly exchanging facts to allow a patient to exercise autonomy.
- Clinicians caring for patients with cognitive-behavioral syndromes often face unique challenges arising from impairments in patient capacity (understanding and appreciation of the illness).
- Impairments in capacity, along with the impact of the information, will determine the timing and content of information told to the patient, and the level of involvement of a care partner as the patient's proxy. While a structured diagnostic disclosure process is recommended, it always has to be tailored to the individual patient and care partner(s). Competent, ethical medicine relies on a doctor and patient freely and openly exchanging facts to allow a patient to exercise autonomy.

Considerations for Implementation

- Clinicians caring for patients with cognitive-behavioral syndromes often face unique challenges arising from impairments in patient capacity (understanding and appreciation of the illness).
- Impairments in capacity, along with the impact of the information, will determine the timing and content of information told to the patient, and the level of involvement of a care partner as the patient's proxy. While a structured diagnostic disclosure process is recommended, it always has to be tailored to the individual patient and care partner(s).

RECOMMENDATION 11: In communicating diagnostic findings the clinician should honestly and compassionately inform both the patient and their care partner of the following information using a structured process: the name, characteristics, and severity of the cognitive-behavioral syndrome; the disease(s) likely causing the cognitive-behavioral syndrome; the stage of the disease; what can be reasonably expected in the future; treatment options and expectations; potential safety concerns; and medical, psychosocial, and community resources for education, care planning and coordination, and support services (Strength of Recommendation A).

Rationale

- The purpose of diagnostic disclosure is to accurately and compassionately explain to the patient and care partner(s) the illness they are facing.
- When a clinician communicates the diagnosis, stage, prognosis, and options for care of an illness, a patient (and care partner) can exercise his/her autonomy.
- A standardized approach to the communication of the diagnosis, stage, and prognosis creates structure so that the clinician conveys a large amount of information in a cohesive and supportive manner and assesses the patient's understanding and appreciation of the information, engaging in a dialogue to personalize the communication of diagnostic information to the individual(s).
- Diagnostic disclosure for patients with cognitive impairment presents important challenges: a patient may not be able to understand or appreciate the information because of the nature of their impairments including, in some cases, lack of insight. In this case, the involvement of a care partner is critical.

Considerations for Implementation

- The patient and care partner's informational needs, the patient's capacity, and the clinician's judgment about the likely impact of diagnostic information on the patient and care partner will guide the process, content, and timing of the information shared with the patient and their care partner. The clinician should deliver the personalized education necessary for the patient and care partner to understand the diagnosis, its implications, and to develop the foundation for care planning.
- The clinician may decide, based on impairments in the patient's capacity, to use different methods to disclose the diagnosis to the patient and to the care partner(s).

RECOMMENDATION 12: A patient with atypical findings or in whom there is uncertainty about how to interpret the evaluation, or that is suspected of having an early-onset or rapidly progressive cognitive-behavioral condition, should be further evaluated expeditiously, usually including referral to a specialist (Strength of Recommendation A).

Rationale

- Delirium and rapidly progressive dementia (usually defined as developing subacutely within weeks or months) are considered to be urgent medical problems requiring rapid, and in some cases inpatient, evaluation and management.
- Atypical, rapidly progressive or early-onset (young age of onset, age < 65 years) dementias pose unique diagnostic and care challenges due to the potential for a broad differential diagnosis that may require comprehensive neuropsychiatric evaluation; Tier 3 and 4 studies (see Recommendation 15); and specialist assessment, interpretation, or management.
- Atypical dementia presentations are not uncommon, but symptom recognition and accurate diagnosis are frequently delayed for several years.
- Patients with atypical forms of neurodegenerative dementias may have substantially different care and management needs and considerations regarding safety than patients with typical presentations of dementia due to AD.
- Delays in accurate diagnosis and appropriate management of patients with atypical and early-onset dementias may cause substantial distress, harm, and costs to patients, families, and society, especially when a patient is working and/or raising children at home.

Considerations for Implementation

- The diagnosis of delirium may be clinically straightforward or may be challenging depending on the presentation and medical context, but in all settings requires urgent or emergent care for diagnosis and management (Box 3).
- The diagnostic evaluation of a patient with rapidly progressive dementia requires urgency and is usually complex, often requiring specialist consultation.
- The evaluation of a patient with atypical or early-onset cognitive impairment or dementia requires proactive and expedited management by the evaluating clinician and should usually involve prompt specialist referral.
- Atypical examination findings in patients with suspected cognitive-behavioral syndromes may include: (1) attentional impairments difficult to differentiate between dementia and delirium, (2) prominent language or social-behavioral abnormalities, (3) sensory or motor dysfunction of cerebral origin, (4) cognitive performance that may be confounded by high or low educational/occupational attainment.

RECOMMENDATION 13: A specialist evaluating a patient with cognitive or behavioral symptoms should perform a comprehensive history and office-based examination of cognitive, neuropsychiatric, and neurologic functions, aiming to diagnose the cognitive-behavioral syndrome and its cause(s) (Strength of Recommendation A).

- See Dickerson BC et al.³² for specialists for rationale and considerations for implementation of Recommendations 13 and 15 through 19.

RECOMMENDATION 14: Neuropsychological evaluation is recommended when office-based cognitive assessment is not sufficiently informative. Specific examples are when a patient or caregiver report concerning symptoms in daily life, but the patient performs within normal limits on a cognitive examination, or when the examination of cognitive-behavioral function is not normal but there is uncertainty about interpretation of results due to a complex clinical profile or confounding demographic characteristics. The neuropsychological evaluation, at a minimum, should include normed neuropsychological testing of the domains of learning and memory (in particular delayed free and cued recall/recognition); attention, executive function, visuospatial function, and language (Strength of Recommendation A).

Rationale and Considerations for Implementation

- The neuropsychological evaluation may detect very mild but clinically important cognitive impairment which a mental status examination (see Recommendation 6) using brief validated cognitive tests (see Recommendation 7)—such as those done in most office examinations—may not capture.
- The neuropsychological evaluation can provide recommendations for potential further studies and a care plan that considers a patient-centered profile of strengths and limitations and can inform the differential diagnosis of potential etiologies.
- Neuropsychological evaluation can aid in distinguishing neuropsychiatric disorders from the effects of medical and emotional comorbidities or of confounding patient characteristics such as limited or advanced education or language limitations.
- Neuropsychological evaluation should be considered when a clinician needs to better delineate the cognitive functional status or to define the cognitive-behavioral syndrome or when there are complex psychosocial, medical, or demographic characteristics or significant confounding conditions.
- The referring clinician should provide a consultation question that the neuropsychological evaluation can be structured to answer.

RECOMMENDATION 15: When diagnostic uncertainty remains, the clinician can obtain additional (Tier 2–4) laboratory tests guided by the patient's individual medical, neuropsychiatric, and risk profile (Strength of Recommendation A).

RECOMMENDATION 16: In a patient with an established cognitive-behavioral syndrome in whom there is continued diagnostic uncertainty regarding cause(s) after structural imaging has been interpreted, a dementia specialist can obtain molecular imaging with fluorodeoxyglucose (FDG) PET to improve diagnostic accuracy (Strength of Recommendation B).

RECOMMENDATION 17: In a patient with an established cognitive-behavioral syndrome in whom there is continued diagnostic uncertainty regarding cause(s) after structural imaging with or without FDG PET, a dementia specialist can obtain CSF according to appropriate use criteria for analysis of amyloid beta (A β)₄₂ and tau/phosphorylated tau (p-tau) profiles to evaluate for AD neuropathologic changes (Strength of Recommendation B).

RECOMMENDATION 18: If diagnostic uncertainty still exists after obtaining structural imaging with or without FDG PET and/or CSF A β ₄₂ and tau/p-tau, the dementia specialist can obtain an amyloid PET scan according to the appropriate use criteria to evaluate for cerebral amyloid pathology (Strength of Recommendation B).

RECOMMENDATION 19: In a patient with an established cognitive-behavioral syndrome and a likely autosomal dominant family history, the dementia specialist should consider whether genetic testing is warranted. A genetic counselor should be involved throughout the process (Strength of Recommendation A).

TABLE 1 Diagnostic criteria for mild cognitive impairment and dementia.**NIA-AA diagnostic criteria for mild cognitive impairment³⁹**

Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)

Objective evidence of impairment in one or more cognitive domains (i.e., formal or "bedside" testing to establish level of cognitive function in multiple domains)

Preservation of independence in functional abilities

Not demented

DSM-5 diagnostic criteria for mild neurocognitive disorder⁴⁰

Evidence of modest cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a mild decline in cognitive function; and
2. A modest impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

The cognitive deficits do not interfere with capacity for independence in everyday activities (i.e., complex instrumental activities of daily living such as paying bills or managing medications are preserved, but greater effort, compensatory strategies, or accommodation may be required).

The cognitive deficits do not occur exclusively in the context of delirium.

The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

NIA-AA diagnostic criteria for dementia⁴¹

Dementia is diagnosed when there are cognitive or behavioral (neuropsychiatric) symptoms that:

1. Interfere with the ability to function at work or at usual activities; and
2. Represent a decline from previous levels of functioning and performing; and
3. Are not explained by delirium or major psychiatric disorder.

Cognitive impairment is detected and diagnosed through a combination of:

- a. History taking from the patient and a knowledgeable informant and
- b. An objective cognitive assessment, either a "bedside" mental status examination or neuropsychological testing. Neuropsychological testing should be performed when the routine history and bedside mental status examination cannot provide a confident diagnosis.

The cognitive or behavioral impairment involves a minimum of two of the following domains:

- a. Impaired ability to acquire and remember new information
Symptoms include: repetitive questions or conversations, misplacing personal belongings, forgetting events or appointments, getting lost on a familiar route.
- b. Impaired reasoning and handling of complex tasks, poor judgment
Symptoms include: poor understanding of safety risks, inability to manage finances, poor decision-making ability, inability to plan complex or sequential activities.
- c. Impaired visuospatial abilities
Symptoms include: inability to recognize faces or common objects or to find objects in direct view despite good acuity, inability to operate simple implements, or orient clothing to the body.
- d. Impaired language functions (speaking, reading, writing)
Symptoms include: difficulty thinking of common words while speaking, hesitations; speech, spelling, and writing errors.
- e. Changes in personality, behavior, or comportsment
Symptoms include: uncharacteristic mood fluctuations such as agitation, impaired motivation, initiative, apathy, loss of drive, social withdrawal, decreased interest in previous activities, loss of empathy, compulsive or obsessive behaviors, socially unacceptable behaviors.

DSM-5 diagnostic criteria for major neurocognitive disorder⁴⁰

Evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:

1. Concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function; and
2. A substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment.

The cognitive deficits interfere with independence in everyday activities (i.e., at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications).

The cognitive deficits do not occur exclusively in the context of delirium.

The cognitive deficits are not better explained by another mental disorder (e.g., major depressive disorder, schizophrenia).

Abbreviations: DSM-5, Diagnostic and Statistical Manual of Mental Disorders Fifth Edition; NIA-AA, National Institute on Aging–Alzheimer's Association.

TABLE 2 Cognitive-behavioral syndromes (syndromic diagnosis) and the differential diagnosis for diseases that cause them (etiologic diagnosis).

Cognitive-behavioral syndrome	Major clinical features	Differential diagnosis of neuropathologic etiology(ies)
Progressive amnesic syndrome (single or multi-domain)	Difficulty with learning and remembering new information, sometimes as the main feature, often accompanied by other features (e.g., executive dysfunction, depression, anxiety)	Usually AD Often AD with co-pathologies (AD + VCID, AD + LBD > AD + VCID + LBD) Sometimes hippocampal sclerosis, argyrophilic grain disease, pure VCID, pure LBD, TDP-43 proteinopathy/LATE, PART Rarely FTLD
Progressive aphasic syndrome (e.g., PPA or progressive aphasic multi-domain syndrome)	Speech and language impairments including word-finding difficulty (anomia), agrammatism, speech sound errors, impaired repetition (often due to auditory-verbal working memory impairment), impaired comprehension, impaired reading (alexia), impaired writing (agraphia)	Usually logopenic variant PPA is due to AD, less commonly FTLD Usually semantic variant PPA is due to FTLD-TDP43, rarely FTLD-tau or AD Usually non-fluent variant PPA is due to FTLD-tau, sometimes FTLD-TDP43, rarely AD
Progressive visuospatial dysfunction (e.g., posterior cortical atrophy syndrome)	Difficulty with visual and/or spatial perception and cognition, often with limb apraxia (difficulty planning or performing learned motor tasks or movements), alexia, agraphia, acalculia, and related cognitive dysfunction localizable to posterior cortical regions	Usually AD Sometimes FTLD-CBD or AD + LBD Rarely LBD Very rarely FTLD-TDP43
Progressive dysexecutive and/or behavioral syndrome (e.g., bvFTD)	Changes in executive function (judgment, problem solving, reasoning) with or without apathy or changes in personality or social or emotional behavior	Frequently FTLD (FTLD-tau or FTLD-TDP43) Frequently AD or AD + VCID Sometimes FTLD-PSP, FTLD-CBD, or VCID Rarely LBD
Progressive cognitive-behavioral-parkinsonism syndrome (e.g., dementia with Lewy bodies syndrome or PDD syndrome)	Fluctuating levels of cognitive impairment, recurrent visual hallucinations, spontaneous extrapyramidal motor features and a history of rapid eye movement (REM) sleep behavior disorder (RBD)	Often LBD Often LBD with AD Sometimes LBD with FTLD or VCID Rarely FTLD-CBD or FTLD-PSP
Progressive cortical cognitive-somatosensorimotor syndrome (e.g., corticobasal syndrome)	Cortical sensorimotor (e.g., limb apraxia) and cognitive difficulties especially including executive dysfunction, with asymmetric rigidity and other motor dysfunction	Often CBD Sometimes AD, FTLD-PSP, FTLD-Pick's or FTLD-TDP43 Rarely LBD
Progressive supranuclear palsy syndrome (e.g., PSP Richardson's syndrome)	Postural instability, supranuclear gaze palsy, with varying degrees of cognitive, behavioral, or other movement symptoms	Usually FTLD-PSP Sometimes FTLD-CBD Rarely LBD

Note: The syndromic diagnosis is defined by the nature of the cognitive and/or behavioral domain most prominently impacted. There is a probabilistic—not deterministic—relationship between syndromic diagnosis and etiologic diagnosis. AD neuropathologic changes can be associated with many clinical syndromes; multiple etiologies are likely in individuals older than 85 years. VCID may be the primary etiology or a contributor to a host of syndromes.^{31,42} Korsakoff's syndrome, limbic encephalitis, anoxic brain injury, traumatic brain injury, temporal lobe epilepsy, sequelae of herpes encephalitis may cause amnesic syndromes but are usually distinguishable by history. In addition, cognitive-behavioral impairment may be a feature of other rare diseases including Huntington's disease, FTD with ALS, Creutzfeldt-Jakob disease, multiple-system atrophy, etc.

Abbreviations: AD, Alzheimer's disease (referring specifically to the neuropathologic changes); bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; FTLD, frontotemporal lobar degeneration (referring specifically to the neuropathologic changes; many neuropathologists consider FTLD-tau to include the neuropathologic entities of Pick's disease, PSP, and CBD); LATE, limbic-predominant age-related TDP-43 encephalopathy; LBD, Lewy body disease (referring specifically to the neuropathologic changes); PART, primary age-related tauopathy; PDD, Parkinson's disease dementia; PPA, Primary Progressive Aphasia; PSP, progressive supranuclear palsy; VCID, vascular contributions to cognitive impairment and dementia.

To accomplish the three steps of the diagnostic formulation, the evaluation follows a multi-tiered approach so the clinician can select assessments and tests that follow a structured process but that are tailored to the individual patient's circumstances. Depending on the proficiency of the practitioner and the profile of the patient, this evaluation can be initiated and, in many situations, completed in any clinical practice setting. The three steps of the diagnostic formula-

tion may be relatively straightforward to determine by following a process of seven core elements (Figure 1) and using the first tier of assessment and diagnostic tests in a primary care setting (Figure 2), or they may require additional consultation (e.g., neuropsychological evaluation) and tiers of assessments and tests in the primary care (Figure 2), specialty (Figure 3), or dementia subspecialty settings (Figure 4).

BOX 2: Brain-healthy behaviors

Accruing evidence indicates that there are a variety of potentially modifiable risk factors for dementia.^{43–48} In their report, Livingston et al. identified three mid-life risk factors for dementia, including hearing loss, hypertension, and obesity.⁴⁷ In later life, five potentially modifiable risk factors include smoking, depression, physical inactivity, social isolation, and diabetes. Although it is impossible to completely eliminate these risks, estimates suggest that risk could be reduced by $\approx 20\%$ if these factors were adequately addressed. Additional evidence is cited in this report indicating that patients with MCI or dementia may benefit—even after symptoms are clearly present—from brain-healthy behaviors to reduce modifiable risk factors for dementia.⁴⁷ Several ongoing studies are evaluating the efficacy of multifaceted lifestyle interventions as preventative approaches or to treat progressive decline in people with dementia.

Although a small group of studies suggest that primary care clinicians are not aware of this evidence, they have a positive attitude toward the promotion of brain health and would like a risk prediction tool and more time to promote brain health.⁴⁹ An evidence-based consensus⁵⁰ recommended that clinicians perform individualized risk assessment and counseling, focusing on the American Heart Association Life's Simple 7.⁴⁴ These include the promotion of four health-related behaviors: non-smoking status, physical activity at goal levels, body mass index $< 25 \text{ kg/m}^2$, healthy diet consistent with current guidelines; and three health-related factors: untreated blood pressure $< 120/< 80 \text{ mm Hg}$, untreated total cholesterol $< 200 \text{ mg/dL}$, and fasting blood glucose $< 100 \text{ mg/dL}$. Citing substantial evidence, they also recommend the pursuit of cognitively stimulating and rewarding activities.⁵⁰ Screening and evaluating for obstructive sleep apnea and excessive alcohol use are also important.

We recommend that primary care clinicians work toward bringing this evidence into their practice by performing a personalized assessment of dementia risk factors in any middle-aged or older adult and providing counseling on “brain-healthy behaviors.”⁵¹ In many settings, approaches similar to those taken for diabetes treatment and prevention are worth considering, including the development of a “champion” member of the team who provides a summary of evidence and motivational information.⁴⁹ If a patient has sought evaluation for symptoms of cognitive decline and been determined to be cognitively normal or experiencing subjective cognitive decline, clinicians should take the opportunity to engage the patient in promoting brain-healthy behaviors while continuing to monitor cognitive function longitudinally.⁵²

2.2 | DETeCD-ADRD core elements of diagnostic and disclosure process and recommendations

2.2.1 | Core element one: whom to evaluate and how to establish shared goals

The first core element of the process, covered by Recommendations 1 through 3, addresses foundational considerations when initiating and proceeding through a diagnostic evaluation and disclosure process. These include in whom and when to initiate an evaluation; the importance of a patient-centered and collaborative partnership in the goal-setting, diagnostic, and disclosure processes; and the three-step conceptual framework for diagnostic formulation. The DETeCD-ADRD CPG also emphasizes the critical importance—in most situations—of including both the patient and an informant or care partner in the diagnostic and disclosure process.

Recommendation 1 applies the basic tenets of a high-quality medical approach to the evaluation of symptoms of cognitive or behavioral decline.^{36,53–55} The timely evaluation of an individual with cognitive or behavioral symptoms concerning for MCI or dementia represents best medical practice.^{16,20,22,56–60}

Any middle-aged or older patient who self-reports—or whose spouse, family, or other informant (or clinician) reports concern regarding symptoms of cognitive, behavioral, or functional decline—

should undergo an evaluation to determine whether they might have a cognitive-behavioral syndrome arising due to specific neuropathologic changes (Recommendation 1). A clinician should not assume “normality” or ascribe cognitive or behavioral symptoms to “normal aging” without an appropriate evaluation.⁵⁶ The optimal approach to the evaluation of a patient with suspected cognitive or behavioral impairments, whether at the level of subjective cognitive decline,⁶¹ MCI,⁵⁶ mild behavioral impairment,^{62,63} or dementia, is grounded in the biopsychosocial model of health and illness.^{64,65}

Clinicians evaluating a patient suspected of having a cognitive-behavioral syndrome arising from neurodegenerative disease may face unique challenges arising from impairments that may be present in a patient's awareness of the illness (anosognosia) or understanding and appreciation of medical facts and the ability to use this information to make decisions about medical care or other important activities (capacity). Impairments in awareness and capacity that may be present at the outset or that will arise sooner or later in all patients with dementia due to AD or ADRD dictate the need to engage a care partner in the communication of the diagnosis, optimally from the beginning.

The clinician should use patient-centered communication to develop a partnership with the patient or with the patient and a care partner to (1) establish shared goals for the evaluation process and (2) assess capacity (understanding and appreciation) to engage

EVALUATION OF PATIENT WITH SUSPECTED COGNITIVE IMPAIRMENT

Specialist Setting: General Neurology, Psychiatry, Geriatrics

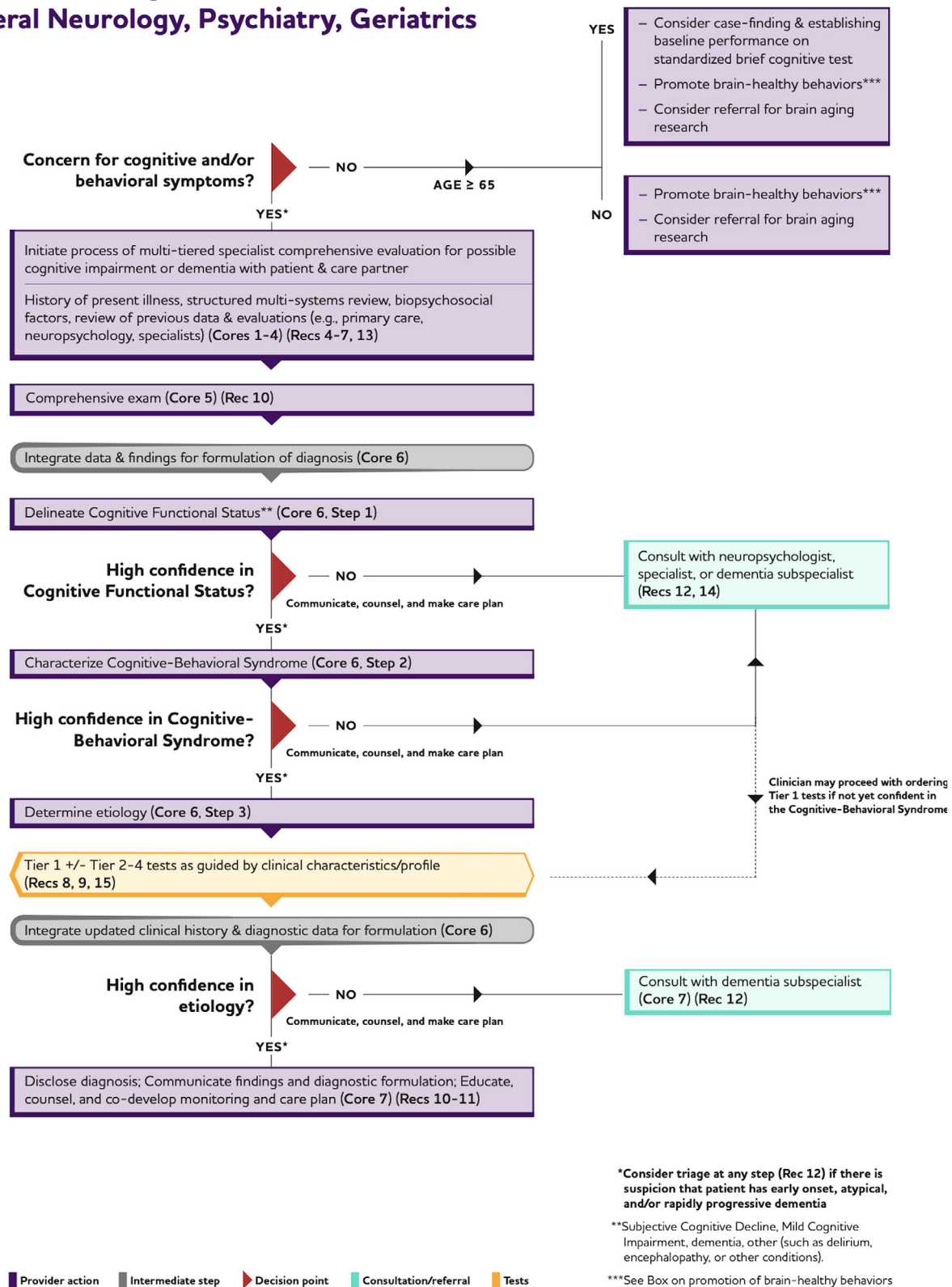


FIGURE 3 In a specialty care setting (usually general neurology, geriatric psychiatry, or geriatrics), this diagram briefly illustrates how each primary care clinical practice recommendation fits into the typical workflow (see Figure 2 for details). Additional detail is provided on how higher tier assessments and diagnostic tests fit into the specialty care workflow. In some specialty care settings, the assessments and tests illustrated in Figure 4 are performed to arrive at the three-step diagnostic formulation. This diagnostic formulation should then be disclosed clearly and compassionately, and a treatment plan can then be initiated.

EVALUATION OF PATIENT WITH SUSPECTED COGNITIVE IMPAIRMENT

Dementia Subspecialist Setting

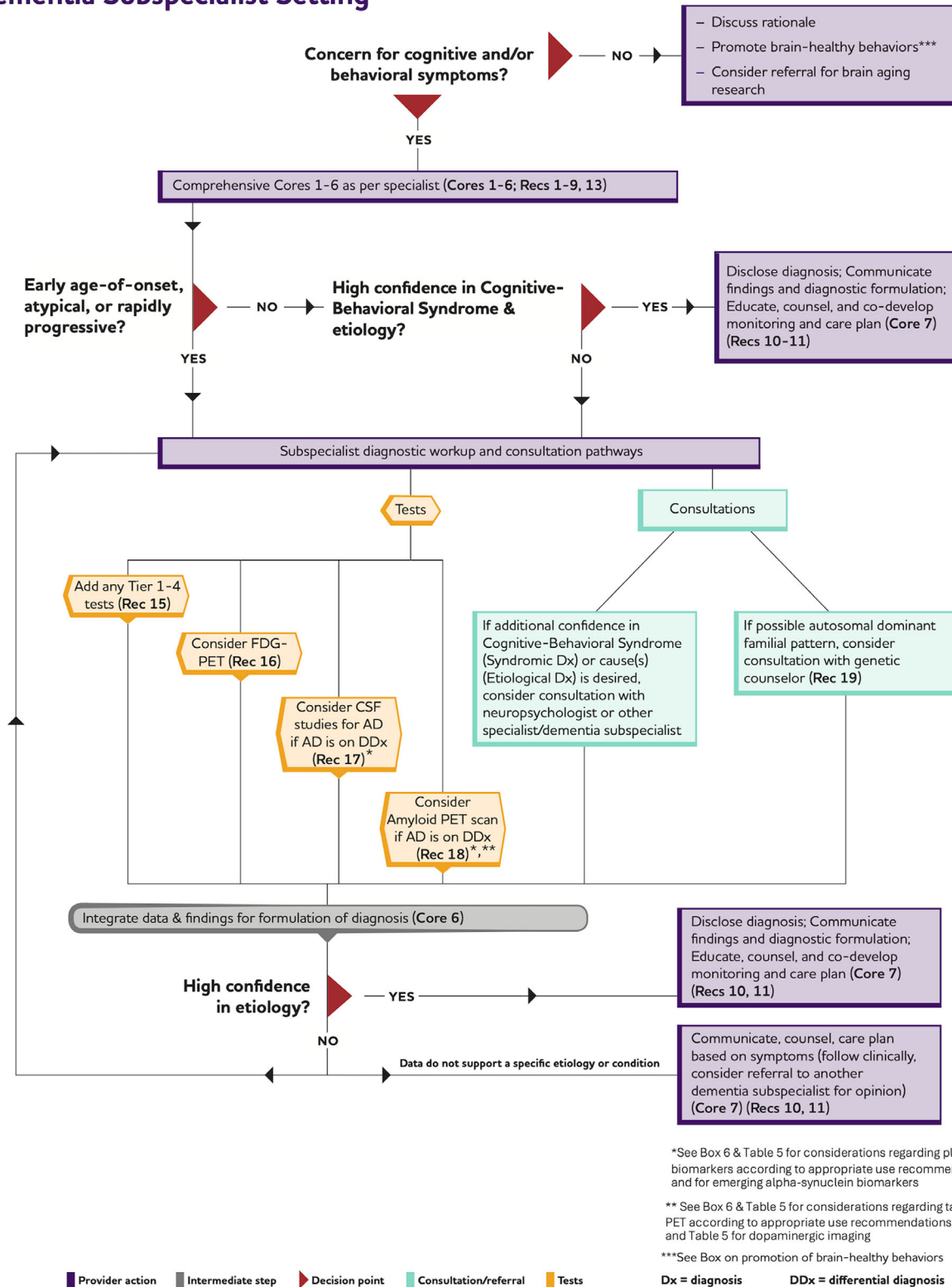


FIGURE 4 In a dementia subspecialty care setting (usually behavioral or geriatric neurology, geriatric or neuropsychiatry, or geriatrics), this diagram briefly illustrates how each primary care or specialty clinical practice recommendation fits into the typical workflow (see Figures 2 and 3 for details). Additional detail is provided on how higher tier assessments and diagnostic tests fit into the subspecialty care workflow to arrive at the three-step diagnostic formulation. This diagnostic formulation should then be disclosed clearly and compassionately, and a treatment plan can then be initiated. CBC, complete blood count; CRP, C-reactive protein; CT, computed tomography; DDx, differential diagnosis; Dx, diagnosis; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; TSH, thyroid-stimulating hormone.

15525279, 0, Downloaded from https://alz-journals.onlinelibrary.wiley.com/doi/10.1002/alz.14333, Wiley Online Library on [06/01/2025]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

in the goal-setting process for the evaluation (Recommendation 2). Such a relationship provides a foundation aiming to ensure that all information necessary for an accurate diagnosis is obtained, that an explanation of the illness being faced is effectively communicated, and that a robust plan of care is formulated and implemented. The provider should convey medical information, assess the patient and care partner's knowledge and appreciation of that knowledge, and offer education and support. Throughout the process, the clinician's assessment of the patient's awareness and capacity should guide the timing and content of the information shared with the patient and their care partner.

Although the triadic clinician–patient–informant relationship is unusual in the practice of adult medicine, it is nonetheless essential to assure that an accurate diagnosis is made, an appropriate explanation of the illness being faced by the patient and family is provided, and a comprehensive and practical plan of care is formulated and implemented. Other consensus recommendations and guidelines also emphasize the critical importance of establishing a triadic relationship that involves a patient-centered communication approach^{66,67} including a care partner, optimally from the beginning of a structured and iterative process (see Figure 1).^{15,56,58,60,68,69}

The practical considerations for achieving the most effective triadic relationship are often complex and can, in some circumstances—and particularly in primary care settings—be challenging to accommodate.^{7,16,18,70} For example, the most honest history from an informant may be best obtained in private. In some primary care settings, privacy concerns may make it difficult to involve an informant in the evaluation process. Some clinician's offices may not be physically or operationally designed to optimally accommodate a patient and care partner. Relationship dynamics between the patient and family members or informant/care partners can be complicated and may necessitate several streams of communication and a separate space. It can be very helpful to start the process with a meeting to establish shared goals for the diagnostic evaluation process.

In most cases, the goal of the evaluation process is to determine whether the patient has a diagnosable brain disease affecting cognition or behavior.⁷¹ The first step—the determination that a person does or does not have dementia—is critical for the clinician to be able to discuss whether the patient needs or will likely need specific supports, including surrogate decision makers. For any individual, differentiation of what is a cognitive–behaviorally impaired versus an unimpaired state requires clinical judgment.^{24,39–41,56,72,73} The determination that a person has MCI or dementia (or mild vs. major neurocognitive disorder in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition [DSM-5] terminology) is the first step of a diagnostic formulation that requires the clinician to integrate reliable history regarding the types, trajectory, and impact of changes in cognitive, behavioral, and daily activity functions with the patient's performance on tests of cognitive function in multiple domains (attention, memory, language, executive function, visual function, socio-emotional behavior).^{39–41} The patient's symptoms and performance on tests are both influenced by a variety of individual factors that have to be considered, including education, occupation, culture, living situation, family or other rela-

tionship dynamics, developmental history, and medical and psychiatric comorbidities (see Table 1).

The second step—determination of the cognitive–behavioral syndrome—facilitates communication about the specific types of impairments the patient has, regardless of the severity and impact of those impairments (i.e., MCI or dementia). While some patients present classically with one of the recognizable cognitive–behavioral syndromes (Table 2), others may not fit so clearly into these syndromic diagnostic criteria. In these cases, additional information or consultation with a specialist may be useful. A neuropsychological evaluation by a neuropsychologist proficient in AD/ADRD assessment is often invaluable in delineating the cognitive–behavioral syndrome in a patient with a complex presentation and can also be very helpful to suggest next steps in the evaluation and management process.

Third, it is important for the clinician to implicate a specific disease and/or condition as the likely cause(s) of cognitive impairment or dementia. While a patient's clinical syndromic profile (cognitive–behavioral syndrome) informs likelihood estimates of underlying disease pathology, there is always a differential diagnosis with regard to the possible neuropathologic changes that may be primarily driving and “responsible” for a given clinical syndrome^{42,74–77} (Table 2). A variety of risk and resilience factors can inform the clinician's thinking about the likelihood of specific diseases (e.g., a strong family history of AD increases the likelihood of AD pathology in a symptomatic individual; multiple cerebrovascular risk factors increase the likelihood of VCID). Each of these major disease entities has clinical diagnostic criteria (Tables 3 and 4), although the field is evolving toward a forward-thinking framework of separation of clinical syndrome from likely neuropathologic changes informed by core and ancillary biomarkers.^{78–80}

2.2.2 | Core elements two through five: history, systems review, risk profile, and exam

Recommendations 4 through 7 provide guidance regarding the next four core elements of the evaluation process, including the use of a structured approach to obtain history and systems review information in the key domains of cognition, daily function, mood and behavior, and sensorimotor function, representing not only the patient's perspective but in most cases also reliable collateral information from an informant. These recommendations also emphasize the importance of eliciting personalized information regarding risk factors for cognitive decline. The clinician should perform a mental status examination that assesses cognition, mood and behavior, and a dementia-focused neurologic examination, using validated tools whenever feasible. A separate article in this special issue provides detailed descriptions of instruments that can be used to facilitate these assessments (Atri A, et al).⁹⁴ It is also fundamentally important to consider psychiatric history and psychiatric disorders in the differential diagnosis in patients with cognitive impairment, recognizing that it is not uncommon for neurologic diseases to present with primary psychiatric symptoms (Box 3).

TABLE 3 NIA-AA core diagnostic criteria for probable AD dementia⁴¹ and for MCI due to AD,³⁹ and AA diagnostic criteria for AD.⁸⁰**Diagnostic criteria for AD****NIA-AA core diagnostic criteria for probable AD dementia**

A diagnosis of **probable AD dementia** can be made when the patient

1. Meets criteria for dementia (see Table 1), and
2. In addition has the following characteristics:
 - A. Insidious onset: symptoms have a gradual onset over months to years, not sudden over hours or days;
 - B. Clear-cut history of worsening of cognition by report or observation; and
 - C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories:
 - a. **Amnesic presentation:** It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text.
 - b. **Non-amnesic presentations:**
 - (i) Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present.
 - (ii) Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
 - (iii) Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
 - D. The diagnosis of probable AD dementia should *not* be applied when there is evidence of
 - a. Substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or
 - b. Core features of dementia with Lewy bodies other than dementia itself; or
 - c. Prominent features of behavioral variant frontotemporal dementia; or
 - d. Prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or
 - e. Evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. If biomarkers of both A β (PET or CSF) and neuronal injury (structural brain MRI, FDG PET, CSF tau) are present, likelihood is high that dementia is due to AD. If both are absent, the dementia is highly likely not due to AD. If they are conflicting, likelihood is intermediate.

NIA-AA core diagnostic criteria for MCI due to AD

1. Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time)
2. Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains)
3. Preservation of independence in functional abilities
4. Not demented

Supportive

1. Evidence of longitudinal decline in cognition, when feasible
2. Rule out vascular, traumatic, medical causes of cognitive decline, where possible
3. Report history consistent with AD genetic factors, where relevant

Likelihood of MCI being due to AD

1. High: biomarkers of both amyloid-beta (PET or CSF) and neuronal injury (structural brain MRI, FDG PET, CSF tau) are present
2. Intermediate: a biomarker of either amyloid-beta or neuronal injury is present and the other is untested; or one is positive and one is negative
3. Low: biomarkers of both A β and neuronal injury are absent

AA diagnostic criteria for AD***Biomarker categorization****Core AD biomarkers**

- Core 1: A β ("A": PET, CSF, plasma) and hyper-phosphorylated tau ("T₁": specific CSF or plasma tau species [p-tau 217, p-tau 181, p-tau 231])
- Core 2: AD tau proteinopathy ("T₂": specific CSF or plasma tau species [p-tau 205, microtubule binding region 243, non-phosphorylated tau fragments], tau PET)

Non-specific processes involved in AD pathophysiology

- N (neurodegeneration or injury): CSF or plasma neurofilament-light, MRI anatomic measures, FDG PET hypometabolism
- I (astrocytic activation): CSF or plasma GFAP

Biomarkers of non-AD pathology

- Vascular brain injury: MRI indicators of infarct(s) and/or white matter hyperintensities
- Alpha-synuclein: CSF alpha-synuclein seed amplification assay

Biological staging (e.g., by PET)

- Stage A (amyloid-positive [A+])
- Stage B (A+, tau positive, medial temporal lobe)
- Stage C (A+, tau positive, moderate neocortical)
- Stage D (A+, tau positive, high neocortical)

Clinical staging for individuals on the AD continuum

- Stage 0 (asymptomatic, deterministic genetic abnormality, no biomarker abnormality)
- Stage 1 (asymptomatic, biomarker evidence for AD)
- Stage 2 (Transitional cognitive/behavioral decline (including subjective cognitive decline))
- Stage 3 (MCI)
- Stage 4 (mild dementia)
- Stage 5 (moderate dementia)
- Stage 6 (severe dementia)

Abbreviations: A β , amyloid beta; AA, Alzheimer's Association; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; NIA, National Institute on Aging; PET, positron emission tomography; p-tau, phosphorylated tau.

*As this manuscript was in press, an international working group published an alternative proposal for contemporary clinical diagnostic criteria for Alzheimer's disease, maintaining the tradition of viewing it as a clinical-biological construct.⁷³

TABLE 4 Diagnostic criteria for major forms of non-AD dementia (AD-related dementia).

Diagnostic criteria for various types of ADRD	
Behavioral variant frontotemporal dementia	81
Primary progressive aphasia ^a	40,82
Dementia with Lewy bodies/Parkinson's disease dementia	40,83
Vascular dementia/vascular cognitive impairment	40,84–86
LATE	87
Progressive supranuclear palsy	88
Corticobasal degeneration	89
Amyotrophic lateral sclerosis with frontotemporal dementia	90
Huntington's disease	91,92
Creutzfeldt-Jacob disease	93

Abbreviations: AD, Alzheimer's disease; LATE, Limbic-predominant Age-related TDP-43 encephalopathy; PPA, primary progressive aphasia.

^aPPA can be an atypical presentation of AD, especially when characteristics are consistent with the logopenic variant of PPA.

BOX 3: Psychiatric disorders and dementia

The interplay between cognitive impairment and psychiatric symptoms is complex. Traditionally, new-onset depression in an older adult has been on the list of treatable forms of dementia, formerly referred to as pseudodementia.^{95–97} Yet, it has become clear that changes in mood are very common early symptoms of AD or ADRD. For example, in one study of data from nearly 2000 cognitively unimpaired participants in the National Alzheimer's Coordinating Center database who subsequently developed MCI or dementia, more than half had depression or irritability symptoms prior to cognitive impairment.⁹⁸ According to the DSM-5, core symptoms of depression include difficulty thinking, concentrating, and decision making. Thus, a patient presenting with such symptoms should always be evaluated for other symptoms of depression and this diagnostic possibility should be considered.⁹⁹ Further complicating the matter, specific types of primary neurologic etiologies of dementia can be very difficult to differentiate from primary psychiatric disorders because psychiatric symptoms are common early clinical features, including FTLD, LBD, prion diseases, Huntington's disease, and paraneoplastic and autoimmune encephalopathies.¹⁰⁰ Neuropsychological assessment or dementia subspecialist assessment may be helpful.¹⁰¹

A past medical history of a variety of primary psychiatric disorders is associated with an increased risk of dementia in later life, including not only major depressive disorder but also post-traumatic stress disorder, bipolar disorder, and psychotic disorders.¹⁰² The causal direction of the associ-

ation between psychiatric disorders and dementia remains unclear. Psychiatric symptoms may be risk factors for future dementia or may represent early symptoms in patients with neuropathologic changes associated with dementia. Many studies investigating associations between psychiatric disorders and dementia have only included relatively short follow-up periods. Therefore, given the long duration of accumulation of some neuropathologic changes leading to dementia prior to overt cognitive and functional impairment, new-onset psychiatric symptoms in older adults may represent early symptoms of a disease that will ultimately become obvious as dementia due to AD or ADRD. These observations have led to the development of the clinical construct of mild behavioral impairment.¹⁰³ In some cases, it may not be clear whether a patient's symptoms are most likely explained by a primary psychiatric disorder or a neurodegenerative or other neuropsychiatric disease; thus, this construct may be useful in indicating this ambiguity as further diagnostic evaluation is performed, and as treatment for primary psychiatric symptoms is implemented. Although not yet clinically validated, risk algorithms are being developed to support individualized prognostication in patients with MCI demonstrate the importance of assessing mood.¹⁰⁴ Because of this complexity, many experts are advocating for studies with longer follow-up periods and sufficient biomarker evaluations to determine whether psychiatric symptoms/disorders represent primary psychiatric conditions that are risk factors and drivers for later developing neurodegenerative pathologic changes that then lead to dementia or whether psychiatric symptoms in some older persons are early manifestations of neuropathologic changes that precede cognitive and functional impairment in the clinical course of AD/ADRD.

Recognizing these challenges, the Lancet Commission report focused their 2024 meta-analysis on seven studies with a 10- to 14-year follow-up period after a diagnosis of depression, summarizing their findings as supporting mid-life depression as a modifiable risk factor for dementia: "The effect of medication and therapy for depression in reducing the risk of dementia suggest the importance of treating depression both for quality of life and because it might reduce the risk of dementia in the future." It is widely recognized that the diagnosis and treatment of depression in older adults is often more complex than in younger adults,^{105,106} hence a high index of suspicion and an interdisciplinary and coordinated approach is required.

When considering risk profile, it is important to recognize that a majority of individuals older than age 80 with cognitive impairment harbor more than one type of brain pathological change.^{77,107,108} Older persons with AD neuropathological changes often have concomitant changes related to VCID—including macroinfarcts, microinfarcts, atherosclerosis, arteriosclerosis, cerebral amyloid angiopathy—as well

as other concomitant neurodegenerative diseases (e.g., LBD, TDP-43 proteinopathy, hippocampal sclerosis).⁷⁴⁻⁷⁷ In addition, many older adults with cognitive impairment have other potentially contributing conditions (e.g., obstructive sleep apnea, use of cognitively impairing medications, excessive alcohol consumption) that can exacerbate cognitive or behavioral symptoms. Therefore, it is not uncommon in older individuals and those with multiple comorbidities that a cognitive-behavioral syndrome has multiple etiologies, which when causing dementia-level impairment is called mixed etiology dementia.^{75,109} Patients with mixed etiology dementia are more likely to present with atypical or non-amnesic symptoms, and the identification of these factors may also provide opportunities for risk mitigation and optimization of care and management, particularly when cardiac, cerebrovascular, sleep, medication/supplement, or alcohol/substance-related risk factors are present.

2.3 | Core element six: iterative diagnostic formulation and multi-tiered diagnostic testing

By following recommendations to this sixth core element in the evaluation process (see Figures 1, 2, and 3), the clinician should have integrated information about risk profile, history of symptoms, and examination findings to develop an opinion regarding the cognitive functional status and, at least preliminarily, a cognitive-behavioral syndromic diagnosis, if present. There should also be sufficient information for most primary care clinicians to arrive at a first decision point with regard to whether consultative input should be obtained (i.e., from a neuropsychologist, specialist, or dementia subspecialist). In the primary care setting, two or more problem-focused visits would usually be required to arrive at this point in the diagnostic evaluation process, especially when involving an informant/care partner and allowing sufficient time to assess cognition via a validated standardized instrument.

To achieve the goals of this three-step diagnostic formulation, the DETeCD-ADRD CPG recommends a structured and multi-tiered approach to assessment and testing that begins with a fundamental set of Tier 1 assessments and tests, supplemented as needed by other tests tailored to the patient (see Figures 2-3). The clinician should formulate the results of the Tier 1 assessments and tests and decide which, if any, additional tests may be required to gain sufficiently high confidence in the presence or absence of a specific diagnosis. A stepped approach to diagnostic evaluation of potential cognitive impairment or dementia is also a cornerstone of other national, European and international guidelines including the UK National Institute for Health and Care Excellence 2018 Guidelines on dementia diagnosis and care,⁵⁸ Canadian (5th Canadian Consensus Conference on Diagnosis and Treatment of Dementia) guidelines,⁶⁰ the World Health Organization mhGAP 2016 Intervention Guide,¹¹⁰ and the 2024 European Intersocietal Recommendations for the biomarker-based diagnosis of neurocognitive disorders.¹¹¹ It is ultimately each clinician who, depending on her or his proficiency, the available data and resources, and the goals of evaluation, must—in partnership with each patient-care partner dyad—

guide the evaluation process to achieve the desired confidence in the syndromic and etiological diagnosis.

Recommendations 8 and 9 provide guidance regarding the basic (Tier 1) diagnostic tests, including a cognitive laboratory panel and structural neuroimaging, that should be routinely obtained in all patients with a cognitive-behavioral syndrome to inform a confident etiological diagnosis. Importantly, Recommendations 8 through 11 apply to fewer patients than those who begin the process, as many patients in whom there is an initial concern that prompts the evaluation process will, once Recommendations 1 through 7 are followed, be assessed with high confidence to have a cognitive functional status of “cognitively unimpaired,” and will not require further testing or evaluation (see Figure 2). Conversely, whether in the primary or specialty setting, for most individuals with typical presentations of AD dementia, the relevant information often would be available at this point to arrive at a confident clinical diagnosis of the likely etiology and to proceed with a disclosure visit emphasizing that such a diagnosis remains probabilistic and clinical judgment based and is not biomarker confirmed. Molecular biomarker confirmation is necessary for consideration of new disease-modifying therapies that target amyloid plaques (see Box 6).¹¹²

Several readily treatable common comorbid conditions, including infections, dehydration, hypothyroidism (TSH), and vitamin B₁₂ deficiency, are often observed and may contribute to cognitive or behavioral symptoms, and may cause subacute or acute clinical decompensation (see Box 4 on delirium). Acute mental status changes may be solely due to such conditions, but acute-on-chronic decompensations are usually an indication that a patient with a chronic brain disease causing progressive cognitive decline has developed a common comorbid condition.

A shotgun approach to first-tier diagnostic testing is not recommended as it is costly and can be harmful. A judicious and stepwise approach that prioritizes common and treatable conditions, and less invasive and more cost-effective testing, is recommended as the first-tier approach to diagnostic testing in a patient suspected of having a cognitive-behavioral syndrome due to AD/ADRD. Such approaches to routine lab testing in AD/ADRD have been recommended in specialty society practice parameters,^{57,59,68} health-care systems such as the Veterans Health Administration,¹²² and in guidelines by world, European Intersociety Consensus Recommendations, and national health service authorities and commissions,^{20,58,60,110,111,123} but lack consistency, detail, a multi-disciplinary perspective, and specificity to the United States.¹²⁴

A description of first-line routine laboratory testing as “labs for reversible causes of dementia” can be misleading; the term “cognitive lab panel” may be more suitable. The conditions being evaluated in such a panel are rarely the primary etiology of a gradually progressive cognitive-behavioral syndrome, but often exacerbate cognitive or behavioral impairment in individuals with underlying neurodegenerative diseases and related disorders (e.g., VCID). It is highly unlikely for a hormonal or vitamin deficiency, or metabolic, infectious, autoimmune, toxic, neoplastic, or paraneoplastic condition to mimic the clinical

BOX 4: Delirium

Delirium (also known as encephalopathy, confusional state, or altered mental status) is a sometimes life threatening but often preventable clinical syndrome that is especially common in older vulnerable adults.⁴⁰ Delirium, which is defined as an acute disorder of cognition and attention, often occurs during the course of a medical illness or after surgery (commonly while a person is in the hospital). Delirium often occurs in a person who is already cognitively impaired due to AD or ADRD, but may arise in a person who has not yet been diagnosed with cognitive impairment or dementia due to AD/ADRD or other cause. When delirium is superimposed on a preexisting neurodegenerative dementia, there are important risk stratification and prognostic implications, including accelerated cognitive and functional decline; increased length of hospital stay; higher rates of rehospitalization, institutionalization, and death; and greater costs compared to dementia alone.¹¹³ It is critical to diagnose delirium because it represents a medical emergency, which if left untreated may be fatal or lead to devastating and irreversible cognitive and functional losses.¹¹³

Delirium is a clinical diagnosis involving acute onset and fluctuating course of cognitive, behavioral, and/or sensorimotor symptoms; inattention; impaired level of consciousness; and disturbance of cognition indicating disorganization of thought (e.g., disorientation, memory impairment, or alteration in language).¹¹³ Delirium usually occurs in the context of medical conditions including infection, toxic-metabolic disorders, electrolyte and hydration disturbances, drugs, hypoxia, or organ failure. Supportive features of the syndrome include alterations in sleep-wake cycle; perceptual disturbances, such as hallucinations or misperceptions; delusions; inappropriate or unsafe behavior; and emotional lability. In typical delirium, acute changes in cognition, behavior, attention, and level of consciousness develop on timescales of hours to days, and may fluctuate within minutes to hours depending on the delirium subtype (hyperactive, hypoactive, mixed).

The foundation of the delirium diagnosis rests on an estimate of the patient's previous baseline level of cognition, function, and behavior. The clinician must interview a knowledgeable informant to determine the time course, nature, and trajectory of changes, and examine the patient to establish current levels of cognitive function. The assessment of the patient with suspected delirium benefits greatly from the use of a validated brief cognitive assessment instrument to delineate spot performance (e.g., one of the forms of the Confusion Assessment Method (CAM))^{114,115} or a similar instrument.¹¹³ Repeated assessments are helpful because cognitive status often varies substantially within a day due to fluctuations in arousal, attention, and psychomotor state. In parallel, the clinician should obtain appropriate labs and studies to establish and treat the cause(s) of and factors contributing to delirium. Simultaneously, measures should be initiated to prevent delirium complications; and delirium symptoms should be managed using non-pharmacological and, in severe cases, pharmacological strategies.¹¹⁶ Delirium severity should be measured over time to ensure appropriate response and resolution.

The time course and nature of cognitive and behavioral abnormalities can help differentiate delirium from dementia, psychosis, mania, or severe depression. From a diagnostic perspective, the most useful characteristics of typical delirium are an acute change in mental status or behavior, fluctuations in arousal or level of consciousness, and inattention. Some patients experience a hypoactive delirium,¹¹⁷⁻¹¹⁹ with cognitive and motor slowing and even a sedated appearance, which is more common among older individuals and is associated with greater risk of morbidity and mortality.¹²⁰ Atypical, subsyndromal, and mild chronic forms of delirium must also be recognized and treated accordingly. Some causes of these forms of delirium include sleep disturbances, heavy alcohol intake, or the use of cognitively deleterious medications in vulnerable older individuals.¹²¹

phenotype of typical AD/ADRD; it is more likely for a subsyndromal delirium caused by these conditions to secondarily becloud and decompensate cognitive-behavioral function in an individual with underlying AD/ADRD pathological changes. It is also possible, though very uncommon, for some of these conditions to primarily cause atypical dementia syndromes: reports of very rare instances (with insufficient long-term follow-up) notwithstanding, meta-analyses suggest that 0.3% to 0.6% of dementia syndromes may be at least partially "reversible"; while in ≈ 9% of dementia syndromes a common comorbid condition may be observed.¹²⁵

The DETeCD-ADRD Workgroup aimed to provide practical guidance for Tier-1 lab testing via a cognitive lab panel that should be obtained in all or almost all patients evaluated for suspected cognitive-behavioral syndromes due to their relatively low cost, wide

availability, and acceptable yield as a broad evaluation for common comorbid conditions. The workgroup adopted a multidisciplinary and US health-care-centric perspective to estimate risk-reward calculus by integrating usual practice, recommendations from other guidelines and practice parameters,^{20,57-60,68,110,111,122,124} and the limited evidence to otherwise support or refute the utility of cognitive lab panel tests for common comorbid conditions.⁵⁹

The cognitive lab panel (Table 5) recommended by the workgroup includes screening tests for TSH and vitamin B12 deficiency, which are common in older adults, can cause neuropsychiatric symptoms and decompensation of cognitive-behavioral syndromes, and their treatment can improve symptoms. Homocysteine is included because hyperhomocysteinemia is associated with functional B12 deficiency (and may not always readily detected by B12 levels in blood),

TABLE 5 Multiple tiers of tests considered in the evaluation of patients with or suspected of having cognitive impairment.

Tier	Type	What	Who/how	Why
1	Blood "cognitive lab panel" (Rec. 8)	TSH, vitamin B12, homocysteine, CBC with differential, complete metabolic panel (including calcium, magnesium, liver function tests), ESR, CRP	Who: Obtain in almost all individuals assessed How: Usually obtain all tests in this tier	Broad and relatively inexpensive tests for common conditions in older individuals that can contribute to cognitive and behavioral impairments
	Imaging (Rec. 9)	Brain MRI without gadolinium—if unavailable or contraindicated then obtain non-contrast head CT		Brain MRI (or CT if MRI is unavailable or contraindicated) (Rec. 9), assessing: atrophy patterns (hippocampal and cortical atrophy in medial temporal and lateral temporal and parietal lobes are consistent with AD; frontal or anterior temporal atrophy are consistent with FTD; infarcts, leukoaraiosis, and microhemorrhages; non-degenerative conditions (e.g., hydrocephalus, mass lesions)
2	Blood	ANA, HgbA1c, lipid profile, folate, Lead, Lyme antibody, RPR, HIV, SPEP, methylmalonic acid (MMA), PT, PTT	Who: Obtain in some individuals based on clinical features (clinical risk profile from history, exam or lab/studies; other medical comorbidities) (**including people for whom the clinician aims to obtain a high confidence diagnosis of AD)	Some Tier 2-4 tests can be obtained in some individuals based on clinical characteristics (Rec. 15)
	Imaging	Chest plain film/x-ray ^a	How: Obtain one or a few tests in this tier depending on targeted clinical question	
	Urine	Urinalysis, ^a urine culture ^a		
	Other	Sleep study: for obstructive sleep apnea or REM sleep disorder (LBD)		
3	Blood	TPO, anti-TGA, FTA-ABS, ACE, ANCA, viral antibody studies (hepatitis B/C, EBV, CMV)	Who: Obtain in few individuals including those with atypical clinical profiles* or rapid progression	Most Tier 3 and 4 tests should be done by or in consultation with a specialist/subspecialist (see ¹²⁶ for review)
	Urine	UPEP, Bence-Jones Proteins	How: Obtain one or more tests in this tier to evaluate a patient for a specific condition	TPO & TGA to assess for Hashimoto's encephalopathy/SREAT
	CSF	AD CSF biomarker panel ($A\beta_{42}$, tau, phospho-tau and ratios) (Rec. 17)**; consider obtaining cell count, glucose, total protein, and other CSF tests depending on condition being considered		*Assessment of possible early age-of-onset or atypical AD or ADRD may include brain FDG-PET (or SPECT) scan (Rec. 16). **When AD is a possibility and high confidence is desired
	Imaging	Lyme PCR; viral PCRs and cultures, VDRL, T. pallidum PCR MR or CT angiogram of head and neck, carotid ultrasound, brain MRI with gadolinium or head CT with contrast, chest films		consider analysis of specific in vivo AD biomarkers such as CSF AD panel (Rec. 17) or amyloid PET (Rec. 18). Diagnostic confirmation with molecular biomarkers is required for anti-amyloid therapies (see Box 6).
	Other	Brain FDG PET (or SPECT) scan* (Rec. 16) Brain amyloid PET scan** (Rec. 18) EEG, dopamine transport SPECT or PET imaging (altered in LBD, PDD > PSP and CBD), cardiac scintigraphy (altered in LBD)		

(Continues)

TABLE 5 (Continued)

Tier	Type	What	Who/how	Why
4	Blood	Paraneoplastic antibody panel, anti-voltage-gated potassium channel (VGKC) antibody, non-Lyme tick borne disease panel (ehrlichiosis, babesiosis, anaplasmosis, rickettsiosis, Powassan), copper & ceruloplasmin, tumor markers, rheumatological studies	Who: Obtain in rare cases, atypical cases or in rapid progression, when etiology remains uncertain or index of suspicion is raised by evolving clinical trajectory or results of earlier testing	Tier 4 tests investigate rare, highly atypical or rapidly progressive dementia syndromes (see ¹²⁶ for review)
	Urine	24 hour urine collection for heavy metals, porphyria and/or copper	How: One or more tests in this tier would be obtained if a specific etiology is being considered	
	CSF	Protein 14-3-3, neuron specific enolase (NSE), T. whipplei PCR, paraneoplastic antibody panel, anti-voltage-gated potassium channel (VGKC) antibody, cytology, flow cytometry, other stains and cultures for infectious agents (bacterial, fungal, AFB)		
	Imaging	CT of chest, abdomen, pelvis; cerebral angiogram; whole body PET scan		
	Other [biopsy]	Biopsies: Brain and/or meningeal vessels; temporal artery; skin; small intestine; or muscle biopsy		
	Genetic	Autosomal dominant AD or ADRD genetic mutations*** (PSEN2, PSEN1, APP) (Rec 19), FTLD genetic mutations (MAPT, GRN, C9orf72), Huntington genetic mutation		***When there is a 2 or more generational history of AD or dementia syndrome suggestive of autosomal dominant pattern or in early age-of-onset. All genetic tests should be performed and disclosed with involvement of genetic counseling when possible (Rec. 19).
X	Blood	A β , hyperphosphorylated tau, neurofilament light chain (NFL), glial fibrillary acidic protein (GFAP), etc.	Who: Patients suspected of having cognitive impairment or dementia due to a particular etiology typically in a specialist setting	Subspecialty molecular biomarkers are emerging as commercial tests but at the time of this writing have not been validated in most clinical practice settings and diverse populations; ¹²⁷ reimbursement is not yet available. Tau PET is FDA approved but not yet widely available or reimbursed. ¹²⁸
	CSF, skin	Alpha synuclein ^{129,130}	How: One or more tests in this tier would be obtained if a specific etiology is being considered	This is a rapidly evolving field. See Box 6 and 2024 AA Revised Criteria for diagnosis and staging of AD ⁸⁰ for more information and caveats. See also 2024 biological diagnosis of Lewy body diseases. ⁷⁹
	Imaging	Brain tau PET scan ¹³¹		

Note: Tier 1 tests involve a blood cognitive lab panel and structural brain imaging that should be obtained in all or almost all individuals to establish likely etiology(-ies). Tests listed in Tier 2–4 are representative of tests that could be ordered with increasing selectivity based on an individual's clinical characteristics. Tier X are clinically emerging in specialist/subspecialist settings but may not be validated in diverse real-world populations and clinical settings, widely accessible, reimbursed or readily interpreted without high proficiency.¹²⁶

Abbreviations: AA, Alzheimer's Association; A β , amyloid beta; ACE, angiotensin converting enzyme; AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; AFB, acid fast bacilli; ANCA, antineutrophil cytoplasmic antibodies; CBC, complete blood count; CBD, corticobasal degeneration; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein-Barr virus; ESR, erythrocyte sedimentation rate; FDA, US Food and Drug Administration; FDG, fluorodeoxyglucose; FTA-ABS, fluorescent treponemal antibody absorption; FTLD, frontotemporal lobar degeneration; HIV, human immunodeficiency virus; LBD, Lewy body disease; PCR, polymerase chain reaction; PDD, Parkinson's disease dementia; PET, positron emission tomography; PSP, progressive supranuclear palsy; PT, prothrombin time; PTT, partial thromboplastin time; RPR, rapid plasma reagin; SPECT, single photon emission computed tomography; SREAT, steroid responsive encephalopathy associated with thyroiditis; TGA, thyroglobulin antibodies; TPO, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.

^a Delirium work-up first tier (see Box 3 on delirium)—in addition to Tier 1 labs, these tests should also be considered in all or nearly all individuals being assessed for delirium or an acute change in mental status.

cardio- and cerebrovascular risk, and VCID. Other panel tests are informative about the potential existence of common comorbid conditions such as dehydration (e.g., suggestive with a blood urea nitrogen:creatinine ratio > 20:1), hypo/hyponatremia, hypomagnesemia, hypercalcemia (and hypocalcemia), hypo/hyperglycemia, anemia, uremia, and hepatic dysfunction. Finally, ESR and CRP are included as broad, non-specific, and inexpensive screens for insidious systemic processes including inflammatory/autoimmune, infectious, or neoplastic processes (e.g., undetected lung, liver, or colon cancer) which may change management and prognosis.

Brain MRI without contrast, when available and not contraindicated, is appropriate for evaluation of AD/ADRD.^{111,132} In the past, the major role of structural neuroimaging in dementia assessment was to assist in the exclusion of non-neurodegenerative etiologies of cognitive impairment or dementia (such as tumors, inflammatory conditions, infectious processes, etc.) or the identification of features of unusual forms of dementia (such as prion diseases).^{59,132-134} In contemporary practice, structural brain images may reveal atrophy patterns supportive of a particular neurodegenerative disease diagnosis.¹³³⁻¹³⁵ Strong evidence supports the utility of brain MRI against gold-standard neuropathologic examinations.¹³⁶ For example, in some patients presenting with a history and examination typical for an early clinical stage of suspected AD, the brain MRI may show clear evidence of atrophy in the medial temporal lobes and lateral temporal and parietal cortices with ventricular enlargement.^{135,137} When a proficient clinician's hypothesis is that the patient's cognitive impairment is likely due to AD with relatively little else in the differential diagnosis, and a brain MRI is supportive of this hypothesis, the clinician may be reasonably confident in the clinical diagnosis, although specific molecular biomarkers are required to confirm the diagnosis for treatment with disease-modifying therapy. In other cases, there may not be evidence of abnormality, or the abnormalities may not be consistent with those hypothesized from the clinical presentation. In these cases, additional higher-tier testing may be warranted. Finally, MRI plays a critical role in the detection of evidence of microhemorrhage associated with cerebral amyloid angiopathy,¹³⁸ which influences risk-benefit considerations for the use of anticoagulants and is a critical element of appropriate patient selection and monitoring for amyloid-related imaging abnormalities in patients who receive disease-modifying therapies.^{112,139}

While multiple barriers to timely diagnosis and appropriate disclosure of AD/ADRD exist in primary care, individuals with typical AD dementia can and should be readily diagnosed with confidence in the primary care setting. By gaining proficiency with the testing and processes recommended in this guideline, most PCPs should find it relatively straightforward to suspect and then diagnose dementia likely due to AD in a patient with a typical presentation of gradually progressive memory loss and difficulty with judgment and problem solving, and often spatial and/or temporal orientation, which have impacted ADLs, and in whom cognitive lab panel and brain MRI are also supportive (i.e., unrevealing in the former and consistent with AD in the latter). However, some patients—especially those who are relatively young—may not only present with an unusual history of subtle, atypical, or

rapidly progressive symptoms but may also exhibit unusual signs on office-based examination. Delirium and rapidly progressive dementia (usually defined as developing subacutely within weeks or months) are considered urgent medical problems requiring rapid, and in some cases inpatient, evaluation and management.

Atypical features may include prominent focal cognitive abnormalities (e.g., aphasia, cortical visual dysfunction), sensorimotor impairment (e.g., visual field cut, limb apraxia or rigidity, myoclonus, eye movement abnormalities, incoordination, gait abnormalities), or profound mood and behavioral symptoms (e.g., disinhibition, manic-like behavior, flat or indifferent affect, or severe depressive or anxious mood or psychotic thought content).¹⁴⁰⁻¹⁴⁴ Patients with such signs on examination require an approach with a broader differential diagnosis, which often warrants specialist examination and distinct testing and studies to arrive at a diagnosis and appropriate interdisciplinary care plan.

Other patients may have a history and examination that are incongruent: for example, a patient may not have a history suggestive of delirium but on examination may be highly inattentive or exhibit signs suggestive of a toxic-metabolic encephalopathy or a related syndrome. Still other patients may present with a history of substantial cognitive-behavioral change in daily life yet have what appears to be a normal examination in an initial office encounter. In patients whose examination may be difficult to interpret in the primary care setting, it is critical to consider and facilitate referral to a specialist with expertise in dementia; and to strongly consider neuropsychological evaluation. Evaluation for suspected rare or rapidly progressive dementia is complex, includes a very broad differential diagnosis, and is best performed by a dementia subspecialist.^{126,145,146}

Recommendations 12 through 14 provide guidance regarding referral to a specialist or a neuropsychologist and the elements of these assessments. Recommendations 15 through 19 provide guidance regarding hierarchical use of Tier 2 to 4 diagnostic tests (specialized labs, imaging, genetic testing) and consultations, if needed, to determine cause(s) of (and potential contributors to) the cognitive-behavioral syndrome with a high level of confidence. Importantly, Recommendations 12 through 19 apply to fewer and fewer patients and circumstances still and the strength of these recommendations varies. For additional detail on the specialist or dementia subspecialist guideline, see Dickerson BC, et al.³² aimed toward specialists.

2.4 | Core element seven: diagnostic disclosure

Recommendations 10 and 11 provide guidance regarding the seventh core element of the process—the communication of diagnostic findings and recommended management and follow-up care.¹⁴⁷ The patient and care partner's understanding and appreciation of the illness—together with the clinician's judgment—should guide education, communication, and documentation of diagnostic findings and disclosure. In this context, the clinician should honestly and compassionately communicate the name/stage of the syndrome and the disease causing it; treatment options and expectations; prognosis;

BOX 5: Health equity and disparities in AD/ADRD

There is a great need to better understand the incidence and prevalence of ADRD and to appropriately tailor services for underrepresented communities and people of color.^{2,159-161} Incidence of dementia appears to be highest in Black, Hispanic/Latino Caribbean, and Native American populations; intermediate in Latinx, Mexican American, and non-Latino White populations; and lowest in Japanese American and Asian American populations. Prevalence of dementia appears to be highest in Black and Caribbean Hispanic/Latinx populations.^{159,162} The prevalence rates are likely underestimated, and better data are needed, particularly in Native American, most Asian American, and Pacific Islander populations.^{159,163,164}

Studies of genetic risk factors and molecular biomarkers of AD in underrepresented minoritized backgrounds have consistently reported differences from non-Latinx White populations.¹⁶⁵⁻¹⁶⁸ These studies suggest that the apolipoprotein E (APOE) ε4 allele and traditional AD pathological biomarkers are likely not the major factors that account for the observed differences in risk, incidence, and prevalence of AD in underrepresented populations. At least some of the differences in incidence and prevalence likely relate to variations in medical comorbidities, health-related behaviors, and sociocultural and environmental factors^{2,164,169} that confer increased AD and ADRD vulnerability (or other as yet unknown genetic or biological factors).¹⁷⁰ Such factors may include differences in chronic stress, smoking, exposure to pollution, and inequitable access to education, a healthy diet, and health care.^{160,171} The complex interplay among these factors may influence the pathobiological disease processes leading to AD or ADRD in the brain, neuroimmune responses to these pathologic changes, or other risk and resilience factors that are ultimately expressed as alterations in brain circuit function underlying dementia symptoms.^{172,173}

Pervasive health-care system inequities for people of color and underrepresented and underserved populations hinder the diagnosis of cognitive-behavioral impairment and dementia due to ADRD.^{2,174} People of color and underrepresented populations have less access to health care, and family members may be less able to access help they need when faced with challenges of caring of adults with cognitive-behavioral impairments. Lack of access to medical services, care, and appropriate resources can result in more rapid cognitive decline, increased hospitalization rates from comorbid medical conditions, and excessive financial and caregiver burdens.^{3,174} The combination of disparities in access to health care and differences in disease biomarker characteristics in individuals with symptoms of cognitive impairment who are from underrepresented backgrounds compounds the challenges in early diagnosis and will likely lead to delays in access to appropriate treatments. In parallel with emerging evidence that collaborative dementia care management in primary care is associated with better health outcomes and is cost effective,¹⁷⁵ numerous studies are being launched to try to improve the efficiency of the diagnostic process in primary care in underserved communities.¹⁷⁶

Ongoing progress to raise awareness, diversify the practitioner workforce, and to evolve clinical and research practices are needed to mitigate health inequities. It is essential to develop and implement tailored practices to improve diversity, inclusion, and equity in access to health-care resources and research opportunities for people of color and underrepresented populations.^{2,163} Although differences in modifiable risk factors for dementia such as control of blood pressure, cholesterol, and glucose among racial and ethnic groups may contribute to ongoing health disparities, some health-care systems in certain regions of the country have demonstrated the elimination of racial disparities in at least some of these modifiable risk factors in their beneficiaries except for Blacks.¹⁷⁷ Finally, better access and inclusion of Blacks, Hispanic/Latinos, Asian Americans, Pacific Islanders, and Native Americans in clinical trials and observational studies are crucial to advance the biopsychosocio-environmental understanding of ADRD, to develop more effective treatments, and to provide greater care and hope for all facing the increasing scourge of dementing disorders.^{2,170}

and potential safety concerns—and the certainties, likelihoods, and unknowns related to these—and medical, psychosocial, and community resources for education, care planning and coordination, and support services. A separate article in this special issue provides guidance about principles of the diagnostic disclosure process as well as when immediate or full diagnostic disclosure may not be recommended or feasible.¹⁴⁸

3 | DISCUSSION

Improved diagnostic approaches for AD and ADRD that have tangible clinical benefits will be effective and of value in primary care

if the diagnostic procedures can be efficient (with respect to time, effort, and costs), widely available, and sufficiently accurate and interpretable without high expertise. In parallel, therapeutic research must move forward toward new evidence-based pharmacotherapies, other biological interventions, behavioral interventions, and care and support interventions that improve outcomes. In addition to the federal agencies devoting growing resources to these diseases, guided strategically in part by the National Alzheimer's Project Act Advisory Council, grass-roots and advocacy organizations are catalyzing public-private-industry partnerships that should help the field work toward our common goal of timely and accurate diagnosis, appropriate disclosure, and better management for people living with these serious

BOX 6: Diagnostic assessment in the era of amyloid plaque-lowering monoclonal antibody disease-modifying therapies

In June 2021, the US Food and Drug Administration (FDA) granted accelerated approval for aducanumab (Aduhelm), an A β -directed plaque-lowering monoclonal antibody (mAb) indicated for the treatment of AD in patients with MCI or mild dementia ("early-stage AD"), but the Centers for Medicare Services (CMS) did not support payment for aducanumab, limiting its use.^{178,179} Its development has been discontinued. In January 2022, the FDA granted accelerated approval for lecanemab (Leqembi), another amyloid plaque-lowering mAb indicated for the treatment of early-stage AD.¹¹² This was followed in July 2023 by the traditional (full) FDA approval of lecanemab with the CMS agreeing to reimburse for its use when appropriate patients are registered in a CMS-approved patient registry. Protocols and care pathways for lecanemab administration have made it available to patients, particularly in specialty clinical practices. On July 2, 2024, the FDA gave traditional approval for donanemab (Kisunla), a third plaque-lowering mAb. In October 2023, CMS eliminated the national coverage determination for amyloid PET, thus making it reimbursable in clinical practice for Medicare beneficiaries. Several new CSF assays for amyloid and tau have also received FDA clearance.

The availability of these disease-modifying therapies creates a demand for timely detection, accurate diagnosis, and appropriate treatment options for early AD that could overwhelm an unprepared health-care system.¹⁸⁰ Providing treatment with amyloid plaque-lowering mAbs requires high proficiency and sufficient resources including close collaborations with comprehensive multi-disciplinary teams.¹¹² With too few specialists currently available to respond to the possible number of patients who are candidates for treatment, there are opportunities to forge new models of hub-and-spoke dementia specialist–primary care collaborations and peer-to-peer consultation to partially fill these needs and respond to workforce gaps. Health-care systems around the country are working to respond to this need, which will likely require new partnerships among community organizations, primary care clinicians, memory-care experienced nurses and nurse practitioners, and specialists.^{181–183}

The DETeCD-ADRD CPG Workgroup reviewed the 19 recommendations in the context of these FDA and CMS decisions. As guidance on the practical use of this new class of medications is developed and revised diagnostic criteria for AD evolve, the role, availability, and reimbursement of companion diagnostic biomarkers in the evaluation of patients with MCI or mild dementia will change. In addition, adjustments may be needed to accommodate the segment of the patient population who might warrant referral primarily for specialized elements of the diagnostic evaluation to determine whether a patient is a candidate for amyloid-lowering therapy. And finally, the use of structural brain imaging and genetics will change because brain MRI scans are required for monitoring for amyloid-related imaging abnormalities (ARIA) and APOE genotype influences ARIA risk.^{112,139} Thus, an MRI may need to be repeated and APOE testing (and the genetic counseling that should accompany genetic testing) may need to be obtained for treatment planning (not for diagnostic evaluation purposes). With those points of potential adjustment in mind, the workgroup believes these guidelines and the evidence and principles that support them will likely change minimally in the short term in the context of amyloid-lowering therapy, yet we plan to re-evaluate them soon as this class of medications gains greater traction in clinical practice; as more accurate and broadly validated (in diverse clinical populations and settings) AD plasma biomarkers become available and reimbursed; as tau PET's clinical utility and accessibility increase; and as sufficiently clinically accurate biomarkers for AD and other ADRD are developed, validated, and become accessible.^{127,128,153–158}

illnesses. Many in the field are enthusiastic for new approaches that may provide primary care clinicians with more actionable information within their own practices or that will help with decision making regarding referrals, including digital biomarkers (e.g., wearables to monitor aspects of physiology, behavior, or sensorimotor functions¹⁴⁹ and self-administered remote computerized cognitive and behavioral testing¹⁵⁰) and plasma biomarkers,^{151,152} which are demonstrating remarkable potential for detecting forms of A β , p-tau, and other disease-related proteins in blood samples but require further assessment and validation in real-world and diverse populations and clinical settings.^{153–158} Appropriate use criteria and EU/US Clinical Trials in Alzheimer's Disease Task Force recommendations for blood-based biomarkers do not recommend their use as stand-alone biomarkers in clinical practice, although cautious use in subspecialty clinics with confirmation using CSF or PET has been encouraged.^{127,152} Furthermore, it is critical to recognize that a variety of factors appear to

alter the clinicopathologic relationships and biomarker characteristics of these disorders in minoritized populations who are under-represented in AD and ADRD research and clinical practice studies (Box 5).

The field is evolving rapidly, and although we expect that the fundamental principles outlined in the DETeCD-ADRD CPG recommendations will stand the test of time, advances in specific technologies and their validation in more diverse non-research cohorts and real-world clinical settings will likely lead to the need to update this CPG within the next few years; especially now that disease-modifying therapies for AD are approved (Box 6) and plasma biomarkers are becoming more accurate and being validated in real-world populations and settings.¹⁵⁵ Ongoing studies of other specific etiologies of cognitive impairment and dementia, such as chronic traumatic encephalopathy (Box 7), are continuing to expand our understanding of the variety of disease processes that can lead to dementia.

BOX 7: Chronic traumatic encephalopathy

Chronic traumatic encephalopathy (CTE) is a neurodegenerative disease leading to dementia that is associated with exposure to repetitive head impacts, including those sustained in contact sports and military service.¹⁸⁴ The diagnosis of CTE can only be made at present by neuropathologic examination demonstrating a unique pattern of p-tau deposition.¹⁸⁵ A diagnosis of dementia due to CTE in life is not yet possible to make. Given that the 2014 research diagnostic criteria for the traumatic encephalopathy syndrome (TES) showed high sensitivity (97.3%) but low specificity (20.2%), an expert consensus panel published a report in 2021 on provisional research National Institute of Neurological Disorders and Stroke Consensus Diagnostic Criteria for TES, which requires (1) substantial exposure to repetitive head impacts from contact sports, military service, or other causes; (2) core clinical features of cognitive impairment and/or neurobehavioral dysregulation; (3) a progressive course; and (4) that the clinical features are not fully accounted for by any other neurologic, psychiatric, or medical conditions.¹⁸⁶ Cognitive symptoms include core impairments in episodic memory and/or executive function (potentially with symptoms in other domains as well). Behavioral symptoms include poor regulation or control of emotions and/or behavior, including (but not limited to) explosiveness, impulsivity, rage, violent outbursts, having a short fuse (exceeding what might be described as periodic episodes of minor irritability), or emotional lability (often reported as mood swings)—not transiently occurring in the context of life events, for example, divorce, death of loved one, and financial problems. The panel stated that these diagnostic criteria for TES are meant primarily for research purposes and should be used cautiously in clinical and medicolegal settings, avoiding equivalence with a diagnosis of CTE, and using appropriate care when communicating a diagnosis of TES.

A sufficient level of expertise must be developed by PCPs (i.e., physicians, nurse practitioners, physicians' assistants) to proficiently evaluate, diagnose, and manage most persons with typical and non-complicated AD or ADRD. Dementia subspecialists, geriatricians, general neurologists and general psychiatrists are far too few in number to care for the majority of persons with later life disorders of cognition or behavior. Given that frontline providers are also held accountable for expertise in dozens of other common conditions, we recognize the importance of unbiased professional educational curricula to assist PCPs in maintaining currency and proficiency with this rapidly evolving field. Such curricula must address access barriers to timely and appropriate evaluation of patients with cognitive and behavioral disorders. Development of efficient linkages to specialty care sponsored by health systems will be critical to make expert consultation available where it is needed, and to facilitate access to specialized treatment protocols for appropriate patients. We hope that this guideline supports efforts to assist primary care and specialty providers in harnessing the resources necessary for high quality diagnostic evaluation and management of the millions of Americans with cognitive-behavioral impairment or dementia due to AD or ADRD.

4 | CONCLUSIONS

This guideline aims to empower all clinicians, regardless of specialty or practice setting, to collaborate in close alignment with patients and care partners to take a systematic patient-centered approach to the timely evaluation of cognitive or behavioral symptoms suggestive of AD or ADRD. The evaluation process may lead to an AD or ADRD diagnosis, or it may lead to opportunities to optimize and promote brain-healthy strategies and to treat comorbid medical conditions to mitigate risk of cognitive and functional decline, or to both.^{20,47,48} In all

cases, the evaluation process should lead to a diagnostic formulation that is communicated clearly and compassionately to the patient and care partner, along with a discussion of management and prognosis. It should also lead to a multipronged plan to address—through direct treatment, risk factor identification and reduction, educational and psychosocial support, and monitoring—the symptoms of concern that can affect quality of life, health status, and major life choices including current and future care needs and priorities, finances, and personal and public safety.

AUTHOR CONTRIBUTIONS

Alireza Atri and Bradford C. Dickerson had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: all authors. Acquisition, analysis, or interpretation of data: all authors. Drafting of the manuscript: Alireza Atri and Bradford C. Dickerson. Critical revision of the manuscript for important intellectual content: all authors. Administrative, technical, or material support: Alireza Atri, Bradford C. Dickerson, and Maria Carrillo. Supervision: Alireza Atri, Bradford C. Dickerson, and Maria Carrillo.

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Alzheimer's Association staff agreed with the co-chairs about the need for this guideline, contracted with Avalere and the Pacific Northwest Evidence-based Practice Center, worked with the co-chairs to select the expert panel members, and provided administrative support and oversight. The expert panel designed the approach to the review of the evidence; review and interpretation of the data; and preparation, review, and approval of the guideline and the comprehensive report.

CONFLICT OF INTEREST STATEMENT

Bradford C. Dickerson: consulting for Acadia, Alector, Arkuda, Biogen, Eisai, Med Learning Group, Quanterix; on DSMB for Lilly, Merck; royalties from Cambridge University Press, Elsevier, Oxford University Press, Up To Date. Alireza Atri: consulting for Acadia, AriBio, AZ Therapies, Biogen, Eisai, JOMDD, Lundbeck, Life Molecular Imaging, Merck, ONO, Prothena, Roche/Genentech, Novo Nordisk, Qynapse, Vaxxinity; royalties from Oxford University Press. Carolyn Clevenger: none. Jason Karlawish: on a DSMB for Linus Health. David Knopman: on a DSMB for DIAN TU. Pei-Jung Lin: consulting for Lilly. Mary Norman: none. Chiadi Onyike: consulting for Acadia Pharmaceuticals, Reata Pharmaceuticals, Otsuka Pharmaceutical, Eisai Pharmaceutical, Lykos Therapeutics, Zevra Therapeutics. Mary Sano: consulting for Eisai, NovoNordisk, Otsuka Lundbeck. Susan Scanland: employee of Dementia Connection, LLC; consulting for Axsome, BioXcel, Eisai, Genentech, Lundbeck, Otsuka. Maria Carrillo: employee of Alzheimer's Association. Author disclosures are available in the [supporting information](#).

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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