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PERSPECTIVE

The 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 specialty care

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Abstract

US clinical practice guidelines for the diagnostic evaluation of cognitive impairment due to Alzheimer's disease (AD) or a related dementia (ADRD) are two decades old. This evidence-based guideline was developed to empower all clinicians to implement a structured approach for evaluating a patient with symptoms that may represent clinical AD/ADRD. An expert workgroup conducted a review of 7374 publications (133 met inclusion criteria) and developed recommendations as steps in an evaluation process. This summary briefly reviews core recommendations and details special-

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ist recommendations 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 primary care recommendations. If clinicians use the recommendations in 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 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 specialty practice settings, forming key 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 primary care 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 AD 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, which in aggregate is a major public health burden.[1–3] Although some primary care providers (PCPs) are comfortable diagnosing and managing patients with dementia, many PCPs, hospitalists, and emergency room specialists express a preference and refer patients with cognitive symptoms to neurologists, geriatricians, or geriatric psychiatrists.[3] Evidence shows that timely diagnosis is associated with meaningful medical and psychosocial benefits[4–11] as well as reduced societal and health-care costs.[2,4,6,12] Barriers to timely diagnosis and disclosure of MCI or dementia due to AD/ADRD are multifactorial, but many could be mitigated by development and adoption of contemporary evidence-based clinical practice guidelines for the diagnostic evaluation of suspected MCI or dementia, incorporating current perspectives on the essential roles of biomarkers in specialty practice.

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), as summarized in the companion article focused on primary care.[13] 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

RESEARCH IN CONTEXT

1. **Systematic review**: Through a modified-Delphi approach and guideline-development process (7,374 publications were reviewed; 133 met inclusion criteria) an expert workgroup developed recommendations as steps in a patient-centered evaluation process.
2. **Interpretation**: This summary focuses on recommendations appropriate for a specialty 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.
3. **Future directions**: If clinicians use this guideline and healthcare systems provide adequate resources, outcomes should improve in most patients in most practice settings.

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.

Here, we briefly summarize the core elements of a high-quality patient-centered evaluation and disclosure process that are appropriate for primary care and any other practice setting (additional details on these elements are summarized in the companion article) and provide specific information on the recommendations aimed toward specialists and dementia subspecialists.

2 | METHODS

The methods used in the DETeCD-ADRD CPG workgroup process are described in the companion article focused on primary care and supplementary material (see supporting information Material). The first 11 recommendations are described in detail in the companion article and summarized very briefly here. Recommendations 12–19 focus on steps in the process typically performed by specialty and subspecialty practitioners and are detailed here (see Box 1 for complete recommendations).

2.1 | Framework of the DETeCD-ADRD guideline

As detailed in the companion article focused on primary care, 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). The second step is to characterize the patient's cognitive–behavioral syndrome, which sets prior probabilities for the likely underlying cause(s) (and potential contributing factors, conditions, and disorders) and plays a critical role in guiding diagnostic decision making. Finally, the third step is for the clinician to generate and narrow the differential diagnosis of the brain disease(s) or disorder(s) 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), medical conditions (e.g., sleep apnea), and factors (e.g., effects of medications or substance use) that may cause or contribute to cognitive or behavioral symptoms. 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 on brain-healthy behaviors in companion manuscript for primary care).[13,17]

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 are tailored to the individual patient's circumstances. The three steps of the diagnostic formulation may be relatively straightforward to determine by following a process of seven core elements and using the first tier of assessment and diagnostic tests in a primary care setting, or they may require additional consultation (e.g., neuropsychological evaluation) and tiers of assessments and tests in the primary care, specialty, or dementia subspecialty settings.

2.2 | DETeCD-ADRD core elements of diagnostic and disclosure process and recommendations: A brief summary

The first 11 recommendations, briefly summarized here, are detailed in the companion article. These recommendations follow a series of seven core elements as illustrated in Figure 1.

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. The DETeCD-ADRD CPG emphasized the critical importance—in most situations—of including both the patient and an informant or care partner in the diagnostic and disclosure process.

BOX 1: DETeCD-ADRD Recommendations

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

Rationale and considerations for the Implementation of Recommendations 1–12 are detailed in Atri et al.[13]

RECOMMENDATION 2: 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 in the goal-setting process for the evaluation. (Strength of Recommendation A)

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)

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 (ADL and instrumental ADL [IADL]), (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)

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)

RECOMMENDATION 6: In a patient being evaluated for cognitive or behavioral symptoms, the primary 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)

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

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)

RECOMMENDATION 9: In a patient being evaluated for 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)

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)

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)

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)

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)

Rationale and Considerations for Implementation

- An evaluation by a specialist, optimally a dementia subspecialist, should be strongly considered if a patient presents with atypical cognitive abnormalities (e.g., aphasia, apraxia, agnosia), sensorimotor dysfunction (e.g., cortical visual abnormalities, movement or gait disorders), severe mood/behavioral disturbance (e.g., profound anxiety, depression, apathy, psychosis, or changes in personality), rapid progression, or fluctuating course (e.g., suggestive of potential superimposed delirium, LBD, or VCID).
- In patients with features of an atypical dementia syndrome, a dementia subspecialist may be needed to perform, integrate, and interpret history, complex findings on examination, and test results to determine the patient's cognitive functional status, cognitive–behavioral syndrome, and/or likely cause(s).

- Specialized neurobehavioral assessments and neurologic examinations are also used to monitor status, as well as to disentangle the adverse effects of prior or current treatments (e.g., parkinsonism, dyskinesias, cognitive side effects, sleep and mood changes) from the symptoms of disease(s) and comorbid conditions.

RECOMMENDATION 14: Neuropsychological evaluation is recommended when office-based cognitive assessment is not sufficiently informative. Specific examples are when a patient or caregiver reports 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 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)

Rationale

- When confident diagnosis requires data beyond that provided by routine testing (see Recommendations 8 and 9), the clinician should pursue a judicious and selective approach to ordering additional tests that are personalized to the patient's biopsychosocial and clinical profiles and consider the ordering clinician's proficiency and resources (e.g., via specialist input) to interpret test results.
- Few studies, reports, and consensus recommendations[14] are available to guide clinicians in choosing when and what testing should be performed for less common or rare conditions that can either contribute to or primarily cause cognitive and behavioral impairment.
- Tiered categorization to broadly stratify diagnostic tests based on epidemiological and risk/cost-benefit considerations is justified.

Considerations for Implementation

- Clinicians should use a deliberate, personalized, and judicious approach, as opposed to a broad-based ("shotgun") approach to diagnostic testing.
- When a more confident etiological diagnosis is needed, primary clinicians may consider ordering tests listed under Tier 2 (see Table 4) in some individuals as guided by their assessment of the patient's clinical characteristics and risk profile.
- Tests listed under Tiers 3 or 4 (see Table 4) should be considered highly selective in very few individuals, often with the guidance and interpretation of a specialist or dementia subspecialist; these may include testing for atypical, rare, or rapidly progressive conditions in the evaluation of some individuals with atypical clinical profiles when diagnostic uncertainty remains regarding etiology (see Recommendations 16–19).

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) positron emission tomography (PET) to improve diagnostic accuracy. (Strength of Recommendation B)

Rationale

- FDG PET is a measure of cellular glucose metabolism, which is usually reduced in patients with dementia due to AD, FTLD, LBD, and other neurodegenerative diseases with a topographic pattern consistent with the neurologic localization of symptoms.
- FDG PET is not a marker of a specific molecular pathology but rather is a marker of cellular dysfunction (considered to represent, at least in part, synaptic dysfunction). The topographic (spatial) pattern of hypometabolism is probabilistically associated with particular neurodegenerative pathologic changes with a predilection for those regions of the brain (the sensitivities and specificities for specific disease-related pathologic changes are reviewed below).
- In patients with an established cognitive–behavioral syndrome, whether in MCI or dementia stages, in whom there is concern for AD or another neurodegenerative disease as a potential etiology but when diagnostic uncertainly remains after a comprehensive workup including brain MRI, FDG PET may provide valuable information that influences diagnostic confidence.

Considerations for Implementation

- FDG PET may be considered and is more likely to be useful in cognitively or behaviorally impaired patients in whom the etiological diagnosis is equivocal, when there is only an intermediate level of diagnostic confidence, or when having very high confidence in the etiological diagnosis is needed. Those may include individuals at very early clinical stages (e.g., early MCI) or those with atypical clinical presentations or syndromes.
- In individuals with severe stage dementia with global impairments FDG PET is not helpful in determining etiological diagnosis and should be avoided as it is likely to show diffuse and global hypometabolism regardless of underlying cause(s).
- The interpretation of FDG PET images is not always straightforward, and like other biomarkers, the clinician should consider the pretest probability of potential diagnostic etiology (-ies); the age, clinical presentation, and risk profile of the patient; and the possibility of multiple pathologies when ordering and interpreting results.
- When FDG PET is not available, a single photon emission computed tomography (SPECT) scan may be considered.

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 cerebrospinal fluid (CSF) according to appropriate use criteria for analysis of amyloid beta (Aβ)42 and tau/phosphorylated tau (p-tau) profiles to evaluate for AD neuropathologic changes. (Strength of Recommendation B)

Rationale

- AD CSF biomarkers are sensitive and specific for the detection of the likely presence of Aβ neuritic plaques and hyperphosphorylated tau-related neurofibrillary tangles, the two core molecular features of AD pathologic change.
- In patients with MCI or dementia and an established cognitive–behavioral syndrome, in whom there is concern for AD as a potential etiology but when diagnostic uncertainty remains after a comprehensive workup, AD CSF biomarkers may provide valuable information that influences diagnostic confidence.
- In some patients with MCI, AD CSF biomarker results may provide helpful prognostic information.
- CSF biomarkers that are sensitive and specific for non-AD ADRD pathologic changes, such as primary tauopathies, TDP-43, and vascular-ischemic brain injury are not yet available in clinical practice. Alpha-synuclein biomarkers from CSF and skin for LBD are emerging and require further validation in diverse patient populations and practice settings.
- CSF biomarker results directly impact medical decision making regarding the use of disease-modifying therapies and is a sufficient test for establishing the presence of amyloid-beta pathology which must be confirmed prior to initiating treatment.

Considerations for Implementation

- AD CSF biomarkers are more likely to be useful in cognitively impaired patients in whom the etiological diagnosis is equivocal, when there is only an intermediate level of diagnostic confidence, or when having very high confidence in the etiological diagnosis is needed. Those may include individuals at very early clinical stages (e.g., early MCI) or with atypical clinical presentations.
- The interpretation of AD CSF biomarker measures is not always straightforward, and like other AD and ADRD biomarkers, requires the clinician to consider pretest probability, the age and clinical presentation and profile of the patient, the possibility of multiple pathologic processes, and the age-related increasing incidence of brain amyloid and tau pathology.
- AD CSF biomarkers are typically reserved for the dementia specialist practice setting and appropriate use criteria are available to guide obtaining CSF for analysis in suspected AD.
- Although it is always important to consider patient-specific risk factors, a lumbar puncture for the purposes of obtaining AD CSF biomarkers is generally considered to be a safe and well-tolerated procedure in the hands of an experienced clinician; and is commonly performed in dementia subspecialty settings in the United States and in many European countries as part of a diagnostic evaluation.

RECOMMENDATION 18: If diagnostic uncertainty still exists after obtaining structural imaging with or without FDG PET and/or CSF Aβ42 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)

Rationale

- Amyloid PET is sensitive and specific for the detection of the likely presence of Aβ neuritic plaques, one of the two core molecular features of AD pathologic change.
- In patients with an established cognitive–behavioral syndrome whether MCI or dementia, in whom there is concern for AD as a potential etiology but when diagnostic uncertainty remains after a comprehensive workup, amyloid PET may provide valuable information that influences diagnostic confidence and management.
- Amyloid PET is more likely to be useful in cognitively impaired patients in whom the etiological diagnosis is equivocal, when there is only an intermediate level of diagnostic confidence, or when having very high confidence in the etiological diagnosis is needed. Those may include individuals at very early clinical stages (e.g., early MCI) or with atypical clinical presentations.[15,16]

- Amyloid PET results directly impact medical decision making regarding the use of disease-modifying therapies and is a sufficient test for establishing the presence of amyloid-beta pathology which must be confirmed prior to initiating treatment.

Considerations for Implementation

- The interpretation of amyloid PET images is not always straightforward, and like other AD biomarkers, requires the clinician to consider pretest probability, the age and clinical presentation and profile of the patient, the possibility of multiple types of pathologies, and the age-related increasing incidence of brain amyloid pathology.
- Amyloid PET is typically reserved for the dementia subspecialist practice setting, and should only be ordered according to appropriate use criteria.

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)

Rationale

- Although uncommon, some patients with cognitive–behavioral syndromes due to AD or ADRD harbor genetic mutations that are deterministic and highly penetrant (i.e., known to predictably cause the pathophysiologic disease process with which they are associated with a very high likelihood).
- The identification of a deterministic genetic mutation that is known to be associated with AD or ADRD in a patient with a cognitive–behavioral syndrome increases confidence in the etiology—for example, in a patient suspected of having dementia due to AD or FTLD, the identification of a known disease-causing genetic mutation places the patient in a "definite" diagnostic category according to current diagnostic criteria.
- Deterministic genetic mutations associated with AD or ADRD usually are inherited with an autosomal dominant pattern, and often cause symptoms at a relatively young age (often but not always < 65).

Considerations for Implementation

- Guidelines on whom to test usually emphasize the presence of a pedigree (family history) consistent with an autosomal dominant inheritance pattern of dementia or a related condition, or a young patient with dementia. It may take substantial time and effort to collect and document the relevant information in the family history. The ascertainment of information necessary to document the patient's pedigree often benefits from the involvement of a genetic counselor.
- The decision to perform genetic testing should be made in partnership with the patient and family after appropriate education regarding the potential implications of such testing for the patient and blood relatives. This education and counseling process, ultimately leading to a decision regarding whether to perform genetic testing and the interpretation and disclosure of genetic test results requires specialized expertise and proficiency and should be done, when possible, with an experienced genetic counselor involved.
- Considerations regarding the potential clinical utility of evaluating probabilistic genetic risk variants, such as apolipoprotein E (*APOE*) genotype, are different from considerations regarding testing for deterministic genetic mutations.

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 AD or an ADRD (Recommendation 1). 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 the patient's capacity (understanding and appreciation) to engage in the goal-setting process for the evaluation (Recommendation 2). Such a relationship provides a foundation 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. 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. A separate article in this special issue summarizes the challenges of and provides guidance on the assessment of capacity in patients with mild cognitive impairment.[23]

In most cases, the goal of the evaluation process is to determine whether the patient has an identifiable brain disease affecting cognition or behavior, formulated in three steps (Recommendation 3). For any given individual, differentiation of what is cognitively behaviorally impaired versus an unimpaired state requires clinical judgment.[24–30] The first step of the diagnostic formulation is to determine whether a person has subjective cognitive decline,[31] MCI,[25] mild behavioral impairment,[32,33] or dementia[34] (or mild vs. major neurocognitive disorder in Diagnostic and Statistical Manual of Mental Disorders Fifth Edition terminology; see Table 1 of companion article for primary care). This first-level diagnosis 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

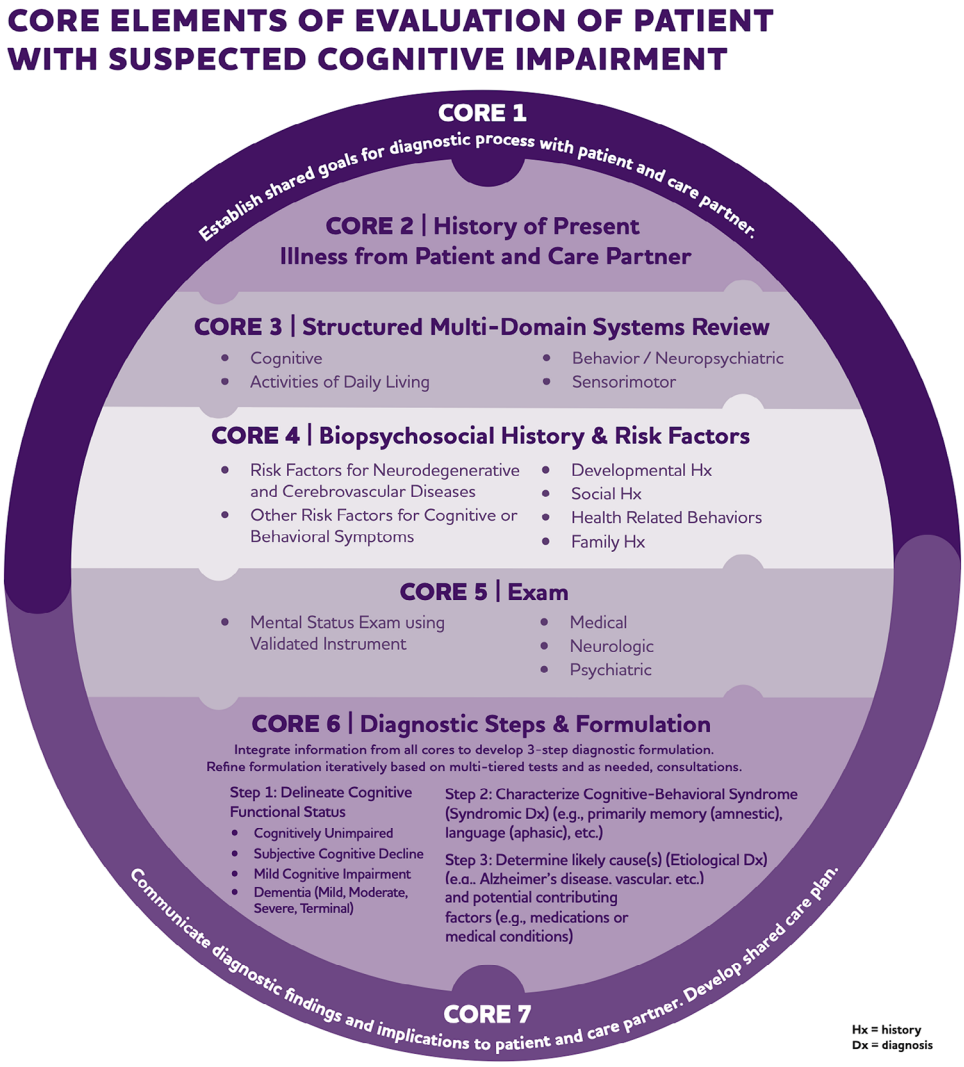

FIGURE 1 For patients who may be exhibiting symptoms and/or signs of cognitive impairment due to AD or ADRD, the three steps of the diagnostic formulation may be accomplished by following a process of seven core elements. AD, Alzheimer's disease; ADRD, Alzheimer's disease and related dementias; Dx, diagnosis,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

behavior).[24–26,34] 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 relationship dynamics, developmental history, and medical and psychiatric comorbidities. This first step is critical for the clinician to be able to evaluate whether the patient needs or may need specific support, including a surrogate decision maker(s).

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, others may not fit so clearly into these syndromic categories (Tables 1–3). In these cases, additional information or consultation with a subspecialist may be useful. An evaluation by a neuropsychologist proficient in the assessment of AD/ADRD is often invaluable in delineating the cognitive–behavioral syndrome in a patient with a complex presentation and can also be very helpful to suggest the 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, if one is identifiable (Tables 1–3). While a patient's 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 syndrome[35–38] (Table 1). A variety of risk and resilience factors (Recommendation 6) 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 2 and 3), although the field is evolving toward a forward-thinking framework of separation of clinical

TABLE 1 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 multidomain)	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 multidomain 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, and 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 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
PSP 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: AD (referring specifically to the neuropathologic changes); FTLD (referring specifically to the neuropathologic changes; many neuropathologists consider FTLD-tau to include the neuropathologic entities of Pick's disease, PSP, and CBD); LBD (referring specifically to the neuropathologic changes); PART; VCID; LATE. Note that Korsakoff's Syndrome, limbic encephalitis, anoxic brain injury, traumatic brain injury, temporal lobe epilepsy, and 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 amyotrophic lateral sclerosis, Creutzfeldt–Jakob disease, multiple system atrophy, etc. 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.[35,38]
Abbreviations: AD, Alzheimer's disease; bvFTD, behavioral variant frontotemporal dementia; CBD, corticobasal degeneration; FTLD, frontotemporal lobar degeneration; LATE, limbic-predominant age-related TDP-43 encephalopathy; LBD, Lewy body disease; PART, primary age-related tauopathy; PDD, Parkinson's disease dementia; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy, REM, rapid eye movement; VCID, vascular contributions to cognitive impairment and dementia.

syndrome from likely neuropathologic changes informed by core and ancillary biomarkers.[28,39,40,161]

The 2024 revision of the diagnostic and staging criteria for AD (Table 2C)—which has generated criticisms[41,43,44]—focuses on core and ancillary biomarkers and is meant to serve as a bridge between research and clinical care.[39] Commentary on the criteria by two authors clarifies that biomarker testing should be done in symptomatic patients for whom AD is in the differential diagnoses and when establishing a biological diagnosis would be beneficial to the patient. Such a scenario includes (but is not limited to) consideration of anti-amyloid immunotherapies or symptomatic treatments.[47] The authors also clarify that they do not currently recommend AD biomarker testing for clinical purposes in individuals without any cognitive symptoms, primarily because there are not yet any approved interventions for preclinical AD.[47] 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.[48]

TABLE 2A National Institute on Aging–Alzheimer's Association core diagnostic criteria for probable AD dementia.[34]

Probable AD dementia
A diagnosis of probable AD dementia can be made when the patient: 1. Meets criteria for dementia (see Table 1 in companion article for primary care), 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. Amnestic 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-amnestic 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 PPA or non-fluent/agrammatic variant PPA; or e. Evidence for another concurrent, active neurological disease, or non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Note: Biomarker evidence may increase the certainty that the basis of the clinical dementia syndrome is the AD pathophysiological process. If biomarkers of both amyloid beta (PET or CSF) and neuronal injury (structural brain MRI, FDG PET, CSF tau) are present, the 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, the likelihood is intermediate.
Abbreviations: AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; PPA, primary progressive aphasia.

TABLE 2B National Institute on Aging–Alzheimer's Association diagnostic criteria for MCI due to AD.[25]

Clinical criteria for MCI 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 the 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 Aβ (PET or CSF) and neuronal injury (structural brain MRI, FDG PET, CSF tau) are present 2. Intermediate: A biomarker of either Aβ or neuronal injury is present and the other is untested, or one is positive and one is negative 3. Low: biomarkers of both Aβ and neuronal injury are absent

Abbreviations: Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography.

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. 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

TABLE 2C National Institute on Aging–Alzheimer's Association diagnostic criteria for AD.[39]*

Biomarker categorization

- Core AD biomarkers
  - Core 1: Aβ ("A": PET, CSF, plasma) and hyper-phosphorylated tau ("T_1": specific CSF or plasma tau species [p-tau 217, p-tau 181, p-tau 231])
  - Core 2: AD tau proteinopathy ("T_2": specific CSF or plasma tau species [p-tau 205, MTBR-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: Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; GFAP, glial fibrillary acidic protein; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; 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.[48]

TABLE 3 Diagnostic criteria for major forms of non-AD dementia (AD-related dementia).

Behavioral variant frontotemporal dementia	162
PPA[a]	163
Dementia with Lewy bodies/Parkinson's disease dementia	40,161,164
Vascular dementia/vascular cognitive impairment	165–167
LATE	42
PSP	168
Corticobasal degeneration	169
ALS-FTD	170
Huntington's disease	171,172
Creutzfeldt–Jacob disease	173

Abbreviations: AD, Alzheimer's disease; ALS-FTD, amyotrophic lateral sclerosis with frontotemporal dementia; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy.
[a]PPA can be an atypical presentation of AD, especially when characteristics are consistent with the logopenic variant of PPA.

separate article in this special issue provides detailed descriptions of instruments that can be used to facilitate these assessments.[174]

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.[45,46] Older persons with AD neuropathological changes often have concomitant changes related to vascular disease—including macroinfarcts, microinfarcts, atherosclerosis, arteriosclerosis, cerebral amyloid angiopathy—as well as other neurodegenerative diseases (e.g., LBD, TDP-43 proteinopathy, hippocampal sclerosis, argyrophilic grain disease).[36,46,49,50] 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. It is always important to keep in mind the potential contribution of a primary psychiatric disorder, recognizing that it may be difficult to differentiate from a symptom of an emerging neurodegenerative disease (see Box 3 on psychiatric disorders and dementia in companion manuscript for primary care).[13] Therefore, it is not uncommon, in older individuals and those with multiple comorbidities, that a cognitive–behavioral syndrome has a "mixed etiology," which when causing dementia-level impairment is called mixed etiology dementia.[49,51,52] Patients with mixed etiology dementia are more likely to present with atypical or non-amnestic 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.

2.2.3 | Core element six: Iterative diagnostic formulation and multitiered diagnostic testing

By following recommendations to this sixth core element in the evaluation process, the clinician should be able to integrate 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 about whether consultative input should be obtained (i.e., from a neuropsychologist, specialist physician, or dementia subspecialist).

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 Figure 2). 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 is also a cornerstone of other national, international, and intersocietal guidelines.[37,53–55]

Basic (Tier 1) diagnostic tests, including a cognitive laboratory panel (Recommendation 8) and structural neuroimaging (Recommendation 9) 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 some 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.[18]

Several readily treatable common comorbid conditions, including infections, dehydration, hypothyroidism, and vitamin B_{12} deficiency, may contribute to cognitive or behavioral symptoms and may cause subacute or acute clinical decompensation (see Box 4 on delirium in companion article for primary care).[13] 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 description of first-line routine laboratory testing as "labs for reversible causes of dementia" can be misleading; the conditions being evaluated are rarely the primary etiology of a gradually progressive cognitive–behavioral syndrome but may exacerbate cognitive or behavioral impairment in individuals with underlying neurodegenerative diseases and related disorders (e.g., VCID).[56] The DETeCD-ADRD Workgroup aimed to provide practical guidance for Tier 1 "cognitive lab panel" testing (Table 4) 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. 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,[10,11,14,37,53–55,57–60] and limited evidence.[57]

Brain MRI without contrast, when available and not contraindicated, is appropriate for evaluation of AD/ADRD.[11,37,62] 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).[57,62–64] In contemporary practice, structural brain images may reveal atrophy patterns probabilistically suggestive of a particular neurodegenerative disease diagnosis;[63–65] in some practice settings, quantitative volumetric measures may be obtained from MRI scans. Atrophy patterns seen on brain MRI predict neuropathological findings with a high level of accuracy,[66] although not as high as molecular biomarkers. 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.[65,67] When a proficient clinician's hypothesis is that the patient's cognitive impairment is likely due to AD 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 and 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,[68] and is a critical element of appropriate patient selection and monitoring for amyloid-related imaging abnormalities (ARIA) in patients who receive disease-modifying therapies.[18,69]

2.2.4 | 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 follow-up care. These require that the patient and care partner's understanding and appreciation of the illness—together with the clinician's judgment—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 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 the principles of the diagnostic disclosure process as well as when immediate or full diagnostic disclosure may not be recommended or feasible.[70]

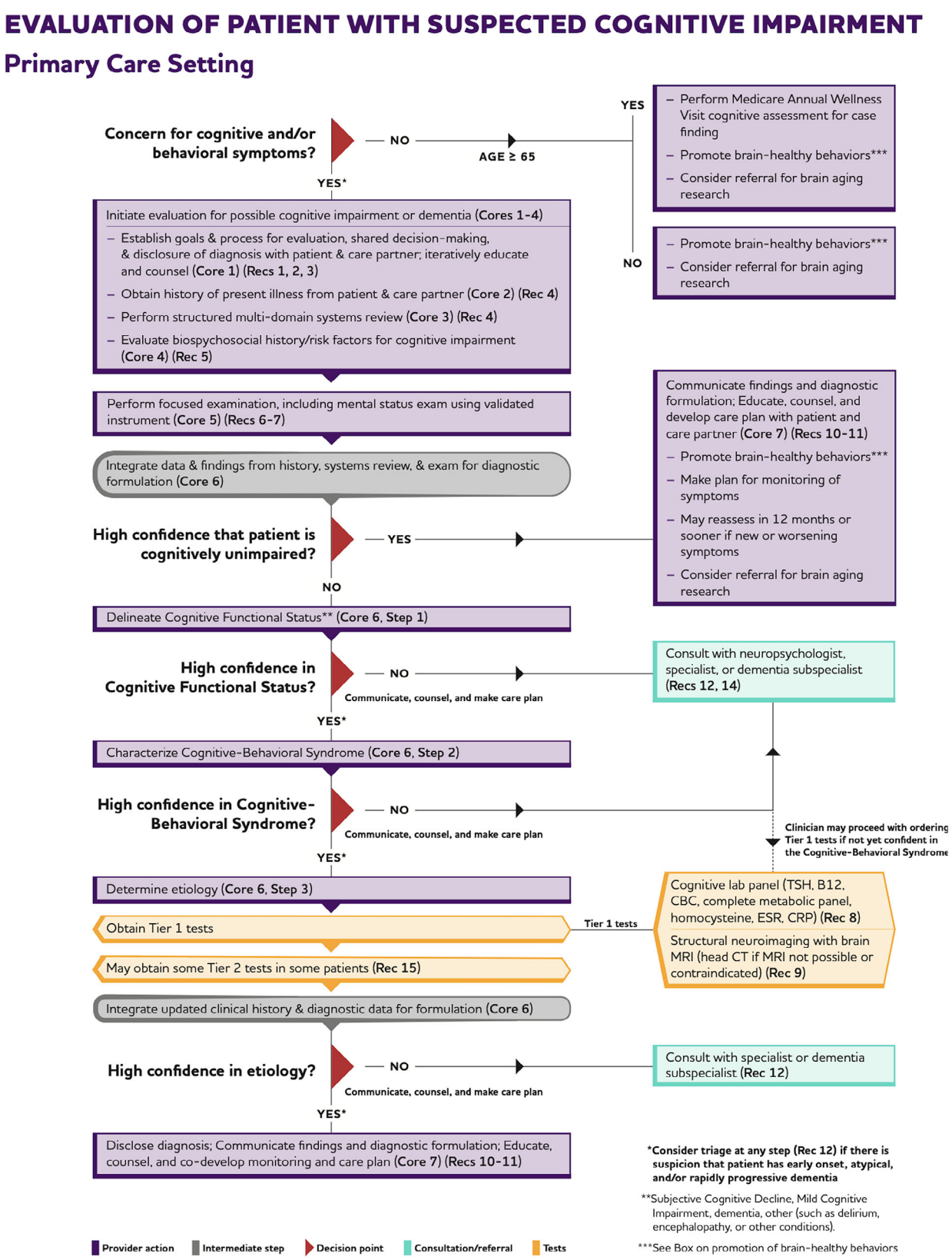

FIGURE 2 In a primary care setting, this diagram shows the implementation of the seven core elements of the diagnostic evaluation process, illustrating how each clinical practice recommendation fits into the typical workflow, using the first tier of assessments and diagnostic tests. Ultimately, the goal 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.

TABLE 4 Multiple tiers of tests to be considered in the evaluation of patients with or suspected of having cognitive impairment.

Tier	Type	What	Who/how	Why
1	Serum "cognitive lab panel" (Rec. 8)	TSH, vitamin B12, homocysteine, CBC with differential, complete metabolic panel (including calcium, magnesium, and 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	Serum	ANA, HgbA1c, lipid profile, folate, ammonia[d], lead, Lyme antibody, RPR, HIV, SPEP, MMA, PT, PTT	Who: Obtain in some individuals based on clinical features (clinical risk profile from history, exam, or lab/studies; other medical comorbidities) How: Obtain one or a few tests in this tier depending on the targeted clinical question	Some Tier 2–4 tests can be obtained in some individuals based on clinical characteristics (Rec. 15)
	Imaging	Chest plain film/x-ray[d]		
	Urine	Urinalysis[d], urine culture[d]		
	Other	sleep study: for obstructive sleep apnea or REM sleep disorder (LBD)		
3	Serum	TPO, antithyroglobulin antibodies (TGA), FTA-ABS, ACE, ANCA, viral antibody studies (hepatitis B/C, EBV, CMV)	Who: Obtain in fewer individuals including those with atypical clinical profiles or rapid progression or in whom specific molecular diagnosis is desired, such as for therapeutic decision-making purposes How: Obtain one or more tests in this tier to evaluate a patient for a specific condition	Most Tier 3 and 4 tests should be done by or in consultation with a specialist/subspecialist TPO & TGA to assess for Hashimoto's Encephalopathy/SREAT **Assessment of possible early age-of-onset or atypical AD or ADRD may include a brain FDG PET (or SPECT) scan* (Rec. 16). *When AD is a possibility but the diagnosis is uncertain consider the analysis of specific in vivo AD biomarkers such as the CSF AD panel* (Rec. 17). *Consider brain amyloid PET scan when AD is a consideration but diagnosis is uncertain* (Rec. 18). Diagnostic confirmation with molecular biomarkers is required for anti-amyloid therapies (see Box 2)
	Urine	UPEP, Bence–Jones proteins		
	CSF	*AD CSF biomarker panel ($A\beta_{42}$, tau, phospho-tau)* (Rec. 17)*; consider obtaining cell count, glucose, total protein, and other CSF tests depending on the condition being considered Lyme PCR; viral PCRs and cultures, VDRL, T. pallidum PCR		
	Imaging	MR or CT angiogram of head and neck, carotid ultrasound, Brain MRI with gadolinium or head CT with contrast, Chest films *Brain FDG PET (or SPECT) scan** (Rec. 16) *Brain amyloid PET scan** (Rec. 18)		
	Other	EEG, dopamine transport SPECT or PET imaging (altered in LBD, PDD > PSP, and CBD), cardiac scintigraphy (altered in LBD)		

(Continues)

TABLE 4 (Continued)

Tier	Type	What	Who/how	Why
4	Serum	Paraneoplastic antibody panel, autoimmune antibody panel, anti-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 ref. [175] 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, NSE, T. whipplei PCR, paraneoplastic antibody panel, autoimmune antibody panel, anti-VGKC antibody, cytology, flow cytometry, other stains and cultures for infectious agents (bacterial, fungal, AFB)		
	Imaging	CT of chest, abdomen, and 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	Aβ, hyperphosphorylated tau, NfL, GFAP, etc.[159]	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; reimbursement is not yet available. Tau PET is FDA approved but not yet widely available or reimbursed.[16] This is a rapidly evolving field. *See* Box 2 and AA Revised Criteria for diagnosis and staging of AD[39] for more information and caveats. See also 2024 biological diagnosis of Lewy body diseases.[40,161]
	CSF, skin	alpha-synuclein[176,177]	How: One or more tests in this tier would be obtained if a specific etiology is being considered	
	Imaging	Brain tau PET scan[16]		

Note: Tier 1 tests involve a serum 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 selectively 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.[21]

Abbreviations: AA, Alzheimer's Association; Aβ, amyloid beta; ACE, angiotensin converting enzyme; AD, Alzheimer's disease; ADRD, Alzheimer's disease and related disorders; AFB, acid-fast bacillus; ANA, antinuclear antibody; CBC, complete blood count; CBD, corticobasal degeneration; CMV, cytomegalovirus; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computed tomography; EBV, Epstein–Barr virus; EEG, electroencephalogram; FDA, US Food and Drug Administration; FTA-ABS, fluorescent treponemal antibody absorption; FTLD, frontotemporal lobar degeneration; GFAP, glial fibrillary acidic protein; HIV, human immunodeficiency virus; LBD, Lewy body disease; MMA, methylmalonic acid; NfL, neurofilament light chain; NSE, neuron-specific enolase; 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; TGA, thyroglobulin antibodies; TPO, thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone; VGKC, voltage-gated potassium channel.

[d]Delirium work-up first tier (see Box 4 on delirium in companion primary care article)—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.

2.3 | DETeCD-ADRD recommendations for elements of the diagnostic evaluation process typically performed in specialty or subspecialty care settings

In addition to the core elements of the diagnostic evaluation process and their implementation in the first 11 recommendations, which should be considered in all settings, we provide additional recommendations applicable to the specialist settings. Recommendations 12 and 13 pertain to whom to refer to a specialist and what would usually be expected from a specialist's evaluation. Recommendation 14 summarizes guidance regarding neuropsychological referral and assessment. Recommendations 15 through 19 provide a framework for the hierarchical use of Tier 2 to 4 diagnostic tests (specialized labs, imaging, genetic testing) and consultations, if needed, to determine the cause(s) of (and potential contributors to) the cognitive–behavioral syndrome with a high level of confidence. Recommendations 12 through 19 apply to fewer and fewer patients who are going through this process; the strength of these recommendations applies to this smaller group of patients who are deemed to need more specialized evaluation.

2.4 | Which patients might be considered for a referral to a specialist?

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. An evaluation by a specialist or a dementia subspecialist should be strongly considered if a patient presents with atypical cognitive abnormalities (e.g., aphasia, apraxia, agnosia), sensorimotor dysfunction (e.g., cortical visual abnormalities, movement or gait disorders), accompanying mood/behavioral disturbance (e.g., profound anxiety, depression, apathy, psychosis, or changes in personality), rapid progression, or fluctuating course (e.g. suggestive of potential superimposed delirium, LBD, or VCID; Figure 3). Delirium and rapidly progressive dementia (usually defined as developing within weeks or months) are urgent medical problems requiring prompt examination, and in some cases, in-patient evaluation and management. 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 young-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.

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 may 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 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.[37,71–73]

Specialized neurobehavioral assessments and neurologic examinations are also used to monitor status, as well as to disentangle the adverse effects of prior or current treatments (e.g., parkinsonism, dyskinesias, cognitive side effects of medications, sleep and mood changes) from the symptoms of disease(s) and comorbid conditions.[74] Recommendation 12 provides additional detail on patient characteristics that warrant specialist referral.

2.5 | What constitutes a specialist or dementia subspecialist evaluation?

The dementia subspecialist uses a detailed behavioral neurologic or neuropsychiatric evaluation to identify key symptoms and signs of abnormal brain function, which may narrow or expand the differential diagnosis of the cognitive–behavioral syndrome and likely etiology, as detailed in Recommendation 13.[38,75,76] This requires methodical and nuanced consideration of the exam data in the context of the history and depends on the knowledge, experience, and advanced proficiency that subspecialist training and practice confers. The clinical formulation of the patient's cognitive–behavioral syndrome sets prior probabilities on likely etiology (-ies), and guides tiered selection of potential referrals and/or diagnostic tests—psychometric instruments, neuropsychological evaluation (Recommendation 14), CSF or other biofluid assays, brain imaging, and other studies (Recommendations 15–19)—and their interpretation.[35,37,38]

When neuropsychiatric or sensorimotor dysfunction is a presenting or prominent feature, specialist or dementia subspecialist involvement provides added value as these problems increase the morbidity, care burden, and resource use associated with a dementia, and are important drivers of costs including emergency department visits, hospital admission, length of stay, and transfer to residential care.[77–83] It is essential to capture these problems in a succinct clinical formulation and to incorporate them into an individualized care plan. For example, a patient whose cognitive functional status and syndromic formulation is mild dementia with amnesic and dysexecutive features would be expected to require a different plan of care than a patient whose formulation is partially similar (mild dementia with amnesic and dysexecutive features) but is also accompanied by anxiety, sleep disturbance, and extrapyramidal motor dysfunction.[61]

Management of patients with atypical or more complex cognitive–behavioral syndromes is often best handled through a comprehensive and interdisciplinary team approach that may include not only a dementia subspecialist(s) (see Figure 4) but also, potentially, a

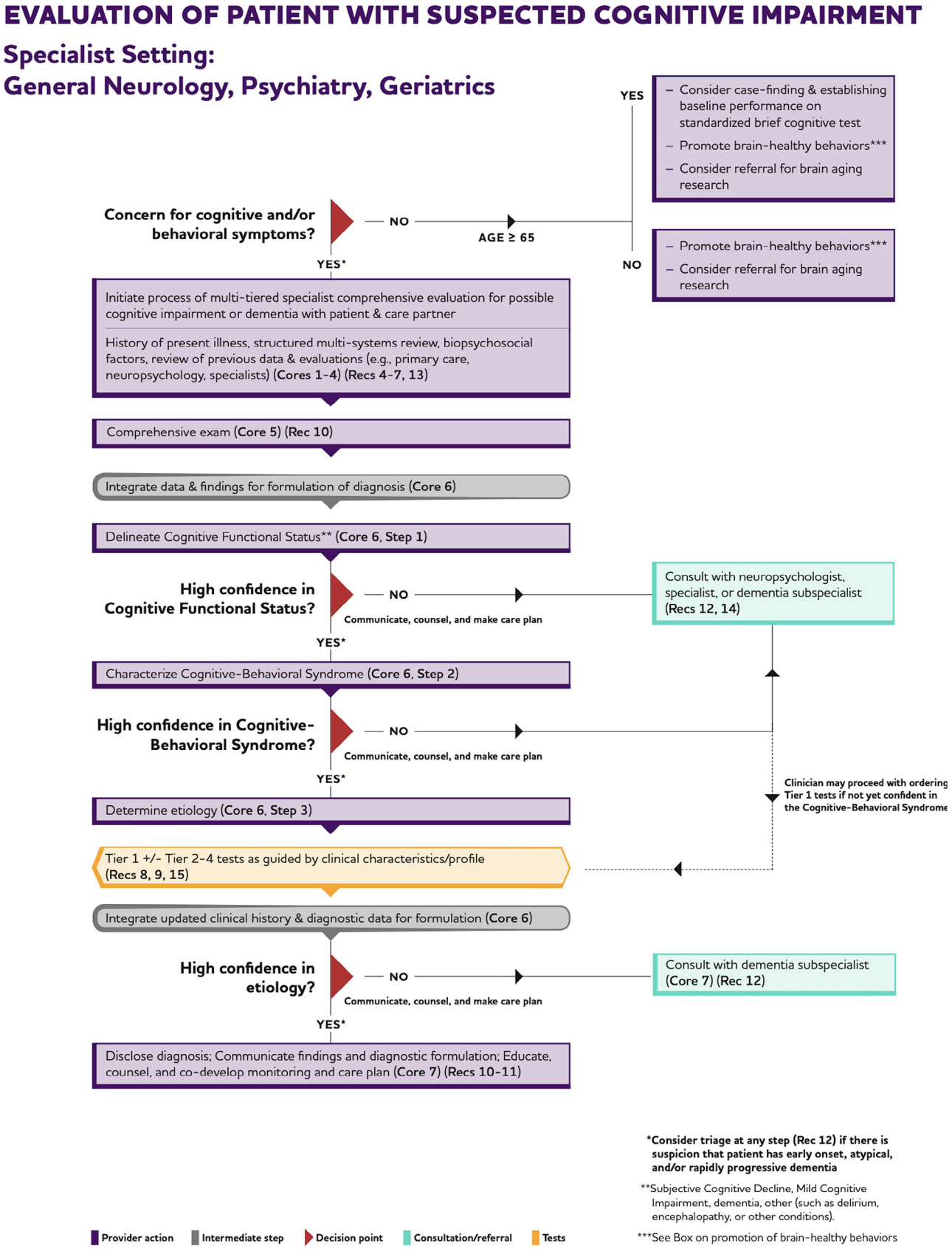

FIGURE 3 In a specialty care setting (usually general neurology, geriatric psychiatry, or geriatrics), this diagram briefly illustrates how each primary care clinical practice recommendation fits into the typical workflow (see Figure 2 for details). Additional detail is provided on how higher tier assessments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

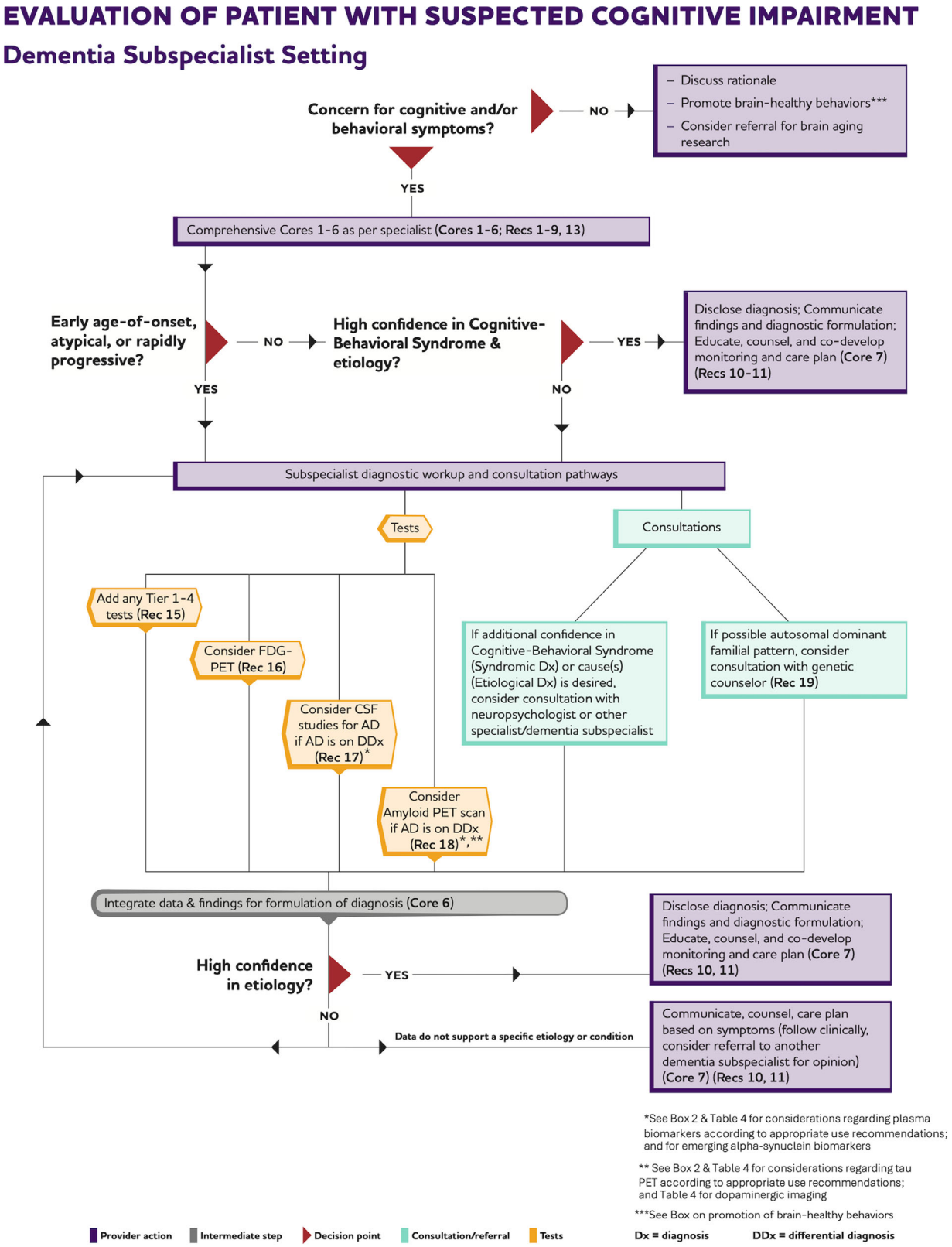

FIGURE 4 In a dementia subspecialty care setting (usually behavioral or geriatric neurology, geriatric or neuropsychiatry, or geriatrics), this diagram briefly illustrates how each primary care or specialty clinical practice recommendation fits into the typical workflow (see Figures 2 and 3 for details). 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.

neuropsychologist; a social worker, nurse, and/or case manager; a speech–language pathologist; a physical or occupational therapist; and/or a genetic counselor. The goal in every case is to devise a comprehensive and personalized clinical diagnostic formulation that then informs the implementation of a multidisciplinary care plan that appropriately uses behavioral, psychosocial, and environmental interventions, resources, and supports; pharmacologic management as warranted; and potentially rehabilitative or compensatory and supportive therapies to mitigate the impact of the illness on the patient–care partner dyad, and her/his family and community.

2.6 | When should referral for neuropsychological assessment be considered and what should be expected?

As detailed in Recommendation 14, a neuropsychological evaluation should be considered when a patient's circumstances or presentation is complex or when symptoms are mild or unusual.[84–90] If a patient has characteristics such as little or extensive education or if there are language or cultural considerations, neuropsychological evaluations may be required to achieve an accurate diagnosis.[88] Similarly, if patients have comorbidities whose symptoms may present as cognitive impairment—such as sensory or motor impairments (e.g., poor hearing or vision), movement disorder, stroke, brain injury, polypharmacy, substance abuse, depression, anxiety, post-traumatic stress disorder, learning disability, or attention deficit disorder—a neuropsychological evaluation should be strongly considered.[90,91]

The neuropsychological evaluation goes beyond the administration of psychometric cognitive tests: it involves the interpretation of a history from the patient and an informant augmented with symptom questionnaires and integrated with the patient's performance on norm-based cognitive and behavioral testing to develop a specialized diagnostic formulation that can delineate cognitive functional status, characterize the cognitive–behavioral syndrome, and suggest a differential diagnosis of likely cause(s). The evaluation can also provide recommendations for potential further studies and a care plan that considers a patient-centered profile of strengths and limitations, as well as opportunities and threats to the quality of life, health, and well-being of the patient and others. The neuropsychological evaluation may detect very mild but clinically important cognitive impairment which a mental status examination using brief validated cognitive tests—such as those done in most office examinations—may not capture. The report from a neuropsychological evaluation should include a formulation of overall cognitive functional status, cognitive–behavioral syndrome, and likely etiology as well as patient-centered recommendations for further studies, if warranted, and a comprehensive care plan for the patient including caregiver and environmental support and safety. A separate article in this special issue provides additional detail about the role of neuropsychological assessment in this patient population.[92]

2.7 | What additional diagnostic testing might a specialist or dementia subspecialist consider?

Beyond AD and ADRD, the list of conditions or diseases that can contribute to or cause cognitive or behavioral impairment and dementia syndromes is extensive, and the clinical approach to differential diagnosis and testing for less common syndromes is complex and often requires dementia subspecialist assessment.[37,71–73] The high strength assigned to Recommendation 15 about tiered specialized testing was motivated by the workgroup's consensus, consistent with other international guidelines and practice parameters,[10,14,37,53,54,57–59,93] that a shotgun approach to dementia diagnostic testing is wasteful and potentially harmful and that while many patients can be confidently diagnosed using a thorough clinical evaluation and Tier 1 diagnostic tests,[14,56] some patients require more specialized diagnostic and biomarker testing.[37]

Less widely available diagnostic tests and tests for less common comorbidities or conditions associated with dementia were classified into Tiers 2 to 4 (Table 4). Individual circumstances will lead clinicians to pursue a judicious approach to ordering these additional tests in some individuals depending on the complexity of the patient, the proficiency of the clinician, the availability of resources, and the desired level of diagnostic certainty.

Tests listed in Tier 2 are reasonable to obtain in some patients when there is suspicion for one of these etiologies based on clinical characteristics, risk profile, or the results of other lab tests or diagnostic studies. Tests listed under Tiers 3 and 4 are warranted only under special circumstances and include tests typically performed by a specialist or dementia subspecialist when diagnostic uncertainty remains regarding the etiology of cognitive impairment, including when there may be atypical or rare or rapidly progressive conditions. Tests listed under 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.[19–22]

In the following sections, we focus on FDG PET, CSF analyses for amyloid and tau, and amyloid PET. These three types of tests, as well as newer fluid and imaging biomarkers, can provide invaluable and, in some cases, highly accurate data that often helps increase confidence in the etiology of the cognitive–behavioral syndrome—and in some cases may help assess the severity of the disease. These three modalities were vetted by the workgroup for use in the diagnosis of AD (and in the case of FDG PET for ADRD). At the time the guideline was finalized, the strength of recommendation for these three biomarkers was lower than for the other recommendations. New evidence and greater accessibility in the context of disease-modifying therapies will require a reconsideration of the strength of these recommendations. The workgroup fully expects that fluid and imaging biomarker testing for suspected neurodegenerative diseases in the context of cognitive–behavioral impairment and dementia will play a much larger role in the next few years as AD and ADRD diagnostics and therapeutics advance in all clinical settings.

2.8 | When should FDG PET imaging be considered?

FDG PET is a measure of cellular glucose metabolism, which is usually reduced with particular patterns in patients with dementia due to AD, FTLD, LBD, and other neurodegenerative diseases, indicating synaptic dysfunction.[94] As detailed in Recommendation 16, FDG PET may be considered in cognitively or behaviorally impaired patients in whom the etiological diagnosis is equivocal, when there is only an intermediate level of diagnostic confidence, or when having very high confidence in the etiological diagnosis is needed. Those may include individuals at very early clinical stages (e.g., early MCI) or those with atypical clinical presentations or syndromes. The interpretation of FDG PET images requires proficiency and clinical-radiographic correlation; it is not always straightforward, and like other biomarkers, should incorporate pretest probability based on the clinical presentation and risk profile of the patient, and the possibility of multiple pathologies.

In 2004, CMS approved reimbursement of FDG PET for the purposes of differential diagnosis of AD versus FTLD. For differentiating AD versus FTLD, autopsy studies have shown that FDG PET has 80% to 99% sensitivity, 63% to 98% specificity, and 87% to 89.2% accuracy.[95] For AD versus LBD, FDG PET has 70% to 92% sensitivity, 74% to 100% specificity, and 72% to 96% accuracy.[95] The preponderance of high-level evidence and consensus recommendations indicate that FDG PET adds value to the diagnostic workup of patients with MCI or dementia suspected of being due to neurodegenerative disease.[11,95]

In symptomatic patients with AD (who are known based on biomarkers to have elevated brain amyloid and tau), the topography and magnitude of FDG PET abnormalities closely parallels the distribution and amount of tau pathology as measured by tau PET and atrophy as measured by MRI.[96] FDG PET provides a topographic view of the extent of AD-related neurodegenerative pathology that is useful for diagnosis and may also be useful for staging or prognosis. In addition, unlike the CSF or amyloid PET, FDG PET also offers the prospect of support for non-AD "mimics" such as hippocampal sclerosis[97] or TDP-43 proteinopathy.[42,94,98] On the other hand, amyloid PET and CSF amyloid/tau ratios (see next two sections) offer greater specificity than FDG PET for the biology of AD. Thus, FDG PET and CSF amyloid/tau ratios provide complementary information in some cases that increases confidence in diagnosis and prognosis.[37,99]

Despite its value, FDG PET continues to face challenges in being used in the diagnostic evaluation of patients suspected of having AD/ADRD. Clinicians and their nuclear medicine colleagues need to be familiar with its utility and have access to a facility in which high-quality PET imaging, reporting, and interpretation are performed. In addition, private insurance reimbursement for FDG PET in the diagnostic evaluation of dementia or cognitive impairment is inconsistent. Some insurance companies erroneously classify FDG PET as "experimental" in the evaluation of individuals suspected of having dementia, but that is simply incorrect: the evidence base to strongly support the clinical utility of FDG PET, when considered as part of an evaluation process of AD/ADRD under the special conditions of Recommendation 16, are clear and unequivocal.

2.9 | When should CSF analysis be considered?

In some patients with an established cognitive–behavioral syndrome thought to be due to AD, a dementia subspecialist may wish to obtain information about whether the patient has biomarker evidence of AD neuropathologic changes, the key elements of which are Aβ plaques and paired helical filament hyperphosphorylated tau neurofibrillary tangles. While blood-based biomarkers are clinically emerging and being validated in real-world and diverse populations and clinical settings, at present, the most accurate, widely validated, and accessible method for obtaining this information is through examination of CSF;[11,19–22] appropriate use criteria for clinical indications are available[100] and there are multiple FDA-approved CSF tests that are covered by CMS and private payors in the United States. Molecular amyloid PET imaging (see Recommendation 18), which can provide highly detailed information on the spatial distribution and burden of amyloid-plaque pathology, was recently approved by CMS for Medicare Administrative Contractors (MACs) for coverage outside a national coverage determination coverage-with-evidence development (NCD CED) framework (October 2023); however, it remains associated with much higher costs relative to CSF testing and is constrained by limited accessibility.

Because CSF is obtained via lumbar puncture, this procedure is usually performed by a specialist, often a neurologist. AD CSF biomarkers are useful in cognitively impaired patients in whom the etiological diagnosis is equivocal, where there is only an intermediate level of diagnostic confidence, or when having very high confidence in the etiological diagnosis is needed (such as in the consideration of a patient's candidacy for AD disease-modifying therapy). Those may include individuals at very early clinical stages (e.g., early MCI) or with atypical clinical presentations. CSF biomarker analysis in the evaluation of a patient with MCI or dementia should be performed after Tier 1 studies—structural MRI and laboratory tests tailored to the patient—have been obtained. In this context, Recommendation 17 is also consistent with other international clinical practice guidelines[37,53,54] and steering committee recommendations of the US Veterans Health Administration.[60]

In CSF, a decreased concentration of one form of Aβ (Aβ42) is a marker of amyloid neuritic plaques in the brain, while an increased concentration of total tau (t-tau) reflects injury to neurons, and an increased concentration of specific isoforms of hyperphosphorylated tau can not only reflect neurofibrillary tangles but also correlate highly as measures of amyloid plaques.[19,21,39,101] A ratio of t-tau to Aβ42, Aβ42 to Aβ40, or p-tau181 (or p-tau217) to Aβ42 are at present the best-performing markers of AD neuropathologic changes, and are more accurate than individual levels of these proteins alone.[39,102] These CSF biomarkers of AD have been validated against autopsy, and ratio values of CSF Aβ42 have been further validated against amyloid

PET imaging, with overall values for sensitivity and specificity of 85% to 90% and 80% to 84%, respectively.[100]

Vigorous efforts are underway worldwide to explore CSF for biomarkers of other neurodegenerative diseases—including specific markers of FTLD[103] and synucleinopathies,[104,176] and for biomarkers of neurodegeneration that may be less specific to these pathologic conditions such as neurofilament light chain (a marker of axonal neuronal injury) and neurogranin (a marker of synaptic dysfunction).[101,105,106] When the differential diagnosis is broader in the evaluation of a patient with rapidly progressive or atypical cognitive–behavioral or other neurologic symptoms, CSF may be a critically important test when there is a suspicion for infectious disease, immune-mediated encephalitis, prion disease (e.g., Creutzfeldt–Jacob disease), subacute cerebrovascular or demyelinating disease, or cancer presenting with primary neurologic symptoms (paraneoplastic syndrome).[102]

Both the lumbar puncture and the AD-related assay are reimbursed by Medicare (CMS) and usually also by other payors in the United States. The assays are often performed in centralized laboratories as send-outs from local labs. Global efforts are working to better standardize CSF amyloid and tau threshold values across laboratories as new assays are continually developed.[107,108] The interpretation of results in the clinical context, however, may be difficult, because a sizeable percentage of cognitively normal older adults harbor these pathologic markers of AD, with the percentage increasing with age over ≈ 60 (20%–40% of cognitively normal older adult patients have AD pathological changes[109–111]). That is, just because a patient with cognitive impairment has abnormal amyloid and tau biomarkers does not mean AD is the etiology primarily driving or even potentially substantially contributing to cognitive impairment. Furthermore, a substantial proportion of older adult patients with what appears clinically to be probable AD dementia are found to have multiple types of pathologic changes at autopsy, including other proteinopathies and evidence of VCID; emerging evidence suggests that co-pathologies may influence CSF AD biomarker findings.[50,112–115] And much of the research to date has not included ethnically and racially diverse participants.

Finally, when considering a lumbar puncture, it is always important to assess safety and communicate risks and burdens appropriately to patients.[116] The safety of lumbar puncture for CSF collection in the evaluation of patients suspected of having AD has been well established in many thousands of patients.[117–127] The most critical element of the safety and tolerability of this procedure is the experience and proficiency of the clinician, and knowledge of the potential contraindications to lumbar puncture, including use of anticoagulant medications, some blood clotting disorders, recent seizures, intracranial lesions associated with increased intracranial pressure, papilledema, and impaired consciousness.[116,128]

2.10 | When should amyloid PET be considered?

Three PET tracers have been validated and approved by the US FDA for the detection of cerebral amyloid plaques, with high sensitivity (89%–98%) and specificity (88%–100%) rates against an autopsy gold standard,[129,130] including florbetapir, flutametamol, and florbetaben. An Amyloid Imaging Taskforce (AIT) developed appropriate use criteria, recommending the use of amyloid PET to be appropriate in the evaluation of a patient with persistent or progressive MCI, especially because a negative amyloid PET scan in a patient with amnestic MCI would strongly weigh against AD as the etiology, and would open the differential diagnosis to other etiologies, including other neurodegenerative diseases, VCID, or other medical or psychiatric contributors.[15,16] Non-AD neurodegenerative diseases also may cause amnestic MCI including hippocampal sclerosis, argyrophilic grain disease,[131] primary age-related tauopathy[132,133] or TDP-43 proteinopathy/LATE.[42,134–136] A positive amyloid PET scan in a patient with MCI indicates that amyloid plaques are present but does not necessarily pinpoint the cause as AD (because cerebral amyloid plaques may coexist with other pathologies).

The AIT recommended that an amyloid PET scan be considered in a patient who meets appropriate use criteria after a comprehensive diagnostic evaluation is performed by a dementia expert, which is consistent with our recommendation that it be considered a higher tier test only after other tests are completed, interpreted, and an assessment that integrates their findings is performed. Moreover, the workgroup placed consideration of amyloid PET after FDG PET because FDG PET is useful for the evaluation of patients with a wide variety of diseases causing dementia and therefore applies to a broader segment of the population.[95] The workgroup did not require that FDG PET be obtained prior to considering amyloid PET; this decision depends on the individual clinical circumstances and the judgment of the specialist. Because the frequency of a positive amyloid PET scan in cognitively normal older adults increases substantially with age,[137] it is important to consider the possibility of multiple pathological changes, and potentially multiple etiologies, in older adults with cognitive impairment. Although amyloid PET has clearly been shown useful in the diagnostic evaluation of a patient suspected of having cognitive impairment due to AD, until October 2023, it was only accessible for coverage in the United States through the VA Healthcare System. However, with the advent of traditional approval of the amyloid plaque-lowering monoclonal antibody drug lecanemab in July 2023, and given the important role amyloid PET can play in the evaluation of patients' eligibility for disease-modifying therapies targeting amyloid-plaques, it was finally approved by CMS for reimbursement in October 2023 (see Box 2).

A new AIT updated the appropriate use criteria for amyloid PET and added criteria for tau PET.[16] Many of the principles concur with the original AIT. The use of amyloid PET is considered appropriate in the evaluation of a patient with clinically typical or atypical or young-onset MCI or dementia possibly due to AD, in patients with equivocal or inconclusive CSF biomarkers, to inform prognostication in MCI, or to determine eligibility for anti-amyloid therapy. The AIT viewed inappropriate uses of amyloid PET to include people who are cognitively unimpaired, patients with subjective cognitive decline who are not at elevated risk of AD based on age, *APOE* genotype, or family history; to determine dementia severity or track progression; or in people with MCI or dementia suspected of being due to LBD.

BOX 2: Diagnostic assessment in the era of amyloid plaque–lowering monoclonal antibody disease-modifying therapies

In June 2021, the US FDA granted accelerated approval for aducanumab (Aduhelm), an Aβ-directed plaque-lowering monoclonal antibody (mAb) indicated for the treatment of AD in patients with MCI or mild dementia ("early-stage AD"), but the CMS did not support payment for aducanumab, limiting its use.[138,139] Its development and sale has been discontinued. In January 2022, the FDA granted accelerated approval for lecanemab (Leqembi), another plaque-lowering mAb Aβ-directed antibody indicated for the treatment of early-stage AD.[18] 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 June 10, 2024, an FDA external advisory panel voted unanimously to recommend 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 in recent years. A separate article in this special issue discusses how the availability of these new treatments is transforming clinical diagnostic practice.[140]

The availability of these disease-modifying therapies may create a demand for timely detection, accurate diagnosis, and appropriate treatment options for early AD that could overwhelm an unprepared health-care system.[141] Providing treatment with amyloid plaque-lowering mAbs requires high proficiency and sufficient resources including close collaborations with comprehensive multidisciplinary teams.[18] 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 nurse practitioners, and specialists.[142–144]

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 evolves, 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. Finally, the use of structural brain imaging and genetics will change because brain MRI scans are required for monitoring for ARIA[1,18] and *APOE* genotype influences ARIA risk. 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.[19–22]

2.11 | When should genetic counseling and testing be considered?

Although uncommon, some patients with cognitive–behavioral syndromes due to AD or ADRD harbor pathogenic genetic mutations that are deterministic and highly penetrant (i.e., known to predictably cause the pathophysiologic disease process with which they are associated with a very high likelihood).[145] The identification of a deterministic genetic mutation known to be associated with AD or ADRD in a patient with a cognitive–behavioral syndrome increases confidence in the etiology—for example, in a patient suspected of having dementia due to AD or FTLD, the identification of a pathogenic genetic mutation places the patient in a "definite" diagnostic category according to current diagnostic criteria. Deterministic genetic mutations associated with AD or ADRD usually are inherited with an autosomal dominant pattern, and often cause symptoms at a relatively young age (often but not always in people younger than 65 years old).

Guidelines on whom to test usually emphasize the presence of a pedigree (family history) consistent with an autosomal dominant inheritance pattern of dementia or a related condition, or a young patient with dementia. It may take substantial time and effort to collect and document the relevant information in the family history. The decision to perform genetic testing should be made in partnership with the patient and family after appropriate education regarding the potential implications of such testing for the patient and blood relatives. This education and counseling process, ultimately leading to a decision regarding whether to perform genetic testing and the interpretation and disclosure of genetic test results requires specialized expertise and proficiency and should be done, when possible, with an experienced genetic counselor involved.

A growing array of probabilistic genetic risk factors for AD have been and are being identified, which should be considered separately from deterministic genetic abnormalities.[146] The strongest probabilistic genetic risk factor for AD is the *APOE* gene. Considerations regarding the potential clinical utility of evaluating probabilistic genetic risk variants, such as *APOE* genotype, are different from considerations regarding testing for deterministic genetic mutations. The workgroup agreed with a variety of guidelines and expert groups who have recommended against testing for this risk allele in the diagnostic evaluation of individual patients suspected of having MCI or dementia due to AD.[147–150,53,57,60] The workgroup appreciated the potential for *APOE* allele genetic testing to become useful in future clinical practice as part of composite diagnostic biomarker panels, but at the time of this writing the preponderance of current evidence does not support its broad clinical utility in diagnostic evaluation. Counseling and testing for *APOE* genotype play an important role in safety considerations, patient-centered risk-benefit discussions, and shared decision making involved in amyloid-modifying therapies (see Box 2). However, in those cases, *APOE* genotyping would be for therapeutic decision making rather than diagnostic evaluation purposes.[18,138,139]

3 | DISCUSSION

In specialty practice, diagnostic approaches for AD and ADRD are evolving rapidly and rest on the foundation of "a comprehensive diagnostic approach," which has not been previously described in a clinical practice guideline. As AD/ADRD therapeutic advances are made, diagnostic criteria are being refined and extended from research to clinical settings. The workgroup appreciates that imaging biomarkers, including tau PET (approved by the FDA in 2020[151]) and plasma biomarkers[21,102] as well as digital biomarkers (e.g., wearables to monitor aspects of physiology, behavior, or sensorimotor functions[152] and self-administered remote computerized cognitive and behavioral testing[153]) are emerging from the research arena and making their way into clinics now; and that they will be increasingly clinically validated, accessible, and implemented in the coming years to facilitate more timely, accurate, and effective detection, diagnosis, monitoring and progression of cognitive-behavioral impairment and AD/ADRD. Many in the field are particularly enthusiastic about plasma biomarkers,[154] which are demonstrating remarkable potential for detecting forms of Aβ, hyperphosphorylated tau, and other proteins in blood samples. Multiple separate articles in this special issue provide further discussion on a variety of topics related to blood-based biomarkers.[155–158] We welcome this progress and appreciate that as new tests and biomarkers become clinically available, they will need to be adequately assessed for utility and accessibility and appropriate use criteria will be needed to guide recommendations for their use in clinical practice settings. Appropriate use criteria for blood-based biomarkers were recently published, and do not recommend their use as stand-alone biomarkers in clinical practice, although cautious use in subspecialty clinics with confirmation using CSF or PET was encouraged.[159] 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 (see Box 5 on health equity and disparities in AD/ADRD in the companion article for primary care[13]) and real-world clinical settings, will likely lead to the need to update this CPG soon. With the rapidly evolving diagnostic and therapeutic landscape in AD, particularly surrounding anti-amyloid plaque-lowering mAbs (see Box 2) and increasingly accurate plasma biomarkers being assessed in real-world populations and clinics, we plan to revise this CPG to accommodate the elements of the diagnostic evaluation process necessary to determine whether and how patients, care partners, and society may benefit. Furthermore, ongoing studies of other specific etiologies of cognitive impairment and dementia, such as chronic traumatic encephalopathy (see Box 7 in companion article for primary care[13]) and limbic-predominant age-related TDP-43 encephalopathy (LATE; see article in this special issue on new diagnostic criteria for this entity[42]), are continuing to expand our understanding of the variety of disease processes that can lead to dementia.

Because there are far too few dementia subspecialists, geriatricians, neurologists, and psychiatrists to care for the majority of persons with age-related disorders of cognition or behavior, a sufficient level of expertise must be developed by primary care providers—the physicians, nurse practitioners, physicians' assistants, and others who first encounter and care for the majority of the patients with these illnesses—to proficiently evaluate, diagnose, and manage most persons with typical and non-complicated AD or ADRD. Close partnerships for co-evaluation and co-management between specialty and primary care are critical given the tremendous numbers of patients with these diseases. This starts with unbiased professional educational curricula to assist primary care providers and specialists in maintaining currency and proficiency in this rapidly evolving field. Such curricula must acknowledge the limitations of the health-care system that may contribute to challenges in the timely and appropriate evaluation of patients with cognitive and behavioral disorders and barriers to access to services for the care of persons with cognitive and behavioral disorders. The development of efficient linkages to specialists supported by health systems will be critical to making expert consultation and co-management available where it is needed. We hope that this guideline will empower and support efforts to assist primary care and specialty providers in harnessing the resources necessary for high-quality, efficient, and effective diagnostic evaluation and management of the millions of Americans with cognitive–behavioral impairment or dementia due to AD or ADRD.

4 | CONCLUSIONS

The purpose of this guideline is to empower all clinicians, regardless of specialty or practice setting, to work in close alignment with the patient and care partner to take a systematic, evidence-informed, and effective approach to the patient-centered evaluation and disclosure 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.[10,160] In all cases, the evaluation process should lead to a diagnostic formulation that is communicated clearly to the patient and care partner, along with a discussion of the 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 well-being, and major life choices including current and future care needs and priorities, finances, and personal and public safety.

AUTHOR CONTRIBUTIONS

Drs. Alireza Atri and Bradford C. Dickerson had full access to all of the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. *Concept and design*: Bradford C. Dickerson, Alireza Atri, Carolyn Clevenger, Jason Karlawish, David Knopman, Pei-Jung Lin, Mary Norman, Chiadi Onyike, Mary Sano, Susan Scanland, and Maria Carrillo. *Acquisition, analysis, or interpretation of data*: Bradford C. Dickerson, Alireza Atri, Carolyn Clevenger, Jason Karlawish, David Knopman, Pei-Jung Lin, Mary Norman, Chiadi Onyike, Mary Sano, Susan Scanland, and Maria Carrillo. *Drafting of the manuscript*: Alireza Atri, and Bradford C. Dickerson. *Critical revision of the manuscript for important intellectual content*: Bradford C. Dickerson, Alireza Atri, Carolyn Clevenger, Jason Karlawish, David Knopman, Pei-Jung Lin, Mary Norman, Chiadi Onyike, Mary Sano, Susan Scanland, and Maria Carrillo. *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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CONFLICT OF INTEREST STATEMENT

Dickerson: consulting for Acadia, Alector, Arkuda, Biogen, Eisai, Med Learning Group, Quanterix, DSMB: Lilly, Merck; royalties from Cambridge University Press, Elsevier, Oxford University Press, Up To Date. 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. Clevenger: none. Karlawish: DSMB for Linus Health. Knopman: DSMB for DIAN TU. Lin: consulting for Lilly. Norman: none. Onyike: consulting for Acadia Pharmaceuticals, Reata Pharmaceuticals, Otsuka Pharmaceutical, Eisai Pharmaceutical, Lykos Therapeutics, Zevra Therapeutics. Sano: consulting for Eisai, NovoNordisk, Otsuka Lundbeck. Scanland: employee of Dementia Connection, LLC; consulting for Axsome, BioXcel, Eisai, Genentech, Lundbeck, Otsuka. 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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