American College of Radiology
ACR Appropriateness Criteria®
Dementia

Variant 1:　　　　　**Adult. Mild cognitive impairment not meeting criteria for dementia. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
Amyloid PET/CT brain	Usually Appropriate	☢☢☢
CT head without IV contrast	Usually Appropriate	☢☢☢
FDG-PET/CT brain	Usually Appropriate	☢☢☢
MRI head without and with IV contrast	May Be Appropriate	O
Tau PET/CT brain	May Be Appropriate (Disagreement)	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢

Variant 2:　　　　　**Adult. Cognitive impairment with memory deficits. Suspect Alzheimer disease with typical clinical presentation. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
Amyloid PET/CT brain	Usually Appropriate	☢☢☢
FDG-PET/CT brain	Usually Appropriate	☢☢☢
MR spectroscopy head without IV contrast	May Be Appropriate	O
CT head without IV contrast	May Be Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	May Be Appropriate	☢☢☢
Tau PET/CT brain	May Be Appropriate	☢☢☢
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢

Variant 3: Adult. Cognitive impairment with memory deficits. Suspect Alzheimer disease with atypical clinical presentation. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
Amyloid PET/CT brain	Usually Appropriate	☢☢☢
CT head without IV contrast	Usually Appropriate	☢☢☢
FDG-PET/CT brain	Usually Appropriate	☢☢☢
Tau PET/CT brain	Usually Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	May Be Appropriate (Disagreement)	☢☢☢
SPECT or SPECT/CT brain striatal	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢

Variant 4: Adult. Known Alzheimer disease considering therapy with antiamyloid monoclonal antibodies. Pretreatment imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
Amyloid PET/CT brain	Usually Appropriate	☢☢☢
Tau PET/CT brain	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢

Variant 5:   **Adult. Known Alzheimer disease undergoing therapy with antiamyloid monoclonal antibodies. Posttreatment imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
Amyloid PET/CT brain	May Be Appropriate (Disagreement)	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
CT head without IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢
Tau PET/CT brain	Usually Not Appropriate	☢☢☢

Variant 6:   **Adult. Cognitive impairment with behavioral abnormalities or progressive aphasia. Suspect frontotemporal dementia. Initial imaging.**

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
CT head without IV contrast	Usually Appropriate	☢☢☢
FDG-PET/CT brain	Usually Appropriate	☢☢☢
Amyloid PET/CT brain	May Be Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢
Tau PET/CT brain	Usually Not Appropriate	☢☢☢

Variant 7:   Adult. Cognitive impairment with visual hallucinations or Parkinsonian symptoms. Suspect dementia with Lewy bodies. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
CT head without IV contrast	Usually Appropriate	☢☢☢
FDG-PET/CT brain	Usually Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Appropriate	☢☢☢
MRI head without and with IV contrast	May Be Appropriate (Disagreement)	O
SPECT or SPECT/CT brain perfusion	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
Amyloid PET/CT brain	Usually Not Appropriate	☢☢☢
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
Tau PET/CT brain	Usually Not Appropriate	☢☢☢

Variant 8:   Adult. Cognitive impairment with recent stroke or stepwise decline. Suspect vascular dementia. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
MRA head without IV contrast	May Be Appropriate	O
MRA neck without and with IV contrast	May Be Appropriate	O
MRA neck without IV contrast	May Be Appropriate	O
CT head without IV contrast	May Be Appropriate (Disagreement)	☢☢☢
CTA head and neck with IV contrast	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRA head without and with IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
Amyloid PET/CT brain	Usually Not Appropriate	☢☢☢
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢
Tau PET/CT brain	Usually Not Appropriate	☢☢☢

Variant 9:   Adult. Cognitive impairment with gait disturbance or urinary incontinence. Suspect normal pressure hydrocephalus. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without IV contrast	Usually Appropriate	O
CT head without IV contrast	Usually Appropriate	☢☢☢
DTPA cisternography	May Be Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
MRI head without and with IV contrast	Usually Not Appropriate	O
Amyloid PET/CT brain	Usually Not Appropriate	☢☢☢
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢
Tau PET/CT brain	Usually Not Appropriate	☢☢☢

Variant 10:   Adult. Rapidly progressive dementia. Initial imaging.

Procedure	Appropriateness Category	Relative Radiation Level
MRI head without and with IV contrast	Usually Appropriate	O
MRI head without IV contrast	Usually Appropriate	O
CT head without IV contrast	Usually Appropriate	☢☢☢
MR spectroscopy head without IV contrast	Usually Not Appropriate	O
MRI functional (fMRI) head without IV contrast	Usually Not Appropriate	O
Amyloid PET/CT brain	Usually Not Appropriate	☢☢☢
CT head with IV contrast	Usually Not Appropriate	☢☢☢
CT head without and with IV contrast	Usually Not Appropriate	☢☢☢
FDG-PET/CT brain	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain perfusion	Usually Not Appropriate	☢☢☢
SPECT or SPECT/CT brain striatal	Usually Not Appropriate	☢☢☢
Tau PET/CT brain	Usually Not Appropriate	☢☢☢

DEMENTIA

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Summary of Literature Review

Introduction/Background

Dementia is a common chronic syndrome in adults, affects up to 47 million people worldwide, and is expected to affect 131 million people by the year 2050 [1]. In the United States, the prevalence of dementia is 15% in people >68 years of age and constitutes the fifth leading cause of death in patients >65 years of age [1]. Complications of dementia can lead to great morbidity and mortality and can pose a diagnostic and management challenge for patients, their families, and clinicians. Dementia is defined by chronic and acquired significant impairment in a single domain or loss of two or more cognitive functions by brain disease or brain injury [1].

The core clinical criteria for all-cause dementia include cognitive or behavioral/neuropsychiatric symptoms—which interfere with the ability to function at work or usual activities, represent a decline from a previous level of function and performance, and are not explained by delirium or a major psychiatric disorder—and that cognitive impairment is detected and diagnosed through a combination of thorough clinical history and objective cognitive assessment. Furthermore, the cognitive or behavioral impairment must involve impairment of a minimum of two of the following domains: the ability to acquire and remember new information, reasoning and judgement, visuospatial abilities, impaired language, or changes in personality or behavior [2]. Patients with mild cognitive impairment (MCI) have impairment in one or several cognitive domains but of a mild degree, interfering minimally with daily living and functioning [2].

Multiple etiologies of dementia exist and are primarily caused by neurodegenerative diseases such as Alzheimer disease (AD), frontotemporal dementia (FTD), and dementia with Lewy bodies (DLB) as well as other diseases such as vascular dementia (VaD) and normal pressure hydrocephalus (NPH). Rapidly progressive dementias (RPD) can be the result of a wide variety of etiologies, to include prion diseases, atypical or rapid onset of neurodegenerative diseases, infectious/inflammatory conditions, neoplastic and paraneoplastic conditions, vascular conditions, and toxic/nutritional and metabolic disorders. Imaging plays a central role in the diagnosis of various dementias, and now also plays a key role in the selection and monitoring of patients with AD undergoing targeted antiamyloid monoclonal antibody (MAB) therapy.

Initial Imaging Definition

Initial imaging is defined as imaging at the beginning of the care episode for the medical condition defined by the variant. More than one procedure can be considered usually appropriate in the initial imaging evaluation when:

- There are procedures that are equivalent alternatives (ie, only one procedure will be ordered to provide the clinical information to effectively manage the patient's care)

OR

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- There are complementary procedures (ie, more than one procedure is ordered as a set or simultaneously where each procedure provides unique clinical information to effectively manage the patient's care).

Discussion of Procedures by Variant

Variant 1: Adult. Mild cognitive impairment not meeting criteria for dementia. Initial imaging.

MCI is defined by mildly impaired performance on neuropsychological cognitive tests but with little impact on the ability to perform instrumental activities of daily living [1]. As such, patients with MCI do not meet clinical criteria for dementia. It is important to note that although the term MCI generally refers to cognitive impairment due to AD, MCI can also be a symptomatic predementia phase of non-AD dementias. Two categories of MCI exist: amnestic and nonamnestic. The former is characterized by reduced memory performance, whereas the latter is characterized by reduced performance on nonmemory cognitive functions such as language. MCI can also be categorized as single or multiple domains depending on the number of cognitive areas affected. Some patients with MCI will progress to dementia, whereas others will remain stable. Some patients have fluctuating cognitive impairment, which has been seen in conditions such as DLB, cerebrovascular disease, psychiatric disorders, and medication use [1]. A clinical workup of MCI and dementia requires a thorough clinical history, physical examination, neuropsychiatric testing, laboratory analysis, and occasionally cerebrospinal fluid (CSF) testing. Neuroimaging is an adjunct to the clinical and laboratory workup.

The goal of imaging in patients with MCI not meeting criteria for dementia is to assess for potentially treatable structural brain abnormalities such as an intracranial mass or subdural hematomas, which may mimic MCI, and to identify imaging features that may indicate an increased risk of later developing a neurodegenerative disease such as AD or VaD. Identification of treatable structural brain abnormalities, which might mimic symptoms of MCI, will improve patient outcomes by allowing for timely intervention. Identification of imaging findings, which might increase risk of future development of a neurodegenerative disease, would provide prognostic information for clinicians, patients, and their family members and help initiate earlier neuropsychiatric and medical therapy.

Amyloid PET/CT Brain

Brain amyloid PET/CT has been shown to be positive in up to 60% of patients with MCI, and there is a correlation between amyloid burden and cognitive test performance in patients with MCI [3]. Patients with MCI and positive brain amyloid PET/CT are more likely to progress to AD than patients with MCI and negative amyloid PET/CT [4]. Patients with MCI and positive amyloid PET/CT have greater cognitive decline than those with negative amyloid PET/CT [5]. Patients with MCI related to AD pathology are less likely than patients with dementia to manifest typical brain atrophy patterns of AD and are more likely to benefit from undergoing brain amyloid PET/CT [6]. Brain amyloid PET/CT results in a change in diagnosis of suspected etiology of cognitive impairment in up to 25% to 44% of patients, increasing diagnostic confidence [7,8]. Amyloid PET/CT and fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-PET/CT are complementary and when combined have better accuracy at predicting conversion of patients with MCI to AD [9].

Appropriate Use Criteria (AUC) for amyloid PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10]. This AUC document states that amyloid PET/CT is appropriate in the following scenarios: patients with MCI or dementia who are <65 years of age and for whom AD is suspected, patients with MCI or dementia consistent with amnestic AD pathology with onset at ≥65 years of age, patients with MCI or dementia that could be consistent with AD but has atypical features, patients with MCI or dementia with equivocal or inconclusive results on CSF biomarkers, and to inform the prognosis of patients with MCI due to suspected AD pathology [10]. This AUC document determined that the use of amyloid PET/CT was rarely appropriate in patients with MCI or dementia and conclusive CSF biomarker results [10].

CT Head With IV Contrast

There is no relevant literature to support CT head with intravenous (IV) contrast for the use of initial imaging in patients with MCI not meeting criteria for dementia.

CT Head Without and With IV Contrast

There is no relevant literature to support CT head without and with IV contrast for the use of initial imaging in patients with MCI not meeting criteria for dementia.

CT Head Without IV Contrast
CT head without IV contrast can detect some abnormalities such as large intracranial masses, subdural hematomas, or other structural abnormalities, which may produce clinical symptoms of MCI. CT head can also demonstrate presence or absence of brain atrophy, which may provide information about future conversion to dementia.

FDG-PET/CT Brain
Patients with MCI who progress to dementia have been shown to have lower FDG uptake in the temporal and parietal cortex, whereas a negative FDG-PET/CT indicates that progression from MCI to dementia is unlikely [11]. Patients with MCI have demonstrated AD patterns of hypometabolism in the posterior cingulate and hippocampi; this was seen in up to 79% of patients with MCI in multiple domains and 31% of patients with amnestic MCI [12]. Patients with MCI and with reduced cortical uptake in the temporal and parietal lobes and posterior cingulate on brain FDG-PET/CT predicts conversion from MCI to AD with an accuracy of more than 80% [13]. Amyloid PET/CT and FDG-PET/CT are complementary and when combined have better accuracy at predicting conversion of patients with MCI to AD [9]. Brain FDG-PET/CT results in a change in diagnosis in up to 32% of patients with MCI [14]. Patients with MCI who later converted to DLB and AD have different patterns of FDG hypometabolism, with diminished FDG metabolism in the parieto-occipital and temporal regions in those progressing to DLB versus medial temporal lobe and posterior cingulate hypometabolism in those progressing to AD [15].

MR Spectroscopy Head Without IV Contrast
Ratios of N-acetylaspartate (NAA) to myoinositol (myI) and creatine (Cr) have been shown to correlate with cognitive scores over time and may distinguish patients with MCI from those with AD [16]. Elevated ratios of myI/Cr and choline (Cho)/Cr and reduced NAA/Cr ratios may predict development of AD in patients with MCI [17,18]. Decreased NAA/Cr ratios have been demonstrated in patients with MCI compared with healthy patients [18].

MRI Functional (fMRI) Head Without IV Contrast
Patients with MCI demonstrated abnormally decreased default mode network functional connectivity and decreased task-related default mode network deactivations compared with healthy patients [19]. Hyperactivation in various brain regions has been demonstrated in patients with MCI who later converted to AD; this finding may help identify patients with MCI who are at risk of conversion to AD [20]. The diagnostic usefulness of functional MRI (fMRI) is not yet validated in routine clinical practice [21].

MRI Head Without and With IV Contrast
MRI findings in patients with MCI can be detected without the use of IV contrast. There is insufficient evidence to support the use of MRI head without and with IV contrast for the initial imaging of patients with MCI not meeting criteria for dementia.

MRI Head Without IV Contrast
A finding of hippocampal atrophy in older patients with MCI may predict later conversion to AD with 80% accuracy, but this finding has also been seen in older patients without cognitive deficits [11,13]. Volumetric hippocampal volume, entorhinal cortex thickness, and supramarginal gyrus thickness measurements have been used for risk stratification in MCI cohorts; voxel-based volumetry has demonstrated reduced volume in the medial temporal, lateral temporal, and parietal lobes in patients with MCI [13,22]. Brain atrophy on MRI correlates with tau deposition, and the degree of medial temporal lobe and hippocampal atrophy in patients with MCI is a diagnostic marker for AD [23]. Apparent diffusion coefficient (ADC) values in patients with amnestic MCI have been shown to be higher than in healthy patients in the left limbic regions, whereas patients with AD have demonstrated higher ADC values in the hippocampi, cingulate, temporal, and frontal lobes; as such, diffusion-weighted imaging (DWI) can help distinguish patients with MCI from healthy patients and can support a diagnosis of MCI [24]. MRI has an increased accuracy of predicting conversion from MCI to AD when combined with brain amyloid PET/CT [25].

SPECT or SPECT/CT Brain Perfusion
There is no relevant literature to support brain perfusion single-photon emission CT (SPECT) or SPECT/CT for the use of initial imaging in patients with MCI not meeting criteria for dementia.

SPECT or SPECT/CT Brain Striatal
There is no relevant literature to support brain striatal SPECT or SPECT/CT for the use of initial imaging in patients with MCI not meeting criteria for dementia.

Tau PET/CT Brain

Brain tau PET/CT shows a significant increase in cortical tau deposition in patients with MCI compared with normal patients, providing in vivo evidence of underlying tau pathology in patients with a high probability of converting to AD [26]. Brain tau PET/CT positivity correlates with amyloid PET/CT positivity, FDG-PET/CT findings, and cognitive functions [27].

AUC for brain tau PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10]. Brain tau PET/CT was deemed to be of uncertain usefulness in patients with MCI or dementia consistent with amnestic AD with onset at ≥65 years of age and patients with MCI or dementia with recent conclusive, equivocal, or inconclusive CSF biomarker results [10].

Variant 2: Adult. Cognitive impairment with memory deficits. Suspect Alzheimer disease with typical clinical presentation. Initial imaging.

The prevalence of dementia in the United States is estimated at up to 10% of individuals older than age 65 [28]. AD is the most common cause of dementia in this age group and represents a significant public health problem. Age is the most important risk factor for dementia; other risk factors include female sex, Black race, Hispanic ethnicity, and genetic factors such as apolipoprotein E ε4 variant [1]. AD is characterized by the accumulation of beta-amyloid plaques and misfolded tau 3R and 4R protein neurofibrillary tangles [28].

In 2011, the National Institute on Aging and Alzheimer's Association working group proposed specific terminology for patients with dementia due to AD: probable AD, possible AD, and probable or possible AD with evidence of the AD pathophysiological process. Designations of probable and possible AD are used in the clinical setting, whereas probable or possible AD dementia with evidence of the AD pathophysiologic process is used in research. The typical clinical syndrome and presentation of AD occurs in patients >65 years of age and encompasses several stages, from the asymptomatic phase to the symptomatic predementia phase (MCI due to AD) and the dementia phase. Transition between phases is gradual and often subtle in typical presentations of AD. There is greater diagnostic uncertainty earlier in the disease course [2].

Evidence of the AD pathophysiologic processes are indicators of brain amyloid-beta protein deposition and evidence of downstream neuronal degeneration and injury. Evidence of brain amyloid-beta deposition include positive brain amyloid PET/CT and low CSF amyloid beta 42 [2]. Evidence of downstream neuronal degeneration and injury include elevated CSF tau (total and phosphorylated), brain FDG-PET/CT demonstrating hypometabolism in the temporal and parietal cortex, and disproportionate atrophy in the medial, basal, and lateral temporal lobe and medial parietal cortex on structural brain MRI [2]. At the time of publication of these definitions in 2011, routine biomarker testing, including imaging, was not recommended despite the fact that positive biomarkers increase certainty that dementia is due to AD. In 2014, the diagnostic framework was modified to state that a diagnosis of AD requires the presence of a clinical AD phenotype (typical or atypical) and a pathophysiologic biomarker consistent with the presence of AD pathology [29]. A newer classification scheme was proposed in 2018 emphasizing AD biomarkers: the "A/T/N" system [30]. "A" refers to amyloid beta, assessed with brain amyloid PET/CT or CSF amyloid beta 42. "T" refers to tau, assessed with CSF phosphorylated tau or brain tau PET/CT. "N" refers to neurodegeneration or neuronal imaging, assessed with brain FDG-PET/CT, structural MR, or CSF total tau. Revised criteria for diagnosis and staging of AD from the Alzheimer's Association workgroup was recently published in June 2024, emphasizing the definition of AD as a biological process rather than a clinical syndrome and the importance of early-changing Core 1 biomarkers (eg, amyloid PET) in the diagnosis of AD versus later-changing Core 2 biomarkers (eg, tau PET) in the prognosis of AD [10,31].

The goal of imaging in patients with cognitive impairments and memory deficits who are suspected to have AD with a typical clinical presentation is to assess for potentially treatable structural brain abnormalities, which may mimic a typical clinical presentation of AD, and to identify imaging features that support or refute a clinical diagnosis of AD. Identification of treatable structural brain abnormalities, which might mimic symptoms of AD, will improve patient outcomes by allowing for timely intervention. Identification of imaging findings supportive of a diagnosis of AD would provide prognostic information for clinicians, patients, and their family members and help initiate earlier neuropsychiatric and medical therapy. For patients with mild symptoms or early stage dementia, who are potential candidates for therapy with antiamyloid monoclonal antibodies, the reader can also refer to Variant 4.

Amyloid PET/CT Brain

Patients with AD have been shown to demonstrate amyloid retention on brain amyloid PET/CT in areas of the cortex known to contain large amounts of amyloid deposition on postmortem specimens and correlates with areas

of hypometabolism on brain FDG-PET/CT; it is a reliable biomarker for AD and is positive in more than 86% of patients with high specificity [32-35]. In the preclinical stage of AD, amyloid PET/CT is positive in areas of normal FDG-PET/CT metabolism [36]. The characteristic pattern of uptake in patients with AD is symmetric, diffuse uptake throughout the cortical gray matter with sparing of the cerebellum [28]. Brain amyloid PET/CT discriminates between patients with AD and healthy patients [37]. Positive brain amyloid PET/CT can also distinguish between patients with AD and FTD, although it can be positive in older patients with FTD and those with the apolipoprotein ε4 genotype [3,38]. Positive brain amyloid PET/CT is required before treatment with antiamyloid MAB therapy, further detailed elsewhere in this narrative. Brain amyloid PET/CT has a higher sensitivity than brain MRI and brain FDG-PET/CT for the diagnosis of AD [25]. Patients undergoing brain amyloid PET/CT require fewer follow-up imaging studies after amyloid PET/CT, which has demonstrated usefulness in young patients, patients with atypical presentations, and patients with multiple potential causes of cognitive impairment; these patients are less likely to manifest typical atrophy patterns of AD on MRI and are more likely to benefit from brain amyloid PET/CT for diagnosis [6]. In patients with dementia of uncertain etiology, brain amyloid PET/CT has been shown to result in a change in diagnosis, increase in diagnostic confidence, and alteration of clinical management with greater diagnostic value than brain FDG-PET/CT [7,8,39]. A negative brain amyloid PET/CT usually excludes a diagnosis of AD [40,41]. When used together, brain FDG-PET/CT and brain amyloid PET/CT have a combined sensitivity of 97% and a specificity of 98% for AD pathology, and mixed dementia should be considered when amyloid and FDG-PET/CT are incongruent [42].

AUC for brain amyloid PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10]. This AUC document states that brain amyloid PET/CT is appropriate in the following scenarios: patients with MCI or dementia who are <65 years of age and in whom AD is suspected, patients with MCI or dementia consistent with amnestic AD pathology with onset at ≥65 years of age, patients with MCI or dementia that could be consistent with AD but has atypical features, patients with MCI or dementia with equivocal or inconclusive results on CSF biomarkers, and to inform the prognosis of patients with MCI due to suspected AD pathology [10]. The usefulness of brain amyloid PET/CT to inform prognosis of patients presenting with dementia due to clinically suspected AD pathology was uncertain [10]. This AUC document determined that the use of brain amyloid PET/CT was rarely appropriate in patients with MCI or dementia and conclusive CSF biomarker results [10].

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the use of initial imaging in patients with suspected AD and a typical clinical presentation.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the use of initial imaging in patients with suspected AD and a typical clinical presentation.

CT Head Without IV Contrast
CT head without IV contrast can demonstrate treatable structural lesions, which may result in clinical symptoms mimicking a typical clinical presentation of AD, such as subdural hematomas or intracranial mass lesions. CT can also demonstrate detection of hippocampal atrophy and other atrophy patterns, which may be seen with AD [43].

FDG-PET/CT Brain
On brain FDG-PET/CT, AD manifests as hypoperfusion involving the parietal and temporal lobes, precuneus, and posterior cingulate gyrus [28]. This finding has a sensitivity of up to 95% and a specificity of up to 73% for differentiating AD from non-AD dementias and has a greater accuracy than MRI and brain perfusion SPECT for the diagnosis of AD [44,45]. Brain FDG-PET/CT has a sensitivity of up to 96% and a specificity of up to 100% for discriminating between patients with AD and healthy patients [12]. Brain FDG-PET/CT also has a greater accuracy for diagnosis of AD than the use of clinical criteria alone and can help distinguish between AD and FTD based upon patterns of brain hypometabolism [11,14].

MR Spectroscopy Head Without IV Contrast
MR spectroscopy demonstrates altered ratios of brain metabolites in patients with AD, particularly in the mesial temporal lobes and hippocampi, however, by the time MR spectroscopy becomes abnormal, hippocampal atrophy is typically present. An abnormal NAA to myI ratio is a dependable diagnostic measure distinguishing patients with AD from healthy patients, with a sensitivity of 83% and a specificity of 98%, although this modality is considered

a secondary diagnostic tool to increase confidence in a clinical diagnosis [16]. Patients with AD demonstrate lower NAA/Cr ratios in the posterior cingulate gyri than normal patients [17].

MRI Functional (fMRI) Head Without IV Contrast
Patients with AD demonstrate abnormally decreased default mode network connectivity and decreased task-related default mode network deactivations compared with normal patients [19]. The diagnostic usefulness of fMRI is not yet validated in routine clinical practice [21].

MRI Head Without and With IV Contrast
Imaging findings of AD can be demonstrated without the use of IV contrast. There is no relevant literature to support MRI head without and with IV contrast for the use of initial imaging in patients with suspected AD and a typical clinical presentation.

MRI Head Without IV Contrast
Brain MRI without IV contrast can demonstrate regional atrophy patterns suggestive of AD. Brain atrophy patterns correlate with tau deposition and are a valid biomarker for AD [23]. The earliest structural change is volume loss in the entorhinal cortex, with hippocampal atrophy occurring later [28]. Volumetric techniques can be used for quantitative assessment of parenchymal atrophy and are considered the reference standard method of quantifying brain atrophy, but they are time intensive and may require postprocessing software [13]. DWI can demonstrate increased ADC values in the hippocampi, cingulum, parahippocampal gyri, and temporal and frontal lobes compared with healthy patients and can thus support a diagnosis of AD [24]. Diffusion tensor imaging can demonstrate reduced fractional anisotropy in the precuneus in patients with AD compared with healthy patients [46]. MRI perfusion with arterial spin labeling shows similar patterns of abnormalities as brain FDG-PET/CT in patients with AD [47]. Brain MRI is necessary if antiamyloid MAB therapy is to be considered.

SPECT or SPECT/CT Brain Perfusion
A specific pattern of bilateral posterior hypoperfusion on brain perfusion SPECT increases the likelihood of a diagnosis of AD rather than other neurodegenerative disorders such as VaD and FTD [48]. Brain perfusion SPECT or SPECT/CT is considered an adjunct to other structural, functional, and metabolic imaging modalities. The sensitivity of brain perfusion SPECT is lower than that of clinical criteria [45]. However, brain perfusion SPECT has been shown to be superior to MR perfusion methods in diagnosing patients with AD [49].

SPECT or SPECT/CT Brain Striatal
A normal pattern of radiotracer uptake in the striatum on brain striatal SPECT or SPECT/CT can help distinguish patients with AD from those with DLB; abnormal striatal uptake can indicate coexistent AD in patients with suspected DLB [50]. However, there is no relevant literature to support brain striatal SPECT or SPECT/CT for the use of initial imaging in patients with suspected AD and a typical clinical presentation.

Tau PET/CT Brain
Tau radiotracer uptake on brain tau PET/CT corresponds with Braak staging (entorhinal cortex, followed by limbic system and hippocampus, followed by remaining cortex) and is a reliable biomarker for tau pathology and AD [28,51]. Patients with AD demonstrate greater tau avidity on brain tau PET/CT in patients with AD compared with patients with non-AD dementias [52,53]. Brain tau PET/CT has a 93% diagnostic accuracy rate for prodromal AD or AD dementia [54].

AUC for brain tau PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10]. This AUC document states that brain tau PET/CT is appropriate for patients with MCI or dementia who are <65 years of age and in whom AD is suspected, patients with MCI or dementia that could be consistent with AD but has atypical clinical features, and to inform the prognosis of patients with MCI or dementia due to clinically suspected AD [10]. Brain tau PET/CT was deemed to be of uncertain usefulness in patients with MCI or dementia consistent with amnestic AD with onset at ≥65 years of age and patients with MCI or dementia with recent conclusive, equivocal, or inconclusive CSF biomarker results [10].

Variant 3: Adult. Cognitive impairment with memory deficits. Suspect Alzheimer disease with atypical clinical presentation. Initial imaging.

Dementia due to AD with a typical clinical presentation of AD is detailed in Variant 2. An atypical clinical presentation of AD is one that meets core clinical criteria of cognitive impairment in multiple domains, which interfere with instrumental activities of daily living and functioning, but has a sudden or rapid onset or the onset occurs at a younger age (<65 years of age) [2]. In some cases, a rapid onset of AD symptoms may be approached

as an RPD, which is discussed elsewhere in this narrative. Early onset AD occurs in up to 3% of patients with AD [55]. Atypical variants of AD present a diagnostic challenge to clinicians and often result in delays in diagnosis or misdiagnosis. Besides early onset, atypical AD variants include amnestic variant (early onset AD), visuospatial variant AD (posterior cortical atrophy [PCA]), language variant AD (logopenic variant primary progressive aphasia ([PPA]), behavioral variant/dysexecutive variant AD, and motor variant AD (corticobasal syndrome due to AD [55]. Patients with atypical presentations of AD have typically been excluded from many studies and clinical trials due to their clinical symptoms or age [27]. Clinical diagnosis in patients with atypical presentations of AD is often difficult due to the variable and often nonamnestic phenotype, which can have significant overlap with other neurodegenerative diseases such as FTD or DLB [27]. In this population, biomarkers, particularly imaging, play an important role in diagnosis.

The goal of imaging in patients with cognitive impairments and memory deficits who are suspected to have AD with an atypical clinical presentation such as early age of onset (<65 years of age) is to assess for potentially treatable structural brain abnormalities, which may mimic an atypical clinical presentation of AD and to identify imaging features that support or refute a clinical diagnosis of AD. Advanced molecular imaging plays a greater role in confirming a diagnosis of AD when the clinical presentation is atypical. Identification of treatable structural brain abnormalities, which might mimic symptoms of AD, will improve patient outcomes by allowing for timely intervention. Identification of imaging findings supportive of a diagnosis of AD would provide prognostic information for clinicians, patients, and their family members and help initiate earlier neuropsychiatric and medical therapy.

Amyloid PET/CT Brain
Patients with AD have been shown to demonstrate amyloid retention on brain amyloid PET/CT in areas of cortex known to contain large amounts of amyloid deposition on postmortem specimens; it is a reliable biomarker for AD and is positive in more than 86% of patients with high specificity [32-35]. The characteristic pattern of uptake in patients with AD is symmetric, diffuse uptake throughout the cortical gray matter with sparing of the cerebellum [28]. Brain amyloid PET/CT discriminates between patients with AD versus healthy patients [37]. Positive brain amyloid PET/CT can also distinguish between patients with AD and FTD [3]. Brain amyloid PET/CT has a higher sensitivity than brain MRI and brain FDG-PET/CT for the diagnosis of AD [25]. Patients undergoing brain amyloid PET/CT require fewer follow-up imaging studies after amyloid PET/CT, which has demonstrated usefulness in young patients, patients with atypical presentations, and patients with multiple potential causes of cognitive impairment; these patients are less likely to manifest typical atrophy patterns of AD on MRI and are more likely to benefit from brain amyloid PET/CT for diagnosis [6]. In patients with dementia of uncertain etiology, brain amyloid PET/CT has been shown to result in a change in diagnosis, increase in diagnostic confidence, and alteration of clinical management with greater diagnostic value than brain FDG-PET/CT [7,8,39]. A negative brain amyloid PET/CT can exclude a diagnosis of AD [40,41]. When used together, brain FDG-PET/CT and brain amyloid PET/CT have a combined sensitivity of 97% and a specificity of 98% for AD pathology, and mixed dementia should be considered when amyloid and FDG-PET/CT are incongruent [42]. Positive brain amyloid PET/CT is required before treatment with antiamyloid MAB therapy, further detailed elsewhere in this narrative.

Patients with early onset or atypical presentations of AD demonstrated positive brain amyloid PET/CT in approximately 64% of patients, leading to a change in diagnosis of nearly 67%, improved confidence in the diagnosis of 81.5%, and altered patient management in 80% of cases [56]. Baseline brain amyloid PET/CT can distinguish patients with early onset AD from early onset non-AD dementias [27]. Patients with early onset or other atypical clinical manifestations of AD are less likely to manifest typical atrophy patterns of AD, and brain amyloid PET/CT is most useful for diagnosis in these patients [6]. Brain amyloid PET/CT has also shown benefit in patients with atypical AD presentations with indeterminate or inconclusive findings on brain MRI; in these patients, brain amyloid PET/CT can support a diagnosis of AD when positive and exclude AD when negative, thus raising the possibility of a different neurodegenerative disorder [41]. Positive brain amyloid PET/CT is predictive of cognitive and functional decline among patients with atypical presentations of AD [5].

AUC for brain amyloid PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10]. This AUC document states that brain amyloid PET/CT is appropriate in patients presenting with MCI or dementia that could be consistent with AD pathology but has atypical features such as a nonamnestic clinical presentation, rapid or slow progression of disease, or an etiologically mixed presentation [10].

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the use of initial imaging in patients with suspected AD and an atypical clinical presentation.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the use of initial imaging in patients with suspected AD and an atypical clinical presentation.

CT Head Without IV Contrast
CT head without IV contrast can demonstrate treatable structural lesions, which may result in clinical symptoms mimicking an atypical clinical presentation of AD, such as subdural hematomas or intracranial mass lesions. CT can also demonstrate detection of hippocampal atrophy and other atrophy patterns, which may be seen with AD [43].

FDG-PET/CT Brain
On brain FDG-PET/CT, AD manifests as hypoperfusion involving the parietal and temporal lobes, precuneus, and posterior cingulate gyrus [28]. This finding has a sensitivity of up to 95% and a specificity of up to 73% for differentiating AD from non-AD dementias, and it has a greater accuracy than MRI and brain perfusion SPECT for the diagnosis of AD [44,45]. Brain FDG-PET/CT has a sensitivity of up to 96% and a specificity of up to 100% for discriminating between patients with AD from healthy patients [12]. Brain FDG-PET/CT also has greater accuracy for diagnosis of AD than the use of clinical criteria alone and can help distinguish between AD and FTD based upon patterns of brain hypometabolism [11,14].

In patients with autosomal dominant AD in the asymptomatic phase and with subjective cognitive decline, there is poor evidence for the use of brain FDG-PET/CT [57]. The presence of hypometabolism on brain FDG-PET/CT in the parieto-temporo-occipital cortex and cingulate cortex is a hallmark of PCA, distinguishing it from DLB when there is hypometabolism in the association visual cortex, sparing the posterior cingulate gyrus [58].

MR Spectroscopy Head Without IV Contrast
MR spectroscopy demonstrates altered ratios of brain metabolites in patients with AD, particularly in the mesial temporal lobes and hippocampi, however, by the time MR spectroscopy becomes abnormal, hippocampal atrophy is typically present. An abnormal NAA to myI ratio is a dependable diagnostic measure distinguishing patients with AD from healthy patients, with a sensitivity of 83% and a specificity of 98%, although this modality is considered a secondary diagnostic tool to increase confidence in a clinical diagnosis [16]. Patients with AD demonstrate lower NAA/Cr ratios in the posterior cingulate gyri than normal patients [17].

MRI Functional (fMRI) Head Without IV Contrast
Patients with AD demonstrate abnormally decreased default mode network connectivity and decreased task-related default mode network deactivations compared with normal patients [19]. The diagnostic usefulness of fMRI is not yet validated in routine clinical practice [21].

MRI Head Without and With IV Contrast
Imaging findings of AD can be demonstrated without the use of IV contrast. There is no relevant literature to support MRI head without and with IV contrast for the use of initial imaging in patients with suspected AD and an atypical clinical presentation.

MRI Head Without IV Contrast
Brain MRI without IV contrast can demonstrate regional atrophy patterns suggestive of AD. Brain atrophy patterns correlate with tau deposition and are a valid biomarker for AD [23]. The earliest structural change is volume loss in the entorhinal cortex, with hippocampal atrophy occurring later, but this pattern may differ depending on AD anatomic variants [28,59]. Volumetric techniques can be used for quantitative assessment of parenchymal atrophy and are considered the reference standard method of quantifying brain atrophy, but they are time intensive and may require postprocessing software [13]. DWI can demonstrate increased ADC values in the hippocampi, cingulum, parahippocampal gyri, and temporal and frontal lobes compared with healthy patients and can thus support a diagnosis of AD [24]. Diffusion tensor imaging can demonstrate reduced fractional anisotropy in the precuneus in patients with AD compared with healthy patients [46]. MRI perfusion with arterial spin labeling shows similar patterns of abnormalities as brain FDG-PET/CT in patients with AD [47]. Brain MRI is necessary if antiamyloid MAB therapy is to be considered.

SPECT or SPECT/CT Brain Perfusion

A specific pattern of bilateral posterior hypoperfusion on brain perfusion SPECT increases the likelihood of a diagnosis of AD rather than other neurodegenerative disorders such as VaD and FTD [48]. Brain perfusion SPECT or SPECT/CT is considered an adjunct to other structural, functional, and metabolic imaging modalities. The sensitivity of brain perfusion SPECT is lower than that of clinical criteria [45]. However, brain perfusion SPECT has been shown to be superior than MR perfusion methods in diagnosing patients with AD [49].

SPECT or SPECT/CT Brain Striatal

In patients with an atypical clinical presentation of AD, certain clinical or imaging features may indicate the possibility of DLB such as rapid eye movement (REM) sleep behavior disorder, hallucinations, or Parkinsonian findings. A normal pattern of radiotracer uptake in the striatum on brain striatal SPECT or SPECT/CT can help distinguish patients with AD from those with DLB alone or comorbid DLB with AD; abnormal striatal uptake in a patient with an atypical presentation of AD could indicate a diagnosis of DLB or other Parkinsonian syndrome [50].

Tau PET/CT Brain

Brain tau PET/CT in patients with atypical variants of AD to include nonamnestic AD, PCA, and logopenic variant PPA demonstrated uptake in specific areas correlating with cognitive function, thus, tau PET can be of use in diagnosis of atypical clinical phenotypes of AD [60]. Tau radiotracer uptake on brain tau PET/CT is greater in patients with PCA than DLB [61].

AUC for brain tau PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10]. This AUC determined that the use of brain tau PET/CT is appropriate in patients presenting with MCI or a dementia syndrome that could be consistent with AD pathology but has atypical features such as a nonamnestic clinical presentation, rapid or slow progression, or an etiologically mixed presentation [10].

Variant 4: Adult. Known Alzheimer disease considering therapy with antiamyloid monoclonal antibodies. Pretreatment imaging.

Treatment of AD has traditionally been focused on symptomatic therapies. Recently, the FDA has approved MAB therapy targeting amyloid plaques such as lecanemab for the treatment of early or mild AD. Patients who are potential candidates for antiamyloid therapy must meet clinical criteria for AD with biomarker evidence of amyloid pathology such as positive amyloid PET imaging or positive CSF biomarkers, although at the time of this writing blood biomarkers are not accurate enough [62]. Appropriate patient selection with imaging before the initiation of therapy is of the utmost importance to ensure appropriate efficacy and safety. Certain exclusion criteria for antiamyloid MAB therapy based on MRI findings were used in clinical trials, which include a hemorrhage >10 mm in diameter, 4 or more microhemorrhages <10 mm in diameter, evidence of superficial siderosis, evidence of vasogenic edema, significant white matter hyperintensities, multiple lacunar infarcts, or any infarcts involving a major vascular territory [62]. Other findings such as evidence of cerebral contusions, encephalomalacia, aneurysms and vascular malformations, infection, and brain tumors other than meningiomas or arachnoid cysts excluded patients from clinical trials [62]. Finally, evidence of cerebral amyloid angiopathy-related inflammation (CAA-ri) or amyloid-beta related angiitis (ABRA), which confers increased risk for amyloid-related imaging abnormalities (ARIA), also exclude patients from receiving antiamyloid MAB therapy. Imaging features indicating probable CAA-ri include unifocal or multifocal asymmetric T2 hyperintensities involving subcortical white matter; one or more peripheral hemorrhagic lesions to include microhemorrhages, macrohemorrhages, or superficial siderosis; and absence of neoplastic and infectious findings [62]. In order to screen patients for exclusionary MRI findings, patients must have undergone an MRI within 12 months of initiation of antiamyloid MAB therapy; CT is inadequate for pretherapy screening [62].

The goal of initial imaging in patients with known AD who will potentially consider antiamyloid MAB therapy is to select patients who are candidates for therapy. Brain imaging is necessary to identify structural brain lesions, which would preclude safe antiamyloid treatment and would identify patients at greater risk of developing complications of therapy such as ARIA.

Amyloid PET/CT Brain

In addition to a clinical diagnosis of MCI or AD, a positive biomarker for AD such as positive amyloid PET imaging or CSF findings indicative of AD (elevated phosphorylated tau and low amyloid beta 42) is required by appropriate use recommendations before the initiation of antiamyloid MAB therapy [62].

AUC for brain amyloid PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024, which stated that the use of brain amyloid PET/CT is appropriate to determine eligibility for treatment with an approved amyloid-targeting therapy [10].

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the use of initial imaging of patients with AD considering therapy with MAB.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the use of initial imaging of patients with AD considering therapy with MAB.

CT Head Without IV Contrast
Although CT head can demonstrate acute intracranial pathology such as intracranial hemorrhage, large intraparenchymal mass lesions and mass effect, encephalomalacia, parenchymal contusions, and parenchymal edema, it lacks sensitivity for detection of certain imaging findings, which would exclude patients from antiamyloid MAB therapy, particularly CAA-ri/ABRA, microhemorrhages, significant white matter lesions, intracranial infection, and superficial siderosis. Appropriate use recommendations state that CT is inadequate for detection of imaging findings, which might exclude patients from considering antiamyloid MAB therapy [62].

FDG-PET/CT Brain
There is no relevant literature to support FDG-PET/CT brain for the use of initial imaging for patients with AD considering therapy with MAB.

MR Spectroscopy Head Without IV Contrast
There is no relevant literature to support MR spectroscopy for the use of initial imaging for patients with AD considering therapy with MAB.

MRI Functional (fMRI) Head Without IV Contrast
There is no relevant literature to support fMRI for the use of initial imaging for patients with AD considering therapy with MAB.

MRI Head Without and With IV Contrast
IV contrast is not necessary to detect imaging findings, which might exclude patients from antiamyloid MAB therapy. However, it may increase detection of findings of which can be seen in CAA-ri/ABRA, central nervous system (CNS) infection, and brain tumors.

MRI Head Without IV Contrast
Clinical guidelines regarding eligibility for antiamyloid MAB therapy mandate patient screening with MRI within 12 months of initiation of antiamyloid MAB therapy to detect certain exclusionary criteria, which might increase the risk of ARIA and their related complications [62]. MRI must include standard sequences such as DWI, T2 fluid-attenuated inversion recovery (FLAIR), and T2* gradient-echo (GRE) or susceptibility-weighted imaging (SWI). Imaging on a 3T unit provides greater sensitivity for detection of abnormalities, particularly microhemorrhages. Imaging findings, which would exclude patients from therapy with antiamyloid MABs, include intraparenchymal macrohemorrhages >10 mm in diameter, 4 or more microhemorrhages <10 mm in diameter, superficial siderosis, vasogenic edema, significant white matter signal abnormalities, multiple lacunar infarcts, major vascular territory infarcts, parenchymal contusions, encephalomalacia, aneurysms and vascular malformations, CNS infection, brain tumors other than meningiomata or arachnoid cysts, and evidence of CAA-ri/ABRA [62]. For more details or recommendations on imaging protocols and reporting templates, the American Society of Neuroradiology website provides educational resources and webinar recordings.

SPECT or SPECT/CT Brain Perfusion
There is no relevant literature to support brain perfusion SPECT or SPECT/CT for the use of initial imaging for patients with AD considering therapy with MAB.

SPECT or SPECT/CT Brain Striatal
There is no relevant literature to support brain striatal SPECT or SPECT/CT for the use of initial imaging for patients with AD considering therapy with MAB.

Tau PET/CT Brain

Although tau pathology is a hallmark of AD, patients may have positive amyloid PET imaging with negative tau PET imaging, leading to potential false negatives. As such, AUC recommend the use of amyloid PET imaging rather than tau PET imaging before the initiation of antiamyloid MAB therapy [62].

AUC for brain tau PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024, which stated that the use of brain tau PET/CT is appropriate to determine eligibility for treatment with an approved amyloid-targeting therapy, although the recommendation was slightly less strong than for brain amyloid PET/CT [10].

Variant 5: Adult. Known Alzheimer disease undergoing therapy with antiamyloid monoclonal antibodies. Posttreatment imaging.

Posttreatment monitoring of patients undergoing antiamyloid MAB therapy is mandated by appropriate use recommendations to screen for development of ARIA, which constitute the predominant neurologic complication associated with this therapy [62,63]. ARIA are theorized to be caused by an inflammatory response to MAB treatment against amyloid, which results in increased vascular permeability leading to edema and extravascular extravasation of blood products and proteinaceous fluid [63]. Two forms of ARIA are described: ARIA-E, referring to edema and/or effusion, and ARIA-H, referring to hemorrhage [63]. Both forms of ARIA are only detectable on noncontrast brain MRI and cannot be reliably detected on CT. ARIA-E presents as parenchymal edema and/or sulcal "effusions" characterized by increased parenchymal T2 signal potentially with associated mass effect and nonsuppression of sulcal CSF signal on T2 FLAIR images, respectively. ARIA-H manifests as parenchymal microhemorrhages and/or superficial siderosis [63]. ARIA-E was detected in up to 35% to 36% of patients undergoing therapy with aducanumab in the EMERGE and ENGAGE phase 3 trials, in up to 26.7% of patients undergoing therapy with donanemab in the TRAILBLAZER-ALZ phase 2 and phase 3 trials, and in up to 12.6% of patients undergoing therapy with lecanemab in the CLARITY AD phase 3 trial [64]. ARIA-H has incidence ranging from 15% to 20% in clinical trials [63]. ARIA-E and ARIA-H can be graded as mild, moderate, and severe. The main differential diagnosis of ARIA is CAA-ri/ABRA because there is significant overlap in imaging findings between the entities; the discriminating feature between the 2 is the history of antiamyloid MAB therapy. Other entities in the differential diagnosis for ARIA-E include posterior reversible encephalopathy syndrome, posterior multifocal leukoencephalopathy, subacute infarcts, subarachnoid hemorrhage, artifactual CSF nonsuppression on T2 FLAIR, meningitis, and vasculitis; differential considerations for ARIA-H include hypertensive microhemorrhages, CAA, and diffuse axonal injury [63].

Regular monitoring at specified intervals with brain MRI for the detection of ARIA is required by clinical use recommendations for patients undergoing antiamyloid MAB therapy. Patients undergoing therapy with lecanemab, for example, should undergo pretreatment MRI within 12 months of initiation of therapy and routine posttreatment MRIs during therapy before the fifth, seventh, and fourteenth infusions [62]. MRI can also be performed at any time if patients develop clinical signs and symptoms that may indicate development of ARIA. Mandatory MRI sequences include DWI, T2 FLAIR, and T2* GRE or SWI. Management of ARIA is determined by clinical symptoms and MRI grading severity. Detection of ARIA-E or ARIA-H may require modification of the antiamyloid MAB therapy regimen such as temporary or permanent cessation of treatment and/or the use of other therapies such as corticosteroids or antiepileptic treatment [63,65,66].

The goal of posttreatment imaging in patients with known AD who are undergoing antiamyloid MAB therapy is to detect the development of treatment complications known as ARIA. The development of ARIA may result in a change in management of antiamyloid therapy such as temporary or permanent cessation of therapy and may also require subspecialty care in a facility adequately equipped to care for patients with ARIA.

Amyloid PET/CT Brain

Brain amyloid PET/CT was used as an outcome measure in clinical trials for antiamyloid MAB therapy, including for stopping therapy in a study of the antiamyloid MAB donanemab [66,67]. AUC for brain amyloid PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024, which stated that the use of brain amyloid PET/CT was appropriate to monitor response of patients who have received an approved amyloid-targeting therapy [10]. However, it should be noted that although brain amyloid PET/CT can measure amyloid plaque removal, it cannot assess for ARIA; only brain MRI is able to detect ARIA. There is no other relevant literature to support brain amyloid PET/CT for the use of posttreatment monitoring in patients with AD undergoing therapy with MAB outside of clinical trials.

CT Head With IV Contrast

There is no relevant literature to support CT head with IV contrast for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

CT Head Without and With IV Contrast

There is no relevant literature to support CT head without and with IV contrast for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

CT Head Without IV Contrast

Although CT head without IV contrast may detect parenchymal edema and acute intracranial hemorrhage, it lacks sensitivity for the detection of ARIA and therefore should not be used for posttreatment monitoring in patients with AD undergoing antiamyloid MAB therapy [62].

FDG-PET/CT Brain

There is no relevant literature to support brain FDG-PET/CT for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

MR Spectroscopy Head Without IV Contrast

There is no relevant literature to support MR spectroscopy for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

MRI Functional (fMRI) Head Without IV Contrast

There is no relevant literature to support fMRI for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

MRI Head Without and With IV Contrast

Although the use of IV contrast may increase conspicuity of leptomeningeal inflammation, it is not considered necessary for posttreatment monitoring of patients with AD undergoing antiamyloid MAB therapy.

MRI Head Without IV Contrast

MRI of the brain without IV contrast is required for posttreatment monitoring of patients undergoing antiamyloid MAB therapy to detect ARIA-E and ARIA-H complications [63]. A noncontrast brain MRI can also be performed if a patient develops clinical signs and symptoms that may indicate ARIA. Detection of ARIA may require temporary or permanent cessation of antiamyloid MAB therapy depending on the type and severity. A surveillance protocol should include at a minimum DWI, T2 FLAIR, and T2* GRE or SWI sequences. For more details or recommendations on imaging protocols and reporting templates, the American Society of Neuroradiology website provides educational resources and webinar recordings.

SPECT or SPECT/CT Brain Perfusion

There is no relevant literature to support brain perfusion SPECT or SPECT/CT for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

SPECT or SPECT/CT Brain Striatal

There is no relevant literature to support brain striatal SPECT or SPECT/CT for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

Tau PET/CT Brain

AUC for brain tau PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024, which stated that the usefulness of brain tau PET/CT was uncertain for monitoring response among patients who have received an approved amyloid-targeting therapy [10]. It should be noted that this modality cannot assess for ARIA. There is no other relevant literature to support brain tau PET/CT for the use of posttreatment monitoring in patients with AD undergoing therapy with antiamyloid MAB.

Variant 6: Adult. Cognitive impairment with behavioral abnormalities or progressive aphasia. Suspect frontotemporal dementia. Initial imaging.

FTD encompasses a group of neurodegenerative diseases characterized by progressive language deficits and aphasia, executive function deficits, and behavioral abnormalities. FTD was first described by Pick in 1892 in a patient with presenile dementia, aphasia, and frontal and temporal brain atrophy [68]. It is the third most common dementia in patients >65 years of age with a prevalence of up to 26%, with 10% of cases occurring in patients <45 years of age [28,68,69]. There are multiple subtypes or variants of FTD with different clinical and imaging

phenotypes, which reflect underlying neuropathologic findings of neuronal or astrocytic tau or TDP-43 inclusions in the affected areas of the brain [68]. Subtypes include behavioral variant FTD, PPAs (with semantic FTD or nonfluent agrammatic PPA variants), and motor neuron disease–associated FTD. The clinical symptoms of FTD occasionally overlap with DLB. Like DLB, clinical guidelines assign the modifiers of "probable" or "possible" FTD based upon a combination of clinical features and biomarkers such as structural or functional imaging abnormalities [68].

The goal of imaging in patients with cognitive impairment, behavioral abnormalities, and/or progressive aphasia who are suspected to have FTD is to assess for potentially treatable structural brain abnormalities, which may mimic a clinical presentation of FTD, and to identify imaging features that support or refute a clinical diagnosis of FTD. Identification of treatable structural brain abnormalities that might mimic symptoms of FTD will improve patient outcomes by allowing for timely intervention. Identification of imaging findings supporting a diagnosis of FTD would provide prognostic information for clinicians, patients, and their family members and help initiate earlier neuropsychiatric and medical therapy.

Amyloid PET/CT Brain
Brain amyloid PET/CT is uncommonly positive in patients with FTD, occurring in up to 9%. Negative brain amyloid PET/CT can differentiate FTD from AD in up to 80% of cases, essentially excluding a diagnosis of AD [3,70]. Rare instances of positive brain amyloid PET/CT in suspected cases of FTD are thought to be related to false-positive results, incorrect clinical diagnosis, or mixed pathology [70].

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the use of initial imaging in patients with suspected FTD.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the use of initial imaging in patients with suspected FTD.

CT Head Without IV Contrast
CT head without IV contrast can detect some abnormalities such as large intracranial masses, subdural hematomas, or other structural abnormalities, which may produce a clinical syndrome mimicking FTD. CT head can also demonstrate presence or absence of atrophy patterns that can be seen in FTD.

FDG-PET/CT Brain
Brain FDG-PET/CT can demonstrate asymmetric hypometabolism in the frontal and temporal lobes, with sparing of the precuneus and occipital lobes, and is effective at differentiating FTD from AD and DLB [11,28,68]. Brain FDG-PET/CT is most useful when combined with structural MRI, leading to a sensitivity of 96% and a specificity of 73%; brain FDG-PET/CT has higher usefulness than brain perfusion SPECT [68].

MR Spectroscopy Head Without IV Contrast
Patients with FTD have lower NAA/Cr ratios than patients with DLB in the posterior cingulate gyri, which can differentiate FTD from DLB [17].

MRI Functional (fMRI) Head Without IV Contrast
Functional brain MRI can demonstrate decreased activation in the frontal and parietal cortex in early FTD when compared with early AD [71]. Increased functional connectivity with conventional and task-based fMRI can be seen in patients with FTD [19]. These structural and functional connectivity alterations can be seen in patients with presymptomatic FTD [72].

MRI Head Without and With IV Contrast
MRI findings of FTD can be depicted without the use of IV contrast material. There is insufficient evidence to support the use of MRI head without and with IV contrast for the initial imaging of patients with suspected FTD.

MRI Head Without IV Contrast
Structural brain MRI without IV contrast demonstrates classic atrophy patterns of FTD, which predominantly affect the frontal and temporal lobes with characteristic "knifelike gyri" and are typically seen in advanced cases. The subtypes of FTD have more specific atrophy patterns: behavioral variant FTD demonstrates asymmetric involvement of the anterior temporal lobes, prefrontal cortices, insula, anterior cingulate, striatum, and thalamus, whereas PPA variants demonstrate asymmetric anteroinferior temporal lobe atrophy worse on the left than the right

[28]. Volumetric techniques, particularly cortical thickness measurements, are useful for FTD diagnosis [73,74]. Advanced imaging techniques such as diffusion tensor imaging can demonstrate high sensitivity for assessing white matter damage in FTD and have been shown to be more accurate in classifying FTD subtypes than atrophy patterns [75]. MRI perfusion with arterial spin labeling can help distinguish FTD from AD; FTD demonstrates bilateral frontal hypoperfusion, whereas AD demonstrates hypoperfusion in the parietal and posterior cingulate regions [70].

SPECT or SPECT/CT Brain Perfusion

The presence of bilateral anterior brain hypoperfusion on brain perfusion SPECT increases the odds of a diagnosis of FTD rather than other dementias such as AD, DLB, and VaD [48]. However, brain FDG-PET/CT has greater usefulness in the initial imaging of patients with suspected FTD.

SPECT or SPECT/CT Brain Striatal

There is no relevant literature to support brain striatal SPECT or SPECT/CT for the use of initial imaging in patients with suspected FTD.

Tau PET/CT Brain

Several FTD subtypes are characterized by neuronal or glial tau inclusions. However, brain tau PET/CT has limited sensitivity and specificity [28,76]. Positive brain tau PET/CT has been demonstrated in some variants of FTD such as PPA. In FTD semantic variant PPA, associated not with tau but with TDP-43 PET/CT, it is often positive, but positivity was less pronounced than in patients with AD. When positive, areas of tau uptake corresponded to areas of cortical atrophy and areas related to specific language functions impaired in the various subtypes of PPA [53,77,78]. Ultimately, brain tau PET/CT's usefulness in FTD is yet unknown [28].

Variant 7: Adult. Cognitive impairment with visual hallucinations or Parkinsonian symptoms. Suspect dementia with Lewy bodies. Initial imaging.

DLB is the second most common primary neurodegenerative disease in older patients after AD, accounting for 10% to 25% of dementia cases [28,68]. Clinical symptoms of DLB overlap with those of AD, making it sometimes difficult to distinguish the 2 diseases, which coexist in the brain of about 50% of older patients with DLB. DLB is a synucleinopathy characterized by the presence of Lewy bodies on neuropathologic specimens, belonging to the same family of diseases of Parkinson disease dementia and idiopathic Parkinson disease [68]. Lewy bodies are made up of aggregates of misfolded alpha-synuclein proteins, which spread throughout the brain and cause damage to cortical neurons in addition to dopaminergic neurons in the substantia nigra and basal ganglia [28]. Like in Parkinson disease, amyloid and tau pathology are occasionally present in DLB [79].

Guidelines regarding the diagnosis of DLB divides patients into probable or possible cases based upon clinical features and biomarkers. The hallmark clinical features are fluctuating cognitive impairment, visual hallucinations, REM sleep-related behavioral disorder, and parkinsonism. A diagnosis of "probable" DLB requires 2 or more of the hallmark clinical features. Alternately, a diagnosis of "probable" DLB can be made if a patient has 1 clinical feature plus 1 biomarker to include abnormal brain striatal SPECT or SPECT/CT, abnormal reduced myocardial I-123 MIBG scintigraphy, or confirmation of REM sleep disorder on polysomnography. A patient will be designated as having "possible" DLB if there are positive biomarkers but no clinical symptoms, or 1 clinical feature without biomarker evidence [68].

The goal of imaging in patients with cognitive impairment, visual hallucinations, and/or Parkinsonian symptoms who are suspected to have DLB is to assess for potentially treatable structural brain abnormalities, which may mimic a clinical presentation of DLB and to identify imaging features which support or refute a clinical diagnosis of DLB. Identification of treatable structural brain abnormalities, which might mimic symptoms of DLB, will improve patient outcomes by allowing for timely intervention. Identification of imaging findings supporting a diagnosis of DLB would provide prognostic information for clinicians, patients, and their family members and help initiate earlier neuropsychiatric and medical therapy.

Amyloid PET/CT Brain

Brain amyloid PET/CT is positive in up to 29% of patients with DLB and in up to 63% in patients with DLB older than 80 years of age [3,38]. However, patients with DLB demonstrated lower binding of amyloid beta on brain amyloid PET/CT than patients with AD [80]. AUC for brain amyloid PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024, which stated that the use of brain amyloid PET/CT was rarely appropriate in patients presenting with prodromal Lewy body disease or DLB [10].

CT Head With IV Contrast

There is no relevant literature to support CT head with IV contrast for the use of initial imaging in patients with suspected DLB.

CT Head Without and With IV Contrast

There is no relevant literature to support CT head without and with IV contrast for the use of initial imaging in patients with suspected DLB.

CT Head Without IV Contrast

CT head without IV contrast can detect some abnormalities such as large intracranial masses, subdural hematomas, or other structural abnormalities, which may produce a clinical syndrome mimicking DLB. CT head can also demonstrate presence or absence of hippocampal atrophy, which may help discriminate between AD and DLB.

FDG-PET/CT Brain

Brain FDG-PET/CT may demonstrate findings of decreased metabolism in the temporal, parietal, and occipital lobes as well as the cerebellum [11]. The presence of hypometabolism in the occipital lobes is a distinguishing feature of DLB, which can distinguish it from AD [79]. The "cingulate island sign," or preservation of FDG metabolism in the posterior cingulate gyrus, is a biomarker for DLB and can help distinguish DLB from AD; the presence of the cingulate island sign is associated with preserved memory and processing speed [81]. Lateral occipital cortex hypometabolism and preserved posterior cingulate metabolism are the most sensitive and specific brain FDG-PET/CT findings, respectively [79]. Abnormal occipital lobe hypometabolism on FDG-PET/CT can be indicative of "probable" DLB [68].

MR Spectroscopy Head Without IV Contrast

Patients with DLB have been found to have normal NAA/Cr ratios in the posterior cingulate region compared with patients with AD, FTD, and VaD; as such, MR spectroscopic findings may help to differentiate patients with DLB from AD [17,82].

MRI Functional (fMRI) Head Without IV Contrast

Patients with DLB have been found to demonstrate abnormal default mode network functional connectivity and task-related deactivations compared with normal patients [19]. There is reduced activation of temporo-occipital regions during visual tasks [21].

MRI Head Without and With IV Contrast

MRI findings of DLB can be depicted without the use of IV contrast material. There is insufficient evidence to support the use of MRI head without and with IV contrast for the initial imaging of patients with suspected DLB.

MRI Head Without IV Contrast

MRI of the head without IV contrast can demonstrate structural lesions and abnormalities such as neoplasms or subdural hematomas, which may result in clinical symptoms of DLB. Compared with AD, DLB has less pronounced volume loss of the mesial temporal lobe structures and hippocampi as demonstrated on volumetric MRI [68,83]. In comparison, patients with isolated AD demonstrated greater atrophy in the left cuneus, lateral occipital, and parahippocampal regions when compared with patients with coexistent AD and DLB [84]. Loss of the swallow tail sign, akin to that seen in Parkinson disease, has been demonstrated on SWI of patients with DLB [28]. DWI findings of elevated ADC values in the right hippocampus could differentiate patients with DLB from those with MCI [85]. Diffusion tensor imaging findings of reduced fractional anisotropy and higher mean diffusivity has been demonstrated in the precuneus in patients with DLB when compared with healthy patients, and patients with DLB demonstrated reduced fractional anisotropy in the precuneus compared with patients with AD [46].

SPECT or SPECT/CT Brain Perfusion

Brain perfusion SPECT or SPECT/CT in patients with DLB demonstrates a pattern of occipital hypoperfusion compared with patients with AD [86]. In patients with clinical symptoms of both AD and DLB, brain perfusion SPECT or SPECT/CT with I-123 N-isopropyl-p iodoamphetamine (Iofetamine) may show decreased striatal perfusion, which indicates the presence of DLB, although it does not exclude the presence of AD pathology [50]. In patients with an isolated REM sleep disorder (a prodromal condition of DLB), brain perfusion SPECT can demonstrate a specific perfusion signature, which can predict future conversion to DLB [87].

SPECT or SPECT/CT Brain Striatal

A normal pattern of brain striatal SPECT or SPECT/CT using dopamine transporter analogues demonstrates symmetric uptake in the caudate nuclei and putamina, with a normal comma shape [68]. Brain striatal SPECT and

SPECT/CT using Iodine-123 Ioflupane can demonstrate loss of dopamine transporter volume in the putamina manifested as loss of the normal comma shape, which can occur in disorders such as DLB and Parkinson disease [68]. Because clinical symptoms of AD and DLB overlap and patients can have coexistent AD and DLB pathology, brain striatal SPECT or SPECT/CT can demonstrate loss of striatal activity, indicating the presence of DLB [50]. Reduced striatal uptake has a sensitivity of 78% and a specificity of 90% for the differentiation of DLB from AD [68]. In patients with prodromal clinical signs and symptoms of DLB, brain striatal SPECT or SPECT/CT may facilitate earlier diagnosis [88]. Quantitative methods of measuring brain striatal uptake have shown promise for discriminating patients with DLB from those without DLB [89]. Use of brain striatal SPECT or SPECT/CT can help support findings on MRI and brain FDG-PET/CT and could be indicative of "probable" DLB.

Tau PET/CT Brain
Brain tau PET/CT positivity is variable and generally minimal in patients with DLB [90,91]. Since clinical features and some imaging features of the AD variant posterior cerebral atrophy such as occipital hypometabolism overlap with DLB, brain tau PET/CT could be considered to differentiate between the 2 entities, because brain tau PET/CT is likely to demonstrate higher tau uptake in PCA than DLB [61]. AUC for brain tau PET PET/CT were recently published by the Society of Nuclear Medicine Imaging and Molecular Imaging in June 2024 [10], which stated that brain tau PET/CT is of uncertain usefulness in patients presenting with prodromal Lewy body disease or DLB [10]. There is insufficient evidence to support its use in the initial imaging of patients with suspected DLB.

Variant 8: Adult. Cognitive impairment with recent stroke or stepwise decline. Suspect vascular dementia. Initial imaging.

VaD, also known as vascular cognitive impairment (VCI), is the second most common cause of clinical dementia after AD and comprises 15% to 20% of clinically diagnosed dementia in North America and Europe, with higher incidence in Asia and developing countries [92]. The underlying pathophysiology is neuronal damage and loss of white matter connectivity as a result of ischemia, infarcts, and hemorrhage [93]. There is an overlap of clinical symptoms of cognitive impairment between VaD, AD, and MCI. Mixed vascular and Alzheimer pathology has a prevalence of up to 38% in some neuropathologic studies, with the probability of mixed disease increasing with age [92]. It is postulated that VaD and AD are mechanistically linked, but the relationship is not well defined [93]. Risk factors for development of VaD/VCI include cardiovascular risk factors such as hypertension, dyslipidemia, type 2 diabetes mellitus, smoking, and atrial fibrillation [92]. These risk factors directly contribute to different types of cerebrovascular diseases such as atherosclerosis (leading to large vessel thrombosis, artery-to-artery embolic events, or cardioembolic events), arteriolosclerosis (leading to small vessel and lacunar infarcts, white matter disease, and microhemorrhages), and microvascular disease [92]. CAA also is a causal etiology in VaD/VCI, in which deposition of beta-amyloid in small vessels leads to intraparenchymal hemorrhage, white matter disease, and microinfarcts [92]. Inherited cerebrovascular disorders such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy caused by a mutation in the notch3 gene can also result in a clinical syndrome of VaD/VCI in addition to symptoms of migraine, strokes, and psychiatric symptoms [94]. Treatment and prevention of VaD/VCI is targeted to detect and diminish vascular risk factor.

Diagnosis of VaD/VCI relies on clinical history, neurologic examination, and neuropsychiatric testing. Symptoms of VaD/VCI are variable and depend upon the regions of the brain affected. The classic description of VaD/VCI is that of "stepwise" progression of cognitive impairment. Four clinical patterns of VCI are now recognized based upon the Vascular Impairment of Cognition Classification Consensus Study: subcortical ischemic VaD, poststroke dementia, multi-infarct dementia, and mixed dementia [92]. The role of imaging in the diagnosis of VaD/VCI is to increase confidence in the clinical diagnosis and to demonstrate evidence of superimposed or alternate pathology. The absence of vascular lesions such as prior infarcts and hemorrhage, the presence of specific atrophy patterns on structural brain imaging, or different patterns of brain metabolism and perfusion on FDG-PET/CT or brain perfusion SPECT/CT may help distinguish VaD from alternate dementia diagnoses [95].

The goal of imaging in patients with cognitive impairment with recent stroke and/or stepwise decline who are suspected to have VaD is to assess for potentially treatable structural brain abnormalities, which may mimic a clinical presentation of VaD, and to identify imaging features, which support or refute a clinical diagnosis of VaD. Identification of treatable structural brain abnormalities, which might mimic symptoms of VaD, will improve patient outcomes by allowing for timely intervention. Identification of imaging findings supporting a diagnosis of VaD would provide prognostic information for clinicians, patients, and their family members and help initiate earlier neuropsychiatric and medical therapy.

Amyloid PET/CT Brain
Brain amyloid PET/CT was found to be positive in up to 25% of patients with a clinical diagnosis of VaD [3]. Brain amyloid PET/CT can also support a diagnosis of subcortical VaD and poststroke dementia [96]. Because positive amyloid PET/CT is an imaging biomarker of AD, positive amyloid PET/CT in a patient with structural imaging findings of VaD would support the diagnosis of a mixed dementia.

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the initial imaging of patients with suspected VaD.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the initial imaging of patients with suspected VaD.

CT Head Without IV Contrast
CT head without IV contrast is an option for the initial imaging patients of patients with suspected VaD. Although there are no pathognomonic CT findings for VaD, CT can demonstrate acute intracranial hemorrhage, encephalomalacia, extensive white matter disease, parenchymal atrophy, and ventricular size; CT cannot readily detect microhemorrhages or superficial siderosis [92,95]. Although CT is relatively insensitive for acute infarcts, it can detect stroke mimics such as intracranial mass lesions.

CTA Head and Neck With IV Contrast
Although CT angiography (CTA) of the head and neck can detect evidence of cerebrovascular disease involving the cervical and intracranial arteries such as vascular occlusions, stenosis, atherosclerosis, and vasculopathy, it cannot establish a diagnosis of VaD. Neurovascular imaging may be useful in this clinical scenario as a complementary procedure when ordered in conjunction with structural imaging of the brain (eg, head CT).

FDG-PET/CT Brain
Brain FDG-PET/CT can demonstrate hypometabolism with a patchy, predominantly anterior distribution, which correlates with vascular lesions on structural brain MRI and is distinct from AD [28,97,98]. Thus, brain FDG-PET/CT is effective at differentiating AD from VaD. Differentiating FTD from VaD on brain FDG-PET/CT could be more difficult given similarities between the imaging findings and, as such, correlation with structural MRI and other clinical features, and is often needed [97].

MR Spectroscopy Head Without IV Contrast
Infarcts can demonstrate metabolic changes, which can occur in VaD. Elevated lactate relative to Cho and Cr as well as increased Cho/NAA and Cr/NAA ratios can be seen in infarcts; in contrast, white matter lesions can demonstrate increased Cho/NAA ratios [99]. Patients with VaD as well as other dementias were found to have lower NAA/Cr ratios than normal patients in the posterior cingulate gyri [17].

MRA Head Without and With IV Contrast
Although MRA of the head can detect evidence of intracranial vascular occlusions or stenosis, it cannot establish a diagnosis of VaD. MRA findings of cerebrovascular disease can be depicted without the use of IV contrast material. There is insufficient evidence to support the use of MRA head without and with IV contrast for the initial imaging of patients with suspected VaD.

MRA Head Without IV Contrast
Although MRA of the head can detect evidence of intracranial vascular occlusions or stenosis, it cannot establish a diagnosis of VaD. Neurovascular imaging may be useful in this clinical scenario as a complementary procedure when ordered in conjunction with structural imaging of the brain (eg, brain MRI).

MRA Neck Without and With IV Contrast
Although MRA of the neck can detect evidence of cerebrovascular disease, it cannot establish a diagnosis of VaD. Neurovascular imaging may be useful in this clinical scenario as a complementary procedure when ordered in conjunction with structural imaging of the brain (eg, brain MRI).

MRA Neck Without IV Contrast
Although MRA of the neck can detect evidence of cerebrovascular disease, it cannot establish a diagnosis of VaD. Neurovascular imaging may be useful in this clinical scenario as a complementary procedure when ordered in conjunction with structural imaging of the brain (eg, brain MRI).

MRI Functional (fMRI) Head Without IV Contrast
There is no relevant literature to support fMRI for the initial imaging of patients with suspected VaD.

MRI Head Without and With IV Contrast
MRI findings of VaD can be depicted without the use of IV contrast material. There is insufficient evidence to support the use of MRI head without and with IV contrast for the initial imaging of patients with suspected VaD.

MRI Head Without IV Contrast
MRI is more sensitive than CT for detecting the presence of encephalomalacia related to infarcts. Classic MRI findings in VaD include encephalomalacia from multiple cortical and subcortical infarcts, small but strategically placed lacunar infarcts, microhemorrhages, and white matter disease [28]. MRI with T2 FLAIR imaging can distinguish lacunar infarcts from perivascular spaces, the latter of which are also associated with vascular risk factors and small vessel disease [97]. Specific MRI findings such as the presence of multiple lacunar infarcts, white matter signal changes in the corpus callosum, anterior temporal lobes, and external capsule may be a clue to a diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy [94]. MRI findings of white matter lesions involving the corpus callosum in a patient with cognitive impairment, headaches, retinal artery abnormalities, and vestibulocochlear symptoms may indicate a diagnosis of Susac syndrome. Diffusion tensor imaging findings have been shown to correlate with cognitive/executive function in patients with VaD [100]. The presence of microhemorrhages does not correlate with cognitive performance in VaD but could represent CAA or chronic hypertension depending on their pattern of distribution, with deep gray nuclei involvement in the latter and peripheral involvement and superficial siderosis in the former [92,101].

In a study, a subset of patients with mixed VaD and AD were found to have specific imaging characteristics such as higher burden of white matter lesions with a frontal predominance, higher fractional anisotropy in normal-appearing white matter, and lower transverse relaxation rates within white matter lesions, suggesting that structural MRI with diffusion tensor imaging could help distinguish mixed dementia from pure VaD and AD [102]. Hippocampal volume loss is typically absent in pure VaD but present in AD or mixed dementia [92].

SPECT or SPECT/CT Brain Perfusion
Brain perfusion SPECT or SPECT/CT can demonstrate a "patchy" pattern of hypoperfusion, which can increase the likelihood of a diagnosis of VaD rather than AD, which tends to demonstrate a bilateral posterior pattern of hypoperfusion [48].

SPECT or SPECT/CT Brain Striatal
There is no relevant literature to support brain striatal SPECT or SPECT/CT for the initial imaging of patients with suspected VaD.

Tau PET/CT Brain
There is no relevant literature to support brain tau PET/CT for the initial imaging of patients with suspected VaD.

Variant 9: Adult. Cognitive impairment with gait disturbance or urinary incontinence. Suspect normal pressure hydrocephalus. Initial imaging.
NPH is a clinical syndrome characterized by a triad of gait disturbance, urinary incontinence, and cognitive impairments, which was first described by Hakim and Adams in 1965 [103]. Additional features include a normal CSF pressure on lumbar puncture, findings of communicating hydrocephalus on neuroimaging, and clinical improvement following CSF diversion (shunting) [103]. NPH is estimated to have a prevalence of 3.7% in patients >65 years of age and is a potentially reversible etiology of dementia following CSF diversion [103,104]. Patients typically present late in the course of the disease due to the slow and gradual nature of symptom onset, with gait alterations occurring early and cognitive impairment occurring later [104]. NPH can be comorbid with other neurodegenerative diseases, such as AD, which is detected in 20% to 57% of patients with NPH [105].

Classic imaging features of NPH include ventriculomegaly out of proportion to the degree of brain parenchymal volume loss, enlargement of lateral ventricular frontal and temporal horns, periventricular white matter T2 signal changes, thinning of the corpus callosum, a posterior callosal angle of 90 degrees or less, relative effacement of sulci near along the high convexities near the vertex and disproportionate enlargement of the sylvian fissures, a flow void in the cerebral aqueduct, and lack of an obstructing lesion. The combined findings of ventriculomegaly, sulcal effacement near vertex along the high convexities, and enlarged sylvian fissures are often described as disproportionately enlarged subarachnoid space hydrocephalus [106]. Disproportionately enlarged subarachnoid

space hydrocephalus is considered a subcategory of NPH and may correlate with positive response to shunting [106].

Clinical practice guidelines published by the American Academy of Neurology have concluded that shunting is potentially effective in idiopathic NPH, with a 96% chance of subjective improvement and 83% chance of improvement on timed gait testing at 6 months [103]. Predictors of clinical improvement following shunting include positive response to CSF drainage or repeated lumbar punctures and elevated outflow resistance during a CSF infusion test, and certain neuroimaging findings [103].

The goal of imaging of patients with cognitive impairment and gait disturbance and/or urinary incontinence with suspected NPH is to exclude other structural brain abnormalities, which could mimic clinical features of NPH and to identify imaging features supportive of a diagnosis of NPH. Imaging also allows for the identification of prognostic imaging features, which may determine the likelihood of a patient's response to surgical intervention, as well as the presence of additional comorbid neurodegenerative diseases in order to guide appropriate therapy. The benefit of imaging in these patients is to direct timely appropriate medical and/or surgical care, which could in turn improve patient outcomes and diminish morbidity.

Amyloid PET/CT Brain
A major differential consideration of cognitive impairment in patients with suspected NPH is AD. Brain amyloid PET/CT can detect comorbid AD pathology in patients with NPH and may help determine who will benefit from shunting [105]. However, there is insufficient evidence to support brain amyloid PET/CT for the initial imaging of patients with suspected NPH.

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the initial imaging of patients with suspected NPH.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the initial imaging of patients with suspected NPH.

CT Head Without IV Contrast
CT head without IV contrast can identify classic imaging findings of NPH, to include ventriculomegaly, a narrowed posterior callosal angle, effaced sulci along the high convexities and widened sylvian fissures, and periventricular white matter hypoattenuation, although MRI has a higher sensitivity for the latter finding [104]. However, CT cannot detect a cerebral aqueduct flow void and may be unable to detect small obstructing lesions along the course of the ventricular system, which might result in noncommunicating hydrocephalus.

DTPA Cisternography
In patients with NPH, diethylenetriamine pentaacetic acid (DTPA) cisternography is characterized by persistent radiotracer activity in the lateral ventricles and absence of radiotracer activity over the cerebral convexities on delayed imaging [106]. The use of SPECT/CT may provide better anatomic localization of radiotracer activity than planar imaging. Although some studies have shown that DTPA findings of NPH may correlate with positive response to shunting, clinical practice guidelines conclude that evidence is insufficient to proceed with shunting based upon DTPA cisternography findings alone [103,106].

FDG-PET/CT Brain
Brain FDG-PET/CT does not reliably demonstrate classic imaging findings of NPH, and there is insufficient evidence to support brain FDG-PET/CT for the initial imaging of patients with suspected NPH. Brain FDG-PET/CT can demonstrate a pattern of hypometabolism in the dorsal striatum with preserved cortical metabolism, which may help distinguish NPH from healthy patients and those with other dementias [107]. Brain FDG-PET/CT may also identify a comorbid neurodegenerative disease based upon metabolic patterns [105]. Postshunting increase in glucose metabolism on brain FDG-PET/CT was associated with clinical improvement in patients with NPH [105].

MR Spectroscopy Head Without IV Contrast
MR spectroscopy is typically not used for the initial imaging of patient with suspected NPH, because it cannot detect classic structural imaging biomarkers. Whereas NAA/Cho and NAA/Cr ratios in patients with NPH are significantly reduced relative to healthy control patients, MR spectroscopy cannot reliably distinguish between patients with NPH and other dementias [108]. Furthermore, MR spectroscopy findings do not correlate with CSF diversion outcomes in patients with NPH [108].

MRI Functional (fMRI) Head Without IV Contrast
There is no relevant literature to support fMRI brain without IV contrast for the initial imaging of patients with suspected NPH.

MRI Head Without and With IV Contrast
Because the imaging findings of NPH can be demonstrated on noncontrast brain MRI, contrast is not necessary for initial imaging. There is no relevant literature to support MRI head without and with IV contrast for the initial imaging of patients with suspected NPH.

MRI Head Without IV Contrast
MRI brain without IV contrast readily detects imaging findings of NPH. These findings include ventriculomegaly out of proportion to the degree of brain parenchymal atrophy with an Evans Index of >0.3 (the Evans Index is the ratio of the maximal frontal horn width to the maximal width of the inner table of the calvarium), high convexity tight sulci and widened sylvian fissures, lack of obstructing lesions along the course of the ventricular system, widened frontal and temporal horns, a posterior callosal angle of 90 degrees or less, periventricular white matter T2 signal abnormality, and a flow void in the cerebral aqueduct [104]. Patients with suspected NPH and a high velocity aqueductal flow void measured on phase contrast MRI and an abnormal CSF infusion test are more likely to have a positive response to shunting [103]. An anterior callosal angle measurement can also differentiate between patients with NPH and AD with a high sensitivity and specificity [104]. Diffusion tensor imaging findings of reduced fractional anisotropy in certain brain regions can help distinguish between patients with NPH and AD [104]. MRI with arterial spin labeling perfusion can demonstrate reduced relative cerebral blood flow in the periventricular white matter, basal ganglia, and thalami [104].

SPECT or SPECT/CT Brain Perfusion
In patients with suspected NPH, patients with impaired cerebral blood flow reactivity to acetazolamide challenge on brain perfusion SPECT imaging are possibly more likely to respond to shunting [103]. However, brain perfusion SPECT or SPECT/CT does not reliably demonstrate classic imaging features of NPH.

SPECT or SPECT/CT Brain Striatal
There is no relevant literature to support brain striatal SPECT or SPECT/CT for the initial imaging of patients with suspected NPH.

Tau PET/CT Brain
There is no relevant literature to support brain tau PET/CT for the initial imaging of patients with suspected NPH.

Variant 10: Adult. Rapidly progressive dementia. Initial imaging.
Prototypical dementia syndromes such as AD, FTD, DLB, and VaD typically have a slow, insidious, or gradual onset over the course of several years. Although there is no clear definition of a RPD, the term is applied to a clinical syndrome that progresses from first symptom onset to clinical dementia in less than 1 to 2 years, with many occurring over the course of weeks to months [109]. RPDs have a vast array of clinical presentations, and the differential diagnosis for a RPD is quite broad. A retrospective review of 2,535 patients with RPD referred to a subspecialty RPD clinic at a large institution over the course of 13 years revealed prion diseases in 75% and nonprion diseases in 25%; of the 622 patients evaluated in-person at the institution, prion diseases made up 56% and nonprion diseases made up 44% [109].

A simplistic approach to the differential diagnosis of a RPD is to use 3 broad categories: atypical presentation of a typical dementia syndrome, prion disease, and other. Atypical presentations of typical dementia syndromes such as AD, FTD, DLB, corticobasal degeneration, progressive supranuclear palsy, multiple system atrophy, and Huntington disease can occur in early onset or genetic variants of those diseases [110]. Prion diseases resulting in RPD include sporadic and acquired Creutzfeldt-Jakob disease (CJD) and genetic prion diseases [109]. The differential diagnosis of nonneurodegenerative and nonprion disease RPD is tremendously diverse and includes infectious etiologies, HIV and AIDS-related etiologies, inflammatory and autoimmune conditions, malignancy and paraneoplastic etiologies, toxic, nutritional, and metabolic etiologies, and neurovascular conditions [110]. Each category of disease carries unique clinical features and specific clinical, laboratory, and imaging testing requirements.

Clinical evaluation and diagnosis of a RPD includes a thorough clinical history and physical examination, neuropsychiatric testing, comprehensive laboratory investigation to include analysis of various CSF biomarkers,

electroencephalography (EEG) in some cases, and imaging. Imaging is a mainstay in the clinical workup. A presentation of RPD should prompt an urgent workup because many, but not all, RPDs are reversible and treatable.

The goal of imaging of patients with RPD is to assess for imaging evidence of suspected prion disease or nonprion disease (eg, autoimmune encephalitis), which could result in a clinical presentation of RPD. Prompt identification of either prion disease or a nonprion related structural abnormality can inform prognosis and may allow for the timely initiation of appropriate therapy, thereby potentially improving patient outcomes.

Initial imaging of patients with suspected prototypical dementia syndromes such as MCI, typical and atypical presentations of AD, FTD, DLB, VaD, and NPH are discussed elsewhere in this narrative. Imaging of patients with movement disorders with neurodegenerative diseases, neuroinflammatory diseases, cerebrovascular diseases, altered mental status, and delirium are discussed in other ACR Appropriateness Criteria.

Amyloid PET/CT Brain
There is no relevant literature to support brain amyloid PET/CT for the initial imaging of patients with RPD. However, brain amyloid PET/CT may be considered later in the clinical investigation if there is clinical suspicion of an atypical presentation of a neurodegenerative disease resulting in RPD.

CT Head With IV Contrast
There is no relevant literature to support CT head with IV contrast for the initial imaging of patients with RPD.

CT Head Without and With IV Contrast
There is no relevant literature to support CT head without and with IV contrast for the initial imaging of patients with RPD.

CT Head Without IV Contrast
CT head without IV contrast can detect the presence of structural lesions, which may result in a clinical presentation of RPD, such as subdural hematomas, large intracranial mass lesions, hydrocephalus, parenchymal attenuation changes related to various underlying conditions, and other acute intracranial pathology that may necessitate urgent clinical management. However, tissue contrast resolution of CT is low compared with MRI, and CT without IV contrast cannot readily detect many of the varied pathology which can result in a RPD presentation, particularly prion disease.

FDG-PET/CT Brain
There is no relevant literature to support brain FDG-PET/CT for the initial imaging of patients with RPD. However, brain FDG-PET/CT may be considered later in the clinical investigation if there is clinical suspicion of an atypical presentation of a neurodegenerative disease resulting in RPD.

MR Spectroscopy Head Without IV Contrast
There is no relevant literature to support MR spectroscopy of the brain without IV contrast for the initial imaging of patients with RPD. However, MR spectroscopy may have usefulness later in the clinical workup of RPD when specific entities in a differential diagnosis are being evaluated.

MRI Functional (fMRI) Head Without IV Contrast
There is no relevant literature to support fMRI of the brain without IV contrast for the initial imaging of patients with RPD.

MRI Head Without and With IV Contrast
MRI of the brain without and with IV contrast is central to the imaging workup of RPD. MRI possesses the appropriate tissue contrast, sensitivity, and specificity to detect various prion-related, neurodegenerative, and other diverse etiologies of RPD. The addition of contrast can potentially increase sensitivity and specificity for detection of various etiologies of RPD, specifically infectious, inflammatory, and neoplastic/paraneoplastic etiologies.

Prion-related causes of RPD such as CJD are readily demonstrated on MRI and manifest as hyperintense signal on T2 and T2 FLAIR sequences and DWI sequences, with cortical and deep gray matter involvement. When the deep gray nuclei are involved, the "hockey stick" or "pulvinar" sign are often present, which is caused by confluent high signal in the dorsomedial and posterior thalami; this sign is seen in variant and other forms of CJD and are more sensitive than positive 14-3-3 protein in CSF and periodic sharp wave complexes on EEG [111]. One study comparing MRI findings in patients with RPD caused by prion disease and nonprion disease demonstrated that negative DWI effectively excludes a diagnosis of prion disease and that specific DWI positive patterns differentiate CJD from other causes of RPD [112].

Structural MRI can depict specific atrophy patterns, which could suggest an atypical presentation of an otherwise typical dementia as an etiology of RPD, although atrophy usually is a late finding in these disorders. MRI can also depict imaging findings of infectious etiologies of RPD, such as viral encephalitides; HIV and AIDS-related causes of RPD such as progressive multifocal leukoencephalopathy, AIDS-dementia complex, toxoplasmosis, and CNS lymphoma; Lyme disease encephalitis; CNS Whipple disease; measles/subacute sclerosing panencephalitis; and neurosyphilis. MRI also has a role in the detection of neuroinflammatory and autoimmune disorders such as multiple sclerosis and other demyelinating disorders, Hashimoto encephalopathy, neurosarcoidosis, CNS vasculitis, glial fibrillary acidic protein astrocytopathy, neuro-Behcet disease, and autoimmune encephalitides. Malignancy-related conditions such as lymphoma, metastatic disease, lymphomatoid granulomatosis, and paraneoplastic limbic encephalitis can result in RPD and are readily demonstrated on MRI. Finally, MRI is useful in detecting a wide array of toxic and metabolic etiologies of RPD such as Wernicke encephalopathy and other nutritional deficiencies, osmotic demyelination syndrome, Wilson disease, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [111]. Dural arteriovenous fistulae have also been reported as etiologies of RPD for which MRI and MRA have a role [113].

MRI Head Without IV Contrast
MRI of the brain without IV contrast is central to the imaging workup of RPD. It possesses the appropriate tissue contrast, sensitivity, and specificity to detect various prion-related, neurodegenerative, and other diverse etiologies of RPD.

Prion-related causes of RPD such as CJD are readily demonstrated on MRI and manifest as hyperintense signal on T2 and T2 FLAIR sequences and DWI sequences, with cortical and deep gray matter involvement. When the deep gray nuclei are involved, the "hockey stick" or "pulvinar" sign are often present, which is caused by confluent high signal in the dorsomedial and posterior thalami; this sign is seen in variant and other forms of CJD and are more sensitive than positive 14-3-3 protein in CSF and periodic sharp wave complexes on EEG [111]. One study comparing MRI findings in patients with RPD caused by prion disease and nonprion disease demonstrated that negative DWI effectively excludes a diagnosis of prion disease and that specific DWI positive patterns differentiate CJD from other causes of RPD [112].

Structural MRI can depict specific atrophy patterns, which could suggest an atypical presentation of an otherwise typical dementia as an etiology of RPD, although atrophy usually is a late finding in these disorders. MRI can also depict imaging findings of infectious etiologies of RPD, such as viral encephalitides; HIV and AIDS-related causes of RPD such as progressive multifocal leukoencephalopathy, AIDS-dementia complex, toxoplasmosis, and CNS lymphoma; Lyme disease encephalitis; CNS Whipple disease; measles/subacute sclerosing panencephalitis; and neurosyphilis. MRI also has a role in detection of neuroinflammatory and autoimmune disorders such as multiple sclerosis and other demyelinating disorders, Hashimoto encephalopathy, neurosarcoidosis, CNS vasculitis, glial fibrillary acidic protein astrocytopathy, neuro-Behcet disease, and autoimmune encephalitides. Malignancy-related conditions such as lymphoma, metastatic disease, lymphomatoid granulomatosis, and paraneoplastic limbic encephalitis can result in RPD and are readily demonstrated on MRI. Finally, MRI is useful in detecting a wide array of toxic and metabolic etiologies of RPD such as Wernicke encephalopathy and other nutritional deficiencies, osmotic demyelination syndrome, Wilson disease, and mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes [111]. Dural arteriovenous fistulae have also been reported as etiologies of RPD for which MRI and MRA have a role [113].

SPECT or SPECT/CT Brain Perfusion
There is no relevant literature to support brain perfusion SPECT or SPECT/CT for the initial imaging of patients with RPD. However, brain perfusion SPECT or SPECT/CT may be considered later in the clinical investigation if there is clinical suspicion of an atypical presentation of a neurodegenerative disease resulting in RPD.

SPECT or SPECT/CT Brain Striatal
There is no relevant literature to support brain striatal SPECT or SPECT/CT for the initial imaging of patients with RPD. However, brain striatal SPECT or SPECT/CT may be considered later in the clinical investigation if there is clinical suspicion of an atypical presentation of a neurodegenerative disease resulting in RPD.

Tau PET/CT Brain
There is no relevant literature to support brain tau PET/CT for the initial imaging of patients with RPD. However, brain tau PET/CT may be considered later in the clinical investigation if there is clinical suspicion of an atypical presentation of a neurodegenerative disease resulting in RPD.

Summary of Highlights

This is a summary of the key recommendations from the variant tables. Refer to the complete narrative document for more information.

- **Variant 1**: For initial imaging of adult patients with MCI not meeting criteria for dementia, MRI brain without IV contrast, CT head without IV contrast, brain amyloid PET/CT, and brain FDG-PET/CT are recommended imaging studies to evaluate for treatable structural brain abnormalities that could mimic a clinical presentation of MCI and demonstrate imaging features, which may increase a patient's likelihood of developing dementia. Advanced MRI techniques such as MR spectroscopy and fMRI are not recommended for initial imaging but may be appropriate later in the imaging workup of these patients. Brain amyloid PET/CT and brain FDG-PET/CT are complementary modalities, which together have greater accuracy at predicting conversion of patients with MCI to AD. The use of IV contrast material is not generally necessary for the initial imaging of patients with MCI not meeting criteria for dementia. Brain perfusion and striatal SPECT/CT is not recommended for initial imaging in these patients.

- **Variant 2**: For initial imaging of adult patients with cognitive impairment and memory deficits in whom AD with a typical clinical presentation is suspected, MRI brain without IV contrast, brain FDG-PET/CT, and brain amyloid PET/CT are recommended to evaluate for treatable structural brain abnormalities that could mimic a clinical presentation of AD and to demonstrate imaging features, which support a clinical diagnosis of AD in conjunction with clinical history and additional biomarkers. The use of IV contrast material is not necessary for initial imaging of these patients. Brain fMRI and brain striatal SPECT/CT are not recommended for initial imaging of patients with a typical clinical presentation of AD. MR spectroscopy, CT head without IV contrast, brain perfusion SPECT/CT, and brain tau PET/CT may be useful as secondary imaging tests later in the clinical evaluation.

- **Variant 3**: For initial imaging of adult patients with cognitive impairment and memory deficits in whom AD with an atypical clinical presentation is suspected, MRI brain without IV contrast, CT head without IV contrast, brain amyloid PET/CT, brain FDG-PET/CT, and brain tau PET/CT are recommended to assess for treatable structural brain abnormalities, which may mimic an atypical clinical presentation of AD and to demonstrate imaging features that support or refute a clinical diagnosis of AD in conjunction with clinical history and other biomarkers. The use of IV contrast material is not necessary for initial imaging of these patients. Brain perfusion and brain striatal SPECT/CT may be useful secondary adjuncts later in the clinical workup but generally are not recommended for initial imaging. MR spectroscopy and brain fMRI are not recommended for initial imaging for these patient.

- **Variant 4**: For pretreatment imaging of adult patients with known AD for whom therapy with antiamyloid monoclonal antibodies is being considered, MRI brain without IV contrast and brain amyloid PET/CT are recommended to demonstrate imaging findings, which may preclude treatment candidates from undergoing therapy and to demonstrate the presence of amyloid in the brain parenchyma, respectively. IV contrast is not necessary for pretreatment imaging in these patients. Although brain tau PET/CT may be an appropriate imaging study for pretreatment imaging for these patients, brain amyloid PET/CT has a lower false-negative rate and is more highly recommended. Other imaging tests, such as CT head, MR spectroscopy, fMRI, brain perfusion SPECT/CT, and brain striatal SPECT/CT are not appropriate imaging tests for this clinical scenario and are not recommended.

- **Variant 5**: The goal of posttreatment imaging in patients with known AD who are undergoing therapy with antiamyloid monoclonal antibodies is primarily to detect the development of complications known as ARIA, which can manifest ARIA-E or ARIA-H. Patients who develop ARIA may require modification or cessation of their antiamyloid MAB therapy regimen. Only brain MRI can demonstrate the findings of ARIA and therefore is the only recommended imaging study for posttreatment imaging in this clinical scenario. A secondary goal of posttreatment imaging is to demonstrate clearance of amyloid from the brain parenchyma, which can potentially be demonstrated with brain amyloid PET/CT. Other imaging modalities such as head CT, MR spectroscopy, fMRI, brain FDG-PET/CT, brain perfusion and brain striatal SPECT/CT, and brain tau PET/CT cannot demonstrate ARIA and are therefore not recommended. IV contrast is not necessary to detect ARIA.

- **Variant 6**: For initial imaging of patients with cognitive impairment with behavioral abnormalities or progressive aphasia in whom FTD is suspected, MRI brain without IV contrast, CT head without IV contrast,

and brain FDG-PET/CT are recommended to assess for treatable structural brain abnormalities, which could mimic a clinical presentation of FTD, and to demonstrate imaging features that support a clinical diagnosis of FTD. Because of the overlap in clinical symptoms of AD and early FTD, brain amyloid PET/CT may be appropriate to assess for AD; in this situation, a negative brain amyloid PET/CT scan rules out a diagnosis of AD and supports a diagnosis of FTD. MRI brain without IV contrast and brain FDG-PET/CT are complementary modalities, which combined have high sensitivity and specificity for diagnosis of FTD. MR spectroscopy, fMRI, brain striatal SPECT/CT, and brain tau PET/CT are not recommended in this clinical scenario. The use of IV contrast is not necessary for initial imaging of these patients.

- **Variant 7**: For initial imaging of patients with cognitive impairment and visual hallucinations or Parkinsonian symptoms in whom DLB is suspected, MRI head without IV contrast, CT head without IV contrast, brain FDG-PET/CT, and brain striatal SPECT/CT are recommended to assess for treatable structural abnormalities, which may mimic a clinical presentation of DLB and to demonstrate imaging features which would support a diagnosis of DLB. IV contrast is generally not necessary for initial imaging in this clinical scenario. MR spectroscopy, fMRI, brain amyloid PET/CT, and brain tau PET/CT are not recommended for initial imaging in this clinical scenario.

- **Variant 8**: For initial imaging of adult patients with cognitive impairment with recent stroke or stepwise decline in whom VaD is suspected, MRI head without IV contrast is recommended to demonstrate treatable brain abnormalities, which might mimic a clinical presentation of VaD, and to demonstrate imaging features supportive of a clinical diagnosis of VaD. CT head without IV contrast may also be appropriate for initial imaging in this clinical scenario, although it is less sensitive for detection of acute infarcts than MRI. Although neurovascular imaging with CTA head and neck with IV contrast, MRA head without IV contrast, MRA neck without IV contrast, and MRA neck without and with IV contrast cannot diagnose VaD on their own, use of these imaging studies may be appropriate as adjunctive imaging tests in the initial workup of patients with suspected VaD to demonstrate neurovascular disease. MRA brain without and with IV contrast, MR spectroscopy, fMRI, brain amyloid PET/CT, brain tau PET/CT, brain perfusion SPECT/CT, brain striatal SPECT/CT, and brain FDG-PET/CT are not recommended for this clinical scenario. IV contrast with structural brain imaging with CT and MRI is not necessary for this clinical scenario.

- **Variant 9**: For initial imaging of patients with cognitive impairment and gait disturbance or urinary incontinence in whom NPH is suspected, MRI brain without IV contrast and CT head without IV contrast are recommended to demonstrate imaging features supportive of a diagnosis of NPH and which may predict a positive response to shunting. DTPA cisternography may be an appropriate initial imaging test to diagnose NPH, but it does not demonstrate imaging features, which may predict positive response to shunting. Imaging studies performed with IV contrast are not necessary for this clinical scenario. MR spectroscopy, fMRI, brain amyloid PET/CT, brain FDG-PET/CT, brain perfusion SPECT/CT, brain striatal SPECT/CT, and brain tau PET/CT are not recommended for initial imaging in this clinical scenario.

- **Variant 10**: For initial imaging of adult patients with RPD, MRI brain without and with IV contrast and MRI brain without IV contrast are recommended imaging tests, which can demonstrate structural abnormalities that may indicate prion-related, neurodegenerative, and other diverse etiologies of RPD such as infectious/inflammatory processes, demyelinating diseases, neoplastic and paraneoplastic processes, toxic/metabolic disorders, and vasculitis/vasculopathies. CT head without IV contrast can also demonstrate the presence of potentially treated structural abnormalities, which may result in RPD such as subdural hematomas, large intracranial mass lesions, hydrocephalus, and parenchymal attenuation changes related to various underlying etiologies. MR spectroscopy, fMRI, brain amyloid PET/CT, CT head with IV contrast, CT head without and with IV contrast, brain FDG-PET/CT, brain perfusion SPECT/CT, brain striatal SPECT/CT, and brain tau PET/CT are not recommended for the initial imaging of RPD.

Supporting Documents

The evidence table, literature search, and appendix for this topic are available at https://acsearch.acr.org/list. The appendix includes the strength of evidence assessment and the final rating round tabulations for each recommendation.

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

Gender Equality and Inclusivity Clause

The ACR acknowledges the limitations in applying inclusive language when citing research studies that pre-dates the use of the current understanding of language inclusive of diversity in sex, intersex, gender and gender-diverse people. The data variables regarding sex and gender used in the cited literature will not be changed. However, this guideline will use the terminology and definitions as proposed by the National Institutes of Health [114].

Appropriateness Category Names and Definitions

Appropriateness Category Name	Appropriateness Rating	Appropriateness Category Definition
Usually Appropriate	7, 8, or 9	The imaging procedure or treatment is indicated in the specified clinical scenarios at a favorable risk-benefit ratio for patients.
May Be Appropriate	4, 5, or 6	The imaging procedure or treatment may be indicated in the specified clinical scenarios as an alternative to imaging procedures or treatments with a more favorable risk-benefit ratio, or the risk-benefit ratio for patients is equivocal.
May Be Appropriate (Disagreement)	5	The individual ratings are too dispersed from the panel median. The different label provides transparency regarding the panel's recommendation. "May be appropriate" is the rating category and a rating of 5 is assigned.
Usually Not Appropriate	1, 2, or 3	The imaging procedure or treatment is unlikely to be indicated in the specified clinical scenarios, or the risk-benefit ratio for patients is likely to be unfavorable.

Relative Radiation Level Information

Potential adverse health effects associated with radiation exposure are an important factor to consider when selecting the appropriate imaging procedure. Because there is a wide range of radiation exposures associated with different diagnostic procedures, a relative radiation level (RRL) indication has been included for each imaging examination. The RRLs are based on effective dose, which is a radiation dose quantity that is used to estimate population total radiation risk associated with an imaging procedure. Patients in the pediatric age group are at inherently higher risk from exposure, because of both organ sensitivity and longer life expectancy (relevant to the long latency that appears to accompany radiation exposure). For these reasons, the RRL dose estimate ranges for pediatric examinations are lower as compared with those specified for adults (see Table below). Additional information regarding radiation dose assessment for imaging examinations can be found in the ACR Appropriateness Criteria® Radiation Dose Assessment Introduction document [115].

Relative Radiation Level Designations		
Relative Radiation Level*	**Adult Effective Dose Estimate Range**	**Pediatric Effective Dose Estimate Range**
⚪	0 mSv	0 mSv
☢	<0.1 mSv	<0.03 mSv
☢☢	0.1-1 mSv	0.03-0.3 mSv
☢☢☢	1-10 mSv	0.3-3 mSv
☢☢☢☢	10-30 mSv	3-10 mSv
☢☢☢☢☢	30-100 mSv	10-30 mSv

*RRL assignments for some of the examinations cannot be made, because the actual patient doses in these procedures vary as a function of a number of factors (eg, region of the body exposed to ionizing radiation, the imaging guidance that is used). The RRLs for these examinations are designated as "Varies."

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