

**American College of Radiology  
ACR Appropriateness Criteria®**

**Clinical Condition:** Dementia and Movement Disorders

**Variant 1:** Probable Alzheimer's disease.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8	This procedure is used in structural evaluation; volumetric determinations are generally not appropriate in routine clinical imaging.	O
MRI head without and with IV contrast	7		O
CT head without IV contrast	6		☼☼☼
FDG-PET/CT head	6	This procedure may be used as a problem-solving technique in differentiating dementias.	☼☼☼☼
CT head without and with IV contrast	4		☼☼☼
CT head with IV contrast	4		☼☼☼
MR spectroscopy head without IV contrast	3		O
MRI functional (fMRI) head without IV contrast	2	This procedure is used for research purposes.	O
Tc-99m HMPAO SPECT head	2		☼☼☼☼
Amyloid PET/CT head	2		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 2:** Possible Alzheimer's disease.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8	This procedure is used in structural evaluation; volumetric determinations are generally not appropriate in routine clinical imaging.	O
MRI head without and with IV contrast	7		O
FDG-PET/CT head	6	This procedure may be used as a problem-solving technique in differentiating dementias.	☼☼☼☼
CT head without IV contrast	6		☼☼☼
CT head without and with IV contrast	5		☼☼☼
CT head with IV contrast	5		☼☼☼
MR spectroscopy head without IV contrast	3		O
Amyloid PET/CT head	3		☼☼☼
Tc-99m HMPAO SPECT head	2		☼☼☼☼
MRI functional (fMRI) head without IV contrast	2		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:** Dementia and Movement Disorders

**Variant 3:** Suspected frontotemporal dementia.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8	This procedure is used in structural evaluation; volumetric determinations are generally not appropriate in routine clinical imaging.	O
MRI head without and with IV contrast	7		O
FDG-PET/CT head	6	This procedure may be used as a problem-solving technique in differentiating dementias.	☼☼☼☼
CT head without IV contrast	6		☼☼☼
CT head without and with IV contrast	4		☼☼☼
CT head with IV contrast	4		☼☼☼
MR spectroscopy head without IV contrast	3		O
MRI functional (fMRI) head without IV contrast	2		O
Tc-99m HMPAO SPECT head	2		☼☼☼☼
Amyloid PET/CT head	2		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 4:** Suspected dementia with Lewy bodies.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8		O
MRI head without and with IV contrast	7		O
FDG-PET/CT head	6		☼☼☼☼
CT head without IV contrast	6		☼☼☼
Tc-99m HMPAO SPECT head	5		☼☼☼☼
CT head without and with IV contrast	5		☼☼☼
CT head with IV contrast	5		☼☼☼
I-123 Ioflupane SPECT head	5		☼☼☼
I-123 IMP SPECT head	5		☼☼☼
MR spectroscopy head without IV contrast	3		O
MRI functional (fMRI) head without IV contrast	2		O
Amyloid PET/CT head	2		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:** Dementia and Movement Disorders

**Variant 5:** Suspected vascular dementia.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without and with IV contrast	8		O
MRI head without IV contrast	7		O
CT head without IV contrast	6		☼☼☼
MRA head without IV contrast	6		O
MRA neck without and with IV contrast	6		O
CTA head and neck with IV contrast	6		☼☼☼
US duplex Doppler carotid	6		O
CT head without and with IV contrast	5		☼☼☼
CT head with IV contrast	5		☼☼☼
FDG-PET/CT head	4		☼☼☼☼
MRA neck without IV contrast	4	Consider this procedure if gadolinium is contraindicated.	O
MRA head without and with IV contrast	3		O
Tc-99m HMPAO SPECT head	2		☼☼☼☼
MR spectroscopy head without IV contrast	2		O
MRI functional (fMRI) head without IV contrast	2		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 6:** Suspected prion disease (Creutzfeld-Jakob, iatrogenic, or variant).

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8	Include diffusion-weighted imaging with this procedure.	O
MRI head without and with IV contrast	7	Include diffusion-weighted imaging with this procedure.	O
CT head without IV contrast	6		☼☼☼
CT head without and with IV contrast	5		☼☼☼
CT head with IV contrast	5		☼☼☼
MR spectroscopy head without IV contrast	5		O
Tc-99m HMPAO SPECT head	5	Consider this procedure for problem solving.	☼☼☼☼
FDG-PET/CT head	5		☼☼☼☼
I-123 IMP SPECT head	3		☼☼☼
MRI functional (fMRI) head without IV contrast	2		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:** Dementia and Movement Disorders

**Variant 7:** Suspected normal pressure hydrocephalus.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8		O
MRI head without and with IV contrast	7		O
CT head without IV contrast	6		☼☼☼
CT head without and with IV contrast	5		☼☼☼
CT head with IV contrast	5		☼☼☼
Cisternography	4		☼☼☼
MR spectroscopy head without IV contrast	3		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 8:** Suspected Huntington disease.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8		O
MRI head without and with IV contrast	7		O
CT head without IV contrast	5		☼☼☼
Tc-99m HMPAO SPECT head	3		☼☼☼☼
FDG-PET/CT head	3		☼☼☼☼
MR spectroscopy head without IV contrast	3		O
CT head without and with IV contrast	3		☼☼☼
CT head with IV contrast	3		☼☼☼
MRI functional (fMRI) head without IV contrast	2		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:** Dementia and Movement Disorders

**Variant 9:** Clinical features suggestive of neurodegeneration with brain iron accumulation.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8		O
MRI head without and with IV contrast	7		O
CT head without IV contrast	5		☼☼☼
CT head without and with IV contrast	4		☼☼☼
CT head with IV contrast	4		☼☼☼
MR spectroscopy head without IV contrast	3		O
MRI functional (fMRI) head without IV contrast	3		O
Tc-99m HMPAO SPECT head	3	Consider this procedure for problem solving.	☼☼☼☼
FDG-PET/CT head	3	Consider this procedure for problem solving.	☼☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 10:** Parkinson disease. Typical clinical features. Responsive to levodopa.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	7	Consider this procedure for problem solving.	O
MRI head without and with IV contrast	7	Consider this procedure for problem solving.	O
CT head without IV contrast	6		☼☼☼
CT head without and with IV contrast	5		☼☼☼
CT head with IV contrast	5		☼☼☼
I-123 Ioflupane SPECT head	4		☼☼☼
Tc-99m HMPAO SPECT head	3		☼☼☼☼
FDG-PET/CT head	3		☼☼☼☼
MR spectroscopy head without IV contrast	3		O
MRI functional (fMRI) head without IV contrast	2		O
Amyloid PET/CT head	2		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Clinical Condition:** Dementia and Movement Disorders

**Variant 11:** Parkinsonian syndrome. Atypical clinical features. Not responsive to levodopa.

Radiologic Procedure	Rating	Comments	RRL*
MRI head without IV contrast	8		O
MRI head without and with IV contrast	7		O
I-123 Ioflupane SPECT head	6		☼☼☼
CT head without IV contrast	5		☼☼☼
CT head without and with IV contrast	4		☼☼☼
CT head with IV contrast	4		☼☼☼
Tc-99m HMPAO SPECT head	3		☼☼☼☼
FDG-PET/CT head	3		☼☼☼☼
MR spectroscopy head without IV contrast	3		O
MRI functional (fMRI) head without IV contrast	2		O
Amyloid PET/CT head	2		☼☼☼
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

**Variant 12:** Motor neuron disease.

Radiologic Procedure	Rating	Comments	RRL*
MRI spine without IV contrast	8	With this procedure, the patient may need multilevel imaging.	O
MRI head without IV contrast	8		O
MRI spine without and with IV contrast	7	With this procedure, the patient may need multilevel imaging.	O
MRI head without and with IV contrast	7		O
CT head without IV contrast	5		☼☼☼
CT head without and with IV contrast	4		☼☼☼
CT head with IV contrast	4		☼☼☼
MR spectroscopy head without IV contrast	3		O
Tc-99m HMPAO SPECT head	3	Consider this procedure for problem solving.	☼☼☼☼
FDG-PET/CT head	3	Consider this procedure for problem solving.	☼☼☼☼
MRI functional (fMRI) head without IV contrast	2		O
<b>Rating Scale:</b> 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate			<b>*Relative Radiation Level</b>

## DEMENTIA AND MOVEMENT DISORDERS

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### **Summary of Literature Review**

#### **Introduction/Background**

Degenerative disease of the central nervous system (CNS) is a growing public health concern. The prevalence of dementia, one of the leading degenerative conditions, is expected to quadruple by 2050 [1]. Other degenerative diseases may affect the extrapyramidal system and the motor system.

Dementia is characterized by a significant loss of function in multiple cognitive domains without affecting the general level of arousal. Several forms are now recognized, including Alzheimer disease (AD), frontotemporal dementia (FTD), Lewy body disease, and the vascular dementias. Although the causes of most dementias remain elusive, genetic research has opened many frontiers in understanding the pathophysiology of heretofore enigmas such as AD [1,2]. Additionally, infectious, vascular, and toxic etiologies have become increasingly more appreciated as causes of cognitive decline. Trauma with brain injury may also be associated with premature dementia.

The extrapyramidal centers are large subcortical nuclear structures from which output systems emerge at several points. Since mediation and control of the corticospinal tract are the most prominent functions of these output systems, lesions of the extrapyramidal nuclei typically result in motor dysfunction and movement disorders of various types. Examples of extrapyramidal diseases include Huntington disease (HD), neurodegeneration with brain iron accumulation (NBIA), and Parkinsonism and its variants.

Finally, motor neuron diseases are a heterogeneous group of syndromes in which the upper and/or lower motor neurons degenerate. Amyotrophic lateral sclerosis (ALS) is the most frequent type of motor neuron disease, although an increasing number of variants are being recognized.

#### **Overview of Imaging Modalities**

Neuroimaging has played an increasing role in the understanding, diagnosis, and management of degenerative diseases of the CNS by supplementing and complementing current clinical tests. Neuroimaging may be divided into structural neuroimaging, which evaluates anatomic changes that occur in neurodegenerative conditions, and functional neuroimaging, which evaluates CNS activities such as blood flow and metabolism in neurodegenerative conditions. For example, structural neuroimaging with computed tomography (CT) and magnetic resonance imaging (MRI) has defined patterns and rates of brain volume loss in AD [3-5]. Moreover, structural neuroimaging may exclude treatable conditions that may present with dementia-like symptoms. Functional neuroimaging with MRI (fMRI), single photon emission CT (SPECT), and positron emission tomography (PET) have greatly assisted in the understanding of blood flow, metabolism, and amyloid deposition in demented patients [6]. Application of MR spectroscopy (MRS) has also yielded novel information about degenerative processes.

Despite tremendous insights into the pathophysiology of neurodegenerative processes provided by advanced imaging, application of these techniques in everyday practice does have certain limitations in patients with neurodegenerative disorders. First of all, frequently observed imaging findings of white-matter disease and

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general atrophy are nonspecific and may not necessarily refine the differential diagnosis of dementia or neurodegeneration [7]. Although many of the newer imaging techniques have penetrated the American markets, some of the advanced modalities are still not widely available in some communities. Additionally, many of these patients are frail and confused and may not tolerate long scanning times. Also, older patients may have significant comorbidities, such as cardiac pacemakers or renal insufficiency, which may limit the choice of available modalities and administration of intravenous contrast agents. Moreover, the cost of imaging must be weighed against its potential benefits, especially because most neurodegenerative diseases are considered incurable, have only limited available palliative medical therapies, and have no current options to slow disease progression. In an older study, Simon and Lubin [8] determined that CT might detect from 1,400 to 15,000 potentially treatable lesions per 100,000 demented patients scanned at an estimated cost of \$49 million in 1985, a cost now certainly much higher. The addition of MRI might allow the identification of 70 to 150 additional treatable cases but would almost double the cost according to these authors. Also, treating selected lesions detected on these scans would not necessarily guarantee return to prepresentation functional status, assuming patients were even appropriate candidates for the proposed treatment [8]. Finally, many of these elderly patients may have more than one condition contributing to the clinical manifestation of neurodegeneration.

### **Discussion of Imaging Modalities by Variant**

#### **Variant 1: Probable Alzheimer's disease.**

#### **Variant 2: Possible Alzheimer's disease.**

The National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA) in 1984 established the criteria for the definite (typical clinical presentation with pathologic verification), probable (typical clinical presentation without pathologic verification), and possible (atypical clinical features but no alternative diagnosis evident without pathologic verification) diagnosis of AD, the most frequent type of dementia in the United States and most European countries. Another related condition, mild cognitive impairment (MCI), is defined as a cognitive decline greater than expected for an individual's age and education level without significantly interfering with activities of daily life [9]. More than half of the patients with MCI progress to dementia within 5 years. The amnesic subtype of MCI may constitute a prodromal stage of AD [9]. In 2007, a revision of the NINCDS and ADRDA criteria for probable AD without pathologic verification was suggested to include typical clinical presentation with a progressive episodic memory defect for 6 months but also at least one abnormal imaging finding or cerebrospinal fluid (CSF) biomarker [10,11]. Imaging biomarkers include hippocampal and other areas of atrophy on volumetric MRI, parietal and temporal glucose hypometabolism on PET using fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) imaging, and abnormal amyloid PET imaging [10-12]. CSF biomarkers include reduced CSF beta-amyloid 42 and increased CSF tau, total and phosphorylated [10-12]. More recently, the National Institute of Aging/Alzheimer's Association workgroups have suggested diagnostic criteria for 3 phases of the disease: preclinical AD, symptomatic predementia, or MCI and AD dementia using these imaging and CSF biomarkers. In the preclinical stage, biomarkers (low CSF beta amyloid and amyloid PET) are markers of latent disease, whereas in the later symptomatic stages of MCI and AD dementia biomarkers (increased CSF tau, FDG-PET, and volumetric MRI) can document the cause of the dementia and may be used to document progression of disease [12]. Although promising, use of biomarkers for such tasks as imaging for the diagnosis of AD and to sort the differential diagnoses of AD is currently limited, partly due to the absence of quantitative metrics for AD. Other dementing illnesses may have abnormal amyloid deposition, and the specificity of CSF biomarkers is not established. Moreover, reliable prediction of progression to dementia in clinically normal patients with demonstrated amyloid deposition is also not established. Patients with suspected dementia should initially undergo clinical testing aimed at confirming the diagnosis, identifying the form or variant, and establishing the etiology.

The primary role of neuroimaging in the workup of patients with probable or possible AD has typically been to exclude other significant intracranial abnormalities, primarily because clinical diagnosis is inexact and the cost of a false-positive clinical diagnosis of AD, especially in cases of MCI, is very high. In general, the imaging findings in structural studies such as MRI are nonspecific but may nevertheless suggest other forms of dementia. Patients with possible AD have a greater incidence of other significant intracranial pathologies detected on neuroimaging studies than patients with probable AD. The American Academy of Neurology (AAN) has recommended that the routine use of structural neuroimaging such as a noncontrast CT or MRI examination may assist with the diagnosis of dementia [7,13]. Advanced methods such as volumetric MRI, amyloid PET, and FDG-PET are not routinely used in community or general practices for the diagnosis or differentiation of forms of dementia [10-12].



### *Positron Emission Tomography*

PET imaging in dementia can be divided into metabolic PET, which uses FDG as a marker for metabolism, and amyloid PET, which uses agents that bind to amyloid deposits within the brain. Metabolic PET imaging has been shown to provide greater diagnostic accuracy when compared with clinical evaluations without functional neuroimaging [7]. Hypometabolism on FDG-PET is thought to be related to decreased synaptic activity and is a biomarker of neurodegeneration or neuronal injury [11]. FDG-PET shows characteristic reductions of regional glucose metabolic rates in patients with probable and definite AD in the parietal, temporal, and posterior cingulate regions but does not reliably distinguish among other forms of dementia [14]. PET accurately discriminates AD patients from normal subjects with a sensitivity of 96% and specificity of 100% [14]. Quantitative FDG-PET measures may improve prediction of the progression to AD in patients with MCI [15]. Although the Centers for Medicare & Medicaid Services (CMS) have made FDG-PET available to Medicare recipients to assist with the diagnosis of dementia in the appropriate clinical setting (eg, to distinguish AD from FTD) in recognition of this usefulness [7], the AAN consensus group did not recommend routine FDG-PET for diagnosing AD [13].

PET has also been used to detect *in vivo* A $\beta$  amyloid in the brains of patients with AD. Until recently, this has been achieved using the carbon-11 Pittsburgh compound-B (PIB). This method, which requires an on-site cyclotron, however, is not widely available in clinical practice because of the very short half-life of this compound [16]. C11-PIB has been used to show that in patients with amnesic MCI, PIB-positive patients with abnormal amyloid deposition are significantly more likely to convert to AD [17]. Recently, three F-18-based amyloid PET agents, F-18 florbetapir, F-18 flutemetamol and F-18 florbetaben, have been approved for use by the Food and Drug Administration. These agents have been shown to be well tolerated, to distinguish patients with AD from healthy controls, and to correlate with amyloid load on pathology at autopsy [18-22]. Amyloid PET, however, may be positive in cognitively normal subjects who do not develop AD and in patients with other forms of non-AD dementia [23]. Although a negative amyloid PET scan likely means a low probability of AD, the patient may still harbor a non-AD neurodegenerative condition. Cortical uptake of amyloid radiotracers correlates with progression of AD [10,12]. Positive amyloid PET and low CSF beta amyloid 42 are considered biomarkers of amyloid deposition in the brain and potential indicators of preclinical AD [12].

The Amyloid Imaging Taskforce, which was convened by the Alzheimer's Association and the Society of Nuclear Medicine and Molecular Imaging, has recently proposed guidelines for the use of amyloid PET [24,25]. The taskforce suggests that amyloid PET may be useful and appropriate in patients with a cognitive complaint and confirmed impairment when AD is in the differential but the diagnosis is uncertain after evaluation by a dementia expert and the knowledge of the presence or absence of amyloid deposition is felt to add to patient care (although currently no treatment can slow AD progression, and the presence of amyloid may not be sufficiently predictive in many cases). The taskforce goes on to cite specific examples where amyloid PET might be useful: persistent or progressive unexplained MCI, possible AD and progressive dementia with early age of onset (65 or younger). The taskforce considered amyloid PET inappropriate in patients with probable AD with typical age of onset, to judge dementia severity, for patients with only unconfirmed cognitive complaints, or in asymptomatic individuals (positive family history, presence of apolipoprotein E, and nonmedical use such as insurance screening). A CMS-convened Medicare Evidence Development and Coverage Advisory Committee that met in January 2013 concluded there was low-to-intermediate confidence that amyloid PET would significantly contribute to the care of these patients. However, in its national coverage decision, CMS concluded that amyloid PET would be covered under a coverage with evidence development (CED) program [26]. The American College of Radiology and the Alzheimer's Association are sponsoring the "Imaging Dementia—Evidence for Amyloid Scanning (IDEAS) Study" (<https://clinicaltrials.gov/ct2/results?term=NCT02420756>), a CMS-approved CED study that is expected to begin accrual in early 2016 of over 18,000 patients.

### *Volumetric Structural Imaging*

CT-based and MRI-based volumetric measurements of the hippocampal formation are significantly smaller in patients with mild AD compared with controls and compared to patients with other forms of dementia. This finding correlates with a neuropathologic hallmark of AD, which is focal atrophy of the hippocampal formation. Although atrophy may be noted on visual inspection of MR images, semiautomated methods are available. Free and commercial software products are available. These techniques are time consuming and have yet to be commonly used in routine clinical practice but are standard in AD research. MRI volumetric calculations permit accurate differentiation of controls from patients with AD in 85%–100% of cases. Baseline and follow-up volumetric MRI predict conversion to AD in patients with MCI [27]. Automated MRI may distinguish between MCI and probable AD and then be a marker for disease severity [28]. A study comparing volumetric MRI to FDG-PET showed no benefit of FDG-PET over volumetric MRI in MCI and mild AD in documenting the

neurodegeneration [29]. Automated MRI volume methods may identify cognitively normal individuals at risk of memory decline [30], and abnormal patterns of atrophy can be seen up to 10 years before the onset of dementia [31,32]. Volumetric MRI, along with FDG-PET and high CSF tau, is felt to be a biomarker of neurodegeneration or neuronal injury and might be able to document and follow disease severity [12,28]. Although it is not as accurate as MRI, CT also permits detection of hippocampal atrophy in AD patients. Medial temporal lobe atrophy has also been observed in patients with MCI compared to cognitively normal individuals [33]. The presence of this sign has a high predictive value for the progression to dementia [9,34]. The AAN did not recommend quantitative volumetry of the hippocampus [13].

#### *Single Photon Emission Computed Tomography*

Regional cerebral blood flow determined using SPECT imaging with Tc-99m hexamethyl propylene amine oxime (HMPAO) shows bilateral temporoparietal or hippocampal hypoperfusion in patients with AD. Whether brain SPECT contributes substantially to diagnostic accuracy after a careful clinical examination using current diagnostic criteria is controversial. Although perfusion MRI is promising, SPECT remains superior in identifying pathologic perfusion [35]. Application of fMRI in dementia is also an emerging technique but remains an investigative tool [6]. An evidence-based review performed by the AAN concluded that SPECT imaging cannot be recommended for either the initial or the differential diagnosis of suspected dementia because it has not demonstrated superiority to clinical criteria [13]. Also, compared with PET, SPECT has a lower diagnostic accuracy and is inferior in its ability to separate healthy controls from patients with true dementia [36,37].

#### *MR Spectroscopy*

Hydrogen-1 MRS may permit identification of mild to moderate AD with a specificity and sensitivity that suggest the potential for clinical usefulness and may predict the conversion of MCI to dementia [38]. Studies of automated MRS for AD diagnosis have reported high sensitivity and moderate specificity. Findings in reported studies have varied, but decreased N-acetylaspartate (NAA) and increased myoinositol (mI) with the use of the NAA:mI ratio show the greatest promise [39]. Prospective studies are still lacking to validate this method for diagnosing AD. Functional MRI, diffusion-tensor MRI, and perfusion MRI have been used in AD and MCI patients but are still considered investigational tools at this time [6].

Of these neuroimaging tests, MR volumetric analysis of the hippocampal formation and PET assessment of regional glucose metabolism are the most diagnostic of AD. Determining the specific clinical applications of either of these studies in patients with probable or possible AD, MCI, or atypical dementias awaits additional investigation.

#### *Summary*

The value of conventional cross-sectional neuroimaging in the evaluation of a patient with possible AD or other dementing disorder is the exclusion of potentially treatable causes of the decline. CT is appropriate to exclude conditions such as subdural hematoma, frontal lobe tumor, or hydrocephalus, and MRI is sensitive to white-matter changes observed in vascular dementia (VaD) [40]. In patients with a diagnosis of probable AD, any of these neuroimaging studies may permit the accuracy to increase from the 80%–85% range to the 90%–100% range depending on the prevalence of the disorder in the subject population. In patients with possible AD or other atypical dementias, these neuroimaging studies may also permit a more accurate diagnosis. Combining volumetric MRI, PET, and CSF biomarkers may improve accuracy of the diagnosis of AD [41]. Volumetric MRI studies, PET studies, and possibly fMRI likely will play an important investigational role in the evaluation of new therapeutic drug strategies for treating AD [42]. Information derived from the Alzheimer's Disease Neuroimaging Initiative is likely to greatly impact the evaluation and management of this dementia [43].

#### **Variant 3: Suspected frontotemporal dementia.**

FTD is a neurodegenerative disorder commonly mistaken for AD. Pathologically, it includes a heterogeneous group of sporadic and familial neuropsychiatric disorders. Pick disease is one of the neuropathological entities of FTD. Unlike AD, which increases in frequency with age, FTD is rare after the age of 75.

MRI may show atrophy of the anterior temporal and frontal lobes. PET studies assessing regional glucose metabolism with FDG show the metabolic disturbance most prominent in the frontal and temporal lobes. SPECT studies assessing regional cerebral perfusion with HMPAO show frontal hypoperfusion. Although PET and SPECT could help to make the differential diagnosis between AD and FTD, they are not recommended for routine use at the present time because of the marked overlap of findings [13].

#### **Variant 4: Suspected dementia with Lewy bodies.**

Dementia with Lewy bodies (DLB) has been identified in a subgroup of demented patients demonstrating Lewy bodies in their brainstem and cortex on autopsy. It is now recognized as the second most prevalent neurodegenerative dementia in the elderly, causing up to 15% of cases [44].

Functional imaging of the dopamine transporter (I-123 Ioflupane) using SPECT may identify a defect in the nigrostriatal pathway that may occur in a variety of disorders including Parkinson disease (PD). I-123 Ioflupane striatal activity tends to be normal in AD and low in DLB and PD, however AD and DLB can coexist in the same patient, potentially confounding results [10,44]. Occipital hypoperfusion has been demonstrated using perfusion SPECT and occipital hypometabolism using PET [45] in DLB. In patients with DLB, MRI shows a preservation of hippocampal and medial temporal lobe volume, no occipital lobe atrophy despite abnormality on functional imaging, and atrophy of the putamen [46]. Striatal volume is low in DLB compared to AD, and the combination of low striatal volume on volumetric MRI and occipital hypoperfusion on perfusion SPECT using N-isopropyl-(iodine-123) p-iodoamphetamine ( $I^{123}$ -IMP) may aid in distinguishing DLB from AD [44].

#### **Variant 5: Suspected vascular dementia.**

Cerebral vascular disease, especially common in the elderly, may lead to VaD [10]. The main clinicopathological subtypes of VaD are large-vessel VaD and small-vessel VaD. Most patients with a diagnosis of VaD have small-vessel disease. Clinical and imaging tests that aid in distinguishing VaD from less treatable forms of dementia may be beneficial. One of the roles of neuroimaging, therefore, is to document the presence or absence of strokes. Although CT can detect the presence or absence of infarctions in patients with dementia, histopathologically verified cases of VaD with normal CT studies have been reported [14]. Thus, MRI is preferable to CT for detecting vascular lesions in patients with dementia.

Differentiation of VaD from either AD with superimposed cerebrovascular disease or mixed AD and VaD is especially difficult. On neuroimaging studies, extensive infarctions (cortical or lacunar or both) and white-matter changes (hyperintense on T2-weighted MRI or hypodense on CT) in a patient with dementia favor a contribution from VaD or mixed VaD and AD over AD. The absence or mild extent of these changes in a patient with dementia argues against a diagnosis of VaD.

FDG-PET in VaD shows multiple focal metabolic defects. SPECT is of little value in differentiating AD from VaD. MRS and fMRI are investigational and, to date, do not appear to clinically help establish a diagnosis of VaD or mixed VaD and AD.

Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy is an autosomal-dominant hereditary small-artery vasculopathy caused by mutations in the notch3 gene on chromosome 19. Clinically, the disease is characterized by migraine with aura, strokes and progressive subcortical dementia, and mood disturbances. MRI in these patients shows focal lacunar infarcts and leukoaraiosis. Lesion load increases with age. Besides familial anamnesis and clinical history, structural MRI changes in these patients help to suggest the diagnosis by showing characteristic hyperintense T2 or fluid-attenuated inversion recovery lesions, which predominate in the frontal, parietal, and anterior temporal cortexes and in the external capsule [47]. Diagnosis is confirmed by skin biopsy or detection of a pathogenic notch3 mutation on direct sequencing.

#### **Variant 6: Suspected prion disease (Creutzfeldt-Jakob, iatrogenic, or variant).**

Creutzfeldt-Jakob disease (CJD) is a fatal neurodegenerative disorder caused the accumulation of an abnormal form of the human prion protein PrP<sup>Sc</sup> in the brain. Recognized forms include sporadic CJD (sCJD), familial CJD (fCJD), variant CJD (vCJD), and iatrogenic CJD (iCJD). Although some variability exists, the most common MRI abnormality, other than progressive atrophy, is hyperintense signal on long-TR images in gray-matter structures, usually in the basal ganglia or thalami, and less commonly in the cortical gray matter. Bilateral hyperintensity on a T2-weighted MRI sequence at the level of the pulvinar (“pulvinar sign”) relative to the signal intensity of the anterior putamen may be useful for diagnosing vCJD [48]. Diffusion-weighted imaging (DWI) may be useful in diagnosing CJD [49]. Cortical diffusion abnormalities were present in 70 of 157 patients (45%) but were visible in 35 of 44 patients (80%) of the available DWI examinations. Basal ganglia were affected in 94 patients (60%), in particular in the caudate nucleus. The most sensitive sequences were DWI (64%) and PD-weighted (63%) [49]. MRI may aid the diagnosis of CJD, and incorporation of MRI in the diagnostic criteria has been proposed for sCJD [50].

Marked cerebral hypometabolism on FDG-PET in the early stages of CJD, when no parenchymal abnormalities are present on MRI, has been described. Similarly, focal hypoperfusion was detected with SPECT using  $I^{123}$ -IMP

before CT or MRI showed any abnormalities. Changes in cerebral metabolites using proton MRS have also been described in patients with CJD.

#### **Variant 7: Suspected normal pressure hydrocephalus.**

Normal-pressure hydrocephalus (NPH) is characterized by the clinical triad of dementia, gait disturbance, and urinary incontinence. Other diagnostic features include normal CSF pressure at lumbar puncture, communicating hydrocephalus documented on MRI or CT, and ventricular influx but no passage of isotope over the convexities on radionuclide cisternography.

Because dementia and other symptoms can be reversible with shunting and because patients with NPH who are not shunted may progress symptomatically, distinguishing responders from nonresponders is important. Several clinical, laboratory, and imaging signs may improve distinction between responders and nonresponders to shunting. Clinical features that favor shunt responsiveness include predominance of gait disturbance, mild to moderate degree of dementia, and rapid clinical progression of urinary incontinence. MRI or CT findings include at least moderate ventriculomegaly (with rounded frontal horns and marked enlargement of the temporal horns and third ventricle) and absence of or only mild cortical atrophy. Increased CSF flow void through the cerebral aqueduct on MRI appears to correlate with a good response to shunt surgery. Cine MRI with inflow technique showing hyperdynamic aqueductal CSF may also help in identifying shunt-responsive NPH patients. SPECT cisternography permits more accurate localization of radionuclide activity than planar cisternography, which partially superimposes different CSF compartments.

Evidence-based guidelines have been developed for diagnosing idiopathic NPH (INPH). In these guidelines, the patients are divided into probable INPH, possible INPH, or unlikely INPH. Brain imaging features for diagnosing probable INPH include ventricular enlargement not entirely attributable to cerebral atrophy or congenital enlargement (Evan index = maximal width of frontal horns/maximal width of inner skull  $>0.3$ ); no macroscopic obstruction of CSF flow; and at least one the following features: enlargement of the temporal horns, callosal angle of  $\geq 40^\circ$ , evidence of altered brain water content, and aqueductal or fourth ventricle flow void on MRI. Other brain imaging findings considered supportive of the diagnosis but not necessary for probable INPH are brain imaging performed before onset of symptoms showing smaller ventricular size; radionuclide cisternogram showing delayed clearance of radiotracer over the cerebral convexities; cine MRI study showing increased ventricular flow rate; and a SPECT acetazolamide challenge showing decreased periventricular perfusion that is not altered by acetazolamide [51].

#### **Variant 8: Suspected Huntington disease.**

HD is inherited in an autosomal-dominant fashion with complete penetrance. Clinical manifestations are choreoathetosis, rigidity, dementia, and emotional disturbance. Neuroimaging and pathology studies both show characteristic atrophy of the caudate and/or putamen. MRI also shows signal changes of the striatum, either hyperintensity or hypointensity on T2-weighted images. Neuronal loss accompanied by loss of myelin and gliosis likely results in the hyperintense signal, and iron accumulation likely accounts for the hypointense signal. Using voxel-based morphometry, it has been shown that patients with HD have significant volume reductions in almost all brain structures, including total cerebrum, total white matter, cerebral cortex, caudate, putamen, globus pallidus, amygdala, hippocampus, brainstem, and cerebellum when compared with healthy age-matched controls [52].

Localized MR spectroscopic studies have found increased lactate concentrations in the occipital cortex of symptomatic HD patients when compared with normal controls. Modification of activation pattern has been demonstrated using fMRI during a time-discriminated task in presymptomatic HD compared to control subjects [53]. SPECT may show hypometabolism of the striatum in HD and in other types of chorea.

#### **Variant 9: Clinical features suggestive of neurodegeneration with brain iron accumulation.**

NBIA is a heterogeneous group of disorders characterized by neurodegeneration and excessive iron deposition in the basal ganglia [54], also formerly known as Hallervorden-Spatz disease. Most patients with NBIA and all of those with the early-onset, rapidly progressive types have mutations in the gene encoding pantothenate kinase 2 (PANK 2) [55]. MRI findings in NBIA correlate with the presence or absence of PANK 2 mutations. All patients with the PANK 2 mutation show bilateral areas of hyperintensity within a hypointense zone in the medial globus pallidus on T2-weighted images. This pattern has been described as the “eye of tiger” [55]. MR imaging may help to distinguish the multiple subtypes of NBIA [56].

### *Other Neurodegenerative Disorders*

Many additional degenerative disorders of the brain have been described, and several organizational classifications have been proposed based on clinical, pathological, and immunohistochemical criteria. One such classification is based on demonstrated intracellular inclusions such as synuclein, a common protein found in the human brain, and tau protein, a protein associated with microtubules. Synucleinopathies include PD, which is characterized as an intraneuronal synucleinopathy with Lewy body inclusions and Lewy neurites, and multiple system atrophy (MSA), which is characterized as a glial cytoplasmic synucleinopathy with glial synuclein inclusions. MSA may be further subdivided into MSA-P, when parkinsonian features predominate, MSA-C, when ataxia predominates, and MSA-A, when autonomic dysfunction predominates. Tauopathies include progressive supranuclear palsy (PSP), corticobasal degeneration (CBD), and AD (previously discussed).

**Variant 10: Parkinson disease. Typical clinical features. Responsive to levodopa.**

**Variant 11: Parkinsonian syndrome. Atypical clinical features. Not responsive to levodopa.**

Parkinsonism may be caused by idiopathic PD, MSA, PSP, CBD, and other neurodegenerative conditions. A diagnosis of idiopathic PD is usually based on patient history and physical examination alone. When clinical signs and symptoms and response to medication are typical of PD, neuroimaging is not required [57]. In patients with unusual clinical features, incomplete or uncertain medication responsiveness, or clinical diagnostic uncertainty, imaging to exclude alternative pathologies may be indicated. MRI findings in PD are nonspecific, but imaging may suggest atypical Parkinsonian variants or secondary Parkinsonism [58].

A diminution of the width of the pars compacta on MRI may be seen in PD, however this sign is not reliably demonstrated in all patients. PET and SPECT tracer studies exploring the presynaptic nigrostriatal terminal function and the postsynaptic dopamine receptors have been unable to reliably classify the various Parkinson syndromes and may not reliably measure disease progression [59,60].

Elevations of lactate within the occipital lobes may be seen on proton MR spectroscopic studies in patients with PD. <sup>18</sup>F-dopa PET may detect frontal changes in PD. I-123 Ioflupane SPECT may improve diagnostic accuracy of a degenerative parkinsonian syndrome in patients with confusing clinical presentations but does not distinguish among the various etiologies of degenerative parkinsonism [61,62]. SPECT with <sup>123</sup>iodobenzamide may predict dopaminergic responsiveness in patients with Parkinsonism. FDG-PET may distinguish PD from other neurodegenerative Parkinsonian syndromes but does not reliably differentiate from among these atypical syndromes [63,64]. Results of FDG-PET studies in suspected early PD have not consistently shown its usefulness in predicting progression to definite disease [64,65].

### *Other Parkinsonian Syndromes*

The various MSA subtypes may have structural MRI findings, though these findings are not present in all patients and are nonspecific when present. Findings include patterns of atrophy and iron deposition. PET with <sup>18</sup>F-dopa does not reliably distinguish PD from MSA.

PSP, also called Steele-Richardson-Olszewski syndrome, is one of the common atypical Parkinsonian syndromes. Structural MRI changes such as putaminal hypointensity, periaqueductal hyperintensity, midbrain atrophy, and other measurements have been described in PSP [66]. However, the clinical usefulness of these imaging features for treatment decisions has not been demonstrated [63,67,68].

**Variant 12: Motor neuron disease.**

ALS is characterized predominantly by degeneration of the corticospinal tract and lower motor neurons. Neuroimaging abnormalities can often be traced from the lower spinal cord to the motor cortex. On MRI, corticospinal tract atrophy and hyperintensity may be seen on T2-weighted sequences. This high signal likely reflects characteristic histologic changes of myelin loss and gliosis. Hypointense signal on T2-weighted sequences may also be found in ALS, due to iron deposition. The anterior and lateral portions of the cord may be atrophic and flattened due to loss of motor neurons in the anterior horns and corticospinal tracts. Magnetization transfer measurements are useful for detecting abnormalities associated with degeneration of the pyramidal tract in patients with ALS [46].

Proton MRS reveals decreased NAA values in the sensorimotor cortex and brainstem of patients with ALS, consistent with neuronal dysfunction or loss, but MRS has not been shown useful in establishing the diagnosis. Involvement of the corticospinal tract in patients with ALS has been demonstrated using diffusion tensor imaging, even at an early stage [69].

## Summary of Recommendations

- The primary function of anatomic neuroimaging studies in evaluating the patient with dementia or movement disorder is to rule out structural causes that may be reversible.
- Lack of sensitivity and specificity of many neuroimaging techniques applied to a variety of neurodegenerative disorders has limited the role of neuroimaging in differentiating types of neurodegenerative disorders encountered in everyday practice.
- Neuroimaging is a valuable research tool and has provided insight into the structure and function of the brain in patients with neurodegenerative disorders.
- Advanced imaging techniques such as fMRI and MRS hold exciting investigative potential for better understanding of neurodegenerative disorders, but they are not considered routine clinical practice at this time.

## 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, both because of 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 to 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.

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”.		

## Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to [www.acr.org/ac](http://www.acr.org/ac).

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The ACR Committee on Appropriateness Criteria and its expert panels have developed criteria for determining appropriate imaging examinations for diagnosis and treatment of specified medical condition(s). These criteria are intended to guide radiologists, radiation oncologists and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. Only those examinations generally used for evaluation of the patient's condition are ranked. Other imaging studies necessary to evaluate other co-existent diseases or other medical consequences of this condition are not considered in this document. The availability of equipment or personnel may influence the selection of appropriate imaging procedures or treatments. Imaging techniques classified as investigational by the FDA have not been considered in developing these criteria; however, study of new equipment and applications should be encouraged. The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination.