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CDI Quality Institute PLE Neurocognitive Disorders AUC

2020 Update

Appropriateness of advanced imaging procedures* in patients with a suspected neurocognitive disorder:

*Including MRI, Functional MRI (fMRI), MR spectroscopy, Diffusion-Tensor Imaging (DTI), CT, Nuclear Medicine, SPECT, PET, and I-MIBG Cardiac Scintigraphy

Abbreviation list:

AAN	American Academy of Neurology
ACR	American College of Radiology
AD	Alzheimer's disease
AIT	Amyloid Imaging Task Force
APA	American Psychiatric Association
aPET	Amyloid positron emission tomography
AUC	Appropriate Use Criteria
bvFTD	Behavioral variant FTD
^{11}C-PIB	C-labelled Pittsburgh compound B
CSF	Cerebrospinal fluid
CT	Computed tomography
DAT	Dopamine transporter
DLB	Dementia with Lewy bodies
DTI	Diffusion tensor imaging
ECD	Ethylcysteinate dimer
EFNS	European Federation of the Neurological Societies
ENS	European Neurological Society
FDG	Fluorodeoxyglucose
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
FTD	Frontotemporal dementia
FTLD	Frontotemporal lobar degeneration
HMPAO	Hexamethylpropyleneamine oxime
iNPH	Idiopathic normal pressure hydrocephalus
MCI	Mild cognitive impairment
MIBG	Meta-iodobenzylguanidine
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
MTL	Medial temporal lobes
NIA-AA	National Institute on Aging and Alzheimer's Association
NICE	National Institute for Health and Care Excellence
NPH	Normal pressure hydrocephalus
PET	Positron emission tomography
PPA	Primary progressive aphasia
SIGN	Scottish Intercollegiate Guidelines Network
SNMMI	Society of Nuclear Medicine and Molecular Imaging
SPECT	Single-photon emission computerized tomography
SUVR	Standardized uptake value ratio
VaD	Vascular dementia

Mild Cognitive Impairment (MCI):

- **Green** – MRI brain without contrast
- **Yellow** – CT head without contrast*
- **Yellow** – Amyloid PET** or FDG-PET** in atypical cases or when an Alzheimer's dementia subtype is suspected, and all of the following apply:
    - at specialist request
    - all other tests (history, physical, structural imaging, lab testing) are inconclusive,
    - other diagnoses have been excluded by MRI or CT and
    - the results will change management
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline
- **Red** – fMRI; MRS; Perfusion (HMPAO or ECD) SPECT; Dopaminergic (DAT) SPECT; I-MIBG cardiac scintigraphy; DTI

* The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

**Amyloid PET and FDG-PET imaging may be useful in the evaluation of patients with amnestic MCI. If positive, these patients can be monitored closely for any progression/conversion to Alzheimer's disease.

Level of Evidence: MRI without contrast: low; MRI with and without contrast, MRI with contrast: n/a; CT without contrast: moderate; CT with and without contrast, CT with contrast: n/a; fMRI: n/a; MRS: n/a; amyloid imaging: low; FDG-PET: low; perfusion SPECT: low; dopaminergic SPECT: low

Notes concerning applicability and/or patient preferences:
Older adults fear cognitive decline and most patients prefer testing that would indicate future AD risk. Some patients may prefer to forgo diagnostic testing, however, because of the emotional distress and social stigma (Wikler et al. 2014; LeCouteur et al. 2013; Grill et al. 2017).

Guideline and PLE expert panel consensus summary:
Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, unless dementia is well established and the subtype diagnosis is clear (*NICE* 2018).

Functional imaging can be of value to diagnose (or exclude) a neurodegenerative dementia in those subjects with cognitive impairment presenting with severe psychiatric disturbances (including depression and agitation) and in cases where proper cognitive testing is difficult (Filippi et al [*EFNS*] 2012, good practice point).

No neuroimaging or laboratory test is currently recommended for predicting MCI progression to dementia in clinical practice. Although specific brain imaging findings are associated with an increased risk of progression, these findings currently lack specificity (Albert et al. [*NIA-AA*] 2011*).

In patients with persistent or progressive unexplained MCI, amyloid PET would be appropriate only in those individuals who the dementia expert has concluded would benefit from greater certainty of the underlying pathology and whose clinical management would change as a result of this greater certainty (Johnson et al. [*AIT, SNMMI, AA*] 2013).

Amyloid imaging is likely to find clinical utility in the stratification of MCI patients into those with and without underlying AD (Filippi et al [*EFNS*] 2012, class III/level B recommendation).

Amyloid imaging is appropriate in the situations listed below for individuals with all of the following characteristics: a) a cognitive complaint with objectively confirmed impairment; b) Alzheimer's disease as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and c) when knowledge of the presence or absence of amyloid-beta pathology is expected to increase diagnostic certainty and alter management (Johnson et al. [*AIT, SNMMI, AA*] 2013).

- Patients with persistent or progressive unexplained mild cognitive impairment
- Patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation, either atypical clinical course or etiologically mixed presentation
- Patients with progressive dementia and atypically early age of onset (usually defined ≤ 65 years).

Amyloid imaging is inappropriate for any of the situations listed below (Johnson et al. [*AIT, SNMMI, AA*] 2013).

- Patients with core clinical criteria for probable Alzheimer's disease with typical age of onset
- To determine dementia severity
- Solely based on a positive family history of dementia or presence of APOE4
- Patients with a cognitive complaint that is unconfirmed on clinical examination
- In lieu of genotyping for suspected autosomal mutation carriers
- In asymptomatic individuals
- Non-medical usage (e.g. legal, insurance coverage, or employment screening)

In patients with MCI whose clinical picture is complicated with potential vascular, traumatic or medical causes of cognitive impairment, amyloid PET may find utility and could be used appropriately to exclude AD pathology effectively as a basis for the clinical syndrome (Johnson et al. [*AIT, SNMMI, AA*] 2013).

Functional MRI, diffusion-tensor MRI, and perfusion MRI have been used in AD and mild cognitive impairment (MCI) patients but are still considered investigational tools at this time (Albert et al. [*NIA-AA*] 2011*; Moonis et al. [*ACR*] 2019).

* The NIA-AA Guideline by Albert et al (2011) did not pass the AGREE II cutoff, but was included because of its direct relevance to the mild cognitive impairment clinical scenario.

Clinical notes:

- Mild cognitive impairment (MCI) is a condition in which individuals demonstrate cognitive impairment with minimal impairment of instrumental activities of daily living (IADL) (Petersen et al. [*AAN*] 2018).
- This change can occur in a variety of cognitive domains, including memory, executive function, attention, language and visuospatial skills. An impairment in episodic memory is seen most

commonly in MCI patients who subsequently progress to AD dementia (Albert et al [*NIA-AA*] 2011).

- Once it has been determined that the patient has cognitive impairment, the clinician must determine the likely primary cause, for example, degenerative, vascular, depressive, traumatic, medical comorbidities or mixed disease. Typically, this information is derived from further historical information and ancillary testing (e.g. neuroimaging, laboratory studies, and neuropsychological assessment) (Albert et al. [*NIA-AA*] 2011).
- For asymptomatic, community-dwelling adults age ≥ 65 years, the *US Preventive Services Task Force* found that the evidence is insufficient to assess the balance of benefits and harms of screening for cognitive impairment (*USPSTF*, 2020).
- The use of biomarkers in patients with MCI is a rapidly evolving field, but to date, there are no biomarkers clearly shown to predict progression in patients with MCI. For patients and families asking about biomarkers in MCI, clinicians should counsel that there are no accepted biomarkers available at this time (Petersen et al. [*AAN*] 2018, Level B recommendation).
- When the cognitive impairment is sufficiently great, such that there is interference with daily function, the patient is diagnosed with dementia (Albert et al. [NIA-AA] 2011).
- The key criteria that distinguish MCI from dementia are preservation of independence in functional abilities (ADLs and IADLs) and lack of significant impairment in social or occupational functioning (Langa & Levine 2014).
- Persons with MCI are at higher risk of progressing to dementia than age-matched controls (Petersen et al. [*AAN*] 2018).
- Appropriate diagnosis of MCI is important in order to assess for reversible causes of cognitive impairment, to help patients and families understand the cause of their cognitive concerns, and to discuss the prognostic possibilities with the provider so they can plan accordingly, although sharing the diagnosis must be balanced with the potential harm of anxieties from diagnosing a patient with a condition that may not progress (Petersen et al. [*AAN*] 2018).
- Very rapid cognitive decline (weeks to months) is not typical of MCI due to Alzheimer disease and should raise concerns for other causes such as neoplasm, metabolic disorders, or prion disease (Langa & Levine 2014).

Imaging notes:

- Structural brain MRI may rule out other potential causes for cognitive decline, such as subdural hematoma, stroke, NPH, or tumor, and should be considered if the history, physical, or laboratory studies suggest one of these causes (Ries et al. 2008).
- Volumetric MRI can be used as a second-line imaging test for aiding in the diagnosis once the patient has been seen by a specialist. Medial temporal lobe atrophy has been noted to correlate with cognitive decline and nonfunctional test accumulation and is seen in patients with MCI compared with normal patients (Moonis et al. [*ACR*] 2019).
- A standard structural MRI protocol should include a high-resolution structural volumetric (3D) T1-weighted gradient echo, transverse T2 FSE/TSE, FLAIR sequences and transverse T2*-gradient echo sequences. Routine contrast administration [as part of a standard MRI protocol] is not indicated (Filippi et al. [*EFNS*] 2012).
- If 3D T1-weighted techniques are unavailable, coronal oblique T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD (Filippi et al. [*EFNS*] 2012).
- A positive Aβ biomarker and a positive biomarker of neuronal injury confers the highest likelihood that AD pathophysiological processes are the cause of the cognitive dysfunction (Albert et al. (*NIA-AA*] 2011).

- In patients with MCI syndrome, negative biomarkers for both Aβ and neuronal injury strongly suggests that the MCI is not secondary to AD (Albert et al. [*NIA-AA*] 2011).
- Normal FDG PET scan findings, in the presence of the suspicion of dementia, make a neurodegenerative diagnosis less likely (Filippi et al. *[EFNS]* 2012).
- AD-like metabolic patterns in patients with MCI are predictive of conversion to AD within several years (Filippi et al. [*EFNS*] 2012).

Evidence update (2017-present and selected articles from guideline references):
Smailagic et al. (2018) conducted a systematic review update on the accuracy of ^{18}F-FDG-PET for detecting MCI at baseline that clinically converts to Alzheimer's disease (AD) at follow-up. Quality assessment using QUADAS 2 was performed independently and blindly by two reviewers. Meta-analysis was not conducted due to heterogeneity across studies. Included studies (n = 24) showed highly variable accuracy. Analysis for conversion of MCI to AD dementia showed sensitivity values ranged from 25–100% with specificity values ranging from 24–100%. The authors conclude that systematic assessment of ^{18}F-FDG-PET studies for prediction of conversion from MCI to AD dementia reveals many studies have methodological limitations according to Cochrane diagnostic test accuracy gold standards, and accuracy remains highly variable. There is some evidence of higher and more consistent accuracy in studies using computer aided metrics in specialized clinical settings. Further evidence of the clinical validity and utility of ^{18}F-FDG PET in people with MCI is needed (moderate level of evidence).

Fantoni et al. (2018) conducted a systematic review of 12 studies on the value added by amyloid PET (aPET) imaging in cognitively impaired subjects. Data was abstracted by consensus among two observers and assessed for bias. Clinical utility was measured by diagnostic change, diagnostic confidence, and patient management before and after aPET. For 1,142 cases with aPET as key biomarker, 31.3% of diagnoses were revised, vs. 3.2% of diagnoses changed in the delayed aPET control group ($p < 0.0001$). Increased diagnostic confidence following aPET was found for 62.1% of 870 patients. Management changes with aPET were found in 72.2% of 740 cases (vs. 55.5% of 299 cases in control group) ($p < 0.0001$). The diagnostic value of aPET in appropriate use criteria patients or when FDG/CSF were additionally available did not substantially differ from value of aPET alone. The authors conclude that the data support utility of aPET in diagnostic decision-making, confidence of diagnosis, and management of patients with cognitive impairment (moderate level of evidence).

Shea et al. (2018) performed a systematic review and meta-analysis of 13 studies (n = 1,489) to determine the impact of amyloid PET (Aβ-PET) imaging on etiological diagnosis and clinical management in the memory clinic setting. Meta-analysis revealed a pooled effect of change in diagnoses of 35.2% (95% CI 24.6–47.5). Sub-analyses showed that the pooled effect in change in diagnoses if Aβ-PET was used under the appropriate use criteria (AUC) or non-AUC criteria were 47.8% (95% CI 25.9–70.5) and 29.6% (95% CI: 21.5–39.3), respectively. The pooled effect of a change of diagnosis from Alzheimer's disease (AD) to non-AD and from non-AD to AD were 22.7% (95% CI: 17.1–29.5) and 25.6% (95% CI: 17.6–35.8), respectively. The pooled effect leading to a change of management was 59.6% (95% CI 39.4–77.0). The authors conclude that Aβ-PET has a highly significant impact on both changes in diagnosis and management among patients seen at a specialty memory clinic (moderate level of evidence).

Martinez et al. (2017) conducted a systematic review of three studies (n = 448) to determine the diagnostic test accuracy of F-florbetapir PET for detecting people with MCI who will clinically progress to AD or other forms of dementia at follow-up. Progression from MCI to AD in those with follow-up between two-four years had sensitivity of 67% (95% CI: 30-93) and specificity of 71% (95% CI: 54-85) by visual assessment. Progression from MCI to AD in those with follow-up between one to less than two

years had a sensitivity of 89% (95% CI: 78-95) and a specificity of 58% (95% CI: 53-64) by visual assessment, and a sensitivity of 87% (95% CI: 76-94) and a specificity of 51% (95% CI: 45-56) by quantitative assessment by the standardized uptake value ratio. The authors conclude that although sensitivity was good in one included study, considering the poor specificity and limited data available in the literature, routine use of F-florbetapir PET cannot be recommended in clinical practice to predict the progression from MCI to AD (low level of evidence).

Smailagic et al. (2015) conducted a systematic review of 14 studies (n = 421) evaluating the diagnostic accuracy of F-FDG PET in detecting individuals with MCI at baseline who would clinically convert to AD dementia or other forms of dementia at follow-up. The sensitivities for conversion from MCI to AD were between 25%-100% and specificities between 15%-100%. From the summary receiver operating characteristic (ROC) curve, estimated sensitivity was 76% (95% CI, 53.8-89.7) at the included study median specificity of 82%. This equated to a positive likelihood ratio of 4.03 (95% CI, 2.97-5.47), and a negative likelihood ratio of 0.34 (95% CI, 0.15-0.75). At the median specificity of 82%, the estimated sensitivity was between 74%-76%. The authors conclude that, given the considerable variability of specificity values and lack of defined thresholds for determination of test positivity in the included studies, the current evidence does not support the routine use of F-FDG- PET scans in clinical practice in people with MCI (low level of evidence).

Zhang et al. (2014) conducted a systematic review and meta-analysis of nine studies to determine the diagnostic accuracy of C-labelled Pittsburgh compound B-(^{11}C-PIB) PET scan for detecting participants with MCI at baseline who will clinically convert to AD or other forms of dementia. Of the 274 participants included, 112 developed AD. Based on the included studies, the median proportion converting was 34%. The studies varied in how PIB scans were done and interpreted. Sensitivities were between 83%-100%, and specificities between 46%-88%. Because of variation in thresholds and measures of C-PIB amyloid retention, the authors could not calculate summary sensitivity and specificity. They estimated from the fitted summary ROC curve that sensitivity was 96% (95% CI: 87-99) at the included study median specificity of 58%. This equated to a positive likelihood ratio of 2.3 and a negative likelihood ratio of 0.07. The authors conclude that, although the good sensitivity achieved in some included studies is promising for the value of ^{11}C-PIB-PET, given the heterogeneity in the conduct and interpretation of the test and the lack of defined thresholds for determination of test positivity, its routine use in clinical practice cannot be recommended (low level of evidence).

Rabinovici et al. (2019) longitudinally evaluated the association between amyloid PET (aPET) and change in clinical management among Medicare beneficiaries with MCI or dementia from 595 U.S. sites. All participants met criteria that etiology of cognitive impairment was unknown, AD was a diagnostic consideration, and knowledge of PET results was expected to change diagnosis and management. Primary end point was change in management between pre- and post-PET visits, assessed by composite outcome including drug therapy and counseling. The study was powered to detect a 30% or greater change in MCI and dementia groups. A total of 11,409 patients were included in the analysis (median age 75). aPET results were positive in 3,817 patients with MCI (55.3%) and 3,154 patients with dementia (70.1%). The composite end point changed in 4,159 of 6,905 patients with MCI (60.2% [95%CI, 59.1%-61.4%]) and 2,859 of 4,504 patients with dementia (63.5% [95%CI, 62.1%-64.9%]), (P < .001). Etiologic diagnosis changed from AD to non–AD in 2,860 of 11,409 patients (25.1% [95%CI, 24.3%-25.9%]) and from non–AD to AD in 1,201 of 11,409 (10.5% [95%CI, 10.0%-11.1%]). The authors conclude that use of aPET among Medicare beneficiaries with dementia or MCI was associated with changes in clinical management within 90 days (moderate level of evidence).

Ding et al. (2019) examined whether a deep learning algorithm could be trained to predict final clinical diagnoses in patients undergoing ^{18}F-FDG PET of the brain, and how the algorithm compares with current standard clinical reading methods in differentiation of patients with AD (n = 243), MCI (n = 413), or no evidence of dementia (n = 386). A total of 2109 imaging studies among 1002 patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and 40 imaging studies from a retrospective independent test set were collected, and final clinical diagnosis at follow-up was recorded. The designed algorithm was trained on 90% of the ADNI data set and tested on both the remaining 10% and independent test set, with performance compared to three nuclear medicine physicians. The algorithm achieved area under the ROC curve of 0.98 (95% CI: 0.94-1.00) when evaluated on predicting final clinical diagnosis of AD in the independent test set (82% specificity, 100% sensitivity), an average of 75.8 months prior to final diagnosis, which outperformed reader performance (57% sensitivity, 91% specificity; P < .05). The authors conclude that a deep learning algorithm can predict the final diagnosis of AD from ^{18}F-FDG PET imaging studies of the brain with high accuracy and robustness across external test data (moderate level of evidence).

de Wilde et al. (2018) assessed association of amyloid PET (aPET) with changes in diagnosis, diagnostic confidence, and treatment in two memory clinic cohorts (n = 507, mean age 65). A neurologist determined pre- and post-aPET diagnosis for each patient, consisting of both clinical syndrome (e.g., MCI) and suspected etiology (AD or non-AD), with a confidence level of 0-100%. 164 patients (32%) had AD dementia, 70 (14%) non-AD dementia, 114 (23%) MCI, and 159 (31%) subjective cognitive decline. aPET results were positive for 242 patients (48%). Suspected etiology changed for 125 patients (25%) after undergoing aPET, more often due to a negative (82 of 265 [31%]) than a positive (43 of 242 [18%]) PET result (P < .01). Post-PET changes in suspected etiology occurred more often in older (> 65 years: 74 of 257 [29%]) vs. younger (< 65 years: 51 of 250 [20%]) (P < .05) patients. The authors conclude that both amyloid-positive and amyloid-negative results had substantial associations with changes in diagnosis and treatment in patients with and without dementia (moderate level of evidence).

Fischbach-Boulanger et al. (2018) evaluated whether T1-weighted (T1WI) or T2-weighted (T2WI) imaging allowed the best visual evaluation of hippocampal atrophy among 100 patients with MCI and 50 with AD. Visual qualitative ratings were made by four independent operators according to medial temporal lobe atrophy score based either on T1WI or T2WI. These evaluations were compared for interobserver reproducibility, concordance with a quantitative volumetric measure, discrimination power between groups, and correlation with neuropsychological tests. The medial temporal lobe atrophy score evaluated on either T1WI or T2WI exhibited similar interobserver variability and accordance with quantitative volumetric evaluation. However, the visual evaluation on T2WI seemed to provide better discrimination power between AD and MCI for both left (T1WI, P = 0.0001; T2WI, P = .00007072) and right (T1WI, P = 0.008; T2WI, P = 0.001) hippocampus, and a higher overall correlation with neuropsychological tests (moderate level of evidence).

Quaranta et al. (2018) assessed whether ability to predict progression from amnestic MCI (aMCI) to dementia is improved by considering the presence of SPECT perfusion abnormalities at baseline. A total of 42 aMCI subjects completed the Episodic Memory Score (EMS) and SPECT imaging at baseline and were followed for two-year period. A total of 15 subjects (36%) progressed to AD. The EMS predicted progression from aMCI to dementia with a high level of sensitivity (93%) and a lower level of specificity (67%), but the association of neuropsychological (EMS) and SPECT data (hypoperfusion in the Posterior Cingulate Cortex) increased the accuracy (to 90%) in predicting conversion from aMCI to AD. The association of results obtained by aMCI patients on memory tests and perfusion SPECT may improve the accuracy in detecting subjects who will progress to dementia (low level of evidence).

Lan et al. (2017) compared three neuroimaging biomarkers to predict progression to dementia in 88 subjects with MCI (vs. 40 healthy controls). All subjects had a 3T MRI and two PET scans, one with Pittsburgh compound B ([^{11}C] PIB) and one with fluorodeoxyglucose ([^{18}F]FDG). Subjects were followed up to 4 years. [^{11}C] PIB, [^{18}F]FDG standard uptake value ratio (SUVR) and hippocampus volume were associated with time to progression to dementia. [^{11}C]PIB BPND and [^{18}F]FDG SUVR were independently predictive, while hippocampus volume had independent predictive properties to [^{11}C] PIB BPND, but did not add predictive power when combined with [^{18}F]FDG SUVR data. The authors concluded that PET imaging with both [^{11}C] PIB and [^{18}F]FDG may help determine which MCI subjects are likely to progress to AD (moderate level of evidence).

Fayed et al. (2017) conducted a prospective study of 48 patients to assess accuracy of MRS and brain volumetry in MCI to predict conversion to probable AD. Patients fulfilling criteria of MCI had conventional MRI followed by MRS, and T1-3D on 1.5T MR. After 3 years, 15 (31.2%) had converted to AD. Themyo-inositol in the occipital cortex and glutamate+glutamine (Glx) in the posterior cingulate cortex predicted conversion to probable AD at 46.1% sensitivity and 90.6% specificity (PPV was 66.7%, NPV was 80.6%, with overall accuracy of 77.8%). The volume of the third ventricle, total white matter and entorhinal cortex predict conversion to probable AD at 46.7% sensitivity and 90.9% specificity (PPV was 70%, NPV was 78.9%, with overall accuracy of 77.1%). Combining volumetric measures in addition to MRS measures, the prediction to probable AD has a 38.5% sensitivity and 87.5% specificity (PPV of 55.6%, NPV of 77.8%, with overall accuracy of 73.3%). The authors conclude that while MRS or brain volumetric measures may serve as noninvasive tools to monitor progression to dementia in patients with MCI, their routine use in clinical settings is not supported (moderate level of evidence).

Inui et al. (2017) evaluated long-term prediction of MCI to AD conversion among 72 patients using F-FDG-PET and MRI. PET scores over 5 years were found to have accuracy of 60% with 53% sensitivity and 84% specificity in predicting conversion. Visual interpretation of PET images predicted conversion to AD with overall 82% diagnostic accuracy, 94% sensitivity, and 53% specificity. The accuracy of volume-based morphometry (VBM) analysis on MRI presented little fluctuation through 5 years and was highest (73%) at 5-year follow-up, with 79% sensitivity and 63% specificity. The authors concluded that 18F-FDG-PET visual assessment showed high performance for predicting conversion to AD from MCI, particularly in combination with neuropsychological tests. Structural MRI focused on the medial temporal area showed stable predictive value throughout the 5-year course (low level of evidence).

Possible Alzheimer's disease (AD) *:

- **Green** – MRI brain without contrast
- **Yellow** - CT head without contrast**
- **Yellow** – Amyloid PET or FDG-PET in atypical cases or to differentiate AD from FTD, and all of the following apply:
    - at specialist request
    - all other tests (history, physical, structural imaging, lab testing) are inconclusive
    - other diagnoses have been excluded by MRI or CT and
    - the results will change management
- **Yellow** – Perfusion (HMPAO or ECD) SPECT in atypical cases or to differentiate AD from FTD, and all of the following apply:
    - at specialist request
    - all other tests (history, physical, structural imaging, lab testing) are inconclusive
    - other diagnoses have been excluded by MRI or CT
    - the results will change management and
    - PET imaging is not available
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline
- **Red** – fMRI; MRS; Dopaminergic (DAT) SPECT; I-MIBG cardiac scintigraphy; DTI

*A diagnosis of possible Alzheimer's disease is made in either of the following circumstances (McKhann et al 2011):

A. **Atypical course** – meets core clinical criteria in terms of nature of cognitive deficits for AD dementia, but either with sudden onset or demonstrates insufficient historical detail or objective cognitive documentation of progressive decline.
B. **Etiologically mixed presentation** – meets all core clinical criteria for AD dementia but has evidence of another concomitant neurological disease, medical comorbidity, or medication use that could have substantial effect on cognition.

** The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

Level of Evidence: MRI without contrast: moderate; MRI with and without contrast, MRI with contrast: n/a; CT without contrast: moderate; CT with and without contrast, CT with contrast: n/a; fMRI: high; MRS: low; FDG-PET: moderate; amyloid imaging: low; perfusion SPECT: low; dopaminergic SPECT: low

Notes concerning applicability and/or patient preferences: Older adults fear cognitive decline and most patients prefer testing that would indicate future AD risk. Some patients may prefer to forgo diagnostic testing, however, because of the emotional distress and social stigma (Wikler et al. 2014; LeCouteur et al. 2013; Grill et al. 2017).

Guideline and PLE expert panel consensus summary:
Structural imaging should be carried out at least once in the diagnostic work-up of patients with suspected dementia and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (Filippi et al [*EFNS*] 2012, good practice point; Hort et al. [*EFNS*] 2010).

Offer structural imaging to rule out reversible causes of cognitive decline and to assist with subtype diagnosis, unless dementia is well established and the subtype diagnosis is clear (*NICE* 2018).

Structural imaging should be used in the evaluation of every patient affected by dementia. CT and standard MRI are used to exclude secondary causes for dementia such as tumor and inflammatory disease, including abscess or normal-pressure hydrocephalus (Sorbi et al. [*EFNS/ENS*] 2012, Level A recommendation).

The use of a structural neuroimaging study, such as CT or MRI scan, is generally recommended as part of an initial evaluation [for patients with dementia], although clinical practice varies. Imaging is particularly important for those with a subacute onset (less than 1 year), symptom onset before age 65, vascular risk factors…or possible focal lesion (*APA Work Group on Alzheimer's Disease and other Dementias* 2007). *The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions, such as FTLD* (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010*). The panel expressed concern about interobserver reliability of structural imaging and thought that structural imaging for neurocognitive disorders should be interpreted by specialists in neuroimaging* (PLE expert panel consensus opinion).

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus. Multi-detector row CT is the best alternative for patients who cannot undergo MRI (Filippi et al [*EFNS*] 2012, good practice point).

For Alzheimer's disease, both CT and MRI are highly accurate in correctly ruling out the diagnosis, but both types of scans have only low to moderate ability to correctly identify patients with this condition (Health Quality Ontario 2014). *The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions, such as FTLD* (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010). *The panel expressed concern about interobserver reliability of structural imaging and thought that this is best performed in a subspecialty setting* (PLE expert panel consensus opinion).

Multislice CT and coronal MRI may be used to assess hippocampal atrophy to support a clinical diagnosis of AD (Hort et al. [*EFNS*] 2010, level B recommendation).

MRI indices such as hippocampal volumetry can support clinical diagnosis of early AD (SIGN 2006).

Although typical cases of dementia may not benefit from routine SPECT or PET imaging, these tools are recommended in cases where diagnosis remains in doubt after clinical and structural MRI work-up and in particular clinical settings (Filippi et al. [*EFNS*] 2012, class II/level A recommendation).

If the diagnosis is uncertain and Alzheimer's disease is suspected, consider FDG-PET or perfusion SPECT if FDG-PET is unavailable (*NICE* 2018). *The PLE expert panel agreed with this statement, but noted that these scans should be used primarily for differentiating AD from FTD, and should be used in an appropriate subspecialty setting* (PLE expert panel consensus opinion).

FDG PET and perfusion SPECT are useful adjuncts when diagnosis [of AD] remains in doubt (Hort et al. [*EFNS*] 2010, level B recommendation).

SPECT may be used in combination with CT to aid the differential diagnosis of dementia when the diagnosis is in doubt (*SIGN* 2006, C recommendation).

SPECT perfusion and MRI morphometric imaging are useful to distinguish DLB from AD (Sorbi et al. [*EFNS*/*ENS*] 2012).

Dopaminergic SPECT is useful to differentiate AD from DLB (Hort et al. [*EFNS*] 2010, level A recommendation).

Amyloid imaging is likely to find clinical utility in the following fields (Filippi et al [*EFNS*] 2012):

i The stratification of MCI patients into those with and without underlying AD (class III, level B);
ii The evaluation of early-onset AD patients, as these patients often present with atypical symptoms, or patients with clinically atypical presentations, as these are pathologically heterogeneous syndromes that are variably associated with AD pathology (class III, level C);
iii The differential diagnosis between AD and FTD, because amyloid plaques are not part of the FTLD pathological spectrum (class III, level C).

Amyloid imaging is <u>appropriate</u> in the situations listed below for individuals with all of the following characteristics: a) a cognitive complaint with objectively confirmed impairment; b) Alzheimer's disease as a possible diagnosis, but when the diagnosis is uncertain after a comprehensive evaluation by a dementia expert; and c) when knowledge of the presence or absence of amyloid-beta pathology is expected to increase diagnostic certainty and alter management (Johnson et al. [*AIT, SNMMI, AA*] 2013).

- Patients with persistent or progressive unexplained mild cognitive impairment
- Patients satisfying core clinical criteria for possible Alzheimer's disease because of unclear clinical presentation, either atypical clinical course or etiologically mixed presentation
- Patients with progressive dementia and atypically early age of onset (usually defined <u>≤</u> 65 years)

Amyloid imaging is <u>inappropriate</u> for any of the situations listed below (Johnson et al. [*AIT, SNMMI, AA*] 2013).

- Patients with core clinical criteria for probable Alzheimer's disease with typical age of onset
- To determine dementia severity
- Solely based on a positive family history of dementia or presence of APOE4
- Patients with a cognitive complaint that is unconfirmed on clinical examination
- In lieu of genotyping for suspected autosomal mutation carriers
- In asymptomatic individuals
- Non-medical usage (e.g. legal, insurance coverage, or employment screening)

Amyloid PET may be appropriate only in those individuals in whom there is substantial doubt about of whether the dementia is based on AD pathology. The sources of doubt are (i) the presence of an unusual course (e.g. sudden or episodic)…, or (ii) the presence of a comorbid condition that confounds the interpretation of the clinical data (Johnson et al. [*AIT, SNMMI, AA*] 2013).

Amyloid PET is appropriate in the scenario in which a relatively young patient presents with a progressive impairment that has feature of AD dementia as well as of a non-AD dementia (Johnson et al. [*AIT, SNMMI, AA*] 2013).

For patients with *cognitive decline, suspected Alzheimer disease, initial imaging*, the *American College of Radiology* recommends MRI head without IV contrast or CT head without IV contrast (*usually appropriate*). F-18 amyloid PET/CT brain or FDG-PET/CT brain *may be appropriate* (Moonis et al [*ACR*] 2019).

Functional MRI, diffusion-tensor MRI, and perfusion MRI have been used in AD patients but are still considered investigational tools at this time (Moonis et al. [*ACR*] 2019).

Diffusion-tensor imaging (DTI) MRI distinguishes [FTD] from AD and controls (and AD from controls) (Sorbi et al. [*EFNS*/*ENS*] 2012, level B recommendation). *The PLE expert panel thought that this was a rather strong statement, and that it would be more appropriate to state that DTI MRI can support the differentiation of FTD from AD*. *The use of DTI was also downgraded because of concerns over availability in the community outpatient setting* (PLE expert panel consensus opinion).

Post-contrast T1 images are only recommended in patient with a suspicion of infection or inflammatory disorder [or tumor] (Filippi et al. [*EFNS*] 2012).

<u>Clinical notes:</u>

- AD pathology can manifest itself with clinically atypical presentations; memory is not the primary deficit, but visuospatial and visuoperceptual and/or language disturbances are prominent symptoms (Filippi et al. [*EFNS*] 2012).
- Atypical presentations are more often seen in early-onset AD patients (Filippi et al. [*EFNS*] 2012).
- **Amnestic presentation** is the most common syndromic presentation of AD dementia. The deficits include impairment in learning and recall of recently learned information (McKhann et al. 2011).
- **Nonamnestic presentations** of AD dementia include (McKhann et al. 2011):
    - **Language presentation** – the most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
    - **Visuospatial presentation** – the most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
    - **Executive dysfunction** – the most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
- **Posterior cortical atrophy** (PCA) is a neurodegenerative syndrome with typical age of onset between 50-65 years, characterized by a progressive, often dramatic and relatively selective decline in visuospatial, visuoperceptual, literacy, and praxic skills. The progressive neurodegeneration affecting parietal, occipital, and occipito-temporal cortices which underlies PCA is attributable to AD in the majority of patients (Crutch et al. 2012).

- The **logopenic variant of primary progressive aphasia (PPA)** appears to represent a nonamnestic form of AD (Sorbi et al. [*EFNS*/*ENS*] 2012; McKhann et al. 2011), and is characterized by impaired single-word retrieval in spontaneous speech and naming, impaired repetition of sentences and phrases, and at least three of the following: speech (phonologic) errors in spontaneous speech and naming; spared single-word comprehension and object knowledge; spared motor speech; absence of frank agrammatism (Gorno-Tempini et al. 2011).

Imaging notes:

- The primary role of neuroimaging in the workup of patients with probable or possible AD has typically been to exclude other significant intracranial abnormalities (Moonis et al. [*ACR*] 2019).
- Volumetric MRI can be used as a second-line imaging test for aiding in the diagnosis [of AD] (Moonis et al [*ACR*] 2019).
- A standard structural MRI protocol should include a high-resolution structural volumetric T1-weighted scan transverse T2-weighted and FLAIR sequences and transverse T2*-gradient echo sequence. Routine contrast administration [as part of a standard MRI protocol] is not indicated (Filippi et al. [*EFNS*] 2012).
- If 3D T1-weighted techniques are unavailable, coronal oblique T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD compared with cognitively normal subjects (Filippi et al. [*EFNS*] 2012).
- T1-weighted images should be carefully evaluated to assess specific patterns of focal atrophy, especially in the MTL, biparietal regions and posterior cingulate cortex (as seen in AD), temporal pole and/or frontal lobes (as seen in FTD), parietal/occipital lobe (as seen in PCA), putamen, and midbrain and frontal lobe (as seen in PSP) (Filippi et al. [*EFNS*] 2012).
- Coronal T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD compared with cognitively normal subjects (Filippi et al. [*EFNS*] 2012).
- The presence of temporoparietal atrophy is highly associated with AD (Filippi et al. [*EFNS*] 2012).
- Combining MTL measures with other potentially informative markers, such as posterior cingulate cortex and precuneus volumetric measures, are likely to improve diagnostic confidence in AD patients, mainly in younger cases (Filippi et al. [*EFNS*] 2012).
- In cases of atypical AD presentations, the involvement of the MTL is reported less consistently than that of lateral temporal and medial parietal regions (Filippi et al. [*EFNS*] 2012).
- Early-onset AD patients (i.e., < 65 years) show less prominent MTL atrophy and greater involvement of the parietal, lateral temporal, and frontal regions compared to late-onset cases (Filippi et al. [*EFNS*] 2012).
- Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans (*NICE* 2018).
- FDG-PET accurately discriminates AD patients from normal subjects with a sensitivity of 96% and specificity of 100% (Moonis et al. [*ACR*] 2019). Negative amyloid scans indicate absence of AD pathology with a high level of accuracy (class III, level B), but healthy elderly controls might have positive amyloid scans, so their predictive value in isolation is not clear (Filippi et al. [*EFNS*] 2012).
- CMS has made FDG-PET available to Medicare recipients to assist with the diagnosis of dementia in the appropriate clinical setting (e.g., to distinguish AD from FTD) (Moonis et al. [*ACR*] 2019).
- In most cases, advanced image registration techniques are needed to pick up subtle structural changes over time, but these are restricted to research use or clinical trials (Filippi et al. [*EFNS*] 2012).

Evidence update (2010-present):
Shea et al. (2018) performed a systematic review and meta-analysis of 13 studies (n = 1,489) to determine the impact of amyloid PET (Aβ-PET) imaging on etiological diagnosis and clinical management in the memory clinic setting. Meta-analysis revealed a pooled effect of change in diagnoses of 35.2% (95% CI 24.6–47.5). Sub-analyses showed that the pooled effect in change in diagnoses if Aβ-PET was used under the appropriate use criteria (AUC) or non-AUC criteria were 47.8% (95% CI 25.9–70.5) and 29.6% (95% CI: 21.5–39.3), respectively. The pooled effect of a change of diagnosis from Alzheimer's disease (AD) to non-AD and from non-AD to AD were 22.7% (95% CI: 17.1–29.5) and 25.6% (95% CI: 17.6–35.8), respectively. The pooled effect leading to a change of management was 59.6% (95% CI 39.4–77.0). The authors conclude that Aβ-PET has a highly significant impact on both changes in diagnosis and management among patients seen at a specialty memory clinic (moderate level of evidence).

Rabinovici et al. (2019) longitudinally evaluated the association between amyloid PET (aPET) and change in clinical management among Medicare beneficiaries with MCI or dementia from 595 U.S. sites. All participants met criteria that etiology of cognitive impairment was unknown, AD was a diagnostic consideration, and knowledge of PET results was expected to change diagnosis and management. Primary end point was change in management between pre- and post-PET visits, assessed by composite outcome including drug therapy and counseling. The study was powered to detect a 30% or greater change in MCI and dementia groups. A total of 11,409 patients were included in the analysis (median age 75). aPET results were positive in 3,817 patients with MCI (55.3%) and 3,154 patients with dementia (70.1%). The composite end point changed in 4,159 of 6,905 patients with MCI (60.2% [95%CI, 59.1%-61.4%]) and 2,859 of 4,504 patients with dementia (63.5% [95%CI, 62.1%-64.9%]), (P < .001). Etiologic diagnosis changed from AD to non–AD in 2,860 of 11,409 patients (25.1% [95%CI, 24.3%-25.9%]) and from non–AD to AD in 1,201 of 11,409 (10.5% [95%CI, 10.0%-11.1%]). The authors conclude that use of aPET among Medicare beneficiaries with dementia or MCI was associated with changes in clinical management within 90 days (moderate level of evidence).

Ding et al. (2019) aimed to evaluate whether a deep learning algorithm could be trained to predict final clinical diagnoses in patients who underwent ^{18}F-FDG PET of the brain and how the algorithm compares with current standard clinical reading methods in differentiation of patients with AD (n = 243), MCI (n = 413), or no evidence of dementia (n = 386). A total of 2109 imaging studies from 1002 patients from the Alzheimer's Disease Neuroimaging Initiative (ADNI) and 40 imaging studies from a retrospective independent test set were collected, and final clinical diagnosis at follow-up was recorded. The designed algorithm was trained on 90% of the ADNI data set and tested on both the remaining 10% and independent test set, with performance compared to three nuclear medicine physicians. The algorithm achieved area under the ROC curve of 0.98 (95% CI: 0.94-1.00) when evaluated on predicting final clinical diagnosis of AD in the independent test set (82% specificity, 100% sensitivity), an average of 75.8 months prior to final diagnosis, which outperformed reader performance (57% sensitivity, 91% specificity; P < .05). The authors conclude that a deep learning algorithm can predict the final diagnosis of AD from ^{18}F-FDG PET imaging studies of the brain with high accuracy and robustness across external test data (moderate level of evidence).

Ossenkoppele et al. (2018) conducted a cross-sectional study to examine discriminative accuracy of [^{18}F]flortaucipir for AD vs. non-AD neurodegenerative disorders among 719 patients at 3 centers (mean age 68.8). The proportions of patients who were amyloid-β positive were 26.3%, 65.9%, 100%, and 23.8% among cognitively normal controls, MCI, AD dementia, and non-AD dementia patients, respectively. [^{18}F]flortaucipir uptake in the medial-basal and lateral temporal cortex showed 89.9% (95% CI, 84.6%-93.9%) sensitivity and 90.6% (95% CI, 86.3%-93.9%) specificity using the threshold based on

controls (SUVR, 1.34), and 96.8% (95%CI, 92.0%-99.1%) sensitivity and 87.9% (95%CI, 81.9%-92.4%) specificity using the Youden Index–derived cutoff (SUVR, 1.27) for distinguishing AD from all non-AD neurodegenerative disorders. The AUCs for all 5 [^{18}F]flortaucipir regions of interest (ROIs) were higher (range, 0.92-0.95) compared with the 3 volumetric MRI measures (range, 0.63-0.75; all ROIs P < .001). The authors conclude that among patients with established diagnoses at a memory disorder clinic, [^{18}F]flortaucipir PET was able to discriminate AD from other neurodegenerative diseases (moderate level of evidence).

Zwan et al. (2017) assessed the diagnostic impact of the amyloid-positron emission tomography (PET) imaging agent flutemetamol in 211 early-onset dementia patients, in terms of change in (confidence in) diagnosis and patient management plan. Pre-PET diagnosis was AD in 144 patients (68.3%), FTD in 28 (13.3%), other dementia in 19 patients (9.0%), and non-neurodegenerative diagnosis in 20 patients (9.5%). 18F-flutemetamol PET increased diagnostic confidence from 69 +/- 12% before to 88 +/- 15% after PET (P < .01). This significant increase in diagnostic confidence was seen in 183 patients (87%). 18F-flutemetamol PET results led to change in patient management plan for 79/211 (37%) patients; 42% for those with positive PET vs. 29% for those with negative PET (P < .05). The authors concluded that amyloid PET may have added value over standardized diagnostic work-up in early-onset dementia patients with uncertain clinical diagnosis (moderate level of evidence).

Bensaidane et al. (2016) investigated the clinical utility of amyloid PET in the differential diagnosis of 28 patients (age $\leq$ 65 years) with atypical/unclear dementia presentation. Diagnostic changes occurred in 9 (32%) cases and physician confidence in diagnosis increased by 44% as a result of amyloid PET scan. Knowledge of amyloid PET status significantly improved caregivers' outcomes in domains of anxiety, depression, disease perception, future anticipation and quality of life. The authors concluded that amyloid PET has an additive role in atypical dementia with an unclear diagnosis (low level of evidence).

Grill et al. (2017) examined amyloid imaging's effect on the diagnostic experience of 26 patients with possible AD and their families. A total of 20 patients had amyloid PET (18 positive scan) and 6 declined imaging. Patient-caregiver dyads felt emotional relief by knowing amyloid results and expressed that these results helped them plan for the future. The authors concluded that amyloid imaging may provide information that patients and families find useful from a practical and emotional standpoint (low level of evidence).

Laforce et al. (2010) retrospectively examined the role of FDG-PET in the diagnosis of atypical/unclear dementia in 94 patients in a memory care setting. Clinicians thought that PET helped clarify dementia diagnosis in 56% of cases, confirmed clinical impression in 16% of cases, and had no impact in 28% of cases. FDT-PET findings were associated with change in clinical diagnosis in 29% of cases. Global concordance rate between initial clinical diagnosis and FDG-PET diagnosis was 31.9% (Kappa = 0.23, P <.0001). The authors concluded that the addition of PET to investigation of atypical/unclear cases of dementia helped generate a more accurate diagnosis, and initiation of earlier treatment (low level of evidence).

Probable Alzheimer's disease (AD)*:

- **Green** – MRI brain without contrast
- **Yellow** - CT head without contrast**
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline**
- **Orange** – Amyloid PET, except in cases with atypical presentations at specialist request when all other tests are inconclusive and the results will change management
- **Red** – fMRI; MRS; FDG-PET; Perfusion (HMPAO or ECD) SPECT; Dopaminergic (DAT) SPECT; I-MIBG cardiac scintigraphy; DTI

*Probable Alzheimer's disease is generally defined as dementia with insidious onset, a clear history of cognitive worsening, cognitive deficits (amnestic or nonamnestic) evident on history and examination, and no evidence of another concurrent active neurological disease, medical comorbidity, or use of medication (McKhann et al. 2011).

** The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

Level of Evidence: MRI without contrast: moderate; MRI with and without contrast, MRI with contrast: n/a; CT without contrast: moderate; CT with and without contrast, CT with contrast: n/a; fMRI: high; MRS: low; FDG-PET: low; perfusion SPECT: low; dopaminergic SPECT: low

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Structural imaging should be carried out at least once in the diagnostic work-up of patients with AD and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (Filippi et al [*EFNS*] 2012, good practice point; Hort et al. [*EFNS*] 2010;).

Structural imaging should be used in the evaluation of every patient affected by dementia. CT and standard MRI are used to exclude secondary causes for dementia such as tumor and inflammatory disease, including abscess or normal-pressure hydrocephalus (Sorbi et al. [*EFNS/ENS*] 2012, Level A recommendations).

The use of a structural neuroimaging study, such as CT or MRI scan, is generally recommended as part of an initial evaluation [for patients with dementia], although clinical practice varies. Imaging is particularly important for those with a subacute onset (less than 1 year), symptom onset before age 65, vascular risk factors…or possible focal lesion (*APA Work Group on Alzheimer's Disease and other Dementias* 2007). *The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to*

changes that may indicate specific conditions, such as FTLD (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus. Multi-detector row CT is the best alternative for patients who cannot undergo MRI (Filippi et al [*EFNS*] 2012, good practice point).

MRI is superior to conventional CT in the evaluation of medial temporal lobes (MTL) atrophy. However, the possibility of evaluating the pattern of atrophy using CT has improved with the advent of multi-detector row CT, owing to the availability of high-resolution coronally reformatted images (Hort et al. [*EFNS*] 2010). *The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions, such as FTLD* (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

For Alzheimer's disease, both CT and MRI are highly accurate in correctly ruling out the diagnosis, but both types of scans have only low to moderate ability to correctly identify patients with this condition (*Health Quality Ontario* 2014). *The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions, such as FTLD* (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010). *Additionally, the committee noted that imaging alone cannot rule out a neurocognitive disorder diagnosis* (PLE expert panel consensus opinion).

MRI indices such as hippocampal volumetry can support clinical diagnosis of early AD (*SIGN* 2006).

For patients with *cognitive decline, suspected Alzheimer disease, initial imaging*, the *American College of Radiology* recommends MRI head without IV contrast or CT head without IV contrast (*usually appropriate*). F-18 amyloid PET/CT brain or FDG-PET/CT brain *may be appropriate* (Moonis et al [*ACR*] 2019).

Multislice CT and coronal MRI may be used to assess hippocampal atrophy to support a clinical diagnosis of AD (Hort et al. [*EFNS*] 2010, level B recommendation).

Functional MRI, diffusion-tensor MRI, and perfusion MRI have been used in AD and mild cognitive impairment (MCI) patients but are still considered investigational tools at this time (Moonis et al. [*ACR*] 2019).

Amyloid imaging is not yet recommended for routine use in the clinical setting, especially in the diagnostic work-up of patients with straightforward clinical AD as these patients are very likely to have positive scans (Filippi et al. [*EFNS*] 2012, class III/level B recommendation).

Post-contrast T1 images are only recommended in patients with a suspicion of infection, [tumor,] or inflammatory disorder (Filippi et al. [*EFNS*] 2012).

Follow up with serial MRI is useful in a clinical setting to document [AD] progression (Hort et al. [*EFNS*] 2010). *The PLE expert panel thought that findings on serial MRI may not be useful and do not complement clinical findings indicating progression of dementia (PLE expert panel consensus opinion).*

Clinical notes:

- **Amnestic presentation** is the most common syndromic presentation of AD dementia. The deficits include impairment in learning and recall of recently learned information (McKhann et al. 2011).
- **Nonamnestic presentations** of AD dementia include (McKhann et al. 2011):
    - **Language presentation** – the most prominent deficits are in word-finding, but deficits in other cognitive domains should be present.
    - **Visuospatial presentation** – the most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present.
    - **Executive dysfunction** – the most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present.
- **Posterior cortical atrophy** (PCA) is a neurodegenerative syndrome with typical age of onset between 50-65 years, characterized by a progressive, often dramatic and relatively selective decline in visuospatial, visuoperceptual, literacy, and praxic skills. The progressive neurodegeneration affecting parietal, occipital, and occipito-temporal cortices which underlies PCA is attributable to AD in the majority of patients (Crutch et al. 2012).
- The **logopenic variant of primary progressive aphasia (PPA)** appears to represent a nonamnestic form of AD (Sorbi et al. [*EFNS*/*ENS*] 2012; McKhann et al. 2011), and is characterized by impaired single-word retrieval in spontaneous speech and naming, impaired repetition of sentences and phrases, and at least three of the following: speech (phonologic) errors in spontaneous speech and naming; spared single-word comprehension and object knowledge; spared motor speech; absence of frank agrammatism (Gorno-Tempini et al. 2011).
- Typical late-onset AD is radiologically characterized by global atrophy, especially in the medial temporal lobe (hippocampus and entorhinal cortex) (*Health Quality Ontario* 2014; Filippi et al. [*EFNS*] 2012).
- The presence of temporoparietal atrophy is highly associated with AD (Filippi et al. [*EFNS*] 2012).
- Do not rule out Alzheimer's disease based solely on the results of CT or MRI scans (*NICE* 2018).

Imaging notes:

- The primary role of neuroimaging in the workup of patients with probable or possible AD has typically been to exclude other significant intracranial abnormalities (Moonis et al. [*ACR*] 2019).
- A standard structural MRI protocol should include a high-resolution structural volumetric (3D) T1-weighted gradient echo, transverse T2 FSE/TSE, FLAIR sequences and transverse T2*-gradient echo sequences. (Filippi et al. [*EFNS*] 2012).
- If 3D T1-weighted techniques are unavailable, coronal oblique T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD compared with cognitively normal subjects (Filippi et al. [*EFNS*] 2012).
- T1-weighted images should be carefully evaluated to assess specific patterns of focal atrophy, especially in the MTL, biparietal regions and posterior cingulate cortex (as seen in AD), temporal pole and/or frontal lobes (as seen in FTD), parietal/ occipital lobe (as seen in PCA), [dementia with Lewy bodies], putamen, and midbrain and frontal lobe (as seen in PSP) (Filippi et al. [*EFNS*] 2012).
- Combining MTL measures with other potentially informative markers, such as posterior cingulate cortex and precuneus volumetric measures, are likely to improve diagnostic confidence in AD patients, mainly in younger cases (Filippi et al. [*EFNS*] 2012).

Evidence update (2017-present and selected articles from guideline references):
Canu et al. (2017) explored whether combining structural and resting state functional MRI could aid differentiation between 62 early onset probable AD (EOAD) patients, 27 behavioral variant of FTD (bvFTD) patients, and 48 age-matched healthy controls. All patients showed a distributed pattern of brain alterations relative to controls. Compared to bvFTD, EOAD patients showed bilateral inferior parietal cortical thinning and decreased default mode network functional connectivity. Compared to EOAD, bvFTD patients showed bilateral orbitofrontal and temporal cortical thinning, and white matter (WM) damage of the corpus callosum, bilateral uncinate fasciculus, and left superior longitudinal fasciculus. Random forest analysis showed left inferior parietal cortical thickness (accuracy 0.78, specificity 0.76, sensitivity 0.83) and WM integrity of the right uncinate fasciculus (accuracy 0.81, specificity 0.96, sensitivity 0.43) were best predictors of clinical diagnosis. The combination of cortical thickness and DT MRI measures was able to distinguish patients with EOAD and bvFTD with accuracy 0.82, specificity 0.76, sensitivity 0.96. The authors concluded that a multiparametric MRI study is useful to identify brain alterations specific to EOAD and bvFTD. A severe cortical involvement suggests EOAD, while prominent WM damage might be indicative of bvFTD (low level of evidence).

Frontotemporal degeneration / frontotemporal dementia (FTD) spectrum disorder:

- **Green** – MRI brain without contrast
- **Yellow** – CT head without contrast*
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Yellow** – Amyloid PET or FDG-PET in atypical cases or to differentiate AD from FTD, and all of the following apply:
    - at specialist request,
    - all other tests (history, physical, structural imaging, lab testing) are inconclusive,
    - other diagnoses have been excluded by MRI or CT, and
    - the results will change management
- **Yellow** – Perfusion (HMPAO or ECD) SPECT in atypical cases or to differentiate AD from FTD, and all of the following apply:
    - at specialist request,
    - all other tests (history, physical, structural imaging, lab testing) are inconclusive,
    - other diagnoses have been excluded by MRI or CT,
    - the results will change management, and
    - PET imaging is not available
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline
- **Red** – fMRI; MRS; Dopaminergic (DAT) SPECT; I-MIBG cardiac scintigraphy; DTI

* The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

Level of Evidence: MRI without contrast: moderate; MRI with and without contrast, MRI with contrast: n/a; CT without contrast: very low for diagnostic accuracy; CT with and without contrast, CT with contrast: n/a; fMRI: very low; MRS: very low; FDG-PET: low; amyloid imaging: insufficient; perfusion SPECT: low; dopaminergic SPECT: insufficient; I-MIBG cardiac scintigraphy: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Structural imaging should be carried out at least once in the diagnostic work-up of patients with dementia and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (Filippi et al [*EFNS*] 2012, good practice point).

Although the diagnosis of FTD is primarily clinical, neuroimaging serves several purposes: exclusion of other structural brain abnormalities that could clinically mimic FTD, differentiation of FTD from other

neurodegenerative disorders (most commonly AD), and classification of the known subtypes of FTD (Moonis et al [*ACR*] 2019).

Structural imaging should be used in the evaluation of every patient affected by dementia. CT and standard MRI are used to exclude secondary causes for dementia such as tumor and inflammatory disease, including abscess or normal-pressure hydrocephalus (Sorbi et al. [*EFNS/ENS*] 2012, Level A recommendation).

The use of a structural neuroimaging study, such as CT or MRI scan, is generally recommended as part of an initial evaluation [for patients with dementia], although clinical practice varies. Imaging is particularly important for those with a subacute onset (less than 1 year), symptom onset before age 65, vascular risk factors…or possible focal lesion (*APA Work Group on Alzheimer's Disease and other Dementias* 2007). *The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions, such as FTLD* (PLE expert panel consensus opinion; Hort et al. *[EFNS]* 2010*).*

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus. Multi-detector row CT is the best alternative for patients who cannot undergo MRI (Filippi et al [*EFNS*] 2012, good practice point).

If the diagnosis is uncertain and frontotemporal dementia is suspected, use either FDG-PET or perfusion SPECT. Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests (*NICE* 2018).

SPECT and PET perfusion and metabolic techniques are highly useful in FTLD diagnosis (Sorbi et al. [*EFNS*/*ENS*] 2012, level C recommendation).

PET accurately discriminates AD patients from normal subjects with a sensitivity of 96% and specificity of 100%. FDG-PET/CT head may be used as a problem solving technique in differentiating dementias [e.g., AD vs. FTD] (Moonis et al. [*ACR*] 2019).

Functional neuroimaging using brain positron emission tomography (PET) scans may contribute to diagnostic specificity in certain instances [differentiating between AD and FTD] (*APA Work Group on Alzheimer's Disease and other Dementias* 2007).

Amyloid imaging is likely to find clinical utility for the differential diagnosis between AD and FTD, because amyloid plaques are not part of the FTLD pathological spectrum (Filippi et al [*EFNS*] 2012): class III, level C).

For patients with *suspected frontotemporal dementia, initial imaging*, the *American College of Radiology* recommends MRI head without IV contrast or CT head without IV contrast (*usually appropriate*). FDG-PET/CT brain *may be appropriate* (Moonis et al [*ACR*] 2019).

Diffusion-tensor imaging (DTI) MRI distinguishes frontotemporal lobar degeneration (FTLD) from AD and controls (and AD from controls) (Sorbi et al. [*EFNS*/*ENS*] 2012, level B recommendation). *The PLE expert panel thought that this was a rather strong statement, and that it would be more appropriate to state*

that DTI MRI can support the differentiation of FTD from AD. The use of DTI was also downgraded because of concerns over availability in the community outpatient setting (PLE expert panel consensus opinion).

Post-contrast T1 images are only recommended in patient with a suspicion of infection, [tumor,] or inflammatory disorder [or tumor] (Filippi et al. [*EFNS*] 2012).

Clinical notes:

- Frontotemporal degeneration/frontotemporal dementia is a clinically and pathologically heterogeneous group of disorders characterized collectively by relatively selective progressive atrophy and neuronal loss of the frontal and/or temporal lobes (Sorbi et al. [*EFNS*/*ENS*] 2012).
- Frontotemporal lobe degeneration represents the pathologic process whereas frontotemporal dementia refers to a clinical syndrome (Filippi et al. [*EFNS*] 2012).
- Behavioral variant FTD (bvFTD) represents half of all cases, and is characterized by personality changes and inappropriate social and interpersonal conduct (*Health Quality Ontario* 2014; Sorbi et al. [*EFNS*/*ENS*] 2012).
- Primary progressive aphasia (PPA) involves changes in the ability to communicate-to use language to speak, read, write, and understand what others are saying. Problems with memory, reasoning, and judgment are not apparent at first but can develop over time (*National Institute on Aging,* 2017). There are three types of PPA, categorized by the kind of language problems seen at first:
    - The semantic variation of PPA is characterized by speech that is smooth or fluent but devoid of information or specific labels or meanings (*Health Quality Ontario* 2014; Sorbi et al. [*EFNS*/*ENS*] 2012).
    - The nonfluent/agrammatic variant of primary progressive aphasia (PPA), also known as progressive nonfluent aphasia, is characterized by hesitant, agrammatical and effortful speech, including problems with findings words and naming objects (*Health Quality Ontario* 2014; Sorbi et al. [*EFNS*/*ENS*] 2012).
    - The logopenic variant of PPA is characterized by impaired single-word retrieval in spontaneous speech and naming, impaired repetition of sentences and phrases, and at least three of the following: speech (phonologic) errors in spontaneous speech and naming; spared single-word comprehension and object knowledge; spared motor speech; absence of frank agrammatism (Gorno-Tempini et al. 2011). The logopenic variant of PPA appears to represent a nonamnestic form of AD (Sorbi et al. [*EFNS*/*ENS*] 2012: McKhann et al. 2011).
- Two rare neurological disorders associated with FTD, corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP) occur when parts of the brain that control movement are affected. These disorders may also affect thinking and language abilities (*National Institute on Aging*, 2017):
    - Corticobasal degeneration (CBD) is characterized by asymmetric cortical dysfunction, often affecting motor control of a limb, along with executive dysfunction, rigidity, a jerky postural tremor, myoclonus, dystonia, and a gait disorder. Speech may be disrupted owing to apraxia or non-fluent aphasia (Budson & Solomon 2016). The clinical features suggestive of CBD in the absence of pathological confirmation are referred to as "corticobasal syndrome" (CBS).
    - Progressive supranuclear palsy (PSP) is an uncommon atypical parkinsonian syndrome, clinically characterized by prominent postural instability and falls, vertical supranuclear gaze palsy, and frontal-subcortical dementia (Stamelou & Oertel 2017).

Imaging notes:

- A standard structural MRI protocol should include a high-resolution structural volumetric (3D) T1-weighted gradient echo, transverse T2 FSE/TSE, FLAIR sequences and transverse T2*-gradient echo sequences. Routine contrast administration [as part of a standard MRI protocol] is not indicated (Filippi et al. [*EFNS*] 2012).
- The role of volumetric imaging in FTD diagnosis has become one of emerging importance (PLE expert panel opinion). If 3D T1-weighted techniques are unavailable, coronal oblique T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD compared with cognitively normal subjects (Filippi et al. [*EFNS*] 2012).
- T1-weighted images should be evaluated to assess specific patterns of focal atrophy, especially in the temporal pole and/or frontal lobes (as seen in FTD) (Filippi et al. [*EFNS*] 2012).
- The pattern of atrophy is more useful than atrophy of single regions in the differential diagnosis of [bv]FTD compared with AD: knife-like, severe frontotemporal atrophy combined with dilatation of frontal horn, and an anterior greater than posterior gradient is suggestive of a diagnosis of FTD (Filippi et al. [*EFNS*] 2012; Sorbi et al. [*EFNS*/*ENS*] 2012).
- A normal structural MRI scan should prompt the clinician to reconsider a diagnosis of bvFTD, if clinically severe, and semantic variant PPA (Filippi et al. [*EFNS*] 2012). *The PLE expert panel noted that structural MRI is not specific in the diagnosis of semantic variant PPA* (PLE expert panel consensus opinion).
- Use of amyloid PET in FTD is limited to the exclusion of underlying amyloid brain pathology that can be seen in cases of AD with atypical presentation (Moonis et al [*ACR*] 2019).
- Although an overlap of functional abnormalities between FTD and AD has been shown to occur, the presence of posterior temporal and parietal brain hypoperfusion or hypometabolism is predictive of a pathological diagnosis of AD, whereas a disproportionate reduction in frontal perfusion/metabolism is more common in FTD cases (Filippi et al. [*EFNS*] 2012).
- FDG-PET is an established tool for differentiating FTD and AD and classifying different FTD subtypes. FDG-PET has a sensitivity of 60% and a positive predictive value of 78.5% for differentiating the subtypes of FTD (Moonis et al [*ACR*] 2019).
- CMS has made FDG-PET available to Medicare recipients to assist with the diagnosis of dementia in the appropriate clinical setting (e.g., to distinguish AD from FTD) (Moonis et al. [*ACR*] 2019).
- Tc-99m HMPAO SPECT has been found to be useful in distinguishing FTD from AD and VaD with a pattern of bilateral anterior hypoperfusion. Tc-99m HMPAO SPECT may be used as an adjunct to clinical evaluation and CT but it is not a first-line test (Moonis et al [*ACR*] 2019).
- Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests (*NICE* 2018).

Evidence update (2017-present and select articles from guideline references):

Archer et al. (2015) conducted a systematic review of 11 studies (n = 1117) to determine the diagnostic accuracy of rCBF SPECT for diagnosing FTD in populations with suspected dementia and in the differential diagnosis of FTD from other dementia subtypes. Sensitivities and specificities for differentiating FTD from non-FTD ranged from 0.73-1.00 and from 0.80-1.00, respectively, for the 3 multiple-headed camera studies. Sensitivities were lower for the 2 single-headed camera studies: one with a sensitivity and specificity of 0.40 (95% CI, 0.05-0.85) and 0.95 (95% CI, 0.90-0.98), respectively, and the other a sensitivity and specificity of 0.36 (95% CI, 0.24-0.50) and 0.92 (95% CI, 0.88-0.95), respectively. Eight of the 11 studies which used SPECT to differentiate FTD from AD used multiple-headed camera SPECT. Of these, 5 used a case-control design, reporting sensitivities between 0.52-1.00,

and specificities between 0.41-0.86. The remaining 3 studies used a cohort design, reporting sensitivities between 0.73-1.00, and specificities between 0.94-1.00. The 3 studies that used single-headed camera SPECT reported sensitivities between 0.40-0.80, and specificities between 0.61-0.97. The authors concluded that no recommendation can be made for the use of rCBF SPECT in the diagnosis of FTD on the basis of the findings (low level of evidence).

Kramer et al. (2018) investigated the sensitivity of DTI and FDG-PET to detect cerebral alterations in early stage bvFTD. A total of 30 patients with early stage bvFTD (no atrophy on conventional MRI) underwent neuropsychological exam, cerebral 3T MRI with DTI analysis, and FDG-PET. After 12-month follow-up, all patients fulfilled bvFTD diagnosis. Individual FDG-PET data showed 20 patients exhibited a "typical" pattern for bvFTD with bifrontal and/or temporal hypometabolism (bvFTD/PET+), and 10 patients showed a "non-typical"/normal pattern (bvFTD/PET-). DTI data were compared with 42 healthy controls. DTI voxel-based group analyses revealed microstructural degeneration in bifrontal and bitemporal areas in bvFTD/PET+ and bvFTD/PET- groups. However, when comparing individual DTI data analysis with FDG-PET, DTI appeared to be less sensitive. Neuropsychological symptoms were considerably related to neurodegeneration within frontotemporal areas identified by DTI and FDG-PET. The authors conclude that DTI seems to be an interesting tool for detection of functionally relevant neurodegenerative alterations in early stages of bvFTD. However, it seems to be less sensitive than FDG-PET, and therefore improvement of individual DTI analysis is necessary (low level of evidence).

Canu et al. (2017) explored whether combining structural and resting state functional MRI could aid differentiation between 62 early onset probable AD (EOAD) patients, 27 behavioral variant of FTD (bvFTD) patients, and 48 age-matched healthy controls. All patients showed a distributed pattern of brain alterations relative to controls. Compared to bvFTD, EOAD patients showed bilateral inferior parietal cortical thinning and decreased default mode network functional connectivity. Compared to EOAD, bvFTD patients showed bilateral orbitofrontal and temporal cortical thinning, and white matter (WM) damage of the corpus callosum, bilateral uncinate fasciculus, and left superior longitudinal fasciculus. Random forest analysis showed left inferior parietal cortical thickness (accuracy 0.78, specificity 0.76, sensitivity 0.83) and WM integrity of the right uncinate fasciculus (accuracy 0.81, specificity 0.96, sensitivity 0.43) were best predictors of clinical diagnosis. The combination of cortical thickness and DT MRI measures was able to distinguish patients with EOAD and bvFTD with accuracy 0.82, specificity 0.76, sensitivity 0.96. The authors concluded that a multiparametric MRI study is useful to identify brain alterations specific to EOAD and bvFTD. A severe cortical involvement suggests EOAD, while prominent WM damage might be indicative of bvFTD (low level of evidence).

Meyer et al. (2017) attempted to validate the diagnostic utility of structural MRI in predicting behavioral variant frontotemporal dementia (bvFTD) in 52 patients with known bvFTD and 52 age and sex matched controls. Disease severity was 5.5± 3.5 or 7.7 ±4.2 as measured with the Clinical Dementia Rating scale (CDR) and the FTLD-modified Clinical Dementia Rating scale (FTLD-CDR). A region-of-interest approach focusing on frontotemporal, insular regions, and basal ganglia resulted in a diagnostic accuracy of bvFTD of 84.6%. The authors concluded that MRI can individually identify bvFTD with high accuracy in multi-center imaging data, paving the road to personalized diagnostic approaches in the future (low level of evidence).

Suspected dementia with Lewy bodies (DLB):

- **Green** – MRI brain without contrast
- **Yellow** – CT head without contrast*
- **Yellow** – Dopaminergic (DAT) SPECT to distinguish DLB from (PCA variant) AD when clinical criteria are non-diagnostic
- **Yellow** – I-MIBG cardiac scintigraphy to distinguish DLB from (PCA variant) AD when clinical criteria are non-diagnostic and DAT SPECT is not available or indeterminate
- **Yellow** – FDG-PET to distinguish DLB from (PCA variant) AD when clinical criteria are non-diagnostic and DAT SPECT is not available or non-diagnostic
- **Yellow** – Perfusion (HMPAO or ECD) SPECT to distinguish DLB from (PCA variant) AD when clinical criteria are non-diagnostic and DAT SPECT is not available or non-diagnostic
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline
- **Red** – fMRI; MRS; amyloid PET; DTI

* The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

Level of Evidence: MRI without contrast, MRI with and without contrast: moderate; MRI with contrast: n/a; CT without contrast: very low; CT with contrast: n/a; fMRI, MRS: insufficient; FDG-PET, perfusion SPECT, dopaminergic SPECT: moderate; I-MIBG cardiac scintigraphy: low

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Structural imaging should be carried out at least once in the diagnostic work-up of patients with dementia and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (Filippi et al [*EFNS*] 2012, good practice point).

Structural imaging should be used in the evaluation of every patient affected by dementia. CT and standard MRI are used to exclude secondary causes for dementia such as tumor and inflammatory disease, including abscess or normal-pressure hydrocephalus (Sorbi et al. [*EFNS/ENS*] 2012, Level A recommendation).

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus. Multi-detector row CT is the best alternative for patients who cannot undergo MRI (Filippi et al [*EFNS*] 2012, good practice point).

SPECT perfusion and MRI morphometric imaging are useful to distinguish DLB from AD (Sorbi et al. [*EFNS/ENS*] 2012).

Dopaminergic SPECT is useful to distinguish DLB from [PCA variant] AD, especially when there are no clear extrapyramidal symptoms and signs [or there is atypical presentation] (Filippi et al. [*EFNS*] 2012, class I/level A recommendation).

Dopaminergic SPECT can be useful in differentiating DLB from long-term psychiatric patients on neuroleptic drugs, whose parkinsonism may be drug-induced (Filippi et al. [*EFNS*] 2012, good practice point).

SPECT pre-synaptic dopamine transporter imaging is useful to distinguish DLB from non-DLB dementias (Sorbi et al. [*EFNS*/*ENS*] 2012, level B recommendation).

If the diagnosis is uncertain and dementia with Lewy bodies is suspected, use I-FP-CIT SPECT. If I-FP-CIT SPECT is unavailable, consider I-MIBG cardiac scintigraphy. Do not rule out dementia with Lewy bodies based solely on normal results (*NICE* 2018).

SPECT may be used in combination with CT to aid the differential diagnosis of dementia when the diagnosis is in doubt (*SIGN* 2006, C recommendation).

For patients with *suspected dementia with Lewy bodies, initial imaging*, the *American College of Radiology* recommends MRI head without IV contrast or CT head without IV contrast (*usually appropriate*). I-123 ioflupane SPECT/CT brain or FDG-PET/CT brain *may be appropriate* (Moonis et al [*ACR*] 2019).

Clinical notes:

- Lewy body dementia (LBD) accounts up to 15% of cases, with classic features of Parkinsonism, visual hallucinations, and fluctuating cognition and level of alertness (*Health Quality Ontario* 2014; Sorbi et al. [*EFNS*/*ENS*] 2012).
    - DLB fluctuations are typically delirium-like, occurring as spontaneous alterations in cognition, attention and arousal. They include waxing and waning episodes of behavioral inconsistency, incoherent speech, variable attention, or altered consciousness that involves staring or zoning out (McKeith et al. 2017).
    - Recurrent, complex visual hallucinations occur in up to 80% of patients with DLB and are a frequent clinical signpost to diagnosis. Patients are typically able to report these experiences, as are observant caregivers (McKeith et al. 2017).
    - Spontaneous parkinsonian features, not due to antidopaminergic medications or stroke, are common in DLB, eventually occurring in over 85% (McKeith et al. 2017).
    - REM sleep behavior disorder (RBD) is a parasomnia manifested by recurrent dream enactment behavior that includes movements mimicking dream content and associated with an absence of normal REM sleep atonia. RBD occurs frequently in autopsy-confirmed cases compared with non-DLB (76% vs. 4%) (McKeith et al. 2017).
- Supportive clinical features of DLB include: severe sensitivity to antipsychotic agents; postural instability; repeated falls; syncope or other transient episodes of unresponsiveness; severe autonomic dysfunction; hypersomnia; hyposmia; systematized delusions; apathy; anxiety; and depression (McKeith et al. 2017).

- PET imaging shows increased Aβ brain deposition in > 50% of patients with DLB, limiting its value to distinguish between AD and DLB (McKeith et al. 2017).

Imaging notes:

- No established structural MRI pattern is characteristic for DLB (Filippi et al. [*EFNS*] 2012; Sorbi et al. [*EFNS*/*ENS*] 2012). However, the absence of MTL atrophy on CT or MRI may be suggestive of a diagnosis of DLB compared with AD (Filippi et al. [*EFNS*] 2012).
- Similar to AD, a diffuse pattern of global grey matter atrophy including temporal, parietal, frontal, and insular cortices may occur in DLB (Filippi et al. [*EFNS*] 2012).
- Parietal occipital atrophy is associated with the hallucinations and visual-spatial disorders of DLB (Sorbi et al. [*EFNS*/*ENS*] 2012).
- A standard structural MRI protocol should include a high-resolution structural volumetric (3D) T1-weighted gradient echo, transverse T2 FSE/TSE, FLAIR sequences and transverse T2*-gradient echo sequences. Routine contrast administration [as part of a standard MRI protocol] is not indicated (Filippi et al. [*EFNS*] 2012).
- Volumetric MRI can be done as a secondary test to support the diagnosis [of DLB] (Moonis et al [*ACR*] 2019).
- If 3D T1-weighted techniques are unavailable, coronal oblique T1-weighted sequence can be used to assess MTL atrophy (Filippi et al. [*EFNS*] 2012).
- Supportive biomarkers, consistent with DLB that help the diagnostic evaluation, but without clear diagnostic specificity, include the following (McKeith et al. 2017):
    - Relative preservation of medial temporal lobe structure on CT/MRI scan
    - Generalized low uptake on SPECT/PET perfusion/metabolism scan, reduced occipital activity, and the posterior cingulate island sign on FDG-PET imaging
    - Prominent posterior slow-wave EEG activity with periodic fluctuations in the pre-alpha/theta range.
- Occipital hypometabolism, particularly in the primary visual cortex, may be more common in DLB than AD on a group basis (Filippi et al. [*EFNS*] 2012). However, on individual scans, the appearances of DLB and [PCA variant] AD can be identical. Moreover, occipital hypometabolism is not a specific marker for DLB and can be associated with AD (Filippi et al. [*EFNS*] 2012).
- Generalized low uptake on FDG-PET/CT with occipital hypometabolism has been demonstrated and is a useful supportive imaging biomarker. However, FDG-PET/CT is a second level examination for the evaluation of DLB (Moonis et al [*ACR*] 2019).
- If one or more of the following is found, associated with one or more core clinical features, probable DLB should be diagnosed (McKeith et al. 2017):
    - Reduced DAT update in basal ganglia demonstrated by SPECT or PET imaging
    - Reduced uptake on I-MIBG myocardial scintigraphy
    - Polysomnography (PSG) confirmation of REM sleep without atonia.
- In the present guidelines, decreased dopamine transporter uptake is of the greatest importance among various neuroimaging findings and is listed as one of the suggestive features. Functional imaging of the dopamine transporter (I-123 Ioflupane) using SPECT might identify a defect in the nigrostriatal pathway that occurs in a variety of disorders including DLB and Parkinson disease (Moonis et al [*ACR*] 2019).
- A negative ^{123}I-FP-CIT scan does not necessarily exclude a diagnosis of probable DLB, as around 20% of individuals with probable DLB appear to have normal scans (Filippi et al. [*EFNS*] 2012).

Evidence update (2017-present and selected articles from guideline references):
Donaghy et al. (2018) studied the relationship between amyloid deposition, clinical profile, gray matter volume, and brain perfusion in patients with dementia with Lewy bodies (DLB, n = 37), Alzheimer's disease (n = 20), and controls (n = 20). All patients underwent a thorough clinical assessment, 3T MRI, and early- and late-phase ^{18}F-Florbetapir PET-CT to assess cortical perfusion and amyloid deposition, respectively. There were no significant differences between amyloid-positive and amyloid-negative DLB cases in age (P=.78), overall cognitive impairment (P=.83), level of functional impairment (P=.80), or any other clinical or cognitive scale, nor any significant differences in hippocampal or gray matter volumes. Amyloid-positive DLB cases had lower medial temporal lobe perfusion (P=.03) than amyloid-negative cases. The authors conclude that amyloid deposition was not associated with differences in clinical or neuropsychological profiles in DLB, and the presence of amyloid in DLB cannot be identified on the basis of clinical and other imaging features (low level of evidence).

Mishima et al. (2016) conducted a meta-analysis of 45 studies (n = 7461) to quantitatively synthesize data on test performance in differentiating dementia with Lewy bodies from other dementias. Metaiodobenzylguanidine (MIBG) scintigraphy and dopamine transporter (DAT) single photon emission computed tomography (SPECT) showed, respectively, excellent (summary kappa = 0.85; 95% CI, 0.74-0.96) and good (summary kappa = 0.71; 95% CI, 0.43-0.99) agreement. MIBG scintigraphy appeared superior to fluorodeoxyglucose–positron emission tomography (summary kappa = 0.53; 95% CI, 0.36-0.69) and cerebral blood flow SPECT (summary kappa = 0.40; 95% CI, 0.33-0.47). For differentiating DLB from AD, CSF t-tau levels (summary kappa = 0.68; 95% CI, 0.55-0.82) performed comparably to MIBG scintigraphy and DAT SPECT. The authors concluded that MIBG scintigraphy and DAT SPECT are highly concordant with standard diagnostic criteria in differentiating DLB from non-DLB dementias (moderate level of evidence).

Barrou et al. (2014) evaluated the influence of I-FP-CIT SPECT on diagnosis and treatment strategies in 46 elderly patients with mild dementia and suspicion of DLB. Patients were stratified into three groups: probable DLB (N = 14; mean age 82), possible DLB (N = 21; mean age 82), or other than DLB (N = 11; mean age 83). Dementia diagnoses were revised in 37% of cases and Levodopa was stopped in 67% cases based on I-FP-CIT-SPECT results. The authors concluded that I-FP-CIT SPECT has a significant impact on dementia diagnoses and treatment decisions, even in cases of definite parkinsonism or probable DLB (low level of evidence).

Kobayashi et al. (2017) evaluated the extent to which diagnostic accuracy can be increased by using different combinations of brain perfusion SPECT (bp-SPECT), MIBG scintigraphy, and DAT-SPECT in 34 consecutive patients (mean age 75 years) with DLB based on consensus diagnostic criteria. MIBG scintigraphy (79%) and Dopamine-transporter (DAT) SPECT (79%) had better sensitivity for characteristic abnormalities in DLB than bp-SPECT (53%). The combination of the three modalities could increase sensitivity for diagnosis of DLB to 100%. The authors concluded that the combination of bp-SPECT, MIBG scintigraphy, and DATSPECT imaging may lead to a marked improvement in DLB diagnosis (low level of evidence).

Suspected vascular dementia:

- **Green** – MRI brain without contrast
- **Yellow** – CT head without contrast*
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline
- **Red** – fMRI; MRS; FDG-PET; amyloid PET; Perfusion (HMPAO or ECD) SPECT; Dopaminergic (DAT) SPECT; I-MIBG cardiac scintigraphy; DTI

* The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

Level of Evidence: MRI without contrast, MRI with and without contrast: moderate; MRI with contrast: n/a; CT without contrast, CT with and without contrast: very low for comparative diagnostic accuracy; CT with contrast: n/a; fMRI, MRS, FDG-PET, amyloid imaging, perfusion SPECT, dopaminergic SPECT, I-MIBG cardiac scintigraphy: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Structural imaging should be carried out at least once in the diagnostic work-up of patients with dementia and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (Filippi et al. [*EFNS*] 2012, good practice point).

Structural brain imaging is an essential element for the diagnosis of vascular dementia, and without it vascular dementia will be 'possible' at best (Filippi et al. [*EFNS*] 2012).

Structural imaging should be used in the evaluation of every patient affected by dementia. CT and standard MRI are used to exclude secondary causes for dementia such as tumor and inflammatory disease, including abscess or normal-pressure hydrocephalus (Sorbi et al. [*EFNS/ENS*] 2012, Level A recommendation).

If the dementia subtype is uncertain and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT (*NICE* 2018).

The use of a structural neuroimaging study, such as CT or MRI scan, is generally recommended as part of an initial evaluation [for patients with dementia], although clinical practice varies. Imaging is particularly important for those with a subacute onset (less than 1 year), symptom onset before age 65, vascular risk factors…or possible focal lesion (*APA Work Group on Alzheimer's Disease and other Dementias* 2007).

The PLE expert panel recommended MRI as the preferred approach for structural imaging of patients with suspected vascular dementia, as MRI is more sensitive to subtle small-vessel vascular changes than CT (PLE expert panel consensus opinion; Filippi et al. [*EFNS*] 2012; Hort et al. [*EFNS*] 2010).

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus. Multi-detector row CT is the best alternative for patients who cannot undergo MRI (Filippi et al [*EFNS*] 2012, good practice point).

If the dementia subtype is uncertain and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT. Do not diagnose vascular dementia based solely on vascular lesion burden (*NICE* 2018).

Although CT can detect the presence or absence of infarctions in patients with dementia, histopathologically verified cases of vascular dementia with normal CT studies have been reported. Thus, MRI is preferable to CT for detecting vascular lesions in dementia patients (Moonis et al. [*ACR*] 2019).

Both CT and MRI perform well in depicting large-vessel infarcts, MRI is more sensitive to subtle small-vessel vascular changes than CT. T2-weighted and FLAIR sequences are highly sensitive for detecting major stokes as well as small strategic infarcts and small-vessel ischaemic white matter damage (Filippi et al. [*EFNS*] 2012).

Both CT and MRI are useful for detecting a vascular component of dementia. There is a lack of evidence that MRI is superior to CT (*Health Quality Ontario* 2014, GRADE: Low). *The PLE expert panel recommended that MRI is the procedure of choice in to evaluate dementia associated with infarction* (PLE expert panel consensus opinion).

For patients with *suspected vascular dementia, initial imaging*, the *American College of Radiology* recommends MRI head without IV contrast or CT head without IV contrast (usually appropriate). (Moonis et al [*ACR*] 2019). *The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions* (PLE expert panel consensus opinion; Hort et al. [EFNS] 2010).

FDG-PET in vascular dementia shows multiple focal metabolic defects. SPECT is of little value in differentiating Alzheimer's disease from vascular dementia. MRS and fMRI are investigational and do not appear to clinically help establish a diagnosis of vascular dementia or mixed vascular dementia and Alzheimer's disease (Moonis et al. [ACR] 2019).

<u>Clinical notes:</u>

- The Diagnostic and Statistical Manual of Mental Disorders – 5th Edition (*American Psychiatric Association*, 2013) defines vascular neurocognitive disorder as follows:
    A. Criteria met for major or mild neurocognitive disorder
    B. Clinical features are consistent with a vascular etiology, as either of the following:
        a. Onset of the cognitive deficits is temporally related to one or more cerebrovascular events

b. Evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function

C. Evidence of the presence of cerebrovascular disease from history, physical examination, and/or neuroimaging considered sufficient to account for the neurocognitive deficits.

D. Clinical criteria supported by neuroimaging evidence of significant parenchymal injury attributed to cerebrovascular disease*

E. Neurocognitive syndrome is temporally related to one or more documented cerebrovascular events*

F. Both clinical and genetic (e.g., cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) evidence of cerebrovascular disease are present*

*If D, E, or F are present, probable vascular neurocognitive disorder is diagnosed; otherwise, possible vascular neurocognitive disorder should be diagnosed.

- It is particularly difficult to attribute clinical significance to evidence of cerebrovascular disease in patients with cognitive impairment. Vascular changes on CT or MRI do not preclude a diagnosis of degenerative dementia, especially in older age. A diagnosis of vascular dementia should only be made where the vascular lesion(s) can explain the cognitive deficit (Filippi et al. [*EFNS*] 2012).
    - Bilateral infarcts in the area of the anterior cerebral artery, infarcts in the area of the posterior cerebral artery, association areas, or watershed regions are thought to be causative of large-vessel vascular dementia (Filippi et al. [*EFNS*] 2012).
    - Extensive white matter lesions involving $\geq$ 25% of the white matter, or multiple basal ganglia, thalamic and frontal white matter lacunar infarcts, or bilateral thalamic lesions are considered relevant radiological lesions associated with small-vessel vascular dementia (Filippi et al. [*EFNS*] 2012).

Imaging notes:

- A standard structural MRI protocol should include a high-resolution structural volumetric (3D) T1-weighted gradient echo, transverse T2 FSE/TSE, FLAIR sequences, transverse T2*-gradient echo and DWI sequences. Routine contrast administration [as part of a standard MRI protocol] is not indicated (Filippi et al. [*EFNS*] 2012).
- If 3D T1-weighted techniques are unavailable, coronal oblique T1-weighted sequence can be used to assess MTL atrophy to support a clinical diagnosis of AD compared with cognitively normal subjects (Filippi et al. [*EFNS*] 2012).
- DWI sequences can be useful to identify recent infarcts in patients with vascular dementia, transient global amnesia or vasculitis (Filippi et al. [*EFNS*] 2012).

Evidence update (2017-present): No low, moderate, or high level evidence was found which addresses the clinical scenario above.

Suspected normal pressure hydrocephalus (NPH):

- **Green** – MRI brain without contrast
- **Yellow** – CT head without contrast*
- **Yellow** – MRI brain with contrast to characterize abnormalities seen on initial MRI brain without contrast or CT head; CT head with contrast to characterize abnormalities seen on initial CT head without contrast
- **Orange** – MRI brain with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline; CT head with and without contrast, except when concerned for an intracranial neoplasm or infectious/inflammatory disease as an etiology in atypical cases, or when there is rapid neurological decline*
- **Orange** – In-111 DTPA cisternography with SPECT/CT, except at specialist request when all other tests are inconclusive and the results will change management
- **Orange** – Perfusion (HMPAO or ECD) SPECT, except at specialist request when all other tests are inconclusive and the results will change management
- **Orange** – Dopaminergic ([^{123}I]FP-CIT, DAT) SPECT, except at specialist request when all other tests are inconclusive and the results will change management
- **Red** – fMRI; MRS; FDG-PET; amyloid PET; I-MIBG cardiac scintigraphy; DTI

* The PLE expert panel recommends MRI as the preferred approach for structural imaging of patients with a suspected neurocognitive disorder, as MRI is more sensitive to subtle vascular changes and to changes that may indicate specific conditions (PLE expert panel consensus opinion; Hort et al. [*EFNS*] 2010).

Level of Evidence: MRI without contrast, MRI with and without contrast: moderate; MRI with contrast: n/a; CT without contrast: very low; CT with and without contrast, CT with contrast: n/a; fMRI, MRS, amyloid imaging: very low; FDG-PET, perfusion SPECT, dopaminergic SPECT, I-MIBG cardiac scintigraphy: insufficient

Notes concerning applicability and/or patient preferences: none

Guideline and PLE expert panel consensus summary:
Structural imaging should be carried out at least once in the diagnostic work-up of patients with dementia and serves at least three purposes: to exclude other potentially treatable diseases, to recognize vascular lesions and to identify specific findings to help distinguish different forms of neurodegenerative types of dementia (Filippi et al [*EFNS*] 2012, good practice point).

Structural imaging should be used in the evaluation of every patient affected by dementia. CT and standard MRI are used to exclude secondary causes for dementia such as tumor and inflammatory disease, including abscess or normal-pressure hydrocephalus (Sorbi et al. [*EFNS/ENS*] 2012, Level A recommendation).

MRI is currently the imaging modality of choice for assessing subjects with suspected dementia. However, where MRI is not available or contraindicated, CT scans can usefully exclude major space occupying lesions, large infarcts and hydrocephalus. Multi-detector row CT is the best alternative for patients who cannot undergo MRI (Filippi et al [*EFNS*] 2012, good practice point).

MRI is recommended for diagnosis [of NPH]. CT may be used when MRI is contraindicated. The diagnosis of iNPH should be suspected based on both symptomatic and imaging findings (Mori et al. 2012).

Morphological brain imaging by CT and MRI is essential for screening and clinical diagnosis of iNPH. Although no study has compared the diagnostic performance of CT and MRI, MRI is suitable for detecting morphological changes, and coronal sections are particularly useful in evaluating the condition of the sulci over the high cerebral convexity (Mori et al. 2012, grade B recommendation).

The presence of one of the triad symptoms and MRI features consistent with DESH (disproportionate distribution of CSF between the superior and inferior subarachnoid spaces) is highly predictive of a positive tap test and shunt responsiveness (Mori et al. 2012, grade B recommendation).

Because of the invasiveness and low diagnostic accuracy of CT or RI cisternography, it is not necessary for the diagnosis of iNPH; however, it may be useful in identifying obstructions in the circulation of CSF (Mori et al. 2012, grade C2 recommendation).

For patients with *suspected idiopathic normal-pressure hydrocephalus, initial imaging*, the *American College of Radiology* recommends MRI head without IV contrast or CT head without IV contrast (*usually appropriate*). In-111 DTPA cisternography or Tc-99m HMPAO SPECT/CT brain *may be appropriate* (Moonis et al [*ACR*] 2019). *Because of high false positive and high false negative rates, the expert panel thought that CT or RI cisternography has limited applicability in the work up of NPH. The expert committee thought that volumetric imaging with respect to the DESH criteria represents the primary diagnostic technique in making a diagnosis of NPH and predicting shunt responsiveness in patients with appropriate symptoms* (PLE expert panel consensus opinion).

The value of magnetic resonance spectroscopy (MRS) as a test to investigate the clinical course, such as conditions before and after shunt surgery, has not been established (Mori et al. 2012).

The usefulness of diffusion tensor imaging (DTI) to differentiate iNPH and AD has been reported. However, the diagnostic value of the white matter evaluation by DTI has not been established (Mori et al. 2012).

Clinical notes:

- Normal pressure hydrocephalus is a syndrome which classically presents with dementia, gait disturbance and urinary incontinence, and is associated with ventricular dilation and normal cerebrospinal fluid pressure. The symptoms can be reversed by CSF shunt surgery (Mori et al. 2012).
- NPH can be either idiopathic (iNPH) or secondary to known risk factors. iNPH constitutes the majority of cases (Isaacs et al. 2018).
    - iNPH is primarily observed in patients age $\geq$ 65 years and clinically characterized by the presence of neurologic gait impairment plus additional features of a symptom triad – cognitive impairment and urinary incontinence (Isaacs et al. 2018).
    - Secondary NPH may result from subarachnoid hemorrhage or meningitis (Mori et al. 2012).

Imaging notes:

- MRI 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 (Moonis et al [*ACR*] 2019).
- The finding of tight high convexity subarachnoid spaces can differentiate iNPH from cerebral atrophy in patients with Alzheimer's disease with high sensitivity and specificity (Mori et al. 2012).
- MRI sections through the posterior commissure, and the posterior half of the cingulate sulcus is narrower than the anterior half on sagittal MRI sections (the anterior half is narrower or equal to the posterior half in healthy individuals). Both signs are also useful in the differentiation of iNPH from Alzheimer's disease (Mori et al. 2012, grade C1 recommendation).
- A standard structural MRI protocol should include a high-resolution structural volumetric (3D) T1-weighted gradient echo, transverse T2 FSE/TSE, FLAIR sequences and transverse T2*-gradient echo sequences. Routine contrast administration [as part of a standard MRI protocol] is not indicated (Filippi et al. [*EFNS*] 2012).
- Perfusion of the cortices at the high convexity, and medial parietal and frontal lobes is relatively increased due to increased gray matter density and decreased CSF spaces in these regions, which are useful in differentiating iNPH from other dementia illnesses including Alzheimer's disease (Mori et al. 2012).
- Tc99m HMPAO SPECT/CT is a second-level test to stratify patients with INPH who may benefit from shunting (Moonis et al [*ACR*] 2019).
- 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 can also help in identifying shunt-responsive NPH patients (Moonis et al [*ACR*] 2019). The diagnostic value of CSF flow studies has not been established, however and it is controversial as to whether it predicts shunt response (Mori et al. 2012; expert panel opinion).
- Radioisotope cisternogram using In-111-diethylenetriamine pentaacetic acid (DTPA) shows delayed clearance of radiotracer over the cerebral convexities and abnormal reflux of radiotracer into the ventricles (Moonis et al [*ACR*] 2019). *Because of high false positive and high false negative rates, the expert panel thought that CT or RI cisternography has limited applicability in the work up of NPH* (PLE expert panel consensus opinion).

Evidence update (2010-present):

Kockum et al. (2019) constructed a radiological scale, composed of morphological signs of iNPH, and compared it with clinical symptoms. A total of 168 patients (mean age 75) had brain CT and neurological exam to assess clinical symptoms according to Hellstrom's iNPH scale. Two radiologists, blinded to clinical data, independently evaluated and measured eight radiological parameters: Evans' index, callosal angle, size of temporal horns, narrow high-convexity sulci, dilated Sylvian fissures, focally dilated sulci, periventricular hypodensities and bulging of lateral ventricular roof. Linear regression showed that all parameters except ventricular roof bulging were significantly associated with clinical iNPH symptoms. The seven remaining parameters were summarized into a total iNPH Radscale score ranging from 0-12. There was significant correlation ($r = 0.55$, $P < 0.001$) between total iNPH Radscale score and clinical symptoms. Inter-rater agreement for included radiological parameters was high (intraclass correlation, 0.74–0.97). The authors conclude that the iNPH Radscale may become a valuable diagnostic screening tool, allowing a structured radiological assessment (moderate level of evidence).

Allali et al. (2018) compared [^{123}I]FP-CIT SPECT imaging (visual rating and semiquantitative values) among iNPH (n = 26) and iNPH mimics (n = 30). Patients were visually categorized as having normal or abnormal [^{123}I]FP-CIT SPECT. For quantification of [^{123}I]FP-CIT SPECT imaging, the authors calculated striatal binding ratios (SBR) using automated brain analysis while applying locally established (age-adjusted) reference limits. Normal SBR [^{123}I]FP-CIT SPECT was present in 69.2% of iNPH and 37.9% of mimics (p value = .02), while visual rating did not differ between the two groups. Normal SBR [^{123}I]FP-CIT SPECT values were associated with diagnosis of iNPH, even after adjusting for white matter changes and comorbidities (adjusted OR: 4.17; 95% CI 1.26–13.80). The authors conclude that semi quantitative [^{123}I]FP-CIT SPECT evaluation, but not visual assessment, discriminates iNPH patients from their mimics (low level of evidence).

Garcia-Armengol et al. (2016) compared the prognostic value of pulse amplitude on intracranial pressure (ICP) monitoring and disproportionately enlarged subarachnoid space (DESH) on MRI for predicting surgical benefit after shunt placement in 89 patients with suspected iNPH. Positive DESH findings measured by MRI had sensitivity of 79.4% and specificity of 80.8% for predicting shunt responders. Fifty-five patients had positive DESH findings, with presence of DESH findings having PPV and NPV of 90.9% and 61.8%, respectively. High ICP pulse amplitude had sensitivity of 84.4%, specificity of 88%, PPV of 94.7% and NPV of 61.8% for predicting shunt responders. The authors concluded that both positive DESH findings and high ICP pulse amplitude support diagnosis of iNPH and provide additional diagnostic value for predicting shunt-responsive patients; high ICP amplitude was more accurate than positive DESH findings, although it is an invasive test (moderate level of evidence).

Brix et al. (2017) conducted a retrospective analysis of a cross-sectional observational study on the diagnostic accuracy of the Evan's Index (EI) on MRI imaging in determining pathological ventricular enlargement in 534 patients with iNPH, AD, and healthy matched controls (CTR). New age- and sex-based EI normal cutoffs were determined for patients with AD and elderly controls, for male/female: 65-69 years (0.34/0.32), 70-74 years (0.36/0.33), 75-79 years (0.37/0.34) and 80-84 years (0.37/0.36). Proposed cut-offs for EI in men and women aged 65-84 differentiated between iNPH and CTR with sensitivity of 80% and for different age and sex categories of AD and CTR with sensitivity and specificity of 0%-27% and 91%-98%, respectively. The authors concluded that the range of EI measurements in healthy elderly is wide, and a cut-off value of 0.3 cannot be used to differentiate between normal and enlarged ventricles in individual cases. The proposed EI thresholds from the present study show good sensitivity for the iNPH diagnosis (low level of evidence).

Benedetto et al. (2017) described a new quantitative method (SILVER index) to assess disproportionally enlarged subarachnoid spaces and hydrocephalus (DESH) on CT scans and to evaluate its prognostic value. A total of 55 patients (29 with probable iNPH and 26 matched healthy controls) were included. The mean value of the SILVER index was 11.52 ± 14.27 in the study group and 1.68 ± 0.98 in the control group (P < .0001) with area under the ROC curve of 0.903 (95% CI, 0.813-0.994). A cut-off value for the SILVER index of 3.75 was extrapolated with sensitivity and specificity of 0.828 and 0.962 respectively. The authors concluded that the SILVER index is a reliable tool to easily quantify DESH on CT scans of patients with suspected iNPH. Its high sensitivity and specificity should encourage further investigations to confirm its clinical utility (low level of evidence).

Cagnin et al. (2015) studied the accuracy of a simplified callosal angle measure in differentiating iNPH from DLB and AD using conventional brain MRI in 76 patients. iNPH showed a significantly decreased mean callosal angle value compared to AD, DLB, and controls (iNPH = 109 ± 9; DLB = 136.9 ± 8.2; AD = 135.4 ± 11.3; Controls = 138.5 ± 5.2; P < .00001). The development of a callosal cut-off angle of 123

(derived by the mean -3SD of the control group), which would differentiate iNPH, had an accuracy of 96% (sensitivity 100%, specificity 95.4%). By ROC analysis, the area under the curve was 0.99 (95% CI: 0.97-1).The authors concluded that this simplified callosal angle measure represents an accurate, reproducible, and easy marker of iNPH (low level of evidence).

Craven et al. (2016) calculated the predictive value of the DESH sign on brain imaging in predicting clinical responsiveness to ventricular shunt placement in 103 patients. All patients had probable iNPH, CT or MRI prior to shunt placement, and at least 1 year follow-up. The DESH sign had an estimated PPV of 77% and NPV of 25% in predicting shunt response at follow-up. The authors concluded that the DESH sign demonstrates a low NPV; DESH-negative patients should still undergo prognostic tests for iNPH, such as an extended lumbar drainage protocol, and should not be excluded from shunt insertion (low level of evidence).

Kojoukhova et al. (2015) examined the diagnostic accuracy of multiple radiologic markers in idiopathic NPH (iNPH) vs. 24 hour intraventricular pressure monitoring in 390 patients with NPH and brain imaging (CT or MRI). iNPH was more likely in patients with severe volumetric disproportion between the suprasylvian and sylvian subarachnoid spaces than in those without disproportion (OR 7.5, 95% CI, 4.0-14.1, P < .0001) and mild disproportion (OR 2.6, 95% CI, 1.4-4.6, P = .001). Narrow temporal horns (OR per 1 mm 0.91, 95% CI, 0.84-0.98, P = .014) were also associated with an iNPH diagnosis. None of the preoperative radiologic markers were significantly related to shunt procedure response. The authors concluded that visually evaluated disproportion was the most useful radiological marker in iNPH diagnostics. Narrower temporal horns also supported an iNPH diagnosis, possibly since atrophy was more pronounced in the non-NPH than iNPH group (low level of evidence).

Miskin et al. (2017) assessed the diagnostic performance of traditional manual MR measures of NPH (Callosal angle (CA) and Evans Index (EI)) vs. automated volumetric methods in differentiating NPH from non-NPH on MR in 106 patients with NPH, AD, and matched controls. The traditional model using CA and EI demonstrated 89.6%-93.4% accuracy and average area under the curve of 0.96 in differentiating patients with NPH from patients without NPH, while the regression model using volumetric predictors of gray and white matter was 94.3% accurate. The authors concluded that CA and EI may serve as a screening tool to help differentiate patients with NPH from patients without NPH, which would allow for designation of patients for further volumetric assessment (low level of evidence).

Rinne et al. (2012) conducted a multicenter pooling of cross-sectional studies on the diagnostic accuracy of [^{18}F]flutemetamol PET imaging compared to histopathologic staining for fibrillary amyloid B in cortical biopsies of 52 patients with NPH. Biopsy site and contralateral [^{18}F]flutemetamol standardized uptake value ratios (SUVRs) were significantly associated with neuritic plaque burden (r spearman's = 0.61, P = .0001 for both), as was the composite SUVR with biopsy pathology (r spearman's = 0.74, P < .0001). Sensitivity and specificity by majority read were 93% and 100%, respectively. The authors concluded that noninvasive in vivo [^{18}F]flutemetamol PET imaging demonstrates strong concordance with histopathology for brain fibrillar amyloid B, supporting its promise as a tool to assist physicians with earlier detection of the disease process and making diagnostic decisions about concomitant AD and other diseases associated with brain amyloidosis (low level of evidence).

Exclusions:

- Suspected prion disease (e.g., Creutzfeld-Jakob Disease)
- Traumatic brain injury (TBI) / chronic traumatic encephalopathy (CTE)
- Neurodegeneration with excessive iron degeneration
- Movement disorders as primary diagnostic disorder (including Parkinson's disease, limbic encephalitis, Huntington's disease)
- Pediatric patients
- Pregnant patients
- Suspected malignancy
- Arterial spin labelling
- Resting state functional MRI
- Electroencephalography (EEG)
- Artificial intelligence, deep learning
- Acute altered mental status (AMS) / delirium

AUC Revision History:

Revision Date:	New AUC Clinical Scenario(s):	Posting Date:	Approved By:
04/07/2020	n/a	04/13/2020	CDI Quality Institute's Multidisciplinary Committee

Information on our evidence development process, including our conflicts of interest policy is available on our website at **https://www.mycdi.com/ple**