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Article type    : Guidelines

**EANM-EAN recommendations for the use of brain ^{18}F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in neurodegenerative cognitive impairment and dementia: Delphi consensus**

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Running title: FDG-PET recommendations in dementia

## Abstract

**Background**: Recommendations for using FDG-PET to support the diagnosis of dementing neurodegenerative disorders are sparse and poorly structured.

**Methods**: We defined 21 questions on diagnostic issues and on semi-automated analysis to assist visual reading. Literature was reviewed to assess study design, risk of bias, inconsistency, imprecision, indirectness and effect size. Critical outcomes were sensitivity, specificity, accuracy, positive/negative predictive value, area under the receiving operating characteristic curve, and positive/negative likelihood ratio of FDG-PET in detecting the target conditions. Using the Delphi method, an expert panel voted for/against the use of FDG-PET based on published evidence and expert opinion.

**Results**: Of the 1435 papers, 58 provided proper quantitative assessment of test performance. The panel agreed on recommending FDG-PET for 14 questions: diagnosing mild cognitive impairment due to Alzheimer's disease (AD), frontotemporal lobar degeneration (FTLD) or dementia with Lewy bodies (DLB); diagnosing atypical AD and pseudodementia; differentiating between AD and DLB, FTLD, or vascular dementia, between DLB and FTLD, and between Parkinson's disease (PD) and progressive supranuclear palsy; suggesting underlying pathophysiology in corticobasal degeneration and progressive primary aphasia, and cortical dysfunction in PD; using semi-automated assessment to assist visual reading. Panelists did not support FDG-PET use for preclinical stages of neurodegenerative disorders, for amyotrophic lateral sclerosis (ALS) and Huntington disease (HD) diagnoses, and ALS or HD-related cognitive decline.

**Conclusions**: Despite limited formal evidence, panelists deemed FDG-PET useful in the early and differential diagnosis of the main neurodegenerative disorders, and semiautomated assessment helpful to assist visual reading. These decisions are proposed as interim recommendations.

1. Background

Advancing knowledge on the pathophysiology of dementing neurodegenerative disorders and the increasing pressure for cost-effectiveness require systematic assessment and validation of biomarkers performance, including FDG-PET, to define efficient diagnostic procedures (1). In USA, Medicare accepted to reimburse FDG-PET in 2004 (2), for differential diagnosis between Alzheimer's disease (AD) and frontotemporal dementia (FTD). A heterogeneous reimbursement picture is found in Europe, where national or private insurance reimbursement is guaranteed with different

restrictions, with the exception of Germany (1). In 2007, the International Working Group (IWG) research criteria (3) included FDG-PET as a biomarker for prodromal AD. In 2011, the U.S. National Institute on Aging and the Alzheimer Association (NIA-AA) criteria regarded FDG-PET as a biomarker of neuronal injury, supporting the diagnosis of Mild Cognitive Impairment (MCI) due to AD at the stage of MCI, (4) -consistent with the IWG concept of prodromal AD. In 2014, the IWG categorized FDG-PET as a *topographical* biomarker detecting downstream neurodegeneration. As such, it is considered able to track disease stage, although it is less specific than biomarkers of brain amyloidosis and tauopathy in detecting the underlying pathophysiology (IWG-2 criteria (5)). Although the downstream nature of hypometabolism and its limited specificity restrict its ability to diagnose the pathophysiology of neurodegenerative disorders, many clinicians are convinced that FDG-PET, as a biomarker of neurodegeneration, is a highly relevant tool in clinical practice, allowing exclusion of neurodegeneration and differentiation of patterns of hypometabolism positively contributing to diagnosis, as in the case of FTLD (6, 7), DLB (8), and PSP (9). A comprehensive review of available data till 2010, supporting the clinical utility of the exam in the differential diagnosis of dementing conditions, further supports this view (10). Regarding AD, a recent Cochrane review found an exceedingly large variability of FDG-PET performance in detecting AD in MCI patients (11), reflecting the heterogeneity of MCI criteria between studies and the inadequate follow-up period of many studies (12).

This scenario led the EANM and the European Academy of Neurology (EAN) to endeavor to achieve consensus-based recommendations for clinical use in the diagnosis of a large set of neurodegenerative disorders, based on the expertise of clinicians proficient in FDG-PET use and research, and on the available scientific evidence on the utility of the investigation. A preamble introducing these recommendations is in Supplemental material 1.

1.1 Aims of the EANM-EAN task force

The clinical role of FDG-PET was already quoted in previous European Federation of Neurological Societies (EFNS) dementia (13), neuroimaging (14) and EANM procedure (15) guidelines, but specific clinical recommendations on FDG-PET have never been released. Following the publication of the second edition of the procedure guidelines, the EANM-NIC decided to target neurologists and other clinicians involved in dementia management with more direct information to facilitate proper use of FDG-PET. The EANM-NIC and the Neuroimaging and Dementia study groups of the EAN (formerly study groups of the EFNS) thus converged to prepare common recommendations on the use of FDG-PET in the clinical practice of dementia. They appointed seven panelists, four from EANM and three from EAN, to produce recommendations taking into consideration the incremental value of FDG-PET, as added on clinical-neuropsychological examination, for the diagnosis and management of patients with dementing neurodegenerative disorders of different types. Consensus recommendations have been produced based on the expertise of panelists, who were also informed about the availability and quality of evidence, assessed based on the EFNS guidance (16).

2. Methods

The evidence assessment procedure is described in detail elsewhere (17). All the procedures were conducted through telematic contacts. The panelists drafted and circulated twenty-one PICO (Population, Intervention, Comparison, Outcome) questions, whose literature search was then assigned to each panelist (minimum: two PICO questions each). Peer-reviewed papers addressing such questions until November 2015 were searched using strings harmonized across the 21 PICOs in one or more databases among Embase and PubMed. Only original studies published in English were considered, excluding reviews and management guidelines. We considered all papers reporting on FDG-PET use independently of the acquisition technique, either static or dynamic. The vast majority of studies used static acquisition and thus evidence on absolute quantification of glucose consumption is lacking. Evidence was assessed based on study design (including availability of validated measures of test performance, gold/reference standard, head-to-head comparison with comparator, blinding, patient recruitment and accounting), inconsistency, imprecision, indirectness, applicability and effect size.

As acceptable diagnostic studies (18, 19), we included cross-sectional studies provided they reported the critical outcomes, such as sensitivity, specificity, accuracy, positive/negative predictive value (PPV/NPV), area under the curve (AUC), or positive/negative likelihood ratios (LR+/LR-). Clinical confirmation or conversion at follow-up or biomarker-based diagnosis were considered as acceptable reference standards, where pathological confirmation was not available. In cases where pathology confirmation was available, no minimum sample size was set for study inclusion. Otherwise, a minimum sample size of 30 was set for frequent disorders, and lower thresholds for less frequent disorders. Effect size for sensitivity, specificity and accuracy was considered small with values between 50-70%, medium (71-80%), or large (81-100%). These and other data were extracted and reported in the PICO tables available at https://drive.google.com/open?id=0B0_JB3wzTvbpVFYtUGxHdGZWYmc. (Suppl Mater 2).

The Delphi voting procedure (20) was performed using a web-based platform. Panelists accessed the questionnaire, the tables reporting the data extraction, summaries of available evidence and, from round II, statistics and the anonymized answers by the other panelists from previous rounds. For each PICO question, panelists had to vote for or against supporting clinical use based on the collected evidence and on their expertise, and to justify their answers. Consensus was defined when at least 5 out of 7 panelists converged on the same decision.

In our terminology, we distinguished syndromes from pathophysiologies. This is consistent with current NIA-AA and IWG criteria (21), but less consistent with the diagnostic criteria of other disorders, for which the prodromal stage is not yet defined (as, for example FTLD). However, a diagnosis of "possible bv-FTD" (6) can be formulated in MCI patients; as well, the DLB community is working at the definition of "prodromal DLB"(8). Thus, the distinction between disease stages and

pathophysiology is indeed required also for non-AD neurodegenerative disorders. Regarding FTLD, unless differently referenced [e.g., (6)], we adopted the inclusive 1998 definition (22), treating separately only the linguistic variant where specified.

**3. Results**

The evidence assessment for the 21 literature searches, available at https://drive.google.com/open?id=0B0_JB3wzTvbpVFYtUGxHdGZWYmc (Suppl Mater 2), is reported in detail in dedicated review papers (23-29) and briefly summarized in the pertinent sections below. All panelists filled the whole questionnaire at each of the 4 rounds. The output of the project consists of the recommendations consensually generated through the Delphi procedure, where panelists based their votes on both their own expertise and on the available evidence. Basically, decisions reflected the well-accepted concept that FDG-PET allows to differentiate between presence and absence of neuronal injury, no matter what type of neurodegeneration. Tables 1 and 2 summarize the recommendations for the 21 PICO. Panelists supported the use of FDG-PET in those PICOs involving the diagnosis of disorders at the MCI stage (Section 3.1) and when already indicated for typical patterns of neurodegeneration in the disease-specific diagnostic criteria (Section 3.3) (3-9, 14, 30) (Table 1). Instead, they did not support the use of FDG-PET in individuals without objective cognitive impairment (Section 3.2) (31, 32).

3.1 *Use of FDG-PET in MCI patients*

The panel voted to support the use of FDG-PET whenever a neurodegenerative disorder is suspected to be the underlying cause of an MCI condition (Table 1, (24)). This included the conditions of AD, FTD, and DLB. Literature searches, assessment and consensual decisions answered the PICO questions whether *FDG-PET should be performed, as adding diagnostic value (in terms of increased accuracy, and versus pathology or biomarker-based diagnosis or conversion at follow-up) as compared to standard clinical/neuropsychological assessment alone, to detect (3.1.1) AD, (3.1.2) FTD, and (3.1.3) prodromal dementia with Lewy bodies (DLB) in patients with persistent MCI of uncertain origin.*

*3.1.1 FDG-PET to support the diagnosis of AD in MCI (PICO 1)*

Critical outcomes for this question were available in 13 of the examined papers (24). These papers found a very large range of values. Sensitivity ranged between 38 to 98%, specificity between 41-97%, accuracy 58.4-100% (33-45). Similarly, AUC ranged from 0.66 to 0.97 (33, 36-40, 45); PPV: 41-85.2%; NPV: 77-95% (33, 37, 39-41). Only one paper reported LR values, obtaining LR+=8.14 and LR-=0.12 (45). Aside from these inconsistencies, possibly due to the tools employed (e.g., PALZ, SPM, SVM, meta-ROI) and to patients heterogeneity (converter/non converter, amnestic/multi-domain, MCI due AD, or undefined MCI) (24, 46), we did not detect other substantial risks of bias. The typical hypometabolic pattern in MCI converting to AD included posterior cingulate and temporo-parietal areas. The consensual recommendation was defined on Delphi Round II, with 6 panelists voting for

clinical use, since FDG-PET allows a better short-term prognosis of AD dementia conversion as compared to biomarkers of amyloidosis, and may also identify non-Alzheimer types of neurodegeneration early in the course of the disease.

### 3.1.2 FDG-PET to support the diagnosis of FTLD in MCI (PICO 2)

Critical outcomes were not available in any of the examined papers, denoting lack of objective data on possible incremental diagnostic value of FDG-PET in this case. The consensual recommendation was defined on Delphi Round II, with 6 panelists deciding to recommend clinical use. Indeed, FTLD may be hard to recognize, especially in the prodromal stage where behavioral changes may mimic psychiatric disorders and cognitive impairment is absent or subtle, a stage that might be defined as mild behavioral (rather than cognitive) impairment. Functional neuroimaging with FDG-PET is required by current diagnostic criteria for probable bv-FTD at the dementia stage (6). Since synaptic failure is an early phenomenon, frontotemporal hypometabolism can be detected when the patient presents with the first behavioral or cognitive symptoms, or both, without being demented. In many specialized memory clinics and in dedicated neurological and psychiatric units, the use of FDG-PET to ascertain FTLD in this clinical scenario is already part of clinical routine workup. 'FTD phenocopies' have been identified, i.e., patients with behavioral disturbances of varied aetiologies that mimic FTD (47), but normal metabolism at FDG-PET (48). Therefore, a normal FDG-PET is particularly valuable to exclude a neurodegenerative disease.

### 3.1.3 Use of FDG-PET to support the diagnosis of DLB in MCI (PICO 3)

Measures of accuracy were not available in any of the examined papers. The consensual recommendation was defined on Delphi Round IV, with 5 panelists recommending clinical use of FDG-PET. Besides its negative predictive value, the presence of the posterior cingulate island sign (i.e., relatively preserved metabolism in the posterior cingulate area) and occipital hypometabolism (49, 50) at the stage of MCI support a diagnosis of DLB. However, in the first instance Dopamine transporter brain SPECT (8, 51), $^{18}$F-18 DOPA PET or $^{123}$I-MIBG cardiac scintigraphy (52) should be sought as more informative investigations.

### 3.2 Preclinical conditions

The use of FDG-PET is not supported in any of the preclinical conditions assessed by the panel (25). Literature searches, assessment and consensus answered the PICO questions whether *FDG-PET should be performed, as adding diagnostic value (in terms of increased accuracy, and versus conversion to MCI) as compared to standard clinical/neuropsychological assessment alone, to detect early signs of neurodegeneration in* (3.2.1) *patients with subjective cognitive decline (SCD),* (3.2.2) *asymptomatic subjects with risk factors for AD (based on APOE ε4 status or amyloid positivity)*, and (3.2.3) *asymptomatic subjects with familial forms of AD.*

*3.2.1 FDG-PET in subjective cognitive decline (SCD, PICO 4)*

Critical outcomes were not available in any of the examined papers. Also based on this lack of evidence, agreement was achieved on Delphi Round I, with 6 panelists deciding not to recommend clinical use, consistent with current diagnostic criteria (31, 32). FDG-PET should still be reserved for research purposes.

3.2.2 *FDG-PET in asymptomatic subjects at risk for AD (PICO 5)*

Risk for AD was based on APOE ε4 status or amyloid positivity. Critical outcomes were not available in any of the examined papers. Agreement was achieved on Delphi Round I, with 5 panelists deciding not to recommend clinical use since the degree of hypometabolism in individual asymptomatic patients at risk of AD is usually insufficient to consider FDG-PET as a tool of additional prognostic value, particularly when compared with ApoE4 or amyloid positivity. Therefore, FDG-PET should be regarded only within well defined, ethic committee-approved research studies, but definitively not in clinical practice.

3.2.3 *FDG-PET in asymptomatic subjects with familial forms of AD (PICO 6)*

Critical outcomes were available in 2 of the examined papers (53, 54). These found 100% of sensitivity, 83-100% specificity range and 97-100% accuracy range (25). They included only 13 asymptomatic autosomal-dominant Alzheimer's disease (ADAD) due to Presenilin-1 mutation and 30 non-carriers. Data showed that the posterior cingulate cortex hypometabolism assessed semi-quantitatively could discriminate ADAD from controls with high sensitivity and specificity, although with large confidence intervals. Concerns listed regarded the applicability of the index test and a possible risk of bias in patient selection. Significant hypometabolism in the precuneus could be detected in mutation carriers 10 years before expected symptom onset and at the age of onset, but inconsistently across studies (25). Agreement was achieved on Delphi Round III, with 5 panelists deciding not to recommend clinical use as a diagnosis of Alzheimer's disease or prognosis of imminent dementia is of limited value and ethically questionable as long as disease modifiers are not available, and time-to-conversion cannot be accurately defined. In cases of familial AD, FDG-PET may potentially be applied to detect or rule out the onset of neurodegeneration but preferably not in clinically completely asymptomatic cases. Once therapeutic tools become available, then FDG-PET might be considered for predicting short- and medium-term conversion to dementia.

*3.3 Use of FDG-PET to discriminate between different forms of dementia*

The use of FDG-PET is supported to facilitate differential diagnosis among different forms of dementia (26). Literature searches, assessment and consensual decisions answered the PICO questions whether *FDG-PET should be performed, as adding diagnostic value (in terms of increased accuracy, and versus pathology, biomarker-based diagnosis or diagnosis at follow-up) as compared to standard clinical/neuropsychological assessment alone, to differentiate: among main forms of*

*dementia in patients with dementia and either atypical presentation or atypical course (3.3.1); between DLB and AD (3.3.2); between AD and FTLD (3.3.3); between DLB and FTLD (3.3.4); between AD and Vascular dementia (VaD) (3.3.5); to unveil brain dysfunction related to cognitive deterioration in patients with Parkinson's disease (PD) and cognitive impairment (3.3.6); to differentiate PSP from PD (3.3.7); depressive pseudo-dementia from neurodegenerative disorders associated with depressive symptoms in elderly patients with depression and cognitive deficit (3.3.8); to point to the diagnosis of the underlying pathological process in patients with corticobasal syndrome (CBS) (3.3.9); of the different clinical variants (nonfluent/agrammatic form, semantic, logopenic) of primary progressive aphasias (PPA) and thus to guide towards the underlying pathophysiology (3.3.10).*

3.3.1 *FDG-PET in atypical presentation or atypical course (PICO 7)*

Critical outcomes were available in 4 of the examined papers (26). These studies included particularly heterogeneous samples, so the main results are summarized separately for each paper. After FDG-PET-based diagnosis in patients with 'atypical/unclear dementia', a diagnostic change in 59.5% of the patients, and increased prescription of cholinesterase inhibitors (from 13.8% to 38.3%) were reported (55). In a clinically heterogeneous population of AD patients (AD-memory, AD-language and AD-visuospatial) distinct hypometabolism distribution was found in the AD-language dominant (left inferior frontal and left temporo-parietal; AUC=0.82, p=0.011) and AD-visuospatial dominant presentations (bilateral occipito-parieto-temporal, AUC=0.85, p=0.009; right posterior cingulate cortex/precuneus and right lateral parietal, AUC=0.69, p=0.045) (56). A trend was also observed for AD-memory dominant cases, with AUC=0.65 (p=0.062) for hypometabolism in bilateral inferior frontal, cuneus and inferior temporal, and right inferior parietal. The logopenic variant of PPA (lvPPA) and typical AD dementia could be discriminated (AUC=0.89) based on the right medial temporal and posterior cingulate gyri, the left inferior, middle and superior temporal lobes, and left supramarginal gyrus (57). Patients with posterior cortical atrophy (PCA) could be distinguished from DLB with 83% sensitivity, 85% specificity and 83% accuracy, and from the pooled AD and DLB with 83% sensitivity, 93% specificity, 90.9% accuracy and 91% AUC (58). Early onset AD were included in the search, but no papers were found reporting critical outcomes.

The consensual recommendation was defined on Delphi Round I, with 6 panelists voting for clinical use, as FDG-PET information in patients with atypical appearance or disease course may point towards reasons other than AD. This includes other forms of neurodegeneration (e.g., FTLD-spectrum), or non-neurodegenerative causes (e.g., depression) in the absence of hypometabolism.

*3.3.2 FDG-PET to differentiate between DLB and AD (PICO 8)*

Measures of accuracy were available in 11 of the examined papers (26). However, the majority of these papers had only baseline clinical diagnosis as the reference standard, with only two studies, including a total of 23 DLB and 31 AD patients, quantifying test performance appropriately. On the whole, these papers found a 70-92% sensitivity range, 74-100% specificity range and 72-96%

accuracy range (49, 58-66); 0.77-0.91 AUC range (49, 62, 65-67); and 86% PPV, 85% NPV and 4.46 positive likelihood ratio (LH+) value (59). A similar profile of cerebral hypometabolism was observed in AD and DLB, with the exception of the marked hypometabolism in the visual cortex in DLB and the relative posterior cingulate preservation (cingulate island sign).

The consensual recommendation was defined on Delphi Round I, with 6 panelists voting for clinical use to discriminate DLB and AD. The reason for the positive response by the majority of the panelists was based on the available data, providing relatively good quality of evidence for the ability of FDG-PET to discriminate DLB from AD. Although presynaptic dopaminergic pathway radiopharmaceuticals is more accurate in differentiating DLB from AD, FDG-PET is useful in those centers where this investigation is unavailable or in the infrequent DLB cases with a normal presynaptic dopaminergic imaging. The inclusion of FDG-PET in the new criteria for DLB (8) as a *supportive* biomarker (a scan not showing hypometabolism in the occipital lobes does not exclude DLB) also contributed to panelists' decision.

### 3.3.3 FDG-PET to differentiate AD from FTLD (PICO 9)

Critical outcomes were available in 5 of the examined papers (26). These papers found 80-99% sensitivity range, 63-98% specificity range and 87-89.2% accuracy range (65, 68-70); 0.91-0.97 AUC range (65, 70), 98% PPV, 74% NPV, 29.88 LR+, 0.25 LR- (70), and an increased accuracy for the classification of FTLD with respect to AD by using semi-quantitative assessment of FDG-PET (71).

The consensual recommendation was defined on Delphi Round I, with 7 panelists supporting clinical use. Occasionally, differentiating FTLD from AD on clinical-neuropsychological grounds may be challenging. In most cases, the hypometabolic patterns of FTLD and AD are clearly separated, with the differential involvement of the prefrontal, insular and anterior cingulate cortex, basal ganglia, and sometimes the crossed cerebellar diaschisis in FTLD, and the posterior cingulate cortex and precuneus hypometabolism in AD. Despite a relatively low quantitative evidence, FDG-PET is approved to discriminate FTD and AD in the US (2), and included in the clinical criteria of both bv-FTD (6) and PPA (7). However, there are still cases where a diagnosis cannot be reached based on clinical-neuropsychological evaluation and FDG-PET, since fronto-parietal hypometabolism may sometimes be found in both disease, especially at the dementia stage. In those cases, either CSF biomarker analysis or amyloid PET can clarify. One should be aware, though, that AD pathology may co-exist in FTLD patients, with possible amyloid positivity unrelated to the clinical syndrome (72). In these cases, a clear FTLD pattern on FDG-PET helps the diagnosis.

### 3.3.4 FDG-PET to differentiate between DLB and FTLD (PICO 10)

Critical outcomes were available in only 1 of the examined papers. Mosconi and colleagues (73) reported 71% sensitivity, 65% specificity, 66% accuracy and 68% AUC of FDG-PET in distinguishing between DLB and FTLD patients. However, values were obtained using only the clinical diagnosis as the reference standard. The remaining papers provide only evidence of correlated patterns of atrophy (26). A consensual recommendation was defined at Delphi Round II, with 6 panelists voting for clinical use. The reason given by the majority of panelists was based on the different patterns of metabolism associated with the two conditions, FTLD showing frontal and anterior-temporal hypometabolism and DLB displaying additional posterior involvement (visual and parieto-temporal) and relative posterior cingulate preservation (cingulate island sign). Although most cases can be differentiated clinically, there are some overlapping features, and misdiagnosis between the two conditions has been documented in autopsy cases (74-76). This is particularly relevant in the presence of parkinsonism, that may be present in both conditions, with dopamine transporter uptake on SPECT possibly abnormal in both disorders (75). The inclusion of FDG-PET in the FTD criteria (6) and the new DLB criteria (8) also contributed to the panelists decision.

### 3.3.5 Use of FDG-PET to differentiate between AD and VaD (PICO 11)

Using a fully automated voxel-based multivariate technique, AD, VaD and controls were identified with 100% accuracy, sensitivity and specificity; however, the test sample was the same used to train the algorithm (77). Associated patterns of hypometabolism include the thalamus, brainstem and cerebellum in VaD, as opposed to the posterior cingulate and temporo-parietal pattern of AD patients (77-79). However, this was not confirmed in other studies (80, 81). A key problem with the concept of VaD, and possibly a reason for inconsistencies, lies in the difficulty of using a clinical reference-standard and in the issue of mixed pathologies, where disentangling the relative weight of neurodegeneration and vascular lesions on the cognitive impairment may be difficult. Specifically, in patients with dementia and prominent vascular lesions on structural imaging, dementia is not necessarily due to vascular pathology. Rather, AD with concomitant vascular lesions often causes the clinical syndrome. The existing literature is therefore particularly limited in this case as no study has included pathological diagnosis as the gold standard. Comparisons across studies are also problematic because of the variable inclusion criteria for VaD. Nonetheless, a consensual recommendation for clinical use was achieved in Round II, 5 panelists supporting the utility of FDG-PET in identifying AD in patients with vascular pathology if the characteristic AD pattern of bilateral posterior temporo-parietal hypometabolism is present, and provided that hypometabolic regions are not co-localized with large vessel cortical or sub-cortical infarcts on a structural scan.

### 3.3.6 FDG-PET to identify PD-related neurodegeneration associated with cognition (PICO 12)

Quantitative assessments of the discrimination accuracy of patterns of hypometabolism in this condition are not available (29). A consensual recommendation was achieved on Delphi Round IV, with 5 panelists voting for clinical use. Panelists mostly based their recommendation on the grounds that patients with PD dementia or MCI have a typical pattern of hypometabolism, mainly in the

posterior regions. The absence of this typical pattern therefore raises the possibility of an alternative diagnosis, including depressive pseudodementia or an atypical Parkinsonian syndrome. In addition, the ability of FDG-PET to predict future decline in cognition may allow to identify patients suitable for cholinesterase inhibitor therapy at an early PD stage. After the deadline for literature review (November 2015), other relevant papers not included in the present evaluation of evidence have been published, which are consistent with this recommendation (82-84) .

### 3.3.7 FDG-PET to discriminate PSP from PD (PICO 13)

Critical outcomes were available in 2 of the examined papers, for a total of 36 PSP and 32 PD patients. These papers found a 52.9-75% sensitivity range, 80-100% specificity range and 67.6-83.9% accuracy range (85, 86) and 0.80 AUC (86). Additional outcomes were reported in 3 papers (87-89) in which a two-step classification was used, consisting of a first separation of PD from atypical parkinsonisms, and a subsequent separation of PSP from other atypical parkinsonisms. In these studies, FDG-PET demonstrated a good sensitivity in distinguishing PD from atypical parkinsonisms (range 83-86%) but moderate sensitivity in differentiating PSP from CBD and MSA (range 73-88%). Specificity and PPV were both greater than 90% in distinguishing PD from atypical parkinsonisms and atypicals between each other. The NPV in differentiating PD versus atypicals was moderate (range 76-83%). The 5 studies had a moderate risk of bias regarding the reference standard (in two studies it is not clear whether the FDG-PET reader was blind to clinical diagnosis) and the index test (2 papers did not report sufficient detail to allow replication). Moreover, low applicability arose because all studies included a very selected population and used a semi-quantitative method of image analysis.

A consensual recommendation to support clinical use was defined on Delphi Round III. The five panelists supporting clinical use considered that in a typical PSP patient, FDG-PET can usefully highlight hypometabolism in the medial frontal gyrus, anterior cingulate cortex, pons, and ventral striatum. These findings are usually not found in PD patients who show normal or even increased striatal metabolism. FDG-PET may be particularly useful in the early stages (i.e., within the first 2 years from symptom onset), when the accuracy of clinical diagnosis is limited. Although of lower spatial resolution, perfusion SPECT shows essentially the same pattern (90, 91). It should be said that the majority of these abnormalities are rather symmetrical and difficult to assess based on visual analysis alone, especially in the early stage. Therefore, the use of semi-automated quantification in comparisons with age-matched healthy controls is particularly useful to highlight these symmetrical abnormalities and assist visual reading. This PSP-related metabolic pattern has been highlighted also with covariance analyses and used for differential diagnosis from PD (87, 92, 93). However, data remain largely incomplete when considering the several PSP phenotypes (such as PSP-Parkinsonism or pure akinesia with gait freezing, for instance), often leading to less severe or incomplete patterns as compared to the full-blown Richardson's syndrome. Finally, the EANM procedural guidelines (15) and also the latest criteria for PSP diagnosis by the Movement Diagnosis Society (9) support the use of FDG PET to differentiate between Parkinson's disease and atypical parkinsonian syndromes.

### 3.3.8 FDG-PET to discriminate depressive pseudo-dementia (PICO 14)

No references were obtained for this PICO questions. The consensual recommendation was defined on Delphi Round II, with 7 panelists voting for clinical use. Depressive pseudo-dementia is a relatively uncommon problem but one that is critical not to miss because of its potential reversibility. Evidence from formal studies on the utility of FDG-PET in this scenario is entirely lacking. Nonetheless, although the recommendation is based on anecdotal observation, there was unanimous consensus supporting the use of FDG-PET. The rationale is based, in part, on the fact that FDG-PET abnormalities are a function of disease severity. As such, a patient who appears to have dementia—based on both clinical interview and objective neuropsychological examination—should always have obvious abnormalities on FDG-PET. Therefore, a normal FDG-PET examination in this circumstance offers strong evidence for a pseudo-dementia, while a typical pattern of hypometabolism for one of the degenerative dementias argues against pseudo-dementia, although subtle frontal hypometabolism may be present in psychiatric patients. Finally, it must be stressed that this recommendation relates specifically to the scenario of what appears to be an established dementia, but not to the more common situation of deciding whether very mild or subjective deficits have a psychiatric versus degenerative basis—see sections 3.1-4. Given the total lack of evidence, however, the panel encourages specific research on this topic.

### 3.3.9 FDG-PET to discriminate the underlying pathological process in patients with corticobasal syndrome (PICO 15)

Critical outcomes were available in 2 of the examined papers. These studies (94, 95) used amyloid-PET as the gold standard and tested the ability of FDG-PET in predicting AD pathology in 39 patients with corticobasal syndrome. They found 91-95% sensitivity range, 58-75% specificity range and 73-82% accuracy range. Taswell et al. (86) reported also PPV = 68%, NPV = 97%, LH+ = 3.90 and negative likelihood ratio (LH-) value=0.06. We found a low risk of bias for all items and moderate applicability concerns.

Consensus was achieved on Delphi Round I, six panelists supporting clinical use. The demonstration of asymmetry in cortical metabolism should entail hypometabolism in the hemisphere contralateral to the hemi-body with akinetic-rigid Parkinsonism and apraxia.

Hypometabolism is mainly found in motor and premotor cortices, but can also involve the prefrontal or posterior parietal and lateral temporal cortex, and the cingulate gyrus. Often, basal ganglia and thalamus are hypometabolic in the same hemisphere harboring cortical hypometabolism. This heterogeneity is consistent with the variety of diseases causing CBS, which mainly include CBD, PSP, AD, FTLD, or combinations thereof. Prevalent parietal lobule and posterior cingulate hypometabolism is consistent with AD; anterior cingulate and associated frontal cortex hypometabolism suggests PSP or FTD; and basal ganglia hypometabolism supports CBD and PSP. Therefore, the future challenge consists of identifying specific FDG-PET patterns associated to these different underlying pathologies. Such studies should be based on multi-tracer PET studies including Tau- and amyloid-PET, if pathological gold-standard is unavailable.

*3.3.10 Use of FDG-PET to discriminate clinical presentations and point toward molecular pathologies in PPAs (PICO 16)*

Critical outcomes were available for 4 papers, with very heterogeneous results(27). Using semi-quantitative assessment, PPA variants were discriminated with 86.2% sensitivity, 66.7% specificity, and 84% accuracy (96). Differentiation among the three variants showed 91.6% sensitivity, 100% specificity and 97% accuracy for the non-fluent/agrammatic variant (nfv-PPA); 100%, 93.1% and 94% for the semantic variant (sv-PPA), and 78.6%, 94.4% and 87% for the logopenic variant (lv-PPA). The PPV 100% for nfv-PPA, 60% for sv-PPA and 91.7% for nfv-PPA, and the NPV 95.2% for av-PPA, 100% for sv-PPA and 85% for lv-PPA. Bilateral hypometabolism in the temporo-parietal cortex had 50% sensitivity and 100% specificity in detecting AD pathology, while normal temporo-parietal cortex had 38% sensitivity and 100% specificity in detecting non-AD pathology (97). Both lateral temporal and hippocampal metabolic asymmetry showed 83% sensitivity in predicting amyloid negative lv-PPA. Together, they had 100% specificity in predicting amyloid negative lv-PPA (98). The PPV in predicting AD pathology was >90% both in lv-PPA and nfv-PPA, while NPV was greater in nfv-PPA (96%) and sv-PPA (92%) than in lv-PPA (81%)(94).

Notwithstanding the heterogeneity of results, consensus was achieved on Round I, 6 panelists supporting clinical use. Differentiating the three types of PPAs is a clinical challenge. Since the publication of current diagnostic criteria (7), their overlap has been repeatedly reported clinically and on imaging (99, 100). Although amyloid PET enhances discrimination of patients with AD-based PPA from the others, current diagnostic criteria state that clinical diagnosis may be supported by the typical atrophy or metabolic pattern characterizing the three forms (7). Given that synaptic failure is an earlier phenomenon than atrophy, FDG-PET may be particularly valuable for diagnosis where a typical atrophy pattern is not apparent.

*3.4 Use of FDG-PET in ALS and HD*

*Literature searches and assessment and decisions answered whether FDG-PET should be performed, as adding diagnostic value (in terms of increased accuracy, and versus clinical confirmation) as compared to standard clinical/neuropsychological assessment alone, to: confirm a clinical suspicion of ALS in patients with or without cognitive impairment* (3.4.1); *detect brain dysfunction related to cognitive deterioration in patients with ALS (3.4.2); to pick early signs of neurodegeneration in patients with a genetic risk of Huntington disease (3.4.3); and discriminate frontal-lobe hypometabolism responsible for cognitive deterioration in patients with Huntington disease(3.4.4).* The panel did not support the clinical use of FDG-PET for any of these aims (23).

*3.4.1 FDG-PET in the diagnosis of ALS (PICO 17)*

Critical outcomes on FDG-PET diagnostic utility in ALS were available in 2 of the examined papers (23), denoting 94.8-95.4% sensitivity, 80.0-82.5% specificity and 91.8-93.2% accuracy in distinguishing ALS patients from controls (101, 102). However, a comparison with ALS-mimic

disorders, which is mandatory to test the specificity of these markers, is still lacking. In addition, other neuroimaging tools such as structural and diffusion tensor MRI may be in a better position to help with diagnosis and differential diagnosis (103).

Based on this background, agreement was achieved on Delphi Round II, with 7 panelists deciding not to support clinical utility of FDG PET in the diagnosis of ALS at the moment. It should be considered that according to the revised El Escorial criteria, ALS diagnosis relies on the clinical detection of motor neuron signs in multiple body segments supported by electrophysiological testing (104). However, although these guidelines have been repeatedly shown to be useful inclusion criteria for clinical trials, concerns have been raised regarding their use in clinical practice (105, 106). The false-negative rate has been estimated to be as high as 11%, while the average delay from the symptom onset to diagnosis is 11 months (107, 108). Future research may assess whether incorporating neuroimaging techniques, such as MRI and FDG-PET, into the standard diagnostic algorithm might increase confidence level and improve time to diagnosis.

### 3.4.2 FDG-PET to detect cognitive-related brain dysfunction in ALS (PICO 18)

Critical outcomes were not available in any of the examined papers. No agreement was reached through the Delphi procedure, with 4 panelists supporting clinical utility. Panelists recognized that functional neuroimaging with FDG-PET, additionally or alternatively to structural MRI, is required by the current diagnostic criteria for probable FTD at the dementia stage (6). However, the clinical utility of FDG-PET in ALS patients with cognitive and/or behavioural changes not reaching the threshold for a full FTD diagnosis is more controversial. Indeed, comprehensive cognitive and behavioral testing is enough to determine the presence of cognitive and/or behavioral involvement (109). In agreement with the recently published criteria (109), the panelists felt that in these patients FDG-PET may be adequate for research purposes, but it should not be recommended for clinical use.

### 3.4.3 FDG-PET to detect neurodegeneration in patients with genetic risk of HD (PICO 19)

Critical outcomes were available in only 1 of the examined papers, where the caudate FDG-PET uptake identified conversion from asymptomatic preclinical HD gene carriers to clinical HD with AUC=0.94 (110). However, agreement was achieved on Delphi Round II, with 6 panelists deciding not to support clinical use. Although striatal hypometabolism may be an earlier finding as compared to striatal volume loss on MRI, the present lack of effective neuroprotective drugs does not justify routine use of FDG-PET to predict conversion.

### 3.4.4 FDG-PET to detect frontal-lobe hypometabolism responsible for cognitive deterioration in patients with HD (PICO 20)

Critical outcomes were available in only 1 of the examined papers, including only 8 subjects. This found greater hypometabolism in HD patients compared to healthy controls in the prefrontal and premotor regions, and a significant correlation between frontal lobe hypometabolism and cognitive performances, as measured by a series of script generation and script sorting tasks (111). Agreement was achieved on Delphi Round III, with 5 panelists deciding not to support clinical use because FDG-PET would not add clinically useful information to neuropsychological assessment in a known HD patient.

### 3.5 Requirement of semi-automated assessment (PICO 21)

To assess the opportunity to support the use of semi-automated assessment to assist visual reading in the clinical setting, the literature search, assessment and Delphi voting answered the PICO question: "*Should automated assessment of FDG-PET scans be required, as adding sufficient information (in terms of increased accuracy, and versus pathology, biomarker-based diagnosis or conversion at follow-up) as compared to visual reading as taken alone, to optimize the diagnostic work-up of patients with dementing neurodegenerative disorders?*"

Critical outcomes were available in 9 of the examined papers (28). The level of confidence between visual assessment and SPM-Maps differed significantly (2.07 versus 2.4; p=0.003) in the paper by Perani et al. (71). Visual assessment with and without 3D-SSP had non-significant difference in sensitivity (83% versus 82%), improved specificity (75% versus 41%, p<0.01) and AUC 88% versus 72% (p=0.017) respectively, with a mean increase in confidence rating of 0.7 (p=0.048) (112). Finally, visual assessment differed significantly from 3D-SSP (AUC: 0.94 versus 0.99, p=0.043) in Burdette et al. paper (113). ROI analysis and 3D-SSP were the most frequently used tools, followed by SPM and PALZ score. The subjects involved in the selected studies suffered from different neurodegenerative disorders. Risk of bias was due to imprecision, use of reference standard (follow-up diagnosis rather than pathology confirmation), and applicability of the index test.

The consensual recommendation was achieved on Delphi Round I, 6 panelists supporting the additional use of semi-automated processing to assist visual reading in clinical settings. The visual reading by an expert remains the reference tool to identify abnormalities and to generate a report, according to the EANM procedure guidelines (15, 42, 114, 115), and the semi-quantitative automated assessment of images is considered helpful to assist visual reading, especially to less experienced readers (42). Indeed, such automated assessment can provide confirmation on the statistical significance of the abnormalities that they appreciate visually, and disambiguate doubtful areas of abnormalities. This is relevant for non-expert readers because the limited experience on the wide range of normality leads to both over- and under-estimation of abnormal scans. Anyways, semi-automated assessment can help, increasing specificity and confidence, also expert readers.

Several tools are available allowing semi-quantification and comparison with an age-matched database of healthy controls, either commercially or freely available. They substantially differ in the choice of region chosen for normalization (whole brain or, dependent on the choice of the examiner, pons, thalami, or cerebellum), strategies of analysis (i.e., voxel- or Volume-of-Interest-based), and composition of the healthy control group. While some tools contain only fixed age-matched control groups, others may be preferable as they allow to build-up customized controls also taking into account further relevant covariates, such as gender and education. Finally, correction for atrophy is not embedded in the majority of these tools; the weight of atrophy may be assessed visually through coregistration of PET to the CT scan acquired contextually with PET for attenuation correction, or partial volume effect-correction software could be used. The 3D-SSP routine (Neurostat) (https://neurostat.neuro.utah.edu/) for example has an atrophy correction mechanism. The differences among the several automated tools of semi-quantification are relevant as they impact significantly the incremental value of semi-automated assessment, as shown in head-to-head comparisons with visual reading (114, 115).

**4. Discussion**

With this work, we outlined recommendations for using FDG-PET as an add-on to clinical and neuropsychological examination in the diagnosis of neurodegenerative disorders as good clinical practice points based on consensus by expert panelists. Assessments of the evidence on the incremental utility of FDG-PET over clinical assessment alone for each PICO question assisted panelist decisions. Clinical use of FDG-PET was deemed appropriate for all cases of MCI and dementia, with the exception of ALS and HD, but was not supported for preclinical conditions. Moreover, the panel recommended the use of semi-automated assessment to assist visual reading.

Although proper quantitative assessment of the incremental value of FDG-PET over clinical diagnosis is still limited (23-29), the panel felt that the collection of more robust formal evidence may require a relatively long time and may not at all be feasible for all the various types of neurodegenerative disorders individually. The Panel concludes that altogether a great amount of data has been collected, convincingly demonstrating the value of FDG-PET to detect patterns and extent of neuronal dysfunction across the spectrum of neurodegenerative disorders with high sensitivity. This type of *in vivo* information currently cannot be obtained by any other diagnostic test. Being aware of the mentioned limitations, the information provided by FDG-PET in the diagnostic procedure may thus be considered as *supportive* or *not supportive* of the diagnostic hypothesis, and should always be used *in addition* to conventional clinical and neuropsychological assessments. Although less desirable than providing demonstrated substantial incremental diagnostic value, such support helps importantly in the large uncertainty characterizing clinical diagnosis, especially when pathophysiological biomarkers are not available and when questions on onset and extent of neuronal dysfunction are at issue. Anyway, these recommendations are based on literature that is not yet fully mature for leading to evidence-based prescriptions. Thus, we wish to underline that these are interim recommendations, based on the best of current (i.e., up to end of 2015) knowledge, and liable to change as more complete evidence is generated. We also underline that

the lack of support for clinical use in some conditions should not be read as a recommendation for not using, but rather as a current lack of reasons for supporting clinical use.

The lack of support of FDG-PET use for preclinical conditions is consistent with current clinical criteria, recommending to formulate clinical diagnoses only for symptomatic patients (31, 32). This does not exclude the application of the test in selected cases to answer specific individual questions and use in clinical trials Regarding the fact that FDG-PET is able to document onset of neuronal injury, e.g. in amyloid-positive patients, it may become highly valuable as a tool for patient selection and monitoring as soon as disease-modifying drugs become available. Also consistent with current clinical criteria (4, 6-9, 30)  and regulatory approval (2), the support of clinical use of FDG-PET in diagnosing prodromal and dementia stages of most neurodegenerative disorders was based on its ability to detect neurodegenerative processes, and to inform about location and extent of neuronal dysfunction at early stages. Finally, its negative predictive value allows the exclusion of neurodegeneration in MCI patients with symptoms due to depression, other psychiatric conditions, drug effect or abuse, and other systemic conditions; an exclusionary function that is necessary as an early step in the diagnostic work-up.

Panelists did not support the additional use of FDG-PET to diagnose HD and ALS nor to detect evidence of brain dysfunction justifying a cognitive decline accompanying these conditions. Consensus in these cases was due to the greater informative value of other types of examination, which could not be disregarded although the focus of this exercise was on the incremental value of FDG-PET versus clinical and neuropsychological diagnoses, rather than versus other biomarkers. Formal comparisons of FDG-PET with other biomarkers should be performed to define a cost-effective algorithm for diagnosis in dementia (1, 116). However, solving standardization issues (e.g., for scan reading or normality threshold) may also overcome some of the current heterogeneity in FDG-PET diagnostic performance (116, 117). Again, the panel decision would not get in the way of an individual application of FDG-PET in the diagnostic workup of HD or ALS in selected cases based on specific clinical questions, nor should it be read as an active indication not to perform the exam positively based on demonstrated evidence against clinical use.

The literature reviews (23-29) (Suppl Mater 2) outlined specific methodological issues to be overcome to improve formal evidence of efficiency of FDG-PET in the diagnostic procedure. The lack of direct quantification of patient outcomes (health, quality of life, mortality, institutionalization) following FDG-PET-based diagnosis is a main limitation not solvable in the short term. However, even accepting accuracy studies as proxies for more appropriate patient management (18, 19), many limitations remain. Indeed, demonstration of diagnostic improvement after FDG-PET is limited by the lack of pathology confirmation and of head-to-head comparison between FDG-PET and clinical assessment versus the same gold standard (118). In addition, the frequent use of mere baseline clinical diagnosis as the reference standard conveys the limitation of the intrinsic circularity between hypometabolic patterns and clinical syndromes, and prevents computation of test performance independent of the actual prevalence of the disorder in the examined population. This may be due

to the absence of stakeholders, specific to FDG-PET and the so-called 'orphan' drugs: no company ever having exclusivity on the radiopharmaceutical, rigorous expensive studies are scarce. While addressing these issues as research priorities to boost the achievement of evidence-based guidelines, in this work we optimized the informative value from available studies and provided an interim consensus guidance. Also for this set of reasons, these recommendations are defined late compared to other diagnostic appropriate use criteria, e.g. those for amyloid-PET (119), that are also based on expert consensus, being defined in the complete lack of data on clinical utility. With frequent gaps in formal evidence, the use of clinicians' experience should at present be seen as interim evidence.

In conclusion, the present inter-societal task force provided consensual recommendations for the clinical use of FDG-PET as a supportive tool in the diagnosis of the main dementing disorders. Notwithstanding the interim value of these recommendations, EAN and EANM keep that clinicians will benefit from this collation of best current evidence and expert opinion.

**Conflicts of interest**

Flavio Nobili: received personal fees and non-financial support from G.E. healthcare, non-financial support from Eli-Lilly and grants from Chiesi Farmaceutici.

Javier Arbizu: received grants from Eli-Lilly & Co, Piramal and G.E. Healthcare.

Femke Bouwman: none

**REFERENCES**

1.      Frisoni GB, Boccardi M, Barkhof F, Blennow K, Cappa S, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. *Lancet Neurol*. 2017;**16**:661-76.

2.      Decision Memo for Positron Emission Tomography (FDG) and Other Neuroimaging Devices for Suspected Dementia (CAG-00088R). 2004; https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=104.

3.      Dubois B, Feldman HH, Jacova C, Dekosky ST, Barberger-Gateau P, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol.* 2007;**6**:734-46.

4.      Albert MS, DeKosky ST, Dickson D, Dubois B, Feldman HH, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*. 2011;**7**:270-9.

5.      Dubois B, Feldman HH, Jacova C, Hampel H, Molinuevo JL, et al. Advancing research diagnostic criteria for Alzheimer's disease: the IWG-2 criteria. *Lancet Neurol*. 2014;**13**:614-29.

6.      Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain.* 2011;**134**:2456-77.

7.      Gorno-Tempini ML, Hillis AE, Weintraub S, Kertesz A, Mendez M, et al. Classification of primary progressive aphasia and its variants. *Neurology.* 2011;**76**:1006-14.

8.      McKeith IG, Boeve BF, Dickson DW, Halliday G, Taylor JP, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology.* 2017;**89**:88-100.

9.      Hoglinger GU, Respondek G, Stamelou M, Kurz C, Josephs KA, et al. Clinical diagnosis of progressive supranuclear palsy: The movement disorder society criteria. *Mov Disord*. 2017;**32**:853-64.

10.     Bohnen NI, Djang DS, Herholz K, Anzai Y, Minoshima S. Effectiveness and safety of 18F-FDG PET in the evaluation of dementia: a review of the recent literature. *J Nucl Med*. 2012;**53**:59-71.

11.     Smailagic N, Vacante M, Hyde C, Martin S, Ukoumunne O, et al. (1)(8)F-FDG PET for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI). *The Cochrane database of systematic reviews*. 2015;**1**:Cd010632.

12.     Morbelli S, Garibotto V, Van De Giessen E, Arbizu J, Chetelat G, et al. A Cochrane review on brain [(1)(8)F]FDG PET in dementia: limitations and future perspectives. *Eur J Nucl Med Molec Imag*. 2015;**42**:1487-91.

13.     Sorbi S, Hort J, Erkinjuntti T, Fladby T, Gainotti G, et al. EFNS-ENS Guidelines on the diagnosis and management of disorders associated with dementia. *Eur J Neurol.* 2012;**19**:1159-79.

14.     Filippi M, Agosta F, Barkhof F, Dubois B, Fox NC, et al. EFNS task force: the use of neuroimaging in the diagnosis of dementia. *Eur J Neurol.* 2012;**19**:e131-40, 1487-501.

15.     Varrone A, Asenbaum S, Vander Borght T, Booij J, Nobili F, et al. EANM procedure guidelines for PET brain imaging using [18F]FDG, version 2. *Eur J Nucl Med Molec Imag*.  2009;**36**:2103-10.

16.     Leone MA, Brainin M, Boon P, Pugliatti M, Keindl M, et al. Guidance for the preparation of neurological management guidelines by EFNS scientific task forces - revised recommendations 2012. *Eur J Neurol*. 2013;**20**:410-9.

17.     Boccardi M. Clinical use of F-fluorodeoxyglucose Positron Emission Tomography (FDG-PET) in dementia. *Eur J Neurol*. 2017;**24**(1 SI):761.

18.     Hsu J, Brozek JL, Terracciano L, Kreis J, Compalati E, et al. Application of GRADE: making evidence-based recommendations about diagnostic tests in clinical practice guidelines. *Implementation science*. IS. 2011;**6**:62.

19.     Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, et al. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *Br Med J* 2008;**336**:1106-10.

20.     Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CF, et al. Consensus development methods, and their use in clinical guideline development. *Health Technol Assessm*. 1998;**2**:i-iv, 1-88.

21.    Dubois B, Feldman HH, Jacova C, Cummings JL, Dekosky ST, et al. Revising the definition of Alzheimer's disease: a new lexicon. *Lancet Neurol*. 2010;**9**:1118-27.

22.    Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, et al. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. *Neurology.* 1998;**51**:1546-54.

23.    Agosta F, Altomare D, Festari C, Orini S, Gandolfo F, Boccardi M, et al. Clinical utility of FDG-PET in amyotrophic lateral sclerosis and Huntington's disease. *Eur J Nucl Med Molec Imag*. 2018; doi: 10.1007/s00259-018-4033-0. [Epub ahead of print].

24.    Arbizu J, Festari C, Altomare D, Walker Z, Bouwman F, Rivolta J, et al. Clinical utility of FDG-PET for the clinical diagnosis in MCI. *Eur J Nucl Med Molec Imag*. 2018; doi: 10.1007/s00259-018-4039-7. [Epub ahead of print].

25.    Drzezga A, Altomare D, Festari C, Arbizu J, Orini S, Herholz K, et al. Diagnostic utility of 18F-Fluorodeoxyglucose positron emission tomography (FDG-PET) in asymptomatic subjects at increased risk for Alzheimer's disease. *Eur J Nucl Med Molec Imag*. 2018; doi: 10.1007/s00259-018-4032-1. [Epub ahead of print].

26.    Nestor PJ, Altomare D, Festari C, Drzezga A, Rivolta J, Walker Z, et al. Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia. *Eur J Nucl Med Molec Imag*. 2018; doi: 10.1007/s00259-018-4035-y. [Epub ahead of print].

27.    Bouwman F, Orini S, Gandolfo F, Altomare D, Festari C, Agosta F, et al. Diagnostic utility of FDG-PET in the differential diagnosis between different forms of primary progressive aphasia. *Eur J Nucl Med Molec Imag*. 2018; doi: 10.1007/s00259-018-4034-z. [Epub ahead of print].

28.    Nobili F, Festari C, Altomare D, Agosta F, Orini S, Van Laere K, et al. Automated assessment of FDG-PET for differential diagnosis in patients with neurodegenerative disorders. *Eur J Nucl Med Molec Imag*. 2018; doi: 10.1007/s00259-018-4030-3. [Epub ahead of print].

29.    Walker Z, Gandolfo F, Orini S, Garibotto V, Agosta F, Arbizu J, et al. Clinical utility of FDG-PET in Parkinson's disease and atypical Parkinsonisms associated to dementia *Eur J Nucl Med Molec Imag*. 2018; In press (EJNM-D-18-00397).

30.    McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*. 2011;**7**:263-9.

31.    Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia*. 2011;**7**:280-92.

32.    Dubois B, Hampel H, Feldman HH, Scheltens P, Aisen P, et al. Preclinical Alzheimer's disease: Definition, natural history, and diagnostic criteria. *Alzheimer's & dementia*. 2016;**12**:292-323.

33.     Arbizu J, Prieto E, Martinez-Lage P, Marti-Climent JM, Garcia-Granero M, et al. Automated analysis of FDG PET as a tool for single-subject probabilistic prediction and detection of Alzheimer's disease dementia. *Eur J Nucl Med Molec Imag*. 2013;**40:**1394-405.

34.     Cabral C, Morgado PM, Campos Costa D, Silveira M. Predicting conversion from MCI to AD with FDG-PET brain images at different prodromal stages. *Comput Biol Med.* 2015;**58**:101-9.

35.     Chetelat G, Desgranges B, de la Sayette V, Viader F, Eustache F, et al. Mild cognitive impairment: Can FDG-PET predict who is to rapidly convert to Alzheimer's disease? *Neurology.* 2003;**60**:1374-7.

36.     Choo IH, Ni R, Scholl M, Wall A, Almkvist O, et al. Combination of 18F-FDG PET and cerebrospinal fluid biomarkers as a better predictor of the progression to Alzheimer's disease in mild cognitive impairment patients. *J Alzheimer's dis*. 2013;**33**:929-39.

37.     Drzezga A, Grimmer T, Riemenschneider M, Lautenschlager N, Siebner H, et al. Prediction of individual clinical outcome in MCI by means of genetic assessment and (18)F-FDG PET. *J Nucl Med.* 2005;**46**:1625-32.

38.     Gray KR, Wolz R, Heckemann RA, Aljabar P, Hammers A, et al. Multi-region analysis of longitudinal FDG-PET for the classification of Alzheimer's disease. *NeuroImage*. 2012;**60**:221-9.

39.     Herholz K, Westwood S, Haense C, Dunn G. Evaluation of a calibrated (18)F-FDG PET score as a biomarker for progression in Alzheimer disease and mild cognitive impairment. *J Nucl Med*. 2011;**52**:1218-26.

40.     Ito K, Fukuyama H, Senda M, Ishii K, Maeda K, et al. Prediction of Outcomes in Mild Cognitive Impairment by Using 18F-FDG-PET: A Multicenter Study. *J Alzheimer's dis.* 2015;**45**:543-52.

41.     Landau SM, Harvey D, Madison CM, Reiman EM, Foster NL, et al. Comparing predictors of conversion and decline in mild cognitive impairment. *Neurology.* 2010;**75**:230-8.

42.     Morbelli S, Brugnolo A, Bossert I, Buschiazzo A, Frisoni GB, et al. Visual versus semi-quantitative analysis of 18F-FDG-PET in amnestic MCI: an European Alzheimer's Disease Consortium (EADC) project. *J Alzheimer's dis*. 2015;**44**:815-26.

43.     Mosconi L, Perani D, Sorbi S, Herholz K, Nacmias B, et al. MCI conversion to dementia and the APOE genotype: a prediction study with FDG-PET. *Neurology.* 2004;**63**:2332-40.

44.     Toussaint PJ, Perlbarg V, Bellec P, Desarnaud S, Lacomblez L, et al. Resting state FDG-PET functional connectivity as an early biomarker of Alzheimer's disease using conjoint univariate and independent component analyses. *NeuroImage.* 2012;**63**:936-46.

45.     Young J, Modat M, Cardoso MJ, Mendelson A, Cash D, et al. Accurate multimodal probabilistic prediction of conversion to Alzheimer's disease in patients with mild cognitive impairment. *NeuroImage: Clinical*. 2013;**2**:735-45.

46.     Boccardi M, Festari C, Arbizu J, Orini S, Gandolfo F, Altomare D, et al. Diagnostic utility of FDG-PET in detecting Alzheimer's disease in patients with persistent MCI of uncertain origin. *Eur J Neurol.* 2017;**24**(1 SI):447-8.

47.     Gossink FT, Dols A, Kerssens CJ, Krudop WA, Kerklaan BJ, et al. Psychiatric diagnoses underlying the phenocopy syndrome of behavioural variant frontotemporal dementia. *J Neurol Neurosurg Psychiatry.* 2016;**87**:64-8.

48.     Kipps CM, Hodges JR, Fryer TD, Nestor PJ. Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. *Brain*. 2009;**132**:2566-78.

49.     Lim SM, Katsifis A, Villemagne VL, Best R, Jones G, Saling M, et al. The 18F-FDG PET cingulate island sign and comparison to 123I-beta-CIT SPECT for diagnosis of dementia with Lewy bodies. *J Nucl Med.* 2009;**50**:1638-45.

50.     Graff-Radford J, Murray ME, Lowe VJ, Boeve BF, Ferman TJ, Przybelski SA, et al. Dementia with Lewy bodies: basis of cingulate island sign. *Neurology.* 2014;**83**:801-9.

51.     McKeith I, O'Brien J, Walker Z, Tatsch K, Booij J, Darcourt J, et al. Sensitivity and specificity of dopamine transporter imaging with 123I-FP-CIT SPECT in dementia with Lewy bodies: a phase III, multicentre study. *Lancet Neurol*. 2007;**6**:305-13.

52.     Tiraboschi P, Corso A, Guerra UP, Nobili F, Piccardo A, Calcagni ML, et al. (123) I-2beta-carbomethoxy-3beta-(4-iodophenyl)-N-(3-fluoropropyl) nortropane single photon emission computed tomography and (123) I-metaiodobenzylguanidine myocardial scintigraphy in differentiating dementia with lewy bodies from other dementias: A comparative study. *Ann Neurol.* 2016;**80**:368-78.

53.     Scholl M, Almkvist O, Axelman K, Stefanova E, Wall A, et al. Glucose metabolism and PIB binding in carriers of a His163Tyr presenilin 1 mutation. *Neurobiol Aging*. 2011;**32**:1388-99.

54.     Mosconi L, Sorbi S, de Leon MJ, Li Y, Nacmias B, et al. Hypometabolism exceeds atrophy in presymptomatic early-onset familial Alzheimer's disease. *J Nucl Med*. 2006;**47**:1778-86.

55.     Laforce R, Jr., Buteau JP, Paquet N, Verret L, Houde M, et al. The value of PET in mild cognitive impairment, typical and atypical/unclear dementias: A retrospective memory clinic study. *Am J Alzh Dis other dement*. 2010;**25**:324-32.

56.     Laforce R, Jr., Tosun D, Ghosh P, Lehmann M, Madison CM, et al. Parallel ICA of FDG-PET and PiB-PET in three conditions with underlying Alzheimer's pathology. *NeuroImage: Clinical*. 2014;**4**:508-16.

57.     Madhavan A, Whitwell JL, Weigand SD, Duffy JR, Strand EA, et al. FDG PET and MRI in logopenic primary progressive aphasia versus dementia of the Alzheimer's type. *PloS one.* 2013;**8**:e62471.

58.     Spehl TS, Hellwig S, Amtage F, Weiller C, Bormann T, et al. Syndrome-specific patterns of regional cerebral glucose metabolism in posterior cortical atrophy in comparison to dementia with Lewy bodies and Alzheimer's disease--a [F-18]-FDG pet study. *J Neuroimaging*. 2015;**25**:281-8.

59.     Firbank MJ, Lloyd J, Williams D, Barber R, Colloby SJ, et al. An evidence-based algorithm for the utility of FDG-PET for diagnosing Alzheimer's disease according to presence of medial temporal lobe atrophy. *Br J Psychiat*. 2016;**208**:491-6.

60.     Higuchi M, Tashiro M, Arai H, Okamura N, Hara S, et al. Glucose hypometabolism and neuropathological correlates in brains of dementia with Lewy bodies. *Experim Neurol.* 2000;**162**:247-56.

61.     Ishii K, Imamura T, Sasaki M, Yamaji S, Sakamoto S, et al. Regional cerebral glucose metabolism in dementia with Lewy bodies and Alzheimer's disease. *Neurology.* 1998;**51**:125-30.

62.     Ishii K, Soma T, Kono AK, Sofue K, Miyamoto N, et al. Comparison of regional brain volume and glucose metabolism between patients with mild dementia with lewy bodies and those with mild Alzheimer's disease. *J Nucl Med.* 2007;**48**:704-11.

63.     Koeppe RA, Gilman S, Joshi A, Liu S, Little R, et al. 11C-DTBZ and 18F-FDG PET measures in differentiating dementias. *J Nucl Med*. 2005;**46**:936-44.

64.     Minoshima S, Foster NL, Sima AA, Frey KA, Albin RL, et al. Alzheimer's disease versus dementia with Lewy bodies: cerebral metabolic distinction with autopsy confirmation. *Ann Neurol*. 2001;**50**:358-65.

65.     Mosconi L, Tsui WH, Herholz K, Pupi A, Drzezga A, Lucignani G, et al. Multicenter standardized 18F-FDG PET diagnosis of mild cognitive impairment, Alzheimer's disease, and other dementias. *J Nucl Med*. 2008;**49**:390-8.

66.     O'Brien JT, Firbank MJ, Davison C, Barnett N, Bamford C, et al. 18F-FDG PET and perfusion SPECT in the diagnosis of Alzheimer and Lewy body dementias. *J Nucl Med*. 2014;**55**:1959-65.

67.     Kono AK, Ishii K, Sofue K, Miyamoto N, Sakamoto S, et al. Fully automatic differential diagnosis system for dementia with Lewy bodies and Alzheimer's disease using FDG-PET and 3D-SSP. *Eur J Nucl Med Molec Imag.* 2007;**34**:1490-7.

68.     Foster NL, Heidebrink JL, Clark CM, Jagust WJ, Arnold SE, et al. FDG-PET improves accuracy in distinguishing frontotemporal dementia and Alzheimer's disease. *Brain.* 2007;**130**:2616-35.

69.     Poljansky S, Ibach B, Hirschberger B, Manner P, Klunemann H, et al. A visual [18F]FDG-PET rating scale for the differential diagnosis of frontotemporal lobar degeneration. *Eur Arch Psychiat Clin Neurosci.* 2011;**261**:433-46.

70.     Rabinovici GD, Rosen HJ, Alkalay A, Kornak J, Furst AJ, et al. Amyloid vs FDG-PET in the differential diagnosis of AD and FTLD. *Neurology.* 2011;**77**:2034-42.

71. Perani D, Della Rosa PA, Cerami C, Gallivanone F, Fallanca F, et al. Validation of an optimized SPM procedure for FDG-PET in dementia diagnosis in a clinical setting. *NeuroImage: Clinical.* 2014;**6**:445-54.

72. Ossenkoppele R, Jansen WJ, Rabinovici GD, Knol DL, van der Flier WM, van Berckel BN, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. *JAMA.* 2015;**313**:1939-49.

73. Mosconi L, De Santi S, Brys M, Tsui WH, Pirraglia E, et al. Hypometabolism and altered cerebrospinal fluid markers in normal apolipoprotein E E4 carriers with subjective memory complaints. *Biol Psychiat.* 2008;**63**:609-18.

74. Walker Z, Jaros E, Walker RW, Lee L, Costa DC, et al. Dementia with Lewy bodies: a comparison of clinical diagnosis, FP-CIT single photon emission computed tomography imaging and autopsy. *J Neurol Neurosur Psychiat.* 2007;**78**:1176-81.

75. Morgan S, Kemp P, Booij J, Costa DC, Padayachee S, et al. Differentiation of frontotemporal dementia from dementia with Lewy bodies using FP-CIT SPECT. *J Neurol Neurosur Psychiat*. 2012;**83**:1063-70.

76. Claassen DO, Parisi JE, Giannini C, Boeve BF, Dickson DW, et al. Frontotemporal dementia mimicking dementia with Lewy bodies. *Cognit Behav Neurol.* 2008;**21**:157-63.

77. Kerrouche N, Herholz K, Mielke R, Holthoff V, Baron JC. 18FDG PET in vascular dementia: differentiation from Alzheimer's disease using voxel-based multivariate analysis. *J Cereb Blood Flow Metab.* 2006;**26**:1213-21.

78. Seo SW, Cho SS, Park A, Chin J, Na DL. Subcortical vascular versus amnestic mild cognitive impairment: comparison of cerebral glucose metabolism. *J Neuroimag.* 2009;**19**:213-9.

79. Mielke R, Pietrzyk U, Jacobs A, Fink GR, Ichimiya A, et al. HMPAO SPET and FDG PET in Alzheimer's disease and vascular dementia: comparison of perfusion and metabolic pattern. *Eur J Nucl Med.* 1994;**21**:1052-60.

80. Szelies B, Mielke R, Herholz K, Heiss WD. Quantitative topographical EEG compared to FDG PET for classification of vascular and degenerative dementia. *Electroencephal clin Neurophysiol.* 1994;**91**:131-9.

81. Duara R, Barker W, Loewenstein D, Pascal S, Bowen B. Sensitivity and specificity of positron emission tomography and magnetic resonance imaging studies in Alzheimer's disease and multi-infarct dementia. *Eur Neurol.* 1989;**29** (Suppl 3):9-15.

82. Mattis PJ, Niethammer M, Sako W, Tang CC, Nazem A, Gordon ML, et al. Distinct brain networks underlie cognitive dysfunction in Parkinson and Alzheimer diseases. *Neurology*. 2016;**87**:1925-33.

83. Firbank MJ, Yarnall AJ, Lawson RA, Duncan GW, Khoo TK, Petrides GS, et al. Cerebral glucose metabolism and cognition in newly diagnosed Parkinson's disease: ICICLE-PD study. *J Neurol Neurosurg Psychiat*. 2017;**88**:310-6.

84.    Pilotto A, Premi E, Paola Caminiti S, Presotto L, Turrone R, Alberici A, et al. Single-subject SPM FDG-PET patterns predict risk of dementia progression in Parkinson disease. *Neurology*. 2018;**90**:e1029-e37.

85.    Mudali D, Teune LK, Renken RJ, Leenders KL, Roerdink JB. Classification of Parkinsonian syndromes from FDG-PET brain data using decision trees with SSM/PCA features. *Computat Mathem Meth Med.* 2015; 136921.

86.    Srulijes K, Reimold M, Liscic RM, Bauer S, Dietzel E, et al. Fluorodeoxyglucose positron emission tomography in Richardson's syndrome and progressive supranuclear palsy-parkinsonism. *Mov Disord*. 2012;**27**:151-5.

87.    Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, et al. Differential diagnosis of parkinsonism: a metabolic imaging study using pattern analysis. *Lancet Neurol.* 2010;**9**:149-58.

88.    Tripathi M, Tang CC, Feigin A, De Lucia I, Nazem A, et al. Automated Differential Diagnosis of Early Parkinsonism Using Metabolic Brain Networks: A Validation Study. *J Nucl Med.* 2016;**57**:60-6.

89.    Hellwig S, Amtage F, Kreft A, Buchert R, Winz OH, et al. [(1)(8)F]FDG-PET is superior to [(1)(2)(3)I]IBZM-SPECT for the differential diagnosis of parkinsonism. *Neurology.* 2012;**79**:1314-22.

90.    Varrone A, Pagani M, Salvatore E, Salmaso D, Sansone V, et al. Identification by [99mTc]ECD SPECT of anterior cingulate hypoperfusion in progressive supranuclear palsy, in comparison with Parkinson's disease. *Eur J Nucl Med Molec Imag.* 2007;**34**:1071-81.

91.    Kimura N, Hanaki S, Masuda T, Hanaoka T, Hazama Y, et al. Brain perfusion differences in parkinsonian disorders. *Mov Disord.* 2011;**26**:2530-7.

92.    Niethammer M, Eidelberg D. Metabolic brain networks in translational neurology: concepts and applications. *Ann Neurol.* 2012;**72**:635-47.

93.    Eckert T, Tang C, Ma Y, Brown N, Lin T, Frucht S, et al. Abnormal metabolic networks in atypical parkinsonism. *Mov Disord.* 2008;**23**:727-33.

94.    Taswell C, Villemagne VL, Yates P, Shimada H, Leyton CE, et al. 18F-FDG PET Improves Diagnosis in Patients with Focal-Onset Dementias. *J Nucl Med*. 2015;**56:**1547-53.

95.    Sha SJ, Ghosh PM, Lee SE, Corbetta-Rastelli C, Jagust WJ, et al. Predicting amyloid status in corticobasal syndrome using modified clinical criteria, magnetic resonance imaging and fluorodeoxyglucose positron emission tomography. *Alzh Res & Ther.* 2015;**7**:8.

96.    Matias-Guiu JA, Cabrera-Martin MN, Garcia-Ramos R, Moreno-Ramos T, Valles-Salgado M, et al. Evaluation of the new consensus criteria for the diagnosis of primary progressive aphasia using fluorodeoxyglucose positron emission tomography. *Dement Geriat Cognit Disord.* 2014;**38**:147-52.

97.    Nestor PJ, Balan K, Cheow HK, Fryer TD, Knibb JA, et al. Nuclear imaging can predict pathologic diagnosis in progressive nonfluent aphasia. *Neurology.* 2007;**68**:238-9.

98.     Whitwell JL, Duffy JR, Strand EA, Machulda MM, Senjem ML, et al. Clinical and neuroimaging biomarkers of amyloid-negative logopenic primary progressive aphasia. *Brain & Language.* 2015;**142**:45-53.

99.     Wicklund MR, Duffy JR, Strand EA, Machulda MM, Whitwell JL, et al. Quantitative application of the primary progressive aphasia consensus criteria. *Neurology*. 2014;**82**:1119-26.

100.    Louwersheimer E, Keulen MA, Steenwijk MD, Wattjes MP, Jiskoot LC, et al. Heterogeneous Language Profiles in Patients with Primary Progressive Aphasia due to Alzheimer's Disease. *J Alzheimer's dis.* 2016;**51**:581-90.

101.    Van Laere K, Vanhee A, Verschueren J, De Coster L, Driesen A, et al. Value of 18fluorodeoxyglucose-positron-emission tomography in amyotrophic lateral sclerosis: a prospective study. *JAMA Neurol.* 2014;**71**:553-61.

102.    Pagani M, Chiò A, Valentini MC, Oberg J, Nobili F, et al. Functional pattern of brain FDG-PET in amyotrophic lateral sclerosis. *Neurology.* 2014;**83**:1067-74.

103.    Chiò A, Pagani M, Agosta F, Calvo A, Cistaro A, et al. Neuroimaging in amyotrophic lateral sclerosis: insights into structural and functional changes. *Lancet Neurol.* 2014;**13**:1228-40.

104.    Brooks BR, Miller RG, Swash M, Munsat TL. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lat Sclerosis Oth Motor Neuron Dis*. 2000;**1**:293-9.

105.    Agosta F, Al-Chalabi A, Filippi M, Hardiman O, Kaji R, et al. The El Escorial criteria: strengths and weaknesses. *Amyotroph Lat Scler & Frontotemp Degen*. 2015;**16**:1-7.

106.    Belsh JM. ALS diagnostic criteria of El Escorial Revisited: do they meet the needs of clinicians as well as researchers? *Amyotroph Lat Sclerosis Oth Motor Neuron Dis*. 2000;**1** (Suppl 1):S57-60.

107.    Mitchell JD, Callagher P, Gardham J, Mitchell C, Dixon M, et al. Timelines in the diagnostic evaluation of people with suspected amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND)--a 20-year review: can we do better? *Amyotroph Lat Sclerosis Oth Motor Neuron Dis*. 2010;**11**:537-41.

108.    Cellura E, Spataro R, Taiello AC, La Bella V. Factors affecting the diagnostic delay in amyotrophic lateral sclerosis. *Clin Neurol Neurosurg.* 2012;**114**:550-4.

109.    Strong MJ, Abrahams S, Goldstein LH, Woolley S, McLaughlin P, et al. Amyotrophic lateral sclerosis - frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. *Amyotroph Lat Scler & Frontotemp Degen*. 2017;**18**:153-74.

110.    Ciarmiello A, Giovacchini G, Orobello S, Bruselli L, Elifani F, et al. 18F-FDG PET uptake in the pre-Huntington disease caudate affects the time-to-onset independently of CAG expansion size. *Eur J Nucl Med Molec Imag*. 2012;**39**:1030-6.

111.    Allain P, Gaura V, Fasotti L, Chauvire V, Prundean A, et al. The neural substrates of script knowledge deficits as revealed by a PET study in Huntington's disease. *Neuropsychologia*. 2011;**49**:2673-84.

112.    Lehman VT, Carter RE, Claassen DO, Murphy RC, Lowe V, et al. Visual assessment versus quantitative three-dimensional stereotactic surface projection fluorodeoxyglucose positron emission tomography for detection of mild cognitive impairment and Alzheimer disease. *Clin Nucl Med.* 2012;**37**:721-6.

113.    Burdette JH, Minoshima S, Vander Borght T, Tran DD, Kuhl DE. Alzheimer disease: improved visual interpretation of PET images by using three-dimensional stereotaxic surface projections. *Radiology.* 1996;**198**:837-43.

114.    Caroli A, Prestia A, Chen K, Ayutyanont N, Landau SM, et al. Summary metrics to assess Alzheimer disease-related hypometabolic pattern with 18F-FDG PET: head-to-head comparison. *J Nucl Med.* 2012;**53**:592-600.

115.    Pagani M, De Carli F, Morbelli S, Oberg J, Chincarini A, et al. Volume of interest-based [18F]fluorodeoxyglucose PET discriminates MCI converting to Alzheimer's disease from healthy controls. A European Alzheimer's Disease Consortium (EADC) study. *NeuroImage: Clin.* 2015;**7**:34-42.

116.    Garibotto V, Herholz K, Boccardi M, Picco A, Varrone A, et al. Clinical validity of brain fluorodeoxyglucose positron emission tomography as a biomarker for Alzheimer's disease in the context of a structured 5-phase development framework. Neurobiol Aging. 2017;**52**:183-95.

117.    Frisoni GB, Bocchetta M, Chetelat G, Rabinovici GD, de Leon MJ, et al. Imaging markers for Alzheimer disease: which vs how. *Neurology.* 2013;**81**:487-500.

118.    Boccardi M. Clinical use of F-fluorodeocyglucose Positron Emission Tomography (FDG-PET) in dementia. *Eur J Neurol.* 2017;**24**(1 SI):761.

119.    Johnson KA, Minoshima S, Bohnen NI, Donohoe KJ, Foster NL, Herscovitch P, et al. Appropriate use criteria for amyloid PET: a report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association. *Alzheimer's & dement*. 2013;**9**:e-1-16.

**Table 1.**

| PICO N | PICO question | Delphi decision (Round, n panelists) | Reasons for final decision |
|---|---|---|---|
| 1 | Support diagnosis of MCI due to AD | YES (Round II, 6 vs 1) | Negative predictive value; diagnostic and prognostic value. |
| 2 | Support diagnosis of MCI due to FTLD | YES (Round II, 6 vs 1) | Negative predictive value; typical hypometabolism. |
| 3 | Support diagnosis of MCI due to DLB | YES (Round IV, 5 vs 2) | Negative predictive value; typical hypometabolism. |
| 7 | Support diagnosis of Atypical AD | YES (Round I, 6 vs 1) | Useful to discriminate AD from other conditions. |
| 8 | Support differential diagnosis between DLB and AD | YES (Round I, 6 vs 1) | Useful to discriminate the two conditions. |
| 9 | Support differential diagnosis between AD and FTLD | YES (Round I, 7 vs 0) | Useful to discriminate the two conditions. |
| 10 | Support differential diagnosis between DLB and FTLD | YES (Round II, 6 vs 1) | Useful to discriminate the two conditions. |
| 11 | Support differential diagnosis between AD and VaD | YES (Round II, 5 vs 2) | Useful to discriminate the two conditions. |
| 12 | Detect PD-related dysfunction | YES (Round IV, 5 vs 2) | Sensitive to cortical involvement before cognitive deficits. |
| 13 | Support differential diagnosis between PSP and PD | YES (Round III, 5 vs 2) | Typical hypometabolic patterns. |
| 14 | Support differential diagnosis between depressive pseudodementia and neurodegeneration | YES (Round II, 7 vs 0) | Exclusionary value. |
| 15 | Support diagnosis of CBS | YES (Round I, 6 vs 1) | Typical hypometabolism. |
| 16 | Support diagnosis of PPA | YES (Round I, 6 vs 1) | More sensitive than MRI. Required in PPA diagnostic criteria. |
| 21 | Use semiautomated assessment to assist visual reading | YES (Round I, 6 vs 1) | Helpful, especially non-experienced readers, but also to the experienced ones. |

PICO questions leading to support of clinical use of FDG-PET to guide the diagnostic procedure. III and IV columns denote the Delphi round in which agreement was achieved, number of panelists voting for-against supporting clinical use, and main reasons for the expressed votes. MCI: mild cognitive impairment; AD: Alzheimer's disease; FTLD: frontotemporal lobar degeneration; DLB: dementia with Lewy bodies; VaD: vascular disease; PD: Parkinson's disease; PSP: progressive supranuclear palsy; CBS: cortico-basal syndrome; PPA: primary progressive aphasia.

**Table 2.**

| PICO N | PICO question | Delphi decision (Round, n panelists) | Reasons for final decision |
|---|---|---|---|
| 4 | Detect early neurodegeneration in SCD | NO (Round I, 1 vs 6) | Only for research purposes. |
| 5 | Detect early neurodegeneration in individuals at risk for AD | NO (Round I, 1 vs 6) | Only for research purposes. |
| 6 | Detect early neurodegeneration in ADAD | NO (Round III, 2 vs 5) | Only for research purposes. |
| 17 | Confirm ALS diagnosis | NO (Round II, 0 vs 7) | Other methods are more useful. |
| 18 | Detect ALS-related dysfunction | Undecided (Round IV, 4 yes vs 3 no) | Diagnostic and prognostic value in selected cases. |
| 19 | preclinical HD | NO (Round II, 1 vs 6) | Only for research purposes. |
| 20 | HD-related decline | NO (Round III, 2 vs 5) | Only for research purposes. |

PICO questions for which, at present, there are no reasons for panelists to support clinical use of FDG-PET for diagnostic decisions. III and IV columns denote round in which agreement was achieved, number of panelists voting for-against supporting clinical use, and main reason for the expressed votes. SCD: subjective cognitive decline; AD: Alzheimer's disease; ADAD: autosomal dominant Alzheimer's disease; ALS: amyotrophic lateral sclerosis; HD: Huntington's disease. * Regarded as a negative vote since at least 5 consensual votes were required for defining consensus.