European Association of Nuclear Medicine and European Academy of Neurology recommendations for the use of brain ^{18}F-fluorodeoxyglucose positron emission tomography in neurodegenerative cognitive impairment and dementia: Delphi consensus

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Background and purpose: Recommendations for using fluorodeoxyglucose positron emission tomography (FDG-PET) to support the diagnosis of dementing neurodegenerative disorders are sparse and poorly structured.

Methods: Twenty-one questions on diagnostic issues and on semi-automated analysis to assist visual reading were defined. 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 receiver 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 papers 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 pseudo-dementia; differentiating between AD and DLB, FTLD or vascular dementia, between DLB and FTLD, and between Parkinson's disease and progressive supranuclear palsy; suggesting underlying pathophysiology in corticobasal degeneration and progressive primary aphasia, and cortical dysfunction in Parkinson's disease; using semi-automated assessment to assist visual reading. Panellists did not support FDG-PET use for pre-clinical stages of neurodegenerative disorders, for amyotrophic lateral

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sclerosis and Huntington disease diagnoses, and for amyotrophic lateral sclerosis or Huntington-disease-related cognitive decline.

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

Background

Advancing knowledge on the pathophysiology of dementing neurodegenerative disorders and the increasing pressure for cost-effectiveness require systematic assessment and validation of biomarker performance, including F-18 fluorodeoxyglucose positron emission tomography (FDG-PET), to define efficient diagnostic procedures [1]. In the 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 US 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 [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 frontotemporal lobar degeneration (FTLD) [6,7], dementia with Lewy bodies (DLB) [8] and progressive supranuclear palsy (PSP) [9]. A comprehensive review of available data up to 2010, supporting the clinical utility of the examination 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 European Association of Nuclear Medicine (EANM) and the European Academy of Neurology (EAN) to endeavour 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 given in Data S1.

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 Neuroimaging Committee decided to target neurologists and other clinicians involved in dementia management with more direct information to facilitate proper use of FDG-PET. The EANM Neuroimaging Committee 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 panellists, four from the EANM and three from the 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 the panellists, who were also informed about the availability and quality of evidence, assessed on the basis of EFNS guidance [16].

Methods

The evidence assessment procedure is described in detail elsewhere [17]. All the procedures were conducted through telematic contacts. The panellists drafted and circulated 21 PICO (Population,

Intervention, Comparison, Outcome) questions, whose literature search was then assigned to a panellist (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 of Embase and PubMed. Only original studies published in English were considered, excluding reviews and management guidelines. All papers reporting on FDG-PET use independently of the acquisition technique, either static or dynamic, were considered. 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], cross-sectional studies were included provided they reported the critical outcomes, such as sensitivity, specificity, accuracy, positive/negative predictive value (PPV/NPV), area under the receiver operating characteristic curve (AUC) or positive/negative likelihood ratios (LR+/ LR−). Clinical confirmation or conversion at follow-up or biomarker-based diagnosis was considered as an acceptable reference standard 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% and 70%, medium with values 71%–80% or large with values 81%–100%. These and other data were extracted and reported in the PICO tables available at https://drive.google.com/open?id= 0B0_JB3wzTvbpVFYtUGxHdGZWYmc (Data S2). The full list of selected papers is in Data S3.

The Delphi voting procedure [20] was performed using a web-based platform. Panellists 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 panellists from previous rounds. For each PICO question, panellists had to vote for or against supporting clinical use based on the collected evidence and their expertise, and to justify their answers. Consensus was defined when at least five out of seven panellists converged on the same decision.

In our terminology, syndromes were distinguished 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 behavioural variant frontotemporal dementia (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]), the inclusive 1998 definition [22] was adopted, treating separately only the linguistic variant where specified.

Results

The evidence assessment for the 21 literature searches, available at https://drive.google.com/open?id=0B0_JB3wzTvbpVFYtUGxHdGZWYmc (Data S2), is reported in detail in dedicated review papers [23–29] and briefly summarized in the pertinent sections below. All panellists filled the whole questionnaire at each of the four rounds. The output of the project consists of the recommendations consensually generated through the Delphi procedure, where panellists based their votes on both their own expertise and the available evidence. Basically, decisions reflected the well-accepted concept that FDG-PET allows the presence or absence of neuronal injury to be differentiated, no matter what type of neurodegeneration. Tables 1 and 2 summarize the recommendations for the 21 PICO questions. Panellists supported the use of FDG-PET in those PICOs involving the diagnosis of disorders at the MCI stage (section on 'Use of FDG-PET in MCI patients') and when already indicated for typical patterns of neurodegeneration in the disease-specific diagnostic criteria (section on 'Use of FDG-PET to discriminate between different forms of dementia') [3–9,14,30] (Table 1). Instead, they did not support the use of FDG-PET in individuals without objective cognitive impairment (section on 'Pre-clinical conditions') [31,32].

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) compared to standard

Table 1 PICO questions leading to support of the clinical use of FDG-PET to guide the diagnostic procedure

PICO number	PICO question	Delphi decision (Round, *n* panellists)	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 pseudo-dementia 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 semi-automated assessment to assist visual reading	Yes (Round I, 6 vs. 1)	Helpful, especially non-experienced readers, but also to the experienced readers

The third and fourth columns denote the Delphi round in which agreement was achieved, the number of panellists voting for versus against supporting clinical use, and the main reasons for the expressed votes. AD, Alzheimer's disease; CBS, corticobasal syndrome; DLB, dementia with Lewy bodies; FTLD, frontotemporal lobar degeneration; MCI, mild cognitive impairment; PD, Parkinson's disease; PPA, primary progressive aphasia; PSP, progressive supranuclear palsy; VaD, vascular disease.

clinical/neuropsychological assessment alone to detect AD (section PICO 1), FTD (section PICO 2) and pro-dromal DLB (section PICO 3) in patients with persistent MCI of uncertain origin.

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

Critical outcomes for PICO 1 were available in 13 of the examined papers [24]. These papers found a very large range of values. Sensitivity ranged between 38% and 98%, specificity between 41% and 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, statistical parametric mapping (SPM), support vector machine, meta regions of interest (meta-ROI)] and to patient heterogeneity (converter/non-converter, amnestic/multidomain, MCI due to AD, or undefined MCI) [24,46], other substantial risks of bias were not detected. The

typical hypometabolic pattern in MCI converting to AD included the posterior cingulate and temporoparietal areas. The consensual recommendation was defined in Delphi Round II, with six panellists voting for clinical use, since FDG-PET allows a better short-term prognosis of AD dementia conversion compared to biomarkers of amyloidosis and may also identify non-Alzheimer types of neurodegeneration early in the course of the disease.

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 the possible incremental diagnostic value of FDG-PET in this case. The consensual recommendation was defined in Delphi Round II, with six panellists deciding to recommend clinical use. Indeed, FTLD may be hard to recognize, especially in the prodromal stage where behavioural changes may mimic psychiatric disorders and cognitive impairment is absent or subtle, a stage that might be defined as mild behavioural (rather than cognitive)

Table 2 PICO questions for which, at present, there are no reasons for panellists to support the clinical use of FDG-PET for diagnostic decisions

PICO number	PICO question	Delphi decision (Round, n panellists)	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)[a]	Diagnostic and prognostic value in selected cases
19	Pre-clinical 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

The third and fourth columns denote the round in which agreement was achieved, the number of panellists voting for versus against supporting clinical use, and the main reason for the expressed votes. AD, Alzheimer's disease; ADAD, autosomal-dominant Alzheimer's disease; ALS, amyotrophic lateral sclerosis; HD, Huntington's disease; SCD, subjective cognitive decline. [a]Regarded as a negative vote since at least five consensual votes were required for defining consensus.

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 behavioural 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 work-up. 'FTD phenocopies' have been identified, i.e. patients with behavioural 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.

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 in Delphi Round IV, with five panellists recommending clinical use of FDG-PET. Besides its

NPV, 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 single-photon emission computed tomography (SPECT) [8,51], ^{18}F dihydroxyphenylalanine PET (^{18}F-18 DOPA PET) or ^{123}I metaiodobenzylguanidine (^{123}I-MIBG) cardiac scintigraphy [52] should be sought as more informative investigations.

Pre-clinical conditions

The use of FDG-PET is not supported in any of the pre-clinical 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) compared to standard clinical/neuropsychological assessment alone to detect early signs of neurodegeneration in patients with subjective cognitive decline (SCD) (section PICO 4), asymptomatic subjects with risk factors for AD (based on APOE ε4 status or amyloid positivity) (section PICO 5) and asymptomatic subjects with familial forms of AD (section PICO 6).

FDG-PET in SCD (PICO 4)
Critical outcomes were not available in any of the examined papers. Also, based on this lack of evidence, agreement was achieved in Delphi Round I, with six panellists deciding not to recommend clinical use, consistent with current diagnostic criteria [31,32]. FDG-PET should still be reserved for research purposes.

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 in Delphi Round I, with five panellists 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 compared to apoE4 or amyloid positivity. Therefore, FDG-PET should be regarded only within well defined, ethics-committee-approved research studies, but definitively not in clinical practice.

FDG-PET in asymptomatic subjects with familial forms of AD (PICO 6)
Critical outcomes were available in two of the examined papers [53,54]. These found 100% sensitivity,

83%–100% specificity range and 97%–100% accuracy range [25]. They included only 13 asymptomatic autosomal-dominant AD (ADAD) due to Presenilin-1 mutation and 30 non-carriers. Data showed that the posterior cingulate cortex hypometabolism assessed semiquantitatively 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 in Delphi Round III, with five panellists deciding not to recommend clinical use as a diagnosis of AD 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.

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

The use of FDG-PET is supported to facilitate differential diagnosis between 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) compared to standard clinical/neuropsychological assessment alone to differentiate between main forms of dementia in patients with dementia and either atypical presentation or atypical course (section PICO 7), between DLB and AD (section PICO 8), between AD and FTLD (section PICO 9), between DLB and FTLD (section PICO 10) and between AD and vascular dementia (VaD) (section PICO 11); to unveil brain dysfunction related to cognitive deterioration in patients with Parkinson's disease (PD) and cognitive impairment (section PICO 12); to differentiate PSP from PD (section PICO 13); to discriminate depressive pseudo-dementia from neurodegenerative disorders associated with depressive symptoms in elderly patients with depression and cognitive deficit (section PICO 14); to point to the diagnosis of the underlying pathological process in patients with corticobasal syndrome (CBS) (section PICO 15); and to discriminate the different clinical variants (non-fluent/agrammatic form, semantic, logopenic) of primary progressive aphasias (PPA) and thus to guide towards the underlying pathophysiology (section PICO 16).

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

Critical outcomes were available in four 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 temporoparietal; 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 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 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 when using a multinomial logistic approach including DLB and AD patients [58]. Early onset AD was included in the search, but no papers were found reporting critical outcomes.

The consensual recommendation was defined in Delphi Round I, with six panellists 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.

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, 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 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 in Delphi Round I, with six panellists voting for clinical use to discriminate DLB and AD. The reason for the positive response by the majority of the panellists was based on the available data, providing relatively good quality of evidence for the ability of FDG-PET to discriminate DLB from AD. Although pre-synaptic dopaminergic pathway radiopharmaceuticals are more accurate in differentiating DLB from AD, FDG-PET is useful in those centres where this investigation is unavailable or in the infrequent DLB cases with a normal pre-synaptic 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 the panellists' decision.

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

Critical outcomes were available in five of the examined papers [26]. These papers found 80%–99% sensitivity range, 63%–98% specificity range, 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 semiquantitative assessment of FDG-PET [71].

The consensual recommendation was defined in Delphi Round I, with seven panellists 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 relatively low quantitative evidence, FDG-PET is approved to discriminate FTD and AD in the USA [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 diseases, especially at the dementia stage. In those cases, either cerebrospinal fluid biomarker analysis or amyloid PET can clarify. It should be noted, though, that AD pathology may coexist 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.

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

Critical outcomes were available in only one of the examined papers. Mosconi *et al.* [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 in Delphi Round II, with six panellists voting for clinical use. The reason given by the majority of panellists 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, which 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 panellists' decision.

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 similar to the one 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 temporoparietal 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, five panellists supporting the utility of FDG-PET in identifying AD in patients with vascular pathology if the characteristic AD pattern of bilateral posterior temporoparietal hypometabolism is present, and provided that hypometabolic regions are not colocalized with large vessel cortical or subcortical infarcts on a structural scan.

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 in Delphi Round IV, with five panellists voting for clinical use. Panellists 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 pseudo-dementia or an atypical parkinsonian syndrome. In addition, the ability of FDG-PET to predict future decline in cognition may allow patients suitable for cholinesterase inhibitor therapy to be identified 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].

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

Critical outcomes were available in two 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, 67.6%–83.9% accuracy range [85,86] and 0.80 AUC [86]. Additional outcomes were reported in three 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 corticobasal

degeneration (CBD) and multiple system atrophy (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 five 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 (two papers did not report sufficient detail to allow replication). Moreover, low applicability arose because all studies included a very selected population and used a semiquantitative method of image analysis.

A consensual recommendation to support clinical use was defined in Delphi Round III. The five panellists 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 noted 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 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 PD and atypical parkinsonian syndromes.

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

No references were obtained for this PICO question. The consensual recommendation was defined in Delphi Round II, with seven panellists 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, whilst 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. Given the total lack of evidence, however, the panel encourages specific research on this topic.

FDG-PET to discriminate the underlying pathological process in patients with CBS (PICO 15)

Critical outcomes were available in two 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 CBS. They found 91%–95% sensitivity range, 58%–75% specificity range and 73%–82% accuracy range. Taswell *et al.* [94] reported also PPV = 68%, NPV = 97%, LH+ = 3.90 and LH− = 0.06. A low risk of bias was found for all items and moderate applicability concerns.

Consensus was achieved in Delphi Round I, six panellists 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, the basal ganglia and thalamus are hypometabolic in the same hemisphere harbouring 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 in identifying specific FDG-PET patterns associated with these different underlying pathologies. Such studies should be based on multi-tracer PET studies including tau and amyloid PET, if a pathological gold standard is unavailable.

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

Critical outcomes were available for four papers, with very heterogeneous results [27]. Using semiquantitative assessment, PPA variants were discriminated with 86.2% sensitivity, 66.7% specificity and 84% accuracy [96]. Differentiation between 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 was 100% for nfv-PPA, 60% for sv-PPA and 91.7% for lv-PPA, and the NPV was 95.2% for nfv-PPA, 100% for sv-PPA and 85% for lv-PPA. Bilateral hypometabolism in the temporoparietal cortex had 50% sensitivity and 100% specificity in detecting AD pathology, whilst normal temporoparietal 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% in both lv-PPA and nfv-PPA, whilst NPV was greater in nfv-PPA (96%) and sv-PPA (92%) than in lv-PPA (81%) [94].

Notwithstanding the heterogeneity of the results, consensus was achieved in Round I, six panellists 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.

Use of FDG-PET in amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD)

Literature searches, assessments and decisions answered whether FDG-PET should be performed as

adding diagnostic value (in terms of increased accuracy and versus clinical confirmation) compared to standard clinical/neuropsychological assessment alone to confirm a clinical suspicion of ALS in patients with or without cognitive impairment (section PICO 17); to detect brain dysfunction related to cognitive deterioration in patients with ALS (section PICO 18); to pick early signs of neurodegeneration in patients with a genetic risk of HD (section PICO 19); and to discriminate frontal-lobe hypometabolism responsible for cognitive deterioration in patients with HD (section PICO 20). The panel did not support the clinical use of FDG-PET for any of these aims [23].

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

Critical outcomes on FDG-PET diagnostic utility in ALS were available in two 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 magnetic resonance imaging (MRI) may be in a better position to help with diagnosis and differential diagnosis [103].

Based on this background, agreement was achieved in Delphi Round II, with seven panellists deciding not to support the 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%, whilst the average delay from 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.

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 four panellists supporting clinical utility. Panellists 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 behavioural testing is enough to determine the presence of cognitive and/or behavioural involvement [109]. In agreement with the recently published criteria [109], the panellists felt that in these patients FDG-PET may be adequate for research purposes but it should not be recommended for clinical use.

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

Critical outcomes were available in only one of the examined papers, where the caudate FDG-PET uptake identified conversion from asymptomatic pre-clinical HD gene carriers to clinical HD with AUC = 0.94 [110]. However, agreement was achieved in Delphi Round II, with six panellists deciding not to support clinical use. Although striatal hypometabolism may be an earlier finding 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.

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

Critical outcomes were available in only one of the examined papers, including only eight 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 performance, as measured by a series of script generation and script sorting tasks [111]. Agreement was achieved in Delphi Round III, with five panellists deciding not to support clinical use because FDG-PET would not add clinically useful information to neuropsychological assessment in a known HD patient.

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, adding sufficient information (in terms of increased accuracy, and versus pathology, biomarker-based diagnosis or conversion at follow-up) compared to visual reading taken alone, to optimize the diagnostic work-up of patients with dementing neurodegenerative disorders?'

Critical outcomes were available in nine of the examined papers [28]. The level of confidence between visual assessment and SPM differed significantly (2.07 vs. 2.4; $P = 0.003$) in the paper by Perani *et al.* [71]. Visual assessment with and without three-dimensional stereotactic surface projection (3D-SSP) had shown a non-significant difference in sensitivity (83% vs. 82%), improved specificity (75% vs. 41%, $P < 0.01$) and AUC 88% vs. 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 vs. 0.99, $P = 0.043$) in the 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 a reference standard (follow-up diagnosis rather than pathology confirmation) and applicability of the index test.

The consensual recommendation was achieved in Delphi Round I, six panellists 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 semiquantitative automated assessment of images is considered helpful to assist visual reading, especially for less experienced readers [42]. Indeed, such automated assessment can provide confirmation on the statistical significance of the abnormalities that are appreciated 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 overestimation and underestimation of abnormal scans. Anyway, semi-automated assessment can help, increasing specificity and confidence, also expert readers.

Several tools are available allowing semiquantification and comparison with an age-matched database of healthy controls, either commercially or freely available. They differ substantially 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. Whilst some tools contain only fixed age-matched control groups, others may be preferable as they allow customized controls to be built up 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 between the several automated tools of semiquantification are relevant as they impact the incremental value of semi-automated assessment significantly, as shown in head-to-head comparisons with visual reading [114,115].

Discussion

With this work, recommendations were outlined 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 panellists. Assessments of the evidence on the incremental utility of FDG-PET over clinical assessment alone for each PICO question assisted panellists' 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 pre-clinical 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 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 the 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, it should be underlined that these are

interim recommendations, based on the best of current (i.e. up to the end of 2015) knowledge, and liable to change as more complete evidence is generated. It is also underlined 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 pre-clinical conditions is consistent with current clinical criteria, recommending clinical diagnoses to be formulated 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 the 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 the 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 the location and extent of neuronal dysfunction at early stages. Finally, its NPV 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.

Panellists 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 work-up 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 examination positively based on demonstrated evidence against clinical use.

The literature reviews [23–29] (Data S2) 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 radiopharmaceuticals, rigorous expensive studies are scarce. Whilst addressing these issues as research priorities to boost the achievement of evidence-based guidelines, in this work the informative value from available studies was optimized and an interim consensus guidance was provided. 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 maintain that clinicians will benefit from this collation of best current evidence and expert opinion.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Abbreviations
Data S2. Preamble
Data S3. References

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