Clinical utility of FDG-PET for the differential diagnosis among the main forms of dementia

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ABSTRACT

Aim: to assess the clinical utility of FDG-PET as a diagnostic aid for differentiating Alzheimer's disease (AD; both typical and atypical forms); dementia with Lewy bodies (DLB); frontotemporal lobar degeneration (FTLD); vascular dementia (VaD); and non-degenerative pseudo-dementia.

Methods: a comprehensive literature search was conducted using the PICO model to extract evidence from relevant studies. An expert panel then voted using the Delphi method on six different diagnostic scenarios.

Results: the level of empirical study evidence for the use of FDG-PET was considered good for the discrimination of DLB and AD; fair for discriminating FTLD from AD; poor for atypical AD; and lacking for discriminating DLB from FTLD, AD from VaD, and, for pseudo-dementia. Delphi voting led to consensus in all scenarios within two iterations. Panelists supported the use of FDG-PET for all PICOs—including those where study evidence was poor or lacking—based on its negative predictive value, and, on the assistance it provides when typical patterns of hypometabolism for a given diagnosis are observed.

Conclusion: although overall there is a lack of evidence on which to base strong recommendations, it was generally concluded that FDG-PET has a diagnostic role in all scenarios. Prospective studies targeting diagnostically uncertain patients to assess the added value of FDG-PET would be highly desirable.

Keywords

FDG-PET

Alzheimer's disease

Atypical Alzheimer

Dementia with Lewy bodies

Frontotemporal lobar degeneration

Vascular dementia

Pseudo-dementia

PICO

Delphi

1. BACKGROUND

FDG-PET has long been used to assist the clinical diagnostic work-up of the main forms of dementia and, although inconsistently, is usually reimbursed in Europe for this indication (Table 1). Clinical guidelines for its diagnostic use in dementia are, however, still lacking; this led the European Association of Nuclear Medicine (EANM) and the European Academy of Neurology (EAN) to launch a joint initiative to guide clinicians in the use of the examination. The initiative included a set of 21 clinical questions that were addressed on the basis of literature evidence and expert consensus[1].

In this paper, we report the evidence assessment performed with regard to the added value of FDG-PET in diagnosing and differentiating the main forms of dementing neurodegenerative disorders—namely Alzheimer's disease (AD) both in its typical memory-onset presentation and atypical presentations; frontotemporal lobar degeneration (FTLD); dementia with Lewy bodies (DLB); vascular dementia (VaD); and pseudo-dementia. Consensus recommendations were then formulated.

Six literature searches were performed to assess the quality of evidence supporting the utility of FDG-PET in the differential diagnosis among the above forms of dementing disorders.

2. METHODS

Seven panelists, four from EANM and three from EAN, were appointed to produce recommendations taking into consideration the added value of FDG-PET, as an addition to clinical-neuropsychological examination, for the diagnosis and management of patients with dementing neurodegenerative disorders of different types. Consensus recommendations were developed through a Delphi procedure, where panelists were asked to vote based on their expertise and on the literature evidence, assessed as follows.

Each evidence search and synthesis followed the PICO (Population, Intervention, Comparison, Outcome) approach, and was performed based on PICO question keywords strings which are reported in[2]. One referent panelist per PICO performed the search and extracted an initial long-list of studies. The studies for inclusion in the analysis were then finalised by applying the PICO-specific eligibility criteria (see section 2.2). A methodology group (comprising three with experience in research methods and two clinical researchers) extracted the data from these selected studies; assessed their methodological quality; and performed an assessment on the quality of evidence, based on the EFNS guidance [3] and, in context of the overall literature on FDG-PET [2].

2.1 PICO question(s) for this paper

For this review, the PICO questions asked whether *FDG-PET should be performed to add diagnostic value (in terms of increased accuracy with respect to pathology, biomarker-based diagnosis or diagnosis at follow-up) as compared to standard clinical/neuropsychological assessment alone, to*:

- *differentiate among main variants of AD in patients with either a typical or atypical presentation or course, where, "typical" meant a slowly progressive syndrome characterized by memory and orientation impairment whereas "atypical" referred to presentations characterized by visuospatial or language impairment.*
- *differentiate primary dementias: DLB versus typical AD; typical AD versus FTLD; DLB versus FTLD; typical AD versus VaD.*
- *discriminate depressive pseudo-dementia from any of the neurodegenerative causes of dementia.*

2.2 Eligibility criteria

Only original full papers published in English in international journals were considered, excluding reviews, management guidelines, abstracts and gray literature. Any sample size was accepted if pathology was the reference standard for diagnosis. Without pathological confirmation, the minimum sample size was 5 for atypical forms of AD and 20 for the AD vs FTLD contrast. No sample size limit was set for any of the other PICOs.

2.3 Literature search

The electronic search strategy, developed and tested with panelists, was performed through predefined keyword strings relating to the specific PICO question. These strings included a selection of terms taken from a largely inclusive literature selection in order to capture all variants for the same keyword. The strings were made up of a common part ("FDG-PET") and a part specific to each PICO[2].

Literature searches were performed using Medline, Embase, PubMed, Google Scholar and CrossReference databases, as of November 2015. We adhered to standards of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) in reporting the findings of this review[4] An initial independent screening of all included studies was performed by an expert neurologist who could include additional papers based on personal knowledge or tracking from references of papers. The full texts of these potentially eligible studies were then independently assessed for eligibility by a methodology team member.

2.4 Data extraction and quality assessment

We extracted data considering 80 variables that allowed evaluation of study features, population of interest, index test, and, gold/reference standard. Critical outcomes were validated measures of test performance (accuracy, sensitivity, specificity, AUC, positive and negative predictive values and likelihood ratios). Another outcome, specific to PICO 7, was the added diagnostic value of FDG-PET expressed as change in diagnosis and treatment. Data extractors were DA for PICOs 7, 9, 10; JR for PICO 8; CF for PICO 11; no papers were available for PICO 14. (see[2] in this issue for more detail).

The quality of evidence was consensually assessed within the methodology team based on study design, gold/reference standard, FDG-PET image assessment (visual or semi-quantitative methods), risk of bias, index test imprecision, applicability, effect size, and effect inconsistency. A final assessment of *relative availability of evidence* was formulated, taking into account evidence availability among all of the 21 PICOs. This ranking was summarized as: lacking, poor, fair or good. For further details about data extraction and quality assessment see [2] in this issue.

In our terminology, we distinguished syndromes from pathophysiologies, consistent with current NIA-AA and IWG criteria[5,6]. Regarding FTLD, unless differently referenced (e.g.[7]), we adopted the inclusive 1998 definition[8], treating separately only the linguistic variants where specified.

3. RESULTS

For the 6 PICOs included in this review, only 22 out of the 87 examined papers contained the critical outcomes for the comparison of interest (Figure 1). The diagnoses covered by these PICOs are known to have distinct patterns of hypometabolism. Specifically the profiles are: bilateral predominant medial and lateral temporo-parietal, with less pronounced prefrontal, hypometabolism in typical AD (AD-memory); the same lobar distribution of hypometabolism as typical AD but with marked left hemispheric lateralization for the aphasic form of AD (AD-language); predominant posterior temporo-parietal and occipital hypometabolism for the posterior cortical atrophy (PCA) variant of AD (AD-visuospatial); predominant occipito-parietal hypometabolism with less prominent frontal hypometabolism and relative preservation of the posterior cingulate region for DLB; prefrontal and/or anterior temporal hypometabolism in FTLD; hypometabolism co-localised to ischaemic lesions (on structural imaging)/hypometabolic regions not conforming to the recognized patterns seen for degenerative dementias in VaD; and preserved cerebral metabolism (relative to the apparent degree of cognitive impairment) in pseudo-dementia (Figure 2).

Our data extraction and assessment found evidence lacking (meaning a lack of actual studies as opposed to evidence for lack of utility) for the clinical use of FDG-PET in discriminating VaD from AD, DLB from FTLD, and neurodegenerative dementias from pseudo-dementia. The level of available evidence was rated as poor for differentiating among atypical forms of AD; fair to distinguish between AD and FTLD; and good for differentiating AD from DLB. Nonetheless, consistent with recommendations in disease-specific clinical criteria[1,6,7,9–15] panelists supported clinical use according to known disease related metabolic patterns (Table 2).

3.1 PICO 7: Atypical AD

Among the 73 papers identified and screened by the referent panelist (AD), 15 were sent to the methodology team for data extraction and assessment (see Figure 1 - PICO 7). Five papers were excluded, since comparison was made between patients with atypical dementia patients and healthy people[16–20]. The data extraction table is available at: https://drive.google.com/open?id=0B0_JB3wzTvbpZEd4Z083OThxNDg.

Critical outcomes were available in four of the examined papers (Table PICO 7). These studies included inhomogeneous patient samples, thus the main results are reported separately for each paper. In patients with 'atypical/unclear dementia', an FDG-PET scan led to a diagnostic change in 59.5% of the patients, and to increased prescription of cholinesterase inhibitors from 13.8% to 38.3% [21]. In a population affected by the main AD variants (AD-memory, AD-visuospatial, and AD-language) distinct hypometabolism patterns were found in the AD-language dominant (left inferior frontal and left temporo-parietal; AUC=0.82, p=0.011) and AD-visuospatial dominant (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) presentations. A trend was also found for AD-memory dominant cases (AUC=0.65; p=0.062) for hypometabolism in bilateral inferior frontal, cuneus and inferior temporal regions, and right inferior parietal lobe [22]. The logopenic variant of PPA (lvPPA)—the PPA variant most often associated with AD pathology—could be distinguished from AD-memory (AUC=0.89) based on hypometabolism in the right medial temporal and posterior cingulate gyri, left inferior, middle and superior temporal lobes, and left supramarginal gyrus [23] (see also [24] in this issue for discussion of AD-language in the context of other primary progressive aphasias). Patients affected by PCA could be distinguished from DLB on the basis of FDG-PET pattern 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 [25]. Figure 2 shows some examples of typical hypometabolic patterns in sample patients.

Relative to the 21 PICOs of the whole project [1,2], the availability of formal evidence supporting the utility of clinical use of FDG-PET in differentiating AD dementia with either atypical presentation or atypical course from neurodegenerative disease other than AD was ranked as poor. The consensus recommendation was reached on Delphi Round I (6 out of 7 panelists voted affirmatively for clinical use).

3.2 PICO 8: FDG-PET to differentiate between DLB and AD

One-hundred and twenty-nine papers were identified and screened by the referent panelist (ZW), but only 29 were selected as adequate for assessment and sent to the methodology team (see Figure 1 - PICO 8). Of these, 16 papers were excluded because i) one did not include the population of interest[26]; ii) eight did not compare DLB and AD patients[27–34]; iii) one was an epidemiologic study[35]; iv) two were methodological studies for quantitative analyses of FDG-PET[36,37]; v) and four reported only patterns of hypometabolism (rather than quantitative diagnostic data) [38–41]. The detailed data extraction table is available at: (https://drive.google.com/open?id=0B0_JB3wzTvbpUHhIMVpHTkhBMEU).

Critical outcomes were available in 11 of the examined papers (Table PICO 8). However, the reference standard was clinical diagnosis at baseline in the majority of these papers; only two studies, including a total of 23 DLB and 31 AD patients quantified test performance appropriately. Overall, these papers found a 70-92% sensitivity range, 74-100% specificity range and 72-96% accuracy range [25,33,42–49]; 0.77-0.91 AUC range[44,46,48–50]; and 86% PPV, 85% NPV and 4.46 LH+[42]. Studies reporting only hypometabolic patterns disclosed a partially overlapping profile of brain hypometabolism in AD and DLB, except for a marked hypometabolism in the visual cortex in DLB and relative preservation of metabolism in posterior cingulate cortex (cingulate island sign; see, Figure 2 sections (A) and (D)).

Taking into account the available evidence for the PICOs of the entire project, the level of evidence supporting the clinical utility of FDG-PET in distinguishing between DLB and AD patients was ranked as good. The consensual recommendation was defined on Delphi Round I, since 6 panelists voted for supporting clinical use to discriminate DLB and AD, because of the specific metabolic patterns.

3.3 PICO 9: FDG-PET to differentiate AD from FTLD

Among the 137 papers identified by the panelist (FB), 15 were sent to the methodology team (see Figure 1 - PICO 9). Seven papers were excluded because i) four papers did not report critical

outcomes and did not reach the minimum sample size [30,51–53]; ii) two papers did not compare AD and FTLD patients in a manner that provided useful information for the differential diagnosis[54] and [55]; iii) one paper did not include both target groups (i.e., only FTLD patients) [56]. The data extraction table is available at: (https://drive.google.com/open?id=0B0_JB3wzTvbpUmZtWTFsYkVYY0E).

Critical outcomes were available in five of the selected papers (Table PICO 9). Sensitivity was in the 80-99% range, specificity ranged between 63% and 98%, and accuracy between 87% and 89.2% [48,57–59]. The other values were: 0.91-0.97 AUC range[48,59]; 98% PPV, 74% NPV, 29.88 LR+, 0.25 LR-[59]; and an increased accuracy for the classification of FTLD with respect to AD by using semi-quantitative assessment of FDG-PET [32]. The remaining papers reported only differences in patterns of hypometabolism (figure 2 sections (A) and (E). One study[60] provided quantitative information on the discrimination between AD (or FTLD) and other pathologies, but did not directly compare AD and FTLD. Thus, this information did not address our question (AD vs FTLD+DLB: sensitivity=94%, specificity=86%, AUC=0.90, LR+=6.71, LR-=0.07; FTLD vs AD+DLB: sensitivity=93%, specificity=95%, accuracy=0.94, LR+=18.6, LR-=0.07). Another paper with the same indirect comparisons found that FDG-PET correctly classified 88.1% of AD and 83.9% of FTLD [61]. The remaining paper[62] provided only associated patterns of hypometabolism, describing metabolic differences between AD and HC, FTLD and HC, and AD and FTLD without diagnostic metrics.

With reference to the available evidence for the PICOs of the entire project, the availability of formal evidence supporting diagnostic utility of FDG-PET in distinguishing AD from FTLD patients was ranked as fair. The consensual recommendation was defined on Delphi Round I, with all the seven panelists supporting the clinical diagnostic use because the typical metabolic patterns are backed by some evidence and were judged as very useful for differential diagnosis.

3.4 PICO 10: FDG-PET to differentiate between DLB and FTLD

Among the 80 papers identified by the referent panelist (ZW), 13 were sent to the methodology team (see Figure 1 - PICO 10). Eight papers were excluded since i) three papers were reviews; ii) one was not in English; iii) two did not include the population of interest [34,63]; and iv) two did not compare DLB patients and FTLD patients [45,56]. The data extraction table is available at: https://drive.google.com/open?id=0B0_JB3wzTvbpbUJLeVc3MW8waU0.

Critical outcomes were available in only one of the examined papers (Table PICO 10). This study reported 71% sensitivity, 65% specificity, 66% accuracy and 68% AUC of FDG-PET in distinguishing between DLB and FTLD patients [48]. However, values were obtained using only

the baseline clinical diagnosis as the reference standard. The remaining papers provided only descriptive evidence of the metabolic pattern associated with each disorder. Different patterns of hypometabolism associated with the two disorders consisted of a predominantly posterior hypometabolism in DLB and predominantly anterior hypometabolism in FTLD patients, but also an overlap in several areas (i.e., parietotemporal cortex, posterior cingulate, see, figure 2 sections (D) and (E)).

Relative to the evidence available for the other PICOs, the availability of formal evidence supporting diagnostic utility of FDG-PET in distinguishing DLB from FTLD patients was lacking. Consensual recommendation was reached on Delphi Round II, when 6 panelists voted for clinical use, because all considered the typical metabolic patterns to be useful in supporting the differential diagnosis between the two conditions.

3.5 PICO 11: Use of FDG-PET to differentiate between AD and VaD

The referent panelist (PN) identified sixteen papers that were sent to the methodology team (see Figure 1 - PICO 11). Nine papers were excluded for the following reasons: i) the target samples were missing in five papers [52,64–67]; ii) one study used Oxygen-15 PET rather than FDG-PET [68]; iii) three did not address the comparison of interest [69–71]. The data extraction table is available at https://drive.google.com/open?id=0B0_JB3wzTvbpUVFRN2NPalplZGM.

Critical outcomes were available only in one of the remaining papers (Table PICO 11). With the obvious drawback that the testing sample was the same used to train the algorithm, AD patients, VaD patients and controls were identified with 100% accuracy, sensitivity and specificity by applying a fully-automated, voxel-based multivariate technique [72]. Patterns of hypometabolism associated with VaD patients included thalamus, brainstem and cerebellum, as opposed to AD patients who showed hypometabolism in the posterior cingulate and temporo-parietal cortex [72–74]. These patterns were not, however, replicated in other studies [75,76].

Formal evidence supporting diagnostic utility of FDG-PET in distinguishing AD from VaD patients was considered as lacking. The consensual recommendation was agreed at Delphi Round II, with five panelists voting for supporting clinical use, as they considered that the metabolic pattern typically found in AD patients can help support the differential diagnosis between AD and VaD.

3.6 PICO 14: FDG-PET to discriminate depressive pseudo-dementia

No studies were obtained for this PICO question, therefore we lack evidence about diagnostic utility of FDG-PET in discriminating depressive pseudo-dementia from neurodegenerative disorders

associated with depressive symptoms in elderly patients with depression and cognitive deficits. The consensual recommendation was, however, defined on Delphi Round II, with all the seven panelists voting for clinical use especially taking into consideration the high negative predictive values of FDG-PET, since a normal scan virtually excludes dementia due to a neurodegenerative disease.

4. DISCUSSION

In this paper, we assessed evidence for the utility of FDG-PET in differential diagnosis among the main forms of dementing disorders, specifically: AD, FTLD, DLB, VaD and pseudo-dementia. According to data extraction and assessment, we found no definite evidence for the diagnostic utility of FDG-PET in discriminating DLB from FTLD, VaD from AD, and pseudo-dementia from neurodegenerative disorders. Conversely, we found a fair relative availability of evidence to support the FDG-PET use to differentiate AD from FTLD and a poor relative availability of evidence to distinguish among atypical forms of AD. It should be noted in these instances, that the lack of evidence was due to a paucity of appropriate studies rather than studies with negative results. There was good evidence supporting the use of the exam to differentiate AD from DLB.

Despite the general lack of evidence, consensus was reached supporting the use of FDG-PET for all PICO questions during Delphi voting. It is important to stress, however, that a positive recommendation for use of FDG-PET in a specific clinical circumstance must not be construed as meaning it should be a routine investigation whenever that circumstance arises. When the clinical picture is completely classic for some of the degenerative dementias, addition of an FDG-PET is unlikely to significantly increase diagnostic certainty. For instance, a patient with a progressive disorder characterized by prominent visuospatial and attention deficits; spontaneous parkinsonism; visual hallucination; fluctuation; and REM sleep behavior disorder has probable DLB [13]. Likewise, a patient with progressive changes in behavior and personality characteristic of the behavioral variant of frontotemporal dementia (bvFTD) combined with disproportionate frontal lobe atrophy on structural imaging has probable FTLD[7]. Although in these two vignettes, one would expect FDG-PET to also show characteristic changes, the pre-test probability of the diagnosis is already so high that adding FDG-PET is superfluous. This caveat is already acknowledged in the wording of several national guidelines in Europe (Table 1) which stress that the indication for FDG-PET is in circumstances where the clinical picture and standard structural imaging (i.e. without PET) is ‘unclear’ or ‘in doubt.’ The question then arises as to what defines ‘unclear’ or ‘in doubt’. This is a complex question that should not only take account of the degree

of diagnostic uncertainty but also the implications of an incorrect diagnosis; this can mean that even fairly minor doubt may justify FDG-PET. To illustrate this, consider again a patient whose informant reports behavior and personality changes that are consistent with bvFTD but this time the structural imaging does not show unequivocal frontal lobe atrophy, and, in whom, it is hard to be sure from the informant's account, if the symptoms are truly progressive. This is a common clinical scenario in which bvFTD may still remain the most likely diagnosis; however, now—and in spite of only a fairly subtle change in the clinical information—there is a very real possibility that the patient may not have a degenerative disease at all; this vignette is now also compatible with a so-called FTD phenocopy syndrome. In this scenario, FDG-PET can play a critical role in that frontal hypometabolism offers strong evidence eitherfor the diagnosis of bvFTD [77].

Atypical AD (PICO 7): The occurrence of atypical AD may be difficult to detect at the individual level where merging of multiple biomarkers is often needed to reach the correct diagnosis. In this context, FDG-PET may be especially useful in identifying those with AD pathology in patients presenting with primary progressive aphasia (PPA) and indeed it is included in the current diagnostic criteria for this purpose[11]. For further discussion on the role of FDG-PET in discriminating between the variants of PPA see also[24] in this issue. The PCA variant of AD can sometimes be particularly difficult to diagnose, especially for clinicians with limited experience of the syndrome. Patients often struggle to articulate their difficulties and complaints of visual disturbance in the absence of ocular disease can even lead to misdiagnosis of a functional psychological disorder. This is often further compounded in that the young age of many PCA patients means dementia is not suspected. In this context FDG-PET can prove particularly helpful as it characteristically shows extensive posterior cortical hypometabolism. More complex, however, can be the discrimination of the PCA variant of AD from DLB, although the cingulate island sign is increasingly recognized in DLB and not in AD. The remaining posterior association cortex, however, may disclose largely overlapping regions of hypometabolism between the two conditions.

DLB/ typical AD (PICO 8): 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. Moreover, the inclusion of FDG-PET in the new criteria for DLB[13] as a supportive biomarker also contributed to panelists' decision. In this context, however, the panelists recognized that radiopharmaceuticals targeting the brain presynaptic dopaminergic pathway or cardiac post-ganglionic norepinephrine transporter are more accurate in differentiating DLB from AD. FDG-PET may have a role especially in those centers where these examinations are unavailable.

AD/FTLD (PICO 9): The panelists acknowledged that differentiating FTLD from AD only on clinical-neuropsychological grounds may sometimes be challenging (e.g. in situations where reliable informant history is limited). In most cases, the hypometabolic patterns of FTLD and AD are clearly distinguished. FTLD patients show variable amount of hypometabolism of the prefrontal, insular and anterior cingulate cortex, basal ganglia. Conversely, hypometabolism involves the posterior cingulate cortex, the precuneus and variable degrees of posterior temporal and parietal cortex in AD patients. Some degree of hypometabolism can, however, also be found in parietal cortex in FTLD patients, though this is characteristically less pronounced than the prefrontal lesion. Moreover, some degree of hypometabolism can be found in the frontal association cortex in AD patients and ultimately becomes a universal feature as the disease progresses. The posterior regions are, however, characteristically more severely affected than the frontal lobes. In summary, therefore, although posterior association cortex hypometabolism may occur in FTLD and prefrontal hypometabolism occurs AD, it is the relative gradient—rostral worse than caudal in FTLD and vice versa in AD—that has discriminant value.

Despite relatively few quantitative studies, FDG-PET has been approved to discriminate FTD from AD in the US (Decision Memo for Positron Emission Tomography (FDG) and Other Neuroimaging Devices for Suspected Dementia (CAG-00088R).2004.), and included in the clinical criteria of both bv-FTD[7] and PPA [11]. Moreover, the procedural guidelines of the EANM [78] state that 'Indications include early diagnosis and differential diagnosis of dementing disorders, such as Alzheimer's disease and frontotemporal dementia'. However, there may remain occasional 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, whose degree is generally correlated with the severity of the disease stage. In these cases, amyloid biomarkers may be more informative, albeit with the caveat that a positive amyloid biomarker may be an incidental finding (especially with elderly presentations) in FTLD[79,80] —i.e. minor AD co-pathology in a patient whose dementia is caused by FTLD. In these cases, a clear FTLD pattern on FDG-PET might help point to the causal diagnosis whereas a positive amyloid biomarker along with left posterior temporo-parietal hypometabolism (i.e. the FDG-PET signature of lvPPA) would argue for AD as the causal pathology.

1. DLB/FTLD (PICO 10): The reason given by the majority of panelists for use in this scenario was the clearly different patterns of hypometabolism associated with the two conditions,

FTLD showing frontal and anterior-temporal hypometabolism and DLB displaying mainly posterior involvement (visual cortex and parieto-temporal cortex) and relative posterior cingulate preservation (cingulate island sign). Although some degree of frontal lobe hypometabolism can be found in DLB, it is not predominant. Most cases can be differentiated clinically, meaning that FDG-PET is seldom necessary but there are some overlapping clinical features and misdiagnosis between the two conditions has been reported in autopsy cases[81–83].

Furthermore, parkinsonism may be present in both conditions, and presynaptic dopaminergic imaging may be abnormal in both disorders. The inclusion of FDG-PET in the bvFTD criteria[7] and the new DLB criteria [13] also contributed to the panelists' decision.

AD/VaD (PICO 11): A key problem with the concept of VaD, and possibly a reason for inconsistencies among studies, lies in the huge heterogeneity of VaD patients who differ in terms of etiology, number, location, and extent of vascular lesions. There is also the issue of mixed pathologies, in that a patient with symptomatic vascular lesions can also show AD-pathology. Lastly, in patients with dementia and severe vascular lesions on MRI, dementia may not necessarily be due to vascular pathology—clear-cut temporal and qualitative relationships must be demonstrated as per the criteria on Vascular Cognitive Impairment[84]. In patients with AD and concomitant vascular lesions, it may be hard to establish the relative weight of the two components in causing the clinical dementia. The existing literature in this field is particularly limited as we lack studies with pathological diagnosis as the reference standard. Moreover, the comparison among available studies is problematic because of the variable inclusion criteria for VaD. With these caveats in mind, the consensual recommendation for clinical utility was achieved, supporting the use of FDG-PET in identifying AD in patients with vascular pathology when the characteristic AD pattern of bilateral posterior temporo-parietal hypometabolism can be shown, and provided that these hypometabolic regions are not co-localized with cortical infarcts on structural scans. On this final point, FDG-PET should never be reported without review of the structural imaging; this is good clinical practice in all cases of suspected degenerative brain disease, but none more so than where vascular lesions are suspected.

Pseudo-dementia (PICO 14): Depressive pseudo-dementia is a relatively uncommon problem but it is critical not to miss it because of its potential reversibility. No formal studies on the utility of FDG-PET in this context were identified. Nonetheless, there was unanimous consensus by the panelists to support the use of FDG-PET. The rationale is, firstly, based on the knowledge that FDG-PET abnormalities are a function of disease severity. Thus, a clearly demented patient should

always have obvious abnormalities on FDG-PET. A normal FDG-PET in this instance offers strong evidence supporting pseudo-dementia, while a typical pattern of hypometabolism for one of the degenerative dementias argues against pseudo-dementia (high negative predictive value). It should be noted here that subtle frontal hypometabolism may be found in some patients with severe depression but the hypometabolic profiles corresponding to the degenerative diseases that cause dementia are far from subtle. Finally, it must be stressed that this recommendation specifically applies to a patient with an apparent overt dementia on cognitive testing and not to the more common and challenging situation of deciding whether patients with very mild or even subjective cognitive deficits have a primary psychiatric diagnosis versus the first signs of a degenerative disease (see [85] in this issue for discussion of subjective and mild cognitive impairment).

The key limitation of this work was the paucity, or, in some circumstances, complete lack of evidence on which to base recommendations. Even where evidence exists, limitations in study design often raise questions about the applicability of results to real-world clinical practice. For instance, many studies assess accuracy metrics using baseline clinical diagnosis as the reference-standard. The baseline clinical diagnosis, however, can be incorrect. Both baseline clinical diagnosis and FDG-PET should, therefore, be assessed versus an independent reference standard; ideally this reference should be pathology although a biomarker-based diagnosis may offer a surrogate (if a valid biomarker is available), or, at the very least, versus diagnosis at clinical follow-up (although this last option is better suited to outcome studies in subjective or mild cognitive impairment rather to differential diagnosis). Lack of a definitive reference standard is arguably most pertinent to VaD, in which the vascular risk factors and lesions used to make the ‘diagnosis’ may be incidental/additional findings while the primary cause of the dementia is degenerative.

Even if one assumes that in past studies that used baseline clinical diagnosis as reference standard, this clinical diagnosis was 100% correct, problems still remain. Consider a hypothetical study contrasting AD and FTLD that reports an impressive 90% accuracy for discriminating the two conditions with FDG-PET. If the clinical information was good enough to diagnose patients with 100% accuracy then an accuracy for the diagnostic investigation of 90% no longer looks impressive. Indeed, in Bayesian terms, the test has added nothing. Conversely, interpreting accuracy where—as is probably the case in many studies—the clinical diagnosis was not always correct can unfairly penalize the accuracy results for FDG-PET (e.g. a patient with AD pathology whose FDG-PET also showed the characteristic hypometabolic pattern of AD, but who had been misdiagnosed

clinically as bvFTD, would be recorded as a failure for FDG-PET if clinical diagnosis were being used as the reference standard).

The real worth of FDG-PET—or any diagnostic test for that matter—is not in confirming what was already obvious, but in improving accuracy where some uncertainty exists. In many clinical scenarios there is uncertainty and often only a subtle degree of uncertainty is sufficient for the test to add value. In order to ascertain how much added value, more studies with pathological confirmation as the reference standard—and comparing head-to-head with the accuracy of clinical diagnosis—are essential. It is, at least theoretically, possible that in some circumstances FDG-PET might outperform standard clinical diagnosis, but this is impossible to prove when clinical diagnosis is used as the benchmark. Prospective studies with pathological confirmation require effort and time. On a positive note, however, the definitive information achieved from such an approach likely means that useful information can be found with far fewer cases than in a purely clinical study. Furthermore, the stability of FDG-PET between scanners makes it ideal for pooling data across centres, meaning that many sites, each with only a few datasets, can still play a useful role. Finally, future analyses of diagnostic potential need to adopt more Bayesian approaches to understand the true added value for FDG-PET.

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Table 1. Indication and reimbursement of FDG-PET in the diagnostic work-up for dementia in Europe.

France	INDICATION: early diagnosis of AD / atypical presentation / diagnostic doubt of FTLD. Useful in the diagnosis of probable AD. REIMBURSEMENT: by national health service and private health insurance.
Germany	INDICATION: criteria not defined. REIMBURSEMENT: no. Individual exceptions should be negotiated with private health insurance, but criteria for reimbursement are not clearly defined.
Italy	INDICATION: recommended for the differential diagnosis between AD and VD, and between AD and FTLD.[I] REIMBURSEMENT: by national health service.
Netherlands	INDICATION: FTLD; unexplained dementia. REIMBURSEMENT: by private health insurance.
Spain	INDICATION: no formal indication. In most guidelines: for differential diagnosis of AD with other dementias REIMBURSEMENT: by national health service.
Sweden	INDICATION: used in tertiary clinics when diagnosis is still unclear after ordinary memory assessment. REIMBURSEMENT: by the clinic.[S1-2]
Switzerland	INDICATION: second level investigation in unclear cases, after a visit by a neurologist, psychiatrist or geriatrician, below 80 years of age, MMSE of 10 or higher, max. disease duration of 5 y, no previous brain PET or SPECT.[CH] REIMBURSEMENT: by private health insurance.
UK	INDICATION: to help differentiate between Alzheimer's disease, vascular dementia, and frontotemporal dementia if the diagnosis is in doubt.[UK] REIMBURSMENT: by national health service.

[S1] Lindgren Peter, Ersättning i sjukvården, modeller, effekter ,rekommendationer. SNS förlag,p. 2014, pp. 1-60. ISBN 978-91-86949-56-3

[S2]Jacobsson Fredrik, Lindvall Staffan. Utveckling av hälsa och sjukvårdssystems inom hälso-och sjukvård. En översikt av tillämpning, erfarenheter och utvecklingslinjer.Sverige kommuner och landsting. 2007, pp.5-39 ISBN 978-91-7164-353-7

[C1] Krankenpflege-Leistungsverordnung. Verordnung des EDI über Leistungen in der obligatorischen Krankenpflegeversicherung. https://www.admin.ch/opc/de/official-compilation/2016/4639.pdf

[UK] National Institute for Health and Care Excellence guideline - CG42 (https://www.nice.org.uk/guidance/CG42/chapter/1-Guidance#diagnosis-and-assessment-of-dementia)

Table 2. Evidence and panelists' decisions supporting the use of FDG-PET in the diagnostic work-up of the main forms of dementia. ((What became of PICO 1 to 6 should be made explicit.)) Panelists supported the use of FDG-PET for the other PICO questions (1, [24,86,87], with the exception of those relative to preclinical conditions[85], Huntington disease and amyotrophic lateral sclerosis[88].

PICO	RELATIVE AVAILABILITY OF EVIDENCE	PANELISTS' RECOMMENDATIONS	MAIN REASON FOR FINAL DECISION
7 – Atypical AD	Poor	YES	Different hypometabolic patterns.
8 – DLB vs AD	Good	YES	Different hypometabolic patterns.
9 – AD vs FTLD	Fair	YES	Different hypometabolic patterns.
10 – DLB vs FTLD	Lacking	YES	Different hypometabolic patterns.
11 – AD VS VAD	Lacking	YES	Different hypometabolic patterns.
14 – Pseudo-dementia	Lacking	YES	Exclusionary value.

Figure 1. PRISMA flowchart of selected papers for PICOs 7-11[4] (adapted from Moher et al., 2009).

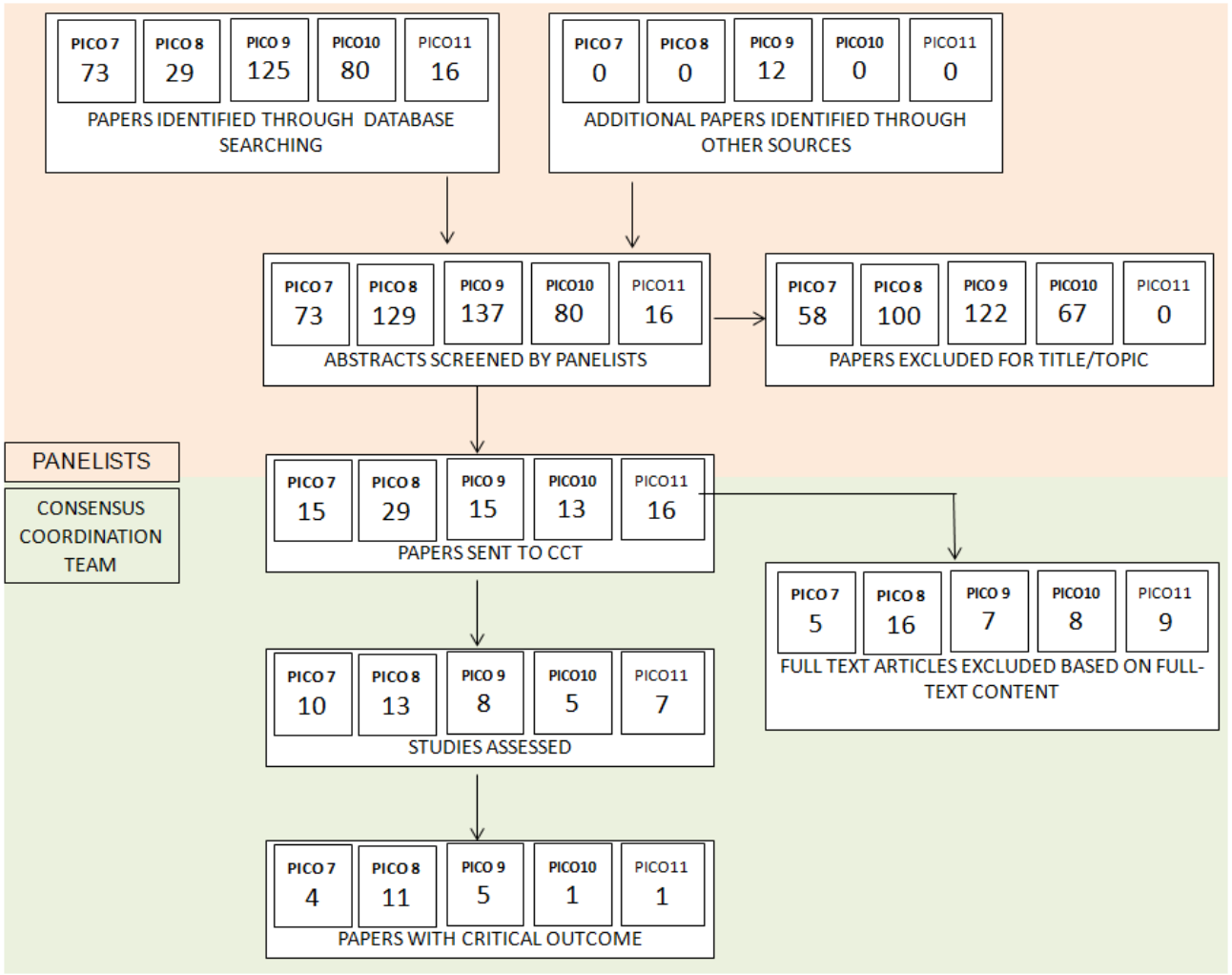

Figure 2. Metabolic patterns associated to atypical AD (B, C) and to the main forms of dementias (A, D, E).

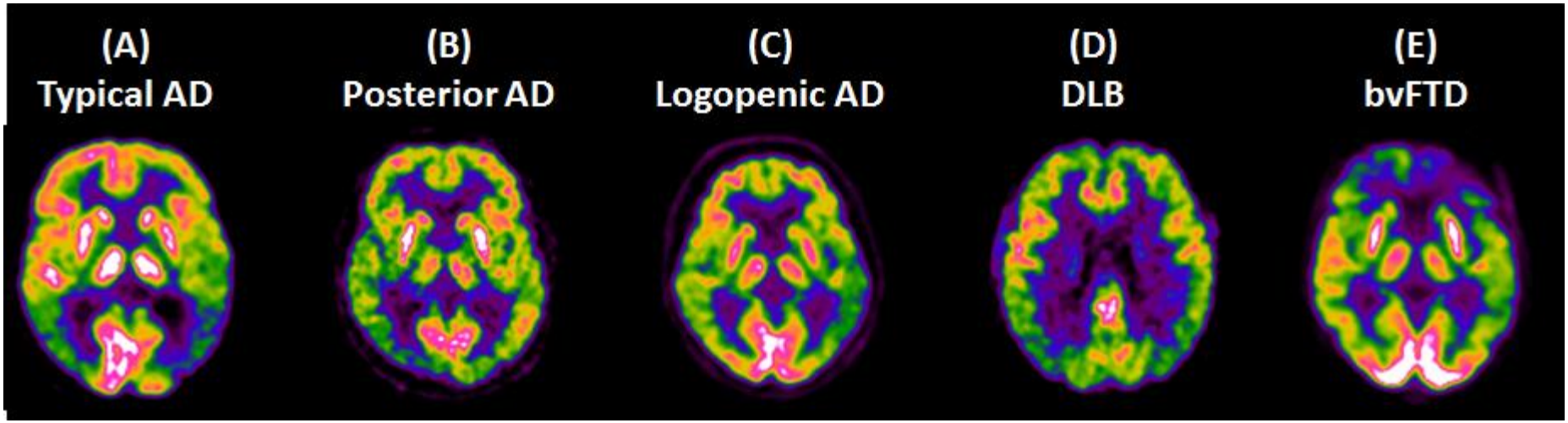
(A)
Typical AD
(B)
Posterior AD
(C)
Logopenic AD
(D)
DLB
(E)
bvFTD

Table PICO 7. Table reports the quality of evidence for each critical outcome. Overall quality of evidence was assessed as described in section 2.4, and ranked among the 21 PICOs of the whole project (1) to provide information about availability of evidence relative to the FDG-PET field (see 3 for further details).

PICO 7: Identify AD dementia with atypical presentation or atypical course											
Critical outcomes	**N. of papers**	**Sample size**	**Gold/ reference standard**	**FDG-PET assessment**	**Risk of bias**	**Index test methods**	**Applicability**	**Effect (CI)**	**Effect assessment**	**Effect inconsistency**	**Outcome quality**
Change in diagnosis	1	37 Atypical unclear dementia	Clinical diagnosis	Visual + Semi-quantitative	Serious	Not serious	Not serious	59.5%	HIGH	NA	VERY LOW
Change in patient management	1	37 Atypical unclear dementia	Clinical diagnosis	Visual + Semi-quantitative	Serious	Not serious	Not serious	Whole sample: Numbers of ChEIs increased significantly from 13.8% to 38.3% following PET scan, partly reflecting the impact of PET on atypical/unclear cases that turned out to be potentially treatable patients with AD.	MODERATE	NA	VERY LOW
Sensitivity	1	6 PCA 12 DLB, 15 AD	Diagnosis at follow-up	Visual + Semi-quantitative	Not serious	Not serious	Not serious	PCA vs DLB: 83% (CI 36-100%) PCA vs (DLB and AD): 83% (CI 36-100%)	HIGH	NA	HIGH
Specificity	1	6 PCA 12 DLB, 15 AD	Diagnosis at follow-up	Visual + Semi-quantitative	Not serious	Not serious	Not serious	PCA vs DLB: 85% (CI 52-98%) PCA vs (DLB and AD): 93% (CI 76-99%)	HIGH	NA	HIGH
Accuracy	1	6 PCA 12 DLB, 15 AD	Diagnosis at follow-up	Visual + Semi-quantitative	Not serious	Not serious	Not serious	PCA vs DLB: 83% (CI 59-96%) PCA vs (DLB and AD): 90.9% (CI 76-98%)	HIGH	NA	HIGH
AUC	3	79 Atypical	2 Biomarker-based diagnosis 1 Diagnosis at follow-up	1 Visual + Semi-quantitative 2 Semi-quantitative	Not serious	Not serious	Serious	Study 1. AD-language: AUC = 82% (CI NA, p=0.011); AD-visuospatial 85% (CI NA, p=0.009); AD-memory: 65% (CI NA, p=0.062). Study 2. lvPPA vs typical AD: 89% (CI: 81-100). Study 3. PCA vs (DLB and AD): 91% (CI NA)	HIGH	NA	HIGH

RELATIVE AVAILABILITY OF EVIDENCE: POOR

Risk of bias: assessment of the study design and other methodological features (e.g., patient selection, clinical diagnostic criteria used)

Index test methods: assessment of index test methodology (e.g., technical details, image analysis methods and statistical analysis).

Applicability: representativeness of the studied population and index test reproducibility in clinical practice (semi-quantitative methods correspond to 'serious' indirectness, visual + semi-quantitative methods correspond to 'not serious' indirectness, due to partial implementation of quantitation in clinical practice).

Effect: lowest and highest values for each critical outcome; when more values were obtained for the same outcome, the highest was reported.

Effect assessment: 51-70% low, 71-80% moderate, 81-100% high.

Effect inconsistency: 'Not serious' if lowest and highest values difference was 0-20, 'serious' 21-40, 'very serious' >40.

Outcome quality: summary of evidence as from all columns.

Table PICO 8. Please see legend for Table PICO 7.

PICO 8: Differentiate DLB from AD											
Critical outcomes	**N. of papers**	**Sample size**	**Gold/ reference standard**	**FDG-PET assessment**	**Risk of bias**	**Index test methods**	**Applicability**	**Effect (CI)**	**Effect assessment**	**Effect inconsistency**	**Outcome quality**
Sensitivity	9	156 DLB 360 AD	Pathology (1) Biomarker-based + follow-up (1) Clinical diagnosis (7)	Visual + Semi-quantitative (4) Semi-quantitative (5)	Not serious	Not serious	Serious	70% (CI 47-87%) – 92% (CI: 61-100%)	HIGH	Serious	MODERATE
Specificity	9	156 DLB 360 AD	Pathology (1) Biomarker-based + follow-up (1) Clinical diagnosis (7)	Visual + Semi-quantitative (4) Semi-quantitative (5)	Not serious	Not serious	Serious	74% (CI: 57-88%) – 100% (CI: 73-100%)	HIGH	Serious	MODERATE

Accuracy	10	176 DLB 380 AD	Pathology (1) Biomarker-based + follow-up (1) Clinical diagnosis (8)	Visual + Semi-quantitative (4) Semi-quantitative (6)	Not serious	Not serious	Serious	72% (CI: 60-82%) – 96% (CI: 92-98%)	HIGH	Serious	MODERATE
AUC	5	117 DLB 312 AD	Clinical diagnosis (5)	Visual + Semi-quantitative (3) Semi-quantitative (2)	Not serious	Not serious	Serious	77.1% (CI NA) – 97% (CI NA, p<0.001)	HIGH	Not serious	VERY LOW
PPV	1	30 DLB 37 AD	Clinical diagnosis (1)	Visual + Semi-quantitative (1)	Not serious	Not serious	Not serious	86% (CI: 66-95%)	HIGH	NA	LOW
NPV	1	30 DLB 37 AD	Clinical diagnosis (1)	Visual + Semi-quantitative (1)	Not serious	Not serious	Not serious	85% (CI: 69-94%)	HIGH	NA	LOW
LR+	1	30 DLB 37 AD	Clinical diagnosis (1)	Visual + Semi-quantitative (1)	Not serious	Not serious	Not serious	4.46* (CI: 2.16–9.20) *AD vs DLB	MODERATE	NA	LOW
RELATIVE AVAILABILITY OF EVIDENCE: GOOD											

Table PICO 9. Please see legend for Table PICO 7.

PICO 9: Differentiate AD from FTLD											
Critical outcomes	**N. of papers**	**Sample size**	**Gold/ reference standard**	**FDG-PET assessment**	**Risk of bias**	**Index test methods**	**Applicability**	**Effect (CI)**	**Effect assessment**	**Effect inconsistency**	**Outcome quality**
Sensitivity	4	312 AD 173 FTLD	Pathology (1) Clinical diagnosis (3)	Visual (3) Semi-quantitative (4)	Not serious	Not serious	Not serious	80% (CI: 67-89) – 99% (CI 96-100)	HIGH	Not serious	LOW
Specificity	4	312 AD 173 FTLD	Pathology (1) Clinical diagnosis (3)	Visual (3) Semi-quantitative (4)	Not serious	Not serious	Not serious	63% (CI: 35-85) – 98% (CI: 87–100)	MODERATE	Serious	LOW
Accuracy	4	253 AD 135 FTLD	Pathology (2) Clinical diagnosis (2)	Visual (3) Semi-quantitative (4)	Not serious	Not serious	Not serious	87% (CI 69-96%) – 89.2% (CI: 75-96)	HIGH	Not serious	HIGH
AUC	2	261 AD	Clinical diagnosis (2)	Visual (1)	Not	Not serious	Serious	0.91 (CI: 0.85-0.97)	HIGH	Not serious	VERY LOW

		107 FTLD		Semi-quantitative (2)	serious			– 0.97 (CI NA, p<0.001)			
PPV	1	62 AD 45 FTLD	Clinical diagnosis (1)	Visual (1) Semi-quantitative (1)	Not serious	Not serious	Not serious	98% (CI: 88-100)	HIGH	NA	VERY LOW
NPV	1	62 AD 45 FTLD	Clinical diagnosis (1)	Visual (1) Semi-quantitative (1)	Not serious	Not serious	Not serious	74% (CI: 59-86)	MODERATE	NA	VERY LOW
LR+	1	62 AD 45 FTLD	Clinical diagnosis (1)	Visual (1) Semi-quantitative (1)	Not serious	Not serious	Not serious	29.88 (CI: 11.61-40.00)	HIGH	NA	VERY LOW
LR-	1	62 AD 45 FTLD	Clinical diagnosis (1)	Visual (1) Semi-quantitative (1)	Not serious	Not serious	Not serious	0.25 (CI: 0.13-0.40)	MODERATE	NA	VERY LOW
Other outcomes (logistic regression results)	1	27 AD 24 FTLD	Diagnosis at follow-up (1)	Visual (1) Semi-quantitative (1)	Not serious	Not serious	Not serious	SPM Maps (beta=1.414; p=0.019) increased concordance and accuracy for the classification of FTLD with respect to AD as compared to Clinical Scenarios (beta=0.671; p=0.291) and Standard FDG Images (beta=−0.041; p=0.945).	NA	NA	MODERATE
RELATIVE AVAILABILITY OF EVIDENCE: FAIR											

Table PICO 10. Please see legend for Table PICO 7.

PICO 10: Differentiate DLB from FTLD											
Critical outcomes	**N. of papers**	**Sample size**	**Gold/ reference standard**	**FDG-PET assessment**	**Risk of bias**	**Index test methods**	**Applicability**	**Effect (CI)**	**Effect assessment**	**Effect inconsistency**	**Outcome quality**
Sensitivity	1	27 DLB 98 FTLD	Clinical diagnosis	Semi-quantitative	Not serious	Not serious	Serious	71% (CI: 50-86)	MODERATE	NA	VERY LOW
Specificity	1	27 DLB 98 FTLD	Clinical diagnosis	Semi-quantitative	Not serious	Not serious	Serious	65% (CI: 55-75%)	LOW	NA	VERY LOW
Accuracy	1	27 DLB 98 FTLD	Clinical diagnosis	Semi-quantitative	Not serious	Not serious	Serious	66% (CI: 57-75%)	LOW	NA	VERY LOW
AUC	1	27 DLB 98 FTLD	Clinical diagnosis	Semi-quantitative	Not serious	Not serious	Serious	68% (CI NA, p<0.01)	LOW	NA	VERY LOW

RELATIVE AVAILABILITY OF EVIDENCE: LACKING

Table PICO 11. Please see legend for Table PICO 7.

PICO 11: Differentiate AD from VaD											
Critical outcomes	**N. of papers**	**Sample size**	**Gold/ reference standard**	**FDG-PET assessment**	**Risk of bias**	**Index test methods**	**Applicability**	**Effect (CI)**	**Effect assessment**	**Effect inconsistency**	**Outcome quality**
Sensitivity	1	51 AD 51 VaD	Clinical diagnosis	Semi-quantitative	Not serious	Very serious	Serious	100% (CI: 93-100%)	HIGH	NA	VERY LOW
Specificity	1	51 AD 51 VaD	Clinical diagnosis	Semi-quantitative	Not serious	Very serious	Serious	100% (CI: 93-100%)	HIGH	NA	VERY LOW
Accuracy	1	51 AD 51 VaD	Clinical diagnosis	Semi-quantitative	Not serious	Very serious	Serious	100% (CI: 96-100%)	HIGH	NA	VERY LOW
RELATIVE AVAILABILITY OF EVIDENCE: LACKING											

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