Diagnostic utility of FDG-PET in asymptomatic subjects at increased risk for Alzheimer's disease

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ABSTRACT

- Purpose: To assess the clinical utility of FDG-PET for detection of early signs of neurodegeneration in conditions of increased risk for Alzheimer's disease (AD) as defined by: subjective cognitive decline (SCD), evidence of cerebral amyloid-pathology, *APOE* ε4-positive genotype or autosomal dominant forms of AD (ADAD) in asymptomatic stages.
- 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 three different diagnostic scenarios.
- Results: The level of empirical study evidence for the use of FDG-PET to detect meaningful early signs of neurodegeneration was considered to be poor for ADAD and lacking for SCD and asymptomatic persons at risk based on *APOE* ε4-positive genotype or cerebral amyloid pathology. Consequently, and consistent with current diagnostic criteria, panelists decided not to recommend routine clinical use of FDG-PET in these situations and to currently mainly reserve it for research purposes.
- Conclusion: Currently, there is limited evidence on which to base recommendations regarding the clinical routine use of FDG-PET to detect diagnostically meaningful early signs of neurodegeneration in asymptomatic subjects with ADAD, with *APOE* ε4-positive genotype or with cerebral amyloid pathology and in subjects with SCD. Future prospective studies are warranted and in part already ongoing aiming to assess the added value of FDG-PET in this context beyond research applications.

Keywords

FDG-PET

Alzheimer's disease

SCD

ADAD

APOE

PSEN1

Amyloidosis

1. BACKGROUND

The lack of international clinical guidelines for the use of FDG-PET in the diagnosis of dementia has led the European Association of Nuclear Medicine (EANM) and the European Academy of Neurology (EAN) to outline joint recommendations aimed to guide clinicians in the use of the exam. The initiative included a set of 21 clinical questions, to be addressed based on literature evidence and expert consensus (Paper Recommendations)[1].

In this paper, we report the evidence assessment performed for the use of FDG-PET for the evaluation of conditions associated with increased risk for Alzheimer's disease (AD). For this review, we considered the following groups to be at increased risk for the development of AD: a) subjects with subjective cognitive decline (SCD), b) asymptomatic subjects carrying the Apolipoprotein E (APOE) ε4 allele c) subjects with evidence of cerebral amyloid-pathology and d) asymptomatic mutation carriers of PSEN1, PSEN2 or APP (leading to autosomal dominant forms of AD. It is important to note that the risk profiles in these groups are fundamentally different.

Subjective cognitive decline (SCD) is currently defined as a self-reported decline of cognitive performance in the absence of objective cognitive dysfunction or depression [2,3]. Subjects with SCD have been demonstrated to have a higher risk to develop incipient AD but they may also suffer from conditions other than AD and the diagnostic classification is still very heterogeneous[4]. Again, prediction of nature or timing of a potentially imminent cognitive decline is currently not reliably possible. Whereas the potential onset of disease may in principle be still years away in APOE ε4 –carriers, amyloid-positive subjects and also subjects with ADAD, the subjective symptoms in SCD indicate that neurodegenerative processes may already be ongoing in some of the affected persons.

Healthy subjects with evidence of cerebral amyloid-pathology, e.g. based on a positive amyloid PET scan, have been considered to be at higher risk for the development of mild cognitive impairment (MCI) and AD[5] . However, to date, several questions with regard to "amyloid-positivity" remain unresolved. The development of amyloid-pathology in the brain has been suggested to precede the onset of symptomatic disease probably for decades. This may also explain the high prevalence of cerebral amyloid-pathology in cognitively (still) healthy elderly subjects. Furthermore, no definite thresholds with regard to pathologically relevant "amyloid-positivity" have yet been defined. A prediction of the onset of symptomatic disease may thus be difficult or impossible in amyloid-positive subjects without additional diagnostic information, e.g. based on markers of neurodegeneration specific to the disease of disease [6].

Carriers of the *APOE* ε4-allele have an increased risk for sporadic AD and the ε4 allele appears to have a gene-dose effect on the age of onset. However, no exact prediction can be made

in the individual subject on the basis of the APOE-genotype alone with regard to the potential onset of cognitive decline[7].

ADAD on the other hand basically inevitably will lead to one of the familial forms of AD which are similar but not identical to the more prevalent sporadic form. Regarding disease onset, patients with ADAD usually suffer from early onset AD. An approximate prediction of symptomatic disease onset may be possible on the basis of the corresponding disease course of the affected parent[8]. However, presence or onset of ongoing preclinical disease may not easily be judged without suitable biomarkers.

Consequently, for all of the mentioned conditions, the evidence of neuronal injury may be crucial to document the onset of manifest neurodegenerative disease and/or prognosis of the future course. Several studies demonstrated abnormal findings using different imaging modalities including FDG-PET in the mentioned risk populations. Research guidelines explicitly recommend to obtain information on neuronal injury in addition to amyloid-status for risk assessment of AD in preclinical stages[6]. However, regarding the potential clinical value of FDG-PET in this context, it needs to be conclusively demonstrated whether abnormalities are specifically bond to the onset of the target neurodegenerative disease and their predictive value in the individual subject regarding the development of AD should be assessed.

Based on this background, three literature searches have been performed to assess the quality of evidence supporting the efficiency of FDG-PET for the evaluation of conditions at risk for AD, encompassing SCD, APOE4 and brain amyloidosis, and ADAD.

2. METHODS.

Seven panelists, four from EANM and three from EAN, were appointed to produce recommendations taking into consideration the incremental value of FDG-PET, as added on clinical-neuropsychological examination, for the evaluation of conditions at risk for AD. Consensus recommendations have been produced through a Delphi procedure based on the expertise of panelists, who were also informed about the availability and quality of evidence, assessed by an independent methodology group as described in Boccardi et al [9].

Briefly, we performed literature searches using harmonized PICO (Population, Intervention, Comparison, Outcome) question keywords edited by the experts, screened the studies for eligibility, extracted the data to assess their methodological quality, and provided an evidence assessment consistent with the EFNS guidance [10] and specific to FDG-PET studies [9].

2.1 PICO question(s) for this paper

For this review, the PICO questions asked whether *FDG-PET should be performed as adding diagnostic value (in terms of increased accuracy, and versus pathology, biomarker-based diagnosis or diagnosis at follow-up) as compared to standard clinical/neuropsychological assessment alone, to pick early signs of neurodegeneration (i) in patients with subjective cognitive impairment; (ii) in asymptomatic subjects with risk factors for AD (based on APOE ε4 status or amyloid positivity); (iii) in asymptomatic subjects with familial forms of AD.*

2.2 Eligibility criteria

Only original full papers published in English on international impacted journals were considered, excluding reviews, management guidelines, abstracts and gray literature. Any sample size was allowed if pathology was the gold standard for diagnosis. Otherwise, a number of 15 subjects was defined *a priori* as the minimum sample size.

2.3 Literature search

Literature searches were performed using Medline database, until November 2015 for PICO 6 and January 2016 for PICOs 4 and 5. A first independent screening of all included studies was performed by a neurologist or by a nuclear medicine physician with expertise in neurodegenerative dementing disorders, who could include additional papers based on personal knowledge or tracking from references of papers. The full text of these potentially eligible studies has then been independently assessed for eligibility by the methodology team.

2.4 Data extraction and quality assessment

The quality of evidence was assessed consensually within the methodology group 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[9]. Data extractors for this review were DA for PICOs 4 and 5 and CF for PICO 6. Critical outcomes were validated measures of test performance (accuracy, sensitivity, specificity, AUC, positive and negative predictive values and likelihood ratios. An additional outcome, specific to PICO 4, was the accuracy in differentiating SCD due to neurodegenerative conditions from subjects without neurodegenerative disorders. This was considered a proxy outcome, the elective one consisting of identification of SCD converters versus non-converters.

A final assessment of relative availability of evidence was formulated, keeping into account all of the 21 PICOs. This ranking was summarized as very poor/lacking, poor, fair or good.

3. RESULTS

For the three PICOs included in this review, of the 170 papers were identified by panelists, 31 reported the comparison of interest and have been examined by the methodology group. Of these, only 2 did contain the critical outcomes, properly quantifying FDG-PET diagnostic utility, and both related to PICO 6 (picking early signs of neurodegeneration in asymptomatic subjects with familial forms of AD; Figure 1). Our assessment denoted that these studies provided limited evidence of utility of FDG-PET in supporting the evaluation of conditions at risk for AD in asymptomatic persons. Panelists decided not to recommend clinical use, consistent with current diagnostic criteria [6,11]. FDG-PET should be predominantly reserved to research purposes (Table 1, [1]).

3.1 PICO 04: FDG-PET in subjective cognitive decline (SCD)

Among the 15 papers identified and screened by the referent panelist (JA), 7 were sent to the methodology group for data extraction and assessment (see Figure 1 - PICO 4). Three papers were excluded; in details, [12,13] used SCD subjects as a control group, to assess the hypometabolism in patients with defined diagnoses; the aim of the third study [14] was to investigate whether depression was correlated to AD-like changes in FDG-PET. The data extraction table is available at (https://drive.google.com/file/d/0B0_JB3wzTvbpcjhUY29fWThIcFE/view?usp=sharing).

Critical outcomes were not available in any of the examined papers, denoting lack of objective evidence in support of an incremental diagnostic value of FDG-PET in this case. Papers were anyway assessed considering the available results, in order to report most of the available information, potentially useful to panelists' decisions. Mosconi and colleagues [15] provided proxy outcomes, reporting that the cerebral metabolic rate of glucose consumption (CMRglc) of the parahippocampal gyrus is able to distinguish SCD from healthy controls with 71% (CI 42-92%) sensitivity, 79% (CI 49-95%) specificity and 75% (CI 55-89%) accuracy. No evidence of conversion nor biomarker confirmation of disorder was available for these SCD subjects. Moreover, this paper should have not entered the analysis as it did not meet the minimum sample size requested for this PICO (involving only 14 SCD ApoE ε4 carriers). The 3 remaining papers reported only patterns of metabolism associated to SCD. Inconsistency of findings among them was serious. The hypometabolism in the precuneus, described in two studies [16,17] was not confirmed

in another study by Brugnolo et al.[18]. We underline that the different hypometabolic patterns identified for SCD subjects cannot be reliably attributed to pathological neurodegeneration due to the study design of these papers.

Taking into account the availability of formal evidence for all of the PICOs within the entire project, the level of evidence about the clinical utility of FDG-PET in detecting early signs of neurodegeneration in SCD subjects was assessed as lacking. Agreement was achieved on Delphi round I, with 6 panelists deciding not to recommend clinical use.

3.2 PICO 05: FDG-PET in asymptomatic subjects at risk for AD

Among the 45 papers identified and screened by the referent panelist (JA), only 11 qualified for further analysis and were sent to the methodology group (see Figure 1 - PICO 5). Of these, [19,20][21]) were excluded, since they did not include the target population. The data extraction table for this PICO is available at (https://drive.google.com/file/d/0B0_JB3wzTvbpZGstOHUwQk5DYTg/view?usp=sharing).

In all of the appropriate papers, subjects were characterized for APOE. Three studies [20,22,23] reported also amyloidosis quantification through cerebrospinal fluid. Critical outcomes were not available in any of the examined papers, denoting lack of objective evidence in support of an incremental diagnostic value of FDG-PET in this case.

Papers were anyway assessed considering the available results in order to report most of the available information, potentially useful to panelists decisions considering the available results. A study by [24] was the only one providing a longitudinal assessment, denoting a longitudinal CMRgl decline in APOE ε4 carriers, as compared to non-carriers, in brain regions typically involved in AD (possibly suggestive of "early signs of neurodegeneration"). Many of the other papers had low risk of bias and good consistency of results. However, with regard to the observed hypometabolism they did not allow to distinguish between acquired neurodegenerative dysfunction versus preexisting differences in baseline metabolism (none of these papers had any follow up, or any data about neither clinical conversion, nor comparison with any independent marker of AD). Thus, the only outcome available in the examined papers was the metabolic pattern associated to subjects having risk factors for AD. Hypometabolism in the precuneus and posterior cingulate associated to presence of the APOE ε4 allele was the most common finding across studies [20,22–28], but the origin and potential diagnostic role of this hypometabolism cannot be further assessed due to the limitations in study design.

Based on these data, the availability of formal evidence on the clinical utility of FDG-PET to pick up early signs of clinically meaningful neurodegeneration in asymptomatic subjects with risk factors for AD was assessed as lacking. Agreement was achieved on Delphi round I, with 5 panelists deciding not to recommend routine clinical use.

3.3 PICO 06: FDG-PET in asymptomatic subjects with familial forms of AD

Among the 110 papers identified by the referent panelist (AD), 13 were eligible for further assessment and sent to the methodology team (see Figure 1 - PICO 6). Among these, seven papers were excluded for the following reason: six studies [29–34] were case reports of new mutation carriers, who already had dementia.[35] defined "familial form" as presence of at least one first-degree relative with a clinical diagnosis of AD, without mutation and included symptomatic subjects. Atypical variants of sporadic AD are described in [36]. The data extraction table is available at https://drive.google.com/file/d/0B0_JB3wzTvbpYmZQWkZiY1FCazQ/view?usp=sharing

Critical outcomes were available in 2 of the examined papers (see Table PICO 6).[37,38] found 100% of sensitivity, 83-100% specificity range and 97-100% accuracy range. These included only 13 asymptomatic ADAD due to Presenilin-1 mutation and 30 non-carriers. Data provided a high level of evidence that the posterior cingulate cortex hypometabolism assessed semi-quantitatively with SPM could discriminate ADAD from controls with high sensitivity and specificity, although with large confidence intervals. Concerns 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 for PSN1, PSN2 and APP carriers [37–42].

Relative to the evidence available for the other PICOs, the availability of formal evidence supporting diagnostic utility of FDG-PET to detect early signs of neurodegeneration in presymptomatic subjects with ADAD, carriers of mutation in PSEN1 was assessed as poor. Agreement was achieved on Delphi Round III, with 5 panelists deciding not to recommend routine clinical use in this population.

4. DISCUSSION

In this paper, we assessed the evidence of utility of FDG-PET for the evaluation of conditions defining an increased risk for AD. We found poor availability of evidence of utility to pick early

signs of neurodegenerations in ADAD, and evidence was lacking for SCD and asymptomatic persons at risk based on *APOE* e4-positivity or brain amyloidosis.

Several previous studies have in general been able to report abnormalities in imaging tests, including FDG-PET in all of the mentioned risk populations. The reasons proposed during the Delphi panel not to support the use of FDG-PET as a routine clinical diagnostic tool in populations with increased risk for AD mainly relied on the lack of convincing evidence regarding the neurodegenerative nature of the lower metabolism observed in the mentioned risk populations as well as the missing information on their individual predictive value.

PICO 4- SCD: In SCD, characteristic hypometabolic changes have been described in some studies [16,17] but were missing in others[18]. This heterogeneity in the findings may mirror the heterogeneity in the diagnostic group of SCD overall, possibly as a consequence of the differing criteria for SCD as well as of the variability of underlying pathologies. Nevertheless, it is possible that abnormal findings in some SCD-subjects may be predictive for future decline to AD, particularly if additional AD-risk factors such as *APOE* ε4-positive genotype or cerebral amyloid-pathology or a positive family history in a direct relative can be identified [15,43,44]. In theory, evidence of FDG-PET showing hypometabolism in posterior cingulate gyrus and pre-cuneus could allow the early detection of neurodegeneration in selected subjects. To date, however, it has not yet been demonstrated conclusively that hypometabolic changes in SCD reflect AD-type of neurodegeneration or that they would be prognostically relevant. Thus, FDG-PET should currently still be predominantly reserved to research purposes and cannot yet be recommended for routine clinical use in this group.

PICO 5- At risk for AD due to cerebral amyloid-pathology or APOE ε4-positivity in asymptomatic subjects: Amyloid-positivity in MCI has been demonstrated to be predictive for conversion to dementia [45] and a higher risk of cognitive decline has also been demonstrated in asymptomatic amyloid-positive subjects [5]. According to recent research guidelines, a marker of neuronal injury to amyloid-positivity increases the level of confidence that the subject has Alzheimer's disease at a preclinical stage [6]. FDG-PET may in principle play this role to capture the onset of neurodegeneration in amyloid-positive asymptomatic subjects. However, the long presymptomatic period of amyloid-buildup, presumably lasting for decades, limits the utility of FDG-PET for clinical purposes in this group. Similar limitations apply to the clinical application of FDG-PET in the diagnostic assessment of asymptomatic APOE ε4-carriers. Hypometabolic changes have been

described in asymptomatic APOE ε4-carriers. On the one hand, the topographical overlap with the typical abnormalities in AD as well as the gene-dose effect on these changes suggests that the procedure does detect neurodegenerative changes. However, the detection of such abnormalities even in young APOE ε4-carriers[28] at risk for AD at old age raises questions with regard to the diagnostic/prognostic value of these findings particularly with regard to prediction of the time of symptomatic onset.

Thus, for both risk groups discussed here, the selection of subjects possibly benefiting from further diagnostic assessment as well as the definition of the appropriate time for the diagnostic imaging procedure may hardly be possible on clinical grounds in subjects free from any cognitive symptoms. Furthermore, at least to date the prognostic value and the therapeutical relevance of an abnormal FDG-PET scan with regard to potential time to conversion would be unclear in both groups. Therefore, FDG-PET should currently be applied only within research studies in these groups.

PICO 6- ADAD: Detection of hypometabolic abnormalities resembling the typical findings in AD have been observed in ADAD even years before onset[38,42,46,47]. These results generally suggest, but not prove, that neurodegenerative changes may be captured with FDG-PET in ADAD before clinical onset of disease. Also, the clinical value of these findings remains difficult to interpret regarding the fact that these subjects were free of cognitive impairment and that information about the time-to-conversion to symptomatic disease may not be easily derived from these imaging findings. Interestingly, in a study on presymptomatic ADAD, Benzinger and colleagues reported that linear extrapolation of the FDG-PET data would have created the appearance of increased glucose metabolism 25 years before the estimated age of clinical onset[42]. Thus, it may be difficult to draw clinical conclusions in ADAD on the basis of FDG-PET and further longitudinal studies are warranted. Generally, a diagnosis of Alzheimer's disease or prognosis of imminent dementia is of limited value and ethically questionable as long as disease modifiers are not available, and time-to-conversion cannot be accurately defined. In cases of familial AD, FDG-PET may potentially be applied to detect or rule out the onset of neurodegeneration but preferably not in clinically completely asymptomatic cases. Once therapeutic tools become available, FDG-PET might be considered as a useful biomarker to detect early ongoing neurodegeneration and identify subjects eligible for therapy as well as to measure therapy response.

The decision of the panel not to recommend FDG-PET for clinical routine application in the mentioned risk-populations does not automatically imply that this method may never be valuable to answer individual questions in these subjects. Ongoing studies may provide further evidence on this matter. In general, this literature search has not focused on combinations of the mentioned risk factors e.g. APOE ε4-positive status plus SCD [15] or amyloid-positivity plus SCD [48]. Particularly this type of risk-enrichment may allow to define groups of subjects who could potentially benefit from adding FDG-PET as a marker of neuronal injury. However, also for these scenarios, systematic studies documenting the individual value would be warranted.

To improve the quality of future studies in this context, it would be advantageous to sharpen the definition of some of the risk conditions per se. Whereas the assessment of the APOE-genotype or evidence of ADAD provides unequivocal information, the definition of SCD is still very heterogeneous and no standardized thresholds for amyloid-positivity are currently established.

On the other hand, limitations are still present also in the validation of FDG-PET. Despite its very long use in clinical routine, neither definite thresholds for test-positivity nor standardized reading procedures are in place[49]. Furthermore, the considerable variation of findings in controls and atrophy in non-AD conditions may be a major confounding factor. Thus the minor changes in PCC and precuneus seen in a few group-comparisons e.g. in ADAD or amyloid-positive subjects may not translate to individual diagnostic use. To improve on that, it may be necessary to optimize and standardize image reconstruction parameters as well as to establish a tighter control of definition and functional state of control subjects.

The literature reviews [22,31–38] brought to light that specific methodological issues have so far limited the collection of formal evidence of efficiency of FDG-PET in the diagnostic work-up of subjects with increased risk for AD. The unknown and potentially very long gap between the imaging test and the actual onset of disease represents another limitation. At the asymptomatic stage, some 10 years can be expected before subjects develop manifest dementia, even in presence of preclinical disease. Very few studies can do that long follow-up without substantial attrition. Thus, existing literature is quite sparse. Even if it could be demonstrated that FDG-PET can be predictive so long before clinical disease onset, the value of such an information would be questionable without access to disease modifying therapies. On the other hand, studies indicate that the predictive power of FDG PET may be best in the last 2 to 3 years before onset of actual dementia. Thus, with regard to clinical relevance, it

could be expedient to focus formal efforts to validate the diagnostic value on that period [49].

Another problem lies in the lack of quantitative information on longitudinal patient outcomes (health, quality of life, mortality, institutionalization) following FDG-PET-based diagnosis. Even when accepting accuracy studies as proxies for more appropriate patient management [26,27] many of these limitations remain. Furthermore, the validation of PET-results in risk populations is limited by the lack of pathology confirmation and the diagnostic improvement after FDG-PET is difficult to judge without head-to-head comparison between FDG-PET and clinical assessment versus the same gold standard[22]. 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. As for many PET-tracers, the lack of dedicated support of an industry sponsor with exclusive rights to the tracer limits the performance of expensive clinical trials. For future trials it could be recommended to use biomarker-based diagnosis as the reference standard, to monitor test performance quantitatively and in a standardized manner and a to perform a systematic blinded comparison between FGD-PET and clinical diagnosis.

It can be expected that further data will be collected with regard to the time-course of disease in the risk-populations discussed here, as well as on the diagnostic value of various imaging biomarkers. These data may change the conclusions drawn by the panel in this study.

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Figure 1. PRISMA flowchart of selected papers for PICOs 4-6 [50]

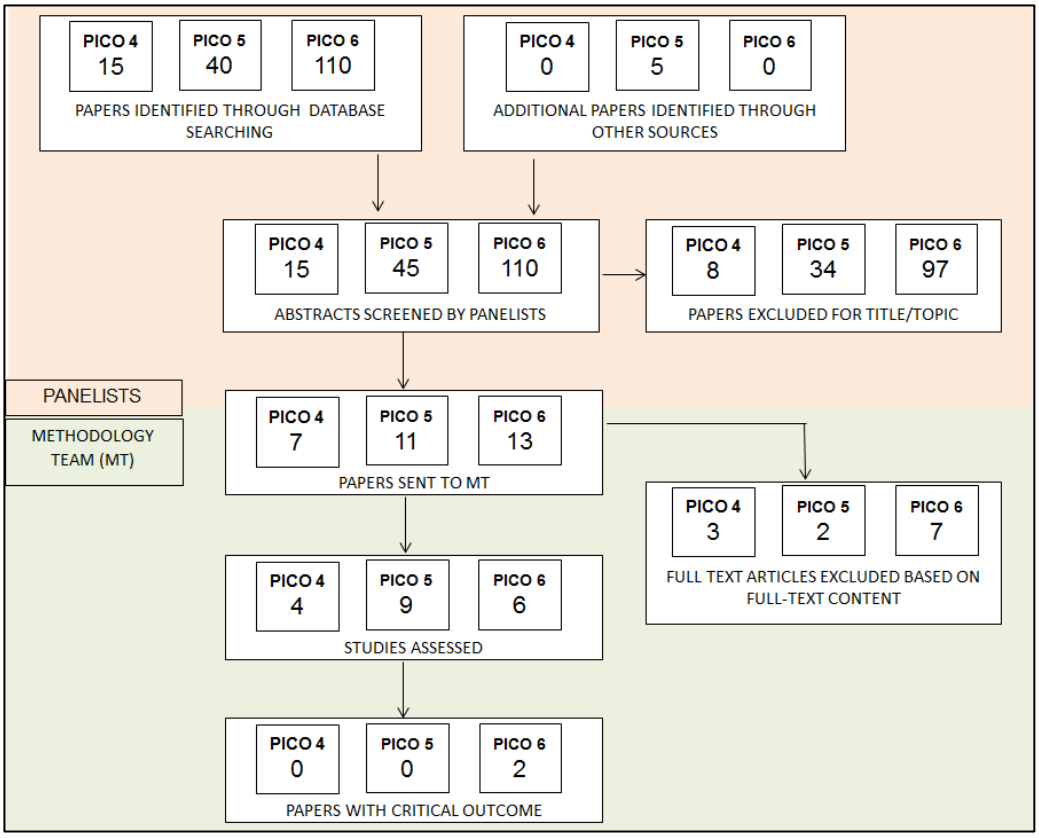

Table 1. Availability of evidence and panelists' decisions supporting the use of FDG-PET in the evaluation of conditions at risk for Alzheimer's disease

PICO	RELATIVE AVAILABILITY OF EVIDENCE	PANELISTS' RECOMMENDATIONS	MAIN REASONS FOR FINAL DECISION
4 – SCD	Lacking	NO	Only for research purposes.
5 – At risk for AD	Lacking	NO	Only for research purposes.
6 – ADAD	Poor	NO	Only for research purposes.

Table PICO 1. Table reports the quality of evidence for each critical outcome.

PICO6: Differentiate subjects with autosomal dominant AD (ADAD) from healthy people											
Critical outcomes	**N. of papers**	**Sample size**	**Gold/reference standard**	**FDG-PET assessment**	**Risk of bias**	**Index test method**	**Applicability**	**Effect (CI)**	**Effect assessment**	**Effect inconsistency**	**Outcome quality**
Sensitivity	2	13 ADAD 30 Non-carriers	Mutation status (PSEN1)	Semi-quantitative	Not serious	Not serious	Serious	100% (CI: 59-100%) – 100% (CI: 85-100%)	HIGH	Not serious	HIGH
Specificity	2	13 ADAD 30 Non-carriers	Mutation status (PSEN1)	Semi-quantitative	Not serious	Not serious	Serious	83% (CI: 36-100%) – 100% (CI: 59-100%)	HIGH	Not serious	HIGH
Accuracy	2	13 ADAD 30 Non-carriers	Mutation status (PSEN1)	Semi-quantitative	Not serious	Not serious	Serious	97% (CI: 82-100%) – 100% (CI: 77-100%)	HIGH	Not serious	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.

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