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Scottish Intercollegiate Guidelines Network (SIGN) Guidance on Dementia. The investigation of suspected dementia (SIGN 168) with focus on biomarkers.

Graham A Mackay, Claire Gall, Ravi Jampana, Carolyn Sleith, Gregory Lip.

Affiliations below.

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Abstract:
This is an executive summary of the recent guidance produced by the SIGN dementia guideline group with regards to the investigation of suspected dementia. This is a sub-section of the broader SIGN 168 guideline released in November 2023. The guideline group included clinicians with expertise in Old Age Psychiatry, Neurology, Radiology and Nuclear Medicine supported by colleagues from the SIGN and Healthcare Improvement Scotland (HIS) teams. There was representation from carers and support organisations with experience of dementia, to ensure the recommendations were appropriate from the perspective of the people being assessed for possible dementia and their carers. As the 2018 National Institute for Health and Clinical Excellence (NICE) dementia review, included a review of the evidenced investigation of dementia, the SIGN guideline development group decided to focus on a review on the up to date evidence regarding the role of imaging and fluid biomarkers in the diagnosis of dementia.
In order to give context to the consideration of more advanced diagnostic biomarker investigations, the guideline and this summary includes the NICE guidance on the use of standard investigations as well as more specialist investigations. The evidence review supports consideration of the use of structural imaging, nuclear medicine imaging and established Alzheimer's cerebrospinal fluid (CSF) biomarkers (amyloid and tau) in the diagnosis of dementia. Although routine use of amyloid PET imaging was not recommended, its potential use, under specialist direction, in patients with atypical or young onset presentations of suspected Alzheimer's dementia was included as a clinical good practice point.

Corresponding Author:
MB chB, MD(hons) Graham A Mackay, Aberdeen Royal Infirmary, Neurology, Foresterhill, AB25 2ZN Aberdeen, United Kingdom of Great Britain and Northern Ireland, graham.mackay2@nhs.scot, grahammackay@doctors.org.uk

Affiliations:
Graham A Mackay, Aberdeen Royal Infirmary, Neurology, Aberdeen, United Kingdom of Great Britain and Northern Ireland
Claire Gall, Queen Elizabeth University Hospital, Neurology, Glasgow, United Kingdom of Great Britain and Northern Ireland
Ravi Jampana, Queen Elizabeth University Hospital, Neuroradiology, Glasgow, United Kingdom of Great Britain and Northern Ireland
Carolyn Sleith, Health Improvement Scotland, Knowledge Management Team, Edinburgh, United Kingdom of Great Britain and Northern Ireland
Gregory Lip, University of Liverpool, Liverpool Centre for Cardiovascular Science, Liverpool, United Kingdom of Great Britain and Northern Ireland

Scottish Intercollegiate Guidelines Network (SIGN) Guidance on Dementia. The investigation of suspected dementia (SIGN 168) with focus on biomarkers. Executive Summary

Graham Andrew Mackay[1], Claire Gall[2], Ravi Jampana[3], Carolyn Sleith[4], Gregory Y. H. Lip[5]; on behalf of the SIGN Dementia Guideline Development Group

1. Department of Neurology, Aberdeen Royal Infirmary, Foresterhill, Aberdeen, AB25 2ZN
2. Department of Neurology, Queen Elizabeth University Hospital, 1345 Govan road, Glasgow G51 4TF, United Kingdom
3. Department of Neuro-radiology, Queen Elizabeth University hospital, 1345 Govan road, Glasgow G51 4TF, United Kingdom
4. Healthcare improvement Scotland
5. Liverpool Centre for Cardiovascular Science at University of Liverpool, Liverpool John Moores University and Liverpool Heart & Chest Hospital, Liverpool, United Kingdom; and Danish Center for Health Services Research, Department of Clinical Medicine, Aalborg University, Aalborg, Denmark

Correspondence: Dr Graham MacKay (graham.mackay2@nhs.scot)

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In order to give context to the consideration of more advanced diagnostic biomarker investigations, the guideline and this summary includes the NICE guidance on the use of standard investigations as well as more specialist investigations. The evidence review supports consideration of the use of structural imaging, nuclear medicine imaging and established Alzheimer's cerebrospinal fluid (CSF) biomarkers (amyloid and tau) in the diagnosis of dementia. Although routine use of amyloid PET imaging was not recommended, its potential use, under specialist direction, in patients with atypical or young onset presentations of suspected Alzheimer's dementia was included as a clinical good practice point.

Introduction

While a diagnosis of dementia can often be made following a clinical and cognitive assessment by an experienced clinician, it is not always possible to make a definite diagnosis. In addition, the subtype of dementia may not always be apparent, but its recognition may be important in guiding future prognosis and treatment options. There is an understandable drive toward trying to provide patients with a more accurate diagnosis as early as possible, to allow them and their carers to plan their futures and in consideration of potential treatments. An evaluation of the potential role of investigations in providing additional information to support the diagnosis of dementia subtypes for patients in life is therefore of vital importance.

This article is an executive summary of the recent guidance produced by the SIGN dementia guideline development group with regards to the investigation of suspected dementia, which is a sub-section of the broader SIGN 168 guideline released in November 2023 [1]. The guideline is based on a detailed review of the evidence, which provides clinicians with guidance on the diagnostic evaluation of patients based on the suspected dementia subtypes being considered.

The multidisciplinary guideline group included clinicians with expertise in Old Age Psychiatry, Neurology, Radiology and Nuclear Medicine supported by colleagues from the SIGN and Healthcare Improvement Scotland (HIS) teams. There was also representation from carers and support organisations with experience of dementia, to ensure the recommendations were appropriate from the perspective of the people being assessed for possible dementia and their carers.

Methodological Considerations

The development of the guideline followed established SIGN methodology based on a systematic review of the evidence. SIGN is a collaborative network of clinicians, other healthcare professionals, and patient organisations and is part of NHS Healthcare Improvement Scotland. Further details about SIGN and the guideline development methodology are contained in *SIGN 50: A Guideline Developer's Handbook* (see www.sign.ac.uk)[2].

The National Institute for Health and Clinical Excellence (NICE) published a comprehensive guideline on the assessment, management and support for people living with dementia and their carers for England and Wales in December 2018 [3]. To avoid duplication of effort,

SIGN used and updated evidence tables produced by NICE, where appropriate, as a basis for the guidelines considered judgments..

As the 2018 NICE dementia review [3], included a review of the accepted evidenced investigation of dementia, the SIGN guideline development group decided to focus on a review of the up to date evidence regarding the role of imaging and fluid biomarkers in the diagnosis of dementia. The findings of the review are summarised in this paper. In order to give context to the consideration of more advanced diagnostic biomarker investigations, the guideline and this summary includes the NICE guidance on the use of more standard investigations as well as more specialist investigations [3].

The evidence for this guideline was collected from Cochrane Library reviews, other published meta-analyses and systematic reviews, other evidence-based management guidelines in dementia, and original scientific papers published in peer-reviewed journals before May 2022.

For each topic, a systematic review of the literature was carried out using an explicit search strategy. Databases searched include Medline, Embase, PsycINFO and the Cochrane Library. The year range covered was 2000–2021. SIGN recommendations are based on systematic reviews of best available evidence, and the strength of the evidence is indicated as levels 1, 2, 3 or 4 (Appendix 1). The evidence ratings given within the guideline are included in bold grey texts with alignment to the right at the end of the related paragraphs in this paper. This is assessed and applied in a formal evidence to recommendations process. SIGN refers to this as “Considered Judgment”. Where evidence supports it a strong or conditional recommendation is made. Recommended best practice (“good practice points”), based on the clinical experience of the guideline development group are also included. Evidence based

"Recommendations" are indicated by the symbol **R** and consensus "Good practice points" by the ✔ symbol in this paper, as well as in the full guideline [1,2].

Summary of evidence search strategies (Appendix 2 and 3).

Results

Initial investigative procedures

Following a comprehensive clinical assessment, further investigations can be considered to help rule out other causes in people presenting with cognitive decline, or to help diagnose dementia subtype in those with a diagnosis of dementia.

The following recommendation is reproduced from the NICE guideline on assessment, management and support for people living with dementia and their carers [3].

4

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

Only consider further tests if:

- it would help to diagnose a dementia subtype and
- knowing more about the dementia subtype would change management.

Diagnosing suspected Alzheimer's disease

In most cases of Alzheimer's disease a diagnosis is made based on clinical symptoms. The gold standard for a diagnosis of Alzheimer's dementia is confirmation of the typical neuropathological findings in people with symptomatic cognitive impairment [4].

Clinical diagnostic criteria for Alzheimer's disease, established by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA),[5] show good sensitivity (98%) but low

specificity (69%) when compared with neuropathological confirmation [6].

3

Positron emission tomography

Positron emission tomography (PET) is a functional imaging technique that uses radioactive substances, known as radiotracers, to visualise changes in metabolic processes and other physiological activities, including blood flow [7]. A ligand that binds to or is taken up by a specific target is labelled with a radioisotope, enabling its visualisation to produce images.

Fluorodeoxyglucose (FDG)-PET, using a tracer taken up by glucose-using cells, is already established for use in dementia diagnosis [3].

Amyloid PET (aPET) utilises a ligand that binds selectively to amyloid plaques. There are three 18F-labelled aPET tracers licensed for use; 18F-Florbetaben (Neuraceq™), 18F-Florbetapir (Amyvid™), and 18F-Flutemetamol (Vizamyl™). The Amyloid Imaging Taskforce report (2013) recommends appropriate-use criteria for aPET in selected patients with MCI, atypical Alzheimer's disease, suspected mixed dementia or young onset dementia [8].

4

There are also tau-specific PET ligands, which enable binding and visualisation of tau proteins in the brain. Tau PET is not considered here.

Interpreting the evidence base

Narrative reviews highlight the difficulties which arise in developing and collating the evidence base on aPET for Alzheimer's disease [8, 9].

- While aPET positivity may correlate well with amyloid brain pathology, amyloid brain pathology does not necessarily equate to Alzheimer's disease dementia.
- Study populations vary in age and stage of dementia as well as with respect to comorbidities. Confounding of studies by age is a problem given that 20–40% of cognitively healthy people aged over 60 have elevated levels of amyloid.

• A variety of research and commercially available tracers are used.

• Methods of processing and interpreting scan images are not standardised. A range of visual and quantitative methods are encountered across the literature.

• Reference standards and how they are applied varies across studies. Gold standard neuropathological diagnosis is rarely used and since postmortem studies recruit patients at the end of life these will over represent participants with the most advanced disease.

• Many outcomes are explored including diagnostic accuracy, clinical utility and prediction of disease progression.

Comparison of aPET and FDG-PET

A diagnostic accuracy study (n=101) compared ante mortem aPET (using the research ligand 11C-Pittsburgh compound B (PIB)) with antemortem FDG-PET for post mortem neuropathological diagnosis of dementia. Participants were recruited from academic memory research centres and there was an emphasis on early-onset dementia (mean age 67.2 years). The scan to post mortem interval was 4.4 years. At post mortem 32 participants had primary Alzheimer's disease, 56 had non-Alzheimer's disease pathology and 13 showed mixed Alzheimer's disease/frontotemporal lobar degeneration. Both aPET and FDG-PET had high accuracy for predicting intermediate-to-high Alzheimer's disease neuropathological change (ADNC) (sensitivity 96% (95% CI 89% to 100%) vs 80% (95% CI 68% to 92%); specificity 86% (95% CI 76% to 95%) vs 84% (95% CI 74% to 93%)). Amyloid PET had statistically significantly better sensitivity than FDG-PET for detection of intermediate high ADNC. There was no significant difference in specificity between the modalities. When the two scans were congruent the sensitivity for determining AD pathology was 97% with specificity 98%. Nine out of 24 participants with incongruent scan findings had co-occurring Alzheimer's

disease and non-Alzheimer's disease pathology [10].

2+

A database modelling study with participants from the Alzheimer Disease Neuroimaging Initiative (ADNI) database (n=319, average age 72–73 years) examined the predictive value of 18F-florbetapir and 18F-FDG-PET for conversion to Alzheimer's disease in people with MCI. FDG-PET had a higher predictive value in the model than aPET. The best prediction accuracy was attained by combining both scans with non-imaging variables including high risk apolipoprotein E and the MMSE [11]. **3**

Amyloid PET for differentiating between Alzheimer's disease and mild cognitive impairment A systematic review with meta-analysis reported pooled weighted sensitivities and specificities for aPET in differentiating patients with Alzheimer's disease from healthy control patients. For F-florbetapir these were 89.6% (95% CI 84.2% to 93.6%) and 87.2% (95% CI 81.7% to 91.6%) respectively (seven studies, n= 181). For F-florbetaben pooled weighted sensitivity was 89.3% (95% CI 82.7% to 94.0%) and specificity was 87.6% (95% CI 80.4% to 92.9%)(four studies, n=131). Meta-analysis of flutemetamol studies was not possible. Most studies in the analysis were case control studies. One study included in the analysis had brain pathology as the reference standard. Participants (n=49, 39 Alzheimer's disease, 10 normal cognitive status) with life expectancy of less than six months were recruited. The sensitivity and specificity for distinguishing participants with Alzheimer's disease from healthy controls was 97.4% and 100% respectively [12].

2+

An overlapping systematic review examined and compared the diagnostic accuracy of the three 18F tracers for Alzheimer's disease where study populations included those with Alzheimer's disease, those with MCI and cognitively normal individuals. Meta-analysis indicated that there was little difference between the accuracy of the tracers and highlighted

that specificity was greater for identifying people with Alzheimer's disease when compared with cognitively normal participants than from distinguishing between people with Alzheimer's disease and those with MCI [13]. **2+**

Amyloid PET for differentiating between Alzheimer's disease and other forms of dementia

A systematic review of the use of 18F-labelled PET tracers identified two studies examining diagnostic accuracy for differentiating between Alzheimer's disease and non-Alzheimer's disease. In the first study (n=107), with clinical judgement as reference standard, sensitivity and specificity for distinguishing between AD and non-AD were low (61.6% and 57.1% respectively). Assessment of external validity of the study was limited as detailed information on the study population was not provided. The second study (n=109) reported high sensitivity for differentiating between Alzheimer's disease (n=30) and frontotemporal lobar degeneration (n=11), dementia with Lewy bodies (n=7), vascular dementia (n=4), and Parkinson disease (n=5). Sensitivity for all groups was 96.7% and specificity ranged from 71.4% to 100%. The small numbers in the studies limit the conclusions which can be drawn [12]. **2+**

Clinical utility of amyloid PET

A systematic review exploring the outcomes measured in clinical utility studies of aPET identified 32 studies (including protocols) published between 2012 and 2020. Twenty five studies (78%) examined impact on diagnosis including change in diagnosis and confidence in diagnosis. Seventeen studies (53%) reported on change in patient management including change of medication, additional investigations, referral for counselling or onto a clinical trial. Few studies looked beyond these clinician-centred outcomes to patient and caregiver-centred outcomes such as anxiety, quality of life and coping [14].

A well-conducted systematic review with literature search [14] identified studies on the clinical utility of aPET where both a pre-aPET working diagnosis and post-aPET final diagnosis were available for study participants with cognitive complaints. Across seven studies (n=1,142) the diagnosis changed due to aPET scan information in 31.3% (n=357) of cases. Where the pre-scan diagnosis was non-Alzheimer's disease (n=338) there were 135 patients who had a positive aPET scan, of whom 100 (74.1%) had their diagnosis changed to Alzheimer's disease.

In subgroup analysis use of aPET led to a change in patient management for 72.2% of those scanned where findings were available immediately (three studies, n=740) compared with 55.5% of control cases (delayed scan reporting, one study, n=299). In a subgroup of patients meeting the appropriate use criteria (two studies, n=211) there was change in patient management for 41.4%.

Diagnostic confidence was assessed in a range of ways and as a subjective measure was dependent on clinician expertise. Across six studies (n=725) the systematic review estimated that aPET increased diagnostic confidence/certainty overall by a mean of 12.7% +/- 35% with a decrease in confidence associated with negative aPET cases [15].

2++

Several additional longitudinal studies published since the systematic review, have each identified changes in diagnosis, diagnostic confidence and/or patient management [16-20]. One study was from the UK. This retrospective single-arm study examined the utility of aPET with 18F-florbetapir for patients attending a tertiary referral clinic. Of 100 patients investigated, most of whom were categorised as having young-onset dementia and/or dementia with atypical clinical features, aPET was positive in 49 patients and led to a change in diagnosis in 30 cases and a change in management in 42 cases, including addition of medication or enrolment into clinical trials [21].

Considerations for the use of amyloid PET

Amyloid PET does not involve a lumbar puncture, a procedure that some people do not find acceptable, which may make it preferable to using CSF biomarkers.

Amyloid PET does involve a scan with radiation exposure. Whilst there is agreement that radiation exposure is detrimental, with repeated or accumulated exposures linked to harmful effects including cancer, there is no agreed cut off. General consensus is that any radiation exposure is potentially harmful. All CT and Nuclear Medicine imaging come under Ionising Radiation Medical Exposure Regulations IR(ME)R [22]. Most health-related exposure works on the principle of ALARA (as low as reasonably achievable).

Doses are variable between centres and scanners. Dose from ionising radiation is measured in milli Sieverts (mSv). The Administration of Radioactive Substances Advisory Committee (ARSAC) guidance (January 2022) gave the following effective dose targets for relevant scans: dopamine transporter single-photon emission computed tomography (DaT) SPECT 4.6 mSv, perfusion SPECT 5.8 mSv, FDG-PET 4.8 mSv, aPET 5.8–6.9 mSv, CT of the brain is around 2 mSv. To put this into context, on average people in the UK are exposed to approximately 2.7 mSv of background radiation per year [23].

In young people with suspected dementia, a brief discussion regarding the benefits and potential effects of the scanning prior to requests should be undertaken. MRI involves no exposure to radiation but has other potential contraindications, for example if the person has a non-MR compatible pacemaker, which should be considered. Local clinical guidance should be followed.

Only one economic analysis of aPET was found, which showed that, in the French healthcare system, aPET was cost effective compared with standard diagnostic assessment and with CSF biomarkers [23]. Amyloid PET cost more to provide, but accrued a greater number of quality-

adjusted life years (QALYs). The patient cohort was followed up for 10 years after diagnosis to capture the longer-term benefits of earlier diagnosis [24].

Cerebrospinal fluid biomarkers

Cerebrospinal fluid (CSF) biomarkers can help diagnose Alzheimer's disease. These are amyloid beta 1–40 and 1–42 (Aβ40, Aβ42), total tau (T-tau) and phosphorylated tau (P-tau). The term 'established CSF biomarker' is used to describe a combination of Aβ42 and/or Aβ40 with either T-tau or P-tau. A reduction in CSF amyloid biomarkers (Aβ42, Aβ40) and elevated tau biomarkers (T-tau, P-tau) is indicative of Alzheimer's disease. There are currently no CSF biomarkers for any other subtypes of dementia [25].

Interpreting the evidence base

Interpretation of the evidence relating to the diagnostic value of biomarkers (whether CSF, blood or imaging based) in diagnosing Alzheimer's disease is challenging. Heterogeneous studies and meta-analyses vary in CSF testing methodology and assays, reference ranges used to define abnormal results, age of participants, length and the quality of follow up and whether neuropathology has been assessed, all of which makes comparison difficult [13].

2+

When assessing the diagnostic accuracy of CSF biomarkers in clinical studies, neuropathological confirmation of the diagnosis is important to establish the rates of Alzheimer's dementia pathology in control participants or as co-pathology in people diagnosed clinically with non-Alzheimer's dementia [26,27].

4

Age is also a consideration, as the post mortem examinations of 20–40% of asymptomatic people older than 80 years (depending on clinical criteria used) show neuropathology of Alzheimer's disease [28-30]. Similar ratios of abnormal CSF Aβ/tau results are seen in

asymptomatic people of this age [13,26].

3, 4

Established CSF biomarkers for differentiating between Alzheimer's disease and other forms of dementia

A Cochrane meta-analysis examined the accuracy of CSF Aβ42 in differentiating Alzheimer's disease dementia from other dementia sub-types [31]. The pooled sensitivity from 13 studies (n=1,704) was 79% (95% CI 0.73 to 0.85) and the pooled specificity was 60% (95% CI 0.52 to 0.67). For differentiating Alzheimer's disease from vascular dementia pooled data from 11 studies (n=1,151) gave sensitivity 79% (95% CI 0.75 to 0.83) and specificity 69% (95% CI 0.55 to 0.81). The corresponding data for differentiating Alzheimer's disease from frontotemporal dementia (17 studies, n=1,948) were sensitivity 85% (95% CI 0.79 to 0.89), specificity 72% (95% CI 0.55 to 0.84). And for differentiating Alzheimer's disease from dementia with Lewy bodies (9 studies, n=1,929) were sensitivity 77% (95% CI 0.70 to 0.83) and specificity 66% (95% CI 0.51 to 0.78). The authors concluded that CSF Aβ42 on its own should not be used to differentiate between Alzheimer's disease dementia and non-Alzheimer's disease dementias.

2++

In clinical practice people may present with less defined clinical phenotypes.

A systematic review and meta-analyses of the diagnostic performance of CSF biomarkers found [31] the pooled ratio between CSF T-tau biomarker concentration in patients with Alzheimer's disease and cognitively healthy control participants was 2.54 (95% CI 2.44 to 2.64, $p<0.0001$ (15 studies, n=18,427)); for CSF P-tau (89 studies, n=12,624) the pooled ratio was 1.88 (95% CI 1.79 to 1.97, $p<0.0001$) and for CSF Aβ42 (131 studies, n=16,790) the pooled ratio was 0.56 (95% CI 0.55 to 0.58, $p<0.0001$). There were similar findings for these CSF biomarkers in distinguishing between people with MCI due to Alzheimer's disease and

people with stable MCI (at two-year follow up). Interpreting the relevance of these findings to clinical practice is difficult due to the variation in reference ranges used across studies. The study authors concluded that there was sufficient consistency in biomarker ratios for them to be used to inform practice. **2**

A Cochrane systematic review examined CSF T-tau and tau/Aβ ratio for diagnosis of Alzheimer's dementia in people with MCI in secondary and tertiary care settings [30]. The NINDS-ADRDA criteria for Alzheimer's disease were used and MCI was defined using either the Petersen [33], revised Petersen criteria [34], and/or Matthew's criteria [35]. Sensitivity ranged from 80% to 96% and specificity ranged from 33% to 95%. It was not possible to combine the studies because the small total number of cases (140). The authors concluded that the biomarkers were more effective at ruling out Alzheimer's disease in people with MCI than ruling it in. **2++**

Established CSF biomarkers and amyloid PET findings

A modelling study based on cross-sectional data from 377 participants with mean age 72.1 explored changes in CSF biomarker trajectories as a function of aPET standardised update volume ratio (SUVR) [28]. There were 135 participants with mild cognitive impairment and 242 who were cognitively unimpaired. No participants had a diagnosis of Alzheimer's disease. Forty percent of the study population had a positive aPET scan. In the model, changes in CSF markers preceded abnormal amyloid deposition as measured by aPET positivity. **2**

Another cross-sectional study (n=64, mean age 66.3) explored data for both aPET and CSF biomarkers alongside clinical diagnoses in people undergoing investigations for cognitive complaints [25]. Forty one of the participants had a clinical diagnosis of AD. Aβ42 (cut-off 706.5 pg/mL) had the strongest correlation with 18F-Flutemetamol PET finding and at this

cut-off had sensitivity and specificity of 87% and 88% respectively, for positive aPET test. **2+**

A further study (n=136) examined concordance between CSF biomarker and 11C-Pittsburgh compound B (PIB) PET findings [30]. Clinical diagnoses that were not informed by biomarker and PET findings were mild cognitive impairment (n=22) non-Alzheimer's dementia (n=34) and Alzheimer's dementia (n=64). There were 16 control participants who had subjective memory complaints but had no abnormalities on cognitive, neurological and psychological investigations. Across all study participants concordance between 11C PIB PET finding and Aβ42 at cut off <550ng/L was 84%. At the wider cut off of 640ng/L it was 90% and when combined with tau biomarker data it was 89%.For people with AD the concordance of 11 C PIB PET with Aβ42 measure at a cut-off of <640 ng/L was 92% whilst for the control group it was 75%. 2+

Considerations for use of biomarkers

The Alzheimer's Association expert group [36] indicated that CSF testing should be arranged by dementia experts following clinical assessment to allow appropriate test counselling, safety screening and consent.

To obtain CSF biomarker samples a lumbar puncture must be undertaken. Although this is an invasive test, the risks are minimal when it is carried out by staff with appropriate training.

A study following up memory clinic attendees undergoing lumbar puncture (n=3,456), included people with a diagnosis of MCI (25.3%) Alzheimer's disease (28.4 %), and other dementia (12.6%) [37]. Adverse effects reported after successful procedures included back pain (17%) and headache (19%).

Another study reported that in cognitively healthy participants, younger people (mean age 28 years) had slightly higher rates of adverse events (14.1 %) than the older control group (12.5

%, mean age 73 years) [38]. A broader review of the safety of lumbar puncture agreed with these findings [39]. **3**

Consensus guidelines from the European Union (EU) Joint Programme – Neurodegenerative Disease Research (JPND) consortium indicated the need for an examination, review of medications and potentially imaging to be undertaken before safe lumbar puncture [40].

4

There are significant costs, given the time required to undertake the procedures, train staff to an appropriate level and have policies for those individuals where the test is technically challenging. There are modest cost implications for the sample couriering transfer and laboratory analysis.

There are few studies on the cost effectiveness of CSF biomarker testing. One study reported that any modelling of the cost effectiveness of such testing is highly influenced by the pretest prevalence of Alzheimer's disease [41]. This study suggested a pretest prevalence of 12.7% after clinical assessment and imaging was required to make the investigation cost effective, requiring a highly clinically selected population from memory clinics. In their model, based on practice, costings and cost-effectiveness modelling from the USA at prices from 2013, the authors concluded that testing established CSF biomarkers was cost effective. It is unclear if these assumptions are generalisable to the Scottish population and healthcare system.

Recommended tests

The following recommendation is reproduced from the NICE guideline on assessment, management and support for people living with dementia and their carers (NG97) [3].

4

R If the diagnosis is uncertain and Alzheimer's disease is suspected, consider either:

- **FDG-PET** (fluorodeoxyglucose-positron emission tomography-CT), **or perfusion SPECT** (single-photon emission CT) if FDG-PET is unavailable

or

- **examining cerebrospinal fluid for:**

  - either total tau or total tau and phosphorylated-tau 181 and

  - either amyloid beta 1–42 or amyloid beta 1–42 and amyloid beta 1–40.

If a diagnosis cannot be made after one of these tests, consider using the other one.

Functional imaging is well-established technique for use in dementia diagnosis and subtyping. Perfusion SPECT is widely available in Scotland, while access to FDG-PET remains extremely limited. Where available FDG-PET should be considered on a case-by-case basis in discussion with regional PET-CT centres.

The NICE guideline states 'amyloid imaging techniques have been licensed for use in the UK,' but makes no recommendation for aPET use [3]. Amyloid PET is not currently widely used in Scotland; it is used only for research purposes and is not routinely available.

R Routine use of amyloid PET in the diagnosis of dementia or mild cognitive impairment is

not recommended.

✔ Amyloid PET may be considered for improving the diagnosis of Alzheimer's dementia in situations where there is still uncertainty following specialist assessment and structural brain imaging, for example in those with an atypical presentations or young-onset dementia.

✔ Any consideration of amyloid PET should follow a full clinical assessment by a dementia

specialist, and discussion of the potential risks from radiation.

✔ Testing of established CSF biomarkers should be arranged by dementia specialists following

clinical assessment. The risks and benefits of undertaking a lumbar puncture should be

discussed with the individual, and any risks managed.

There is insufficient evidence to support the routine clinical use of other blood or CSF biomarkers. Many biomarkers may also be non-specific, reflecting associated comorbidities rather than dementia.

There is a lack of access to biomarker testing as highlighted in a survey of psychiatrists (n=492) working in the UK [42]. At present there are no laboratories within Scotland offering established CSF biomarkers testing.

Diagnosing suspected frontotemporal dementia

NICE guidance indicates that if the dementia subtype is uncertain and frontotemporal dementia is suspected, use either FDG-PET or perfusion SPECT [3].

Do not rule out frontotemporal dementia based solely on the results of structural, perfusion or metabolic imaging tests.

Diagnosing suspected vascular dementia

NICE guidance indicates that if the dementia subtype is uncertain and vascular dementia is suspected, use MRI. If MRI is unavailable or contraindicated, use CT [3].

Do not diagnose vascular dementia based solely on vascular lesion burden. Be aware that young onset vascular dementia has a genetic cause in some people.

Diagnosing suspected dementia with Lewy bodies

NICE guidance indicates that if a diagnosis is uncertain and dementia with Lewy body dementia is suspected, use 123I-FP-CIT SPECT [3].

If 123I-FP-CIT SPECT is unavailable, consider 123I-MIBG cardiac scintigraphy.

Do not however rule out dementia with Lewy bodies based solely on normal results of the above investigations.

Consideration of genetic testing

It is important to recognise that in some patients dementia can be caused by single gene disorders. This may need to be considered in patients with frontotemporal dementia and early-onset Alzheimer's. This may also need to be considered in patients presenting with clinical features such as chorea or motor neurone disease in addition to dementia.

✔ Refer to current national criteria local guidance and protocols.

✔ Consider offering testing with locally available gene panels in individuals with dementia

diagnoses with either:

• age at onset <55 years

• family history of dementia of the same type in a first or second degree relative.

✔ It is important to recognise that gene panels currently test for the common monogenic

causes of some subtypes of dementia. They do not however test for susceptibility genes,

which may also be risk factors within families.

National Services Scotland provides information on genetic testing [43].

Discussion

The evidence review supports consideration of the use of structural imaging, nuclear medicine imaging and established Alzheimer's CSF biomarkers (amyloid and tau) in the diagnosis of dementia. Although, routine use of amyloid PET imaging was not recommended; its potential use, under specialist direction, in patients with atypical or young onset presentations of suspected Alzheimer's dementia was included as a good clinical practice option. A flow chart of the recommended investigation pathway for Alzheimer's dementia is outlined in figure 1.

It is important to recognise that a number of additional imaging and fluid biomarkers have been proposed in supporting the diagnosis of different dementia sub types [44], however at this stage there is insufficient evidence for their inclusion in the guideline. A number of blood biomarkers are being evaluated for example in a range of dementia sub-types. With serological testing having the appeal of being more accessible for use as potential screening tests for a larger number of potential patients [45]. It seems likely that the evidence for the use of fluid and imaging biomarkers will continue its rapid expansion. However, there is potentially important learning for the field in some of the limitations in the evidence gathered for validation purposes, for what many would regard as the established biomarkers of CSF biomarkers (amyloid and tau) and amyloid PET imaging. Despite a large volume of studies being undertaken, over a considerable period of time for these biomarkers, their methodological variability is far from ideal when trying to assimilating data for meta-analysis of the diagnostic value of specific biomarkers. The difficulties of comparability between studies in terms of both the methods of testing biomarkers (with slight variations in the assays used) and the populations under evaluation, likely driven largely by the desire to create

individual new primary research publications, is an issue for the field. As is the lack of neuropathological confirmation in much of the literature. These are important considerations in the methodology for future biomarker studies, as is the consideration of the potential limitations in the evidence of the more established biomarkers in considering whether they should be used as the gold standard against which future biomarkers are tested, rather than confirmatory neuropathology? This is not to discount the importance of the ongoing research into dementia biomarkers, which have the potential to evolve to allow us to make sub-diagnoses earlier and with more certainty, may inform us of important disease mechanisms for future research, may individually or in combination inform us of disease prognosis and progression and may also prove important in differentiating the patients most likely to benefit from future treatments.

Acknowledgements

The authors were tasked with reviewing the evidence regarding in the investigation of suspected dementia, however this was part of the collaborative process involving the wider SIGN dementia guideline development group. In particular we thank Dr Adam Daly the chair of the SIGN dementia guideline development group, as well as Sarah Florida-James and Alan Bigham from the SIGN team for their assistance in co-ordinating the guidelines development. We obtained further specialist review and advice from Professor Alison Murray from Radiology, Dr David Colville from Nuclear medicine and Professor Mary Porteous from clinical genetics.

Authors' statement

All of the authors wrote both the investigation section of the SIGN 168 guideline and this review paper. All authors have written and corrected sections of the guideline and paper. SC

undertook the evidence appraisal and scoring. None of the authors have conflicts of interest to report.

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Key to SIGN evidence statements and recommendations

Levels of evidence

1++ High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias

1– Meta-analyses, systematic reviews, or RCTs with a high risk of bias

2++ High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal

2+ Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal

2– Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal

3 Non-analytic studies, eg case reports, case series

4 Expert opinion

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence; and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that **'should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

Recommended best practice based on the clinical experience of the guideline development group.

NICE has accredited the process used by Scottish Intercollegiate Guidelines Network to produce clinical guidelines. The accreditation term is valid until 31 March 2025 and is applicable to guidance produced using the processes described in SIGN 50: a guideline developer's handbook, 2019 edition (www.sign.ac.uk/our-guidelines/sign-50-aguideline-developers-handbook). More information on accreditation can be viewed at www.nice.org.uk/accreditation

Appendix 2. Evidence tables (by publication in alphabetical order).

<table>
<tr><td colspan="4">Agarwal M, Khan S. Plasma Lipids as Biomarkers for Alzheimer's Disease: A Systematic Review. Cureus. 2020 Dec 10;12(12):e12008. doi: 10.7759/cureus.12008. PMID: 33457117; PMCID: PMC7797449.</td></tr>
<tr><td>Reviewer</td><td colspan="3">Dementia Group</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study Detail/Limitations</td><td>Patient Characteristics</td><td>Intervention</td></tr>
<tr><td>CS:-
General Review (of reviews)
Evidence Level: observational (2)</td><td>Funding: not stated
searched to sept 2020</td><td>Patient Characteristics:
Alzheimer's</td><td>Cholesterol</td></tr>
<tr><td>Notes
No double selection or extraction. No excluded studies listed. No quality of studies assessed. No</td><td colspan="3">Conclusions: This study found an association between plasma lipids and Alzheimer's, proving that plasma lipids can be used as biomarkers for early diagnosis of Alzheimer's disease. It may also help predict the prognosis and stage the disease severity. Further studies are needed to find out the exact mechanism behind these changes.</td></tr>
</table>

CoI of included studies reported. Can be used as a general review.	
Outcome Measures/ Results: Associations	We collected 49 quality appraised articles on the association between plasma lipids and Alzheimer's disease and the genetic mutations in alleles related to cholesterol metabolism and Alzheimer's disease by applying the inclusion and exclusion criteria. Based on the finding of the studies reviewed, we found an association between plasma lipids, polymorphisms in genes associated with cholesterol transport, and Alzheimer's disease. Increased serum low-density lipoprotein (LDL-C), triglycerides (TG), total cholesterol (TC), sphingolipids, 24S hydroxycholesterol (24S-HC), 27O hydroxycholesterol (27O-HC) was associated with Alzheimer's. Decreased high-density lipoprotein (HDL-C) and phospholipids were noticed. Genetic mutations in apolipoprotein E (ApoE), apolipoprotein B (ApoB), apolipoprotein A (ApoA), ATP binding cassette transporter 1 (ABCA1), ATP binding cassette transporter 7 (ABCA7), amyloid precursor protein (APP), cytochrome P450 family 46 subfamilies A member 1 (CYP46A1), presenilin 1 (PSEN1), presenilin 2 (PSEN2) are also associated with increased risk of Alzheimer's disease

Anand K, Sabbagh M. **Amyloid Imaging: Poised for Integration into Medical Practice.** Neurotherapeutics. 2017 Jan;14(1):54-61. doi: 10.1007/s13311-016-0474-y. PMID:

27571940; PMCID: PMC5233621. NOT INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
General Review Evidence Level: 4	Funding: NIA	Patient Characteristics: Alzheimer's	Amyloid Imaging
Notes No appraisal			
Outcome Measures/ Results:	Despite the high sensitivity and specificity of amyloid imaging, it is not commonly used in clinical practice, mainly because it is not reimbursed under current Center for Medicare and Medicaid Services guidelines in the USA. To guide the field in who would be most appropriate for the utility of amyloid positron emission tomography, current studies are underway [Imaging Dementia Evidence for Amyloid Scanning (IDEAS) Study] that will inform the field on the utilization of amyloid positron emission tomography in clinical practice. With the advent of monoclonal antibodies that specifically target amyloid antibody, there is an interest, possibly a mandate, to screen potential treatment recipients to ensure that they are suitable for treatment. In this review, we summarize progress in the field to date.		

Ashford MT, Veitch DP, Neuhaus J, Nosheny RL, Tosun D, Weiner MW**. The search for a convenient procedure to detect one of the earliest signs of Alzheimer's disease: A systematic review of the prediction of brain amyloid status**. Alzheimers Dement. 2021 May;17(5):866-887. doi: 10.1002/alz.12253. Epub 2021 Feb 13. PMID: 33583100. NOT INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: (2)			tests for amyloid beta
Notes Limited databases searched. Embase and google scholar. No excluded studies listed. No publication bias assessed. No CoI of included studies reported.	Conclusions: Conclusions about models are difficult due to study heterogeneity and quality. Promising prediction models used demographic, cognitive/neuropsychological, imaging, and plasma Aβ measures. Further studies using standardized Aβ determination, and improved model validation are required		
Outcome	We identified few high-quality studies due to concerns about Aβ		

Measures/ Results:	determination and analytical issues. The most promising convenient, inexpensive classifiers consist of age, apolipoprotein E genotype, cognitive measures, and/or plasma Aβ. Plasma Aβ may be sufficient if pre-analytical variables are standardized and scalable assays developed. Some models lowered costs associated with clinical trial recruitment or clinical screening

Bergeret S, Queneau M, Rodallec M, Curis E, Dumurgier J, Hugon J, Paquet C, Farid K, Baron JC. **[^{18} F]FDG PET may differentiate cerebral amyloid angiopathy from Alzheimer's disease.** Eur J Neurol. 2021 May;28(5):1511-1519. doi: 10.1111/ene.14743. Epub 2021 Feb 3. PMID: 33460498. NOT INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: cohort (2)	Countries: France Funding: Not stated	Patient Characteristics: CAA vs AD	FDG PET
Notes retrospective	Conclusions: Despite the small sample, our findings are consistent with the previous early-phase amyloid PET study. Thus, [18F]FDG-PET may help differentiate CAA from AD, particularly in cases of amyloid PET positivity. Larger prospective studies, including in CAA-related ICH, are however warranted.		
Outcome Measures/ Results:	**Results:** The SUVr O/PC ratio was significantly lower in CAA versus AD (1.02 ± 0.14 vs. 1.19 ± 0.18, respectively; p = 0.024).		

Bergeron D, Ossenkoppele R, Jr Laforce R. **Evidence-based Interpretation of Amyloid-β PET Results: A Clinician's Tool.** Alzheimer Dis Assoc Disord. 2018 Jan-Mar;32(1):28-34. doi: 10.1097/WAD.0000000000000239. PMID: 29334498.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
Evidence Level: observational (2)	Funding:not stated		
Notes This is not a study type I recognise	This evidence-based approach might provide guidance to clinicians and nuclear medicine physicians to interpret amyloid-β PET results for early and differential diagnosis of patients with progressive cognitive impairment.		
Outcome Measures/ Results: Sensitivity, specificity, NPV, PPV	PPV of PET is highest in young ApoE4− patients with high prePET probability of AD. In older ApoE4+ patients with low pre-PET probability of AD, positive amyloid-β PET scans must be interpreted with caution. A negative amyloid-β PET makes a diagnosis of AD unlikely except in old patients with high pre-PET probability of AD.		

Blazhenets G, Ma Y, Sörensen A, Schiller F, Rücker G, Eidelberg D, Frings L, Meyer PT; Alzheimer Disease Neuroimaging Initiative. **Predictive Value of ^{18}F-Florbetapir and ^{18}F-**

FDG PET for Conversion from Mild Cognitive Impairment to Alzheimer Dementia. J Nucl Med. 2020 Apr;61(4):597-603. doi: 10.2967/jnumed.119.230797. Epub 2019 Oct 18. PMID: 31628215; PMCID: PMC7198373. INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: Cohort (2)	Countries: Germany Funding: National Institutes of Health, Department of Defense etc	Patient Characteristics: MCI to Dementia	18F-Florbetapir and 18F-FDG PET for
Notes A retrospective database study. There is no blinding.	Conclusions: 18F-FDG PET, amyloid PET, and nonimaging variables represent complementary predictors of conversion from MCI to AD. Especially in combination, they enable an accurate stratification of patients according to their conversion risks, which is of great interest for patient care and clinical trials.		
Outcome Measures/ Results: Prediction accuracy	On the basis of the independent validation dataset, the 18F-FDG PET model yielded a significantly higher predictive value than the amyloid PET model. However, both were inferior to the nonimaging model and were significantly improved by the addition of nonimaging variables. The best prediction accuracy was reached by combining 18F-FDG PET, amyloid PET, and nonimaging variables. The combined model yielded 5-y free-of-conversion rates of 100%, 64%, and 24% for the low-, medium- and high-risk groups,		

	respectively

Carswell CJ, Win Z, Muckle K, Kennedy A, Waldman A, Dawe G, Barwick TD, Khan S, Malhotra PA, Perry RJ. **Clinical utility of amyloid PET imaging with (18)F-florbetapir: a retrospective study of 100 patients.** J Neurol Neurosurg Psychiatry. 2018 Mar;89(3):294-299. doi: 10.1136/jnnp-2017-316194. Epub 2017 Oct 10. PMID: 29018162. INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
Evidence Level: Before and After (3)	Countries:England Funding: NIHR	Total No Patients: 100 Patient Characteristics: atypical clinical features	Amyloid PET imaging
Notes No appraisal	Conclusion: young-onset or complex dementia while reducing the overall burden of investigations. It was most useful in younger patients, atypical presentations or individuals with multiple possible causes of cognitive impairment.		
Outcome Measures/ Results: Imaging burden	I was primarily used to investigate patients with atypical clinical features (56 cases) or those that were young at onset (42 cases). MRI features of AD did not always predict positive API (67%), and 6 of 23 patients with MRIs reported as normal were amyloid-PET		

	positive. There were significantly more cases categorised as non-AD dementia post-API (from 11 to 23). Patients investigated when API was initially available had fewer overall investigations and all patients had significantly fewer investigations in total post-API.

Chaudhry A, Houlden H, Rizig M**. Novel fluid biomarkers to differentiate frontotemporal dementia and dementia with Lewy bodies from Alzheimer's disease: A systematic review**. J Neurol Sci. 2020 Aug 15;415:116886. doi: 10.1016/j.jns.2020.116886. Epub 2020 May 11. PMID: 32428759.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: diagnostic (2)	Funding: Medical Research Council and Michael J Fox Foundation	Patient Characteristics: Frontotemporal Dementia and Dementia with Lewy Bodies from Alzheimer's Disease Inclusion Criteria: Exclusion Criteria:	AB42/AB38, AB42/AB40
Notes Can't say if there's been double selection or	Conclusions: Several promising novel biomarkers were highlighted in this review. Combinations of fluid biomarkers were more often useful than individual biomarkers in distinguishing subtypes of dementia. Considering the heterogeneity in methods and results		

extraction. No excluded studies listed. Characteristics of included studies is a diagram, which is a bit unusual. No CoI of included studies reported.	between the studies, further validation, ideally with longitudinal prospective designs with large sample sizes and unified protocols, are fundamental before conclusions can be finalised.
Outcome Measures/ Results: Sensitivity, specificity	The search strategy yielded 614 results, from which, 27 studies were included. When comparing bio-fluid levels in AD and FTD patients, neurofilament light chain (NfL) level was often higher in FTD, whilst brain soluble amyloid precursor protein β (sAPPβ) was higher inpatients with AD. When comparing bio-fluid levels in AD and DLB patients, α-synuclein ensued heterogeneous findings, while the noradrenaline metabolite (MHPG) was found to be lower in DLB. Ratios of Aβ42/Aβ38 and Aβ42/Aβ40were lower in AD than FTD and DLB and offered better diagnostic accuracy than raw amyloid-β (Aβ) concentrations.

Chiotis K, Dodich A, Boccardi M, Festari C, Drzezga A, Hansson O, Ossenkoppele R, Frisoni G, Garibotto V, Nordberg A. **Clinical validity of increased cortical binding of tau ligands of the THK family and PBB3 on PET as biomarkers for Alzheimer's disease in the context of a structured 5-phase development framework.** Eur J Nucl Med Mol Imaging. 2021 Jul;48(7):2086-2096. doi: 10.1007/s00259-021-05277-4. Epub

2021 Mar 15. PMID: 33723628; PMCID: PMC8175292. NOT INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
No appraisal Evidence Level: Opinion (4)		Patient Characteristics: Alzheimer's	Clinical validity of tau PET ligands of the THK family and PBB3
Notes	Conclusions: Much work remains for completing the aims of phases 2 and 3 and replicating the available evidence. However, it is unlikely that the validation process for these tracers will be completed, given the presence of off-target binding and the development of second-generation tracers with improved binding and pharmacokinetic properties.		
Outcome Measures/ Results:	PET radioligands of the THK family discriminate well between healthy controls and patients with AD dementia (phase 2;partly achieved) and recent evidence suggests an accurate diagnostic accuracy at the mild cognitive impairment (MCI) stage ofthe disease (phase 3; partly achieved). The phases 2 and 3 were considered not achieved for PBB3 since no evidence exists aboutthe ligand's diagnostic accuracy. Preliminary evidence exists about the secondary aims of each phase for all ligands.		

Collij LE, Salvadó G, Shekari M, Lopes Alves I, Reimand J, Wink AM, Zwan M,

<table>
<tr><td colspan="4">Niñerola-Baizán A, Perissinotti A, Scheltens P, Ikonomovic MD, Smith APL, Farrar G, Molinuevo JL, Barkhof F, Buckley CJ, van Berckel BNM, Gispert JD; ALFA study; AMYPAD consortium. Visual assessment of [^{18}F]flutemetamol PET images can detect early amyloid pathology and grade its extent. Eur J Nucl Med Mol Imaging. 2021 Jul;48(7):2169-2182. doi: 10.1007/s00259-020-05174-2. Epub 2021 Feb 22. PMID: 33615397; PMCID: PMC8175297. NOT INCLUDED</td></tr>
<tr><td>Reviewer</td><td colspan="3">Dementia Group</td></tr>
<tr><td>Study Type/
Evidence Level</td><td>Study
Detail/Limitations</td><td>Patient
Characteristics</td><td>Intervention</td></tr>
<tr><td>CS:+

Evidence Level:
cohort (2)</td><td>Netherlands
Funding: “la Caixa” Foundation, Alzheimer’s association</td><td>Patient
Characteristics:
Alzheimer’s</td><td>Amyloid pathology</td></tr>
<tr><td>Notes
Retrospective</td><td colspan="3">Conclusion VR is an appropriate method for assessing early amyloid pathology and that grading the extent of visual amyloid positivity could present clinical value.</td></tr>
<tr><td>Outcome Measures/
Results:

visual</td><td colspan="3">VR showed excellent agreement against CL = 12 (κ = .89, 95.2%) and CL = 30 (κ = .88, 95.4%) cut-offs. ROC analysis resulted in an optimal CL = 17 cut-off against VR (sensitivity = 97.9%, specificity = 97.8%). Each additional positive VR region corresponded to a clear increase in global CL. Regional VR was also associated with regional CL quantification. Compared to mCERADSOT-based</td></tr>
</table>

	classification (i.e., any region mCERADSOT > 1.5), VR was in agreement in 89.3% of cases, with 13 true negatives, 12 true positives, and 3 false positives (FP). Regional sparse-to-moderate neuritic and substantial diffuse Aβ plaque was observed in all FP cases. Regional VR was also associated with regional plaque density.

Dulewicz M, Kulczyńska-Przybik A, Mroczko B. **Neurogranin and VILIP-1 as Molecular Indicators of Neurodegeneration in Alzheimer's Disease: A Systematic Review and Meta-Analysis.** Int J Mol Sci. 2020 Nov 6;21(21):8335. doi: 10.3390/ijms21218335. PMID: 33172069; PMCID: PMC7664397.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:- Evidence Level: General review (4)	Funding: European Union	Patient Characteristics: Alzheimer's	CSF levels of Neurogranin and visinin-like protein 1 (VILIP-1)
Notes: There isn't any description of the search in this. Can be treated as a general review. No CoI of included studies reported.	Conclusions: Although, an additional advantage of the protein concentration Ng is the possibility of using it to predict the risk of developing cognitive impairment in normal controls with pathological levels of Aβ1-42. Analyses in larger cohorts are needed, particularly concerning Aβ status		

Outcome Measures/ Results: Associations of cerebrospinal fluid neurogranin	Ng highest levels of RoM were observed in the AD (n=1894) compared to CTRL (n=2051) group (RoM: 1.62). Similarly, the VILIP-1 highest values of RoM were detected in the AD (n=706) compared to CTRL (n=862) group (RoM: 1.34). Concentrations of both proteins increased in more advanced stages of AD. However, Ng seems to be an earlier biomarker for the assessment of cognitive impairment. Ng appears to be related with amyloid beta, and the highest levels of Ng in CSF was observed in the group with pathological Aβ+status.

Fantoni ER, Chalkidou A, O' Brien JT, Farrar G, Hammers A. **A Systematic Review and Aggregated Analysis on the Impact of Amyloid PET Brain Imaging on the Diagnosis, Diagnostic Confidence, and Management of Patients being Evaluated for Alzheimer's Disease**. J Alzheimers Dis. 2018;63(2):783-796. doi: 10.3233/JAD-171093. PMID: 29689725; PMCID: PMC5929301. INCLUDED

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: diagnostic (2)	Funding: GE healthcare searched to Jan 2017	Total No Patients:1531 Patient Characteristics: Alzheimers	Amyloid PET Brain Imaging
Notes	Amyloid PET contributed to diagnostic revision in almost a third of		

No double extraction. No CoI of included studies reported.	cases and demonstrated value in increasing diagnostic confidence and refining management plans
Outcome Measures/ Results: AUC	For 1,142 cases with only aPET, 31.3% of diagnoses were revised, whereas 3.2% of diagnoses changed in the delayed aPET control group ($p < 0.0001$). Increased diagnostic confidence following aPET was found for 62.1% of 870 patients. Management changes with aPET were found in 72.2% of 740 cases and in 55.5% of 299 cases in the control group ($p < 0.0001$). The diagnostic value of aPET in AUC+ patients or when FDG/CSF were additionally available did not substantially differ from the value of aPET alone in the wider population

Hu X, Yang Y, Gong D. **A meta-analysis of cerebrospinal fluid visinin-like protein-1 in alzheimers disease patients relative to healthy controls and mild cognitive impairment patients.** Neurosciences (Riyadh). 2017 Apr;22(2):94-101. doi: 10.17712/nsj.2017.2.20160557. PMID: 28416790; PMCID: PMC5726829.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding: Not stated searched to July 2016	Total No Patients:1151 Patient Characteristics:	cerebrospinal fluid visinin-like protein-1

		Alzheimer's	
Notes **No excluded studies listed.** No CoI of included studies reported.	Conclusions: The CSF VLP-1 in AD patients is higher than that in healthy controls and MCI patients. The changes of VLP-1 in AD patients relative to healthy controls and MCI patients is less pronounced than that of core biomarkers, such as Aβ42, t-tau and p-tau. Population variations, increasing t-tau and decreasing Aβ42 in AD patients relative to healthy controls and MCI patients were the main sources of heterogeneity.		
Outcome Measures/ Results: correlation	Seven studies involved 1151 participants were pooled. The CSF VLP-1 in AD patients was higher than that in healthy controls and MCI patients (pooled Std.MD=0.81, 95% CI: [0.47, 1.16], p		

Jeong DY, Lee J, Kim JY, Lee KH, Li H, Lee JY, Jeong GH, Yoon S, Park EL, Hong SH, Kang JW, Song TJ, Leyhe T, Eisenhut M, Kronbichler A, Smith L, Solmi M, Stubbs B, Koyanagi A, Jacob L, Stickley A, Thompson T, Dragioti E, Oh H, Brunoni AR, Carvalho AF, Kim MS, Yon DK, Lee SW, Yang JM, Ghayda RA, Shin JI, Fusar-Poli P. **Empirical assessment of biases in cerebrospinal fluid biomarkers of Alzheimer's disease: an umbrella review and re-analysis of data from meta-analyses.** Eur Rev Med Pharmacol Sci. 2021 Feb;25(3):1536-1547. doi: 10.26355/eurrev_202102_24862. PMID: 33629323.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
Review of reviews	Funding: NIHR, HEE	Patient	CSF biomarkers

CS:+ Evidence Level: Observations (2)	searched to Jan 2020	Characteristics: Alzheimer's	
Notes Review of reviews. commentary on the number of reviews on each biomarker and their characteristics, rather than about their effectiveness. No excluded studies listed. Quality of studies is not reported individually and characteristics of included studies is collated by biomarker. No CoI of included studies reported.	Conclusions: Our results suggest that there is an excess of statistically significant results and significant biases in the literature of CSF biomarkers for AD. Therefore, the results of CSF biomarkers should be interpreted with caution.		
Outcome Measures/ Results:	A total of 38 meta-analyses on CSF markers from 11 eligible articles were identified and reanalyzed. In 14 (36%) of the meta-		

Heterogeneity, study effects	analyses, the summary estimate and the results of the largest study showed non-concordant results in terms of statistical significance. Large heterogeneity (I2≥75%) was observed in 73% and smallstudy effects under Egger's test were shown in 28% of CSF biomarkers.

Jin M, Cao L, Dai YP. **Role of Neurofilament Light Chain as a Potential Biomarker for Alzheimer's Disease: A Correlative Meta-Analysis.** Front Aging Neurosci. 2019 Sep 13;11:254. doi: 10.3389/fnagi.2019.00254. PMID: 31572170; PMCID: PMC6753203.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:- Evidence Level: General Review (4)	Funding: not stated searched to May 2019	Patient Characteristics: Alzheimer's	Neurofilament light chain
Notes Unclear if double selection or extraction. No excluded studies listed. No quality of studies assessed. For this reason this review will have to	Conclusions: These results show that NFL can be a useful biomarker for improving diagnosis and predicting prognosis in AD patients especially if age weighted.		

be used as a general review. No CoI of included studies reported.	
Outcome Measures/ Results: Correlations	Data from 38 studies (age 68.3 years [95% confidence interval (CI): 65.7, 70.9]; 54 % [95% CI: 50, 57] females) were used. Meta-analyses of correlation coefficients reported by the included studies showed that NFL levels in blood and cerebrospinal fluid (CSF) correlated well (r = 0.59 [95% CI: 0.45, 0.71]; p < 0.0001). NFL levels correlated with MMSE score (r = −0.345 [95% CI: −0.43, −0.25]; p = 0.0001), and age (r = 0.485 [95% CI: 0.35, 0.61]; p = 0.00001). CSF NFL levels correlated with total tau (t-tau; r = 0.39 [95% CI: 0.27, 0.50]; p = 0.0001), phosphorylated tau (p-tau; r = 0.34 [95% CI: 0.19, 0.47]; p = 0.00001), and neurogranin (r = 0.25 [95% CI: 0.12, 0.37]; p = 0.001) but not with beta amyloid (Aβ) (r = 0.00 [95%CI: −0.13, 0.12]; p = 0.937). In meta-regression, MMSE scores were associated inversely with blood NFL (metaregression coefficient (MC) −0.236 [95% CI:−0.40, −0.072; p = 0.008), and age (MC) −0.235 [−0.36, −0.11]; p = 0.001) and positively with CSF Aβ-42 (MC 0.017 [0.010, 0.023]; p = 0.00001). NFL has good correlations with t-tau, and p-tau in CSF and CSF NFL levels correlates well with blood NFL levels.

<table>
<tr><td colspan="4">APOE Status of Early Onset Alzheimer's Disease Variants: A Systematic Review and Meta-Analysis. J Alzheimers Dis. 2020;75(3):827-843. doi: 10.3233/JAD-200052. PMID: 32333592.</td></tr>
<tr><td>Reviewer</td><td colspan="3">Dementia Group</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study Detail/Limitations</td><td>Patient Characteristics</td><td>Intervention</td></tr>
<tr><td>CS:-

Evidence Level: General Review (4)</td><td>Co

Funding: NHMRC</td><td>Patient Characteristics: Early onset Alzheimer’s</td><td>Biomarkers</td></tr>
<tr><td>Notes
No indication of double selection or extraction. No excluded studies listed. No quality of studies assessed. No CoI of included studies reported.</td><td colspan="3">Conclusions: Established CSF biomarkers confirmed quantitative differences between variants of EOAD. EOsAD is enriched with APOE _4, but the level is not higher than generally reported in late-onset AD. The results prompt further exploration of the etiopathogenesis of EOsAD, which accounts for ∼4–10% of all AD cases, but the reasons for the early onset remain poorly understood.</td></tr>
<tr><td>Outcome Measures/ Results: AB40, AB42, t-tau, p-tau, IL6,</td><td colspan="3">In the subset of EOsAD cases without APP, PSEN1/PSEN2 mutations, CSF A_42 and tau levels were higher when compared to the EOsAD group as a whole. Prevalence of the APOE _4 allelewas more elevated in EOsAD relative to controls, and not significantly</td></tr>
</table>

IgG, serum albumin, NfL	elevated in ADAD cases.

Kim BY, Lee SH, Graham PL, Angelucci F, Lucia A, Pareja-Galeano H, Leyhe T, Turana Y, Lee IR, Yoon JH, Shin JI. **Peripheral Brain-Derived Neurotrophic Factor Levels in Alzheimer's Disease and Mild Cognitive Impairment: a Comprehensive Systematic Review and Meta-analysis.** Mol Neurobiol. 2017 Nov;54(9):7297-7311. doi: 10.1007/s12035-016-0192-9. Epub 2016 Nov 4. PMID: 27815832.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding: None searched to Oct 2015	Patient Characteristics: Alzheimer’s and MCI	Peripheral Brain-Derived Neurotrophic Factor
Notes No excluded studies listed. Can’t say if there’s double selection or extraction. The included characteristics is a	Conclusion: In conclusion, this meta analysis shows that peripheral blood BDNF levels seem to be increased in early AD and decreased in AD patients with low MMSE scores respectively compared with their age- and sexmatched healthy referents. At present, however, this could not be concluded from individual studies.		

summary table. No CoI of included studies reported.	
Outcome Measures/ Results: Correlations	Over a total pool of 2061 potential articles, 26 met all inclusion criteria (including a total of 1584 AD patients, 556 MCI patients, and 1294 controls). A meta-analysis of BDNF levels between early AD and controls showed statistically significantly higher levels (SMD [95 % CI]: 0.72 [0.31, 1.13]) with no heterogeneity. AD patients with a low (< 0.0001, I 2 = 85.8 %). There were no differences in blood BDNF levels among AD or MCI patients vs. controls by subgroup analyses according to age, sex, and drug use

Kokkinou M, Beishon LC, Smailagic N, Noel-Storr AH, Hyde C, Ukoumunne O, Worrall RE, Hayen A, Desai M, Ashok AH, Paul EJ, Georgopoulou A, Casoli T, Quinn TJ, Ritchie CW. **Plasma and cerebrospinal fluid ABeta42 for the differential diagnosis of Alzheimer's disease dementia in participants diagnosed with any dementia subtype in a specialist care setting.** Cochrane Database Syst Rev. 2021 Feb 10;2(2):CD010945. doi: 10.1002/14651858.CD010945.pub2. PMID: 33566374; PMCID: PMC8078224.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding:NIHR searched to Feb 2020		AB42

Notes No publication bias assessed. No CoI of included studies reported.	Conclusions: Our review indicates that measuring ABeta42 levels in CSF may help differentiate ADD from other dementia subtypes, but the test isimperfect and tends to misdiagnose those with non-ADD as having ADD. We would caution against the use of CSF ABeta42 alone fordementia classification. However, ABeta42 may have value as an adjunct to a full clinical assessment, to aid dementia diagnosis.
Outcome Measures/ Results: Sensitivity, specificity	We identified 39 studies (5000 participants) that used CSF ABeta42 levels to differentiate ADD from other subtypes of dementia. No studiesof plasma ABeta42 met the inclusion criteria. No studies were rated as low risk of bias across all QUADAS-2 domains. High risk of bias wasfound predominantly in the domains of patient selection (28 studies) and index test (25 studies).The pooled estimates for differentiating ADD from other dementia subtypes were as follows: ADD from non-ADD: sensitivity 79% (95%CI 0.73 to 0.85), specificity 60% (95% CI 0.52 to 0.67), 13 studies, 1704 participants, 880 participants with ADD; ADD from VaD: sensitivity79% (95% CI 0.75 to 0.83), specificity 69% (95% CI 0.55 to 0.81), 11 studies, 1151 participants, 941 participants with ADD; ADD from FTD:sensitivity 85% (95% CI 0.79 to 0.89), specificity 72% (95% CI 0.55 to 0.84), 17 studies, 1948 participants, 1371 participants with ADD; ADDfrom DLB: sensitivity 76% (95% CI 0.69 to 0.82), specificity 67% (95% CI 0.52 to 0.79), nine studies, 1929 participants, 1521 participants withADD. Across all dementia subtypes, sensitivity was greater than specificity, and the balance of

	sensitivity and specificity was dependenton the threshold used to define test positivity.

Lawrence E, Vegvari C, Ower A, Hadjichrysanthou C, De Wolf F, Anderson RM. **A Systematic Review of Longitudinal Studies Which Measure Alzheimer's Disease Biomarkers**. J Alzheimers Dis. 2017;59(4):1359-1379. doi: 10.3233/JAD-170261. PMID: 28759968; PMCID: PMC5611893.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:- General Review Evidence Level: (4)	Funding: Janssen Study Limitations: searched to Aug 2015	Patient Characteristics: Alzheimer's	Biomarkers
Notes Seems like a general statement about the literature base	Conclusion: We have concluded that additional studies with repeat measures over time in a representative population cohort are needed to address the gap in knowledge of AD progression. Based on our analysis, we suggest directions in which research could move in order to advance our understanding of this complex disease, including repeat biomarker measurements, standardization and increased sample sizes.		
Outcome Measures/ Results:			

Lesman-Segev OH, La Joie R, Iaccarino L, Lobach I, Rosen HJ, Seo SW, Janabi M, Baker SL, Edwards L, Pham J, Olichney J, Boxer A, Huang E, Gorno-Tempini M, DeCarli C, Hepker M, Hwang JL, Miller BL, Spina S, Grinberg LT, Seeley WW, Jagust WJ, Rabinovici GD. **Diagnostic Accuracy of Amyloid versus ^{18}F-Fluorodeoxyglucose Positron Emission Tomography in Autopsy-Confirmed Dementia**. Ann Neurol. 2021 Feb;89(2):389-401. doi: 10.1002/ana.25968. Epub 2020 Dec 7. PMID: 33219525; PMCID: PMC7856004. INCLUDED

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: diagnostic (2)	Countries: USA Funding: NIH, Alzheimers association, Blufield, Rainwater	Total No Patients: 101 Patient Characteristics: Alzheimers	Amyloid vs 18F Fluorodeoxyglucose PET
Notes	Conclusions: In our sample enriched for younger onset cognitive impairment, PIB-PET had higher sensitivity than FDG-PET for intermediate–high ADNC, with similar specificity. When both modalities are congruent, sensitivity and specificity approach 100%, whereas mixed pathology should be considered when PIB and FDG are incongruent		

Outcome Measures/ Results: Visual read	One hundred one participants were included (mean age = 67.2 years, 41 females, Mini-Mental State Examination = 21.9, PET-to-autopsy interval = 4.4 years). At autopsy, 32 patients showed primary AD, 56 showed non-AD neuropathology (primarily frontotemporal lobar degeneration [FTLD]), and 13 showed mixed AD/FTLD pathology. PIB showed higher sensitivity than FDG for detecting intermediate–high ADNC (96%, 95% confidence interval [CI] = 89–100% vs 80%, 95% CI = 68–92%, p = 0.02), but equivalent specificity (86%, 95% CI = 76–95% vs 84%, 95% CI = 74–93%, p = 0.80). In patients with congruent PIB and FDG reads (77/101), combined sensitivity was 97% (95% CI = 92–100%) and specificity was 98% (95% CI = 93–100%). Nine of 24 patients with incongruent reads were found to have co-occurrence of AD and non-AD pathologies.

Liao H, Zhu Z, Peng Y. **Potential Utility of Retinal Imaging for Alzheimer's Disease: A Review.** Front Aging Neurosci. 2018 Jun 22;10:188. doi: 10.3389/fnagi.2018.00188. PMID: 29988470; PMCID: PMC6024140.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:- General Review Evidence Level: (4)	Funding: International Collaboration Program of Universities in Guangdong Province Dropouts:	Patient Characteristics: Alzheimer’s	

Notes No appraisal			
Outcome Measures/ Results:	As a projection of the central nervous system (CNS), the retina has been described as a “window to the brain” and a novel marker for AD. Low cost, easy accessibility and non-invasive features make retina tests suitable for large-scale population screening and investigations of preclinical AD. Furthermore, a number of novel approaches in retina imaging, such as optical coherence tomography (OCT), have been developed and made it possible to visualize changes in the retina at a very fine resolution. In this review, we outline the background for AD to accelerate the adoption of retina imaging for the diagnosis and management of AD in clinical practice. Then, we focus on recent findings on the application of retina imaging to investigate AD and provide suggestions for future research directions.		

Liu W, Lin H, He X, Chen L, Dai Y, Jia W, Xue X, Tao J, Chen L. **Neurogranin as a cognitive biomarker in cerebrospinal fluid and blood exosomes for Alzheimer's disease and mild cognitive impairment.** Transl Psychiatry. 2020 Apr 29;10(1):125. doi: 10.1038/s41398-020-0801-2. PMID: 32350238; PMCID: PMC7190828.

Reviewer	Dementia Group		
Study Type/	Study	Patient	Intervention

Evidence Level	Detail/Limitations	Characteristics	
CS:++ Evidence Level: observational (2)	Funding: National Natural Science Foundation of China Dropouts: Study Limitations: searched to Jun 2019	Total No Patients: 4661 Patient Characteristics: Alzheimer's and MCI	neurogranin
Notes No excluded studies listed. No CoI of included studies reported.	Conclusion: These findings provide the clinical evidence that CSF and blood exosomes Ng can be used as a cognitive biomarker for AD and MCI-AD, and further studies are needed to define the specific range of Ng values for diagnosis at the different stages of AD.		
Outcome Measures/ Results: Associations	Results: A total of 24 articles eligible for inclusion and exclusion criteria were assessed, including 4661 individuals, consisting of 1518 AD patients, 1501 MCI patients, and 1642 healthy control subjects. The level of CSF Ng significantly increased in patients with AD and MCI compared with healthy control subjects (SMD: 0.84 [95% CI: 0.70–0.98], P < 0.001; SMD: 0.53 [95% CI: 0.40–0.66], P = 0.008), and higher in AD patients than in MCI patients (SMD: 0.18 [95% CI: 0.07–0.30], P = 0.002), and CSF Ng level of patients with MCI-AD who progressed from MCI to AD was significantly higher than that of patients with stable MCI (sMCI) (SMD: 0.71 [95% CI: 0.25–1.16], P = 0.002). Moreover, the concentration of Ng in blood plasma exosomes of patients with AD		

	and MCI was lower than that of healthy control subjects (SMD: −6.657 [95% CI: −10.558 to −2.755], P = 0.001; and SMD: −3.64 [95% CI: −6.50 to −0.78], P = 0.013), and which in patients with AD and MCI-AD were also lower than those in patients with sMCI (P < 0.001). Furthermore, regression analysis showed a negative relationship between MMSE scores and CSF Ng levels in MCI patients (slope = −0.249 [95% CI: −0.003 to −0.495], P = 0.047). Therefore, the Ng levels increased in CSF, but decreased in blood plasma exosomes of patients with AD and MCI-AD, and highly associated with cognitive declines.

Martínez G, Vernooij RW, Fuentes Padilla P, Zamora J, Flicker L, Bonfill Cosp X. **18F PET with florbetaben for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI).** Cochrane Database Syst Rev. 2017 Nov 22;11(11):CD012883. doi: 10.1002/14651858.CD012883. PMID: 29164600; PMCID: PMC6485979.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding: NIHR Study Limitations: searched to May 2017	Total No Patients: 45 Patient Characteristics: Alzheimer’s and MCI	18F PET

Notes Only 1 study	Conclusions: Although we were able to calculate one estimation of DTA in, especially, the prediction of progression from MCI to ADD at four years follow-up, the small number of participants implies imprecision of sensitivity and specificity estimates. We cannot make any recommendation regarding the routine use of ^{18}F-florbetaben in clinical practice based on one single study with 45 participants. ^{18}F-florbetaben has high financial costs, therefore, clearly demonstrating its DTA and standardising the process of the ^{18}F-florbetaben modality are important prior to its wider use.
Outcome Measures/ Results: Sensitivity, specificity	Progression from MCI to ADD, any other form of dementia, and any form of dementia was evaluated in one study (Ong 2015). It reported data on 45 participants at four years of follow-up; 21 participants met NINCDS-ADRDA criteria for Alzheimer's disease dementia at four years of follow-up, the proportion converting to ADD was 47% of the 45 participants, and 11% of the 45 participants met criteria for other types of dementias (three cases of FrontoTemporal Dementia (FTD), one of Dementia with Lewy body (DLB), and one of Progressive Supranuclear Palsy (PSP)). We considered the study to be at high risk of bias in the domains of the reference standard, flow, and timing (QUADAS-2).MCI to ADD; ^{18}F-florbetaben PET scan analysed visually: the sensitivity was 100% (95% confidence interval (CI) 84% to 100%) and the specificity was 83% (95% CI 63% to 98%) (n = 45, 1 study). Analysed quantitatively: the sensitivity was 100% (95% CI 84% to 100%) and the specificity was 88% (95% CI 68% to 97%) for the

	diagnosis of ADD at follow-up (n = 45, 1 study).MCI to any other form of dementia (non-ADD);^{18}F-florbetaben PET scan analysed visually: the sensitivity was 0% (95% CI 0% to 52%) and the specificity was 38% (95% CI 23% to 54%) (n = 45, 1 study). Analysed quantitatively: the sensitivity was 0% (95% CI 0% to 52%) and the specificity was 40% (95% CI 25% to 57%) for the diagnosis of any other form of dementia at follow-up (n = 45, 1 study).MCI to any form of dementia;^{18}F-florbetaben PET scan analysed visually: the sensitivity was 81% (95% CI 61% to 93%) and the specificity was 79% (95% CI 54% to 94%) (n = 45, 1 study). Analysed quantitatively: the sensitivity was 81% (95% CI 61% to 93%) and the specificity was 84% (95% CI 60% to 97%) for the diagnosis of any form of dementia at follow-up (n = 45, 1 study).

Martínez G, Vernooij RW, Fuentes Padilla P, Zamora J, Bonfill Cosp X, Flicker L. **18F PET with florbetapir for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI).** Cochrane Database Syst Rev. 2017 Nov 22;11(11):CD012216. doi: 10.1002/14651858.CD012216.pub2. PMID: 29164603; PMCID: PMC6486090.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level:	Funding: NIHR Study Limitations: searched to May 2017	Total No Patients: 448 Patient	18F PET

observational (2)		Characteristics: Alzheimer's and MCI	
Notes 3 studies	Conclusions: Although sensitivity was good in one included study, considering the poor specificity and the limited data available in the literature, we cannot recommend routine use of ^{18}F-florbetapir PET in clinical practice to predict the progression from MCI to ADD. Because of the poor sensitivity and specificity, limited number of included participants, and the limited data available in the literature, we cannot recommend its routine use in clinical practice to predict the progression from MCI to any form of dementia. Because of the high financial costs of ^{18}F-florbetapir, clearly demonstrating the DTA and standardising the process of this modality are important prior to its wider use.		
Outcome Measures/ Results: Sensitivity, specificity	We included three studies, two of which evaluated the progression from MCI to ADD, and one evaluated the progression from MCI to any form of dementia. Progression from MCI to ADD was evaluated in 448 participants. The studies reported data on 401 participants with 1.6 years of follow-up and in 47 participants with three years of follow-up. Sixty-one (15.2%) participants converted at 1.6 years follow-up; nine (19.1%) participants converted at three years of follow-up. Progression from MCI to any form of dementia was evaluated in five participants with 1.5 years of follow-up, with three (60%) participants converting to any form of dementia. There were		

	concerns regarding applicability in the reference standard in all three studies. Regarding the domain of flow and timing, two studies were considered at high risk of bias. MCI to ADD; Progression from MCI to ADD in those with a follow-up between two to less than four years had a sensitivity of 67% (95% CI 30 to 93) and a specificity of 71% (95% CI 54 to 85) by visual assessment (n = 47, 1 study).Progression from MCI to ADD in those with a follow-up between one to less than two years had a sensitivity of 89% (95% CI 78 to 95) and a specificity of 58% (95% CI 53 to 64) by visual assessment, and a sensitivity of 87% (95% CI 76 to 94) and a specificity of 51% (95% CI 45 to 56) by quantitative assessment by the standardised uptake value ratio (SUVR)(n = 401, 1 study).MCI to any form of dementia; Progression from MCI to any form of dementia in those with a follow-up between one to less than two years had a sensitivity of 67% (95% CI 9 to 99) and a specificity of 50% (95% CI 1 to 99) by visual assessment (n = 5, 1 study).MCI to any other forms of dementia (non-ADD);There was no information regarding the progression from MCI to any other form of dementia (non-ADD).

Martínez G, Vernooij RW, Fuentes Padilla P, Zamora J, Flicker L, Bonfill Cosp X. **18F PET with flutemetamol for the early diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI).** Cochrane Database Syst Rev. 2017 Nov 22;11(11):CD012884. doi: 10.1002/14651858.CD012884. PMID: 29164602; PMCID: PMC6486287.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding: NIHR Study Limitations: searched to May 2017	Total No Patients: 243 Patient Characteristics: Alzheimer's and MCI	18F PET
Notes Only 2 studies	Conclusions: Due to the varying sensitivity and specificity for predicting the progression from MCI to ADD and the limited data available, we cannot recommend routine use of 18F-flutemetamol in clinical practice. 18F-flutemetamol has high financial costs; therefore, clearly demonstrating its DTA and standardising the process of the 18F-flutemetamol modality is important prior to its wider		
Outcome Measures/ Results: Sensitivity, specificity	Progression from MCI to ADD was evaluated in 243 participants from two studies. The studies reported data on 19 participants with two years of follow-up and on 224 participants with three years of follow-up. Nine (47.4%) participants converted at two years follow-up and 81 (36.2%) converted at three years of follow-up. There were concerns about participant selection and sampling in both studies. The index test domain in one study was considered unclear and in the second study it was considered at low risk of bias. For the		

	reference standard domain, one study was considered at low risk and the second study was considered to have an unclear risk of bias. Regarding the domains of flow and timing, both studies were considered at high risk of bias. MCI to ADD; Progression from MCI to ADD at two years of follow-up had a sensitivity of 89% (95% CI 52 to 100) and a specificity of 80% (95% CI 44 to 97) by quantitative assessment by SUVR (n = 19, 1 study). Progression from MCI to ADD at three years of follow-up had a sensitivity of 64% (95% CI 53 to 75) and a specificity of 69% (95% CI 60 to 76) by visual assessment (n = 224, 1 study). There was no information regarding the other two objectives in this systematic review (SR): progression from MCI to other forms of dementia and progression to any form of dementia at follow-up.

Mo Y, Stromswold J, Wilson K, Holder D, Sur C, Laterza O, Savage MJ, Struyk A, Scheltens P, Teunissen CE, Burke J, Macaulay SL, Bråthen G, Sando SB, White LR, Weiss C, Cowes A, Bush MM, DeSilva G, Darby DG, Rainey-Smith SR, Surls J, Sagini E, Tanen M, Altman A, Luthman J, Egan MF**. A multinational study distinguishing Alzheimer's and healthy patients using cerebrospinal fluid tau/Aβ42 cutoff with concordance to amyloid positron emission tomography imaging.** Alzheimers Dement (Amst). 2017 Mar 6;6:201-209. doi: 10.1016/j.dadm.2017.02.004. PMID: 28349119; PMCID: PMC5357677 INCLUDED

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention

CS:+ Evidence Level: Cohort Level 2	Countries: United States, Netherlands, Norway, Australia	Total No Patients: 343 Patient Characteristics: AD, MCI, non-Alzheimers dementia	amyloid positron emission tomography
Notes PET scans are read by people blinded to assessment	Conclusion: In conclusion, this study demonstrates a robust tau/Ab42 measure that distinguished AD subjects from HC subjects and identified subjects with brain amyloidosis. This cutoff was validated in a second cohort. Our results support the view that CSF tau/Ab42 measures are useful surrogates to amyloid PET to aid in diagnosis of AD, possibly at early stages of disease. Finally, given the robust performance characteristics of this measure, these results support widespread use of tau/Ab42 in clinical settings, including an ongoing phase III trial of a beta-site APP-cleaving enzyme (BACE) inhibitor in a prodromal AD population		
Outcome Measures/ Results: Sensitivity, specificity	Atau/Ab4250.215 cutoff provided 94.8% sensitivity and 77.7% specificity. Concordance with PET visual reads was estimated at 86.9% in aw50%PET positive population. In the validation cohort, the Cut off demonstrated 78.4% sensitivity and 84.9% specificity to distinguish the AD and HC populations.		

Müller EG, Edwin TH, Stokke C, Navelsaker SS, Babovic A, Bogdanovic N, Knapskog AB, Revheim ME. **Amyloid-β PET-Correlation with cerebrospinal fluid biomarkers**

and prediction of Alzheimer´s disease diagnosis in a memory clinic. PLoS One. 2019 Aug 20;14(8):e0221365. doi: 10.1371/journal.pone.0221365. PMID: 31430334; PMCID: PMC6701762.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: diagnostic (2)	Countries: Norway Funding: Civitan Norway Research Foundation for Alzheimer´s disease	Total No Patients: 64 Patient Characteristics:	Amyloid Beta vs CSF
Notes	Conclusions: The present study showed an excellent correlation of Aβ42 in CSF and 18F-Flutemetamol PET and the presented cut-off value for Aβ42 yields high sensitivity and specificity for 18FFlutemetamol PET. 18F-Flutemetamol PET was the best predictor of clinical AD diagnosis.		
Outcome Measures/ Results:	Thirty-two of the 34 patients (94%) in the Flut+ group and nine of the 30 patients (30%) in the Flut- group had a clinical AD diagnosis. There were significant differences in all CSF biomarkers in the Flut+ and Flut- groups. Aβ42 showed the highest correlation with 18F-Flutemetamol PET with a cut-off value of 706.5 pg/mL, corresponding to sensitivity of 88% and specificity of 87%. 18F-Flutemetamol PET was the best predictor of a clinical AD diagnosis. We found a very high interrater agreement for both PET		

	classification and diagnosis.

Olsson B, Lautner R, Andreasson U, Öhrfelt A, Portelius E, Bjerke M, Hölttä M, Rosén C, Olsson C, Strobel G, Wu E, Dakin K, Petzold M, Blennow K, Zetterberg H. **CSF and blood biomarkers for the diagnosis of Alzheimer's disease: a systematic review and meta-analysis.** Lancet Neurol. 2016 Jun;15(7):673-684. doi: 10.1016/S1474-4422(16)00070-3. Epub 2016 Apr 8. PMID: 27068280.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding: Swedish Research Council, Swedish State Support for Clinical Research, Alzheimer's Association, the Knut and Alice Wallenberg Foundation, the Torsten Söderberg Foundation, the Alzheimer Foundation (Sweden), and the Biomedical Research Forum, LLC.	Patient Characteristics: Alzheimer's	CSF and blood biomarkers

	Dropouts: Study Limitations: searched to 2014		
Notes	Conclusions: Core CSF AD biomarkers and NFL, as well as plasma T-tau, are strongly associated with AD. Emerging biomarkers CSF NSE, VLP-1, HFABP, and YKL-40 are moderately associated with AD, while plasma Aβ42 and Aβ40 are not.		
Outcome Measures/ Results:	Of 4521 records identified from PubMed and 624 from Web of Science, 231 articles comprising 15 699 patients with Alzheimer's disease and 13 018 controls were included in this analysis. The core biomarkers differentiated Alzheimer's disease from controls with good performance: CSF T-tau (average ratio 2·54, 95% CI 2·44–2·64, p		

Palmqvist S, Zetterberg H, Blennow K, Vestberg S, Andreasson U, Brooks DJ, Owenius R, Hägerström D, Wollmer P, Minthon L, Hansson O. **Accuracy of brain amyloid detection in clinical practice using cerebrospinal fluid β-amyloid 42: a cross-validation study against amyloid positron emission tomography.** JAMA Neurol. 2014 Oct;71(10):1282-9. doi: 10.1001/jamaneurol.2014.1358. PMID: 25155658.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS/JB:+ Evidence Level:	Countries: Sweden Centres: 3 Funding: European	Total No Patients:118 + 38 Patient	CSF biomarkers vs Amyloid AB or AB42

diagnostic/cohort (2)	Research Council, the Swedish Research Council, the Strategic Research Area MultiPark (Multidisciplinary Research in Parkinson's disease) at Lund University, the Crafoord Foundation, the Swedish Brain Foundation, the Johan and Jakob Söderberg's Foundation, and the Swedish federal government under the ALF agreement Swedish Brain Power. Doses of 18F-flutemetamol injection were sponsored by GE Healthcare.	Characteristics: MCI	

Notes	Conclusions: Cerebrospinal fluid Aβ42 analyzed consecutively in routine clinical practice at an accredited laboratory can be used with high accuracy to determine whether a patient has normal or increased cortical Aβ deposition and so can be valuable for the early diagnosis of Alzheimer disease. Abnormal 18F-flutemetamol retention levels correlate with disease stage in patients with mild cognitive symptoms, but this is not the case for CSF Aβ42 measurements.
Outcome Measures/ Results: CSF Aβ42, total tau, and phosphorylated tau using an enzyme-linked immunosorbent assay (INNOTEST) in clinical samples.	The agreement between Aβ classification with CSF Aβ42 and 18F-flutemetamol positron emission tomography was very high (κ = 0.85). Of all the cases, 92% were classified identically using an Aβ42 cutoff of 647 pg/mL or less. Cerebrospinal fluid Aβ42 predicted abnormal cortical Aβ deposition accurately (odds ratio, 165; 95% CI, 39-693; area under the receiver operating characteristic curve, 0.94; 95% CI, 0.88-0.97). The association was independent of age, sex, APOE (apolipoprotein E) genotype, hippocampal volume, memory, and global cognition (adjusted odds ratio, 169; 95% CI, 25-1143). Using ratios of CSF Aβ42:tau or Aβ42:phosphorylated tau did not improve the prediction of Aβ deposition. Cerebrospinal fluid Aβ42 correlated significantly with Aβ deposition in all cortical regions. The highest correlations were in regions with high 18F-flutemetamol retention (eg, posterior cingulum and precuneus, r = −0.72). 18F-flutemetamol retention, but not CSF Aβ42, correlated significantly with global cognition (r = −0.32), memory function (r = −0.28), and hippocampal volume

	(r = −0.36) among those with abnormal Aβ deposition. Finally, the CSF Aβ42 cutoff derived from the original cohort (647 pg/mL) had an equally high agreement (95%; κ = 0.89) with 18F-flutemetamol positron emission tomography in the validation cohort.

Piersson AD, Mohamad M, Rajab F, Suppiah S. **Cerebrospinal Fluid Amyloid Beta, Tau Levels, Apolipoprotein, and ^{1}H-MRS Brain Metabolites in Alzheimer's Disease: A Systematic Review.** Acad Radiol. 2021 Oct;28(10):1447-1463. doi: 10.1016/j.acra.2020.06.006. Epub 2020 Jul 7. PMID: 32651050.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: (2)		Patient Characteristics: Alzhemier’s	CSF testing
Notes No indication of double selection or extraction. No excluded studies listed. No publication bias assessed. No CoI	Conclusions: NAA, ml, NAA/Cr, NAA/ml and ml/Cr may be potentially useful biomarkers that may highlight functional changes in the clinical stages of AD. The combinations of ml and tau, NAA/Cr and Ab42, and NAA/Cr and tau may support the diagnostic process of differentiating MCI/AD from healthy individuals. Large, longitudinal studies are required to clarify the effect of APOE e4 on brain metabolites.		

of included studies reported.	
Outcome Measures/ Results:	Twenty four articles met the inclusion criteria. Decreased levels of N-acetyl aspartate (NAA), NAA/(creatine) Cr, and NAA/(myoinositol) ml, and increased ml, ml/Cr, Cho (choline)/Cr, and ml/NAA were found in the posterior cingulate cortex/precuneus. Increased ml is associated with increased tau levels, reduced NAA/Cr is associated with increased tau. ml/Cr is negatively correlated with Ab42, and ml/Cr is positively correlated with t-tau. NAA and glutathione levels are reduced in APOE e4 carriers. APOE e4 exerts no modulatory effect on NAA/Cr. There is interaction between APOE e4, Ab42, and ml/Cr.

Rice L, Bisdas S. **The diagnostic value of FDG and amyloid PET in Alzheimer's disease-A systematic review.** Eur J Radiol. 2017 Sep;94:16-24. doi: 10.1016/j.ejrad.2017.07.014. Epub 2017 Jul 20. PMID: 28941755. NOT INCLUDED			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:- Evidence Level: General review (4)		Patient Characteristics: Alzheimers	FDG & Amyloid PET
Notes No indication of	Conclusions: Both techniques have been shown to detect AD with high sensitivity and specificity compared to other neurodegenerative		

double selection or extraction. No excluded studies listed. No quality of studies assessed. No CoI of included studies reported.	processes and cognitively normal age-matched individuals. However, future studies with standardised, uniform thresholds and a lengthier longitudinal follow-up need to be conducted to allow us to make surer conclusions about the future role of PET in clinical practice. In addition, comparison with post-mortem diagnosis, rather than clinical diagnosis with its acknowledged flaws, would result in more powerful statistical outcomes – which is becoming increasingly important given that several disease-modifying AD drugs are now in phase 3 trials.
Outcome Measures/ Results: Sensitivity and specificity	This search resulted in twenty-nine papers on amyloid imaging, twenty-three papers on FDGPET and eight papers which utilized both techniques. Both modalities are considered in turn with regards to their diagnostic accuracy, their role in mild cognitive impairment (MCI) and prognostication, their use in the differential diagnosis of AD and their clinical application. As evidenced from the current literature, both amyloid and FDG-PET meet criteria for suitable biomarkers for the diagnosis of AD. They both indicate pathophysiological processes, albeit at different stages of the Alzheimer's process, and are distinct from normal patterns of aging.

Ritchie C, Smailagic N, Noel-Storr AH, Takwoingi Y, Flicker L, Mason SE, McShane R. **Plasma and cerebrospinal fluid amyloid beta for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI).**

<table>
<tr><td colspan="4">Cochrane Database Syst Rev. 2014 Jun 10;2014(6):CD008782. doi: 10.1002/14651858.CD008782.pub4. PMID: 24913723; PMCID: PMC6465069.</td></tr>
<tr><td>Reviewer</td><td colspan="3">Dementia Group</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study Detail/Limitations</td><td>Patient Characteristics</td><td>Intervention</td></tr>
<tr><td>CS:++

Evidence Level: observational (2)</td><td>Funding: None stated
Study Limitations: searched to Dec 2012</td><td>Total No Patients:1349
Patient Characteristics: dementia and MCI</td><td>AB42</td></tr>
<tr><td>Notes
No publication bias assessed. No CoI of included studies reported.</td><td colspan="3">Conclusions: The proposed diagnostic criteria for prodromal dementia and MCI due to Alzheimer's disease, although still being debated, would be fulfilled where there is both core clinical and cognitive criteria and a single biomarker abnormality. From our review, the measure of abnormally low CSF Aß levels has very little diagnostic benefit with likelihood ratios suggesting only marginal clinical utility. The quality of reports was also poor, and thresholds and length of follow-up were inconsistent. We conclude that when applied to a population of patients with MCI, CSF Aß levels cannot be recommended as an accurate test for Alzheimer's disease.</td></tr>
<tr><td>Outcome Measures/ Results:

Sensitivity,</td><td colspan="3">Alzheimer's disease dementia was evaluated in 14 studies using CSF Aß42. Of the 1349 participants included in the meta-analysis, 436 developed Alzheimer’s dementia. Individual study estimates of sensitivity were between 36% and 100% while the specificities were</td></tr>
</table>

specificity	between 29% and 91%. Because of the variation in assay thresholds, we did not estimate summary sensitivity and specificity. However, we derived estimates of sensitivity at fixed values of specificity from the model we fitted to produce the summary ROC curve. At the median specificity of 64%, the sensitivity was 81% (95% CI 72 to 87). This equated to a positive likelihood ratio (LR+) of 2.22 (95% CI 2.00 to 2.47) and a negative likelihood ratio (LR–) of 0.31 (95% CI 0.21 to 0.48). The accuracy of CSF Aß42 for all forms of dementia was evaluated in four studies. Of the 464 participants examined, 188 developed a form of dementia (Alzheimer's disease and other forms of dementia).The thresholds used were between 209 mg/ml and 512 ng/ml. The sensitivitieswere between 56% and 75% while the specificitieswere between 47% and 76%. Atthe median specificity of 75%,the sensitivity was estimated to be 63% (95% CI 22 to 91) from the meta-analytic model. This equated to a LR+ of 2.51 (95% CI 1.30 to 4.86) and a LR– of 0.50 (95% CI 0.16 to 1.51). The accuracy of CSF Aß42 for non-Alzheimer's disease dementia was evaluated in three studies. Of the 385 participants examined, 61 developed non-Alzheimer's disease dementia. Since there were very few studies and considerable variation between studies, the results were not meta-analysed. The sensitivities were between 8% and 63% while the specificities were between 35% and 67%. Only one study examined the accuracy of plasma Aß42 and the plasma Aß42/Aß40 ratio for Alzheimer's disease dementia. The sensitivity of 86% (95% CI 81 to 90) was the same for both tests while the

	specificities were 50% (95% CI 44 to 55) and 70% (95% CI 64 to 75) for plasma Aß42 and the plasma Aß42/Aß40 ratio respectively. Of the 565 participants examined, 245 developed Alzheimer's dementia and 87 nonAlzheimer's disease dementia. There was substantial heterogeneity between studies. The accuracy of Aß42 forthe diagnosis of Alzheimer's disease dementia did not diGer significantly (P = 0.8) between studies that pre-specified the threshold for determining test positivity (n = 6) and those that only determined the threshold at follow-up (n = 8). One study excluded a sample of MCI non-Alzheimer's disease dementia converters from their analysis. In sensitivity analyses, the exclusion of this study had no impact on our findings. The exclusion of eight studies (950 patients) that were considered at high (n = 3) or unclear (n = 5) risk of bias for the patient selection domain also made no diGerence to our findings.

Ritchie C, Smailagic N, Noel-Storr AH, Ukoumunne O, Ladds EC, Martin S. **CSF tau and the CSF tau/ABeta ratio for the diagnosis of Alzheimer's disease dementia and other dementias in people with mild cognitive impairment (MCI).** Cochrane Database Syst Rev. 2017 Mar 22;3(3):CD010803. doi: 10.1002/14651858.CD010803.pub2. PMID: 28328043; PMCID: PMC6464349.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++	Funding: NIHR	Total No	t-tau,p-tau or p-

Evidence Level: observational (2)	Study Limitations: searched to Jan 2013	Patients:1282 Patient Characteristics: Alzheimers and MCI Inclusion Criteria: Exclusion Criteria:	tau/ABeta ratio
Notes No publication bias assessed. No CoI of included studies reported.	Conclusions: The insufficiency and heterogeneity of research to date primarily leads to a state of uncertainty regarding the value of CSF testing of t-tau,p-tau or p-tau/ABeta ratio for the diagnosis of Alzheimer's disease in current clinical practice. Particular attention should be paid to the risk of misdiagnosis and over diagnosis of dementia (and therefore over-treatment) in clinical practice. These tests, like other biomarker tests which have been subject to Cochrane DTA reviews, appear to have better sensitivity than specificity and therefore might have greater utility in ruling out Alzheimer's disease as the aetiology to the individual's evident cognitive impairment, as opposed to ruling it in. The heterogeneity observed in the few studies awaiting classification suggests our initial summary will remain valid. However, these tests may have limited clinical value until uncertainties have been addressed. Future studies with more uniformed approaches to thresholds, analysis and study conduct may provide a more homogenous estimate than the one that has been available from the included studies we have identified.		
Outcome Measures/	In total, 1282 participants with MCI at baseline were identified in		

Results: Sensitivity, specificity	the 15 included studies of which 1172 had analysable data; 430 participants converted to Alzheimer's disease dementia and 130 participants to other forms of dementia. Follow-up ranged from less than one year to over four years for some participants, but in the majority of studies was in the range one to three years. Conversion to Alzheimer's disease dementia. The accuracy of the CSF t-tau was evaluated in seven studies (291 cases and 418 non-cases).The sensitivity values ranged from 51% to 90%while the specificity values ranged from 48% to 88%. At the median specificity of 72%, the estimated sensitivity was 75% (95% CI 67 to 85),the positive likelihood ratio was 2.72 (95% CI 2.43 to 3.04), and the negative likelihood ratio was 0.32 (95% CI 0.22 to 0.47).Six studies (164 cases and 328 non-cases) evaluated the accuracy of the CSF p-tau. The sensitivities were between 40% and 100% while the specificities were between 22% and 86%. At the median specificity of 47.5%, the estimated sensitivity was 81% (95% CI: 64 to 91), the positive likelihood ratio was 1.55 (CI 1.31 to 1.84), and the negative likelihood ratio was 0.39 (CI: 0.19 to 0.82).Five studies (140 cases and 293 non-cases) evaluated the accuracy of the CSF p-tau/ABeta ratio. The sensitivities were between 80% and96% while the specificities were between 33% and 95%. We did not conduct a meta-analysis because the studies were few and small. Only one study reported the accuracy of CSF t-tau/ABeta ratio. Our findings are based on studies with poor reporting. A significant number of studies had unclear risk of bias for the reference standard,

	participant selection and flow and timing domains. According to the assessment of index test domain, eight of 15 studies were of poor methodological quality. The accuracy of these CSF biomarkers for 'other dementias' had not been investigated in the included primary studies. Investigation of heterogeneity. The main sources of heterogeneity were thought likely to be reference standards used for the target disorders, sources of recruitment, participant sampling, index test methodology and aspects of study quality (particularly, inadequate blinding).We were not able to formally assess the effect of each potential source of heterogeneity as planned, due to the small number of studies available to be included.

Rivero-Santana A, Ferreira D, Perestelo-Pérez L, Westman E, Wahlund LO, Sarría A, Serrano-Aguilar P. **Cerebrospinal Fluid Biomarkers for the Differential Diagnosis between Alzheimer's Disease and Frontotemporal Lobar Degeneration: Systematic Review, HSROC Analysis, and Confounding Factors.** J Alzheimers Dis. 2017;55(2):625-644. doi: 10.3233/JAD-160366. PMID: 27716663.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: diagnostic (2)	Study Limitations: searched to May 2016	Patient Characteristics: Alzheimer's Disease and Frontotemporal Lobar Degeneration	AB42, Tau, phosphorylated tau,

Notes No indication of double data extraction. No excluded studies listed. No publication bias assessed. No CoI of included studies reported.	Conclusions: The p-tau/A_42 ratio has potential for being implemented in the clinical routine for the differential diagnosis between AD and FTLD. It is of utmost importance that future studies report information on confounders such as age, disease duration, and cognitive impairment, which should also stimulate understanding of the role of these factors in disease mechanisms and pathophysiology.		
Outcome Measures/ Results: Sensitivity, specificity,	The p-tau/A_42 ratio showed the best diagnostic performance. No statistically significant effects of the confounders were observed. Nonetheless, the p-tau/A_42 ratio may be especially indicated for younger patients. P-tau may be preferable for less cognitively impaired patients (high MMSE scores) and the t-tau/A_42 ratio for more cognitively impaired patients (low MMSE scores).		

Rossi M, Baiardi S, Teunissen CE, Quadalti C, van de Beek M, Mammana A, Stanzani-Maserati M, Van der Flier WM, Sambati L, Zenesini C, Caughey B, Capellari S, Lemstra AW, Parchi P. **Diagnostic Value of the CSF α-Synuclein Real-Time Quaking-Induced Conversion Assay at the Prodromal MCI Stage of Dementia With Lewy Bodies.** Neurology. 2021 Aug 31;97(9):e930-e940. doi: 10.1212/WNL.0000000000012438. Epub 2021 Jul 1. PMID: 34210822; PMCID: PMC8408510.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+ Evidence Level: Diagnostic (2)	Countries: Italy, Netherlands	Total No Patients: 289 Patient Characteristics: 65-71	α-syn RT-QuIC to CSF samples
Notes This study is in MCI not dementia	These findings indicate that CSF α-syn RT-QuIC is a robust biomarker for prodromal DLB. Further studies are needed to fully explore the added value of the assay to the current research criteria for MCI-LB.		
Outcome Measures/ Results: Sensitivity, specificity	RT-QuIC identified patients with MCI-LB against cognitively unimpaired controls with 95% sensitivity, 97% specificity, and 96% accuracy and showed 98% specificity in neuropathologic controls. The accuracy of the test for MCI-LB was consistent between the 2 cohorts (97.3% vs 93.7%). Thirteen percent of patients with MCI-AD also had a positive test; of note, 44% of them developed 1 core or supportive clinical feature of dementia with Lewy bodies (DLB) at follow-up, suggesting an underlying LB copathology.		

Seeburger JL, Holder DJ, Combrinck M, Joachim C, Laterza O, Tanen M, Dallob A, Chappell D, Snyder K, Flynn M, Simon A, Modur V, Potter WZ, Wilcock G, Savage MJ,

Smith AD. **Cerebrospinal fluid biomarkers distinguish postmortem-confirmed Alzheimer's disease from other dementias and healthy controls in the OPTIMA cohort**. J Alzheimers Dis. 2015;44(2):525-39. doi: 10.3233/JAD-141725. PMID: 25391385.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
No appraisal required Evidence Level:single cohort (3)	Countries: UK Funding: NIHR	Total No Patients:227 Patient Characteristics: Alzheimer's, non-Alzheimer's dementia, controls	CSF specimens
Notes	In a well-characterized, homogeneous population, a single cutoff for baseline CSF A_ and tau markers can distinguish AD with a high level of sens/spec compared to other studies. It may be important to characterize sources of demographic and biological variability to support the effective use of CSF diagnostic assays in the broader AD population.		
Outcome Measures/ Results: t-tau, p-tau, , AB-40, AB-42	Baseline CSF was analysed from 227 participants with AD (97% autopsy-confirmed), mild cognitive impairment (MCI; 73% confirmed), other dementia syndrome (ODS; 100% confirmed), and controls (CTL; 27% confirmed, follow up approximately 9–13 years). Biomarker concentrations were analysed using validated		

	ELISAs. AD patients had lower CSF A_42 and higher t-tau, p-tau, t-tau/A_42, and t-tau/A_40 compared to CTLs, with MCI intermediate. CTL and MCI participants who progressed to AD demonstrated more AD-like profiles. A_40, sA_PP_, and sA_PP_ were lower in AD compared to CTL. High-level discriminators of AD from CTL were t-tau/A_40 (AUROC 0.986, sens/spec of 92%/94%), p-tau/A_42 (AUROC 0.972, sens/spec of 94%/90%), and A_42 (AUROC 0.941, sens/spec of 88%). For discriminating AD from ODS, p-tau/A_42 demonstrated sens/spec of 88%/100% (95%/86% at the AD versus CTL cutoff) and A_42 demonstrated sens/spec of 84%/100% (88%/100% at the AD versus CTL cutoff).

Shi D, Han M, Liu W, Tao J, Chen L. **Circulating MicroRNAs as Diagnostic Biomarkers of Clinical Cognitive Impairment: A Meta-Analysis.** Am J Alzheimers Dis Other Demen. 2020 Jan-Dec;35:1533317520951686. doi: 10.1177/1533317520951686. PMID: 33094634; PMCID: PMC10624042.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Study Limitations: searched to Nov 2018	Patient Characteristics: Alzheimer's and MCI	
Notes	Conclusions: : Our study found that miRNAs have certain		

No CoI of included studies reported.	diagnostic value for cognitive impairment, with high sensitivity and specificity, especially in diagnostics with multiple miRNAs and serumbased miRNA assays.
Outcome Measures/ Results: Sensitivity, specificity	A total of 18 studies involving 729 patients with AD, 283 patients with MCI, and 15 patients with MCI-AD were pooled. The results revealed that the sensitivity and specificity of miRNAs in the diagnosis of AD were 0.78 and 0.79, respectively, and the area under the summary receiver operating characteristic curve (AUSROC) was 0.90. The sensitivity and specificity of miRNAs in the diagnosis of MCI were 0.89 and 0.85, respectively, and the AUSROC was 0.94. The sensitivity and specificity of microRNAs in the diagnosis of MCI-AD were 0.87 and 0.84, respectively, and the AUSROC was 0.92

Showraki A, Murari G, Ismail Z, Barfett JJ, Fornazzari L, Munoz DG, Schweizer TA, Fischer CE. **Cerebrospinal Fluid Correlates of Neuropsychiatric Symptoms in Patients with Alzheimer's Disease/Mild Cognitive Impairment: A Systematic Review**. J Alzheimers Dis. 2019; 71(2):477-501. doi: 10.3233/JAD-190365. PMID: 31424398.

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:+	Funding: Michael's Hospital	Patient Characteristics:	NPS vs CF

Evidence Level: (2)	Foundation. Study Limitations: searched to 2018	Alzheimer's and MCI	
Notes No indication of double selection or extraction. No excluded studies listed. No publication bias assessed. No CoI of included studies reported.	Conclusions: Our study has revealed agitation/aggression as the most *consistent* NPS related to core AD CSF biomarkers. Future studies are required to focus on other neglected NPS domains such as disinhibition. Moreover, why depression was the only NPS inversely associated with core AD CSF pathology remains to be elucidated. Our study also revealed a great degree of heterogeneity, hence calling for a more standardized "objective" approach for the evaluation of NPS.		
Outcome Measures/ Results:	In total, 21 studies qualified for the systematic review. The overall picture regarding the association between NPS and AD CSF biomarkers is conflicting. However, agitation/aggression was significantly and consistently related to core AD CSF biomarkers. Moreover, depression was the only NPS to occasionally be associated with lower core AD CSF pathology.		

Swarbrick S, Wragg N, Ghosh S, Stolzing A. **Systematic Review of miRNA as Biomarkers in Alzheimer's Disease.** Mol Neurobiol. 2019 Sep;56(9):6156-6167. doi: 10.1007/s12035-019-1500-y. Epub 2019 Feb 8. PMID: 30734227; PMCID: PMC6682547.			
Reviewer	Dementia Group		
Study Type/	Study	Patient	Intervention

Evidence Level	Detail/Limitations	Characteristics	
General Review Evidence Level: (4)		Patient Characteristics: Alzheimer's	Mi RNA
Notes No appraisal			
Outcome Measures/ Results:	These deregulated miRNAs were cross-referenced against the miRNAs deregulated in the brain at Braak Stage III. This resulted in a panel of 10 miRNAs (hsa-mir-107, hsa-mir-26b, hsa-mir-30e, hsa-mir-34a, hsa-mir-485, hsa-mir200c, hsa-mir-210, hsa-mir-146a, hsa-mir-34c, and hsa-mir-125b) hypothesised to be deregulated early in Alzheimer's disease, nearly 20 years before the onset of clinical symptoms. After network analysis of the 10 miRNAs, they were found to be associated with the immune system, cell cycle, gene expression, cellular response to stress, neuron growth factor signalling, wnt signalling, cellular senescence, and Rho GTPases.		

Tang W, Wang Y, Cheng J, Yao J, Yao YY, Zhou Q, Guan SH. **CSF sAPPα and sAPPβ levels in Alzheimer's Disease and Multiple Other Neurodegenerative Diseases: A Network Meta-Analysis.** Neuromolecular Med. 2020 Mar;22(1):45-55. doi: 10.1007/s12017-019-08561-7. Epub 2019 Aug 14. PMID: 31414383.

Reviewer	Dementia Group

Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
CS:++ Evidence Level: observational (2)	Funding: Anhui Provincial Natural Science Foundation	Total No Patients:1634 Patient Characteristics: Alzheimer's	CSF sAPPα and sAPPβ
Notes No excluded studies listerd. CoI of included studies reported.	Conclusion: In conclusion, our NMA findings demonstrated that the measurement of CSF sAPPα and sAPPβ levels may be helpful in the diagnosis of early-stage AD, which is conducive to preventive therapy. In the future, a multicentre randomized trial with optimal and standard detection methods, as well as a large sample size, to verify our findings is warranted		
Outcome Measures/ Results:	Twenty studies, comprising ten groups, were eligible and included. Overall, 19 eligible studies with 1634 patients contributed to the analysis of CSF sAPPα levels and 16 eligible studies with 1684 patients contributed to the analysis of CSF sAPPβ levels. CSF sAPPβ levels are significantly higher in AD than in corticobasal syndrome (CBS) and progressive supranuclear palsy (PSP); higher in Control than in Depression, CBS and PSP; higher in Parkinson's disease dementia (PDD) than in CBS and PSP; higher in mild cognitive impairment progressed to AD dementia during the follow-up period (pMCI) than in Depression and PSP; higher in stable mild cognitive impairment (sMCI) than in Depression. With regard to		

	CSF sAPPα levels, there were no significant difference among groups. However, surprisingly, the resultant rankings graphically showed that pMCI populations have the highest levels of CSF sAPPα and sAPPβ. Furthermore, it seemed there was a positive correlation between CSF sAPPα and sAPPβ levels. The measurement of CSF sAPPα and sAPPβ levels may provide an alternative method for the diagnosis of early-stage AD, pMCI, which is conducive to preventive therapy.

Weiner MW, Veitch DP, Aisen PS, Beckett LA, Cairns NJ, Green RC, Harvey D, Jack CR Jr, Jagust W, Morris JC, Petersen RC, Saykin AJ, Shaw LM, Toga AW, Trojanowski JQ; Alzheimer's Disease Neuroimaging Initiative. **Recent publications from the Alzheimer's Disease Neuroimaging Initiative: Reviewing progress toward improved AD clinical trials.** Alzheimers Dement. 2017 Apr;13(4):e1-e85. doi: 10.1016/j.jalz.2016.11.007. Epub 2017 Mar 22. PMID: 28342697; PMCID: PMC6818723. NOT INCLUDED

Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
General review Evidence Level: (4)	Funding: NIH	Patient Characteristics: Alzheimer's and MCI	
Notes Despite the size of this study there is	Conclusion: Taken together, these studies fundamentally deepen our understanding of AD progression and its underlying genetic basis, which in turn informs and improves clinical trial design.		

no methodology to appraise	
Outcome Measures/ Results:	(1) Structural and functional changes, including subtle changes to hippocampal shape and texture, atrophy in areas outside of hippocampus, and disruption to functional networks, are detectable in presymptomatic subjects before hippocampal atrophy; (2) In subjects with abnormal b-amyloid deposition (Aβ+), biomarkers become abnormal in the order predicted by the amyloid cascade hypothesis; (3) Cognitive decline is more closely linked to tau than Aβ deposition; (4) Cerebrovascular risk factors may interact with Aβ to increase white-matter (WM) abnormalities which may accelerate Alzheimer's disease (AD) progression in conjunction with tau abnormalities; (5) Different patterns of atrophy are associated with impairment of memory and executive function and may underlie psychiatric symptoms; (6) Structural, functional, and metabolic network connectivities are disrupted as AD progresses. Models of prion-like spreading of Aβ pathology along WM tracts predict known patterns of cortical Aβ deposition and declines in glucose metabolism; (7) New AD risk and protective gene loci have been identified using biologically informed approaches; (8) Cognitively normal and mild cognitive impairment (MCI) subjects are heterogeneous and include groups typified not only by "classic" AD pathology but also by normal biomarkers, accelerated decline, and suspected non-Alzheimer's pathology; (9) Selection of subjects at risk of imminent decline on the basis of one or more pathologies

	improves the power of clinical trials; (10) Sensitivity of cognitive outcome measures to early changes in cognition has been improved and surrogate outcome measures using longitudinal structural magnetic resonance imaging may further reduce clinical trial cost and duration; (11) Advances in machine learning techniques such as neural networks have improved diagnostic and prognostic accuracy especially in challenges involving MCI subjects; and (12) Network connectivity measures and genetic variants show promise in multimodal classification and some classifiers using single modalities are rivaling multimodal classifiers.

Xu LZ, Li FY, Li BQ, Cao SM, Li Y, Xu J, Jia JP. **Decreased Levels of Insulin-Like Growth Factor-1 Are Associated with Alzheimer's Disease: A Meta-Analysis.** J Alzheimers Dis. 2021;82(3):1357-1367. doi: 10.3233/JAD-210516. PMID: 34151815.			
Reviewer	Dementia Group		
Study Type/ Evidence Level	Study Detail/Limitations	Patient Characteristics	Intervention
Should really reject CS:- Evidence Level: 2	Funding: not stated	Patient Characteristics: Alzheimer’s	Levels of Insulin-Like Growth Factor-1
Notes Heterogeneity is very high. Can’t see the quality	Conclusion: These findings suggest that decreased peripheral and cerebrospinal fluid IGF-1 levels might be a potential marker for the cognitive decline and progression of AD.		

assessment of studies. Publication bias is assessed, but no funnel plots given. No CoI of included studies reported. This is not a good review.	
Outcome Measures/ Results: Levels of Insulin-Like Growth Factor-1	Results: Results of random-effects meta-analysis showed that there was no significant difference between AD patients and healthy control (17 studies; standard mean difference [SMD], –0.01; 95%CI, –0.35 to 0.32) and between MCI patients and healthy control (6 studies; SMD, –0.20; 95%CI, –0.52 to 0.13) in peripheral IGF-1 levels. Meta-regression analyses identified age difference might explain the heterogeneity (p = 0.017). However, peripheral IGF-1 levels were significantly decreased in AD subjects (9 studies; SMD, –0.44; 95%CI, –0.81 to –0.07) and MCI subjects exhibited a decreasing trend (4 studies; SMD, –0.31; 95%CI, –0.72 to 0.11) in studies with sample size ≥ 80. Cerebrospinal fluid IGF-1 levels also significantly decreased in AD subjects (3 studies; SMD, –2.40; 95%CI, –4.36 to –0.43)

Zwan M, van Harten A, Ossenkoppele R, Bouwman F, Teunissen C, Adriaanse S, Lammertsma A, Scheltens P, van Berckel B, van der Flier W. **Concordance between cerebrospinal fluid biomarkers and [11C]PIB PET in a memory clinic cohort.** J

<table>
<tr><td colspan="4">Alzheimers Dis. 2014;41(3):801-7. doi: 10.3233/JAD-132561. PMID: 24705549. NOT INCLUDED</td></tr>
<tr><td>Reviewer</td><td colspan="3">Dementia Group</td></tr>
<tr><td>Study Type/ Evidence Level</td><td>Study Detail/Limitations</td><td>Patient Characteristics</td><td>Intervention</td></tr>
<tr><td>CS/JB:+

Evidence Level: cohort (2)</td><td>Countries:Netherlands
Funding: Internationale Stichting Alzheimer Onderzoek, American Health Assistance Foundation</td><td>Total No Patients:64+34+22+16
Patient Characteristics: Alzheimer’s and MCI</td><td>Cerebrospinal Fluid Biomarkers and [11C]PIB PET</td></tr>
<tr><td>PET images were assessed blind to clinical info and MRI results. This study doesn’t fit the checklist all that well.</td><td colspan="3">Conclusion: Concordance between CSF Aβ42 and [11C]PIB PET was good in all diagnostic groups. Discordance was mostly seen in MCI and AD patients close to the cut-point. These results provide convergent validity for the use of both types of biomarkers as measures of AD pathology.</td></tr>
<tr><td>Outcome Measures/ Results:</td><td colspan="3">Overall, concordance between [11C]PIB PET and CSF Aβ42 (<550 ng/L) was 84%. In discordant cases, [11C]PIB PET was more often AD-positive than Aβ42. When a more lenient Aβ42 cut-point (<640 ng/L) or a combination of Aβ42 and tau was used, concordance with [11C]PIB PET appeared to be even higher (90% and 89%). This</td></tr>
</table>

	difference is explained by a subgroup of mostly MCI and AD patients with Aβ42 levels just above cut-off. Now, in discordant cases, CSF was more often AD-positive than [11C]PIB PET.

Appendix 3. Summary of ongoing Amyloid PET studies (listed by amyloid isotope, Cochrane reviews, 2017) [46-48]

Review	NCT	Link	Completed study link
Flutemetamol [43]	NCT02164643 Longitudinal study of brain amyloid imaging in MEMENTO (MEMENTOAmyGing).	https://clinicaltrials.gov/ct2/show/NCT02164643 Completed	No results posted
	NCT02196116 Amyloid load in elderly population: effect of cognitive reserve (EDUMA).	https://clinicaltrials.gov/ct2/show/NCT02196116 Unknown	No results posted

	EUCTR2011-001756-12-BE Surrogate markers evaluation in pre-demented Alzheimer's disease patients and healthy elderly controls.	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2011-001756-12 Ongoing	No results available
	EUCTR2011-006195-39-BE An open-label study to compare the prognostic value of (18F)Flutemetamol PET-imaging with longitudinal biomarker data in healthy volunteers and patients with mild cognitive impairment.	https://www.clinicaltrialsregister.eu/ctr-search/search?query=2011-006195-39 Ongoing	No results available

	apps.who.int/trialsearch/ Trial2.aspx?		
	JPRN-UMIN000019926 Clinical and neuroimaging study on preclinical Alzheimer's disease. apps.who.int/trialsearch/ Trial2.aspx?	https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000022596 No longer recruiting – considered complete 30/2/2020	Results unpublished
	EUCTR2017-000094-36-E The BioFINDER 2 study improved diagnostics and increased understanding of the pathophysiology of cognitive disorders. NCT03174938 -	https://clinicaltrials.gov/ct2/show/NCT03174938 Recruiting	No results posted
	EUCTR2016-002635-15-NL	https://pubmed.ncbi.nlm.nih.gov/30477432/	

	Study to Identify Factors associated with Resilience to Clinical Dementia at Old Age - 90+ Study.	This is just the protocol – can't find anything else. The Netherlands trial registry doesn't exist anymore	
Florbetapir [44]	JPRN-UMIN000019926 Clinical and neuroimaging study on preclinical Alzheimer's disease	See above	
	NCT01325259 FluoroAv45 imaging research-in Alzheimer's disease (FAIR-AD)	https://clinicaltrials.gov/ct2/show/NCT01325259 Completed	No results posted
	NCT01554202. Multi-modal neuroimaging in Alzheimer's disease	https://clinicaltrials.gov/ct2/show/NCT01554202 Unknown	No results posted

	(IMAP)		
	NCT01638949. Multi-modal neuroimaging in Alzheimer's disease (IMAP+)	https://clinicaltrials.gov/ct2/show/NCT01638949 Unknown	No results posted
	NCT01687153. A study of brain aging in Vietnam war veterans (DOD-ADNI)	https://clinicaltrials.gov/ct2/show/NCT01687153 Completed	No results posted
	NCT01746706. Can the assessment of the subhippocampal region contribute to the detection of early diagnosis of Alzheimer's disease? A validation study	https://clinicaltrials.gov/ct2/show/NCT01746706 Unknown	No results posted

	using PET with florbetapir (AV-45)		
	NCT02164643. Longitudinal study of brain amyloid imaging in MEMENTO (MEMENTOAmyGing)	As above	
	NCT02330510. Amyloid and glucose PET imaging in Alzheimer and vascular cognitive impairment patients with significant white matter disease (MITNEC C6)	https://clinicaltrials.gov/ct2/show/NCT02330510 Recruiting	No results posted
	NCT02343757. Alzheimer's disease imaging with PET/MRI -	https://clinicaltrials.gov/ct2/show/NCT02343757 Terminated	No results posted

	betaamyloid.		
	NCT02854033. Alzheimer's disease neuroimaging initiative 3 (ADNI3) protocol	https://clinicaltrials.gov/ct2/show/NCT02854033 Recruiting	No results posted
Florbetaben [45]	EUCTR2013-004671-12-BE Predictive value of biomarkers in patients with amnestic mild cognitive impairment	https://www.clinicaltrialsregister.eu/ctr-search/trial/2013-004671-12/BE Ongoing	No results
	EUCTR2014-000562-21-NL Amyloid-PET as a diagnostic marker in daily practice	Can't find anything on this. NL trials register doesn't exist	
	EUCTR2014-004244-35-IT	Can't find anything on this	

	Amyloid load in prodromal AD with limbic-predominant phenotype		
	NCT01222351. Measuring brain amyloid plaque load in older adults using BAY 94-9172	https://clinicaltrials.gov/ct2/show/NCT01222351 Active not recruiting	No results posted
	NCT02854033. Alzheimer's disease neuroimaging initiative 3 (ADNI3) protocol	https://clinicaltrials.gov/ct2/show/NCT02854033 recruiting	No results posted

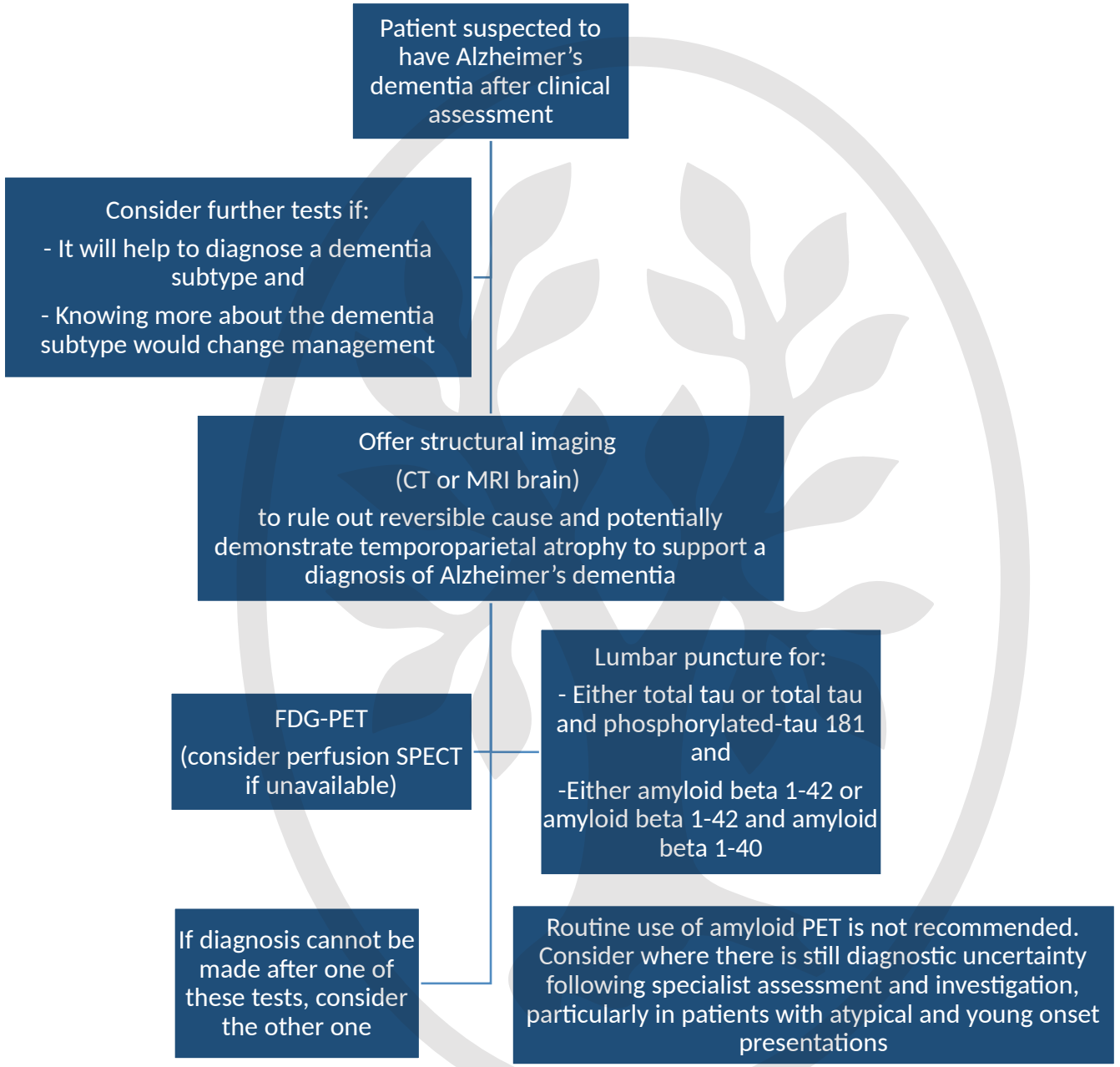

Figure 1. Flowchart of the investigation pathway to consider for the assessment of possible Alzheimer's dementia