Scottish Intercollegiate Guidelines Network Guidance on Dementia: The Investigation of Suspected Dementia (SIGN 168) with Focus on Biomarkers—Executive Summary

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Abstract

This is an executive summary of the recent guidance produced by the Scottish Intercollegiate Guidelines Network (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 teams. There was representation from carers and support organizations 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. To give context to the consideration of more advanced diagnostic biomarker investigations, the guideline and this summary include 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 biomarkers (amyloid and tau) in the diagnosis of dementia. Although routine use of amyloid positron emission tomography 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.

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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 Scottish Intercollegiate Guidelines Network (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 organizations 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 health care professionals, and patient organizations and is part of National Health Service HIS. 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 summarized in this article. 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 performed using an explicit search strategy. Databases searched include Medline, Embase, PsycINFO, and the Cochrane Library. The year range covered was 2000 to 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** [available in the online version]). The evidence ratings given within the guideline are included in bold black texts with alignment to the right at the end of the related paragraphs in this article. This is assessed and applied in a formal evidence to recommendation process. SIGN refers to this as "Considered Judgment." Where evidence supports it a strong or conditional recommendation is made. Recommended best practices ("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 article, as well as in the full guideline.[1,2]

Summary of evidence search strategies (**Appendices 2** and **3** [available in the online version]).

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 (AD) 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 AD, 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 visualize 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 labeled with a radioisotope, enabling its visualization 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) utilizes a ligand that binds selectively to amyloid plaques. There are three 18F-labeled 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 mild cognitive impairment (MCI), atypical AD, suspected mixed dementia, or young-onset dementia.[8] **4**

There are also tau-specific PET ligands, which enable binding and visualization 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 AD.[8,9]

- While aPET positivity may correlate well with amyloid brain pathology, amyloid brain pathology does not necessarily equate to AD 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 to 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 standardized. A range of visual and quantitative methods is encountered across the literature.
- Reference standards and how they are applied vary 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. **4**

Comparison of aPET and FDG-PET

A diagnostic accuracy study ($n = 101$) compared antemortem aPET (using the research ligand 11C-Pittsburgh compound B [PIB]) with antemortem FDG-PET for postmortem neuropathological diagnosis of dementia. Participants were recruited from academic memory research centers and there was an emphasis on early-onset dementia (mean age 67.2 years). The scan to postmortem interval was 4.4 years. At postmortem 32 participants had primary AD, 56 had non-AD pathology, and 13 showed mixed AD/frontotemporal lobar degeneration. Both aPET and FDG-PET had high accuracy for predicting intermediate-to-high AD neuropathological change (ADNC) (sensitivity 96% [95% confidence interval [CI]: 89–100%] vs. 80% [95% CI: 68–92%]; specificity 86% [95% CI: 76–95%] vs. 84% [95% CI: 74–93%]). aPET 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 AD and non-AD pathology.[10] **2+**

A database modelling study with participants from the Alzheimer Disease Neuroimaging Initiative database ($n = 319$, average age 72–73 years) examined the predictive value of 18F-florbetapir and 18F-FDG-PET for conversion to AD 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 nonimaging variables including high-risk apolipoprotein E and the Mini Mental State Examination (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 AD from healthy control patients. For F-florbetapir, these were 89.6% (95% CI: 84.2–93.6%) and 87.2% (95% CI: 81.7–91.6%) respectively (seven studies, $n = 181$). For F-florbetaben pooled weighted sensitivity was 89.3% (95% CI: 82.7–94.0%) and specificity was 87.6% (95% CI: 80.4–92.9%) (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 ADs, 10 normal cognitive status) with life expectancy of less than 6 months were recruited. The sensitivity and specificity for distinguishing participants with AD from healthy controls were 97.4 and 100%, respectively.[12] **2+**

An overlapping systematic review examined and compared the diagnostic accuracy of the three 18F tracers for AD where study populations included those with AD, 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 AD when compared with cognitively normal participants than from distinguishing between people with AD 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-labeled PET tracers identified two studies examining diagnostic accuracy for differentiating between AD and non-AD. In the first study ($n = 107$), with clinical judgement as the 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 AD ($n = 30$) 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-centered outcomes to patient- and caregiver-centered outcomes such as anxiety, quality of life, and coping.[14] **2-**

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 prescan diagnosis was non-AD ($n = 338$), there were 135 patients who had a positive aPET scan, of whom 100 (74.1%) had their diagnosis changed to AD.

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 $12.7\% \pm 35\%$ 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 United Kingdom. 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 categorized 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] **3**

Considerations for the Use of Amyloid PET

aPET does not involve a lumbar puncture, a procedure that some people do not find acceptable, which may make it preferable to using cerebrospinal fluid (CSF) biomarkers.

aPET does involve a scan with radiation exposure. While 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 computed tomography (CT) and Nuclear Medicine imaging come under Ionizing Radiation Medical Exposure Regulations IR(ME)R.[22] Most health-related exposure works on the principle of ALARA (as low as reasonably achievable). **4**

Doses are variable between centers and scanners. Dose from ionizing radiation is measured in milli Sieverts (mSv). The Administration of Radioactive Substances Advisory Committee guidance (January 2022) gave the following effective dose targets for relevant scans: dopamine transporter single-photon emission CT (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 United Kingdom 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. Magnetic resonance imaging (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 health care system, aPET was cost-effective compared with standard diagnostic assessment and with CSF biomarkers.[23] aPET cost more to provide, but accrued a greater number of quality-adjusted life years. The patient cohort was followed up for 10 years after diagnosis to capture the longer term benefits of earlier diagnosis.[24]

Cerebrospinal Fluid Biomarkers

CSF biomarkers can help diagnose AD. These are amyloid β 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 AD. 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 AD 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 make 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 postmortem examinations of 20 to 40% of asymptomatic people older than 80 years (depending on clinical criteria used) show neuropathology of AD.[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 AD dementia from other dementia subtypes.[31] The pooled sensitivity from 13 studies ($n = 1{,}704$) was 79% (95% CI: 0.73–0.85) and the pooled specificity was 60% (95% CI: 0.52–0.67). For differentiating AD from vascular dementia, pooled data from 11 studies ($n = 1{,}151$) gave sensitivity 79% (95% CI: 0.75–0.83) and specificity 69% (95% CI: 0.55–0.81). The corresponding data for differentiating AD from frontotemporal dementia (17 studies, $n = 1{,}948$) were sensitivity 85% (95% CI: 0.79–0.89) and specificity 72% (95% CI: 0.55–0.84). In addition, for differentiating AD from dementia with Lewy bodies (9 studies, $n = 1{,}929$), the sensitivity was 77% (95% CI: 0.70–0.83) and specificity 66% (95% CI: 0.51–0.78). The authors concluded that CSF Aβ42 on its own should not be used to differentiate between AD dementia and non-AD 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[32] the pooled ratio between CSF T-tau biomarker concentration in patients with AD and cognitively healthy control participants was 2.54 (95% CI: 2.44–2.64, $p < 0.0001$ [15 studies, $n = 18{,}427$]); for CSF P-tau (89 studies, $n = 12{,}624$) the pooled ratio was 1.88 (95% CI: 1.79–1.97, $p < 0.0001$) and for CSF Aβ42 (131 studies, $n = 16{,}790$) the pooled ratio was 0.56 (95% CI: 0.55–0.58, $p < 0.0001$). There were similar findings for these CSF biomarkers in distinguishing between people with MCI due to AD and people with stable MCI (at 2-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 AD 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 AD 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 a mean age of 72.1 explored changes in CSF biomarker trajectories as a function of aPET standardized update volume ratio.[28] There were 135 participants with MCI and 242 who were cognitively unimpaired. No participants had a diagnosis of AD. 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 PIB PET findings.[30] Clinical diagnoses that were not informed by biomarker and PET findings were MCI ($n = 22$) 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 <550 ng/L was 84%. At the wider cut-off of 640 ng/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%, while 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 performed 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%), AD (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 Joint Program-Neurodegenerative Disease Research 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 AD.[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 United States at prices from 2013, the authors concluded that testing established CSF biomarkers were cost-effective. It is unclear if these assumptions are generalizable to the Scottish population and health care 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 AD is suspected, consider either:

- **FDG-PET 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 β 1–42 or amyloid β 1–42 and amyloid β 1–40.

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

Functional imaging is a 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 centers.

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

R Routine use of aPET in the diagnosis of dementia or MCI is not recommended.

- aPET 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 presentation or young-onset dementia.
- Any consideration of aPET 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 nonspecific, 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 United Kingdom.[42] At present there are no laboratories within Scotland offering established CSF biomarker testing. **4**

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 recognize 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 neuron 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 recognize 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 aPET 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 ►**Fig. 1**.

It is important to recognize that several 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. Several 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 aPET 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

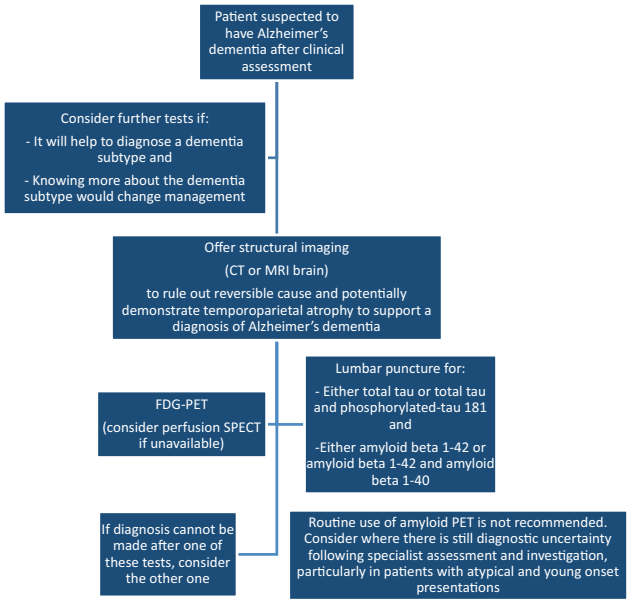

Fig. 1 Flowchart of the investigation pathway to consider for the assessment of possible Alzheimer's dementia.

when trying to assimilate 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.

Authors' Contribution

All of the authors wrote both the investigation section of the SIGN 168 guideline and this review article. All authors have written and corrected sections of the guideline and article. C.S. undertook the evidence appraisal and scoring.

Conflict of Interest

None declared.

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The authors were tasked with reviewing the evidence regarding investigation of suspected dementia; however,

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