Amyloid-PET and ^{18}F-FDG-PET in the diagnostic investigation of Alzheimer's disease and other dementias

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Various biomarkers are available to support the diagnosis of neurodegenerative diseases in clinical and research settings. Among the molecular imaging biomarkers, amyloid-PET, which assesses brain amyloid deposition, and ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET, which assesses glucose metabolism, provide valuable and complementary information. However, uncertainty remains regarding the optimal timepoint, combination, and an order in which these PET biomarkers should be used in diagnostic evaluations because conclusive evidence is missing. Following an expert panel discussion, we reached an agreement on the specific use of the individual biomarkers, based on available evidence and clinical expertise. We propose a diagnostic algorithm with optimal timepoints for these PET biomarkers, also taking into account evidence from other biomarkers, for early and differential diagnosis of neurodegenerative diseases that can lead to dementia. We propose three main diagnostic pathways with distinct biomarker sequences, in which amyloid-PET and ^{18}F-FDG-PET are placed at different positions in the order of diagnostic evaluations, depending on clinical presentation. We hope that this algorithm can support diagnostic decision making in specialist clinical settings with access to these biomarkers and might stimulate further research towards optimal diagnostic strategies.

Lancet Neurol 2020; 19: 951–62

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Introduction

The early and differential diagnosis of neurodegenerative diseases leading to dementia is challenging.[1] The field is moving toward a biological definition of dementia, in which the role of biomarkers in diagnosis is becoming predominant.[2–5] Considering all available biomarkers, amyloid-PET and ^{18}F-fluorodeoxyglucose (^{18}F-FDG)-PET imaging provide valuable and complementary information.[6–14] These biomarkers are used extensively for diagnosis of neurodegenerative diseases in research studies and are recommended in some guidelines for the diagnosis of Alzheimer's disease and several other neurodegenerative diseases.[2,4,10,11,15] For various reasons, including cost, availability, and reimbursement, the generalisation of their use in all clinical settings is not yet feasible. However, many academic memory clinics already use these biomarkers to support assessment and management of patients.[6,9] There is widespread evidence that combining different (PET or non-PET) biomarkers improves diagnostic accuracy.[8,9] However, faced with an arsenal of neuroimaging biomarkers (figure 1), uncertainty has arisen regarding the appropriate combination or order of application of PET imaging for differential diagnosis of dementias, as there is no commonly accepted consensus or theoretical framework concerning how they should be combined. Recommendations for the ordering of these biomarkers into a meaningful sequence or combination are thus needed, to optimise their use.

This Personal View summarises recommendations and conclusions from an interdisciplinary group of experts comprised of nuclear medicine physicians, radiologists, neurologists, geriatricians, psychiatrists, clinical and basic neuroscientists, and patient advocates. These experts met at the European Association of Nuclear Medicine (EANM) Focus Meeting 2 (Jan 2–Feb 2, 2019, Cannes, France) to discuss the role of PET imaging for early and differential diagnosis of neurodegenerative diseases leading to dementia (from here on referred to as neurodegenerative diseases) and to converge on a diagnostic algorithm indicating the recommended order of investigations depending on the clinical presentation. Our aim is not to provide an exhaustive review of the available evidence on the utility of PET imaging in dementia. Instead, we provide a consensual assessment of the optimal use of PET in the diagnostic process from the perspective of a group of experts, including clinicians involved in the care of patients with dementia. We judged biomarkers exclusively on the basis of their diagnostic qualities, whereas other factors, such as geographical differences in their availability or national differences in their reimbursement, are discussed but not taken into account. As such, our recommendations are not intended to replace current guidelines. Rather, they aim at providing a decision aid for situations in which thorough aetiological and biomarker-supported diagnostic assessment is desired and considered meaningful for individual clinical reasons. More specifically, these recommendations are designed to facilitate decisions as to when in the diagnostic process each of the biomarkers can be used and combined in a meaningful way. As this algorithm focuses on the most validated PET imaging biomarkers for dementia, it remains to be seen how the scenario will change in the future, once new PET markers such as tau-PET, new MRI techniques, or fluid biomarkers become available. Consequently, we first outline the current state of evidence on the complementary role of PET imaging in the diagnosis of neurodegenerative diseases and then propose a diagnostic algorithm. We also highlight the main challenges in the clinical implementation of this algorithm, and suggest future research directions.

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PET biomarkers in the differential diagnosis of mild cognitive impairment and dementia

The diagnosis of dementia is particularly difficult in the prodromal stages (when neuropathological changes might be present but symptoms are still mild) and in atypical clinical presentations. In particular, the differential diagnosis between Alzheimer's disease and either frontotemporal lobar degeneration or neurodegenerative parkinsonian syndromes can be very challenging due to overlapping symptoms. Several lines of evidence support the use of PET neuroimaging within the framework of available biomarkers.[5,10–13]

CSF biomarkers

The diagnostic utility of core CSF biomarkers for Alzheimer's disease pathology (Aβ42:Aβ40 ratio, total tau, and phosphorylated tau) is recognised in research guidelines,[16] and these biomarkers are already in clinical use in many European countries in accordance with country-specific regulations. Reference methods and materials for CSF Aβ42 assay standardisation as well as high precision clinical chemistry tests on fully automated instruments are in place, which bodes well for full implementation with uniform reference limits in clinical practice.[17] As compared with PET imaging biomarkers, the diagnostic information derived from CSF analysis is in part overlapping, in part complementary. Both methods provide insights on neurodegeneration, tau, and amyloid pathology. With regard to amyloid detection, both approaches are similarly validated, and agreement between CSF and PET amyloid results is usually good, but not perfect.[18] Despite the fact that CSF and PET imaging biomarkers measure similar pathological processes, they have distinct advantages and disadvantages (table), as previously discussed in greater detail elsewhere.[35] The level of experience, standardisation, and availability at a given centre will have to be considered with regard to the choice of the corresponding biomarker. CSF is less expensive, so a conservative approach could be to use CSF sampling whenever possible. Then, amyloid-PET would only be necessary in a proportion of patients: (1) those who refused lumbar puncture (up to 10%);[36] (2) those in whom CSF sampling is contraindicated (about 5%);[37] or (3) those for whom CSF results are inconclusive due to, for example, technical problems or values close to threshold (about 20%).[38,39]

This approach is confirmed in a setting in which both amyloid-PET and CSF procedures are accessible and reimbursed, such as in Sweden.[40] However, other than imaging, CSF analysis might not answer a number of questions such as location and extent of pathology. Studies also show that amyloid-PET has incremental diagnostic value when done after CSF evaluation.[41,42] Furthermore, disease follow-up and treatment specific therapy monitoring might only be possible by means of suitable neuroimaging biomarkers, as CSF markers would not provide conclusive information on change in extent of pathology or neurodegeneration over time. Finally, the topographic or regional information provided by PET offers valuable information about the earliest pathological stages of amyloid accumulation.[33] In sum, CSF assessment is less expensive, but PET allows better staging and monitoring of the extent and location of pathology.

Performing amyloid-PET as a first-line diagnostic procedure might spare patients multiple visits and unnecessary invasive interventions, which could contribute to a more direct, more comprehensive, and standardised investigation, particularly in diagnostic reference centres such as memory clinics. Furthermore, follow-up and treatment specific therapy monitoring might only be possible by means of suitable neuroimaging biomarkers, as CSF markers for example would not provide conclusive information on change in extent of pathology or neurodegeneration over time. Finally, the topographic or regional information provided by PET can offer valuable information about the earliest pathological stages of amyloid accumulation.[33]

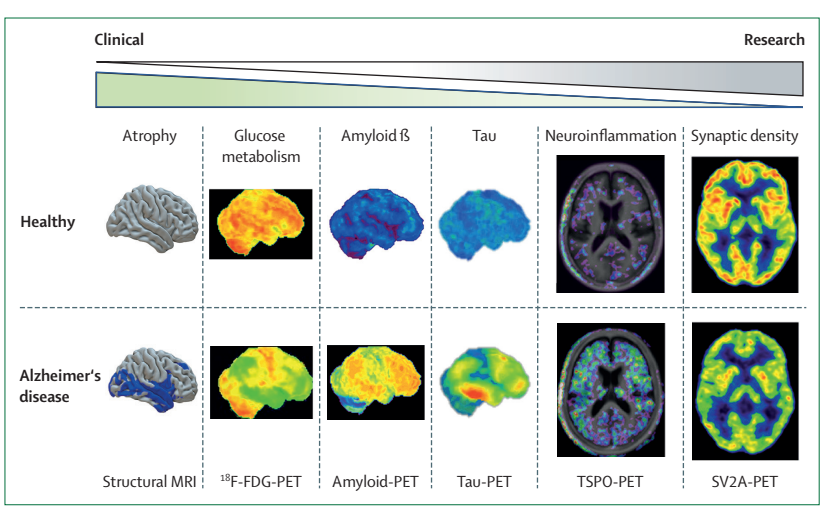

Figure 1: **Neuroimaging obtained with structural MRI or PET using different radiotracers**
The top row shows images from healthy controls and the bottom row from individuals with late-onset Alzheimer's disease. The different neuroimaging techniques are illustrated from the most relevant in clinical setting (left) to the most relevant for research (right). Structural MRI-based Z-score deviations of grey-matter volume in patients compared with controls, displayed in blue on the right hemisphere of a template image. ^{18}F-FDG-PET glucose metabolism are displayed as a 3D-surface projection of the right hemisphere with normal metabolism shown in yellow or red and reduced metabolism in green or blue. Amyloid-PET with ^{11}C-PiB images are displayed as a 3D-surface projection of the right hemisphere, with high amyloid burden indicated in yellow or red and no or low amyloid deposition in green or blue. Tau-PET with ^{18}F-AV-1451 images are displayed as a 3D-surface projection of the right hemisphere, with high tau-tracer retention shown in yellow or red and no or low tau-tracer retention in green or blue. TSPO-PET with ^{11}C-PK11195 images are displayed as axial slices (caudal aspect, frontal to the top) with yellow or red showing elevated TSPO expression reflecting neuroinflammation. SV2A-PET of synaptic density with ^{11}C-UCB-J images are displayed as axial slices (caudal aspect, frontal to the top) with yellow or red showing normal synaptic density and green reflecting reduced synaptic density. ^{18}F-FDG=^{18}F-fluorodeoxyglucose. TSPO=translocator protein. SV2A=synaptic vesicle glycoprotein 2A. Images courtesy of Alexander Drzezga, University of Cologne, Germany; David Brooks, Aarhus University, Denmark; and Ming-Kai Chen, Yale School of Medicine, USA.

^{18}F-FDG-PET imaging

In people with dementia, brain hypometabolism detected with ^{18}F-FDG-PET is a marker of neurodegeneration. It measures regional glucose consumption directly linked to

	PET imaging	CSF measures
Costs	Relatively high	Relatively low
Contraindications	None	Treatment with anticoagulants, spinal defects
Side-effects	The common side-effects (occurring in >1 in 100 and <1 in 10 individuals) reported with fluorinated tracers are: injection site irritation and pain, flushing, increased blood pressure, and headache	The most common side-effect is post-lumbar puncture headache, which occurs in 1–10% of investigations in memory clinic settings;[19,20] more serious side-effects of lumbar puncture, such as infection or brain herniation, might occur albeit very rarely
Variability of the measure across centres and methods	Low[21]	Currently considerable,[22] but commercialised fully automated assays might have helped solving this problem[16]
Individual variability of values in healthy individuals	Low[21]	Quite high, but can be corrected for by measuring changes over time or by using ratio-based approaches[23]
Sensitivity to detect change over time or in the disease course	Low: possibly fast amyloid accumulation during the negative to positive transition,[24] followed by a protracted increase before reaching a plateau	No: stable (studies show that CSF Aβ42 changes 10–20 years before dementia and remains stable during the clinical phase of the disease)[23,25]
Sensitivity for amyloid pathology	91–98%[26-28]	80–96%[29,30]
Specificity for amyloid pathology	87–100%[26-28]	77–82%[29,30]
Information about neurodegeneration or neuronal injury with the same scan or sample	Possible with early phase imaging[31]	Available with total tau (but being questioned), might be with neurofilament amounts but still need validation, confirmation, and standardisation[32]
Information about tau biomarker status with the same scan or sample	Not available	Potentially available with phosphorylated tau amounts
Information on extent of amyloid pathology	Available; distribution of amyloid pathology might indicate the amyloidosis stage[33]	Not available
Information on location of amyloid pathology	Available	Not available
Potential to measure anti-amyloid therapy effects	Conceivable	Conceivable in the future with APP and amyloid β peptides other than Aβ42 (BACE inhibitors would influence Aβ38 and –40 amounts, as well as soluble APPβ in the CSF)[34]

APP=amyloid precursor protein. BACE=β-site amyloid precursor protein cleaving enzyme.

Table: **Comparison of amyloid-PET and amyloid CSF assessments**

the local intensity of brain glutamatergic synaptic and astrocyte activity.[43,44] ^{18}F-FDG-PET allows assessment of the extent and location of hypometabolism, reflecting neuronal dysfunction.

^{18}F-FDG-PET is particularly useful for early diagnosis, as it can show characteristic patterns of Alzheimer's disease neurodegeneration earlier than MRI in individuals with mild cognitive impairment who will go on to develop Alzheimer's dementia.[8,45,46] Previous studies have shown the added value of ^{18}F-FDG-PET over routine CSF or MRI tests to predict development of Alzheimer's disease dementia in people with mild cognitive impairment, especially short-term progression,[8,47,48] with a drop in the misclassification rate from 32% (for CSF or MRI alone) to 20% for ^{18}F-FDG-PET alone, and from 27% for CSF and MRI to 9% when adding ^{18}F-FDG-PET.[47] Insight on short-term (2–3 years) clinical progression is crucial for patients and families to plan for the future and for the clinician to adapt the clinical monitoring, and to target those patients more suitable to undergo therapeutic interventions. On the basis of the typical temporoparietal pattern of hypometabolism, its negative predictive value, ranging from 77% (95% CI 64–87) to 95% (75–100),[49,50] and evidence supporting its validity for clinical use,[9,49,51,52] ^{18}F-FDG-PET is recommended for the evaluation of people with mild cognitive impairment suspected of having underlying Alzheimer's disease. ^{18}F-FDG-PET has also proven to be useful to predict clinical outcome, at the individual level, in people with mild cognitive impairment who have already had an amyloid-PET scan. Thus, a normal ^{18}F-FDG-PET scan would predict clinical stability during follow-up of several years (even in amyloid-positive cases),[53] whereas an abnormal ^{18}F-FDG-PET scan would be associated with increased risk of progressive cognitive deterioration (including in amyloid-negative cases).[54]

^{18}F-FDG-PET is also useful for staging of disease and for differential diagnosis, because the patterns of brain hypometabolism are closely associated with type and severity of cognitive deficits, and are relatively distinct in different neurodegenerative diseases and even among their variants.[8] Characteristic patterns include posterior cingulate and temporal-parietal involvement in Alzheimer's disease, and predominant frontal (in the behavioural variant), perisylvian (in the non-fluent variant), and anterior temporal (in the semantic variant) hypometabolism in frontotemporal lobar degeneration.[8,47,55,56] Specific ^{18}F-FDG-PET hypometabolism patterns also include atypical Alzheimer's disease variants, primary progressive aphasias, and atypical parkinsonisms. ^{18}F-FDG-PET is, therefore, included in the diagnostic criteria of several neurodegenerative diseases: behavioural variant of frontotemporal lobar degeneration;[10] primary progressive aphasias;[11] dementia with Lewy

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***Panel:* A case study**

A 75-year-old man was brought to a neurologist by his wife because of progressive complaints of memory loss and occasional word-finding difficulties. Despite his age, he still worked as a tax-consultant, helping friends and family members with their finances. His clients noticed that he had become slow in finishing the tax filings and recently some of them were returned because they were incomplete and full of mistakes. He was never very good with the computer, but lately his wife had to help him with making wire transfers and writing emails. He had two children and five grandchildren, of whom he sometimes mixed up the names. His wife reported that his gait had also become slower; he used to walk ahead of her during the weekly outings, but now he lags behind.

His Mini-Mental State Examination score was 27 out of 30 and the Montreal Cognitive Assessment score was 20 out of 30, of which the latter is lower than expected and indicative of executive dysfunction more than memory dysfunction. Because of a history of mild hypertension since the age of 40 years and mild diabetes for the past 7 years, both well controlled, the neurologist ordered an MRI, which showed bilateral hippocampal atrophy grade 2 on the Scheltens scale and grade 3 white matter hyperintensities on the Fazekas scale, with five lacunar infarcts in the deep white matter and striatum, indicative of severe small vessel disease. The neurologist doubted whether all the cognitive complaints and findings could be attributed to the vascular damage and wanted to rule out Alzheimer's disease as co-pathology, also in view of the worse prognosis of the combination of both pathologies. She ordered an amyloid-PET scan, which came back negative, ruling out Alzheimer's disease co-pathology. She diagnosed the patient with pure vascular cognitive impairment and increased his vascular care, offering lifestyle advice. The patient and his wife were relieved that Alzheimer's disease was ruled out, subscribed to a fitness programme at their local gym, and put themselves on a Mediterranean diet.

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bodies;[12] and progressive supranuclear palsy.[57] However, the use of ^{18}F-FDG-PET is limited by its inability to give information on neuropathology underlying the detected patterns of hypometabolism.

According to the five-phase strategic roadmap defined to foster clinical validation of biomarkers, ^{18}F-FDG-PET is the PET biomarker that has reached the most advanced phase of validation.[9] Analytical validity (phase 1) is completed, clinical validity (phases 2 and 3) almost achieved, and preliminary evidence for clinical utility (phase 4 and 5) is available.[9]

Amyloid-PET imaging

Amyloid-PET is a neuroimaging technique with standardised tracer-specific visual reading procedures and documented high reproducibility across PET centres. It allows non-invasive, in-vivo detection of amyloid plaques, one of the main neuropathological landmarks of Alzheimer's disease, with very high sensitivity (96%, 95% CI 80–100) and specificity (100%, 78–100) in patients with confirmed Alzheimer's disease who had an autopsy within 1 year of PET imaging.[26] Amyloid-PET also allows detection of amyloid pathology in the clinically atypical variants of Alzheimer's disease such as posterior cortical atrophy, the frontal-executive variant, or in the logopenic variant.[56,58] It does not, however, allow the differentiation between distinct amyloid-positive disorders, which can show similar amyloid-deposition patterns.

Many amyloid tracers have been developed,[59] three of which have reached clinical approval and commercial availability: ^{18}F-florbetapir; ^{18}F-florbetaben; and ^{18}F-flutemetamol. They are essentially equivalent in clinical practice,[8,59] and standardisation approaches have been developed to allow for direct quantitative comparison between the different tracers.[60] A meta-analysis of studies evaluating amyloid-PET's ability to predict mild cognitive impairment conversion to Alzheimer's dementia showed a sensitivity of 93% (95% CI 71·3–99·9) and a specificity of 56% (47·2–64·8).[7] When comparing the ability to predict progression to Alzheimer's dementia, a slightly higher sensitivity has been reported for amyloid-PET over ^{18}F-FDG-PET, although ^{18}F-FDG-PET has a higher specificity and a better accuracy for predicting short-term progression.[21,48] A report from 2019 showed that, in amyloid-positive individuals who were cognitively unimpaired or had mild cognitive impairment, a negative ^{18}F-FDG-PET was associated with clinical stability for several years.[53] This finding might be due to the fact that amyloid pathology can appear long before onset of clinical symptoms. Indeed, positive amyloid scans are found in 10–44% of older people aged 50–90 years who are cognitively unimpaired, with unknown clinical relevance as of yet.[61] Currently, amyloid imaging alone is considered insufficient to predict time to clinical conversion in prodromal and asymptomatic stages. Also, the value of amyloid imaging for disease staging might be poor, as it does not show close correlation with symptom severity and plateaus in later disease stages.[21,62]

Amyloid imaging has almost achieved analytical validity (phase 1) and clinical validity (phases 2 and 3).[9] Yet, more data are needed with use of a harmonised procedure across centres, tracers, and countries (ie, harmonised reading or quantification procedures and thresholds for positivity) to improve reliability of results and information on the effects of covariates (eg, age, sex, *APOE* genotype, disease duration, and comorbidities) on controls and patients. Regarding the clinical utility of amyloid-PET, meta-analyses have consistently shown that amyloid imaging is associated with changes in aetiological diagnosis, increases in diagnostic confidence, and changes in patient management in up to 60% of individuals.[63,64] These changes are more often due to a negative amyloid-PET result and more often in older (>65 years) patients. Such a case study is described in the panel.[65]

Appropriate criteria for amyloid-PET use have been proposed, identifying the following patient populations as the most likely to benefit from the procedure:[66] (1) people with mild cognitive impairment in whom clinical uncertainty exists; (2) patients with a dementia syndrome suggestive of Alzheimer's disease, but with an atypical presentation or suspected mixed cause; and (3) patients with early-onset progressive cognitive decline. A large prospective multicentre trial (IDEAS) done in 2019, including more than 16 000 participants, showed that amyloid-PET in patients selected according to the so-called appropriate use criteria resulted in a change in

management in a relevant proportion (about 60% of patients),[67] which strongly justifies the application of this method in the corresponding population. Other studies have shown that amyloid imaging can also have clinical utility in individuals not fulfilling the appropriate use criteria,[58,68,69] including individuals with clinical probable Alzheimer's disease (who might be amyloid-negative), patients with atypical non-amnestic phenotypes of cognitive impairment who do not fulfil criteria for possible Alzheimer's disease, and individuals with subjective cognitive decline.[51,70,71] Another large multicentre study (AMYPAD-DPMS; EudraCT, 2017-002527-21)[72] is ongoing, including patients beyond appropriate use criteria (eg, fulfilling criteria for probable Alzheimer's disease or for subjective cognitive decline), which could provide answers regarding the clinical effect and utility of amyloid imaging in these populations (appendix p 5).

PET biomarkers in the frontotemporal lobar degeneration spectrum

The complexity of a clinical diagnosis of dementia is well illustrated within the frontotemporal lobar degeneration spectrum, the family of clinically and neuropathologically heterogeneous disorders characterised by progressive degeneration of the frontal or anterior temporal lobes.[71] Symptoms of frontotemporal lobar degeneration can resemble those of Alzheimer's disease, particularly its atypical forms. ^{18}F-FDG-PET has a long-standing role in the diagnosis of frontotemporal lobar degeneration based on signature patterns of hypometabolism associated with specific clinical syndromes.[72–74] Amyloid-PET has proven useful in discriminating Alzheimer's disease from frontotemporal lobar degeneration, as amyloid plaques are a core feature of Alzheimer's disease neuropathology but typically not part of the frontotemporal lobar degeneration neuropathological spectrum.[73,75] The major advantage of amyloid-PET over ^{18}F-FDG-PET is that it can highlight a specific pathology when ^{18}F-FDG-PET cannot inform on the pathological cause underlying a metabolic abnormality.[76] Because of its high sensitivity to detect fibrillar amyloid pathology, a negative amyloid-PET scan can also be used to reliably rule out Alzheimer's disease as the underlying cause in patients with complex presentations such as primary progressive aphasia variants or corticobasal syndrome.[77,78] In general, amyloid-PET is useful when a differential diagnosis between Alzheimer's disease and non-Alzheimer's disease causes of dementia is needed. ^{18}F-FDG-PET can further address differential diagnosis within the frontotemporal lobar degeneration spectrum in patients who are amyloid-negative, or when the final diagnosis is still unclear after amyloid-PET or CSF analyses, (eg, in patients with mixed pathological features).

Neuroimaging biomarkers in parkinsonian syndromes with cognitive decline

Parkinsonian syndromes that can cause dementia include Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy, and corticobasal degeneration. Assessment of integrity of the nigrostriatal dopaminergic pathway with dopamine transporter single-photon emission CT (DaT-SPECT) has been approved by the US Food and Drug Administration and the European Medicines Agency to support the differential diagnosis between dementia with Lewy bodies and Alzheimer's disease. The availability of this tool has increased the diagnostic accuracy for dementia with Lewy bodies, which is usually difficult because of overlapping symptoms with Alzheimer's disease, vascular cognitive impairment, and even frontotemporal lobar degeneration.[12] Some patients with dementia with Lewy bodies might not show all of the core clinical symptoms (eg, they might present with minor or even no apparent parkinsonian symptoms). The use of DaT-SPECT should also be considered in these cases (eg, if other core clinical features of dementia with Lewy bodies such as fluctuating cognition, visual hallucinations, or REM sleep behaviour disorder are observed), especially given the side-effects observed in patients with dementia with Lewy bodies if they are given neuroleptics sometimes prescribed in patients with dementia.[79] Because dopaminergic deficits can be present in all neurodegenerative parkinsonian syndromes, DaT-SPECT cannot be used for the differential diagnosis between these diseases. By contrast, ^{18}F-FDG-PET can distinguish between specific patterns of hypometabolism of Parkinson's disease or dementia with Lewy bodies and all other neurodegenerative parkinsonian syndromes. ^{18}F-FDG-PET has thus been recommended for differential diagnosis within neurodegenerative parkinsonian syndromes by the EANM-European Academy of Neurology taskforce.[80,81] Parkinsonian syndromes are also systemic disorders, and in particular, ^{123}I-meta-iodobenzylguanidine (mIBG) myocardial scintigraphy assessing cardiac sympathetic nerve endings has been included in the clinical flow chart of investigations for the differential diagnosis between Alzheimer's disease and dementia with Lewy bodies, as well as between Parkinson's disease and other neurodegenerative parkinsonian syndromes.[12,82]

Proposed algorithm for differential diagnosis

On the basis of the evidence summarised above on the relative strengths and limitations of each biomarker and their complementarity, but also relying on pragmatic considerations on how to reach a conclusion in a specific clinical situation, we propose a diagnostic algorithm reflecting the optimal combination of biomarkers according to different clinical situations (figure 2). Further information concerning methods used for reaching agreement among the coauthors of this Personal View is provided in the appendix (p 2). In addition to potentially supporting diagnostic decision making in specialised centres, this diagnostic algorithm is proposed as a theoretical framework to guide research and to establish a standard for comparison with alternative algorithms.

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See **Online** for appendix

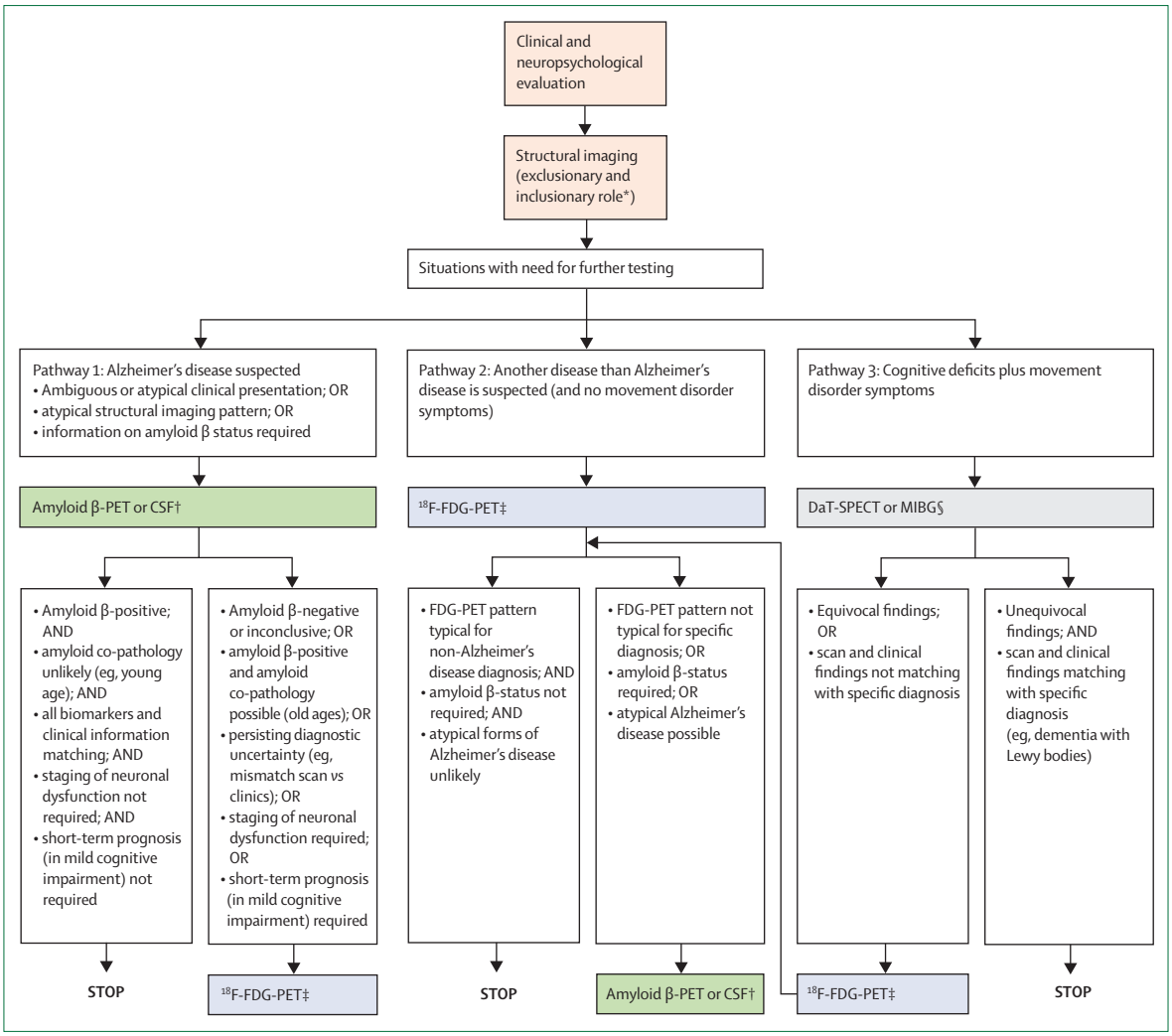

Figure 2: **Proposal for a diagnostic algorithm for early and differential diagnoses of dementia**
This algorithm is a theoretical proposal and further validation of the order of tests is needed (see text for details). ^{18}F-FDG=18F-fluorodeoxyglucose. mIBG=^{123}I-meta-iodobenzylguanidine. *Exclusion of neoplastic, vascular, and inflammatory changes supporting non-neurodegenerative causes and evaluation of topography of atrophy might inform on the neurodegenerative disease (but ^{18}F-FDG-PET might be more sensitive and accurate). †Whatever is established or available and preferred; Amyloid β-PET should always be used if CSF is contraindicated or inconclusive. ‡Age and *APOE* status (when available) might influence the use of ^{18}F-FDG-PET, even before amyloid-PET, especially in individuals with available but inconclusive CSF results. Analyses of ^{18}F-FDG-PET images should also take into account comorbidities (ie, uncontrollable diabetes, brain trauma, chronic ischaemia), as well as some medications (eg, psychotropic drugs or corticosteroids) that might affect the images, as they can alter cerebral metabolism. §^{18}F-FDG-PET can be done before DaT-SPECT or mIBG, particularly if the cortical involvement of neurodegeneration is the diagnostic focus.

Structural imaging as a first step

In situations when biomarker-based diagnostic tests are clinically needed to establish a reliable aetiological diagnosis, structural imaging is recommended as the very first step after clinical and neuropsychological evaluation, before use of other imaging biomarkers. Indeed, structural neuroimaging allows the detection of other pathologies that might be responsible for cognitive decline (eg, hydrocephalus, tumours, or vascular lesions), although the contribution of vascular lesions to the observed cognitive deficits cannot be determined with structural imaging.[83] Furthermore, structural imaging can help assess the presence and degree of comorbidities (eg, vascular) frequently found in neurodegenerative disorders, which can affect the clinical manifestation and can be treatable. In addition, topographical patterns of atrophy assessed by structural imaging are associated with specific neurodegenerative conditions,[84] whereas the overall degree of atrophy is associated with disease-specific clinical features and severity, and tracks the progression of neurodegeneration.[83,85] Regarding the structural imaging modality, MRI has frequently been considered as a superior tool compared with CT for dementia investigation.[86] However, to date, no strong evidence exists for recommending one or the other.

Further tests could be halted if clinical and structural imaging information both converge towards a specific

diagnosis (eg, in patients with memory predominant profile with typical hippocampal atrophy), in patients with a family history of dementia or an *APOE* ε4 genotype when available, or if consequences of the diagnosis are poor meaning that they will not affect patient management (eg, other comorbidities are dominating patient prognosis). However, if tailored therapy is the aim or decisions depend on a conclusive diagnosis and prognosis, additional biomarker assessment is required (referred to in the figure as situations with need for further testing; detailed in appendix p 3).

A three-pathway algorithm

In general, after clinical or neuropsychological evaluation and structural imaging, the added value of other diagnostic biomarkers can be especially high in cases with clinical diagnostic uncertainty (eg, atypical appearance or mixed presentation such as combined cognitive, behavioural, and motor symptoms).[8,9] Moreover, the choice of further diagnostic assessment should account for factors influencing pre-test probability (eg, *APOE* genotype and family history, among others) as well as the potential consequences of the diagnosis. If consequences of the diagnosis are limited (eg, other comorbidities dominate patient prognosis or absent therapeutic alternatives in patients presenting with severe dementia) and once treatable conditions are excluded, there might not be a strong reason to further strive to obtain a diagnosis based on molecular imaging. Also, the diagnostic benefits of additional biomarker tests in the individual situation should be considered. For example, rates of amyloid positivity increase with age in *APOE* ε4 carriers, and the likelihood that the presence of amyloid is not responsible for cognitive decline or predictive of cognitive decline increases in *APOE* ε4 carriers older than 80 years.[87] By contrast, a positive amyloid-PET scan is particularly helpful for considering Alzheimer's disease in the differential diagnosis of patients with early onset dementia, as the a-priori risk of incidental age-related amyloid pathology is low in those younger than 65 years.

These considerations are taken into account in the proposed algorithm indicating three different pathways with distinct sequences of tests for situations in which additional biomarker assessment is required after clinical assessment and structural imaging, with amyloid biomarkers, ^{18}F-FDG-PET, or DaT-SPECT being the preferred subsequent step depending on the clinical presentation. These different pathways are detailed in figure 2.

In pathway 1, preferred if Alzheimer's disease is the suspected diagnosis, analysis of amyloid pathology would be the subsequent next step. Depending on the result, ^{18}F-FDG-PET might be additionally required to obtain further prognostic or diagnostic information (eg, on the extent of neurodegeneration or a specific pattern of hypometabolism and regarding short-term prognosis in mild cognitive impairment). Pathway 2 is recommended if Alzheimer's disease is not the single most probable or suspected diagnosis or for older (>80 years) individuals. If the result of the ^{18}F-FDG-PET scan is conclusive, no further tests are requested (pathway 1); by contrast, if the pattern of ^{18}F-FDG-PET hypometabolism is not conclusive, or if the reliable clarification of neuropathology is clinically relevant, a further amyloid test might be necessary (pathway 2). We would recommend a DaT-SPECT (or mIBG imaging) as the primary test for all situations in which a movement disorder or parkinsonian syndrome is clinically in question;[80] in some cases (ie, abnormal DaT-SPECT), no further test is required (pathway 3), but if further specification is needed (ie, if the DaT-SPECT is normal, or, if it is abnormal, to differentiate between neurodegenerative parkinsonian syndromes), then an additional ^{18}F-FDG-PET is recommended, followed by amyloid-PET if Alzheimer's disease remains a possibility. More details and examples are given in the appendix (p 3).

Practical challenges and limitations of the algorithm

The suggested algorithm is based on existing evidence but also on several assumptions and expert opinion. Thus, several aspects will require further clarification and additional research in the future. Some controversies also remained among the authors, which are further discussed below.

Validation

Our algorithm is a theoretical proposal based on evidence and pragmatic considerations on how to reach a conclusion in a specific clinical situation, reflecting in-depth discussions and expert consensus from various disciplines. It is proposed as a timely model to support and potentially homogenise heterogeneous clinical practice, and to structure research and serve as a basis for future development and comparison to alternative models. There is extensive evidence of analytical and early clinical validity for individual biomarkers, but more evidence is needed on multimodal imaging approaches and, particularly, the order of tests. The systematic validation of each arm of the algorithm will be challenging given the high number of possible combinations. However, the added value for diagnosis of the specific combinations shown in the proposed algorithm will have to be shown and compared with alternative algorithms that might arise based on new evidence or distinct pragmatic considerations.

Practical issues: availability, adverse effects, cost-effectiveness, and sustainability

The widespread and consistent use of biomarkers not only relies on their performance for early and differential diagnoses, but also on more practical issues such as training status of clinicians, availability of and distance to PET scanners and cyclotrons, and adverse effects (table).

These considerations have not been taken into account in this Personal View, because our focus has been purely

on the diagnostic value of the individual biomarkers. Thus, these questions will require attention in future studies.

Because PET imaging can be expensive (the cost of an amyloid-PET scan is €2000–2500 in Europe and US$3000–4500 in the USA), the issue of cost-effectiveness is particularly relevant in the context of absent effective treatment. No sufficient evidence is available yet on the effect of biomarkers on disease burden or cost-effectiveness (phase 5 secondary aim).[9] Overall, an examination with high sensitivity and specificity enhances diagnostic confidence and might reduce costs and the number of patient visits and additional tests, as it has been shown for amyloid-PET imaging.[88,89] Objective evidence from health economic studies is needed to systematically assess cost-effectiveness and ideally considering various situations of treatment availability and efficacy. In addition to cost-effectiveness, medical diagnostic tools might have to be discussed with regard to sustainability in the future. Imaging requires considerable amounts of energy for operation, cooling, and computer technology.[90]

Reimbursement

Reimbursement of imaging tests from health insurers varies considerably across the world.[9] The right-to-know of the patients need to be balanced against the economic status and priorities of the health-care system of each country. Reimbursement of ^{18}F-FDG-PET is mainly provided for the differential diagnosis of Alzheimer's disease versus frontotemporal lobar degeneration in the USA and many European countries. Amyloid-PET is available in most high-income countries, but reimbursement is limited.[9] In 2013, the US Centers for Medicare and Medicaid Services issued a National Coverage Decision concluding insufficient evidence as of yet for its clinical utility to justify general reimbursement.[91] However, they agreed to cover scans in clinical studies investigating whether amyloid-PET improves health outcomes. Health systems are very cautious to endorse any expensive test that might be indicated in a large segment of the population from an economic perspective. This approach could change substantially, once disease-modifying drugs become available.

Ethical aspects of early diagnosis and disclosure of biomarker information

Disclosing information on early ongoing neurodegenerative disease or even prediction involves major ethical considerations. From the patient perspective, the right-to-know and the right-not-to-know should be taken into account. On the one hand, disclosing such serious information can cause anxiety and worry, potentially even long before symptomatic onset of disease and without access to therapy options. On the other hand, early and accurate diagnosis allows individuals and their families to build a care team and seek education and support services. It provides an opportunity to create advance directives and financial planning, enables earlier access to appropriate treatments, and opens opportunities for enrolment in clinical trials. A study concerning the potential benefits of the clinical use of amyloid-PET showed that the majority of 510 patients and caregivers would support use and reimbursement of the test to inform legal (n=446, 87%), financial (n=392, 77%), and long-term health-care (n=345, 68%) choices.[92] Further research is required in this area. In ongoing studies, the context for appropriately disclosing the results of the tests to patients and families are being defined.[93]

Alternatives to the diagnostic algorithm

It needs to be emphasised that the costly and energy-expensive biomarker tests discussed here will not in all cases be able to solve the diagnostic problem, even when applied in a systematic order or combination. Furthermore, the potential benefit for the individual patient needs to be carefully reflected upon when considering the available options for biomarker-supported diagnosis. Depending on the patient (ie, age, stage of disease, psychological status, and comorbidities, among other factors), the diagnostic strategies might considerably deviate from a standardised pathway. It is essential to involve patients and their caregivers in decision-making. Thus, in the clinical investigation of neurodegenerative disorders, the most important factor remains the discussion with the patients and their caregivers about symptoms, the prognosis and the therapeutic options, and the value and the consequences of further diagnostic steps. In light of the often limited therapeutic options at present, other strategies, such as watchful waiting or systematic clinical-neuropsychological follow-up examinations, could represent preferable alternatives.

Controversies regarding disease models

Many questions are unresolved regarding the development of neurodegenerative disorders. In the future, the answers to these questions might affect the way diagnostic questions are asked and how diagnostic algorithms will be drafted. The dominant hypothesis in Alzheimer's disease up to now is the amyloid hypothesis, whereby amyloid deposition is considered as an early causal event.[94] This hypothesis has led to the amyloid deposition, tauopathy, and neurodegeneration (ATN) model,[2] which is well accepted but has also stimulated much debate and criticism.[95–97] Multimodal imaging could allow testing and possible revision of these models, and it has already stimulated consideration of alternative models, including the dual pathway hypothesis, amyloid-independent mechanisms, and the vascular hypothesis.[98–102] However, while drafting the diagnostic algorithm, we aimed to provide a model with diagnostic value largely on the basis of commonly agreed facts, and independently from still controversial concepts and assumptions on disease causality.

Conclusion and future directions

The panellists at the EANM Focus Meeting 2 agreed on recommendations regarding the use of PET imaging

Search strategy and selection criteria

References for this Personal View were identified by searches of PubMed from database inception to Oct 1, 2019, and from references to relevant articles. The search terms (alone or in combination) "Alzheimer's disease", "dementia", "neurodegenerative diseases", "MCI", "imaging", "biomarkers", "PET", "FDG", "amyloid imaging", "amyloid PET", "PIB", "flutemetamol", "florbetapir", "florbetaben", "amyloid markers", "magnetic resonance imaging (MRI)", "CSF biomarkers", "clinical validity", "clinical utility", "clinical acceptance", "management change", AND "diagnostic change" were used. Additional studies cited within the identified papers and known to the authors were also included. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this Personal View.

within the scope of available biomarkers for early and differential diagnosis of neurodegenerative diseases. After clinical and neuropsychological evaluation and structural imaging when needed, the decision on necessity and choice of the next biomarker depends on the specific clinical profile and the individual diagnostic question. Amyloid-PET allows the detection of amyloidosis in vivo in a standardised manner and has high negative predictive value toward Alzheimer's disease. Compared with amyloid CSF biomarkers, amyloid-PET is used to determine the location and extent of pathology, and detect brain areas of earliest amyloid accumulation[33] and changes over time.[59,62] ^{18}F-FDG-PET allows the detection of neurodegeneration with greater sensitivity than structural MRI. Compared with CSF neurodegeneration biomarkers, topographical information on neurodegeneration obtained with ^{18}F-FDG-PET (patterns of hypometabolism) is closely associated with the type and severity of cognitive deficits, making this biomarker particularly useful for differential diagnosis, staging of disease extent, and prediction of short-term progression.[8,54] On the basis of our current knowledge of the respective advantages and disadvantages of each biomarker, together with pragmatic considerations, the authors converged towards a diagnostic algorithm for the optimal combination of biomarkers depending on the clinical condition. The implementation of this algorithm in clinical practice will face challenges associated with practicality, cost-effectiveness, ethics, validation, controversies surrounding the underlying pathophysiological model, and integration of future biomarker developments. Various technologies, other tracers, and biomarkers are under development (appendix p 8), which could open new diagnostic avenues and affect the proposed algorithm. Importantly, advanced approaches and instrumentation, such as integrated PET/MR imaging in combination with dual-phase PET acquisition, could allow the acquisition of multimodal imaging in a one-stop manner, while remaining cost-effective and logistically feasible, thus omitting the need to decide on sequences of tests.[31] Other future options include tau-PET (which obtained FDA-approval for one tracer in the USA in May 28, 2020), synaptic density imaging, inflammation imaging, and blood biomarkers, as well as improvement of PET quantification methods or scanner equipment.

Contributors

GC, JA, HB, VG, IL, SMo, and EvdG are part of the EANM Neuroimaging committee and the EANM Focus 2 Meeting Scientific Committee. JA, HB, VG, IL, SMo, and EvdG contributed equally to this work. FA, FB, DJB, MC, BD, AMF, GBF, OH, KH, BFH, CRJ, AAL, SML, SMi, FN, AN, RO, WJGO, DP, GDR, PS, VV, HZ, and AD were all members of the EANM Focus 2 expert panel, contributed to the content of the study, and reviewed the paper. PS also provided the case study.

Declaration of interests

GC has received research support from the EU's Horizon 2020 research and innovation programme (grant agreement number 667696), Inserm, Fondation d'entreprise MMA des Entrepreneurs du Futur, Fondation Alzheimer, Programme Hospitalier de Recherche Clinique, Région Normandie, Association France Alzheimer et maladies apparentées and Fondation Vaincre Alzheimer (all to Inserm), and personal fees from Fondation d'entreprise MMA des Entrepreneurs du Futur. GBF has received research funds and personal fees from General Electric Healthcare, Avid Lilly, and Life Molecular Imaging. FA reports personal fees from Elsevier, Biogen Idec, and Novartis, outside of the submitted work. JA reports grants from General Electric, Piramal, and Lilly-Avid, personal fees from Biogen and Bayer, personal fees and non-financial support from Araclon and Advanced Accelerator Applications, outside of the submitted work. FB reports consultancies for Bayer-Schering Pharma, Biogen Idec, TEVA, Merck-Serono, Novartis, Roche, Jansen Research, Genzyme-Sanofi, IXICO Ltd, GeNeuro, and Apitope, grants for Amyloid imaging for the Prevention of Alzheimer Disease (Innovative Medicines Initiative), European Progression Of Neurological Disease (H2020), UK Multiple Sclerosis Society, Dutch Multiple Sclerosis Society, National Institute Health Research University College London Biomedical Research Centre. DJB reports grants and personal fees from General Electric Healthcare, outside of the submitted work. AD reports personal fees and non-financial support from General Electric Healthcare, Life Molecular Imaging (Piramal), Lilly, during the conduct of the study, grants, and personal fees and non-financial support from Siemens Healthcare, outside of the submitted work, and has a PSMA patent pending. BD reports personal fees from Biogen-Boehringer Ingelheim and grants from Merck Foundation for IM2A outside of the submitted work. KH reports grants from GlaxoSmithKline, outside of the submitted work. BFH reports research support from General Electric Healthcare, Siemens, and GlaxoSmithKline, outside of the submitted work. CRJ consults for Lilly and serves on an independent data monitoring board for Roche but he receives no personal compensation from any commercial entity. He receives research support from the National Institutes of Health and the Alexander Family Alzheimer's Disease Research Professorship of the Mayo Foundation, and research support from Lilly and Roche, outside of the submitted work. OH has acquired research support (for the institution) from Roche, General Electric Healthcare, Biogen, AVID Radiopharmaceuticals, and Euroimmun. In the past 2 years, he has received consultancy or speaker fees (paid to the institution) from Biogen and Roche. SML reports personal fees from Cortexyme and NeuroVision, outside of the submitted work. SMi reports consultancy for Hamamatsu Photonics. SMo reports speaker's honoraria from General Electric Healthcare. GDR reports grants from the National Institutes of Health, Alzheimer's Association, American College of Radiology, Tau Consortium, Michael J Fox Foundation, Association for Frontotemporal Degeneration, Avid Radiopharmaceuticals, Eli Lilly, General Electric Healthcare, and Life Molecular Imaging and personal fees from Genentech, Merck, Eisai, and Lundbeck, outside of the submitted work. PS reports research support from Medavante, ProBiodrug, EIP Pharma, Novartis AG, and Toyama, outside of the submitted work. VLV reports grants from Life Molecular Imaging, Avid Radiopharmaceuticals, and General Electric Healthcare,

outside of the submitted work. HZ reports that he has served at scientific advisory boards of Roche Diagnostics, Samumed, Wave, and CogRx and has given open lectures sponsored by Alzecure. FN received speaker honoraria from General Electric Healthcare; fees for participation in board from Roche; and consultation fees from BIAL. VG is supported by the Swiss National Science Foundation (projects 320030_169876 and 320030_185028), the Velux foundation (project 1123), the Aetas foundation, and the Association Pour la Recherche sur l'Alzheimer; reports grants from Siemens Healthineers, Life Molecular Imaging, Merck, Cerveau Technologies, Roche, and General Electric Healthcare; and personal fees from Siemens Healthineers and General Electric Healthcare, outside the submitted work.

Acknowledgments

We thank John Bean (Bean Medical Writing, Halle, Belgium; funded by EANM) for providing medical writing services, which included taking the minutes of the EANM Focus 2 meeting, amending text of the Personal View to include EANM Focus Meeting 2 content; editing drafts to improve the accuracy of language, flow, organisation, structure, and overall readability; and checking for grammatical and spelling errors. The authors also thank Susanne Koebe and other EANM staff members for project management. This research was funded by the European Association of Nuclear Medicine and supported by unrestricted grants from Siemens Healthineers, Biogen, Cerveau Technologies, Life Molecular Imaging, and Lilly. These sponsors had no direct or indirect influence on the programme and content of the EANM Focus 2 meeting and the writing or content of this Personal View. FB and BH are supported by the NIHR University College London Hospitals Biomedical Research Centre. The AMYPAD project has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (grant agreement number 115952). The IDEAS study was funded by the Alzheimer's Association, the American College of Radiology, Avid Radiopharmaceuticals (a wholly owned subsidiary of Eli Lilly and Company), General Electric Healthcare, and Life Molecular Imaging (formerly Piramal Imaging). The US Centers for Medicare and Medicaid Services provided coverage for amyloid-PET scans in DEAS under coverage with evidence development.

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