

Chapter 10

Brain imaging using PET and SPECT

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Key points

- Neuroimaging using positron emission tomography (PET) or single-photon emission computed tomography (SPECT) increases the diagnostic accuracy of Alzheimer's disease and dementia with Lewy bodies.
- Applying appropriate use criteria, PET or SPECT neuroimaging may improve the management of patients by revealing specific brain diseases underlying their dementia.
- There is a high demand for diagnostic imaging tests that can identify other brain diseases causative of dementia.



General background

Positron emission tomography (PET) is a functional imaging technique that uses positron-emitting imaging agents to visualise and quantify a wide range of biochemical processes. In individuals with dementia, PET quantifies abnormal protein accumulation and metabolic dysfunctions affecting blood flow and metabolism. The ability to probe the accumulation of abnormal proteins associated with neurodegeneration in vivo offers unprecedented research and clinical application opportunities. There has been tremendous progress in the last 15 years with regards to Alzheimer's disease PET imaging. It is possible to quantify the load of brain amyloid, or neurofibrillary tangles, glucose hypometabolism imposed by disease pathophysiology using PET. Today, PET imaging agents are available for amyloid, neurofibrillary tangles (commonly designated as tau) and neurodegeneration.

A single-photon emission computed tomography (SPECT) scan allows doctors to measure the integrity of the cells affected by Parkinson's and Lewy body's disease in the brain of living people. Like PET, a SPECT scan is a type of nuclear imaging test that uses a radioactive substance and a special camera to create 3-D pictures. Biomarkers generated by these tests permit doctors to diagnose the cause of dementias.

Amyloid imaging agents are biomarkers for brain amyloid pathology. Vizamyl ([18F]flutemetamol), Amyvid ([18F]florbetapir) and Neuraceq ([18F]florbetaben) have been approved by regulatory agencies as amyloid imaging agents for clinical practice. In vivo post-mortem correlations have shown that images of these PET tracers are highly correlated with neuritic plaques (3). Present appropriate-use criteria provide guidance for the utilisation of

Table 1. Types of brain abnormalities measured by PET and SPECT

Disease Process	Amyloid	Tau	Neuronal injury	Dopamine cells
PET	Yes	Yes	Yes	Yes
SPECT	No	No	Yes	Yes

these diagnostic tests in clinical practice. For example, a negative A β -PET scan in a person with dementia will rule out Alzheimer's disease as the underlying aetiology (4,5).

Tau imaging agents are biomarkers for tau pathology. Although there are several PET tau imaging options available to researchers, only Tauvid ([18F]flortaucipir) has been approved by the US Food and Drug Administration for clinical use. Tau imaging serves to diagnose Alzheimer's disease. In contrast with amyloid imaging, the distribution of tau uptake in living patients correlate with clinical symptoms and agrees with the disease staging system proposed by Braak in pathological specimens (6,7).

Brain metabolism measured with [18F]fluodeoxyglucose has been extensively utilised as a clinical tool in neurodegenerative conditions. Abnormal reduction of brain glucose metabolism, or hypometabolism, is a hallmark of neurodegenerative dementias. Hypometabolism from neurons and astrocytes reflects brain synaptic dysfunction. As such, the diagnosis of dementia based on hypometabolism has extensively been utilised to diagnose neurodegenerative conditions (4).

Dopamine nerve terminal imaging provides information regarding the viability of dopaminergic projections in the striatum. 23I-ioflupane is a radioligand that binds to the dopamine transporter located in the presynaptic membrane of dopamine nerve terminals. Images are obtained with SPECT imaging 3 hours after an injection of 123I-ioflupane. In dementia, dopamine transporter imaging can help differentiate Alzheimer's disease from dementia with Lewy bodies (8,9).

Limitation of PET and SPECT imaging agents as dementia biomarkers – The use of PET and SPECT remains limited to a small fraction of people with dementia. Although practical and beneficial in specific clinical circumstances, imaging biomarkers are expensive and not readily accessible or affordable to most healthcare systems worldwide due to the problematic availability of scanners and cyclotrons to produce radiopharmaceuticals.

Table 2. Summary of imaging biomarkers available for degenerative conditions

Methods	Biomarker	Pathophysiologic process		Topographic marker	Neuronal injury
		amyloid	tau		
PET	Amyloid tracer uptake	Yes	No	Yes	No
PET	Tau tracer uptake	No	Yes	Yes	No
PET	Fluorodeoxyglucose	No	No	Yes	Yes
SPECT	Iodinated ioflupane	No	No	Yes	Yes

Survey results

The 1,111 multidisciplinary clinicians who responded, indicated that basic assessments such as history, neurological examination, basic laboratory screening tests, and cognitive assessment are widely used as dementia tests (Chart 1). Due to accessibility limitations and high costs, biomarkers are not always available in many countries

and therefore not included in their clinical practice. That said, 70% of the participants are open to using blood biomarkers in their practice. However, these tests are not yet available in many nations. Once supply distribution is more widely offered, it will fill a gap in their practices and result in more efficient testing protocols (Chart 2).

Are amyloid brain scans (amyloid Positron Emission Tomography) available in your country for people concerned about their cognition?

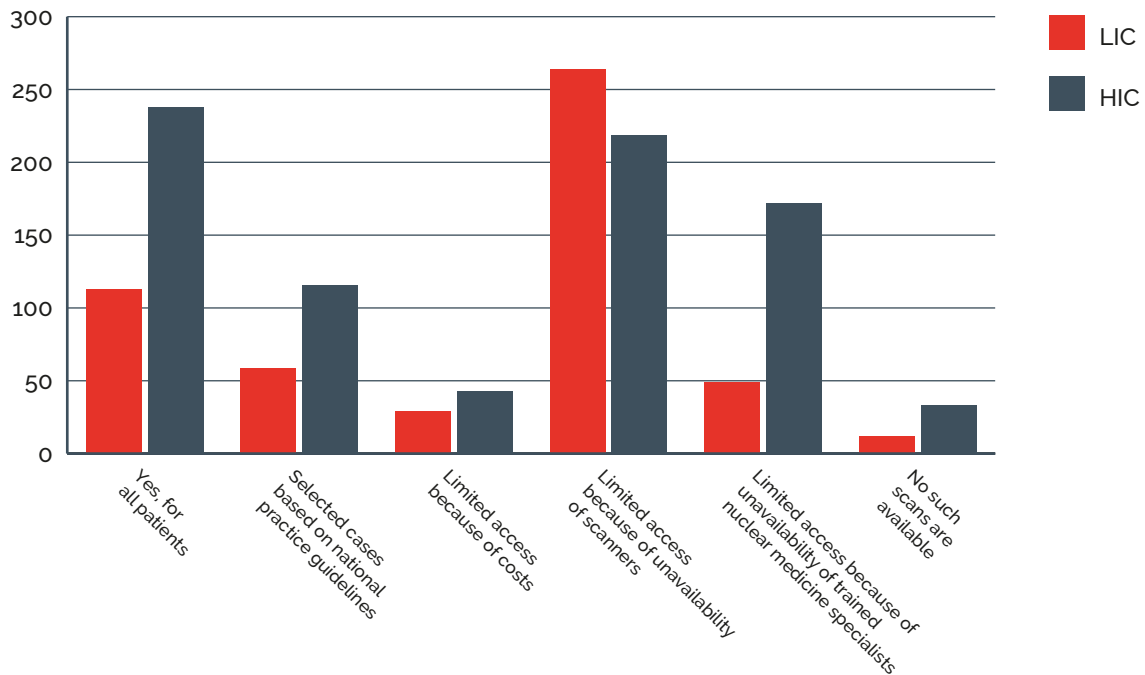


Chart 1. Clinician responses.

Are metabolic brain scans ([¹⁸F]-FDG Positron Emission Tomography) available in your practice for people concerned about their cognition?

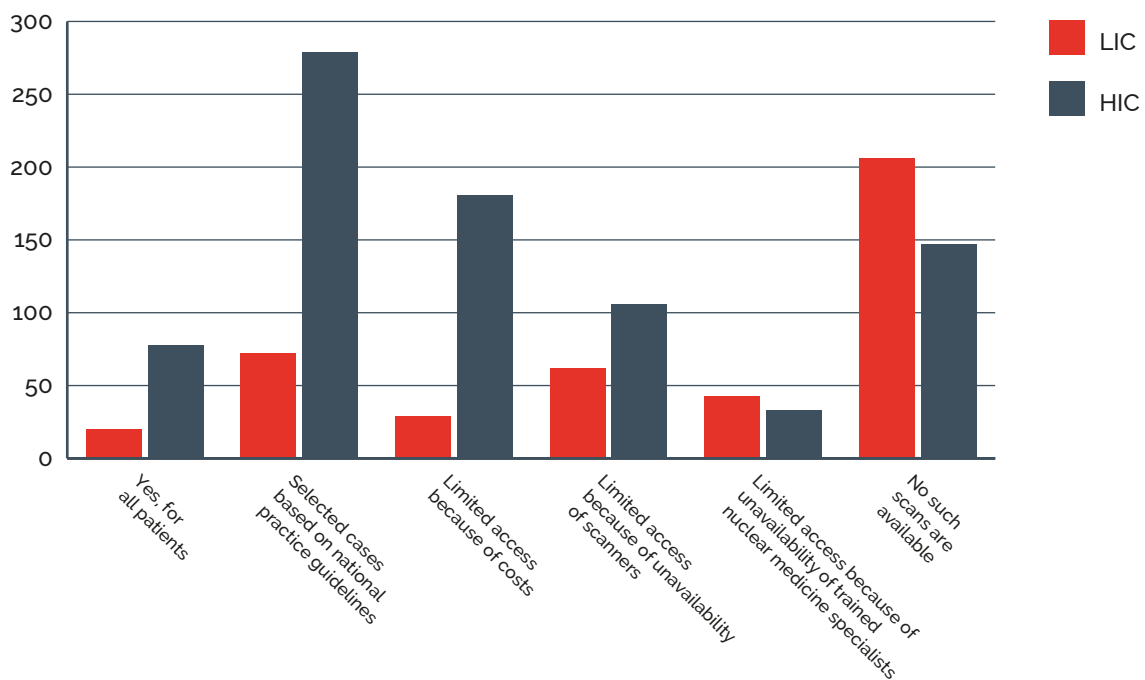


Chart 2. Clinician responses.

Expert essay

Optimal use of anatomic and metabolic brain imaging in the workup of cognitively impaired people

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Currently, clinical evaluation by a cognitive specialist remains the mainstay in the workup of someone with suspected dementia, with both anatomic and metabolic imaging continuing to play a central and complementary role. In general, anatomic imaging refers to computed tomography (CT) and magnetic resonance imaging (MRI), while metabolic brain imaging refers to [18F]-fluorodeoxyglucose (18F-FDG) positron emission tomography (PET). In all cases, it is important to recall that the risk associated with imaging is essentially non-existent and that substantial benefit may be derived in clarifying the diagnosis and ultimately improving the individual's diagnosis management. Finally, while the recommendations below are directly derived from those of the recently published Canadian Consensus Conference on the Diagnosis and Treatment of Dementia, these views are shared by several organisations including those devoted to neurology and imaging (1–3).

Structural imaging is recommended in the workup of people with onset of cognitive symptoms within the past two years (irrespective of rate of progression) as well as in those with unexpected and unexplained decline in cognition and/or functional status in the setting of known dementia regardless of age (1). Either a head CT or MRI is appropriate (2), particularly to assess atrophy and exclude space occupying lesions among other issues. While a head CT including coronal reformatting may be helpful to exclude a space occupying lesion, detect vascular lesions and assess hippocampal atrophy, MRI is generally preferred because of its higher sensitivity for vascular lesions, microhaemorrhages and white matter disease, as well as its ability to exclude space occupying lesions and other features with diagnostic and predictive value (4). When available, a 3 Tesla MRI is preferred to a

1.5 Tesla scanner. The sequences acquired should include: a 3D T1 volumetric sequence (with coronal reformatting), a fluid-attenuation inversion recovery (FLAIR) sequence, T2* (or susceptibility)-weighted imaging as well as T2-weighted and diffusion-weighted imaging (1). A proton density (PD) sequence, although not routinely acquired, may be helpful. Intravenous contrast is not administered, unless there is a clinical indication such as suspected neoplastic, infectious or inflammatory disease. Effort should be made to standardise imaging including equipment and sequences, particularly when follow-up imaging is considered. Interpretation should be done by an experienced individual with consideration to including semi-quantitative scales for medial temporal lobe atrophy and global cortical atrophy (that is, Scheltens and Pasquier scales) as well as white matter disease (namely the Fazekas scale) (5–7).

Metabolic imaging with 18F-FDG PET is recommended in the workup of an individual with a confirmed cognitive impairment who has been evaluated by a cognitive disorders specialist and has had structural imaging but whose underlying pathological process remains unclear (1–3). PET may improve diagnostic accuracy and can lead to a change in medication and use of specialised care, in addition to improved quality of life. While several radioactive drugs (radiopharmaceuticals) may be imaged using PET, 18F-FDG, a radioactive glucose analogue is the most ubiquitous. Uptake of 18F-FDG by cells is detected using PET specific; patterns of decreased uptake correlate to various neurodegenerative diseases (Fig. 1). If 18F-FDG PET is unavailable, assessment of regional cerebral blood flow using single photon emission computed tomography (SPECT) may be helpful (1).

Over the last decade, several additional radiopharmaceuticals have been developed that are useful in the workup of someone with dementia (8). The true strength of imaging is that it provides a non-invasive regional representation of disease pathology. For example, there are ^{11}C - and ^{18}F -labelled radiopharmaceuticals available to image cerebral amyloid including: [^{11}C]-PIB as well as [^{18}F]-florbetapir (AmyvidTM), [^{18}F]-flutemetamol (VizamylTM) and [^{18}F]-florbetaben (NeuraCeqTM). While the presence of cerebral amyloid deposition may be seen in cognitively normal subjects, the absence of cerebral amyloid deposition essentially eliminates the possibility of Alzheimer's disease (Fig. 2). Thus, amyloid PET may provide insight on the pathology underlying dementia and possibly change management. To wit, the results of the IDEAS study reported a change in management pre- and post- amyloid PET in 60% of people with mild cognitive impairment (MCI) and 63% with dementia out of 11,409 subjects 65 years of age or older (9). Currently, accessibility and cost are two of the principal issues limiting use of amyloid PET in the workup of someone with dementia; however, when available amyloid PET can be very helpful. Further, if therapy targeting cerebral amyloid plaque proves beneficial in Phase 3 clinical trials, it is likely that amyloid PET will gain wide utilisation for patient selection and serial amyloid PET may become a more ubiquitous marker of therapy response. Also, over the last few years [^{123}I]-Ioflupane (DaTscanTM) SPECT has become available and may be useful to establish a diagnosis of cognitive impairment linked to dementia with Lewy bodies (DLB) (10). Finally, tau PET is a topic of active research which has already reached the clinical stage with the arrival of a first commercially available agent in the U.S., [^{18}F]-flortaucipir (TauvidTM). Its impact on clinical practice will become clearer within the next few years, particularly given the push to characterise people with dementia in terms of amyloid and tau status in conjunction with an assessment of neurodegeneration (8).

In summary, the workup of a subject suspected of presenting with cognitive deterioration includes a clinical evaluation by a cognitive specialist as well as structural imaging, preferably with a 3Tesla MRI and standard sequences. Metabolic imaging is reserved for individuals where the pathology underlying the cognitive decline remains uncertain. Within the last few years, imaging including amyloid and tau PET as well as [^{123}I]-Ioflupane SPECT have become available. Although not yet part of routine clinical practice, their use is increasing and is likely to become more prevalent pending further development of new therapies for dementia that are on the horizon. The same, with some delay, should happen with tau PET imaging.

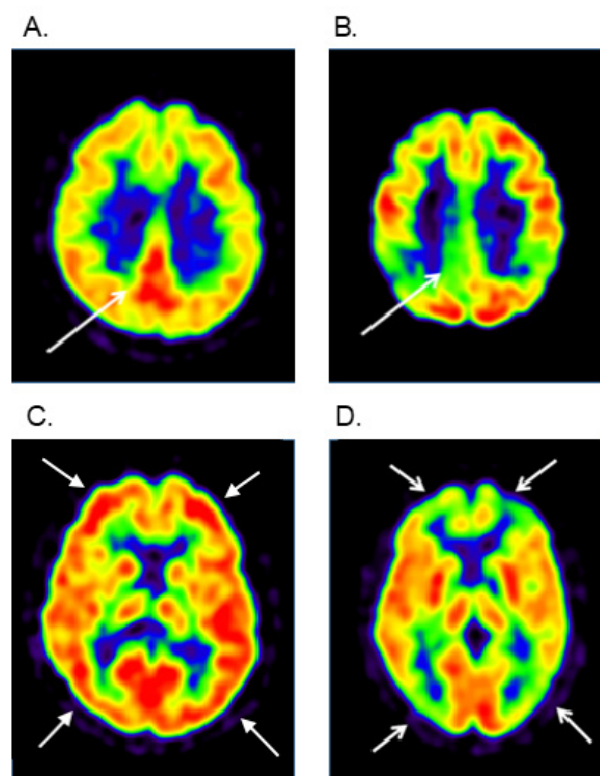


Figure 1. Axial [^{18}F]-fluorodeoxyglucose PET images on the left (A, C) show normal uptake of the radiopharmaceutical. Those on the right (B, D) were obtained from a person with Alzheimer's disease. Arrows point to recognisable differences as being characteristic of the disease.

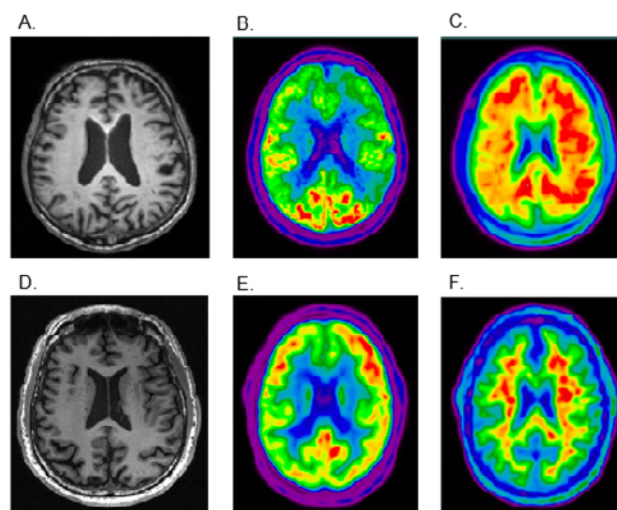


Figure 2. Axial MRI (A,D), [^{18}F]-fluorodeoxyglucose PET (B,E) and [^{18}F]-florbetapir PET (C,F) in two different people; top row: decreased [^{18}F]-fluorodeoxyglucose in the parietal, temporal (not shown), and frontal lobes (B) as well as increased [^{18}F]-florbetapir in the cerebral cortex (C) are characteristic of Alzheimer's disease; bottom row: normal radiopharmaceutical uptake (E, F) (11).

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Expert essay

The impact of amyloid imaging in the diagnosis of dementias

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The diagnosis of Alzheimer's disease and other dementias on purely clinical grounds is challenging due to the complex relationship between clinical presentation and underlying molecular pathology. In vivo biomarkers that detect key elements of Alzheimer's disease pathophysiology can be used to complement the clinical evaluation and provide direct evidence of the core features that define Alzheimer's disease neuropathology, namely amyloid- β (A β) plaques and tau neurofibrillary tangles. Direct visualisation of accumulating A β plaques in people living with Alzheimer's disease was first reported by Klunk and colleagues (1), applying the novel positron emission tomography (PET) radiotracer carbon-11 labelled Pittsburgh Compound-B (PIB). PIB is an analogue of thioflavin-T, a dye that has been used to stain amyloid in autopsy samples for over a century. While the short half-life of the carbon-11 radioisotope (20min) limit the use of PIB to research centres, a number of fluorine-18 (110min half-life) labelled radiotracers have subsequently been developed for clinical use, and three (18F-florbetapir, 18F-florbetaben, 18F-flutemetamol) have been approved by the United States Food & Drug Administration (FDA), the European Medicines Agency and other regulatory agencies.

A β aggregation is an early event in the evolution of Alzheimer's disease, starting decades before symptom onset. On PET, cortical radiotracer uptake is first evident in posterior cingulate-precuneus and prefrontal regions and is later seen throughout large regions of the neocortex (Figure 1). This pattern corresponds to a moderate-frequent density of neuritic plaques on neuropathology. In contrast, people with an absent or low burden of plaques show retention only in the sub-cortical white matter, which reflects non-specific (i.e., not A β -related) tracer binding (Figure 1). While the radiotracers are specific for plaques, A β is strongly related to tau pathology in Alzheimer's disease, with increased A β burden associated with higher Braak stages of neurofibrillary pathology. Braak stages in turn are closely associated with clinical symptoms and decline. Thus, positive amyloid PET can also suggest tau pathology and (in a clinic-based cohort study) has been shown to correspond to intermediate-high overall Alzheimer's disease neuropathological

changes. Importantly, the intensity of amyloid PET signal corresponds only weakly with disease stage, and the topography of binding corresponds weakly with neurodegenerative changes and specific cognitive symptoms. This is in contrast with tau PET signal, which correlates closely with disease progression and spatial distribution of neurodegeneration.

Appropriate Use Criteria have been developed to identify people who would most benefit from amyloid PET in their diagnostic work-up (2). These include individuals with objectively confirmed cognitive impairment seen by a dementia specialist, in whom the cause of impairment is uncertain after a comprehensive evaluation (including cognitive testing, basic labs and brain CT/MRI), Alzheimer's disease is a diagnostic consideration and knowledge of amyloid status is expected to alter diagnosis and management. Amyloid PET may be considered for people with progressive unexplained mild cognitive impairment (MCI), atypical/mixed clinical presentations or early age of onset (under the age of 65). In MCI, positive amyloid PET can confirm the presence of prodromal Alzheimer's disease and increases the likelihood that the person will convert to dementia in the coming 2–5 years. In people with dementia, amyloid PET may be most useful in distinguishing Alzheimer's disease from frontotemporal dementia, an early-onset disease that does not involve A β neuropathology. Conversely, amyloid PET is not useful for distinguishing Alzheimer's disease from other A β -associated conditions, such as dementia with Lewy bodies or cerebral amyloid angiopathy. While the initial Appropriate Use Criteria suggested amyloid PET is inappropriate in older people with a 'typical' (that is, amnesic) Alzheimer's disease presentation, this notion has been challenged by a relatively high rate of negative scans in such people in research studies and clinical trials. Furthermore, it is increasingly recognised that an Alzheimer's disease-like amnesic syndrome can also be caused by other common limbic-predominant pathologies, such as limbic-predominant age-related TDP-43 encephalopathy (3) and primary age-related tauopathy (4). While a negative amyloid PET is always useful in excluding Alzheimer's disease, clinicians should consider the person's age and apolipoprotein E (APOE) genotype in interpreting

the clinical significance of a positive scan. This is because the overall prevalence of amyloid pathology in the general (that is, cognitively unimpaired) population increases with age and in carriers of the APOE4 risk allele. Finally, the presence of amyloid does not exclude another pathology which may be more directly contributing to a person's symptoms.

A number of studies have evaluated the clinical impact of amyloid PET on patient diagnosis and management (5–7). Among these, the Imaging Dementia–Evidence for Amyloid Scanning (IDEAS) study assessed the utility of amyloid PET in over 18,000 Medicare beneficiaries in the US who met Appropriate Use Criteria (5). The study found that amyloid PET was associated with a change in core elements of patient management (use of Alzheimer's disease drugs, use of other drugs that treat dementia or dementia risk factors, counselling about safety and future planning) in over 60% of people. Following PET, the diagnosis changed from Alzheimer's disease to a non-Alzheimer's disease dementia in 25% of cases, and from a non-dementia to Alzheimer's disease in 10%. These results are consistent with those reported in smaller studies (6–7). Future studies will compare health outcomes (rates of hospitalisations, emergency department visits) and overall healthcare utilisation in the IDEAS cohort to a group of matched patients with MCI/

dementia who have not had amyloid PET. In lieu of data on long-term health outcomes, many third-party payers have declined to cover amyloid PET, severely restricting people's access to this diagnostic tool.

Despite its central role in Alzheimer's disease diagnosis, amyloid PET is not a stand-alone tool, and needs to be considered in combination with other tests and biomarkers. The information about molecular pathology provided by amyloid PET can be complemented via imaging markers of neurodegeneration, such as MRI (measuring brain atrophy) or 18F-fluorodeoxyglucose (FDG) PET (measuring glucose metabolism). The combination of amyloid PET and MRI or FDG improves the prediction of conversion from MCI to dementia due to Alzheimer's disease compared to either modality alone (8–9) and improves prediction of a neuropathological diagnosis of Alzheimer's disease (9). Beyond imaging, cerebrospinal fluid measures of A β 42 or the ratio of A β 42/A β 40 are concordant with amyloid PET in classifying individual amyloid status in most cases (~80–90%). CSF markers may be more sensitive than amyloid imaging in early stages of the disease, reflecting changes in soluble A β species that precede detectable aggregation into plaques (10). In the future, emerging plasma markers of A β will facilitate broad access to amyloid biomarkers in clinical care and

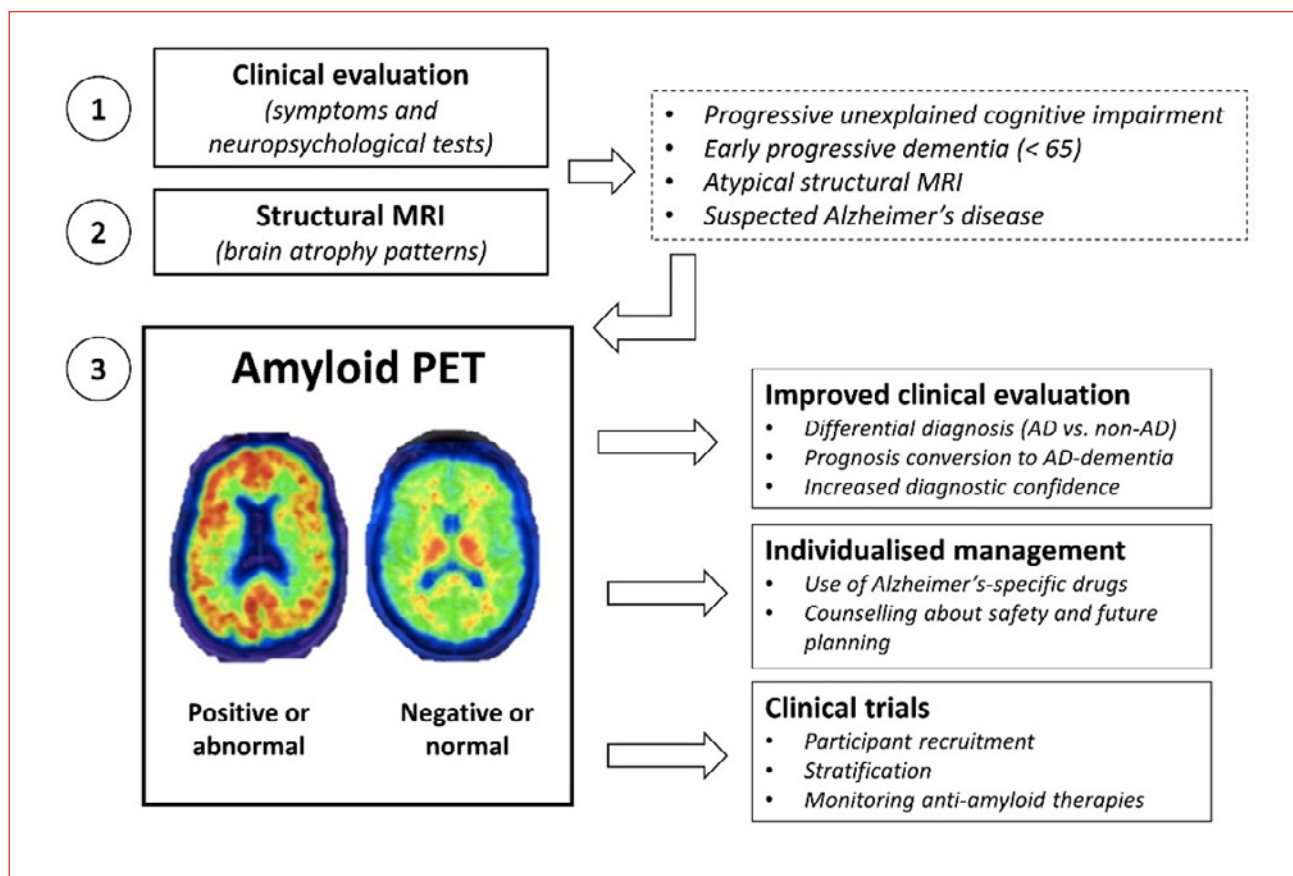


Figure 1. Flowchart of amyloid PET usage in dementia diagnosis, and its impact on clinical evaluation, dementia management and clinical trials. A positive amyloid PET scan (left) shows cortical radiotracer uptake in cortical brain regions, early in posterior cingulate-precuneus and prefrontal regions, while a negative scan (right) shows retention in the sub-cortical white matter, which reflects non-specific tracer binding.

research. However, compared to CSF or plasma, PET provides a better marker for overall brain amyloid burden and a more sensitive measure of longitudinal change.

In addition to its other uses, amyloid PET has played a critical role in Alzheimer's disease drug development. In clinical trials, amyloid PET has been used for subject selection (enabling early identification of pathology) and to measure target engagement for drugs designed to remove plaques. Very recently, the FDA approved the A β -targeting monoclonal

antibody aducanumab for the treatment of Alzheimer's disease, on the grounds that it robustly lowered amyloid PET signal, which was considered a surrogate outcome measure. While the clinical efficacy of the drug remains controversial in light of conflicting trial results, this approval heralds a new era of molecular-specific therapies for Alzheimer's disease. Identifying people who might benefit from these treatments will require broad access to amyloid PET and other biomarkers of A β deposition, and will provide great incentive for an early, biomarker-supported diagnosis of Alzheimer's disease.

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Expert essay

The role of Iodine-123 ioflupane (DaTscan®) SPECT imaging in dementia: what family physicians should know

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Iodine-123 ioflupane (123I-ioflupane, DaTscan®) is a radiopharmaceutical which can be used in combination with Single Photon Emission Tomography (SPECT) in Nuclear Medicine studies in assessing a series of suspected neurodegenerative conditions. Currently, its most frequent application by far is in the field of movement disorders (Parkinson's disease, other parkinsonian syndromes, essential tremor, etc.) (1). Here, the focus will be on the use of this agent in subjects with neurocognitive deterioration, specifically for differentiating Alzheimer's disease from Lewy bodies diseases (this includes dementia with Lewy bodies, and Parkinson's disease with dementia).

Ioflupane is a molecule, which is closely related to cocaine, and both share a number of chemical and pharmacological properties. In particular, they can bind with high affinity to the membrane transporter for dopamine (DAT) found on the surface of dopaminergic (DA) cells (2), especially at synaptic terminals. Under normal conditions, the number of DAT expressed by those cells is relatively constant, and measurements of the quantity of radioactivity found in the brain after injection of 123I-ioflupane with SPECT can serve as an *in vivo*, non-invasive proxy for the regional concentrations of functional DA terminals.

Loss of DA cells from the *substantia nigra* in the mesencephalon has long been known as one of the defining observations made in LBD (3). Lewy bodies, largely composed of a pre-synaptic protein called α -synuclein, are associated with progressive loss of the cells harbouring them and are found in multiple monoaminergic neurons of the brainstem in affected people, especially DA ones (as well as in cholinergic neurons). The brain regions which, in humans, contain the largest number of DA terminals, are the basal ganglia, and 123I-ioflupane SPECT studies specifically assess uptake of the tracer in those nuclei. Subjects presenting with clinical manifestations of a Lewy body dementia overwhelmingly show already significant loss of DA terminals in the basal ganglia by the time they seek medical attention, which is depicted with very high sensitivity by the test, to the extent that a normal study essentially rules out the presence of

a Lewy body dementia. In addition, a well characterised down regulation of the expression of DAT by DA cells in Lewy body dementia (4) increases the sensitivity of the test by further reducing uptake beyond the actual numerical loss of DA terminals bearing DAT.

The test is remarkably safe, with the odds of side effects being extremely low, and involving systematically mild reactions (5). Except for pregnancy (rare in the class of subjects studied) or a history of a previous unexpected reaction to the product, there are no contraindications to its use; in particular, allergies to iodine-containing contrast agents *are not* a contraindication. Preparation for the test is minimal. Approximately one hour before injection, the person will receive a small quantity of non-radioactive iodine such (as Lugol solution or other sources of stable iodine) to block uptake by the thyroid of any radioactive iodine-123, which might be released by ioflupane (standard quality control of the agent ensures that this would be limited to very small amounts in the first place). It is also important to make sure the patient is not taking medication that can interfere with binding of the radiopharmaceutical to DAT, a list of which can be found in the CANM guidelines for Dopamine Imaging in Movement Disorders. (1). The individual should be advised that they need to schedule approximately four hours at the imaging facility, most of which (three hours) is required because of a relatively long uptake period for this molecule after its IV administration. Acquisition of data will last around 30 minutes spent in a SPECT scanner, which only exceptionally induces claustrophobia as those cameras are much more 'open' than an MR scanner for instance.

Visual inspection of the images obtained with SPECT is the recommended approach for diagnosis. Because, as already mentioned, people with clinical manifestations linked to Lewy body dementia already have lost a large portion of their dopaminergic terminals, this is generally quite straightforward. Some borderline cases may benefit from one of several quantification approaches (6), but obtaining high-quality quantification is technically demanding and is often not performed.

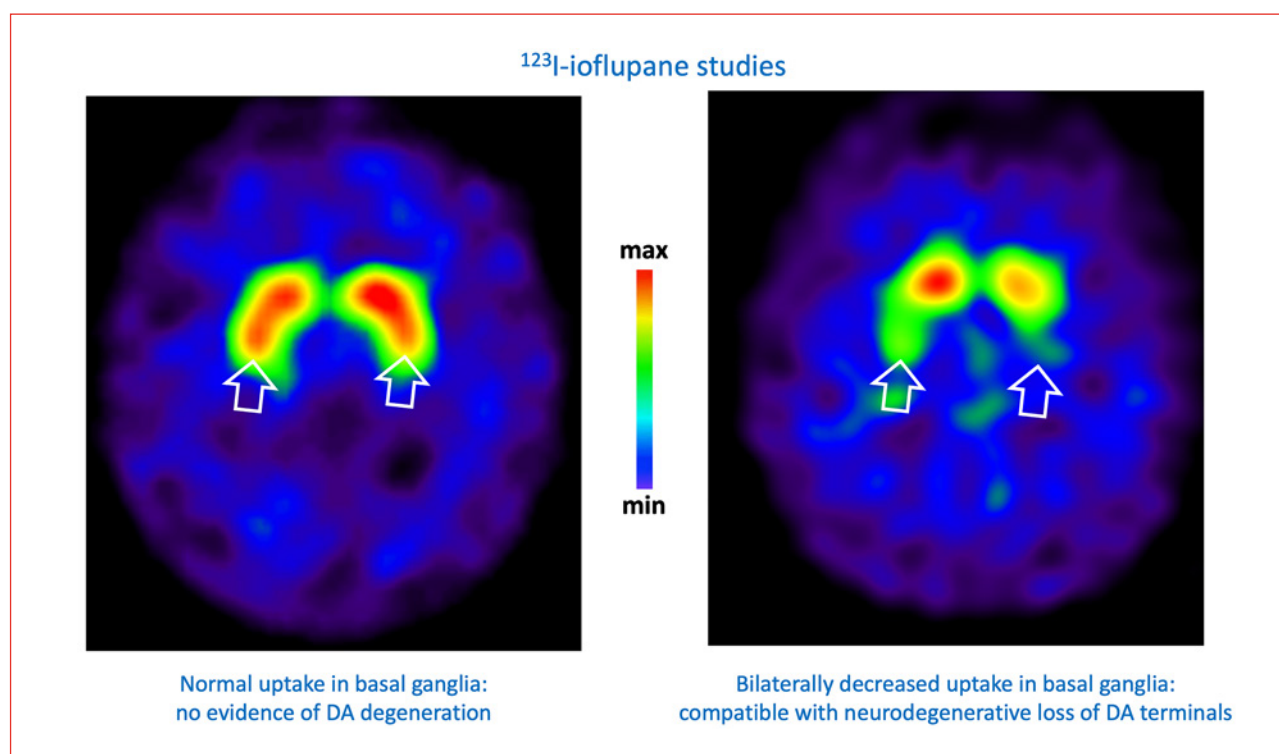


Figure 1. Comparative ¹²³I-ioflupane SPECT imaging after injection illustrating how it identifies suspected dementia with Lewy bodies.

Distinguishing cognitive impairment linked to Alzheimer's disease from that associated to Lewy body dementia (here designating both dementia with Lewy bodies and Parkinson's disease dementia) is an indication to use ¹²³I-ioflupane SPECT imaging which is not approved in all jurisdictions. European authorities have allowed its use under such circumstances, whereas in North America, the use of the product is only authorised for the evaluation of movement disorders, although it is largely used off-label in people with cognitive impairment. Its performance in establishing the correct diagnosis when questions remain after standard evaluation has been obtained (an evolving concept with the arrival of new imaging and liquid biomarkers) is now well recognised

(7); and has led to its inclusion in general recommendations for the evaluation of subjects with cognitive impairment by various organisations (8). Diagnostic accuracy in separating LBD-linked cognitive impairment from Alzheimer's disease is reported to be between 88% and 96%.

Therefore, it is now largely accepted that ¹²³I-ioflupane SPECT imaging, in addition to having an established status as an excellent approach to establish the nature of movement disorders of uncertain aetiology, is a powerful tool for the identification of Lewy body dementia as a cause of cognitive impairment in complex cases where that diagnosis is a clinical possibility.

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Expert essay

Tau PET for the diagnosis and staging of Alzheimer's disease

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The neuropathological signatures of Alzheimer's disease are brain deposits of amyloid- β plaques and hyperphosphorylated tau protein in the form of neurofibrillary tangles (1). The quantification of these pathological processes in the brain of living patients is critical to identifying individuals with underlying Alzheimer's disease pathophysiology, which can provide a more accurate diagnosis of Alzheimer's disease for research and clinical settings. Biomarkers derived from PET (Positron Emission Tomography) imaging, unlike biomarkers measured in blood or CSF (cerebrospinal fluid), offer the unique opportunity to visualise the distribution of the pathology in the human brain. Klunk and colleagues reported the first results showing direct visualisation of Alzheimer's disease pathophysiology in the living human brain with the amyloid- β PET tracer Pittsburgh Compound-B (PIB) more than 15 years ago (2). Since then, several studies have confirmed that amyloid- β PET tracers are valuable tools for identifying Alzheimer's disease pathophysiology (3), which culminated in the United States Food and Drug Administration (FDA) approval of A β PET compounds for clinical use.

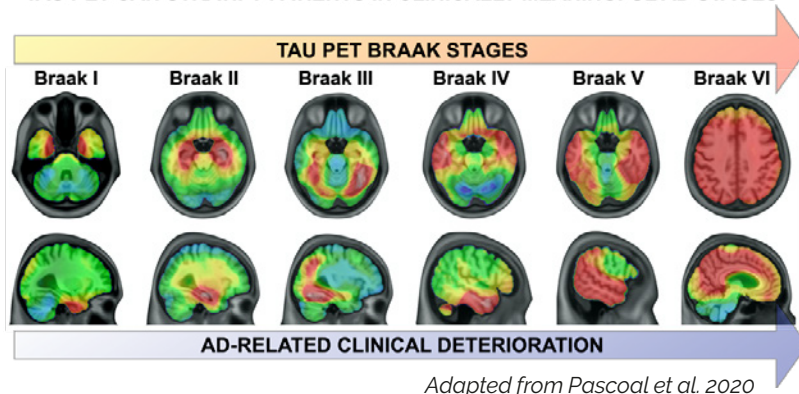
More recently, the field of Alzheimer's disease is increasingly focused on tau PET biomarkers because changes in tau pathology are more closely related to the development of clinical symptoms and post-mortem studies suggest that tau accumulation follows a temporal stereotypical pattern known as Braak stages, suggesting that identifying these stages can help define how far the person is in the course of the disease (4). Several post-mortem studies support that these so-called Braak stages of tau accumulation are closely related to other aspects of Alzheimer's disease pathophysiology, such as amyloid- β deposition, neuronal injury, and cognitive impairment (4). Thus, Braak staging was incorporated in the neuropathological diagnosis criteria of Alzheimer's disease (5). Based on the above-mentioned post-mortem observations, it has been postulated that in vivo Braak staging obtained with tau PET has the potential to stratify patients according to their brain patterns of tau accumulation, offering evidence on the patients' tau pathology and disease stage, which could provide valuable information to clinicians to track Alzheimer's disease progression.

Indeed, tau PET tracers have shown high performance for separate individuals with cognitive impairment due to Alzheimer's disease from other causes of dementia (>85–95%) (6). In addition, several lines of evidence suggest that tau PET can significantly add diagnostic value to amyloid- β PET if used in clinical settings (7). Recognising the potential clinical applicability of tau PET, the US FDA has recently approved the tau PET tracer Tauvid (flortaucipir) for clinical use. To date, Tauvid is the first and only FDA-approved tau tracer to clinically estimate the density and distribution of tau tangles pathology in the brain of adult individuals with cognitive impairment in whom Alzheimer's disease is suspected as a possible aetiology.

Recently, second-generation tau PET tracers (e.g., MK-6240, PI-2620, GTP1, RO948, JNJ-067) have been developed to provide better visualisation of tau pathology (12–16), minimising off-target binding to brain pathologies other than tau and increasing the sensitivity to detect low concentrations of tau tangles pathology.

Studies using the second-generation tau PET tracer MK-6240, which has a high sensitivity to detect tau tangles pathology (~6 times higher than the first-generation tau tracers such as the Tauvid), have shown that tau PET tracers are capable of entirely recapitulating the post-mortem stages proposed by Braak and colleagues (4,6,8). These studies suggest that the stratification of patients into seven Braak-like classes of tau accumulation (Braak 0–VI) can provide invaluable clinical information overlooked by dichotomisation techniques (merely indicating tau positivity or tau negativity). These studies have demonstrated that, in the absence of any other biomarker in clinical practice, patients with a tau PET Braak stage 0 (indicating the absence of tau pathology) could be associated with a very low risk of presenting brain amyloid- β pathology, neurodegeneration, and cognitive impairment, individuals classified as tau PET Braak stage IV or greater with a very high risk of presenting underlying neurodegeneration, and tau PET Braak stages V or VI with likely imminent development of dementia symptoms (6) (Figure). These results highlight that in vivo Braak staging using the novel high-sensitivity tau PET tracers can provide a more comprehensive evaluation of the

TAU PET CAN STRATIFY PATIENTS IN CLINICALLY MEANINGFUL AD STAGES



clinical significance of underlying tau deposition as compared to mere dichotomisation into tau positive and negative classes.

Tau PET tracers are also important to the enrichment and monitoring of clinical trials designed to test novel pharmacological interventions to treat Alzheimer's disease. Years of research on fluid biomarkers (phosphorylated-tau or amyloid- β in CSF and now in the blood) and amyloid- β PET studies have shown severe limitations of these markers for longitudinal quantification of Alzheimer's disease-related

changes at the level of the individual (9). Unlike other available markers of Alzheimer's disease pathophysiology, individuals with cognitive impairment assessed with tau PET show rates of longitudinal tau accumulation at 12–24 months suitable for use as a surrogate marker in clinical trials (10,11). Thus, in addition to its use for diagnosis and staging Alzheimer's disease pathophysiology, tau PET offers a tool capable of testing the effects of drug therapies in reducing the longitudinal progression of Alzheimer's disease pathophysiology over typical clinical trial periods (12–24 months).

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Conclusions

When an individual presents with suspected signs or symptoms of cognitive decline, clinicians will perform the basic dementia assessments such as medical history, neurological examination, basic laboratory screening tests, and cognitive assessment.

Other tools, such as PET and SPECT techniques, that visualise and quantify an extensive list of biochemical processes have undergone much progress in the last fifteen years. However, the availability of PET and SPECT screening methods to diagnose the underlying causes of dementia remains limited worldwide due to cost and accessibility, even in high-income countries.

Although PET can identify Alzheimer's disease pathophysiology, substantial progress has also been achieved for other neurodegenerative conditions.

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