



Evidence-based indications for the use of PET-CT in the United Kingdom 2016

The Royal College of Radiologists, Royal College of Physicians of London, Royal College of Physicians and Surgeons of Glasgow, Royal College of Physicians of Edinburgh, British Nuclear Medicine Society, Administration of Radioactive Substances Advisory Committee



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Contents

Foreword	1	Non-FDG tracers for clinical practice	10
		Indications for non-FDG tracers	10
Indications for 18F-fluorodeoxyglucose (FDG)			
PET-CT	3	Key references	13
Oncology applications	3	Indications for FDG scans	13
Non-oncological applications	8	Indications for non-FDG scans	25

Foreword

Since its introduction into clinical practice in the UK 26 years ago, positron emission tomography (PET) followed by positron emission tomography-computed tomography (PET-CT) has become a key investigative tool in the assessment of cancer and non-cancer medical conditions. The Inter-Collegiate Standing Committee on Nuclear Medicine (ICSCNM) supported the development of PET-CT in the UK through a number of initiatives including the 2003 document *Positron emission tomography – A strategy for provision in the UK*, the forerunner of the publication *PET-CT in the UK. A strategy for development and integration of a leading edge technology within routine clinical practice in the UK*.

The publication of the first version of *Evidence-based indications for the use of PET-CT in the United Kingdom 2012* was a landmark ICSCNM document. Authored by Sally Barrington and Andrew Scarsbrook, it provided, for the first time, a guide to the use of PET-CT in clinical practice and the evidence-base on which this was founded. It was used widely to inform and to shape the commissioning of PET-CT services in the UK and beyond. Now in its third edition, the 2016 version builds on the evidence cited in earlier editions providing an updated review with key references for the use of fluorodeoxyglucose (FDG) and non-FDG PET-CT tracers in malignant and in non-malignant disease. The ICSCNM wish to thank Andrew Scarsbrook and Sally Barrington for updating this invaluable reference guide.

Brian Neilly

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A document prepared for the Intercollegiate Standing Committee on Nuclear Medicine, by members of The Royal College of Radiologists and the Royal College of Physicians.

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This guidance comprises an up-to-date summary of relevant indications for the use of PET-CT, where there is good evidence that patients will benefit from improved disease assessment resulting in altered management and improved outcomes. This document supersedes the previous Evidence based Indications for the use of PET-CT in the United Kingdom guidance published by The Royal College of Physicians in December 2013. New indications and key references are highlighted in red ink for ease of identification. The document will be updated at regular intervals.

The indications are divided into oncological and non-oncological applications then body area/system. This list is not exhaustive and there are cases where PET-CT may be helpful in patients who have equivocal or definite abnormalities on other imaging where PET-CT may alter the management strategy if found to be 'positive' or 'negative'; for example, radical or high-risk surgery. PET-CT would be appropriate in such patients at the discretion of the local Administration of Radioactive Substances Advisory Committee (ARSAC) certificate holder.

Indications for 18F-fluorodeoxyglucose (FDG) PET-CT

Oncology applications

Brain

- Identifying the grade of malignancy where there is uncertainty on anatomical imaging and functional assessment would assist biopsy.
- Suspected relapse where magnetic resonance (MR) is equivocal to inform decisions regarding surgery or radiotherapy planning – see below for alternative PET imaging with 11-Carbon (¹¹C)-methionine or ¹⁸F-fluoroethyltyrosine (FET).
- Assessment of suspected high-grade transformation in low-grade glioma.
- Differentiation of cerebral tumour from atypical infection in immuno-compromised patients with indeterminate lesions on MR/CT.

Head and neck tumours

- Staging of patients where staging is difficult clinically; for example, where there is uncertainty on other imaging or equivocal findings that would preclude radical treatment.
- Staging or restaging of patients with a high risk of disseminated disease such as advanced loco-regional disease and primary sites with a high propensity for disseminated disease such as nasopharyngeal cancer.
- To identify the primary site in patients presenting with metastatic squamous cell carcinoma in cervical lymph nodes, with no primary site identified on other imaging.
- Response assessment 3–6 months' post chemo-radiotherapy.
- To differentiate relapse from treatment effects in patients suspected to have tumour recurrence where magnetic resonance imaging (MRI) is uncertain or equivocal.

Thyroid carcinoma

- Assessment of patients with elevated thyroglobulin levels and negative iodine scintigraphy with suspected recurrent disease.
- To evaluate disease in treated medullary thyroid carcinoma associated with elevated calcitonin levels with equivocal or normal cross-sectional imaging, bone and octreotide scintigraphy – see below for alternative PET imaging with 68 Gallium (⁶⁸Ga)-DOTA-octreotate (DOTATATE), DOTA-1-NaI3-octreotide (DOTANOC) or DOTA-octreotide (DOTATOC).

Lung carcinoma

- Staging of patients considered for radical treatment of non-small cell lung cancer:
 - Specifically National Institute for Health and Care Excellence (NICE) guidelines (2011) recommend PET-CT is used for mediastinal lymph node staging in patients whose disease is potentially suitable for treatment with curative intent, such as those with a low probability of mediastinal malignancy (lymph nodes <1 centimetre [cm] on CT) or in patients with an intermediate probability of mediastinal metastases (nodes between 1–2 cm on CT) and for confirming distant metastases.

- Characterisation of a solid solitary pulmonary nodule with an initial risk of malignancy of >10% (Brock model) where the nodule size is greater than local PET-CT detection threshold (8–10 millimetres [mm]) below which the influence of the partial volume effect is substantial and precludes adequate sensitivity:
 - Especially in the case of failed biopsy, a technically difficult biopsy or where there is a significant risk of a pneumothorax in patients with medical co-morbidities.
 - Smaller nodules in the upper lobes may be considered after discussion with the local ARSAC certificate holder if biopsy and/or CT follow-up are not appropriate.
- Assessment of response to chemotherapy and/or radiation treatment in selected patients who have had an apparently very good response on conventional imaging and surgery is being considered.
- Assessment of suspected disease recurrence:
 - To differentiate between treatment effects and recurrent cancer.
- Staging of patients with small-cell lung cancer with limited disease on CT being considered for radical therapy.

Pleural malignancy

- To guide biopsy in patients with suspected pleural malignancy:
 - With pleural thickening; FDG is less likely to be useful in patients presenting with a pleural effusion only or with a history of previous pleurodesis.
- To exclude extra-thoracic disease in proven mesothelioma in patients considered for multimodality treatment including radical surgery/decortication.

Thymic tumours

- Staging of patients considered for surgical resection.
- Assessment of indeterminate thymic lesions if being considered for radical treatment.

Oesophago-gastric carcinoma

- Staging/restaging of patients with oesophageal or oesophago-gastric carcinoma, suitable for radical treatment, including patients who have received neo-adjuvant treatment.
- Evaluation of suspected recurrence of oesophago-gastric tumours when other imaging is negative or equivocal.

Gastrointestinal stromal tumours

- Staging prior to treatment in patients who are likely to require systemic therapy.
- Response assessment to systemic therapy.

Breast carcinoma

- Assessment of multi-focal disease or suspected recurrence in patients with dense breasts.
- Differentiation of treatment-induced brachial plexopathy from tumour infiltration in symptomatic patients with an equivocal or normal MR.
- Assessment of extent of disease in selected patients with disseminated breast cancer before therapy.
- Assessment of response to chemotherapy in patients whose disease is not well demonstrated using other techniques; for example, bone metastases.

Hepato-pancreatico-biliary cancers

- Staging of patients with potentially operable pancreatic adenocarcinoma where cross-sectional imaging is equivocal for metastatic disease and a positive PET-CT would lead to a decision not to operate.
- Staging of potentially operable primary hepato-biliary malignancy (cholangiocarcinoma, gallbladder carcinoma or hepatocellular carcinoma) where cross-sectional imaging is equivocal for metastatic disease, who are fit for resection and a positive PET-CT would lead to a decision not to operate.
- Suspected recurrence of hepato-pancreatico-biliary cancer in selected patients, where other imaging is equivocal or negative, taking into consideration that up to 30% of pancreatic adenocarcinomas and up to 50% of differentiated hepatocellular carcinomas may not be FDG avid.

See below for other tracers that may be helpful in staging.

Colorectal carcinoma

- Staging of patients with synchronous metastases at presentation suitable for resection or patients with equivocal findings on other imaging; for example, pulmonary or liver lesions.
- Restaging of patients with recurrence being considered for radical treatment and/or **invasive targeted techniques (for example, metastectomy/selective internal radiation therapy [SIRT])**.
- **Assessment of treatment response in patients with rectal carcinoma post (chemo)radiotherapy with indeterminate findings on other imaging.**
- **Assessment of treatment response following targeted therapy (ablative techniques for liver or lung metastases, selective internal radiotherapy for liver metastases) in metastatic colorectal carcinoma when findings on other imaging are inconclusive.**
- Detection of recurrence in patients with rising tumour markers and/or clinical suspicion of recurrence with normal or equivocal findings on other imaging.
- Evaluation of indeterminate pre-sacral masses post-treatment.

Urological malignancy

- Assessment of metastatic renal and ureteric carcinoma in difficult management situations or when standard imaging is inconclusive.
- Assessment of renal carcinoma at staging in selected cases with equivocal findings on other imaging (recognising that ~50% of renal cell carcinoma may not be FDG avid and that the tracer is excreted into the urinary tract).
- Assessment of advanced muscle-invasive bladder carcinoma, which is potentially radically treatable.

See below for alternative PET imaging with non-FDG tracers in prostate malignancy.

Gynaecological malignancy

- Staging or restaging of patients with vulval or uterine (cervix/endometrium) carcinoma considered for exenterative surgery.
- Staging and restaging of patients with locally advanced cervical cancer being considered for radical chemo-radiotherapy.
- **Response assessment of locally advanced cervical cancer after chemoradiotherapy.**
- Suspected recurrence of vulval, endometrial or cervical carcinoma when other imaging is equivocal.
- Detection of tumour in selected patients with ovarian carcinoma who have rising CA125 levels and equivocal or negative imaging.

Testicular malignancy

- Assessment of recurrent disease in patients with metastatic seminoma or teratoma with elevated or rising tumour markers and equivocal or normal anatomical imaging.
- Evaluation of residual masses for patients with seminoma and teratoma, although mature differentiated teratoma may not be FDG avid and cannot be excluded with a negative scan.

Anal and penile carcinoma

- Staging of selected patients considered for radical treatment.

Lymphoma

- Staging of FDG-avid lymphomas.
- Remission assessment of FDG-avid lymphomas after completion of treatment using the five-point scale (Deauville criteria) for response assessment. If there has been a complete metabolic response (CMR) on an interim scan, an end of treatment scan is not required.
- Interim assessment to guide response adapted treatment in selected patients with Hodgkin lymphoma
- Interim assessment to monitor treatment if mid-therapy imaging is performed and to exclude progression in patients with aggressive non-Hodgkin Lymphoma
- Evaluation of suspected relapse for FDG-avid lymphomas in symptomatic patients. *Surveillance imaging is not recommended.*
- Assessment of response to second line treatment and subsequent treatments for FDG-avid lymphoma.
- Staging of suspected post-transplant lympho-proliferative disorder (PTLD).
- Prior to bone marrow transplant to assess remission status and residual volume of disease and suitability for transplant.
- To determine extent and identify a suitable biopsy site in patients with low-grade lymphomas in who there is suspected high-grade transformation.

Myeloma

- FDG PET/CT has prognostic value when used in the initial diagnosis of myeloma, but there is currently insufficient evidence to justify the routine use of PET/CT in all cases of newly diagnosed myeloma. Use in selected patients as follows:
 - To identify patients with smouldering myeloma at high risk of progression to symptomatic disease requiring initiation of treatment in line with revised International Myeloma Working Group Criteria
 - Baseline assessment in patients with non-secretory and oligo-secretory myeloma as a baseline for subsequent response assessment
 - Assessment of patients with apparently solitary plasmacytoma to exclude other sites of disease
 - To assess response or suspected relapse in patients with oligo-secretory or non-secretory myeloma, patients with predominantly extra-medullary disease and patients with solitary plasmacytoma
 - Remission assessment post stem-cell transplantation in patients with absence of para-proteins or light chains in blood, urine and bone marrow in selected cases
 - Assessment of patients with monoclonal gammopathy associated neuropathies (MGAN) to identify plasmacytomas which may be amenable to radiotherapy.

Skin tumours

- Staging of patients with known disseminated melanoma to assess extent of disease prior to treatment.
- To assess for distant disease in patients with melanoma when radical dissection is contemplated (nodal or metastatic disease).
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- To assess response to isolated limb infusion for malignant melanoma.
- **In the assessment of selected patients with Merkel Cell Carcinoma to more accurately stage disease extent where this would alter intended management and for assessment of treatment response and/or suspected recurrence when conventional imaging is inconclusive.**
- To exclude systemic involvement in skin lymphomas **and exclude large cell transformation in Mycosis Fungoides.**
- To exclude primary malignancy where dermatomyositis suspected to represent a paraneoplastic manifestation.

Not indicated for early-stage patients who should undergo sentinel node biopsy.

Musculoskeletal tumours

- Assessment of suspected malignant transformation within plexiform neurofibromas in patients with neurofibromatosis type 1 with delayed imaging recommended at four hours where there is uptake at 60–90 minutes.
- Staging of high-grade sarcomas, unless already proven to have metastatic disease, especially Ewing's sarcoma, rhabdomyosarcoma, leiomyosarcoma, osteosarcoma, malignant fibrous histiocytoma, synovial sarcoma and myxoid liposarcoma.
- Pre-amputation in the setting of a high-grade sarcoma where the detection of distant disease will alter the surgical management.
- To stage patients with metastatic sarcoma considered for liver or lung metastatectomy where anatomical imaging has not identified any extra-thoracic or extra-hepatic disease which would preclude surgery.
- Response assessment in high-grade sarcomas.

Paraneoplastic syndromes

- To detect an occult primary tumour in selected patients with non-metastatic manifestations of neoplastic disease when other imaging is negative or equivocal.

Carcinoma of unknown primary

- Detection of the primary site when imaging and histopathology has failed to show a primary site, where the site of tumour will influence choice of chemotherapy.

Neuroendocrine tumours

- Staging or restaging of selected patients with poorly differentiated neuroendocrine tumours prior to treatment with negative or normal metaiodobenzylguanidine (mIBG) and octreotide scans.
- Assessment of possible multifocal disease in patients with paraganglioma considered for surgery.
- **Assessment of selected patients with adrenocortical carcinoma being considered for invasive treatment where cross-sectional imaging is inconclusive.**

Rare tumours in children and young adults

- Staging of osteosarcoma and response to chemotherapy.
- Staging and response assessment of Ewing's sarcoma.
- PET-CT may be helpful on an individual case basis in paediatric or adolescent patients with:
 - Wilms' tumours
 - Metaiodobenzylguanidine (MIBG)-negative neuroblastoma
 - **Rhabdomyosarcoma**
 - Hepatoblastoma
 - Langerhans' cell histiocytosis.

Non-oncological applications

Neurological applications

- Pre-surgical assessment of medically refractory complex partial seizures where MR is normal, equivocal or conflicts with electroencephalogram (EEG) localisation.
- Evaluation of memory loss/neurological signs suggestive of dementia and differentiation of types of dementia in selected patients.

See below for amyloid imaging which may be helpful in highly selected patients with suspected dementia.

Cardiological indications

- Assessment of myocardial viability in patients with ischaemic heart failure and poor left ventricular function being considered for revascularisation, usually in combination with perfusion imaging with sestamibi/tetrofosmin or ammonia/rubidium.

Vasculitis

- Evaluation of suspected vasculitis in selected cases; for example, to determine the extent and distribution of the disease activity or to exclude underlying malignancy which may be a paraneoplastic phenomenon, resulting in atypical presentations of vasculitis.
- PET-CT would not be indicated in all patients with giant cell arteritis but is of use in patients where conventional investigations are unhelpful and treatment would be altered if ongoing inflammatory disease is confirmed.

Sarcoidosis

- Assessment of activity and distribution of disease at baseline in highly selected cases where there is diagnostic uncertainty using conventional imaging (for example, suspected cardiac sarcoidosis. **May be used in combination with perfusion imaging to assess known or suspected cardiac inflammation in patients with known or suspected sarcoidosis after prolonged fasting**).
- Assessment of disease response where other measures to monitor response are unhelpful and/or in patients with disease resistant to treatment.

Infection imaging

- Detection of site of focal infection in immuno-compromised patients or problematic cases of infection.
- Evaluation of vascular graft **or cardiac implantable device related** infection in selected cases provided sufficient time has elapsed since surgery.

Pyrexia of unknown origin (PUO)

- To identify the cause of a PUO where conventional investigations have not revealed a source.

Non-FDG tracers for clinical practice

The role of FDG in a range of malignancies is established, but there are limitations to using FDG for imaging some tumours. Non-FDG tracers can be used to image a limited number of tumours, which are important for patient care. The exceptions are the potential use of choline derivatives for imaging prostate cancer and the use of amyloid tracers for assessment of patients with cognitive impairment/dementia.

Fluorinated tracers can be produced in a regional cyclotron and transported, such as FDG and fluoro-choline. Generators that are used to produce radionuclides such as ^{68}Ga Gallium can be purchased and the tracers produced in nuclear medicine department radiopharmacies. Other short-lived tracers such as ^{13}N -ammonia and ^{11}C -Carbon-labelled compounds are produced in a cyclotron which needs to be on the same site as the scanner.

It is recognised that cyclotron and generator-produced tracers are available in a few specialist centres and that fluorinated tracers **and generator-produced tracers** may become more widely available. The rationale for using alternative tracers to FDG for these indications is highlighted in italics.

Indications for non-FDG tracers

^{11}C -Methionine (cyclotron-produced short-lived tracer) or ^{18}F -Fluoroethyltyrosine (FET)

^{11}C -Methionine **and ^{18}F -FET** are superior in defining the extent of tumour in low and intermediate grade gliomas compared to FDG, which has limited use because of high uptake in normal brain.

- Assessment of tumour grade and extent in some patients with glioma for staging or suspected recurrence to target biopsy and plan treatment.

^{11}C -Methionine has been reported as having better sensitivity for localising parathyroid tumour than FDG in difficult cases.

- Parathyroid tumour localisation in difficult cases where the tumour has not been found using conventional anatomical and functional imaging techniques.

^{13}N -Ammonia (cyclotron-produced short-lived tracer) ^{82}Rb -Rubidium chloride (generator-produced short-lived tracer)

- Assessment of myocardial perfusion in patients with suspected ischaemic heart disease or to assess the extent of disease in patients with known coronary artery disease (CAD) **or in combination with FDG for assessment of cardiac sarcoidosis (as above).**
- Assessment of perfusion in selected patients with coronary anomalies with congenital disease, after surgery and with Kawasaki's disease.

$^{99\text{m}}\text{Tc}$ -Methyl diphosphonate ($^{99\text{m}}\text{Tc}$)-labelled tracers (sestamibi, tetrofosmin) are widely available and have high sensitivity and specificity for the evaluation of CAD with Single-photon emission computed tomography (SPECT). However, PET tracers have improved sensitivity in some situations, for example, in high-body mass patients where significant attenuation of the inferior and anterior walls limits assessment. ^{13}N -Ammonia allows quantitative assessment of myocardial perfusion to be performed and is better used to assess disease in patients with balanced three vessel disease. Rubidium has improved image quality compared to Technetium $^{99\text{m}}\text{Tc}$ and may be cost-effective compared to $^{99\text{m}}\text{Tc}$ when there is a large throughput of patients (around five cases per day Monday to Friday). Both PET tracers are associated with lower radiation dose than $^{99\text{m}}\text{Tc}$ tracers.

¹¹C-Choline or ¹⁸F-fluoro-choline (both cyclotron-produced but ¹¹C short-lived, ¹⁸F can be transported) and ⁶⁸Ga-prostate-specific membrane antigen (PSMA)

FDG is not taken up by most prostate cancers. FDG is taken up but rapidly dephosphorylated and 'washes out' of the liver and is not useful to image up to 50% of hepatocellular carcinoma (HCC). Choline transport and choline kinase enzymes are over expressed in many malignancies including prostate cancer and HCC. A substantial number of observational studies support the use of choline PET-CT to detect local and distant metastatic disease in prostate cancer with improved accuracy compared to CT and MR. ¹¹C-Choline is generally preferred to ¹⁸F-fluorocholine because it is not excreted in urine but has limited availability. There are two forms of ¹⁸F-fluorocholine available (fluoro-methyl choline and fluoro-ethyl choline) and neither has undergone validation in direct comparison with ¹¹C-choline. ⁶⁸Gallium-PSMA (Prostate Specific Membrane Antigen) is a rapidly emerging alternative tracer for assessment of prostate malignancy with superior diagnostic accuracy compared to choline.

- Evaluation of high-risk patients before curative treatment or to evaluate equivocal findings on conventional imaging such as possible nodal or metastatic disease in patients with prostate cancer where confirmation or exclusion of distant disease would directly influence patient management.
- Suspected recurrence in patients with a rapidly rising prostate-specific antigen (PSA) and negative or equivocal conventional imaging where the results would directly influence patient management.

There is evidence from observational studies suggesting ¹⁸F-fluorocholine improves the accuracy of HCC detection in primary staging and recurrence. Liver transplantation can offer some patients a chance of cure but careful pre treatment assessment is essential.

- Assessment of patients with HCC being considered for transplant or other radical treatment where the results would directly influence patient management.

¹¹C-acetate

- Assessment of HCC.

The combination of FDG and acetate for HCC has been demonstrated to identify more abnormalities to stage the disease than conventional imaging.

⁶⁸Ga-labelled somatostatin receptor (SSR) imaging (generator produced)

- Staging and assessment of suspected recurrence in neuroendocrine tumours (NETs).

Most NETs have low uptake of FDG; however, tracers that bind to somatostatin receptors, which are expressed by these tumours have high uptake. Somatostatin receptor (SSR) scintigraphy using SPECT tracers, for example ¹¹¹In-octreotide, have been in clinical use for a number of years. Newer peptides labelled with ⁶⁸Ga such as DOTATOC and DOTATATE show much higher affinity for NETs. Recently radionuclide treatments using SSR agents have resulted in improved quality of life and survival for patients with NETs and SSR imaging helps to select and manage patients for radionuclide therapy.

¹⁸F-FluoroDOPA (f-dopa) (cyclotron-produced but transportable)

- Assessment of suspected congenital hyperinsulinism.
- Assessment in selected cases of NETs.

There is evidence that F-DOPA may have high uptake in some NETs, mainly carcinoids, and it can be useful to guide surgery in cases of suspected congenital hyperinsulinism.

¹⁸F-Fluoride bone imaging (cyclotron-produced but transportable)

- Assessment of benign and malignant diseases of bone in selected patients.

Sodium ^{18}F -fluoride produces very high-quality images of the skeleton with high uptake in bone and rapid clearance from blood. ^{18}F -Fluoride has been evaluated against $^{99\text{m}}\text{Tc}$ -MDP planar and SPECT imaging in patients with suspected or known metastatic bone disease. These studies show it to be more sensitive and specific than $^{99\text{m}}\text{Tc}$ -MDP scintigraphy, and the addition of CT increases further the specificity of the test.

Uptake times are shorter than conventional bone scintigraphy, 15–30 minutes versus 3–4 hours, and imaging times are shorter 15–30 minutes versus 30–60 minutes suggesting that ^{18}F -fluoride imaging for some patients with bone disease may be an appropriate use of PET-CT.

^{18}F -labelled Amyloid tracer brain imaging (Florbetapir [Amyvid], Florbetaben [Neuraceq], Flutemetamol [Viazmyl]) (cyclotron-produced but transportable)

- Use in highly selected patients with cognitive impairment where i) Alzheimers dementia (AD) is a possible diagnosis but this remains uncertain after comprehensive evaluation by a dementia expert and conventional imaging work-up and ii) where knowledge of the presence or absence of amyloid is expected to increase diagnostic certainty and influence patient management.
- *Currently there is a paucity of evidence of the impact of these tracers on clinical outcomes and the above indication is based on appropriate use criteria developed by the Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association. Amyloid PET imaging detects the presence of human amyloid deposition in the brain. While amyloid plaques are one of the defining pathological features of AD, it is not specific and can be present as part of the normal ageing process and in other clinical syndromes. As a result it is essential that this test is only used in patients who have been fully assessed by an expert clinician and it is considered that amyloid imaging can contribute to diagnosis in combination with clinical assessment and other factors.*
- *Currently there is insufficient evidence to support the use of this technique except in the scenario defined above where the patient has persistent or progressive unexplained memory impairment confirmed by standard medical tests, an unusual clinical presentation and/or an atypically early age of onset.*
- *Inappropriate scenarios for use would include patients 65 years or older who meet standard definitions and tests for AD; where there is no clinical evidence of memory impairment (that is, as a screening tool); to assess the severity of dementia; in asymptomatic patients with a family history of dementia; for non-medical reasons such as pre-employment screening.*

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Indications for FDG scans

General overview

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