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SNMMI PROCEDURE STANDARD/EANM PRACTICE GUIDELINE FOR BRAIN [^{18}F]FDG PET IMAGING version 2.0

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PREAMBLE

The Society of Nuclear Medicine and Molecular Imaging (SNMMI) is an international scientific and professional organization founded in 1954 to promote the science, technology, and practical application of nuclear medicine. The European Association of Nuclear Medicine (EANM) is a professional non-profit medical association that facilitates communication worldwide between individuals pursuing clinical and research excellence in nuclear medicine. The EANM was founded in 1985. The EANM was founded in 1985. SNMMI and EANM members are physicians, technologists, and scientists specializing in the research and practice of Nuclear Medicine.

The SNMMI and EANM will periodically define new guidelines for nuclear medicine practice to help advance the science of nuclear medicine and to improve the quality of service to patients throughout the world. Existing practice guidelines will be reviewed for revision or renewal, as appropriate, on their fifth anniversary or sooner, if indicated.
Each practice guideline, representing a policy statement by the SNMMI/EANM, has undergone a thorough consensus process in which it has been subjected to extensive review. The SNMMI and EANM recognize that the safe and effective use of diagnostic nuclear medicine imaging requires specific training, skills, and techniques, as described in each document. Reproduction or modification of the published practice guideline by those entities not providing these services is not authorized.

These guidelines are an educational tool designed to assist practitioners in providing appropriate care for patients. They are not inflexible rules or requirements of practice and are not intended, nor should they be used, to establish a legal standard of care. For these reasons and those set forth below, both the SNMMI and the EANM caution against the use of these guidelines in litigation in which the clinical decisions of a practitioner are called into question.

The ultimate judgement regarding the propriety of any specific procedure or course of action must be made by the physician or medical physicist in light of all the circumstances presented. Thus, there is no implication that an approach differing from the guidelines, standing alone, is below the standard of care. To the contrary, a conscientious practitioner may responsibly adopt a course of action different from that set forth in the guidelines when, in the reasonable judgement of the practitioner, such course of action is indicated by the condition of the patient, limitations of available resources, or advances in knowledge or technology subsequent to publication of the guidelines.

The practice of medicine includes both the art and the science of the prevention, diagnosis, alleviation, and treatment of disease. The variety and complexity of human conditions make it impossible to always reach the most appropriate diagnosis or to predict with certainty a particular response to treatment.

Therefore, it should be recognized that adherence to these guidelines will not ensure an accurate diagnosis or a successful outcome. All that should be expected is that the practitioner will follow a

reasonable course of action based on current knowledge, available resources, and the needs of the patient to deliver effective and safe medical care. The sole purpose of these guidelines is to assist practitioners in achieving this objective.

I. INTRODUCTION

The purpose of this document is to provide nuclear medicine practitioners in making recommendations, performing, interpreting, and reporting results of PET imaging of the brain using 2-[18F]fluoro-2-deoxy-D-glucose ([18F]FDG).

Nuclear medicine is the medical specialty that uses the tracer principle, most often with radiopharmaceuticals, to evaluate molecular, metabolic, physiologic, and pathologic conditions of the body for the purposes of diagnosis, therapy, and research.

The combination of anatomic information from other modalities may complement the information from tracers providing more information than the sum of the two separately.

The present document considers the work of previous procedure guidelines organizations such as the Society of Nuclear Medicine Molecular Imaging (SNMMI) Brain Imaging Council [Alan D. Waxman, MD; Karl Herholz, MD; David H. Lewis, MD; Peter Herscovitch, MD; Satoshi Minoshima, MD; PhD, Masanori Ichise, MD; Alexander E. Drzezga, MD; Michael D. Devous, Sr., PhD; James M. Mountz, MD, PhD] (*1*), and the European Association of Nuclear Medicine (EANM) Neuroimaging Committee (*2*).
These new practice guidelines incorporate advances in PET technology such as digital PET and hybrid PET/MR systems, dedicated brain PET systems, advances in individual PET semi-quantitative analysis, and current broadening clinical indications (e.g., for encephalitis and brain lymphoma). Further insight has also become available about hyperglycemia effects in patients who undergo brain [^{18}F]FDG-PET. Accordingly, the patient preparation procedure has been updated. Finally, most typical brain patterns of metabolic changes are summarized for neurodegenerative diseases.
The information provided should be taken in the context of local conditions and regulations.

II. GOALS

The goal of this guideline is to achieve a high-quality standard of [^{18}F]FDG brain imaging, to further increase the diagnostic impact of this technique in neurological, neurosurgical, and psychiatric practice.

III. DEFINITIONS

See also the SNMMI Guideline for General Imaging.

A. In the brain, glucose metabolism provides approximately 95% of adenosine triphosphate (ATP) required for brain function. Under physiological conditions glucose metabolism is tightly coupled to neuronal activity. [^{18}F]FDG is suitable for imaging regional cerebral glucose consumption with PET since it accumulates in neuronal tissue depending on facilitated transport of glucose via glucose transporters and hexokinase mediated phosphorylation, as well as the functional interactions between astrocytes and neurons (*3*). Therefore, changes in neuronal activity induced by disease are reflected in an alteration of glucose metabolism. Also, inflammatory processes and malignant tumors exhibit increased glucose metabolism. [^{18}F]FDG-PET is currently the most accurate in-vivo method for the investigation of regional human brain glucose metabolism in health and disease states.

B. The clinical use of [^{18}F]FDG can be regarded as established for a number of diagnostic questions in neurology, neurosurgery, and psychiatry. This information is often complementary to the anatomic detail provided by structural imaging techniques such as CT or MRI. However, functional impairment often precedes structural changes, and may also exist alone.

IV. COMMON CLINICAL INDICATIONS

The following clinical indications especially integrate the EANM and SNMMI recommendations for the use of brain [^{18}F]FDG-PET (*4*).
Common indications for brain PET imaging using [^{18}F]FDG include, but are not limited to the following:

A. Common indications

A.1. **Cognitive impairment and dementia**. In neurodegenerative disorders such as Alzheimer´s disease (AD), changes in synaptic activity occur early in the course of the disease, when macro-structural brain changes cannot yet be detected. Furthermore, tau pathology was shown to mirror brain hypometabolism and clinical symptoms (*5*). In this line, the hypometabolism significantly exceeded atrophy in most altered brain regions, which is however not the case in the hippocampus, suggesting that for such structures synaptic compensatory mechanisms may be taking place, maintaining neuronal activity in spite of structural alteration, (*6*), especially in younger patients. Despite its relatively small dimension, hippocampal hypometabolism is nevertheless more evident in late-onset AD (*7*). Additionally, new categories for neurodegenerative disorders have been recognized including of the transactive response DNA binding protein of 43 kDa (TDP-43) proteinopathy (LATE), primary age-related tauopathy (PART), and argyrophilic grain disease, in conjunction with hippocampus sclerosis which need to be incorporated into the interpretation of [^{18}F]FDG-PET images (*8*). The recognition of

LATE on [^{18}F]FDG PET is particularly important as there is currently no imaging biomarker of TDP-43, and also AD and LATE pathologies overlap significantly in elderly patients.
In AD, [^{18}F]FDG-PET is viewed as a marker of neurodegeneration (N) and progression, and currently included - along with hippocampal volume measured with MRI - in the A/T/N, classification scheme with amyloid-ß (A) and tau (T) (*9*, *10*). A recent study suggests that [^{18}F]FDG-PET is an independent biomarker to predict AD conversion in patients with Mild Cognitive Impairment (MCI) along with amyloid-β and tau, independent of hippocampal volume (*11*) and of amyloid PET status (*12*, *13*). In the diagnostic work-up of patients with suspected AD dementia, the use of [^{18}F]FDG-PET is complementary to A and T biomarkers, respectively amyloid PET and CSF Aβ42 for amyloid biomarkers, and CSF phosphorylated tau and Tau PET for Tau biomarkers (*14*). [^{18}F]FDG-PET is recommended to support early diagnosis of AD in MCI (*15*), early diagnosis of dementia with Lewy bodies (DLB) (in addition to presynaptic dopaminergic imaging which usually is more accurate in this indication) (*16*) and frontotemporal lobar degeneration (FTLD) (*17*). [^{18}F]FDG-PET is also recommended to support the differential diagnosis between: i) AD and FTLD; ii) AD and DLB; iii) FTLD and DLB; iv) AD and vascular dementia when clinical and MRI data are inconclusive; v) differential diagnosis within neurodegenerative parkinsonian syndromes associated with dementia (*15*, *18-20*). In the framework of cognitive impairment workup, a recent consensus-algorithm has been proposed on suitable indications of [^{18}F]FDG-PET, especially emphasizing its great value as a first-line evaluation when a non-AD disorder is clinically suspected (*14*, *21*). Typical topographic patterns of relative hypometabolism associated with AD, FTLD and DLB are summarized in the EANM procedure guidelines for brain PET imaging using [^{18}F]FDG (*2*). Patterns of hypometabolism tend to mirror clinical presentations, and might also help to support diagnostic workup of atypical AD in the framework of posterior cortical atrophy (*22-24*) and primary progressive aphasia (*25*). For sensitivity, specificity, positive and negative predictive value of [^{18}F]FDG-PET in this framework, the reader is referred to the EANM/European Association of Neurology recommendations and to the original publications (*4*). Beyond the differential diagnosis with vascular dementia, [^{18}F]FDG-PET can also be used to help distinguish between cognitive impairment of degenerative diseases from nondegenerative origin, such as in traumatic brain injury (in correlation to MRI using PET/MRI device or fusion (*26*)), idiopathic normal pressure hydrocephalus (showing striatal hypometabolism with preserved cortical metabolism) (*27*), post-acute infection syndrome (showing limbic/paralimbic, brainstem and cerebellar hypometabolisms) (*28-31*), or depression. For the latter, studies report mild to moderate cortical resting-state relative hypometabolism in [^{18}F]FDG-PET involving the frontal, temporal, insular and cingulate areas, especially including the limbic areas, as well as the basal ganglia, in relation with the clinical severity and the therapeutic response (*32-34*), as well as possible pharmacological interferences mostly in group analyses: these possible subtle brain abnormalities associated with depression at individual level usually don't limit the differential diagnosis with neurodegenerative diseases. Interestingly, a normal [^{18}F]FDG-PET scan has relevant negative predictive value at the MCI stage, with less than 10% of patients progressing to degenerative dementia over 3 years (*35*).

A.2. **Movement disorders and parkinsonian syndromes**. [^{18}F]FDG-PET can be used for the differential diagnosis between Parkinson´s disease (PD) and atypical parkinsonian syndromes such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal syndrome (CBS), and the already mentioned DLB (*36, 37*). Typical topographic patterns of cortical and subcortical changes in glucose metabolism of parkinsonian conditions have been described in neurodegenerative parkinsonism based on qualitative interpretation, and semi-quantitative analysis using voxel-based analysis or principal component analyses with estimation of spatial covariance patterns (i.e. metabolic connectivity) (*38-45*). PD patients exhibit relative hypermetabolism in basal ganglia, motor cortex and cerebellar vermis, and variable hypometabolism in cortical associative areas (*46*). However, when PD patients are scanned under dopaminergic treatment, relative hypermetabolism of cerebellar vermis, basal ganglia and motor cortex might be reduced (*47*). Cortical relative hypometabolism in temporo-occipital and parietal regions has also been described in PD-MCI or PD patients that develop PD with dementia at follow-up (*38*). Interestingly, patients with idiopathic rapid eye movement (REM) sleep behavior disorder (iRBD), a prodromal stage of PD, DLB or MSA, present a brain glucose metabolism pattern partially overlapped with the PD-related pattern (*48*). Moreover, a brain metabolic pattern reflecting the risk of phenotypic conversion from iRBD to an overt alpha-synucleinopathy has been demonstrated (*49*).
Unlike PD, atypical parkinsonian conditions exhibit a neurodegeneration of subcortical areas like basal ganglia, mesencephalon or cerebellum with a consequent decrease of synaptic activity in [^{18}F]FDG-PET (*43, 50*). Typical topographic patterns of relative hypo and hypermetabolism associated with PD, PSP, MSA and CBD are summarized in the EANM procedure guidelines for brain PET imaging using [^{18}F]FDG (*2*). PSP is the second most frequent cause of neurodegenerative parkinsonian syndrome after PD/DLB, and the related pattern is expressed in the Richardson syndrome variant as well as other less common PSP variants (*43*). Moreover, [^{18}F]FDG-PET is recommended to support clinical diagnosis of PSP and included as a prognostic biomarker (*51, 52*).

A.3. **Other neurodegenerative motor diseases**. The clinical use of [^{18}F]FDG-PET as biomarker has been also proposed on other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) (*53*). In ALS, the brain metabolic pattern consists of hypometabolism in the primary, pre-, and supplementary motor cortices extending to the frontoparietal cortex and relative hypermetabolism in the cerebellum and brainstem. Metabolism in the medial temporal cortex can range between hyper- and hypometabolism depending on whether the patient has associated frontotemporal dementia. There is a continuum between ALS and frontotemporal dementia (FTD) in which 50% of patients have minor cognitive and behavioral changes, while 10-15% have overt frontotemporal dementia (*54*). In the clinical setting, [^{18}F]FDG brain PET has a prognostic value as patients with frontotemporal hypometabolism have a worse prognosis due to associated frontotemporal dementia. Although, the metabolic pattern is able to discriminate patients from controls with an accuracy higher than 90% (*55-57*), the diagnostic value is limited as the brain metabolic pattern is similar between diseases that mimic the symptoms of ALS (ALS-mimics) and ALS patients (*58*). In HD,

[^{18}F]FDG-PET has only limited clinical value; however, HD patients with atypical (i.e. behavioral/psychiatric) presentations might be submitted to [^{18}F]FDG-PET in the suspect of other diseases and the Nuclear Medicine physician should be able to recognize peculiar pattern of hypometabolism associated with HD. It has been described that the striatal hypometabolism present in HD may identify pre-symptomatic mutation carriers who will develop clinical HD (*59-63*). Besides striatal hypometabolism, HD is associated with a decreased cortical metabolism and an increased thalamic, occipital and cerebellar metabolism (*60*). The respective hypo- and hypermetabolism gradually increases during disease progression and aid selection of patients for clinical trials (*64*).

A.4. **Epilepsy**. The common indication is the presurgical evaluation of focal pharmaco-resistant epilepsy in adults and children to identify the epileptogenic zone using inter-ictal injection (*65-70*). With a better spatial resolution, [^{18}F]FDG-PET has also higher sensitivity than inter-ictal perfusion SPECT, especially in temporal lobe epilepsy (TLE) (84 vs. 66 % in a meta-analysis study) (*71*). Uncoupling of blood flow and metabolism is moreover suspected in epilepsy, with more pronounced cerebral reduction in glucose metabolism than in perfusion. Of note, the inter-ictal brain PET hypometabolism corresponds with the entire irritative zone (i.e. the epileptogenic zone and subsequent neural networks involved in the generation of inter-ictal paroxysms). In this line, extension of hypometabolism to areas beyond the temporal lobe is often found in patients with focal epilepsy, but nevertheless with a great correlation to clinical presentations and stereo-EEG (*66*, *67*). Performance is lower in extra-TLE with identification of the epileptogenic zone in 38-67% of cases (*65*). [^{18}F]FDG-PET is of particular interest in suspected focal cortical dysplasia, also in children, and especially in case of (apparent) negative MRI (*67*). Correlation to brain MRI using PET/MR device or image fusion techniques is particularly important in this framework to identify initially unknown lesions. Interestingly, clinical outcome of cases with positive PET and negative MRI is similar to those with positive MRI (*72*, *73*). Finally, [^{18}F]FDG-PET has good prognostic value for post-surgical outcome, especially in case of limited hypometabolism extent (*66*, *74-76*), and also provides a prognostic value on cognition with more limited hypometabolism associated with a better post-operative cognitive status (*77*, *78*).

A.5. **Encephalitis, including autoimmune encephalitis** (AE) and paraneoplastic limbic encephalitis (PLE), and infectious and post-infectious encephalitis, as well frontier presentations (for example Morvan syndrome (*79*)) and differential diagnosis of inflammatory encephalopathies (for example neuro-lupus (*80*); see Appendix of (*81*) for the whole spectrum of these disorders). With a higher sensitivity, [^{18}F]FDG-PET is especially relevant in patients with negative or inconclusive MRI (*82-85*), both for adults and children (*86*). A recent systematic review and meta-analysis confirms a sensitivity of 80-90% of [^{18}F]FDG-PET with a typical pattern associating global hypometabolism to striatal and limbic relative hypermetabolism (*87*), with also a specificity of 82% against MCI (*88*). Medial temporal changes have been preferentially associated with autoantibodies against intracellular antigens (*89*). This metabolic profile is also used in the follow-up to evaluate therapeutic efficacy, while whole-body PET is

performed to identify cancer in paraneoplastic syndromes or systemic inflammatory localizations (*90*).

A.6 **Neuro-oncology**. Due to the high physiological uptake of [^{18}F]FDG in normal brain grey matter and variable uptake by inflammatory lesions, [^{18}F]FDG-PET has a more limited impact than amino-acid PET - when available - in the imaging of gliomas (*91*). Better contrast between tumor and normal brain tissue as well between grey and white matter can be obtained with a longer time interval from FDG administration to data acquisition (e.g. 60 min up to several hours for tumors) (*92*). A standardized acquisition protocol is nevertheless recommended with a fixed time for starting the acquisition to improve the comparability from different patients or repeated scans. [^{18}F]FDG-PET can be used in the diagnosis of lymphoma, since most primary central nervous system lymphoma (PCNSL) lesions are highly [^{18}F]FDG avid, with homogeneous uptake, and also in the differential diagnosis of non-malignant lesions in patients with AIDS (and particularly Toxoplasma infection) (*93*). The diagnostic accuracy of pre-treatment brain [^{18}F]FDG-PET is high in PCNSL with pooled sensitivity, specificity, positive predictive value and negative predictive value higher than 84% (*94*), with an uptake predictive of the therapeutic response (*95*). PET also contributes to the evaluation of whole-body extension of the lymphoma with less than 5% of false positives in another recent meta-analysis (*96*). Interestingly, amino-acid PET has not demonstrated an additional value over [^{18}F]FDG-PET in PCNSL (*97*). However, in patients with gliomas the role of [^{18}F]FDG-PET is limited as discussed in dedicated procedural guidelines (*98*). If amino-acid PET is not available, [^{18}F]FDG-PET can be used at diagnosis, with increasing [^{18}F]FDG uptake correlated to higher tumor grade and poorer prognosis (*99*), despite overlap between grade I/II and grade III/IV gliomas, with also a prognostic value on survival at recurrence (*100*). [^{18}F]FDG-PET may be used to distinguish radiation necrosis from recurrent tumor, with moderate additional value in comparison to MRI, usually at least 6 to 8 weeks after radiation therapy, with a pooled sensitivity and specificity of 84% on a recent meta-analysis (*91, 98, 101, 102*) for gliomas, and also for brain metastases with reported sensitivities and specificities ranging from 50% to nearly 100% (*103*).

B. Relative Contraindications and limitations

There is no significant contraindication associated with intravenous injection of [18F]FDG, but cautions should be paid to the following conditions.

B.1. In case of PET/MR, patient safety information concerning magnetic field should be carefully screened prior to MRI (including the presence of devices potentially not compatible such as pacemakers, neurostimulators, cochlear implants, non-MRI-compatible metal implants, pumps, etc.; in case of doubt for ocular metal pieces, a low dose X-ray can be performed).

B.2. Pregnancy. For any diagnostic procedure in a woman patient known or suspected to be pregnant, a critical decision is necessary to assess whether the benefits weigh against the possible harm.

B.3. Breast feeding. Women should interrupt breast feeding at least for the first hours after per NRC ACMUI guidance in the USA, although in many European countries 24 hours is recommended.

B.4. Lack of cooperation, or inability to tolerate. Claustrophobia and most important obesity can also be an obvious limitation, especially for PET/MR.
B.5. Uncontrollable hyperglycemia can be a limitation due to the inadequate statistical image quality and gray-to-white matter contrast.

V. QUALIFICATIONS AND RESPONSIBILITIES OF PERSONNEL

A. Physician: All Nuclear Medicine examinations should be performed under the supervision of and interpreted by a physician certified in Nuclear Medicine or Nuclear Radiology by the American Board of Nuclear Medicine or the national equivalent. Physician should maintain their certification in the field of nuclear medicine.
B. Medical Physicist: The medical physicist should be able to practice independently one or more of the subfields of medical physics. National Regulatories and SNMMI consider certification (by the American Board of Science in Nuclear Medicine or by the American Board of Radiology, or the equivalent) and continuing education in the appropriate subfield(s) to demonstrate an individual is competent.
C. Technologist: All nuclear medicine examinations should be performed by a Nuclear Medicine Technologist that is registered/certified in Nuclear Medicine by the NMTCB or national equivalent. The Nuclear Medicine Technologist works under the supervision of the Physician.

VI. PROCEDURE/SPECIFICATIONS OF THE EXAMINATION

See also the SNMMI Guideline for General Imaging.

A. Nuclear Medicine study request

1. Information relevant for the procedure

1.1. History of diseases, especially neurological and psychiatric disorders, and current neurological and psychiatric status including clinical test results, surgery, radiation, or trauma of the brain.
1.2. History of diabetes, and knowledge of patient’s fasting state.
1.3. Patients' ability to lie still for 15 min to 1 hr. If sedation is required, it should be performed as late as possible. The intention should be to administer [^{18}F]FDG at least 30 to 40 min before the sedation.
1.4. Information about recent structural imaging studies (CT, MRI), prior PET (FDG, amyloid or tau imaging) or SPECT brain images, fluid biomarkers (CSF, plasma), blood biochemistry indicative of metabolic dysfunction or systemic disease (e.g. hepatic, thyroid, renal), as well as about functional brain explorations (EEG, neuropsychology) in specific conditions.

1.5. Ongoing necessary therapies are allowed but current medications (and timing of their last administration) must be recorded. This information (including duration and dosage) is particularly relevant for sedatives, psychotropic pharmaceuticals, anti-seizure medication and corticosteroids. Possible effects of these medications on regional metabolic rate of glucose consumption (rCMRglc) have been suggested (*104-106*), but such effects on diagnostic accuracy of [^{18}F]FDG PET have not been addressed systematically.

Use and dosage of corticosteroids, might be particularly relevant for emerging indications of brain [^{18}F]FDG-PET such as AE and PCNSL. In whole-body [^{18}F]FDG-PET, possible false negative results are well-known for inflammatory and autoimmune diseases treated with corticosteroids (*107*, *108*). For brain [^{18}F]FDG-PET, and whenever clinically possible, it is also advised to scan patients before starting (or in any case as soon as possible after initiating) steroid treatment in case of both AE and PCNSL.

Regarding discontinuation of abuse drugs, it should be noted that reports are also available about effects of early abstinence on regional brain metabolism. For example, a shifts in cortical-subcortical metabolic balance has been reported during early abstinence from chronic methamphetamine abuse (*109*). Similarly, it has been shown that acute alcohol administration may decrease brain glucose utilization that may persist through early sobriety in heavy drinkers (*110*).

Finally, in case of parkinsonian patients, the treatment with levodopa might reduce glucose metabolism regionally and consequently modify the defined patterns described in these patients. Therefore, treatments should be recorded whether the examination is conducted in clinically defined “off” or “on” state (*47*).

B. Patient Preparation and Precautions

1 Pre-arrival.
- a. Patient should be fasting for 4 - 6 hours.
- b. Oral hydration with water is encouraged.
- c. Avoid caffeine, alcohol, or drugs that may affect cerebral glucose metabolism.
- d. Required medications should be taken with water.
- e. Intravenous fluid containing dextrose or parenteral feeding should be withheld for 4 – 6 hours.
- f. Pregnancy is a relative contraindication especially during the first trimester.
- g. Refrain from breast feeding for hours per NRC ACMUI guidance in the USA, although in many European countries is recommended 24 hours(*2*, *111*).

– See Society of Nuclear Medicine procedure Guidelines for general imaging.

2. **Pre-injection**
- a. Environment – Should be stable prior to FDG injection and during the subsequent uptake phase.
  - (1) The patient should be placed in a quiet, dimly lit room.

(2) Minor background noise is acceptable, and patients should be awake with eyes open. Closing the eyes could decrease metabolism in the occipital cortex, a cortical region that might be relevant for specific clinical conditions (as in DLB, characterized by hypometabolism of the occipital cortex) (*112*). In any case, a consistent procedure is required in each center to maintain comparability between exams (eyes open/closed), also with respect to the normal control database if semi-quantitative analyses based on voxels or regions/volumes of interest is performed.

(3) The patient should be seated or reclined comfortably.

(5) Place intravenous access at least 10 minutes prior to injection to permit accommodation.

(6) Instruct the patient to relax, not to speak or read and to avoid major movements.

(7) Minimize interaction with the patient during at least 30 minutes postinjection.

b. Blood glucose levels should be checked prior to [18F]FDG administration. Hyperglycemia (>110 mg/dl) gradually reduces brain [18F]FDG uptake due to the increased competition of this radiotracer with endogenous glucose for transport by glucose transporters and for phosphorylation by hexokinase (*113*), (*114*). As a general rule, there is a decrease in [18F]FDG influx rate constant (K_1) quantitatively paralleling blood glucose concentrations, resulting in deterioration of image quality with increasing glucose concentrations. Decreased contrast between white and grey matter uptake can be found, which might, at least in theory, impact diagnostic accuracy (*115*, *116*), but exact relationship between the degree of hyperglycemia and diagnostic accuracy of [18F]FDG PET has not been addressed systematically. In recent years, some reports have suggested that hyperglycemia might enhance hypometabolism in the posterior parieto-occipital cortex (*113*, *117*). These regions encompass the typical AD hypometabolic pattern. Therefore, concerns have been raised about the impact of hyperglycemia on the accuracy of PET in patients with suspected AD (*118*). Very few studies directly addressed this issue, however, and, to date, a measurable effect on scan interpretation has not been proven (*119*) , (*113*). In any case, an examination should be postponed until an acceptable euglycemic state is reached. Notably, acute correction of hyperglycemia with insulin usually does not substantially improve brain image quality, probably because the normalization of an increased intracellular glucose level lags behind the normalization of the plasma glucose level (*120*). Quantitation of regional cerebral glucose metabolism with [18F]FDG-PET also requires steady state situations which are not maintained during falling plasma glucose levels after administration of insulin. Best results for clinical brain [18F]FDG-PET imaging in diabetics can be obtained in an euglycemic condition during correct therapeutic management (*115*, *120*, *121*), but diagnostically acceptable [18F]FDG PET can be obtained at plasma glucose level 160-180 mg/dl.

The use of other molecular imaging modalities can be considered in patients with uncontrolled diabetes (i.e. amyloid PET imaging in the suspect of AD or perfusion SPECT when appropriate for other clinical scenarios) (*118*, *119*).
Interestingly, it has been suggested that hyperglycemia obtained by intravenous infusion of 10% glucose solution could enhance detectability in patients with brain tumors (*112*). Procedural guidelines for PET imaging in glioma should be considered for further details (*122*).

c. Urinary bladder: Before the scanning procedure, patients should void their urinary bladder for maximum comfort during the study and to reduce radiation exposure. Advising the patient to drink water and void the bladder again after the scanning session is also recommended to minimize radiation exposure.

d. For presurgical evaluation of epilepsy (*70*), close monitoring of the patient is required. Such monitoring should start before injection, as soon as the patient arrives in the department, in order to ensure that [^{18}F]FDG is not administered in an ictal/postictal stage. MRI images acquired in combination with PET or prior to it, as well as a well-documented history of seizures before imaging are of critical importance for adequate image interpretation.

3 **Precautions and conscious sedation**

a. Supervision: a continuous supervision of patients during the whole scanning procedure is required. This is particularly important for patients with epilepsy and cognitive impairment.

b. Sedation: In patients with limited ability to cooperate (e.g. due to their cognitive/behavioral disorders) and in whom no contraindications against medical sedation exist, it may be useful to apply conscious sedation (e.g. by a short acting benzodiazepine such as intravenous midazolam). Administration should take place at least 30 to 40 minutes after tracer injection, preferably starting only a few minutes before data acquisition. Sedation should be used with caution and rather be avoided if dynamic acquisitions are performed for quantification of rCMRglc, because of effects of the sedative on glucose metabolism and thus also on brain uptake of [^{18}F]FDG. Appropriate monitoring (pulse-oximetry) should be performed to prevent cardiopulmonary depression, and appropriate antidote/emergency backup should be foreseen. The dose of sedation should be reduced in elderly patients. National regulations in terms of the influence of medical sedation on fitness to drive need to be considered.

C. Radiopharmaceuticals

See the SNMMI and EANM Procedure Guideline for Use of Radiopharmaceuticals

2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG)

1. **Recommended activity**

Adults:

Previous guidelines mentioned 125 – 740 MBq (typically 150 MBq) when scans are performed in 3D-mode (*123*). However, it is important to note that scanner sensitivities vary across systems, and the duration of image acquisition also affects the image quality and the dose needed to achieve optimal image quality. For high sensitivity digital systems (TOF < 400ps) and/or large axial field of view (also called total body) systems, activity might be lowered, probably by a factor of 2 or more, but limited data are at present available to give clear recommendations.

Children:

Activity administered in MBq = 14 x multiple (dosage card)

Administered activities to children may also be lower in case of high sensitivity digital systems or total body PET systems, but should not exceed those recommended in the EANM dosage card v.01.02.2014 (*124*).

For the USA, the previous guidelines for children mentioned 1.85 to 3.7 MBq/Kg, with a minimum of 14 MBq and a maximum of 148 MBq(*125*) .

D. **Protocol/Image acquisition**

1. **Instrumentation**

PET/CT and PET/MR systems that acquire images in list-mode and in 3D are preferred. In addition, new PET/CT and PET/MR systems show increased sensitivity because of increased axial field of views, silicon photomultipliers (“digital PET”) and/or use of time-of-flight technology (*126-131*). These properties can be beneficial in those cases where the injected radioactivity and/or the acquisition time need to be reduced (e.g. pediatric cases or patients with limited ability to cooperate). More recently, dedicated brain PET scanners have been also proposed to reduce costs and installation constraints on full-time cerebral imaging activities, and large axial field of view (LAFOV) PET/CT scanners offer the possibility of whole-body dynamic imaging, which improves compartment modelling.

2. **Positioning of the patient**

Careful positioning of the patient's head is critical, especially for cameras with limited axial field of view. The orbitomeatal line is often used for standardized positioning, and the patient´s head can be fixed in place. To prevent movement artefacts, the patient should be instructed to avoid any movements of the head.

3. **Type of acquisition**.

Depending on the clinical question and type of equipment, [^{18}F]FDG-PET imaging may include:

a. Static acquisition: A single set of tomographic images is obtained after brain uptake. The static image should usually start at a fixed post-injection time, generally 30 to 40 min post-injection (p.i.) for evaluating neuronal activity for the diagnosis of neurological diseases, and 60 min p.i. or delayed (dual-time-point) scanning can be also considered for neurooncological diagnostic purposes (*92, 98*). Preferably, a dynamic reconstruction in several frames (1-to-5-minute frames depending on the total scan time) should be performed to check potential movement artefacts in addition to the static reconstruction. Images should be evaluated by means of visual assessment, complemented by semi-quantitative and/or voxel-based analysis.

b. Dynamic acquisition: multiple sequential sets of tomographic images are acquired from the time of administration of [^{18}F]FDG and up to 60 min post-injection. This acquisition is especially used in clinical settings to correct patient's movements when absolute quantification of rCMRglc is required generally for research purposes (*see paragraph on absolute quantification in G.2.*) and perform parametric analysis or functional activation studies.

4. **Attenuation correction**: this correction is mandatory for [^{18}F]FDG PET brain imaging and is currently performed using CT- or MR-based attenuation correction or using mathematically estimated attenuation maps. Possible motion artefacts between PET and CT acquisitions have to be systematically checked.

a. CT-based attenuation correction. PET/CT systems can use the CT scan for attenuation correction and anatomic correlation. The advantage of a CT scan is that X-rays detection is not impacted by emission photons. Consequently, a CT scan can be performed after the radiopharmaceutical injection. A CT scan can be done for diagnostic purposes, using regular tube current, or just for attenuation correction (i.e., a low-dose CT) with low tube current (typically 10-30 mAs). The latter has the advantage to significantly reduce the CT-related radiation exposure well below 0.5 mSv for most systems. The choice of either type of CT scans depends on the purpose of imaging and the clinical indication. If anatomical information is already available, a low-dose CT for the purpose of attenuation correction can be considered. When performing PET/CT, it is recommended to check for movement between CT and the PET acquisitions, to avoid artefacts in the attenuation correction.

b. MR-based attenuation correction (*132*). For hybrid PET/MR systems, attenuation corrections (AC) need to be derived using either a dedicated MR sequence (MR-AC) or use of CT templates depending on the system's available methods. In most of the systems only MR-AC or CT templates are commercially available now, but

improved and more advanced methods using special image reconstruction algorithms and artificial intelligence (*133-137*) are expected to be offered in future software updates. For MR-AC imaging, the body coil or a dedicated brain/head coil may be required. However, the best performing MR-AC methods work accurately for [^{18}F]FDG brain PET imaging (*138*).

In all cases, it is recommended to visually control the generated attenuation correction maps for unforeseen artefacts arising from metal or dental implants, missing air cavities and missing bones, particularly in MR AC (*139*). The reader should be aware of the possible qualitative and quantitative consequences of these artefacts and take them into consideration when reading or interpreting the PET images. For example, tracer uptake in cortical brain regions may be underestimated by about 20%, while uptake in pons or cerebellum may show upward bias in case air cavities are not correctly considered by the MR-AC. Use of CT templates can overcome these limitations but may also be less accurate in case of abnormal bone anatomy, i.e. the templates assume healthy anatomical bone structures (absence of trauma). The latter can be overcome by separately making individual CT scans and inserting these into the PET/MR reconstruction pipeline for attenuation correction purposes. At present, such a procedure is not routinely available and formally approved on PET/MR systems. With the recent introduction of advanced MR-AC methods, accurate AC can be achieved for brain PET images on PET/MRI hybrid systems (*138*). However, especially in case of pooling PET data collected on PET/CT and PET/MR systems, caution is advised with regard to the quality of the MR-AC data.

c. Mathematically estimated attenuation map. Especially for the new emerging brain-dedicated PET systems which do not acquire attenuation CT data, mathematical estimation of attenuation maps might be applied, like the Chang method which applies a linear attenuation coefficient(*140*) as provided by the manufacturer for clinical use..

5. **Emission scan acquisition**

As already noted, in case of a static image acquisition procedure, the acquisition should not start earlier than 30 min p.i. Better contrast between grey and white matter, as well between tumors and normal brain tissue, can be obtained with a longer time interval between [^{18}F]FDG administration and data acquisition (e.g., 60 min up to several hours for tumors). A standardized acquisition protocol with a fixed time for acquisition start, generally between 30-40 min (for neurological diagnostic purposes) and 60 min p.i. (for neurooncological diagnostic purposes), is recommended to improve comparability between exams of different patients, follow-up scans, or different centers (e.g., as in multicenter trials). Standard protocols on modern hybrid PET/CT or PET/MR system includes list mode acquisition in 3D mode. The duration of emission image acquisition should be related to the minimum required number of detected events. Typically, data are acquired over 10-15 min, possibly less depending on the [^{18}F]FDG dose activity administrated. A whole-body PET/CT scan is particularly recommended in case of

suspected paraneoplastic syndromes, lymphoma, or autoimmune/inflammatory systemic diseases also involving the brain (e.g. neurosarcoidosis). In special circumstances, when moderately agitated patients are examined, acquisition times down to 5 minutes can be used (*141*).

In case of a dynamic procedure, typically a 40 to 60-min 3D dynamic scan depending on the indication is acquired in list-mode shortly before (10s) or simultaneously with the administration of [^{18}F]FDG. During the PET acquisition, it is required to monitor head movement and to correct for any displacements. Use of a dedicated head holder or immobilization device to avoid or limit head movements is recommended. When available, a motion tracking system may be used to detect motion to retrospectively correct for any head displacements. It is beyond these guidelines to recommend motion correction methods as these are not widely available and/or generally accepted. Yet, the reader should be aware that it is important to avoid and/or correct for patient motion in case of long dynamic PET brain studies. After completion of the dynamic scan, the list-mode data can be binned (and reconstructed) into e.g. 20 to 30 successive time frames to capture kinetics in brain tissue over time. Typically, time frames are short (~5 to 30s) on the first 5 minutes of the scan in which the tracer distribution changes rapidly over time, progressively increasing to about 300 s time frames at later uptake times.

6. **Interventions**

Usually, interventions are not necessary to answer routine clinical questions; they are mostly used in research. In the localization of eloquent cortical areas before surgery, stimulation paradigms like language or motor tasks can be performed. Currently, such activation imaging is mostly performed with functional MRI (fMRI). If performed with [^{18}F]FDG-PET to image special clinical states, especially for MRI contraindications (*142-145*), these paradigms usually start at the time of injection and have to be maintained for a time period of at least 30 min (*146*, *147*). Improvement of temporal resolution of PET imaging has also been proposed using continuous infusion of FDG for intervention studies(*148*).

E. Image Processing

Preferably, images are reconstructed using (ordered subset) iterative reconstruction including use of time of flight (TOF) information, when available. Current PET scanners allow matrix sizes as high as 400x400, but it should be at least 128x128 pixels. Using a minimum zoom factor of 2 and the recommended matrix size, the voxel size would be smaller than 2 mm. The number of iterations and subsets applied should be adapted to the manufacturer recommendations because it depends on the specific PET system and TOF performance. Resolution modelling of point spread function (PSF) is also part of a new feature in reconstruction software on many available PET/CT and PET/MR systems. This resolution modelling may be applied to enhance detection of small abnormalities, but it is not yet recommended for either visual or quantitative evaluation due to pronounced Gibbs artefacts resulting of overestimation of small structure uptake with

misinterpretation on activity normalization (*149*, *150*). Different initiatives have emerged during the last years in the US as an effort to standardize brain PET parameters (for instance, ADNI and SCAN ADRC) (*151*, *152*). Recently, the EANM Research GmbH (EARL) stablished as limits of acceptability an observed effective resolution of 5 to 6.5 mm FWHM (*153*, *154*). Depending on the PET system used, a final image resolution of 4-6 mm full width at half maximum (FWHM) typically yields images of adequate resolution and noise. If movement artefacts are observed, it can be helpful to reconstruct the data in short frames (e.g. 5-min frames) and evaluate only those frames that are not affected by patient motion or spatially align the individual frames prior to further analysis. It should be noted that non-attenuated series (that should be reconstructed and archived) could be useful in this setting to check for artifacts and for reporting.

F. **Data display**

- Color scales typically used for the display of the images are spectrum or rainbow scales (*155*), or grey scales with continuous progression from low to high uptake.
- A standardized image display, also in terms of upper/lower color scale thresholding, is advocated to ensure appropriate and best interpretable representation of the reconstructed dataset.
- Internal landmarks can be used for re-orientation to achieve a standardized image display. Current software provided by PET manufactures allows an automatic re-orientation procedure based on the inter-commissural line. A proper reorientation on the coronal view is crucial for visual inspection of the scan. This is as the presence of asymmetry between homologous structures in the two hemispheres is one of the cornerstones of visual reading. For a more accurate inspection of the medial temporal lobe, a second reorientation can be made along the hippocampal axis (the so-called Ohnishi reorientation in which a patients' brain is reoriented 30 degrees upward with respect to the bi-commissural line on sagittal view (*156*), for example for temporal epilepsy or AD.
- The display of additional coronal and sagittal images is recommended.
- Three-dimensional display of the dataset can be helpful for more accurate topographic orientation in some clinical questions.

G. **Quantification**

1. **Semi-quantitative procedures**

Available tools for automated assessment and semi-quantification are currently provided by PET manufacturers and other vendors are used in the clinical settings to improve diagnostic performance of readers (*15*).

Tools for semi-quantification and voxel-analysis provide individual statistical maps (parametric or Z-score maps) aimed to support visual reading and to improve anatomical localization of regions of abnormal metabolism. The user should consider that outputs and parametric maps generated by this software need to be cross evaluated against the visual evaluation results of the native PET images.

a. Operational requirement

- Normal database for individual comparison

Semi-quantification of brain [^{18}F]FDG-PET either relying on a ROI-based or voxel-wise statistical evaluation generally requires comparison between an individual patient's PET image and age-matched databases of PET images obtained from healthy subjects. Commercial packages incorporate their own healthy subject database although in some cases, only limited details are available about the composition/characteristics of this control group. If the software used does not include an embedded normal controls database, the control group must be built locally in each center. This might be challenging and result in suboptimal control groups also from a clinical point of view (lack of follow-up of the controls; simple inclusion of normal scans rather than scans of healthy controls; controls recruited among patients who undergo [^{18}F]FDG-PET for other indications). Finally, in recent years large databases of normal controls have been publicly shared in the framework of research projects and initiatives (*157*, *158*). The availability of these databases might contribute to a further spread of the use of semi-quantitative tools also in a clinical setting; however, preparation, acquisition and reconstruction parameters should be harmonized as much as possible with all parameters used to acquire the normal subject database to reduce the risk of generating bias and inconsistencies.

- Partial volume effect correction (PVC)

Given the spatial resolution of PET and the size of the brain structures that need to be inspected, partial volume effect may degrade "quantitative" accuracy of PET images (*159*, *160*). Because of partial volume/spill-over effect, the intensity of a particular voxel not only reflects the tracer concentration of that voxel, but also that of the surrounding area. However, only some software packages for automated analysis of [^{18}F]FDG PET include PVC. The partial volume effect is a potential confounding factor in PET imaging studies, mainly in cases of neurodegenerative diseases in which it otherwise is unclear whether any observed decrease in the PET signal is caused by atrophy. This potential confounding effect should be taken into consideration for the final interpretation of the scan, as atrophy may also be the result of other (non-neurodegenerative) pathophysiological mechanisms (aging, chronic ischemia, post-encephalitis brain damage, etc).

PVC can at best be applied in case of concomitant or prior acquisition of 3D T1-weighted MR scans. However, at present there is no consensus on which PVC method should be used or recommended. Various methods exist with specific performances. It is also of utmost importance that MR data used during the PET analysis pipeline, either for volume of interest definitions or PVC are of sufficient quality and acquired with 1x1x1mm voxels (or better). It is recommended to correct partial volume effect by the same MR scan and the same sequence to maintain reproducibility between exams. Of note, MR-free PVC corrections methods are available and can be considered as well, when MR data are not available or when harmonized MR image quality cannot be achieved (*153*).

- Intensity normalization

Intensity normalization (or scaling) is needed to allow comparing different PET scans or a PET scan against a normal database (*161*). Accordingly, scaling can be performed by normalizing to the whole brain (proportional or global mean scaling), to predefined reference regions known to be spared in specific clinical settings (i.e. cerebellum, brain stem, pons, primary sensorimotor cortex or grey matter) or on a data-driven basis (*162-166*). The notion of 'intensity normalization' is equivalent to SUVR (Standardized Uptake Value Ratio) used for other molecular brain imaging such as amyloid PET. The underlying assumption is that the reference region used is unaffected by disease or method (e.g. MR-AC, point spread function correction), which needs to be carefully assessed. Intensity normalization is particularly critical when evaluating patients who might show both regions of hypermetabolism and hypometabolism such as patients with AE (*167*). When using software for brain [18F]FDG PET semi-quantification, it is mandatory to consider the count rate normalization approach used. In routine clinical practice, it could be helpful to use whole brain, pons, and cerebellum for normalization, and to carefully compare each semi-quantification output with the visual reading result.

b Voxel-based analytical approaches

In this type of analysis, the minimum unit into which the image is divided is the voxel. Depending on whether the voxel is analyzed as an independent unit (univariate) or the set of voxels and the relationships between them are analyzed these procedures can be classified as univariate or multivariate.

- Univariate image analysis:

Univariate models have the particularity that they analyze each voxel or volume of interest (VOI) of the image independently, which allows differences to be established between groups or individuals in terms of metabolic activity in each voxel.

Different commercial and free-access software are currently extensively used to determine abnormalities of regional [18F]FDG uptake in an observer independent way and to improve diagnostic accuracy in several clinical settings (*69*, *168*, *169*). Here, the following tools are most often employed:

- 3D-SSP (NEUROSTAT) provides a stereotactic surface projection displays. This tool was specifically designed for single-subjects analysis and includes a group of controls (as well as the possibility to replace this built-in group with a database of local controls). It displays results using different reference regions for normalization (whole brain, pons, thalami, and cerebellum) allowing the user to appreciate the effect of the different reference regions on the final results (see above). This algorithm has been used extensively for research and also implemented on commercial workstations.
- SPM was originally designed for voxel-based group comparisons. However, in more recent years, several studies have validated its use for single-subject analysis which can be implemented to support visual reading (*65*). A dementia-customized [18F]FDG-PET template has been made available in recent years including a balanced proportion of [18F]FDG-PET images from control subjects and patients (*4*). The lack of a normal control group embedded within the tool is a

potential limitation for its use in a clinical setting (*see above*). Finally, there is still lack of standardization for SPM processing steps even though these steps can introduce bias and, more generally, can affect final results (this issue is particularly relevant when choosing a reference region instead of using global count density for intensity normalization; *see above*).

- Multivariate image analysis

It is increasingly recognized that neurodegenerative diseases are characterized by stereotyped connectivity changes, and that studying networks provides more insight in pathophysiological mechanisms than separate regions. Against univariate approaches, multivariable models study all the voxels at once, which allows the relationship between them to be studied. Those voxels that present a correlation or variance of their parallel metabolic activity are considered to belong to the same metabolic neural network, so it is assumed that these techniques assess brain metabolic connectivity. Covariance analysis techniques are considered appropriate methods to explore interrelated brain regions based on the glucose metabolism (neuronal networks) (*170*). Such an approach is the Scaled Subprofile Model and Principal Component Analysis (SSM PCA). With this method, disease-related patterns (also referred to as metabolic connectivity networks) have been identified in several neurodegenerative diseases (*40-42*, *44*, *45*, *47*, *59*, *170*, *171*). Disease-related patterns identified by SSM PCA not only delineate the changes in neuronal metabolism related to the disease, but can also be used to quantify the degree of pattern expression in an individual subject (*40-42*, *44*, *45*, *47*, *59*, *170*, *171*).

c Standard uptake value and ratios

For brain tumor imaging typically semi-quantitative estimates of glucose metabolism like standardized uptake value relative to a normal brain region usually in oncology to the contralateral metabolic uptake (SUVR) are used. For such quantification, standardized acquisition times are required. The total activity of administered [^{18}F]FDG and the patient's height and weight for the estimation of body surface are also required. A calibration factor can also be applied as well as for comparative studies between different PET cameras. A static image is sufficient, acquired typically at 60 min. These semi-quantitative estimates can be corrected for blood glucose concentration.

2. **Absolute quantification**

The quantitative assessment of cerebral [^{18}F]FDG/glucose metabolism requires, besides a dynamic emission scan, an arterial input function, i.e. the measurement of plasma [^{18}F]FDG (over time) and glucose concentrations. There is a need for a calibration factor between scanner events in terms of detected events/voxel/s and in vitro (or on-line) measurements of plasma activity concentrations in counts/mL/s (*172*).

Although dynamic image acquisition from the start of injection up to 60min p.i. is considered to be the most accurate procedure, most centers use simplified protocols based on static images in the clinical setting (*173-175*).

At this respect it is worthy to comment that image-derived input function from recently developed highly sensitive LAFOV PET/CT scanners can avoid the need of invasive blood sampling for kinetic modelling of [18F]FDG (*176*).

Glucose metabolism may be derived with either a Patlak plot or a pharmacokinetic model using the dynamic PET series and the arterial input function. The primary outcome parameter, the net influx rate constant Ki then needs to be multiplied with plasma glucose levels to derive the rCMRglc which also take into account the lumped constant. It is required to measure blood glucose levels during the scan, or directly prior to or after the dynamic PET examination.

Estimation of the rCMRglc can be performed by compartmental modelling or using graphical analytic approaches. The quantification can be performed at both region of interest (ROI) or voxel level. In the ROI-based approach, rCMRglc is estimated in different brain regions by fitting the time-activity curve data using the measured arterial curve as input function. In the voxel-based approach, parametric images of rCMRglc can be calculated using Patlak analysis, graphical approach, or a basis function approach.

A correction factor, the so-called "lumped constant" (LC) (*177*), can be used to convert [^{18}F]FDG "metabolism" values to values reflecting glucose metabolism (*174*, *178*). The lumped constant might vary in pathological conditions. For instance, in malignant glioma, a higher LC than the one measured in normal brain has been reported (*179*). Under special physiological conditions, such as prolonged or extreme fasting, a reduction of glucose metabolism has been observed (*180*). For instance, in one PET study conducted in obese patients before and after 3 weeks of fasting, a 50% decrease of rCMRglc was reported, with a 25% decrease of the LC (*181*).

H. Interpretation

1. Visual analysis

- The images should be critically examined during interpretation for presence of movement or attenuation artefacts.
- Variation in color scale, background subtraction or change in contrast can be used to facilitate data interpretation.
- Data interpretation should take into consideration global changes, such as relative cortical hypometabolism and regional decreases or increases in [^{18}F]FDG uptake. Increased uptake can be observed in continue active epileptogenic foci, tumors, inflammation, and pathophysiologically activated brain areas.
    - Known morphological changes like cortical sulci and ventricles enlargement should be considered for the full interpretation of the data. It is helpful to fuse [^{18}F]FDG images with a CT or MRI scan of the individual performed at the same time (PET/CT, PET/MRI) or independently in temporal proximity to the PET scan.

- Presence of localized abnormalities with hypometabolism or hypermetabolism that can be related to e.g. neuroinflammation, structural damage, atrophy, cerebrovascular lesions, and pathophysiological circumstances.
- Accurate evaluation of brain tumors and identification of the metabolically most active part of a brain tumor prior to biopsy.
- Matching of cortical hypometabolism with morphological abnormalities on MRI or with the EEG focus for planning of epilepsy surgery.
- Localization of eloquent cortical areas (e.g. motor, visual, auditive and language) prior to tumor resection.

- Thorough knowledge of the normal physiological tracer distribution and the variants and pitfalls that can occur during image acquisition, processing and interpretation is mandatory in order to provide optimal diagnostic information to referring physicians and patients (*182*).

- 2. **Assisted visual analysis**.

- Several studies have investigated the added value of voxel-based analysis (see above) tools in the clinical setting, and showed higher specificity compared with visual reading, especially (but not only) for the identification of AD-related patterns, thereby increasing diagnostic confidence (*183-187*). On the other hand, sensitivity of visual and automatic analyses has been shown to be relatively similar although visual analysis obviously is affected by the experience of the reader (*15*). Indeed training and experience in the clinical settings are needed to report brain [^{18}F]FDG PET especially given the possibility of subtle defects, as they sometimes occur in the early stages of neurodegenerative disease (*15*). Supporting visual analysis with automated observer-independent approaches is especially suggested for less-skilled readers and, more in general, with the aim to reduce inter-reader variability (*188*).

- It is suitable to have a normal database available, preferably studied on the same type of camera, under the same acquisition circumstances (e.g., eyes open/closed) and using the same type of reconstruction and attenuation correction. Matching spatial resolution is an important parameter needed for optimal database use. This allows assessment of normal variability of regional [^{18}F]FDG uptake and improves diagnostic accuracy.

- Semi-quantitative/voxel-based approaches to [^{18}F]FDG-PET analysis should always be used in conjunction with visual reading (considering visual reading as the first step for images evaluation and mandatory for quality control). Freeware and commercial software are available allowing for semi-quantification or voxel-based analysis based on different methods (*18*, *169*, *189-191*).

VII. DOCUMENTATION and REPORTING

A. Goals of a Nuclear Medicine Report

1. Provide the referring physician with a timely answer to the clinical question within the limits of the test

2. Document the appropriateness, necessity, and performance of the procedure

3. Expedite and assure correct billing

B. **Direct Communication**

See also ACR Practice Guideline for Communication: Diagnostic Radiology

1. Findings likely to have a significant, immediate influence on patient care should be communicated to the requesting physician or an appropriate representative in a timely manner.

2. Actual or attempted communication should be documented as appropriate.

3. Significant discrepancies between an initial and final report should be promptly reconciled by direct communication.

C. **Written Communication**

1. Include the items in section D., Contents of a Nuclear Medicine Report, which are appropriate for a particular study.

2. Many items, such as patient identification or radiopharmaceutical information, can be transferred to the report automatically or entered by a technologist or secretary.

3. The final report should be proofread.

4. Electronic signature instead of a written signature is acceptable if access to the signature mechanism is secure.

5. Copies of the report should be sent to the requesting physician, made available to other identified health care workers, and archived for an appropriate period of time.

D. **Contents of a Nuclear Medicine Report**

1. Study Identification

a. Patient name

b. Other information to uniquely identify the patient such as gender, date of birth, medical record number, or universal patient code

c. Requesting physician and other appropriate health care providers such as the primary care physician

d. Type of study

e. Date of study

g. Study accession number (in a well-integrated information system, the study accession number may not need to be visible)

h. Completion dates and times

2. Clinical Information

a. Indications for the study

b. Other relevant history:
   1. Brief history emphasizing the main reason for the study e.g. memory loss.
   2. Duration of the problem.
   3. Other essential clinical information including medications.
   4. Recent findings on prior nuclear medicine studies.
   5. Findings on other imaging modalities such as MRI

c. Information needed for billing such as referral number, patient status (e.g. inpatient/outpatient), or diagnostic codes (e.g. ICD-9-CM code)

   1. Insurance carriers may not accept phrases such as “rule out” or “possible.”

   2. List the diagnosis to the highest level of specificity known at the time of billing, or if no diagnosis is known, the pertinent symptom or sign that led to the procedure.

3. Procedure Description

a. Radiopharmaceutical (here, [^{18}F]FDG)

b. Administered dose

c. Route of administration

d. Timing of imaging relative to radiopharmaceutical administration

e. Blood glucose level

f. Imaging technique (Instrumentation used i.e. PET with measured attenuation correction, PET with transmission correction, attenuation correction with CT or MRI, or dedicated brain PET scanner with or without CT attenuation correction), including alteration in normal procedure. i.e., whether the images were acquired using a PET/CT or PET/MR system, and procedure performed, such as arterial blood sampling. If CT is acquired for diagnostic purposes, also include a description of the scanning parameters including dosimetry. In cases of PET/MR, report the type of sequences that were acquired during the imaging session (e.g. structural MR, T1-w, T2-w, FLAIR, diffusion weighted, arterial spin labelling, resting-state fMRI, etc).

g. If sedation is performed, briefly describe the procedure, including type of medication and time of sedation in relation to the radiotracer injection.

h. In epileptic patients, briefly describe the procedure of EEG recording, when performed.

i. Complications or patient reactions

4. Description of Findings

a. Significant positive findings as well as pertinent negative findings should be mentioned. Describe whether [^{18}F]FDG PET findings are normal or abnormal. If findings are abnormal, describe the location and intensity of abnormal [^{18}F]FDG uptake. Functional topography can be used as well as anatomical descriptions.

b. Image quality or other causes of study limitations, e.g. patient motion

c. A reference range may be useful for quantitative values.

d. Correlation with other imaging studies should be documented in the report describing the date and type of the prior study. If other studies are not available for correlation, this should also be mentioned in the written report. Comparative data: Comparisons with previous examinations and

reports, if available, have to be part of the report. Furthermore, results of morphological imaging modalities should also be considered for interpretation. Non-diagnostic CT scans only used for attenuation in PET/CT should be used with caution for structural interpretation.

5. Impression

   a. A separate impression should be included for all but the shortest reports.

   b. The impression should address the clinical indication for the scan.

   c. If the PET examination presents a generally accepted disease pattern, this should be said in the conclusion, and if possible, using a statement that indicates the most probable diagnosis considering the pattern only in the context of the clinical presentation and hypothesis. Any (subjective) interpretation not based on such criteria has to be explicitly stated and considered as hypothetical. A differential diagnosis should be given when appropriate.

6. Comments

   a. Study limitations or source of errors(*192*):
      a. Unintended cerebral activation (i.e., visual or motor activation)
      b. Artefacts (patient movement during PET acquisition or between PET and CT/MRI, camera related, induced by inappropriate processing) as well as MR-based AC biases (missing bones, air cavities, metal implants etc)
      c. Psychotropic drugs or corticosteroid use
      d. Sedation
      e. Incomplete intra-venous tracer injection
      f. No or insufficient attenuation correction
      g. Soft tissue or skull uptake following surgery in the area of the skull or brain
      h. Recent radio- or chemotherapy

   b. Recommendations for further procedures, if appropriate

   c. Documentation of direct communication of results including the name of the physician or physician designate and time/date of contact

   d. Comments may be included in the Impression section, especially when brief.

VIII. EQUIPMENT SPECIFICATION

Equipment specification for each procedure is given in the respective procedure guidelines.

IX. QUALITY CONTROL AND IMPROVEMENT, SAFETY, INFECTION CONTROL, AND PATIENT EDUCATION CONCERNS

See also the SNMMI Guideline for General Imaging and EANM Physics Guidelines

Policies and procedures related to quality, patient education, infection control, and safety should be developed and implemented in accordance with the ACR Policy on Quality Control or national equivalence, and Patient Education Concerns appearing elsewhere in the ACR Practice Guidelines and Technical Standards book, or national equivalence.

Physician quality control should also be done regularly to assure consistent, accurate physician interpretation of results.

Equipment performance monitoring should be in accordance with ACR Technical Standards for Medical Nuclear Physics Performance Monitoring of Computed Tomography (CT) and Nuclear Medicine Equipment, or national equivalence.

Information specific to the procedure should also be included in each guideline.

X. RADIATION SAFETY IN IMAGING

See also the SNMMI Guideline for General Imaging, and EANM Dosimetry and Radiopharmaceutical Guidelines

It is the position of SNMMI and EANM that patient exposure to ionizing radiation should be at the minimum level consistent with obtaining a diagnostic examination. Reduction in patient radiation exposure may be accomplished by administering less radiopharmaceutical when the technique or equipment used for imaging can support such an action. Each patient procedure is unique and the methodology to achieve minimum exposure while maintaining diagnostic accuracy needs to be viewed in this light. Radiopharmaceutical dose ranges outlined in this document should be considered as a guide. Dose reduction techniques should be utilized when appropriate. The same principles should be applied when CT is used in a hybrid imaging procedure. CT acquisition protocols should be optimized to provide the information needed while minimizing patient radiation exposure. Minimizing radiation dose is especially important in children.

Infants have a greater relative brain mass (10%) than adults (2-3%), so the percentage uptake of injected [^{18}F]FDG is higher. Although in new-born infants, sufficient image quality may be achieved with an injected dose as low as 10 MBq (*193*)(in part also based on lower tissue attenuation), the advocated minimal dose stated from the pediatric dose card for the EANM is followed in these guidelines.
Estimated radiation doses in adults and children are shown in Table 3.
For CT, the effective dose depends on collimation, scan type (axial, helical) (*194*), but is usually lower than 0.3 mSv for a so-called low dose CT and typically around 2 mSv or lower for a diagnostic high quality CT.

Radiation Dosimetry in Adults

Radiopharmaceutical	Administered Activity * MBq (mCi)	Organ Receiving the Largest Radiation Dose ** mGy per MBq	Effective Dose ** mSv per MBq
2- [^{18}F]- fluoro-2-deoxy-D-glucose ([^{18}F]FDG)	150 - 370 (5 – 10)	Urinary Bladder 0.13	0.019

* Depends on equipment limitations, specific application, and patient compliance.
** Calculations based on: ICRP 128 – Table C31

Radiation Dosimetry in Children

Radiopharmaceutical	Administered Activity * MBq/ Kg (mCi)/Kg	Organ Receiving the Largest Radiation Dose ** mGy /MBq	Effective Dose ** mSv/MBq
2- [^{18}F]- fluoro-2-deoxy- D- glucose ([^{18}F]FDG)	North America: 3.7 (0.1) Europe: 5.18 – 7.4 (0.14 – 0.20)	Urinary Bladder 0.34	0.056

* Depends on equipment limitations, specific application, and patient compliance.
** Calculations based on: ICRP 128 – Table C31

XI. ACKNOWLEDGEMENTS

Committee on Guidelines:

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XII. BIBLIOGRAPHY/REFERENCES

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