Application of Artificial Intelligence (AI) in molecular brain imaging. Perspectives from the EANM.

Or

Perspectives from the EANM on the application of Artificial Intelligence (AI) in molecular brain imaging.

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Abstract:

This paper discusses the opinion of the Neuroimaging Committee of the European Association of Nuclear Medicine regarding the role of artificial intelligence, the unmet needs of AI in standardized applications, and the increasing need for common ethical standards.

The first part of this manuscript offers insight into the fundamentals of artificial intelligence (AI) and provides a general overview of the current role and functions of AI in nuclear medicine neuroimaging. AI methods offer opportunities for image quality enhancement, shortening image acquisition time, and potentially reduced dose of the utilized tracer. In addition, it can facilitate image reading, differential diagnosis and/or predict cognitive decline. Furthermore, AI-based segmentation can eliminate meticulous manual annotation and inter-observer variability and offers help to clinicians with differential diagnosis or automatization of reads (e.g. amyloid positive/negative), prediction of cognitive decline, detection of epileptogenic focus).

In the second part, the current clinical applications of artificial intelligence and its future perspectives in nuclear medicine neuroimaging are reviewed with emphasis on the potential application of AI in brain oncology, neurodegeneration, epilepsy and psychiatric disorders.

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1. Goal

With an increasing availability of diagnostic and therapeutic options for nuclear neuroimaging and open science practices, a larger amount of data has become available, requiring a more complex evaluation (1).

Artificial Intelligence (AI) was first applied in neuroimaging in the early 2000s, when it was combined with functional magnetic resonance imaging (fMRI) to create more precise mapping of the activity of the human brain after various specific stimuli. Despite the potential of the technique being immediately clear, the first reports were pessimistic (2,3). This was because of the combined need for very large amounts of data and contemporary, state-of-the-art computing resources. Solutions became available only in the last decade, which is the reason for today's AI revolution (4).

Much has been written of the potential application of AI in neuroradiology and in most recent times in nuclear imaging in several fields, however, a detailed description of the mechanisms underlying the application of AI in nuclear neuroimaging has not been fully provided (5,6).

Indeed, the Neuroimaging Committee of the European Association of Nuclear Medicine believes that an easy-to understand- and position overview on the principles of AI in nuclear neuroimaging will bring important added value to clinical studies and to clinical teams.

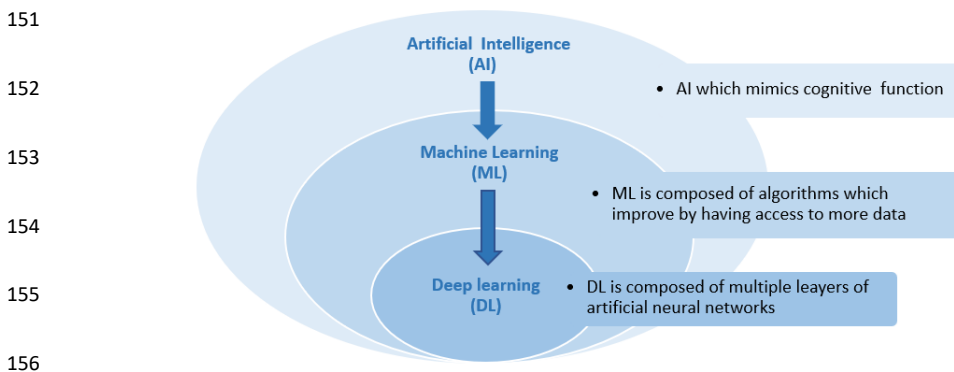## 2. Introduction and background of AI in neuroimaging

Introduction

AI is designed to perform tasks that would otherwise require human labour. AI is a technique which enables programs to mimic human cognitive functions, i.e., human behaviour; therefore, these algorithms can learn from experience. AI essentially learns from processing large amount of data & recognize specific patterns in the dataset (7).

Background and Nomenclature: machine learning vs. deep learning

Machine learning (ML) is a subset of AI programs/algorithms which uses statistical methods on training data and which, by doing so, is able to improve. This is typically an iterative process (the more data we have/insert in the database, the more accurate is the result). In machine learning often the data is structured and pre-processed (e.g. radiomics) using well define features). For instance, ML can differentiate normal brain parenchyma from ischemic parenchyma by using pre-programmed patterns of an infarct (e.g. hypo attenuating brain tissue, obscuration of the basal ganglia, sulci effacement in CT) which are paired with the result in the AI computer database (infarcted brain tissue) (8,9).

Deep learning (DL) is a subset more complex evolution of machine learning. In this learning process, the 'raw' data are presented, and the algorithm learns how to extract the relevant features (Fig. 2) (10).

Figure 2: Relation between AI, Machine Learning and Deep Learning

Artificial Intelligence (AI)
- AI which mimics cognitive function

Machine Learning (ML)
- ML is composed of algorithms which improve by having access to more data

Deep learning (DL)
- DL is composed of multiple leayers of artificial neural networks

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157 DL was inspired by human brain structures/networks; therefore, this algorithm concept
158 is called artificial neural network (ANN). It models artificial neurons that collect input
159 data and weigh each of those inputs. This artificial neuron network operates with an
160 activation function which combines the weighted average of the input into an output
161 signal. This signal is received by connected neurons (Fig. 3) (8,10,11).

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163 **Figure 3:** Schematic structure of a Deep Learning method (Artificial Neural Network)

164 In deep learning the first step is to **i)** collect a large dataset of images / input layer (several MR
165 sequences presented in the left-hand side of the figure). **ii)** Then the computer generates a
166 set of "unusual images" named convolutional layers which is the main building block of CNN
167 and contain abnormal findings (also named filters, e.g. abnormal density, intensity, edge,
168 deviation of anatomical boundaries etc.). **iii)** Then the images are matched with a dataset of
169 pre-acquired images with similar features (see the Fig. below: information of infarct,
170 hemorrhage and metastasis were included in the dataset). Similarly, to what happens in the
171 human brain, which pools information together, the several convolution layers from the images
172 are connected each other. **iiii)** The computer then checks the (millions of) possible combined
173 information (through several fully connected layers to identify a more complex picture
174 (relationship between the features) in the database and will give the results based on the
175 likelihood of similarity. Likewise to human brain, the more information we have, the more
176 probability we have to make a correct assessment. In the same way, the more convolution
177 layer information we feed the AI dataset system, the more accurate results will be generated.
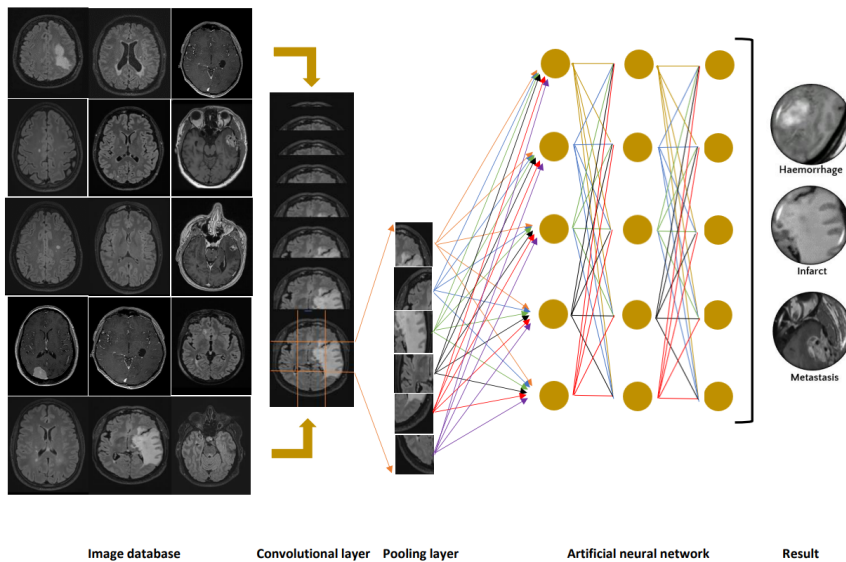
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Image database   Convolutional layer   Pooling layer   Artificial neural network   Result

190   An ANN is able to recognize complex, non-linear patterns in a wide range of complex
191   data set and it can associate them for instance with specific disorders and estimate
192   the onset of disease.

193   The nomenclature of NN/ANN/DL tends to be confusing. Hereafter, we refer to all
194   neural network architectures as ANN, and if it is a conventional ANN, we denote that
195   it is "fully-connected". DL, on the other hand, is a special type of ANN which does not
196   just have fully-connected neural layers, but also has so-called convolutional layers that
197   extract features from input data (Fig. 3) to create output data. Convolution layer
198   consists of one or more filters (or Kernel) with different weights that are used to extract
199   features from the input image (8,10,11).

200   These convolutional kernels are matched to the given input image at each coordinate
201   and generate a "meta-image" (a.k.a. convolved image) which highlights several
202   features such as regions, edges, patterns where the given kernel had a high ratio of
203   matching.

204   This resulting "meta-image' will be weighted and compared to the database into the
205   computer. The training process of ANN is not only of optimizing weights in the fully-
206   connected network, but also to determine the values of the convolutional kernels.
207   Hence, DL operates not only with hand-crafted features (e.g., shallow radiomics) but
208   with learnt features (12–15).

209   Deep learning is the most used algorithm in medical imaging because it can make
210   complex decisions on its own. It is worth to mention that, given the high number of
211   heterogeneous parameters, DL requires a large training dataset to avoid
212   under/overfitting. It is widely used in structural and functional MRI and positron
213   emission tomography (PET) imaging. It is specifically designed for image processing,
214   object identification and segmentation allowing unparalleled accuracy in the field of
215   neuroradiology (16,17).

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3. Physics, clinical aspects, and the need for exhaustive evaluation and validation in neuroimaging

AI algorithms have shown many potential benefits for brain PET and SPECT, mainly related to the physics and clinical aspects of the studies. This section is focused on ensuring these advancements have been rigorously tested and achieved through a reproducible methodology, with a reliable training and verification method and, secondly, defining the corresponding ground-truth for an exhaustive validation and evaluation of AI algorithms.

Lack of generalizability and potential solutions

The crescent interest in AI is not without problems, requiring large validation studies. Consortium datasets have emerge in molecular neuroimaging including Alzheimer's Disease Neuroimaging Initiative (ADNI), Parkinson's Progression Markers Initiative (PPMI) or Open Access Series of Imaging Studies (OASIS), however, more data are still needed to for the complete translation to clinical routine use.

Open standard datasets will be essential for the development of AI, even though it may involve significant costs. One possible cost-efficient solution is to make use of realistic Monte Carlo simulations techniques for generating in silico neuroimaging datasets, thus allowing for data augmentation from patient data (18). Another solution to address this challenge is federated learning, which allows AI to be trained on decentralized datasets from multiple hospitals, while ensuring data privacy and security. Federated learning has been already applied to training of AI models in different brain PET challenges, such as reconstruction, segmentation and denoising using brain PET datasets from multiple institutions (19–21). An even more recent improvement is swarm learning, that combine Federated learning with blockchain technologies to further ensure the robustness of the learning process (22).

The ground-truth for AI models

The ground-truth for a given neuroimaging dataset is often uncertain, difficult to establish and strongly dependent on each application. For instance, ground-truth for AI models aimed at improving the spatial resolution can be obtained from high-resolution phantom studies, the ground-truth for models focused on denoising should be obtained from the corresponding raw data acquired during long scans (23). In

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clinical applications, the ground-truth for AI models providing automated image analysis can be datasets analysed visually and processed manually by experienced nuclear medicine physicians (24). On the other hand, AI models focused on disease detection should use a ground-truth obtained from cases with a definite diagnosis confirmed by clinical follow-up as well as other relevant diagnostic tests or histopathological examination if available (25). Therefore, it is important to have a clear "ground truth" aim before processing and using any AI model; this process requires by all clinicians an understanding of the physics and clinical applications of Artificial intelligence.

4. Image acquisition, reconstruction, segmentation, registration and analysis

In this section we will discuss the potential application of AI to processes of image formation, which include data acquisition and image reconstruction steps (including data correction) and post-processing (including registration, normalization, and analysis).

Acquisition and reconstruction

In the data acquisition stage, deep learning models have been utilized to estimate Time-of-Flight (ToF) and improve the quantitative accuracy and diagnostic confidence of PET images reconstructed without ToF, specifically for brain PET (26,27). In tomographic reconstruction, AI has been employed to enhance the quality of PET and SPECT images by reducing noise and enhancing image contrast during reconstruction (28). Deep learning techniques have also demonstrated effectiveness in providing accurate and generalizable PET attenuation and scatter correction methods (29,30), and, interestingly, attenuation correction methods without CT (31). Finally, generative adversarial networks have been employed for motion correction in brain PET, effectively addressing the challenge of head motion artifacts (32). Also, they can be used to dramatically shorten scan times/activity amounts needed (33).

Segmentation and registration:

In post-processing, AI-based segmentation can overcome the time-consuming and observer-dependent process of manual annotation of brain structures in PET images

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281 (34,35). AI can also assist in the registration of neuroimaging data, via the alignment
282 of images from different imaging modalities or timepoints and learning the mapping
283 between images and different modalities (36). Furthermore, AI can facilitate the
284 extraction of meaningful quantitative parameters from the images, such as, improved
285 amyloid PET quantification without non-specific contributions (37) and amyloid PET
286 quantification without using MRI (38). This advance can contribute to the development
287 and routine accessible use of biomarkers for early diagnosis and personalized
288 treatment. Moreover, AI might provide non-invasive estimations of the arterial input
289 function for brain PET studies, facilitating adoption of absolute quantification in clinical
290 settings (39).

291 ***Interpretability Analysis***

292 Lastly, interpretability and robustness are essential aspects of AI applications in
293 neuroimaging. By improving interpretability and robustness, we can enhance the
294 trustworthiness, and clinical utility of AI models and promote the development and
295 translation of AI technologies in clinical settings. Additionally, we can help identify
296 potential biases, errors, or limitations in the model, which can be addressed to improve
297 its performance and generalizability (40). Similarly, some of the AI methods can be
298 easily supervised. A segmentation task can be easily checked once the segmentations
299 are generated, so the correctness of the segmentation is easily verified/ supervised.
300 Some other tasks of AI cannot be easily supervised and require external validation
301 and, if possible, some explainability testing is of importance. So called explainable AI
302 techniques are rapidly emerging to improve interpretability, including feature
303 visualization, saliency maps, and decision trees. These can reveal the key features
304 and patterns that contribute to the model's predictions or decisions. Another approach
305 is to incorporate robustness measures, such as adversarial training, regularization,
306 and uncertainty quantification, into the AI model to increase its resilience to various
307 types of noise, artifacts, or uncertainties (41).

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5. AI in molecular imaging in neuro-oncology. A review of the current knowledge and perspectives.

In neuro-oncology, one of the specificities of neuro-oncological applications of AI is a relatively rare incidence of brain tumors with an annual global age-standardized incidence of primary malignant brain tumors of about 3 per 100,000 (42), requiring special modelling workflows or data augmentation techniques (43,44). Radiomics studies should follow the IBSI (Image Biomarker Standardization Initiative) guidelines (45). These guidelines cover the image pre-processing, tumor segmentation, and the image biomarker computation. All the extracted radiomics features are used in a modelling step, performed in most of the cases with machine learning models. Studies using deep learning approaches, which can be applied to the entire analysis or to specific parts of the workflow (46), are for the moment scarce.

Machine learning studies

The first studies using AI in neuro-oncology were based on machine learning models with conventional PET features for initial characterization of brain lesions (47), predicting molecular characteristics of gliomas (48–50) including features from multiparametric MRI (48), and search of recurrences (51) with higher diagnostic performances as compared to results obtained only with a conventional approach.

Radiomics studies

Most of the radiomics studies in neuro-oncology focused on amino-acid PET radiotracers in gliomas, at initial diagnosis for grading (52,53) or prediction of important molecular characteristics (54–59) according to the latest WHO classifications of gliomas (60), for prognosis (61–63), for search of recurrences (64–66), including the search for early progression in glioma patients after chemoradiation (67). Interestingly, some studies investigated radiomics derived from both static but also dynamic acquisitions at initial diagnosis (68,69), for the prognosis (70) or search for glioma recurrences (71). The combination of PET radiomics features extracted from several PET radiotracers (64) or in combination with MRI radiomics features (59) is also of interest in the field of neuro-oncology. It is also important to perform radiomics analyses in a multicentric approach ensuring a better guarantee of generalizability of the obtained results (71). Some studies were focused on methodological approaches

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342 regarding patient preparation (72) or PET imagereconstruction processes (73) and
343 their influence on radiomics analyses. Importantly, two methodological studies with
344 ^{18}F-FET relied on the features repeatability (43) and harmonization (44), two crucial
345 steps for considering the generalization of the results obtained. PET radiomics studies
346 in gliomas with other radiotracers than amino-acid ones are limited, with ^{18}F-FDG (74–
347 76) or TSPO PET imaging (44). Table 1 summarizes the main radiomics studies in
348 gliomas compliant with the IBSI guidelines.

349 Radiomics studies in other brain tumors are relatively limited, mainly to brain
350 metastases for the initial differential diagnosis (77) and the search for recurrences
351 (78,79). Rare studies also included primary CNS lymphomas for the differential
352 diagnosis (80,81).

353 ***Deep learning studies***

354 The first studies used deep learning for specific tasks like the tumor segmentation with
355 PET (82,83) or the attenuation correction in PET/MRI (84). More clinically tasks were
356 then investigated with equivalent diagnostic performances than expert consensus for
357 the diagnosis of tumor progression (85), but lower diagnostic performances for the
358 prediction of molecular characteristics (86).

359 ***Perspectives***

360 AI in neuro-oncology is intensively evaluated allowing simplifying steps in radiomics
361 pipeline such as tumor segmentation, increasing data comparability between
362 observers and more importantly extracting new features from the images of brain
363 tumor patients (87). AI is currently primarily represented by radiomics analyses, which
364 must be performed according to the steps described in the IBSI guidelines to ensure
365 standardization of processes (45,88), providing promising results with good diagnostic
366 performances in various clinical indications, including methodological approaches.
367 Some improvements are nevertheless required for the generalization of the observed
368 diagnostic performances, by identifying specific radiomic signatures that are easily
369 transposable across centers. Notably, these efforts concern the feature repeatability
370 and harmonization through well-defined multicentric studies. This is even more
371 meaningful for the field of neuro-oncology since CNS tumors are rare diseases with
372 therefore a limited number of patients, requiring data collection from different centers.

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Studies of PET multi-tracer radiomics analyses and/or combination with multiparametric MRI and clinical parameters are also encouraged. Another important point is that diagnostic performances of radiomics models should systematically be compared to conventional parameters to really appreciate the added value of AI-related methods in each clinical indication before implementation in clinical routine. Finally, an important effort may be developed to make accessible radiomics data accessible at the individual level, providing an additional clinical tool to assist the nuclear medicine physicians in their decisions.

Table 1. Summary of PET radiomics studies compliant with the IBSI guidelines in gliomas

	Radiotracer	Number of Patients	Task	Main finding
Initial diagnosis				
Russo et al., 2021 (53)	[11C]-methionine	56	Grading	AUC of 0.64
Zhou et al., 2021 (57)	[18F]-FET	58	IDH mutation prediction	AUC of 0.91 combining PET and CT features
Li et al., 2021 (68)	[18F]-FET	159	TERTp mutation prediction in glioblastomas	AUC of 0.82
Zaragori et al., 2022 (73)	[18F]-FDOPA	72	IDH mutation and 1p19q codeletion prediction	AUC of 0.83 for IDH mutation and 0.72 for 1p19q codeletion
Zhang et al., 2022 (89)	[18F]-FDG	102	ATRX mutation prediction in IDH-mutant gliomas	AUC of 0.96 combining PET and MRI features
Cao et al., 2022 (77)	[18F]-FDG	100	Differentiation between glioblastoma and brain metastases	AUC of 0.84 combining PET and MRI features
Papp et al., 2023 (56)	[11C]-methionine	35	IDH mutation prediction	Radiomics signature differ according to sex
Prognosis				
Li et al., 2023 (70)	[18F]-FET	141	Survival in newly-diagnosed glioblastomas	AUC of 0.74 combining PET and clinical features
Carles et al., 2021 (62)	[18F]-FET	32	Survival in recurrent glioblastomas	AUC of 0.66 for recurrence location.

				Radiomics signature associated to survival.

Recurrence

Wang et al., 2020 (64)	[18F]-FDG and 11C-methionine	160	Differentiation of treatment-related changes from glioma progression	AUC of 0.91 with an integrated model involving radiomics signature, the mean of tumor-background ratio of 18F-FDG, maximum of TBR of 11C-MET PET, and patient age
Ahrari et al., 2021 (71)	[18F]-FDOPA	85	Differentiation of treatment-related changes from glioma progression	AUC of 0.83
Müller et al., 2022 (66)	[18F]-FET	151	Differentiation of treatment-related changes from glioma progression	AUC of 0.85

Methodological

Gutsche et al., 2021 (43)	[18F]-FET	50	Features repeatability	In tumor VOIs, 73% of first-order features and 71% of features extracted from the gray level co-

				occurrence matrix showed high repeatability.
Bros et al., 2021 (72)	[¹⁸F]-FDOPA	54	Effects of Carbidopa premedication	Carbidopa impacted 81% of radiomics features, no longer significantly modified when using ratios to healthy brain.
Ahrari et al., 2022 (73)	[¹⁸F]-FDOPA	57	Effects of the Point Spread Function deconvolution	AUC of 0.83 vs. 0.79 for the IDH mutation after applying PSFd.
Zounek et al., 2023 (44)	[¹⁸F]-FET and [¹⁸F]-GE-180	19	Features harmonization for pooling data	Feature distributions could be successfully aligned using ComBat except for some features affected by changes in patients rank.

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6. AI in molecular imaging of Epilepsy: A review of the current knowledge and perspectives.

Epilepsy is one of the most common neurological disorders characterized by abnormal excessive firing and synchronisation of neurons leading to seizures. The accurate identification of the epileptogenic foci is essential to avoid misdiagnosis and select the correct treatment, especially when resective surgery is necessary as in drug-resistant epilepsy (90). While nuclear medicine neuroimaging is the key diagnostic tool, allowing to evaluate metabolic, neurotransmission or perfusion abnormalities occurring in people with epilepsy, there is an increasing need to define accurate computer-aided tools to support clinicians. In this context, AI-based tools pave the way for solving such tasks, fostered by the exceptional advancement in the models we have witnessed in the last years. ML and DL are currently explored for diverse tasks as cortical lesion localization (mainly for focal cortical dysplasia - FCD), epileptic focus detection/lateralization and brain region segmentation (e.g., hippocampus), or for the diagnosis and prognosis of different epilepsy types. Still, AI has been mostly applied to MRI or EEG recordings (especially for seizure identification and forecasting), while their exploitation in the nuclear medicine-epilepsy field is still in its infancy, with a few studies largely limited to [^{18}F]FDG-PET briefly reviewed in the followings.

Machine Learning studies

In conventional ML, the classification/regression tasks are combined with an initial step of feature engineering to extract the image-derived phenotypes to be included in the different models. The voxel-wise glucose uptake levels have been used in a few studies (91,92), also combined with dimensionality reduction methods as Principal Component Analysis (PCA) (92). However, regional measures are still the primary choice, usually defined as asymmetry/laterality indices calculated from glucose mean values in a single representative region (93) or in a series of ROIs from common atlases as Anatomical Automatic Labelling Atlas (AAL) or Freesurfer parcellation (94,95). All these measures combined with other ML methods (e.g., support vector machine, random forest and multivariate pattern analysis) have been successfully applied for lateralization tasks in temporal lobe epilepsy (92,93,95), seizure recurrence prediction and prognostic assessment in drug-resistant epilepsy (94,96,97), or disease

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classification (patients vs controls) (91,93), with improved performance compared to conventional and visual approaches.

Deep Learning studies

Besides two pioneering works focusing on epilepsy lateralization with ANNs architectures (98,99), DL has been only recently introduced in such domain. DL has the undeniable advantage of avoiding feature extraction by learning directly from the images, allowing to improve the classification/prediction performance compared to all the other approaches. Only few examples are available in the current literature, aiming at improving the epilepsy lesion characterization (100) or structure segmentation (101). One study evaluated ANN along with other ML-based approaches for predicting surgical outcome in mesial temporal lobe epilepsy (92), and one study focused on the identification of the epileptic foci in paediatric patients with a symmetricity-driven Siamese CNN, going beyond visual assessment and conventional SPM analysis (89). Another used DL to predict an individual patient's "healthy" FDG PET based on their MRI, which was then subtracted from the real FDG PET to identify metabolic lesions (Subtraction Interictal PET Co-registered to MRI, "SIPCOM"), again performing better than conventional SPM analysis (102).

Perspectives

Despite the methodological advancements, AI applications in molecular imaging of epilepsy are still limited and confined to specific epilepsy types, possibly because of the difficulties in finding large (and annotated) datasets to train and generalize the complex AI-based models, the high heterogeneity of patients with epilepsy and the need to perform patient-specific fingerprinting, especially when comes to clinics. Multi-centre initiatives, coupled with advanced DL models (e.g., multi-task CNNs, autoencoders) and data augmentation methods (e.g., generative adversarial networks or large simulated databases) (100), might help to overcome part of such limitations, providing more generalizable models and a precise fine-grained characterization of inter-individual patient variability to progress towards personalized medicine.

Some recent studies have also underlined the importance of combining multi-modal imaging data, such as metabolic PET with structural or functional MRI, often leveraging the value of simultaneous PET/MRI acquisitions. These multi-modal data coupled with AI models can increase the accuracy in predicting the surgical outcomes

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((PET image enhancement using artificial intelligence for better characterization of epilepsy lesions.
Flaus A, Deddah T, Reilhac A, Leiris N, Janier M, Merida I, Grenier T, McGinnity CJ, Hammers A, Lartizien C, Costes N. Front Med (Lausanne). 2022 Nov 16;9:1042706. doi: 10.3389/fmed.2022.1042706. eCollection 2022.))

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PET image enhancement using artificial intelligence for better characterization of epilepsy lesions.
Flaus A, Deddah T, Reilhac A, Leiris N, Janier M, Merida I, Grenier T, McGinnity CJ, Hammers A, Lartizien C, Costes N. Front Med (Lausanne). 2022 Nov 16;9:1042706. doi: 10.3389/fmed.2022.1042706. eCollection 2022. PMID: 36465898

481 (103,104) and detecting focal epilepsy lesions such as FCD (105,106). All these
482 approaches therefore deserve further investigations for fully exploiting their potential
483 and exploring their generalizability in the epilepsy workflow (see the summary of the
484 cited articles in Table 2).

485 **Table 2**: Summary of cited papers

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	Study cohort	Task	AI method	Main finding
Wu et al., 2021 [87]	23 MTLE patients and 24 HC	Classification	MVPA + SVM	AUC of 0.996
Beheshti et al., 2020 [88]	56 TLE patients (MRI negative)	Focus lateralization	T-test Feature ranking + SVM	Accuracy of 96.43%
Peter et al., 2018 [89]	17 TLE patients and 23 HC	Focus lateralization and classification	Lateralization indices + LR	AUC of 0.8 (lateralization); AUC of 0.44 (classification)
Kini et al., 2021 [90]	89 TLE patients	Prediction of long-term seizure recurrence	RF	Mean out-of-bag accuracy of 0.71
Shih et al., 2021 [91]	104 MTLE patients	Focus lateralization	Lateralization indices + 7 ML classifiers	Accuracy of ~ 96% (validation), 100% (test)
Sinclair et al., 2021 [92]	82 MTLE patients	Prediction of surgical outcome	LR, SVM, RF, ANN	AUC of 0.75–0.81
Lee et al., 2000 [93]	261 epilepsy patients	Epilepsy diagnosis (NA, LTLE, RTLE)	ANN + LDA	Average agreement between ANN and human experts of 85% (test)
Kerr et al., 2013 [94]	105 epilepsy patients	Diagnosis and lateralization of TLE	MLP	Accuracy of 88% (RTLE) and 83% (LTLE); accuracy for simultaneous diagnosis and lateralization of 76%
Flaus et al., 2022 [95]	Simulated data and 10 epilepsy patients	PET image quality enhancement	ResNet	Improved image quality; improvement of visual lesion

Study	Dataset	Task	Model	Results
				detection from 38 to 75%
Sundar et al., 2022 [96]	10 HC and 14 non-lesional epilepsy patients (brain dataset)	Segmentation	nnU-Net	89% of the cerebral areas with DSC > 0.80
Zhang et al., 2021 [97]	201 pediatric TLE patients and 24 HC	Focus localization + Classification	Siamese CNN	DSC of 0.51; AUC of 0.92 (classification)
Tang et al., 2022 [98]	141 epilepsy patients	Prediction of seizure outcomes after surgery	ResNet-34 + multi-kernel SVM	AUC from 0.799 to 0.952 (higher for multi-modality)
Wang et al., 2022 [99]	39 mTLE-HS patients and 22 HC	Prediction of seizure outcomes after surgery	GBDT + LR	AUC of 0.905 (multi-modality, test)
Lin et al., 2020 [100]	22 epilepsy patients with FCD	Automatic detection of FCD lesion	XGBoost	Accuracy of 91% (multi-modality)
Tan et al., 2018 [101]	28 epilepsy patients with FCD and 23 TLE patients (MRI negative)	Automatic detection of FCD lesion	SVM	Sensitivity of 93% (multi-modality)

MTLE = mesial temporal lobe epilepsy; HC = healthy controls; MVPA = machine learning-based multivariate pattern analysis; SVM = support vector machine; LR = logistic regression; RF = random forest; ANN = artificial neural network; NA = no abnormal findings; LDA = linear discriminant analysis; MLP = multilayer perceptron; CNN = convolutional neural network; DSC = dice coefficient; mTLE-HS = medial temporal lobe epilepsy due to hippocampal sclerosis; GBDT = gradient boosting decision tree; FCD = focal cortical dysplasia. (Note: all studies used 18F-FDG radiotracer)

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7. AI in molecular imaging of dementia and movement disorders: A review of the current knowledge and perspectives.

The differential diagnosis of neurodegenerative and movement disorders can be quite complex and is highly dependent on the expertise of the reader. Therefore, AI may help in the (early) differential diagnosis, especially for less experienced readers. Multimodal imaging with structural and functional information combined with fluid-based biomarkers is becoming the standard in the diagnostic landscape. In this multimodal setting AI can be particularly helpful for feature selection. Moreover, AI might give additional clues about the prognosis. However, the biggest challenge in the field of AI in neurodegenerative disease is located in a very limited number of available standards of truth assessments, i.e. autopsies in previously imaged patients. In the next paragraphs we will review the AI approaches used in the literature and the perspectives of AI in molecular imaging of degenerative disorders.

Machine Learning studies

Machine learning already showed tremendous success in the differential diagnosis of neurodegenerative disorders by pattern recognition of Parkinsonian syndromes using FDG-PET images more than a decade ago (107). A recent review confirmed that the performance of a multimodal machine learning model using both structural and functional data is higher that single modality models (108). In prodromal AD and Parkinsonian syndromes, artificial intelligence not only showed potential in the early differential diagnosis, but also to predict future pathological protein accumulation and clinical deterioration (109–112). Furthermore, machine learning was evaluated for the discrimination of patients with amyotrophic lateral sclerosis from controls in a prospective study (113). Apart from differential diagnosis and prognosis, Subtype-and-Stage Inference (SuStaIn) modelling was applied for data-driven identification of four major subtypes in the Alzheimer's disease (AD) continuum (108,111,113–115).

Deep Learning studies

Artificial intelligence using deep learning may help to extract hidden information in multimodal imaging approaches of neurodegenerative diseases. For example, it can assist the biomarker discovery, physiology exploration and so on.

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The application of deep learning has been ranged from image quality enhancement (116), biomarker discovery (117,118)) cross-modality synthesis (117,119,120), quantification improvement (37,38), phenotype discovery (121) to clinical differential diagnosis (24,122–124). Brain segmentation, a crucial task to obtain quantitative parameters such as regional volume or radiotracer uptake, has been successfully performed by CNN models with high accuracy and fast processing time (125).

Deep learning models trained on normal data of FDG PET can effectively identify a wide range of brain abnormalities (126). For Alzheimer's disease a multimodal deep learning framework - combining clinical parameters with MRI-data - demonstrated a high accuracy to discriminate between Lewy body, Alzheimer's and vascular dementia (127). Furthermore, a deep learning model using FDG PET scans could demonstrate the cognitive dysfunction in patients with isolated rapid REM sleep behaviour disorder (iRBD) (128). Here, iRBD is considered as a very early preclinical symptom of synucleinopathies such as Parkinson's disease, Lewy body dementia and multiple system atrophy. Also, for prognosis AI with deep learning can help since convolutional neural networks obtained an accuracy of 75% to discriminate between patients with mild cognitive impairment who will progress to Alzheimer and patients with stable mild cognitive impairment (114). Several studies have highlighted the use of deep learning in predicting and differentiating dementia and its related conditions. Deep learning models achieved notable accuracy in predicting MCI's progression to AD and outperformed human readers in predicting AD's final clinical diagnosis (129,130). Other research further emphasized deep learning's accuracy in differentiating and diagnosing various forms of dementia using diverse radiotracers (24,131–133). Deep learning has been effective in classifying and diagnosing movement disorders. Notable results include the consistent accuracy in classifying FDG PET (118,134), DAT PET (124) or SPECT (135,136) imaging and differentiating PD or parkinsonian types.

Several investigations focused on refining image analysis and predictive models using deep learning (137). Studies have shown that deep learning can improve the association between specific amyloid load (37), cognitive signature (138,139), enhance spatial normalization (38), and extract longitudinal trajectories (121). Research has explored the potential of deep learning in generating synthetic PET images of scarce tracers (120), generating MR images from amyloid PET (119), and harmonizing image discrepancies (140,141).

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Perspectives

Future studies need to overcome the lack of validation studies across different centres and the lack of harmonization of generally accepted AI algorithms to aid in diagnosis across the neurodegenerative diseases spectrum. Moreover, all AI models are data-driven, so pre-processing of imaging data plays a crucial role. Therefore, pre-processing software also needs to be harmonized and validated. Accommodation of substantial numbers with standard of truth assessments for validation of AI application in PET imaging of neurodegenerative disorders remains a challenge and may be solved by large cohorts such as BioFINDER or ADNI (142,143). Conversely, PET itself may also be used as a standard of truth assessment for AI driven analysis of fluid biomarkers or omics data with the goal to find cheap and versatile tools for characterization of neurodegenerative disorders.

Table 3: Summary of the cited references as they vary in patient numbers

	Radiotracer	Number of Patients	Task	Main finding
Anomaly discovery				
Choi et al. 2019 (126)	18F-FDG	1303	Unsupervised identification of abnormalities of various disorders	Deep learning trained only by normal data was applicable for identifying wide-range of abnormalities in brain diseases
Dementia				
Lu et al. 2018 (37)	18F-FDG	1242	A multimodal and multiscale deep neural work to predict the risk of MCI in conversion to AD	82.4% accuracy in identifying the individuals with MCI who will convert to AD at 3 years prior to conversion
Ding et al. 2019 (130)	18F-FDG	1042	Convolutional neural network to predict final diagnosis of AD and MCI	Predicted AD final clinical diagnosis 75.8 months earlier, surpassing reader performance
Lee et al. 2022 (117)	18F-FDG	511	Deep learning-based signature from FDG PET to objectively and quantitatively evaluate cognitive function	DL-based cognitive signature using FDG PET discriminated stroke patients with dementia with AUC of 0.75
Etminani et al. 2022 (24)	18F-FDG	757	3D deep learning model to predict final diagnosis of	Superior AUC for predicting final diagnoses: DLB

				AD, DLB, MCI-AD and cognitively normal	96.2%, AD 96.4%, MCI-AD 71.4%, CN 94.7%, surpassing human reader performance.
Son et al. 2020 (131)	18F-Florbetaben	430		Validate DL's feasibility over visual rating for assessing diagnosis in subjects with equivocal amyloid PET	In equivocal scans, DL detected a significant MMSE score change difference over 1.76 years than visual reading
Park et al. 2023 (132)	18F-Flortaucipir	276		DL integrate multimodal data in differentiating of cognitively unimpaired from MCI or AD	AUC of 0.976 for classification of AD and 0.850 for classification of MCI
Jo et al. 2020 (133)	18F-Flortaucipir	300		DL to identify informative features from tau PET for AD classification	Average accuracy of 90.8% based on five-fold cross-validation in classifying AD from cognitively normal
Ryoo et al. 2022 (128)	18F-FDG	50		Test the DL-based cognitive signature derived from AD for cognitive assessment of iRBD	AUC of 0.70 distinguishes RBD-MCI from RBD-nonMCI. The baseline DL-based cognitive signature is significantly higher in iRBD patients who

				experienced cognitive decline over 2 years compared to those who didn't
Movement Disorders				
Wenzel et al. 2019 (135)	123I-FP-CIT	645	deep convolutional neural networks for automatic classification of DAT SPECT	DL achieved consistent accuracy for the classification of DAT SPECT with variable site-, camera-, or scan-specific image characteristics
Shen et al. 2019 (134)	18F-FDG	350	Group Lasso Sparse Deep Belief Network for discriminating PD and normal control subjects based on FDG-PET	DL classification of PD and NC outperformed conventional approaches with strong correlation to UPDRS and H&Y scores
Adams et al. 2021 (136)	123I-FP-CIT	252	DL to predict clinical motor function evaluation scores from longitudinal DAT SPECT and non-imaging clinical measures	DL with DAT SPECT and UPDRS enhances 4-year motor function prediction
Wu et al. 2022 (118)	18F-FDG	2228	Metabolic imaging indices	DL achieved high accuracy in

		based on deep learning to support the differential diagnosis of parkinsonism	differentiating parkinsonism in internal and external tests	
Zhao et al. 2022 (124)	11C-CFT	1017	Decode the discriminative information DAT imaging using DL for the differential diagnosis of parkinsonism	Sensitivity of 90.7%, 84.1%, 78.6% and specificity of 88.4%, 97.5% 93.3% in the blind test for the differential diagnosis of IPD, MSA and PSP
Lu et al. 2023 (129)	18F-Florzolotau		A normalization-free deep-learning model for differentiation of PSP and MSA-P	DL-guided radiomic features correlated with clinical severity of PSP
Quantification & Methodology				
Liu et al. 2021 (37)	11C-PiB	172	Using DL to correct non-specific binding due to cerebrovascular disease	Specific amyloid load after DL-correction increased association with cognitive and functional test scores by up to 67%
Kang et al. 2023 (38)	18F-Flutemetamol, 18F-Florbetaben,	1130	DL-based spatial normalization for automatic quantification of	Quantification using DL-based spatial normalization shows better correlation with that using MRI

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	18F-Florbetapir		amyloid PET without MRI	FreeSurfer than using MRI SPM	
Reith et al. 2021 (139)	18F-Florbetapir	1224	Combine DL-based imaging feature and other clinical data to predict future image features	A root mean squared error of 0.0339 ± 0.0027 for future amyloid SUVR prediction	
Choi et al. 2020 (138)	18F-FDG	1364	DL-based cognitive signature of FDG PET adaptable for PD and AD	DL-based signature developed from AD applies to predict the conversion of MCI to AD and PD dementia	
Hong et al. 2022 (121)	18F-Flortaucipir	1080	Identify the tau trajectory and quantify the tau progression in a data-driven approach with the continuous latent space learned by variational autoencoder	Identified 4 clusters corresponds to different tau progression. The inferred tau trajectory agreed with the Braak staging	
Cross-modality synthesis					
Wang et al. 2021 (120)	18F-FDG	54	Generate synthetic PET images of less-available tracers such as synaptic density and amyloid from FDG PET	SUVR bias for synthesizing 11C-UCB-J: -0.3% ± 7.4% (AD), -0.5% ± 7.3% (CN); for 11C-PiB: -1.3% ± 7.5% (AD), -2.0% ± 6.9% (CN)	

Choi et al. 2018 (119)	18F-Florbetapir	261	Deep generative networks to generate structural MR images from amyloid PET for MR-less quantification	Mean absolute error of SUVR by MR-based method was 0.04 ± 0.03, significantly lower than other MR-less methods.
Kim et al. 2021 (141)	18F-FDG	1533	deep learning based amyloid PET prediction based FDG PET	AUC of 0.86 for predicting amyloid-positive patients using FDG PET in external test
Shah et al. 2022 (140)	11C-PiB, 18F-florbetapir	138	A Residual Inception Encoder-Decoder Neural Network to harmonize the difference between different amyloid PET imaging	Significantly stronger between-tracer correlations (P < .001) were observed after harmonization for both global amyloid burden indices and voxel-wise measurements

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8. AI in molecular imaging in psychiatry: A review of the current knowledge and perspectives.

Diagnosis and evaluation of psychiatric disorders rely almost exclusively on clinical interviews using the Diagnostic and Statistical Manual of Mental Disorders (DSM) nosography, with so far limited impact of neuroimaging beyond the issue of differential diagnosis. Yet, the DSM reliability is regularly questioned by its iterative modifications, lack of reproducibility of current diagnoses, and therapeutic resistance of many patients (144–146). In this context, more transdiagnostic approaches are emerging (147), in -addition to the development of invasive and non-invasive brain stimulation (148), for which relevant biomarkers are crucial to identify brain signatures, guide therapeutics and evaluate their effects (145). PET and SPECT imaging could be particularly relevant to explore such disorders mainly characterized by dysfunction, in the absence of morphological lesions, with the possible implementation of various targets such as the perfusion, metabolism, neurotransmission and neuroinflammation, and especially the individual application of artificial intelligence tools for precision medicine (149,150). In this line, machine learning classification from controls has suggested accurate performance to identify patients with attention-deficit and hyperactivity disorder using multimodal serotoninergic brain PET imaging (151), patients with cocaine dependence using brain perfusion SPECT imaging (152), patients with internet game disorder using metabolic brain PET imaging (153), patients with major depression using serotoninergic PET imaging (154), or brain metabolic PET imaging, also demonstrating the value of this last exploration to predict the response of deep brain stimulation in this context (155). Machine-learned analysis of [^{18}F]FDOPA PET scans of patients with schizophrenia also showed good performance for identifying treatment responders and non-responders, with large potential healthcare cost savings (156). This translation from research to clinical applications will need more numerous multicentric studies, and to be supported by a paradigm change in psychiatry towards modern approaches of precision medicine.

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9. Role of the EANM in advancing the use of AI in molecular brain imaging

As for the whole nuclear medicine community, there is great interest in the molecular brain imaging field to advance the use of AI in research, translational and potentially also in daily clinical routine settings. In good time, the EANM has recognized this desire and leads efforts moving this exciting development forward.

A series of publications of AI in neuroimaging have emerged in the latest years, focusing on several different aspects of this complex modality. As often in the past with methodological imaging advancements, the brain is perfect as the organ of interest to start with testing such new developments. This is not only as multi-modality image co-registration is much easier for the head as compared to other body parts, and as large image databases are easily accessible in case of brain imaging. However, standardization of clinical brain image recording and imaging protocols as well as efficient dissemination of data will be essential before data from different centers can be used as input by AI (157–159).

As with medical imaging in general, in case of molecular brain imaging, the process from data acquisition to diagnosis involves numerous steps (e.g. image reconstruction, image segmentation, extraction of imaging biomarkers, image classification, patient stratification). AI methods have now been developed and tested for one specific step at a time. One could expect in the future that AI based algorithms could automatically handle all steps in a transparent fashion to the user, though, on the other hand, the process still needs to be guided by the clinical needs. Results and type of AI behavior or generalizability need to be evaluated (160–162).

The Neuroimaging committee of the EANM and neuro-nuclear medicine opinion leaders in general believe the future potential of AI will mainly be (i) to increase image quality that would translate into a higher diagnostic accuracy and confidence, (ii) to reduced tracer dose/radiation exposure, (iii) to reduced PET or SPECT scan times, (iv) to standardize and harmonize image data acquisition, processing and analysis across centers, and (v) to improve the reporting/communication of the scan results with the patients, their caregivers and the referring doctors.

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Alexander Hammers:
"Fair AI is close to my heart, and in my opinion still vastly under-recognised - I've added the citation elsewhere but perhaps worth repeating in this summary section along the lines of "Standardisation of clinical data recording and imaging protocols, clear demographic characterisation of controls and patients for Fair AI (REF: Ioannou S et al.), as well as efficient dissemination of data will be essential before data from different centres can be optimally used as input for AI (125 - 127)"
(A study of demographic bias in cnn-based brain mr segmentation
S Ioannou, H Chockler, A Hammers, AP King, ... International Workshop on Machine Learning in Clinical Neuroimaging, 13-22"

In clinical practice, it is difficult to foresee what will be happening in the future in molecular neuroimaging as well in other medical and non-medical fields, e.g. in how far the human being will be replaced by AI.

All these procedures will help even less experts' nuclear physicians, all over the globe, to interpret the images and address the patient to the appropriate specialist, with a timely management.

In our opinion the role of nuclear medicine physicians will be to supervise the work of AI, which will decide on the specific subject the technical parameters to adopt, the scan type, the image reconstruction technique, the count of photons and possible inclusion of scatter, the clinical information/potential risk assessment and or potential treatment options. Incorporation of AI into this envisioned automated workflow (from acquisition and pre-processing to disease and risk identification) will be useful for complex cases that will benefit the most from expert clinical analysis in situations of massive data overflow (157).

Most excitingly, the next years will also show whether AI is, in case of molecular brain imaging, suitable to support or even - at least in some applications - replace the nuclear medicine physician. General pros for AI in this regard are its availability without quality/reproducibility differences on a 24/7 base, stable quality, and a potential to improve over time. As examples, rather straightforward binary decisions like positivity vs. negativity in case of amyloid PET imaging, or rather complex and experience-dependent differential diagnoses like those obtained by FDG PET imaging in dementia disorders or atypical Parkinsonian syndromes might be better obtainable in the future by AI.

The role of nuclear medicine physicians is likely to evolve as soon as these new AI techniques (and us, as nuclear medicine experts should by ourselves drive this developments). will be fully integrated into their practice, and it is therefore important that the acquisition of a basic understanding of these methods and concepts will become part of their training (163), a matter the EANM should likewise focus on.

Nevertheless, there are ongoing challenges to AI in the healthcare system. In clinical practice, the most prominent and time-consuming obstacle is the implementation of AI into the already existing workflow. AI can only function at a high level if it is treated as a fundamental part of the routine protocols rather than a simple add-on within the

system. More specifically, successful integration of AI into the operation of an organization requires at the very least a high computational power of the facility, and proper education of the staff on how to correctly implement AI-generated results, which most likely take years to be implemented satisfactorily. Consequently, successful deployment of AI demands international actions led by the EANM and other stakeholders in the field, including standardized procedures for different AI applications worldwide (164–166).

Taken together, the role of organizations like EANM is to define and foresee these current and potential upcoming issues regarding nuclear medicine related AI applications. With clear objectives, supported by similarly large organizations overcoming these issues can be accelerated (167,168). This also refers to setting up quality standards on publications dealing with AI in molecular imaging (169).

Lastly, another concurrent call for EANM is to set internationally recognized ethical standards for the deployment of AI in nuclear medicine and its associated counterpart fields. The EANM has recently acknowledged a prominent set of ethical principles from Currie et al. (170) for the application of AI in nuclear medicine (Fig. 4), however; as AI algorithms and their reliability will increase, EANM will likely evolve these ethical codes.

Figure 4: Decision making of the ethical principles from Currie et al.

Framework	Professional	Patient
Privacy and security	Fairness and Justice	Beneficience
Mitigation of bias	Safety and Reliabilty	Nonmaleficience
Transparency	Explainability	Human values
Accountablitiy	Decision makig	Equity and Equality
Governance	Collegiality	Autonomy
Inclusiveness		

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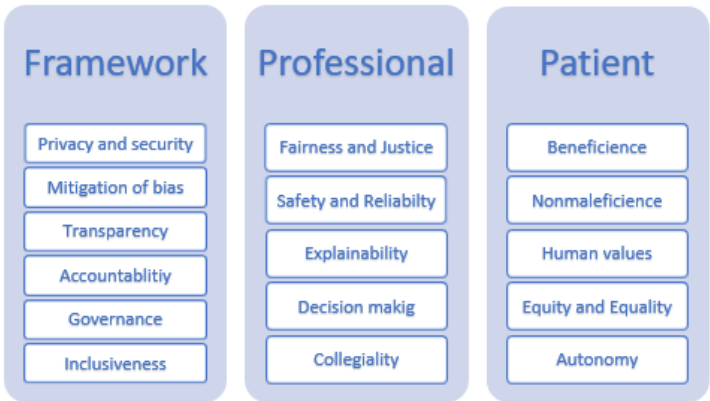
References:

1. Marin JFG, Nunes RF, Coutinho AM, Zaniboni EC, Costa LB, Barbosa FG, et al. Theranostics in nuclear medicine: Emerging and re-emerging integrated imaging and therapies in the era of precision oncology. Radiographics. 2020 Oct 1;40(6):1715–40.

2. Jiang L, Wu Z, Xu X, Zhan Y, Jin X, Wang L, et al. Opportunities and challenges of artificial intelligence in the medical field: current application, emerging problems, and problem-solving strategies. Vol. 49, Journal of International Medical Research. SAGE Publications Ltd; 2021.

3. Smucny J, Shi G, Davidson I. Deep Learning in Neuroimaging: Overcoming Challenges With Emerging Approaches. Front Psychiatry. 2022 Jun 2;13.

4. Bianchini S, Müller M, Pelletier P. Artificial intelligence in science: An emerging general method of invention. Res Policy. 2022 Dec 1;51(10).

5. Decuyper M, Maebe J, Van Holen R, Vandenberghe S. Artificial intelligence with deep learning in nuclear medicine and radiology. Vol. 8, EJNMMI Physics. Springer Science and Business Media Deutschland GmbH; 2021.

6. Cheng Z, Wen J, Huang G, Yan J. Applications of artificial intelligence in nuclear medicine image generation. Vol. 11, Quantitative Imaging in Medicine and Surgery. AME Publishing Company; 2021.

7. Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, et al. Artificial intelligence in healthcare: Past, present and future. Vol. 2, Stroke and Vascular Neurology. BMJ Publishing Group; 2017. p. 230–43.

8. Nenning KH, Langs G. Machine learning in neuroimaging: from research to clinical practice. Vol. 62, Radiologie. Springer Medizin; 2022. p. 1–10.

9. Singh NM, Harrod JB, Subramanian S, Robinson M, Chang K, Cetin-Karayumak S, et al. How Machine Learning is Powering Neuroimaging to Improve Brain Health. Neuroinformatics. Springer; 2022.

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748   10.   Richards BA, Lillicrap TP, Beaudoin P, Bengio Y, Bogacz R, Christensen A, et al. A deep learning

749   framework for neuroscience. Vol. 22, Nature Neuroscience. Nature Publishing Group; 2019.

750   p. 1761–70.

751   11.   Schmidhuber J. Deep Learning in neural networks: An overview. Vol. 61, Neural Networks.

752   Elsevier Ltd; 2015. p. 85–117.

753   12.   Gu J, Wang Z, Kuen J, Ma L, Shahroudy A, Shuai B, et al. Recent advances in convolutional

754   neural networks. Pattern Recognit. 2018 May 1;77:354–77.

755   13.   Chartrand G, Cheng PM, Vorontsov E, Drozdzal M, Turcotte S, Pal CJ, et al. Deep learning: A

756   primer for radiologists. Vol. 37, Radiographics. Radiological Society of North America Inc.;

757   2017. p. 2113–31.

758   14.   Yamashita R, Nishio M, Do RKG, Togashi K. Convolutional neural networks: an overview and

759   application in radiology. Vol. 9, Insights into Imaging. Springer Verlag; 2018. p. 611–29.

760   15.   Najafabadi MM, Villanustre F, Khoshgoftaar TM, Seliya N, Wald R, Muharemagic E. Deep

761   learning applications and challenges in big data analytics. J Big Data. 2015 Dec 1;2(1).

762   16.   Wen D, Wei Z, Zhou Y, Li G, Zhang X, Han W. Deep learning methods to process fmri data and

763   their application in the diagnosis of cognitive impairment: A brief overview and our opinion.

764   Vol. 12, Frontiers in Neuroinformatics. Frontiers Media S.A.; 2018.

765   17.   Yao AD, Cheng DL, Pan I, Kitamura F. Deep learning in neuroradiology: A systematic review of

766   current algorithms and approaches for the new wave of imaging technology. Radiol Artif

767   Intell. 2020 Mar 1;2(2).

768   18.   Paredes-Pacheco J, López-González FJ, Silva-Rodríguez J, Efthimiou N, Niñerola-Baizán A,

769   Ruibal Á, et al. SimPET—An open online platform for the Monte Carlo simulation of realistic

770   brain PET data. Validation for 18F-FDG scans. Med Phys. 2021 May 1;48(5):2482–93.

771   19.   Shiri I, Vafaei Sadr A, Akhavan A, Salimi Y, Sanaat A, Amini M, et al. Decentralized

772   collaborative multi-institutional PET attenuation and scatter correction using federated deep

773   learning. Eur J Nucl Med Mol Imaging. 2023 Mar 1;50(4):1034–50.

774 20. Shiri I, Vafaei Sadr A, Amini M, Salimi Y, Sanaat A, Akhavanallaf A, et al. Decentralized

775   Distributed Multi-institutional PET Image Segmentation Using a Federated Deep Learning

776   Framework. Clin Nucl Med. 2022 Jul 1;47(7):606–17.

777 21. Zhou B, Miao T, Mirian N, Chen X, Xie H, Feng Z, et al. Federated Transfer Learning for Low-

778   Dose PET Denoising: A Pilot Study With Simulated Heterogeneous Data. IEEE Trans Radiat

779   Plasma Med Sci. 2023 Mar 1;7(3):284–95.

780 22. Warnat-Herresthal S, Schultze H, Shastry KL, Manamohan S, Mukherjee S, Garg V, et al.

781   Swarm Learning for decentralized and confidential clinical machine learning. Nature. 2021

782   Jun 10;594(7862):265–70.

783 23. Pain CD, Egan GF, Chen Z. Deep learning-based image reconstruction and post-processing

784   methods in positron emission tomography for low-dose imaging and resolution

785   enhancement. Vol. 49, European Journal of Nuclear Medicine and Molecular Imaging.

786   Springer Science and Business Media Deutschland GmbH; 2022. p. 3098–118.

787 24. Etminani K, Soliman A, Davidsson A, Chang JR, Martínez-Sanchis B, Byttner S, et al. A 3D deep

788   learning model to predict the diagnosis of dementia with Lewy bodies, Alzheimer's disease,

789   and mild cognitive impairment using brain 18F-FDG PET. Eur J Nucl Med Mol Imaging. 2022

790   Jan 1;49(2):563–84.

791 25. Minoshima S, Cross D. Application of artificial intelligence in brain molecular imaging. Vol. 36,

792   Annals of Nuclear Medicine. Springer Japan; 2022. p. 103–10.

793 26. Sanaat A, Akhavanalaf A, Shiri I, Salimi Y, Arabi H, Zaidi H. Deep-TOF-PET: Deep learning-

794   guided generation of time-of-flight from non-TOF brain PET images in the image and

795   projection domains. Hum Brain Mapp. 2022 Nov 1;43(16):5032–43.

796 27. Mehranian A, Wollenweber SD, Walker MD, Bradley KM, Fielding PA, Huellner M, et al. Deep

797   learning–based time-of-flight (ToF) image enhancement of non-ToF PET scans. Eur J Nucl Med

798   Mol Imaging. 2022 Sep 1;49(11):3740–9.

36

799 28. Liu M, Yan P, Lian C, Cao X. Machine Learning in Medical Imaging [Internet]. 2020. Available

800   from: http://www.springer.com/series/7412

801 29. Shiri I, Vafaei Sadr A, Akhavan A, Salimi Y, Sanaat A, Amini M, et al. Decentralized

802   collaborative multi-institutional PET attenuation and scatter correction using federated deep

803   learning. Eur J Nucl Med Mol Imaging. 2023 Mar 1;50(4):1034–50.

804 30. Laurent B, Bousse A, Merlin T, Nekolla S, Visvikis D. PET scatter estimation using deep

805   learning U-Net architecture. Phys Med Biol. 2023 Mar 21;68(6):065004.

806 31. Sari H, Teimoorisichani M, Mingels C, Alberts I, Panin V, Bharkhada D, et al. Quantitative

807   evaluation of a deep learning-based framework to generate whole-body attenuation maps

808   using LSO background radiation in long axial FOV PET scanners. Eur J Nucl Med Mol Imaging.

809   2022 Nov 1;49(13):4490–502.

810 32. Shiyam Sundar LK, Iommi D, Muzik O, Chalampalakis Z, Klebermass EM, Hienert M, et al.

811   Conditional Generative Adversarial Networks Aided Motion Correction of Dynamic 18F-FDG

812   PET Brain Studies. J Nucl Med. 2021 Jun 1;62(6):871–9.

813 33. Chen KT, Schürer M, Ouyang J, Koran MEI, Davidzon G, Mormino E, et al. Generalization of

814   deep learning models for ultra-low-count amyloid PET/MRI using transfer learning. Eur J Nucl

815   Med Mol Imaging. 2020 Dec 1;47(13):2998–3007.

816 34. Oh KT, Lee S, Lee H, Yun M, Yoo SK. Semantic Segmentation of White Matter in FDG-PET

817   Using Generative Adversarial Network. J Digit Imaging. 2020 Aug 1;33(4):816–25.

818 35. Henschel L, Conjeti S, Estrada S, Diers K, Fischl B, Reuter M. FastSurfer - A fast and accurate

819   deep learning based neuroimaging pipeline. Neuroimage. 2020 Oct 1;219.

820 36. Fourcade C, Ferrer L, Moreau N, Santini G, Brennan A, Rousseau C, et al. Deformable image

821   registration with deep network priors: a study on longitudinal PET images. 2021 Nov 22;

822   Available from: http://arxiv.org/abs/2111.11873

823   37.   Liu H, Nai YH, Saridin F, Tanaka T, O' Doherty J, Hilal S, et al. Improved amyloid burden

824   quantification with nonspecific estimates using deep learning. Available from:

825   https://doi.org/10.1007/s00259-020-05131-z

826   38.   Kang SK, Kim D, Shin SA, Kim YK, Choi H, Lee JS. Fast and accurate amyloid brain PET

827   quantification without MRI using deep neural networks. Journal of Nuclear Medicine. 2022

828   Apr 3;jnumed.122.264414.

829   39.   Kuttner S, Wickstrøm KK, Lubberink M, Tolf A, Burman J, Sundset R, et al. Cerebral blood flow

830   measurements with 15O-water PET using a non-invasive machine-learning-derived arterial

831   input function. Journal of Cerebral Blood Flow and Metabolism. 2021 Sep 1;41(9):2229–41.

832   40.   Salahuddin Z, Woodruff HC, Chatterjee A, Lambin P. Transparency of deep neural networks

833   for medical image analysis: A review of interpretability methods. Vol. 140, Computers in

834   Biology and Medicine. Elsevier Ltd; 2022.

835   41.   van der Velden BHM, Kuijf HJ, Gilhuijs KGA, Viergever MA. Explainable artificial intelligence

836   (XAI) in deep learning-based medical image analysis. Vol. 79, Medical Image Analysis. Elsevier

837   B.V.; 2022.

838   42.   Bondy ML, Scheurer ME, Malmer B, Barnholtz-Sloan JS, Davis FG, Il'yasova D, et al. Brain

839   tumor epidemiology: Consensus from the Brain Tumor Epidemiology Consortium. Vol. 113,

840   Cancer. 2008. p. 1953–68.

841   43.   Gutsche R, Scheins J, Kocher M, Bousabarah K, Fink GR, Shah NJ, et al. Evaluation of fet pet

842   radiomics feature repeatability in glioma patients. Cancers (Basel). 2021 Feb 2;13(4):1–15.

843   44.   Zounek AJ, Albert NL, Holzgreve A, Unterrainer M, Brosch-Lenz J, Lindner S, et al. Feasibility of

844   radiomic feature harmonization for pooling of [18F]FET or [18F]GE-180 PET images of

845   gliomas. Z Med Phys. 2023 Feb 1;

846   45.   Zwanenburg A, Vallières M, Abdalah MA, Aerts HJWL, Andrearczyk V, Apte A, et al. The image

847   biomarker standardization initiative: Standardized quantitative radiomics for high-throughput

848   image-based phenotyping. Radiology. 2020 May 1;295(2):328–38.

38

849 46. Hatt M, Krizsan AK, Rahmim A, Bradshaw TJ, Costa PF, Forgacs A, et al. Joint EANM/SNMMI

850   guideline on radiomics in nuclear medicine: Jointly supported by the EANM Physics

851   Committee and the SNMMI Physics, Instrumentation and Data Sciences Council. Eur J Nucl

852   Med Mol Imaging. 2023 Jan 1;50(2):352–75.

853 47. Kebir S, Rauschenbach L, Weber M, Lazaridis L, Schmidt T, Keyvani K, et al. Machine learning-

854   based differentiation between multiple sclerosis and glioma WHO II°-IV° using O-(2-[18F]

855   fluoroethyl)-L-tyrosine positron emission tomography. J Neurooncol. 2021 Apr 1;152(2):325–

856   32.

857 48. Tatekawa H, Hagiwara A, Uetani H, Bahri S, Raymond C, Lai A, et al. Differentiating IDH status

858   in human gliomas using machine learning and multiparametric MR/PET. Cancer Imaging. 2021

859   Dec 1;21(1).

860 49. Kebir S, Weber M, Lazaridis L, Deuschl C, Schmidt T, Mönninghoff C, et al. Hybrid 11 C-MET

861   PET/MRI Combined with "machine Learning" in Glioma Diagnosis According to the Revised

862   Glioma WHO Classification 2016. Clin Nucl Med. 2019 Mar 1;44(3):214–20.

863 50. Blanc-Durand P, Van Der Gucht A, Verger A, Langen KJ, Dunet V, Bloch J, et al. Voxel-based 18

864   F-FET PET segmentation and automatic clustering of tumor voxels: A significant association

865   with IDH1 mutation status and survival in patients with gliomas. PLoS One. 2018 Jun 1;13(6).

866 51. Kebir S, Schmidt T, Weber M, Lazaridis L, Galldiks N, Langen KJ, et al. A preliminary study on

867   machine learning-based evaluation of static and dynamic fet-pet for the detection of

868   pseudoprogression in patients with idh-wildtype glioblastoma. Cancers (Basel). 2020 Nov

869   1;12(11):1–14.

870 52. Pyka T, Gempt J, Hiob D, Ringel F, Schlegel J, Bette S, et al. Textural analysis of pre-

871   therapeutic [18F]-FET-PET and its correlation with tumor grade and patient survival in high-

872   grade gliomas. Eur J Nucl Med Mol Imaging. 2016 Jan 1;43(1):133–41.

873 53. Russo G, Stefano A, Alongi P, Comelli A, Catalfamo B, Mantarro C, et al. Feasibility on the use

874   of radiomics features of 11[C]-MET PET/CT in central nervous system tumours: Preliminary

875   results on potential grading discrimination using a machine learning model. Current

876   Oncology. 2021 Dec 1;28(6):5318–31.

877 54. Zaragori T, Oster J, Roch V, Hossu G, Chawki MB, Grignon R, et al. 18F-FDOPA PET for the

878   Noninvasive Prediction of Glioma Molecular Parameters: A Radiomics Study. Journal of

879   Nuclear Medicine. 2022 Jan 1;63(1):147–57.

880 55. Lohmann P, Lerche C, Bauer EK, Steger J, Stoffels G, Blau T, et al. Predicting IDH genotype in

881   gliomas using FET PET radiomics. Sci Rep. 2018 Dec 1;8(1).

882 56. Papp L, Rasul S, Spielvogel CP, Krajnc D, Poetsch N, Woehrer A, et al. Sex-specific radiomic

883   features of L-[S-methyl-11C] methionine PET in patients with newly-diagnosed gliomas in

884   relation to IDH1 predictability. Front Oncol. 2023 Feb 3;13.

885 57. Zhou W, Huang Q, Wen J, Li M, Zhu Y, Liu Y, et al. Integrated CT Radiomics Features Could

886   Enhance the Efficacy of 18F-FET PET for Non-Invasive Isocitrate Dehydrogenase Genotype

887   Prediction in Adult Untreated Gliomas: A Retrospective Cohort Study. Front Oncol. 2021 Nov

888   19;11.

889 58. Qian J, Herman MG, Brinkmann DH, Laack NN, Kemp BJ, Hunt CH, et al. Prediction of MGMT

890   Status for Glioblastoma Patients Using Radiomics Feature Extraction From 18F-DOPA-PET

891   Imaging. Int J Radiat Oncol Biol Phys. 2020 Dec 1;108(5):1339–46.

892 59. Haubold J, Demircioglu A, Gratz M, Glas M, Wrede K, Sure U, et al. Non-invasive tumor

893   decoding and phenotyping of cerebral gliomas utilizing multiparametric 18F-FET PET-MRI and

894   MR Fingerprinting. Eur J Nucl Med Mol Imaging. 2020 Jun 1;47(6):1435–45.

895 60. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO

896   classification of tumors of the central nervous system: A summary. Neuro Oncol. 2021 Aug

897   1;23(8):1231–51.

898 61. Papp L, Pötsch N, Grahovac M, Schmidbauer V, Woehrer A, Preusser M, et al. Glioma survival

899   prediction with combined analysis of in vivo 11 C-MET PET features, ex vivo features, and

900   patient features by supervised machine learning. Journal of Nuclear Medicine. 2018 Jun

901   1;59(6):892–9.

902 62. Carles M, Popp I, Starke MM, Mix M, Urbach H, Schimek-Jasch T, et al. FET-PET radiomics in

903   recurrent glioblastoma: prognostic value for outcome after re-irradiation? Radiation

904   Oncology. 2021 Dec 1;16(1).

905 63. Wiltgen T, Fleischmann DF, Kaiser L, Holzgreve A, Corradini S, Landry G, et al. 18F-FET PET

906   radiomics-based survival prediction in glioblastoma patients receiving radio(chemo)therapy.

907   Radiation Oncology. 2022 Dec 1;17(1).

908 64. Wang K, Qiao Z, Zhao X, Li X, Wang X, Wu T, et al. Individualized discrimination of tumor

909   recurrence from radiation necrosis in glioma patients using an integrated radiomics-based

910   model. Eur J Nucl Med Mol Imaging. 2020 Jun 1;47(6):1400–11.

911 65. Hotta M, Minamimoto R, Miwa K. 11C-methionine-PET for differentiating recurrent brain

912   tumor from radiation necrosis: radiomics approach with random forest classifier. Sci Rep.

913   2019 Dec 1;9(1).

914 66. Müller M, Winz O, Gutsche R, Leijenaar RTH, Kocher M, Lerche C, et al. Static FET PET

915   radiomics for the differentiation of treatment-related changes from glioma progression. J

916   Neurooncol. 2022 Sep 1;159(3):519–29.

917 67. Lohmann P, Elahmadawy MA, Gutsche R, Werner JM, Bauer EK, Ceccon G, et al. Fet pet

918   radiomics for differentiating pseudoprogression from early tumor progression in glioma

919   patients post-chemoradiation. Cancers (Basel). 2020 Dec 1;12(12):1–17.

920 68. Li Z, Kaiser L, Holzgreve A, Ruf VC, Suchorska B, Wenter V, et al. Prediction of TERTp-mutation

921   status in IDH-wildtype high-grade gliomas using pre-treatment dynamic [18F]FET PET

922   radiomics. Eur J Nucl Med Mol Imaging. 2021 Dec 1;48(13):4415–25.

923 69. von Rohr K, Unterrainer M, Holzgreve A, Kirchner MA, Li Z, Unterrainer LM, et al. Can

924   Radiomics Provide Additional Information in [18F]FET-Negative Gliomas? Cancers (Basel).

925   2022 Oct 1;14(19).

926   70.   Li Z, Holzgreve A, Unterrainer LM, Ruf VC, Quach S, Bartos LM, et al. Combination of pre-

927   treatment dynamic [18F]FET PET radiomics and conventional clinical parameters for the

928   survival stratification in patients with IDH-wildtype glioblastoma. Eur J Nucl Med Mol

929   Imaging. 2023 Jan 1;50(2):535–45.

930   71.   Ahrari S, Zaragori T, Rozenblum L, Oster J, Imbert L, Kas A, et al. Relevance of dynamic18 f-

931   dopa pet radiomics for differentiation of high-grade glioma progression from treatment-

932   related changes. Biomedicines. 2021 Dec 1;9(12).

933   72.   Bros M, Zaragori T, Rech F, Blonski M, Hossu G, Taillandier L, et al. Effects of carbidopa

934   premedication on18 f-fdopa pet imaging of glioma: A multiparametric analysis. Cancers

935   (Basel). 2021 Nov 1;13(21).

936   73.   Ahrari S, Zaragori T, Bros M, Oster J, Imbert L, Verger A. Implementing the Point Spread

937   Function Deconvolution for Better Molecular Characterization of Newly Diagnosed Gliomas: A

938   Dynamic 18F-FDOPA PET Radiomics Study. Cancers (Basel). 2022 Dec 1;14(23).

939   74.   Li L, Mu W, Wang Y, Liu Z, Liu Z, Wang Y, et al. A Non-invasive Radiomic Method Using 18F-

940   FDG PET Predicts Isocitrate Dehydrogenase Genotype and Prognosis in Patients With Glioma.

941   Front Oncol. 2019 Nov 14;9.

942   75.   Kong Z, Jiang C, Zhu R, Feng S, Wang Y, Li J, et al. 18F-FDG-PET-based radiomics features to

943   distinguish primary central nervous system lymphoma from glioblastoma. Neuroimage Clin.

944   2019 Jan 1;23.

945   76.   Zhang L, Pan H, Liu Z, Gao J, Xu X, Wang L, et al. Multicenter clinical radiomics-integrated

946   model based on [18 F]FDG PET and multi-modal MRI predict ATRX mutation status in IDH-

947   mutant lower-grade gliomas. Available from: https://doi.org/10.1007/s00330-022-09043-4

948   77.   Cao X, Tan D, Liu Z, Liao M, Kan Y, Yao R, et al. Differentiating solitary brain metastases from

949   glioblastoma by radiomics features derived from MRI and 18F-FDG-PET and the combined

950   application of multiple models. Sci Rep. 2022 Dec 1;12(1).

951   78.   Lohmann P, Stoffels G, Ceccon G, Rapp M, Sabel M, Filss CP, et al. Radiation injury vs.

952   recurrent brain metastasis: combining textural feature radiomics analysis and standard

953   parameters may increase 18F-FET PET accuracy without dynamic scans. Eur Radiol. 2017 Jul

954   1;27(7):2916–27.

955   79.   Lohmann P, Kocher M, Ceccon G, Bauer EK, Stoffels G, Viswanathan S, et al. Combined FET

956   PET/MRI radiomics differentiates radiation injury from recurrent brain metastasis.

957   Neuroimage Clin. 2018 Jan 1;20:537–42.

958   80.   Wang Y, Kong Z, Lin Y, Jiang C, Li L, Liu Z, et al. 18F-FDG-PET-based Radiomics signature

959   predicts MGMT promoter methylation status in primary diffuse glioma. Cancer Imaging. 2019

960   Aug 19;19(1).

961   81.   Cui C, Yao X, Xu L, Chao Y, Hu Y, Zhao S, et al. Improving the Classification of PCNSL and Brain

962   Metastases by Developing a Machine Learning Model Based on 18F-FDG PET. J Pers Med.

963   2023 Mar 17;13(3):539.

964   82.   Blanc-Durand P, Van Der Gucht A, Schaefer N, Itti E, Prior JO. Automatic lesion detection and

965   segmentation of18F-FET PET in gliomas: A full 3D U-Net convolutional neural network study.

966   PLoS One. 2018 Apr 1;13(4).

967   83.   Jeong JW, Lee MH, John F, Robinette NL, Amit-Yousif AJ, Barger GR, et al. Feasibility of

968   Multimodal MRI-Based Deep Learning Prediction of High Amino Acid Uptake Regions and

969   Survival in Patients With Glioblastoma. Front Neurol. 2019 Dec 17;10.

970   84.   Ladefoged CN, Marner L, Hindsholm A, Law I, Højgaard L, Andersen FL. Deep learning based

971   attenuation correction of PET/MRI in pediatric brain tumor patients: Evaluation in a clinical

972   setting. Front Neurosci. 2019;13(JAN).

973   85.   Paprottka KJ, Kleiner S, Preibisch C, Kofler F, Schmidt-Graf F, Delbridge C, et al. Fully

974   automated analysis combining [18F]-FET-PET and multiparametric MRI including DSC

975   perfusion and APTw imaging: a promising tool for objective evaluation of glioma progression.

976   Eur J Nucl Med Mol Imaging. 2021 Dec 1;48(13):4445–55.

977 86. Matsui Y, Maruyama T, Nitta M, Saito T, Tsuzuki S, Tamura M, et al. Prediction of lower-grade

978   glioma molecular subtypes using deep learning. J Neurooncol. 2020 Jan 1;146(2):321–7.

979 87. Lohmann P, Galldiks N, Kocher M, Heinzel A, Filss CP, Stegmayr C, et al. Radiomics in neuro-

980   oncology: Basics, workflow, and applications. Vol. 188, Methods. Academic Press Inc.; 2021.

981   p. 112–21.

982 88. Chalkidou A, O'Doherty MJ, Marsden PK. False discovery rates in PET and CT studies with

983   texture features: A systematic review. PLoS One. 2015 May 4;10(5).

984 89. Zhang Q, Liao Y, Wang X, Zhang T, Feng J, Deng J, et al. A deep learning framework for 18 F-

985   FDG PET imaging diagnosis in pediatric patients with temporal lobe epilepsy.

986 90. Rogeau A, Lilburn DML, Kaplar Z, Anderson C, Scott CJ, Chowdhury FA, et al. Identifying and

987   troubleshooting the pitfalls of ictal/interictal brain perfusion SPECT studies. Nucl Med

988   Commun. 2023 Sep 4;

989 91. Wu D, Yang L, Gong G, Zheng Y, Jin C, Qi L, et al. Characterizing the hyper- and

990   hypometabolism in temporal lobe epilepsy using multivariate machine learning. J Neurosci

991   Res. 2021 Nov 1;99(11):3035–46.

992 92. Beheshti I, Sone D, Maikusa N, Kimura Y, Shigemoto Y, Sato N, et al. Pattern analysis of

993   glucose metabolic brain data for lateralization of MRI-negative temporal lobe epilepsy.

994   Epilepsy Res. 2020 Nov 1;167.

995 93. Peter J, Khosravi M, Werner TJ, Alavi A. Global temporal lobe asymmetry as a semi-

996   quantitative imaging biomarker for temporal lobe epilepsy lateralization: A machine learning

997   classification study [Internet]. Vol. 21, Hell J Nucl Med. 2018. Available from:

998   www.nuclmed.gr

999 94. Kini LG, Thaker AA, Hadar PN, Shinohara RT, Brown MG, Dubroff JG, et al. Quantitative

1000   [18]FDG PET asymmetry features predict long-term seizure recurrence in refractory epilepsy.

1001   Epilepsy and Behavior. 2021 Mar 1;116.

44

1002 95.   Shih YC, Lee TH, Yu HY, Chou CC, Lee CC, Lin PT, et al. Machine Learning Quantitative Analysis

1003   of FDG PET Images of Medial Temporal Lobe Epilepsy Patients. Clin Nucl Med. 2022 Apr

1004   1;47(4):287–93.

1005 96.   Sinclair B, Cahill V, Seah J, Kitchen A, Vivash LE, Chen Z, et al. Machine learning approaches

1006   for imaging-based prognostication of the outcome of surgery for mesial temporal lobe

1007   epilepsy. Epilepsia. 2022 May 1;63(5):1081–92.

1008 97.   Yankam Njiwa J, Gray KR, Costes N, Mauguiere F, Ryvlin P, Hammers A. Advanced [18F]FDG

1009   and [11C]flumazenil PET analysis for individual outcome prediction after temporal lobe

1010   epilepsy surgery for hippocampal sclerosis. Neuroimage Clin. 2015;7:122–31.

1011 98.   Lee JS, Soo Lee D, Kim SK, Lee SK, Chung JK, Lee MC, et al. Localization of Epileptogenic Zones

1012   in F-18 FDG Brain PET of Patients with Temporal Lobe Epilepsy Using Artificial Neural

1013   Network. Vol. 19, IEEE TRANSACTIONS ON MEDICAL IMAGING. 2000.

1014 99.   Kerr WT, Nguyen ST, Cho AY, Lau EP, Silverman DH, Douglas PK, et al. Computer-aided

1015   diagnosis and localization of lateralized temporal lobe epilepsy using interictal FDG-PET. Front

1016   Neurol. 2013;4 APR.

1017 100.   Yakushev I, Tauber C, Muller F. PET image enhancement using artificial intelligence for better

1018   characterization of epilepsy lesions.

1019 101.   Sundar LKS, Yu J, Muzik O, Kulterer OC, Fueger B, Kifjak D, et al. Fully Automated, Semantic

1020   Segmentation of Whole-Body 18F-FDG PET/CT Images Based on Data-Centric Artificial

1021   Intelligence. J Nucl Med. 2022 Dec 1;63(12):1941–8.

1022 102.   Flaus A, Jung J, Ostrowky-Coste K, Rheims S, Guénot M, Bouvard S, et al. Deep-learning

1023   predicted PET can be subtracted from the true clinical fluorodeoxyglucose PET co-registered

1024   to MRI to identify the epileptogenic zone in focal epilepsy. Epilepsia Open. 2023;

1025 103.   Tang Y, Li W, Tao L, Li J, Long T, Li Y, et al. Machine Learning-Derived Multimodal

1026   Neuroimaging of Presurgical Target Area to Predict Individual's Seizure Outcomes After

1027   Epilepsy Surgery. Front Cell Dev Biol. 2022 Jan 21;9.

1028   104.   Wang J, Guo K, Cui B, Hou Y, Zhao G, Lu J. Individual [18F]FDG PET and functional MRI based

1029   on simultaneous PET/MRI may predict seizure recurrence after temporal lobe epilepsy

1030   surgery. Eur Radiol. 2022 Jun 1;32(6):3880–8.

1031   105.   Lin Y, Mo J, Jin H, Cao X, Zhao Y, Wu C, et al. Automatic analysis of integrated magnetic

1032   resonance and positron emission tomography images improves the accuracy of detection of

1033   focal cortical dysplasia type IIb lesions. European Journal of Neuroscience. 2021 May

1034   1;53(9):3231–41.

1035   106.   Tan YL, Kim H, Lee S, Tihan T, Ver Hoef L, Mueller SG, et al. Quantitative surface analysis of

1036   combined MRI and PET enhances detection of focal cortical dysplasias. Neuroimage. 2018 Feb

1037   1;166:10–8.

1038   107.   Tang CC, Poston KL, Eckert T, Feigin A, Frucht S, Gudesblatt M, et al. Differential diagnosis of

1039   parkinsonism: a metabolic imaging study using pattern analysis. Lancet Neurol. 2010

1040   Feb;9(2):149–58.

1041   108.   Aberathne I, Kulasiri D, Samarasinghe S. Detection of Alzheimer's disease onset using MRI

1042   and PET neuroimaging: longitudinal data analysis and machine learning. Vol. 18, Neural

1043   Regeneration Research. Wolters Kluwer Medknow Publications; 2023. p. 2134–40.

1044   109.   Franzmeier N, Koutsouleris N, Benzinger T, Goate A, Karch CM, Fagan AM, et al. Predicting

1045   sporadic Alzheimer's disease progression via inherited Alzheimer's disease-informed

1046   machine-learning. Alzheimer's and Dementia. 2020 Mar 1;16(3):501–11.

1047   110.   Katako A, Shelton P, Goertzen AL, Levin D, Bybel B, Aljuaid M, et al. Machine learning

1048   identified an Alzheimer's disease-related FDG-PET pattern which is also expressed in Lewy

1049   body dementia and Parkinson's disease dementia. Sci Rep. 2018 Dec 1;8(1).

1050   111.   Saito Y, Kamagata K, Wijeratne PA, Andica C, Uchida W, Takabayashi K, et al. Temporal

1051   Progression Patterns of Brain Atrophy in Corticobasal Syndrome and Progressive

1052   Supranuclear Palsy Revealed by Subtype and Stage Inference (SuStaIn). Front Neurol. 2022

1053   Feb 25;13.

1054   112.   Giorgio J, Jagust WJ, Baker S, Landau SM, Tino P, Kourtzi Z. A robust and interpretable

1055   machine learning approach using multimodal biological data to predict future pathological

1056   tau accumulation. Nat Commun. 2022 Dec 1;13(1).

1057   113.   Van Weehaeghe D, Ceccarini J, Delva A, Robberecht W, Van Damme P, Van Laere K.

1058   Prospective validation of 18F-FDG brain PET discriminant analysis methods in the diagnosis of

1059   amyotrophic lateral sclerosis. Journal of Nuclear Medicine. 2016 Aug 1;57(8):1238–43.

1060   114.   Basaia S, Agosta F, Wagner L, Canu E, Magnani G, Santangelo R, et al. Automated

1061   classification of Alzheimer's disease and mild cognitive impairment using a single MRI and

1062   deep neural networks. Neuroimage Clin. 2019 Jan 1;21.

1063   115.   Vogel JW, Young AL, Oxtoby NP, Smith R, Ossenkoppele R, Strandberg OT, et al. Four distinct

1064   trajectories of tau deposition identified in Alzheimer's disease. Nat Med. 2021 May

1065   1;27(5):871–81.

1066   116.   Wang Y, Yu B, Wang L, Zu C, Lalush DS, Lin W, et al. 3D conditional generative adversarial

1067   networks for high-quality PET image estimation at low dose. Neuroimage. 2018 Jul

1068   1;174:550–62.

1069   117.   Lee R, Choi H, Park KY, Kim JM, Seok JW. Prediction of post-stroke cognitive impairment using

1070   brain FDG PET: deep learning-based approach. Eur J Nucl Med Mol Imaging. 2022 Mar

1071   1;49(4):1254–62.

1072   118.   Wu P, Zhao Y, Wu J, Brendel M, Lu J, Ge J, et al. Differential Diagnosis of Parkinsonism Based

1073   on Deep Metabolic Imaging Indices. J Nucl Med. 2022 Nov 1;63(11):1741–7.

1074   119.   Choi H, Lee DS. Generation of structural MR images from amyloid PET: Application to MR-less

1075   quantification. Journal of Nuclear Medicine. 2018 Jul 1;59(7):1111–7.

1076   120.   Wang R, Liu H, Toyonaga T, Shi L, Wu J, Onofrey JA, et al. Generation of synthetic PET images

1077   of synaptic density and amyloid from 18F-FDG images using deep learning. Med Phys. 2021

1078   Sep 1;48(9):5115–29.

1079   121.   Hong J, Kang SK, Alberts I, Lu J, Sznitman R, Lee JS, et al. Image-level trajectory inference of
1080   tau pathology using variational autoencoder for Flortaucipir PET. Eur J Nucl Med Mol Imaging.
1081   2022 Jul 1;49(9):3061–72.

1082   122.   Suk H Il, Lee SW, Shen D. Latent feature representation with stacked auto-encoder for
1083   AD/MCI diagnosis. Brain Struct Funct. 2015 Mar 1;220(2):841–59.

1084   123.   Esteva A, Kuprel B, Novoa RA, Ko J, Swetter SM, Blau HM, et al. Dermatologist-level
1085   classification of skin cancer with deep neural networks. Nature. 2017 Feb 2;542(7639):115–8.

1086   124.   Zhao Y, Wu P, Wu J, Brendel M, Lu J, Ge J, et al. Decoding the dopamine transporter imaging
1087   for the differential diagnosis of parkinsonism using deep learning. Eur J Nucl Med Mol
1088   Imaging. 2022 Jul 1;49(8):2798–811.

1089   125.   Roy AG, Conjeti S, Navab N, Wachinger C. QuickNAT: A Fully Convolutional Network for Quick
1090   and Accurate Segmentation of Neuroanatomy [Internet]. 2018. Available from:
1091   https://www.sciencedirect.com/science/article/pii/S1053811918321232

1092   126.   Choi H, Ha S, Kang H, Lee H, Lee DS. Deep learning only by normal brain PET identify
1093   unheralded brain anomalies. EBioMedicine. 2019 May 1;43:447–53.

1094   127.   Qiu S, Miller MI, Joshi PS, Lee JC, Xue C, Ni Y, et al. Multimodal deep learning for Alzheimer's
1095   disease dementia assessment. Nat Commun. 2022 Dec 1;13(1).

1096   128.   Ryoo HG, Byun JI, Choi H, Jung KY. Deep learning signature of brain [18F]FDG PET associated
1097   with cognitive outcome of rapid eye movement sleep behavior disorder. Sci Rep. 2022 Dec
1098   1;12(1).

1099   129.   Lu D, Popuri K, Ding GW, Balachandar R, Beg MF, Weiner M, et al. Multimodal and Multiscale
1100   Deep Neural Networks for the Early Diagnosis of Alzheimer's Disease using structural MR and
1101   FDG-PET images. Sci Rep. 2018 Dec 1;8(1).

1102   130.   Ding Y, Sohn JH, Kawczynski MG, Trivedi H, Harnish R, Jenkins NW, et al. A deep learning
1103   model to predict a diagnosis of Alzheimer disease by using 18 F-FDG PET of the brain.
1104   Radiology. 2019 Mar 1;290(3):456–64.

1105   131.   Son HJ, Oh JS, Oh M, Kim SJ, Lee JH, Roh JH, et al. The clinical feasibility of deep learning-

1106   based classification of amyloid PET images in visually equivocal cases. Eur J Nucl Med Mol

1107   Imaging. 2020 Feb 1;47(2):332–41.

1108   132.   Park SW, Yeo NY, Kim Y, Byeon G, Jang JW. Deep learning application for the classification of

1109   Alzheimer's disease using 18F-flortaucipir (AV-1451) tau positron emission tomography. Sci

1110   Rep. 2023 Dec 1;13(1).

1111   133.   Jo T, Nho K, Risacher SL, Saykin AJ. Deep learning detection of informative features in tau PET

1112   for Alzheimer's disease classification. BMC Bioinformatics. 2020 Dec 1;21.

1113   134.   Shen T, Jiang J, Lin W, Ge J, Wu P, Zhou Y, et al. Use of overlapping group LASSO sparse deep

1114   belief network to discriminate Parkinson's disease and normal control. Front Neurosci.

1115   2019;13(APR).

1116   135.   Wenzel M, Milletari F, Krüger J, Lange C, Schenk M, Apostolova I, et al. Automatic

1117   classification of dopamine transporter SPECT: deep convolutional neural networks can be

1118   trained to be robust with respect to variable image characteristics. Eur J Nucl Med Mol

1119   Imaging. 2019 Dec 1;46(13):2800–11.

1120   136.   Adams MP, Rahmim A, Tang J. Improved Motor Outcome Prediction in Parkinson's Disease

1121   Applying Deep Learning to DaTscan SPECT Images. 2021.

1122   137.   Marius De Vries B, Golla SS V, Ebenau J, Verfaillie SCJ, Timmers T, Heeman F, et al.

1123   Classification of negative and positive 18 F-florbetapir brain PET studies in subjective

1124   cognitive decline patients using a convolutional neural network. Eur J Nucl Med Mol Imaging

1125   [Internet]. 2021;48:721–8. Available from: https://doi.org/10.1007/s00259-020-05006-3

1126   138.   Choi H, Kim YK, Yoon EJ, Lee JY, Lee DS. Cognitive signature of brain FDG PET based on deep

1127   learning: domain transfer from Alzheimer's disease to Parkinson's disease. Eur J Nucl Med

1128   Mol Imaging. 2020 Feb 1;47(2):403–12.

1129   139.   Reith FH, Mormino EC, Zaharchuk G. Predicting future amyloid biomarkers in dementia

1130   patients with machine learning to improve clinical trial patient selection. Alzheimer's and

1131   Dementia: Translational Research and Clinical Interventions. 2021;7(1).

1132   140.   Shah J, Gao F, Li B, Ghisays V, Luo J, Chen Y, et al. Deep residual inception encoder-decoder

1133   network for amyloid PET harmonization. Alzheimer's and Dementia. 2022 Dec 1;18(12):2448–

1134   57.

1135   141.   Kim S, Lee P, Oh KT, Byun MS, Yi D, Lee JH, et al. Deep learning-based amyloid PET positivity

1136   classification model in the Alzheimer's disease continuum by using 2-[18F]FDG PET. EJNMMI

1137   Res. 2021;11(1).

1138   142.   Royse SK, Minhas DS, Lopresti BJ, Murphy A, Ward T, Koeppe RA, et al. Validation of amyloid

1139   PET positivity thresholds in centiloids: a multisite PET study approach. Alzheimers Res Ther.

1140   2021 Dec 1;13(1).

1141   143.   Ossenkoppele R, Reimand J, Smith R, Leuzy A, Strandberg O, Palmqvist S, et al. Tau PET

1142   correlates with different Alzheimer's disease-related features compared to CSF and plasma p-

1143   tau biomarkers. EMBO Mol Med [Internet]. 2021 Aug 9;13(8). Available from:

1144   https://www.embopress.org/doi/10.15252/emmm.202114398

1145   144.   Coughlin JM, Horti AG, Pomper MG. Opportunities in precision psychiatry using PET

1146   neuroimaging in psychosis. Vol. 131, Neurobiology of Disease. Academic Press Inc.; 2019.

1147   145.   Henderson TA, van Lierop MJ, McLean M, Uszler JM, Thornton JF, Siow YH, et al. Functional

1148   Neuroimaging in Psychiatry—Aiding in Diagnosis and Guiding Treatment. What the American

1149   Psychiatric Association Does Not Know. Vol. 11, Frontiers in Psychiatry. Frontiers Media S.A.;

1150   2020.

1151   146.   Hellwig S, Domschke K. Update on PET imaging biomarkers in the diagnosis of

1152   neuropsychiatric disorders. Vol. 32, Current Opinion in Neurology. Lippincott Williams and

1153   Wilkins; 2019. p. 539–47.

1154 147. Pagani M, Carletto S, Ostacoli L. PET and SPECT in psychiatry: the past and the future. Vol. 46,

1155   European Journal of Nuclear Medicine and Molecular Imaging. Springer Berlin Heidelberg;

1156   2019. p. 1985–7.

1157 148. Tastevin M, Richieri R, Boyer L, Fond G, Lançon C, Guedj E. Brain PET metabolic substrate of

1158   TMS response in pharmaco-resistant depression. Vol. 13, Brain Stimulation. Elsevier Inc.;

1159   2020. p. 683–5.

1160 149. Fu CHY, Erus G, Fan Y, Antoniades M, Arnone D, Arnott SR, et al. AI-based dimensional

1161   neuroimaging system for characterizing heterogeneity in brain structure and function in

1162   major depressive disorder: COORDINATE-MDD consortium design and rationale. BMC

1163   Psychiatry. 2023 Dec 1;23(1).

1164 150. Boyle AJ, Gaudet VC, Black SE, Vasdev N, Rosa-Neto P, Zukotynski KA. Artificial intelligence for

1165   molecular neuroimaging. Ann Transl Med. 2021 May;9(9):822–822.

1166 151. Kautzky A, Vanicek T, Philippe C, Kranz GS, Wadsak W, Mitterhauser M, et al. Machine

1167   learning classification of ADHD and HC by multimodal serotonergic data. Transl Psychiatry.

1168   2020 Dec 1;10(1).

1169 152. Mete M, Sakoglu U, Spence JS, Devous MD, Harris TS, Adinoff B. Successful classification of

1170   cocaine dependence using brain imaging: A generalizable machine learning approach. BMC

1171   Bioinformatics. 2016 Oct 6;17.

1172 153. Jeong B, Lee J, Kim H, Gwak S, Kim YK, Yoo SY, et al. Multiple-Kernel Support Vector Machine

1173   for Predicting Internet Gaming Disorder Using Multimodal Fusion of PET, EEG, and Clinical

1174   Features. Front Neurosci. 2022 Jun 30;16.

1175 154. Kautzky A, James GM, Philippe C, Baldinger-Melich P, Kraus C, Kranz GS, et al. The influence

1176   of the rs6295 gene polymorphism on serotonin-1A receptor distribution investigated with

1177   PET in patients with major depression applying machine learning. Transl Psychiatry.

1178   2017;7(6).

51

1179   155.   Brown EC, Clark DL, Forkert ND, Molnar CP, Kiss ZHT, Ramasubbu R. Metabolic activity in

1180   subcallosal cingulate predicts response to deep brain stimulation for depression.

1181   Neuropsychopharmacology. 2020 Sep 1;45(10):1681–8.

1182   156.   Veronese M, Santangelo B, Jauhar S, D'Ambrosio E, Demjaha A, Salimbeni H, et al. A potential

1183   biomarker for treatment stratification in psychosis: evaluation of an [18F] FDOPA PET imaging

1184   approach. Neuropsychopharmacology. 2021 May 1;46(6):1122–32.

1185   157.   Kotter E, Ranschaert E. Challenges and solutions for introducing artificial intelligence (AI) in

1186   daily clinical workflow. Available from: https://doi.org/

1187   158.   Pianykh OS, Langs G, Dewey M, Enzmann DR, Herold CJ, Schoenberg SO, et al. Continuous

1188   learning AI in radiology: Implementation principles and early applications. Vol. 297,

1189   Radiology. Radiological Society of North America Inc.; 2020. p. 6–14.

1190   159.   Zwanenburg A, Vallières M, Abdalah MA, Aerts HJWL, Andrearczyk V, Apte A, et al. The image

1191   biomarker standardization initiative: Standardized quantitative radiomics for high-throughput

1192   image-based phenotyping. Radiology. 2020 May 1;295(2):328–38.

1193   160.   Zhou Z, Firestone C. Humans can decipher adversarial images. Nat Commun. 2019 Dec

1194   1;10(1).

1195   161.   Barucci A, Neri E. Adversarial radiomics: the rising of potential risks in medical imaging from

1196   adversarial learning. Vol. 47, European Journal of Nuclear Medicine and Molecular Imaging.

1197   Springer Science and Business Media Deutschland GmbH; 2020. p. 2941–3.

1198   162.   Monsour R. Neuroimaging in the Era of Artificial Intelligence: Current Applications. Federal

1199   Practitioner. 2022 Apr 11;(39 (Suppl 1)).

1200   163.   Xing L, Goetsch S, Cai J. Artificial intelligence should be part of medical physics graduate

1201   program curriculum. Med Phys. 2021 Apr 1;48(4):1457–60.

1202   164.   Sahni NR, Carrus B. Artificial Intelligence in U.S. Health Care Delivery. Drazen JM, Kohane IS,

1203   Leong TY, editors. New England Journal of Medicine [Internet]. 2023 Jul 27;389(4):348–58.

1204   Available from: http://www.nejm.org/doi/10.1056/NEJMra2204673

1205   165.   Bates DW, Auerbach A, Schulam P, Wright A, Saria S. Reporting and implementing

1206   interventions involving machine learning and artificial intelligence. Ann Intern Med. 2020 Jun

1207   2;172(11):S137–44.

1208   166.   Adams R, Henry KE, Sridharan A, Soleimani H, Zhan A, Rawat N, et al. Prospective, multi-site

1209   study of patient outcomes after implementation of the TREWS machine learning-based early

1210   warning system for sepsis. Nat Med. 2022 Jul 1;28(7):1455–60.

1211   167.   Sollini M, Antunovic L, Chiti A, Kirienko M. Towards clinical application of image mining: a

1212   systematic review on artificial intelligence and radiomics. Vol. 46, European Journal of

1213   Nuclear Medicine and Molecular Imaging. Springer; 2019. p. 2656–72.

1214   168.   Hustinx R, Pruim J, Lassmann M, Visvikis D. An EANM position paper on the application of

1215   artificial intelligence in nuclear medicine. Eur J Nucl Med Mol Imaging. 2022 Dec 1;50(1):61–

1216   6.

1217   169.   Buvat I, Orlhac F. The T.R.U.E. Checklist for identifying impactful artificial intelligence-based

1218   findings in nuclear medicine: Is it true? Is it reproducible? Is it useful? Is it explainable? Vol.

1219   62, Journal of Nuclear Medicine. Society of Nuclear Medicine Inc.; 2021. p. 752–4.

1220   170.   Currie G, Hawk KE, Rohren EM. Ethical principles for the application of artificial intelligence

1221   (AI) in nuclear medicine. Vol. 47, European Journal of Nuclear Medicine and Molecular

1222   Imaging. Springer; 2020. p. 748–52.

1223