# Emerging role of artificial intelligence in nuclear medicine

**Citation for published version (APA):**

Jha, A. K., Mithun, S., Rangarajan, V., Wee, L., & Dekker, A. (2021). Emerging role of artificial intelligence in nuclear medicine. *Nuclear Medicine Communications*, *42*(6), 592-601. https://doi.org/10.1097/MNM.0000000000001381

**Document status and date:**
Published: 01/06/2021

**DOI:**
10.1097/MNM.0000000000001381

**Document Version:**
Publisher's PDF, also known as Version of record

**Document license:**
Taverne

Review article

Nuclear Medicine Communications

# Emerging role of artificial intelligence in nuclear medicine

Ashish Kumar Jha[a,b,c], Sneha Mithun[a,b,c], Venkatesh Rangarajan[b,c], Leonard Wee[a] and Andre Dekker[a]

**The role of artificial intelligence is increasing in all branches of medicine. The emerging role of artificial intelligence applications in nuclear medicine is going to improve the nuclear medicine clinical workflow in the coming years. Initial research outcomes are suggestive of increasing role of artificial intelligence in nuclear medicine workflow, particularly where selective automation tasks are of concern. Artificial intelligence-assisted planning, dosimetry and procedure execution appear to be areas for rapid and significant development. The role of artificial intelligence in more directly imaging-related tasks, such as dose optimization, image corrections and image reconstruction, have been particularly strong points of artificial intelligence research in nuclear medicine. Natural Language Processing (NLP)-based text processing task is another area of interest of artificial intelligence implementation in nuclear medicine.** ***Nucl Med Commun*** **42: 592–601** 

**Nuclear Medicine Communications** 2021, **42**:592–601

**Keywords: artificial intelligence, machine learning, nuclear medicine, natural language processing, radiomics**

[a]Department of Radiation Oncology (Maastro), GROW School for Oncology, Maastricht University Medical Centre, Maastricht, The Netherlands, [b]Department of Nuclear Medicine and Molecular Imaging, Tata Memorial Hospital and [c]Homi Bhabha National Institute (HBNI), Deemed University, Mumbai, India

Correspondence to Ashish Kumar Jha, MSc, Department of Nuclear Medicine, Tata Memorial Hospital, Dr. Ernest Borges Road, Parel, Mumbai 400012, India
E-mail: ashish.kumar.jha.77@gmail.com

**Received** 2 December 2020 **Accepted** 15 January 2021



## Introduction

Artificial intelligence applied to clinical workflows and personalized cancer care has attracted immense attention in recent years [1–3]. The strong appeal of artificial intelligence is due in large part to its potential for significantly speeding up mundane clinical tasks through selective automation. In various domains of cancer care, artificial intelligence tools have shown potential to assist with automated diagnosis, segmentations of normal organs and tumor volumes, complex image transformation and interpretation, automated processing of textural reports, as well as other tasks that were previously thought to be the exclusive preserve of human experts. The other strong appeal of artificial intelligence is its potential to 'mine' for diagnostic or prognostic patterns (i.e. a 'signature') among a very large number of potential variables in order to make a reliable prediction of outcome.

In the scope of this article, artificial intelligence shall be defined as a scientific study of mathematical processes (i.e. algorithms) that are able to *approximate* a tightly confined aspect of human cognitive actions, without requiring constant and continuous control by a human operator. The mark of artificial intelligence is therefore computer applications that appear to demonstrate some degree of *autonomy*, *adaptability* and *agnosticism* towards the completion of a narrowly-defined function. Machine learning is a subfield of study in artificial intelligence involving training of mathematical and statistical algorithms, in order to generate the desired output when provided with a given set of inputs. It does so by being exposed to an extremely large number of repeated training episodes whereby the machine is conceptually 'penalized' for every incorrect output and 'rewarded' for every acceptable output. This dependency on a large number of training instances necessarily makes this type of artificial intelligence exceptionally sensitive to the volume, variety, velocity and veracity of the data on which it has to train on; these four V's are immediately recognizable as the signature hallmarks of 'big data' [4,5] (Fig. 1).

Diagnostic and interventional nuclear medicine departments routinely generate huge amounts of data in the form of medical images, text reports and interventional data. With current generation of hybrid scanners such as PET/computed tomography (PET/CT), PET/MRI and single-photon emission tomography (SPECT)/CT scanners, every patient encounter could generate several gigabytes of data in the form of images [6]. These images are interpreted by an imaging expert and textual data are also generated in the form of diagnostic reports. A significant amount of intervention data is also generated in nuclear medicine every day in the form of clinical reports and predosimetry/postdosimetry calculations. Recently, several mathematical algorithms have been developed to extract a vast number of quantitative tumor metrics from medical images in the form of 'radiomic features' [7]. Nuclear medicine data generation is therefore vast, fast, diversified and also highly variable in interpretation, due to human expert subjectivity and variety of scanners from several vendors. Hence, nuclear medicine data clearly qualifies as big data, that satisfies all of the so-called '4 V's' [8].

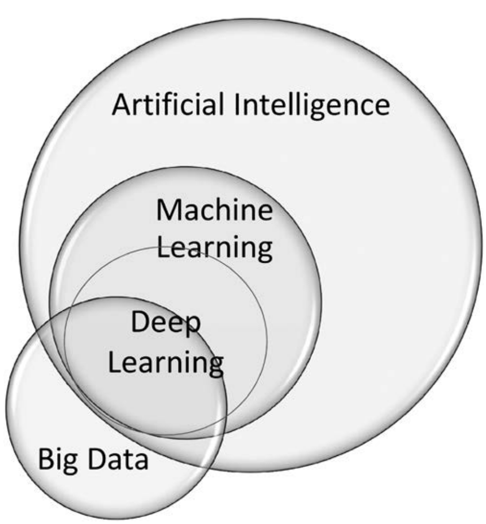

DOI: 10.1097/MNM.0000000000001381

With particular attention to the big imaging data that is found in nuclear medicine, a subfield of machine learning, known as deep learning, has become an extremely powerful artificial intelligence tool for image processing and image analysis. Deep learning algorithms learn composition of data that is represented in a hierarchy of structures of simpler features as a representation of the complex data [5,9]. Deep learning neural networks exploit a vast number of extremely simple computational units, called artificial neurons, which are organized in deep stacks of interconnecting layers [9–11]. Specific deep learning architectures known as convolutional neural networks (CNNs) have been shown to be extremely adaptable to general image-based tasks such as segmentation, object detection and object classification [9–11].

## Radiomics

Radiomics refers to the automated extraction and analysis of quantitative features of an image, such as a PET or a CT, in order to recognize potentially useful diagnostic or prognostic signatures [7]. Therefore, radiomics draws very heavily from technology in both machine learning and deep learning domains, to derive statistical prediction models from ultra-high dimensionality data using regression, decision trees, principal components analysis and ever increasing in recent years, deep learning. The radiomics hypothesis posits that medical images are not simply pictures for qualitative interpretation [7], but can be directly converted into minable data that could be used for personalized cancer care [12]. A typical radiomics analysis cycle is schematically summarized in Fig. 2. This involves the extraction of the region of interest on the image, preprocessing (such as digital image filters and resampling, among others), feature extraction and finally model development with validation [13].

**Fig. 1**




Interdependency of artificial intelligence, machine learning, deep learning and big data.

## Natural Language Processing

Natural Language Processing (NLP) employs machine learning and deep learning tools to aid in the extraction of structured data from natural language sources, such as recorded speech or written text reports or both. There are various well-established applications of NLP in diagnostic and clinical text processing in nuclear medicine such as report classification, report interpretation, sentiment analysis and text generation, etc. [14]. The NLP workflow consists of various steps and is summarized in Fig. 3. The text is first preprocessed by various processes like segmentation in which the text is segmented for sections and sentences. Then certain preposition and conjunction words are removed (stop-word removal). The remaining words are tokenized and normalized by linking to the root word (tokenization and word normalization). The text is then analyzed for grammar and part of speech (syntactic analysis). This is then subject to named entity recognition, concept recognition and relation extraction using relevant ontologies (semantic analysis). Relevant concepts maybe checked for negation using negation detection algorithms. Text features are then extracted and vectorized. The extracted features are used in model development. Models maybe rule-based, machine learning-based or a hybrid of both. The models are developed for defined outcomes and require annotated corpus for training in case of supervised learning. The trained model then undergoes validation with internal data as well as external data. These models maybe developed and applied for the classification of problems, as a part of decision support systems, treatment outcome deduction, summarization or text/report generation.

## Applications of artificial intelligence in nuclear medicine

### Emergence of big data in cancer care

Over the past several years, continuous efforts have been expended to improve quality of patient care and accelerate the pace of cancer research through the ever-increasing use of artificial intelligence and medical big data informatics [15]. Large volumes of routine (standard of care) data related to cancer diagnosis, treatment planning and outcomes are stored as either structured or unstructured form within the confines of the hospital or clinic in the form of medical records [16]. The conversion of such highly granular patient's data into electronic formats has opened up a plethora of opportunities for the cancer research community.

However, realization of clinical and societal value from routine medical big data comes with attendant risks. First and foremost, patient confidentiality must be protected at all times [17,18]. Anonymization, pseudonymization and binding legal data-sharing contracts

**Fig. 2**

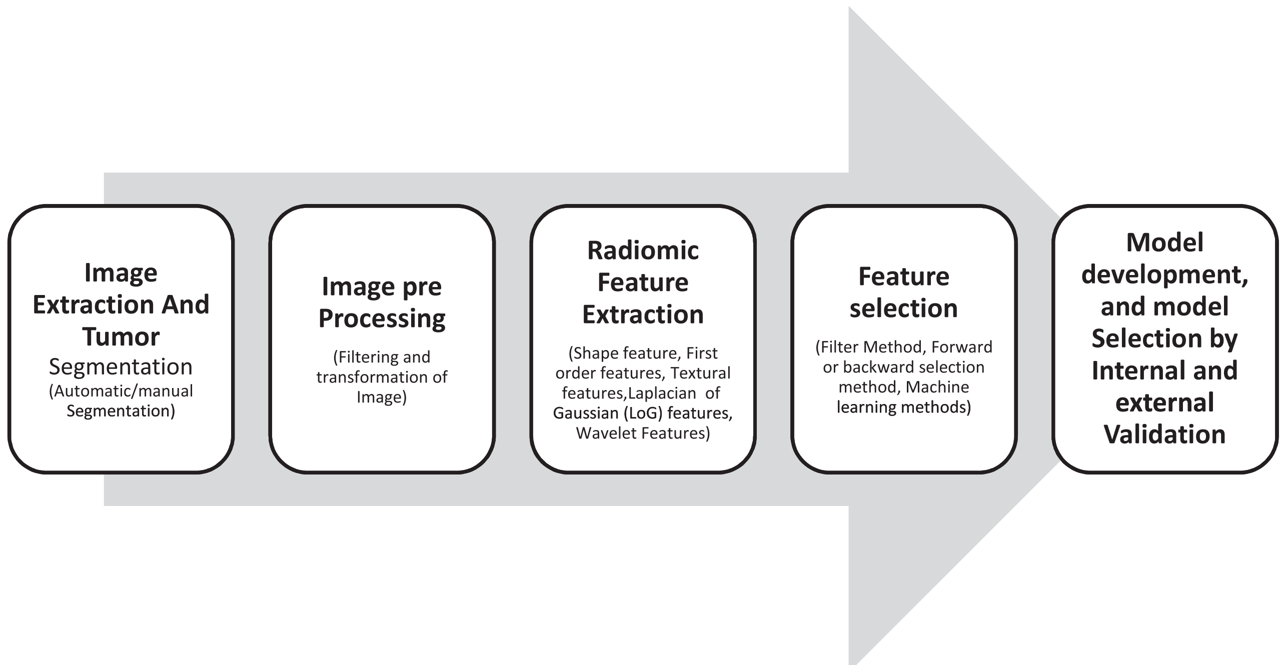



Figure describes radiomic process for radiomic feature extraction, feature selection, model development and model selection by validation process.

all go some way towards protecting confidentiality, and increasingly 'privacy-by-design' paradigms such as distributed learning and federated machine learning [19–21] are being used, where a diverse range of artificial intelligence algorithms can be successfully trained without exposing private individuals' identifiable information outside of the data providers' respective communications network firewalls [22–24]. Second, data quality and provenance issues due to missing data, inexact measurements and undocumented deviations from clinical protocol can lead to serious biases, lack of generalizability and potential patient harm, when developing artificial intelligence models on such data [25]. Last but not least, big data is plagued by interoperability issues such as different formatting standards, idiosyncratic data coding, language barriers and ambiguity in clinical meaning, thus limiting the utilization of this data. The growing impetus behind adherence to Findable-Accessible-Interoperable-Reusable data stewardship standards [26] are beginning to address such problems, thus gradually rendering more big data useable by automated artificial intelligence algorithms.

### Potential benefits of applied artificial intelligence in nuclear medicine

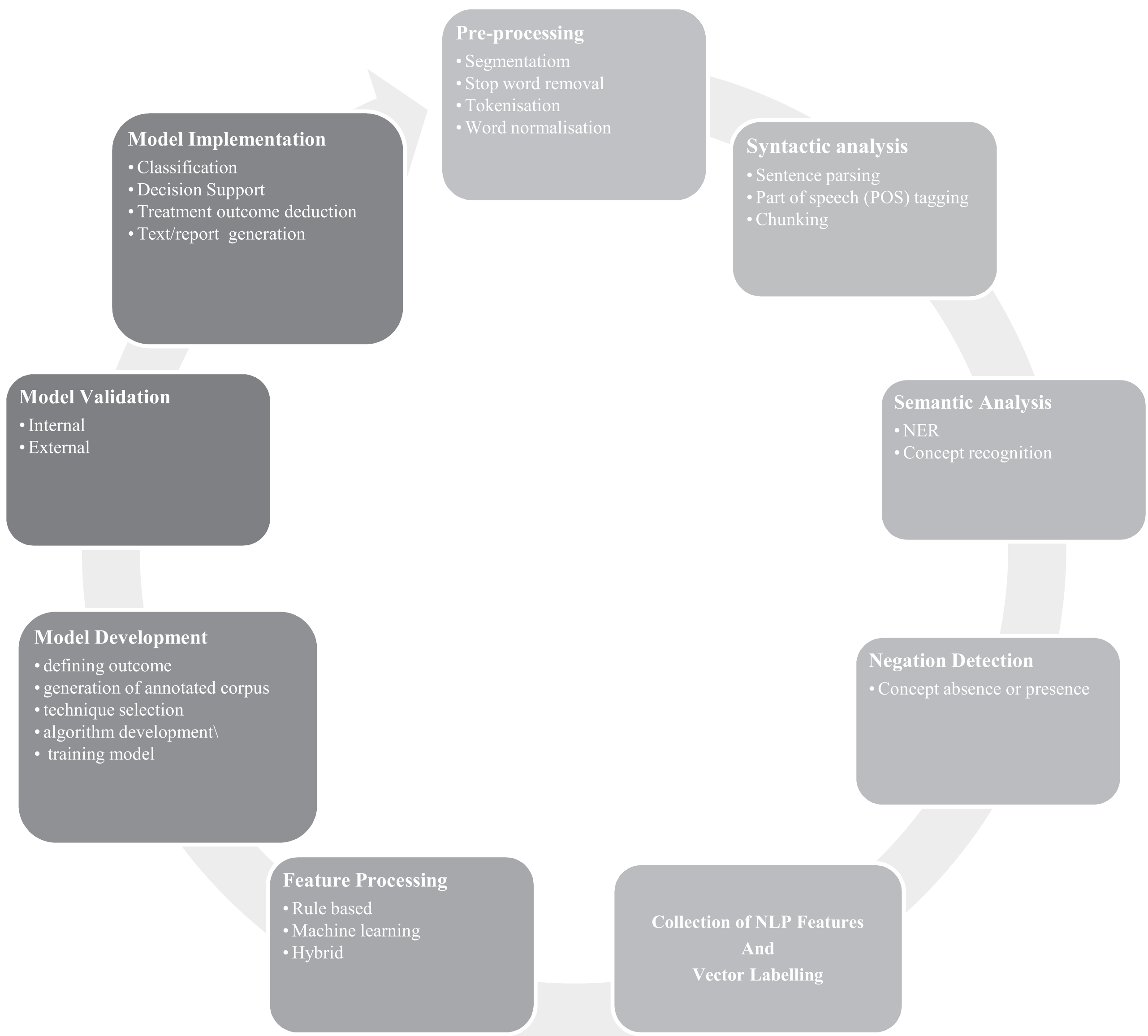
Several retrospective and prospective studies describe different approaches that could support earlier diagnosis and more accurate prognosis of cancer [27–29]. Various aspects of the clinical problem have been examined utilizing genomics, proteomics, radiomics and pathomics signatures [30,31]. These studies identify the potential as well as the limitations of these signatures for the prediction of cancer outcome. The vast majorities of these publications make use of one or more artificial intelligence algorithms, and further integrate data from heterogeneous sources for generating a prediction. The application of artificial intelligence to quantitative medical imaging has shown promising results in cancer diagnosis, prognosis of disease and treatment outcome prediction.

In the following sections, we will discuss the role of artificial intelligence in several parts of the nuclear medicine clinical workflow. The key area of artificial intelligence implementation in nuclear medicine may be grouped into the planning of procedure, execution of procedure, image reconstruction, image interpretation, report generation and implementation of clinical decision support system. These potential domains of application in nuclear medicine are summarized in Fig. 4 and are discussed in detail in the review.

## Planning of nuclear medicine procedure

Nuclear medicine procedures are associated with radiation exposure to the patient and are quite expensive. These procedures require patient specific-preparation (such as fasting prior to scan, cessation of insulin if diabetic, etc.) which has been challenging and required highly skilled human resources to juggle a large number

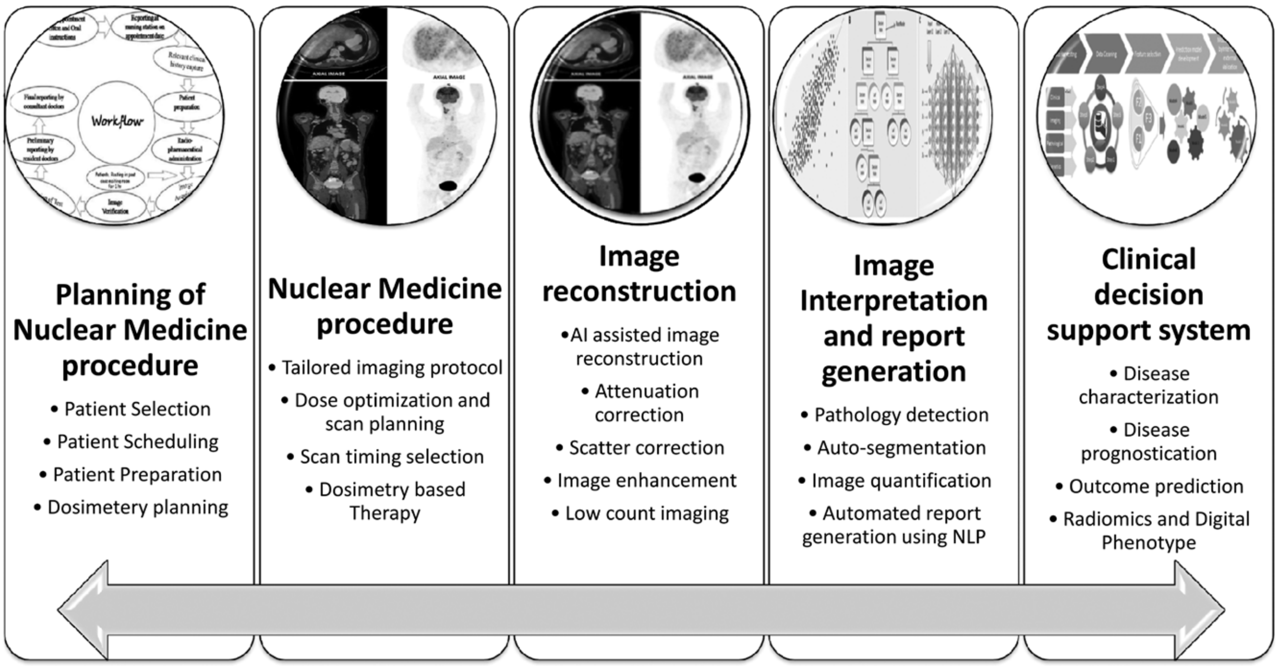
**Fig. 3**




Natural Language Processing (NLP) steps are summarized in this figure.

of these requirements [32]. Diagnostic and therapeutic dosimetry planning requires imaging at multiple time points, image processing and mathematical calculations, all of which are technically demanding and widely seen as a challenging clinical task for nuclear medicine professionals [33]. Artificial intelligence algorithms can play a significant role in optimizing patient scheduling, procedure selection, patient prescan preparation and pre-imaging/treatment dosimetry planning. Ansart *et al.* [34] showed that artificial intelligence-based screening of patients led to an increased number of recruitments as well as reducing the number of expensive PET scans in a clinical trial. Massachusetts General Hospital developed a prediction model using multivariate logistic regression to predict the show or no-show of patient for PET/CT scan [35]. Shi *et al.* [36] have shown that a trained artificial neural network can reduce the individual radiation dosimetry prediction error by between factor 4 and factor 10, in comparison with population-based dosimetry approach in Lu-177-based dosimetry assessment of tumor and various organs. Xie *et al.* [37] have utilized 3D deep convolutional network algorithm for automated segmentation of normal organ and fetus with Dice similarity coefficient between 0.92 and 0.98, which resulted in less than 1% difference in the radiation dose calculation for normal organ and fetus for various radiopharmaceuticals by conventional and artificial intelligence-based segmentation model.

**Fig. 4**




Potential domains of applications of artificial intelligence in the nuclear medicine clinical workflow.

## Optimization of nuclear medicine procedure

Modern generation scanners have started implementing various artificial intelligence approaches [38] that assist with optimization of image quality, scan time and radiation exposure during diagnostic nuclear medicine procedures. During therapeutic procedures, artificial intelligence-based automation can assist with pre-therapeutic and post-therapeutic dosimetry by using artificial intelligence-assisted organ and tumor segmentation, and prediction of either organ and/or tumor dose using single-point imaging, etc. [39,40]. Utilization of artificial intelligence in individualized dose assessment can assist a nuclear medicine physician to implement pre-therapeutic and post-therapeutic personalized dosimetry-based assessment, which is currently not done because the process is very lengthy, cumbersome and requires high expertise to perform the task.

During PET and SPECT examinations, we often require additional imaging or delayed imaging. For example, if a patient is scheduled for a PET scan but there is a lingering suspicion of brain metastasis, he/she may require an extended study that includes scans of the brain. This is currently a decision taken on the spot by a doctor or technologist, and image sets of such scenarios are available in the nuclear medicine department. These image sets can be used to train a deep learning artificial intelligence model to assist in decision making by predicting or scoring the likelihood of a brain metastasis actually being present.

In modern multidetector CT scanners, the tube current, and hence patient exposure, is being modulated in real-time, to minimize investigational radiation dose, but this is not patient-specific because the minimum and maximum tube currents are pre-defined such that the scanner modulates between the specified values [41]. The disadvantage of this is the dose delivered can only be known after the completion of the scan. An artificial intelligence-assisted system may allow us to perform real-time and patient-specific modulation of the tube current value to obtain the best image quality while optimally reducing radiation exposure to the patient [42].

The amount of radioisotope administered to a patient is currently calculated based on body weight, and there is ample margin for empirical (subjective) judgment. This could potentially lead to excess radiation (more than what is needed for the clinical purpose) or else to excessive noise and suboptimal image quality at lower radiation dose. An artificial intelligence-based radioisotope dosing system can be trained with the help of patient demographic data which can suggest the patient-specific required activity in a much more precise manner. This will reduce unnecessary radiation burden to the patient or avoid having to re-do suboptimal scans due to insufficient dose of activity administered.

## Image reconstruction

Nuclear medicine departments have been dealing with the balancing act between radiation doses, longer imaging times, low count density in images, low signal-to-noise ratio, high partial volume effect and low spatial resolution since its inception [43]. Advancements in instrumentation technology and reconstruction technology have addressed these concerns to some degree, in multidetector helical CT and high field-strength MRI [44]. Image reconstruction in nuclear medicine imaging is still unable to catch up to its other radiological imaging counterparts. Nuclear medicine imaging involves various computationally intensive steps including attenuation correction, scatter correction, noise correction and partial volume correction. Reconstruction algorithms in use today range from filtered back projection to newer techniques such as 3D Ordered Subset Expectation Maximization, row-action maximum likelihood algorithm, often in combination with advanced signal processing techniques like partial volume correction and time-of-flight (TOF) correction [45]. These techniques have substantially improved image quality in nuclear medicine without necessarily leading to higher dose in the patient.

Recent literature demonstrates a paradigm shift in image reconstruction in nuclear medicine imaging from analytic predetermined approaches towards a more adaptable, heuristic and potentially more patient-specific approach. Several researchers have examined artificial intelligence-based attenuation correction, scatter correction in PET and SPECT image reconstruction and extensive research is being performed to improve image quality of low count PET scan [46–50]. Hong *et al.* [46] used a CNN to enhance the image resolution of PET scans. Xiang *et al.* [47] have shown promising results with deep learning to improve the image quality with low dose and reduced scan time reconstruction during PET imaging. Wang *et al.* [48] demonstrated the utility of 3D deep convolutional network to predict high-dose PET scan using low administered activity. Kim *et al.* [49] used a de-noising deep learning network with local linear fitting to improve image quality of PET in an iterative reconstruction algorithm. Shiri *et al.* [50] demonstrated the utility of a deep learning residual network to synthetically generate a full-dose myocardial SPECT image from low-dose SPECT data as well as he also demonstrated the utility of artificial intelligence in prediction of full-time acquisition SPECT image from half time acquisition SPECT imaging data.

Multimodality fusion imaging with hybrid scanners has proven to be a significant breakthrough in medical imaging; modalities such as combined-PET/CT have now been established as the modality of choice for cancer imaging [51]. Combined-PET/MRI is another hybrid medical scanner that is rapidly growing its importance in cancer imaging, but it needed to overcome the challenges related to MRI-based attenuation correction in PET for accurate PET imaging and quantification [52]. This can be achieved in number of ways, including the use of deep learning to synthetically generate a radiation attenuation map (in effect, a synthetic CT) directly from MRI. Several analytical techniques have been tested to improve PET attenuation correction in PET/MRI scanners [52]. However, recent literature points towards a growing role of artificial intelligence [53–57] with a particularly active line of study in image corrections. Arabi *et al.* [53] have further shown the feasibility of deep learning to estimate the attenuation correction based solely on TOF PET emission data. Arabi *et al.* [54] also estimated the attenuation and scatter corrections simultaneously in a multitracer neuroimaging study. Shiri *et al.* [55], in a similar kind of study, used deep learning to estimate the joint scatter and attenuation correction in PET image. Hwang *et al.* used a deep learning neural network to apply a Maximum Likelihood reconstruction of Attenuation and Activity algorithm to jointly generate activity and attenuation maps using emission data [56]. Liu *et al.* [57] in another study have used the deep learning technique to generate the attenuation map for PET reconstruction using MRI images.

## Image interpretation and report generation

Image interpretation and reporting of scan are amongst the most important tasks in clinical nuclear medicine as it is in radiology. The entire process involves various steps as image reading, extraction of quantitative data, comparison of a scan with earlier scans (quantitatively and qualitatively), then reporting on the findings with (in general) a clinical interpretation of the significance of the findings. The potential of artificial intelligence here lies in the valuable time saving of nuclear medicine physicians by automatic execution of more mundane jobs in the preparation of the report. Like reading the patient's history from the electronic medical record, the consolidation of the history in the report, quantitative data extraction and comparison often consumes lots of time and leads to reduced output from an expert nuclear medicine physician or radiologist [58–60]. Artificial intelligence tools may be utilized to reduce this burden so that the expert can do more meaningful tasks like interpretation of finding, providing expert opinion and contributing to multimodality treatment groups [58–60].

NLP is an evolving technology that can assist with nuclear medicine report processing in many ways. Several studies have shown the use of NLP in text processing in radiology. Pons *et al.* [14], in their systematic review of literature of NLP in radiology reporting, have identified the potential use of NLP in diagnostic surveillance, cohort building for epidemiologic studies, query-based case retrieval, and quality assessment of radiology practice and clinical support services with level of evidence. These same clinical needs exist in nuclear medicine. Pinto *et al.* [61], in their narrative review, have also emphasized the potential importance of artificial intelligence in processing radiology reporting requirements as well as the importance of enforcing structured reporting to increase the use of artificial intelligence for radiology data-mining.

## Clinical decision support system

Nuclear medicine imaging plays an important role in personalized medicine. A theranostics concept is being used in radionuclide therapy to predict the efficacy of radionuclide therapy [62]. Various parameters like standardized uptake value (SUV), total lesion glycolysis (TLG) and PET Response Criteria in Solid Tumors (PERCIST), etc. have been utilized for disease outcome prognostication [63–65]. Mahadevaiah *et al*. [66] described the use of artificial intelligence in decision support systems in oncology, but very similar concepts will also hold for nuclear medicine. The potential role of artificial intelligence is being explored by several researchers working on the development of various kinds of prediction models for outcome predictions in oncology, such as overall survival (OS), progression-free survival (PFS), loco-regional recurrence, distant metastasis, treatment outcome, toxicity and treatment selection. These studies utilize a range of qualitative, semiquantitative (SUV, TLG and PERCIST) and radiomics features extracted from nuclear medicine images [67–74].

Radiomic features derived from nuclear medicine images have been proposed as a potential digital imaging phenotype for disease-specific personalized predictions of individual outcomes [13]. Sanduleanu *et al*. [67] used a univariate Cox model to show that [F-18]-HX4 PET/CT hypoxia uptake was able to prognose OS and local PFS in head and neck cancer patient treated by chemotherapy [Spearman's correlation coefficient ($\rho_S = 0.77$] ($P < 0.001$). In a multicenter study, Betancur *et al*. [68] showed that a CNN model trained using polar maps of myocardial perfusion imaging (MPI) from SPECT scanners outperformed the human expert diagnosis [area under the curve (AUC): 0.81 vs. 0.78] for detecting obstructive myocardial disease. In an extended study, Betancur *et al*. also developed a prediction model combining clinical information and MPI data to predict the 3-year probability of major cardiac events. They demonstrated that the machine learning technique outperformed clinical decision-making by medical experts (AUC: 0.81 vs. 0.65) for predicting major cardiac events in a cohort of 2619 consecutive patients [69]. A similar study by Rios *et al*. [70] also suggested an improvement of radiomics biomarkers over conventional risk factors (AUC: 0.793 vs. 0.698) when predicting major adverse cardiac events. Shiri *et al*. [71] used a combination of radiomics with genomic sequencing to predict presence of epidermal growth factor receptor (AUC: 0.82) and V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog (KRAS) (AUC: 0.83) mutations from images of nonsmall cell lung cancer (NSCLC) patients. Kidd *et al*. [72] developed an FDG PET-based nomogram (SUVmaximum value and lymph node status) to predict recurrence-free survival (C-stat: 0.741), disease-specific survival (C-stat: 0.739) and OS (C-stat: 0.658) for locally advanced cervical cancer. However, some studies have also reported the poor validation performance of radiomic-based prognostic models. Foley *et al*. [73] performed an external validation of a prognostic model for oesophageal cancer using quantitative PET features and radiomic features but found that these features were unable to discriminate between patient groups with different OS in an independent external validation cohort. van Timmeren *et al*. [74] also performed a multicenter radiomic-based study for treatment response assessment in NSCLC patients; they were able to demonstrate significance of FDG-PET/CT radiomic model in their individual-institution cohort but failed to reproduce this with a multicenter study.

## Summary of review

The emergence of artificial intelligence applications in nuclear medicine appears to be on the verge of contributing significantly throughout the clinical workflow atomization. Initial research suggests an increasing role of artificial intelligence in nuclear medicine imaging, particularly where selective automation of tasks are concerned. Artificial intelligence-assisted planning, dosimetry and procedure execution appear to be areas for rapid and significant development. The role of artificial intelligence in more directly imaging-related tasks, such as dose optimization, image corrections and image reconstruction, have been particularly strong points of artificial intelligence research in nuclear medicine. A further aspect of artificial intelligence research and implementation in nuclear medicine will be disease characterization, prognostication and potentially treatment outcome prediction. The new study of radiomics has been especially active in this field, leading towards the potential for identifying image-based digital signatures of oncological disease that can inform clinical decision-making, and therefore a stepping stone towards individualized cancer care. Artificial intelligence-assisted image interpretation based on deep learning neural networks have the potential to open up a new horizon in quantitative nuclear medicine, and could become a powerful future tool in the hands of nuclear medicine physicians and radiologists. Lastly, an aspect of artificial intelligence that still needs to develop strongly and could be of immense utility in nuclear medicine is domain-specific NLP. Complex NLP tools may help to automate the report generation and clinical interpretation tasks, and likely enrich the clinical interpretation with the aid of quantitative features from radiomics and deep learning analysis.

As a counterpoint to the promising potential future of artificial intelligence in nuclear medicine, one needs to be cognizant of the potential challenges and barriers to widespread artificial intelligence adoption in nuclear medicine clinics. Data, in vast quantities and with large dimensional variety, are the raw material for developing and testing artificial intelligence applications for nuclear medicine. While some data may be found in great abundance (e.g. PET and SPECT images), other types of data may be dispersed across other clinical departments (e.g. chemotherapy treatment details, or radiotherapy delineations, or long-term clinical follow-up) or have become disconnected completely from the radioisotope imaging due to suboptimal data management procedures. It is not simply the image data that needs to be curated and maintained with a view to long-term data sustainability, but it is also the metadata about the investigation that needs to be captured. For example, imaging settings, equipment and scanner software are likely to change rapidly over a short period of time, and we know that differences among vendors' equipment and variation in imaging parameters are a major concern that directly limits the wider applicability of radiomics models [75] and also of deep learning-based image analysis models [76].

A second major barrier to artificial intelligence applicability in nuclear medicine is one of clinical acceptability. This acceptability has two distinct dimensions; clinical acceptability and psychological acceptability. The former requires a detailed and practical process of selecting, commissioning and validating an artificial intelligence tool with realistic and as locally-specific clinical conditions as reasonably possible [66]. This necessarily entails staff training, ongoing quality assurance and careful integration of emerging artificial intelligence tools into the clinical environment with oversight for safety and ethical usage. The latter degree of acceptability is much harder to quantify and define; however, it relates directly to another major topic of research in artificial intelligence, that is, the degree of 'explainability' (or lack thereof) in an artificial intelligence-based decision support system [77]. While a clinician can readily and eloquently supply a rationale for his/her clinical decisions to a qualified peer, to a presiding judge or to an inquiring patient, certain types of artificial intelligence are still lacking in this fundamental rationalizing power of an 'explanation'. For instance, why exactly does an imaging-related signature lead an artificial intelligence-based system to recommend a particular course of action or to suggest a particularly unpleasant prognosis? The risk for the clinician is, either to act upon or else to over-ride such recommendations from an artificial intelligence system (particularly in a question of diagnosis, prognosis or treatment selection). Either of these feels potentially psychologically unsafe in the absence of suitable explanation or justification from an artificial intelligence-based system, leading to deep mistrust or lack of application of artificial intelligence-based nuclear medicine tools.

### Conclusion

The role of artificial intelligence is increasing in prominence in the clinical nuclear medicine workflow, starting from patient preparation to the development of decision support system in medicine. There appears to be ample evidence of development and advancement of artificial intelligence addressing nuclear medicine needs. This is pointing to an ever-increasing role of artificial intelligence in nuclear medicine. In the coming years, the computer science, informatics and clinical specialist fields need to collaborate closely to address some major hurdles related to the long-term sustainability of high-quality data (including imaging metadata) and clinical barriers to the adoption of artificial intelligence.

## Acknowledgements

A.K.J. drafted the article and was principally responsible for the content. S.M., R.K. and V.R. contributed to the review of literature. L.W. and A.D. contributed to the scientific concept, editing and proof-reading of the article.

### Conflicts of interest

This contribution of A.D. and L.W. were supported by The Netherlands Enterprise Agency (RVO) through the Indo-Dutch MWO/MeITy BIONIC project. For the remaining authors, there are no conflicts of interest.

## References

1 Bohr A, Memarzadeh K. The rise of artificial intelligence in healthcare applications. *Artif Intell Healthcare* 2020:25–60.
2 Jiang F, Jiang Y, Zhi H, Dong Y, Li H, Ma S, *et al.* Artificial intelligence in healthcare: past, present and future. *Stroke Vasc Neurol* 2017; **2**:230–243.
3 Wiens J, Shenoy ES. Machine learning for healthcare: on the verge of a major shift in healthcare epidemiology. *Clin Infect Dis* 2018; **66**:149–153.
4 Lee CH, Yoon HJ. Medical big data: promise and challenges. *Kidney Res Clin Pract* 2017; **36**:3–11.
5 Najafabadi MM, Villanustre F, Khoshgoftaar TM, Seliya N, Wald R, Muharemagic E. Deep learning applications and challenges in big data analytics. *J Big Data* 2015; **2**:1.
6 Kharat AT, Singhal S. A peek into the future of radiology using big data applications. *Indian J Radiol Imaging* 2017; **27**:241–248.
7 Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. *Radiology* 2016; **278**:563–577.
8 Morris MA, Saboury B, Burkett B, Gao J, Siegel EL. Reinventing radiology: big data and the future of medical imaging. *J Thorac Imaging* 2018; **33**:4–16.
9 LeCun Y, Bengio Y, Hinton G. Deep learning. *Nature* 2015; **521**:436–444.
10 Lee JG, Jun S, Cho YW, Lee H, Kim GB, Seo JB, Kim N. Deep learning in medical imaging: general overview. *Korean J Radiol* 2017; **18**:570–584.
11 Choi H. Deep learning in nuclear medicine and molecular imaging: current perspectives and future directions. *Nucl Med Mol Imaging* 2018; **52**:109–118.
12 Lambin P, Leijenaar RTH, Deist TM, Peerlings J, de Jong EEC, van Timmeren J, *et al.* Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017; **14**:749–762.
13 van Griethuysen JJM, Fedorov A, Parmar C, Hosny A, Aucoin N, Narayan V, *et al.* Computational radiomics system to decode the radiographic phenotype. *Cancer Res* 2017; **77**:e104–e107.
14 Pons E, Braun LM, Hunink MG, Kors JA. Natural Language Processing in radiology: a systematic review. *Radiology* 2016; **279**:329–343.
15 Liang G, Fan W, Luo H, Zhu X. The emerging roles of artificial intelligence in cancer drug development and precision therapy. *Biomed Pharmacother* 2020; **128**:110255.
16 Dekker AL, Gulliford SL, Ebert MA, Orton CG. Point/Counterpoint. Future radiotherapy practice will be based on evidence from retrospective interrogation of linked clinical data sources rather than prospective randomized controlled clinical trials. *Med Phys* 2014; **41**:030601.
17 Ienca M, Ferretti A, Hurst S, Puhan M, Lovis C, Vayena E. Considerations for ethics review of big data health research: a scoping review. *PLoS One* 2018; **13**:e0204937.
18 Institute of Medicine (US) Committee on Regional Health Data Networks; Donaldson MS, Lohr KN, editors. *Health Data in the Information Age: Use, Disclosure, and Privacy*. Washington (DC): National Academies Press (US); 1994. p. 4. Confidentiality and Privacy of Personal Data. https://www.ncbi.nlm.nih.gov/books/NBK236546/.
19 Sun C, Ippel L, van Soest J, Wouters B, Malic A, Adekunle O, *et al.* A privacy-preserving infrastructure for analyzing personal health data

in a vertically partitioned scenario. *Stud Health Technol Inform* 2019; **264**:373–377.
20 Kazmierska J, Hope A, Spezi E, Beddar S, Nailon WH, Osong B, *et al*. From multisource data to clinical decision aids in radiation oncology: the need for a clinical data science community. *Radiother Oncol* 2020; **153**:43–54.
21 Beyan O, Choudhury A, van Soest J, Kohlbacher O, Zimmermann L, Stenzhorn H, *et al*. Distributed analytics on sensitive medical data: the personal health train. *Data Intell* 2019; **2**:96–107.
22 Tegbaru D, Braverman L, Zietman AL, Yom SS, Lee WR, Miller RC, *et al*. ASTRO journals' data sharing policy and recommended best practices. *Adv Radiat Oncol* 2019; **4**:551–558.
23 Deist TM, Dankers FJWM, Ojha P, Scott Marshall M, Janssen T, Faivre-Finn C, *et al*. Distributed learning on 20 000+ lung cancer patients – the personal health train. *Radiother Oncol* 2020; **144**:189–200.
24 van Soest J, Sun C, Mussmann O, Puts M, van den Berg B, Malic A, *et al*. Using the personal health train for automated and privacy-preserving analytics on vertically partitioned data. *Stud Health Technol Inform* 2018; **247**:581–585.
25 Hamzah FB, Hamzah FM, Razali SFM, Jaafar O, Jamil NA. Imputation methods for recovering streamflow observation: a methodological review. *Cogent Environ Sci* 2020; **6**:1745133.
26 Wilkinson MD, Dumontier M, Aalbersberg IJ, Appleton G, Axton M, Baak A, *et al*. The FAIR guiding principles for scientific data management and stewardship. *Sci Data* 2016; **3**:160018.
27 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**:394–424.
28 Bruni L, Albero G, Serrano B, Mena M, Gómez D, Muñoz J, Bosch FX, de Sanjosé S. *ICO/IARC Information Centre on HPV and Cancer (HPV Information Centre). HumanPapillomavirus and Related Diseases in India. Summary Report.* 2019. https://hpvcentre.net/statistics/reports/IND.pdf. [Accessed 17 March, 2020].
29 Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, *et al*. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999; **340**:1144–1153.
30 Thomas GM. Improved treatment for cervical cancer–concurrent chemotherapy and radiotherapy. *N Engl J Med* 1999; **340**:1198–1200.
31 Yu KH, Snyder M. Omics profiling in precision oncology. *Mol Cell Proteomics* 2016; **15**:2525–2536.
32 Surasi DS, Bhambhvani P, Baldwin JA, Almodovar SE, O'Malley JP. $^{18}$F-FDG PET and PET/CT patient preparation: a review of the literature. *J Nucl Med Technol* 2014; **42**:5–13.
33 Sgouros G, Hobbs RF. Dosimetry for radiopharmaceutical therapy. *Semin Nucl Med* 2014; **44**:172–178.
34 Ansart M, Epelbaum S, Gagliardi G, Colliot O, Dormont D, Dubois B, *et al*.; Alzheimer's Disease Neuroimaging Initiative* and the INSIGHT-preAD study. Reduction of recruitment costs in preclinical AD trials: validation of automatic pre-screening algorithm for brain amyloidosis. *Stat Methods Med Res* 2020; **29**:151–164.
35 Harvey HB, Liu C, Ai J, Jaworsky C, Guerrier CE, Flores E, Pianykh O. Predicting no-shows in radiology using regression modeling of data available in the electronic medical record. *J Am Coll Radiol* 2017; **14**:1303–1309.
36 Shi K, Dong C, Gafita A, Zhao Y. Giles T. Artificial neural network for prediction of post-therapy dosimetry for $^{177}$Lu-PSMA I&T therapy. *J Nucl Med* 2019; **60** (Suppl 1):1185.
37 Xie T, Zaidi H. Estimation of the radiation dose in pregnancy: an automated patient-specific model using convolutional neural networks. *Eur Radiol* 2019; **29**:6805–6815.
38 Zhu B, Liu JZ, Cauley SF, Rosen BR, Rosen MS. Image reconstruction by domain-transform manifold learning. *Nature* 2018; **555**:487–492.
39 Xie T, Akhavanallaf A, Zaidi H. Construction of patient-specific computational models for organ dose estimation in radiological imaging. *Med Phys* 2019; **46**:2403–2411.
40 Xue S, Gafita A, Afshar-Oromieh A, Eiber M, Rominger A, Shi K. Voxel-wise prediction of post-therapy dosimetry for $^{177}$Lu-PSMA I&T therapy using deep learning. *J Nucl Med* 2020; **61** (Suppl 1):1424.
41 Lee CH, Goo JM, Ye HJ, Ye SJ, Park CM, Chun EJ, Im JG. Radiation dose modulation techniques in the multidetector CT era: from basics to practice. *Radiographics* 2008; **28**:1451–1459.
42 Chen H, Zhang Y, Kalra MK, Lin F, Chen Y, Liao P, *et al*. Low-dose CT with a residual encoder-decoder convolutional neural network. *IEEE Trans Med Imaging* 2017; **36**:2524–2535.
43 IAEA Human Health Series. *Quantitative Nuclear Medicine Imaging: concepts, Requirements And Methods*. Vienna: International Atomic Energy Agency; 2014. p. 24. https://www-pub.iaea.org/MTCD/Publications/PDF/Pub1605_web.pdf. [Accessed December 09, 2020].
44 Pichler BJ, Wehrl HF, Judenhofer MS. Latest advances in molecular imaging instrumentation. *J Nucl Med* 2008; **49**:5S–23S.
45 Ozsahin DU, Isa NA, Uzun B, Ozsahin I. Effective analysis of image reconstruction algorithms in nuclear medicine using fuzzy PROMETHEE. 2018 Advances in Science and Engineering Technology International Conferences (ASET); Abu Dhabi; 2018. pp. 1–5.
46 Hong X, Zan Y, Weng F, Tao W, Peng Q, Huang Q. Enhancing the image quality via transferred deep residual learning of coarse PET sinograms. *IEEE Trans Med Imaging* 2018; **37**:2322–2332.
47 Xiang L, Qiao Y, Nie D, An L, Wang Q, Shen D. Deep auto-context convolutional neural networks for standard-dose PET image estimation from low-dose PET/MRI. *Neurocomputing* 2017; **267**:406–416.
48 Wang Y, Yu B, Wang L, Zu C, Lalush DS, Lin W, *et al*. 3D conditional generative adversarial networks for high-quality PET image estimation at low dose. *Neuroimage* 2018; **174**:550–562.
49 Kim K, Wu D, Gong K, Dutta J, Kim JH, Son YD, *et al*. Penalized PET reconstruction using deep learning prior and local linear fitting. *IEEE Trans Med Imaging* 2018; **37**:1478–1487.
50 Shiri I, AmirMozafari Sabet K, Arabi H, Pourkeshavarz M, Teimourian B, Ay MR, Zaidi H. Standard SPECT myocardial perfusion estimation from half-time acquisitions using deep convolutional residual neural networks. *J Nucl Cardiol* 2020. doi: 10.1007/s12350-020-02119-y [Epub ahead of print]
51 Pinilla I, Rodríguez-Vigil B, Gómez-León N. Integrated FDG PET/CT: utility and applications in clinical oncology. *Clin Med Oncol* 2008; **2**:181–198.
52 Chen Y, An H. Attenuation correction of PET/MR imaging. *Magn Reson Imaging Clin N Am* 2017; **25**:245–255.
53 Arabi H, Zaidi H. Deep learning-guided estimation of attenuation correction factors from time-of-flight PET emission data. *Med Image Anal* 2020; **64**:101718.
54 Arabi H, Bortolin K, Ginovart N, Garibotto V, Zaidi H. Deep learning-guided joint attenuation and scatter correction in multitracer neuroimaging studies. *Hum Brain Mapp* 2020; **41**:3667–3679.
55 Shiri I, Arabi H, Geramifar P, Hajianfar G, Ghafarian P, Rahmim A, *et al*. Deep-JASC: joint attenuation and scatter correction in whole-body $^{18}$F-FDG PET using a deep residual network. *Eur J Nucl Med Mol Imaging* 2020; **47**:2533–2548.
56 Hwang D, Kang SK, Kim KY, Seo S, Paeng JC, Lee DS, Lee JS. Generation of PET attenuation map for whole-body time-of-flight $^{18}$F-FDG PET/MRI using a deep neural network trained with simultaneously reconstructed activity and attenuation maps. *J Nucl Med* 2019; **60**:1183–1189.
57 Liu F, Jang H, Kijowski R, Bradshaw T, McMillan AB. Deep learning MR imaging-based attenuation correction for PET/MR imaging. *Radiology* 2018; **286**:676–684.
58 Pesapane F, Codari M, Sardanelli F. Artificial intelligence in medical imaging: threat or opportunity? Radiologists again at the forefront of innovation in medicine. *Eur Radiol Exp* 2018; **2**:35.
59 Nensa F, Demircioglu A, Rischpler C. Artificial intelligence in nuclear medicine. *J Nucl Med* 2019; **60** (Suppl 2):29S–37S.
60 Seifert R, Weber M, Kocakavuk E, *et al*. AI and machine learning in nuclear medicine: future perspectives. *Semin Nucl Med* 2020. In press. doi: 10.1053/j.semnuclmed.2020.08.003
61 Pinto Dos Santos D, Baeßler B. Big data, artificial intelligence, and structured reporting. *Eur Radiol Exp* 2018; **2**:42.
62 Yordanova A, Eppard E, Kürpig S, Bundschuh RA, Schönberger S, Gonzalez-Carmona M, *et al*. Theranostics in nuclear medicine practice. *Onco Targets Ther* 2017; **10**:4821–4828.
63 Pankowska V, Malkowski B, Wedrowski M, Wedrowska E, Roszkowski K. FDG PET/CT as a survival prognostic factor in patients with advanced renal cell carcinoma. *Clin Exp Med* 2019; **19**:143–148.
64 Chen HH, Chiu NT, Su WC, Guo HR, Lee BF. Prognostic value of whole-body total lesion glycolysis at pretreatment FDG PET/CT in non-small cell lung cancer. *Radiology* 2012; **264**:559–566.
65 O JH, Lodge MA, Wahl RL. Practical PERCIST: a simplified guide to PET response criteria in solid tumors 1.0. *Radiology* 2016; **280**:576–584.
66 Mahadevaiah G, Rv P, Bermejo I, Jaffray D, Dekker A, Wee L. Artificial intelligence-based clinical decision support in modern medical physics: selection, acceptance, commissioning, and quality assurance. *Med Phys* 2020; **47**:e228–e235.
67 Sanduleanu S, Hamming-Vrieze O, Wesseling FWR, Even AJG, Hoebers FJ, Hoeben A, *et al*. [18F]-HX4 PET/CT hypoxia in patients with squamous cell carcinoma of the head and neck treated with chemoradiotherapy: prognostic results from two prospective trials. *Clin Transl Radiat Oncol* 2020; **23**:9–15.

68 Betancur J, Hu LH, Commandeur F, Sharir T, Einstein AJ, Fish MB, *et al*. Deep learning analysis of upright-supine high-efficiency SPECT myocardial perfusion imaging for prediction of obstructive coronary artery disease: a multicenter study. *J Nucl Med* 2019; **60**:664–670.
69 Betancur J, Otaki Y, Motwani M, Fish MB, Lemley M, Dey D, *et al*. Prognostic value of combined clinical and myocardial perfusion imaging data using machine learning. *JACC Cardiovasc Imaging* 2018; **11**:1000–1009.
70 Rios R, Hu LH, Einstein A, Sharir T. Prediction of major adverse cardiac events using reduced clinical features in machine learning: results from REFINE SPECT registry. *J Nucl Med* 2020; **61** (Suppl 1): 665.
71 Shiri I, Maleki H, Hajianfar G, Abdollahi H, Ashrafinia S, Hatt M, *et al*. Next-generation radiogenomics sequencing for prediction of EGFR and KRAS mutation status in NSCLC patients using multimodal imaging and machine learning algorithms. *Mol Imaging Biol* 2020; **22**:1132–1148.
72 Kidd EA, El Naqa I, Siegel BA, Dehdashti F, Grigsby PW. FDG-PET-based prognostic nomograms for locally advanced cervical cancer. *Gynecol Oncol* 2012; **127**:136–140.
73 Foley KG, Shi Z, Whybra P, Kalendralis P, Larue R, Berbee M, *et al*. External validation of a prognostic model incorporating quantitative PET image features in oesophageal cancer. *Radiother Oncol* 2019; **133**:205–212.
74 van Timmeren JE, Carvalho S, Leijenaar RTH, Troost EGC, van Elmpt W, de Ruysscher D, *et al*. Challenges and caveats of a multi-center retrospective radiomics study: an example of early treatment response assessment for NSCLC patients using FDG-PET/CT radiomics. *PLoS One* 2019; **14**:e0217536.
75 van Timmeren JE, Leijenaar RTH, van Elmpt W, Wang J, Zhang Z, Dekker A, Lambin P. Test-retest data for radiomics feature stability analysis: generalizable or study-specific? *Tomography* 2016; **2**:361–365.
76 Ker J, Wang L, Rao J, Lim T. Deep learning applications in medical image analysis. *IEEE Access* 2018; **6**:9375–9389.
77 Yang Z, Zhang A, Sudjianto A. Enhancing explainability of neural networks through architecture constraints. *IEEE Trans Neural Netw Learn Syst* 2020; **27**:1–12