

**Reviewer comment:**

The manuscript by Yin, et al is a narrative review of machine learning approaches in molecular imaging. This is overall a timely and well-written manuscript. I particularly like that the authors did not limit themselves to just nuclear medicine molecular imaging, but also included relevant information on optical imaging. Also, the detailed discussion of reconstruction methods will separate this paper from many other reviews in the future. There are some minor grammatical mistakes in the manuscript, but not so many that they detract from the overall quality. I have a few minor suggestions for the authors to consider.

*Reply:* We sincerely thank the reviewer for providing the great suggestions. We have revised the manuscript and a point-to-point response is listed below with all the changes clearly marked in the revision.

**Comment 1:** In the introduction, the phrase “The concept of molecular imaging (MI) was first proposed by Weissleder in 1999. . . .” is not exactly correct. Weissleder first suggested the term in the late 90s, but the concept has a more nebulous timeline. Perhaps a better was to say it is “The term molecular imaging (MI) first came into use in the late 1990s. . . .”

*Reply 1:* We thank the reviewer for pointing it out. The corresponding revision has been made in the first paragraph of the Introduction.

**Changes in the text:** “The term molecular imaging (MI) first came into use in the late 1990s, .....

**Comment 2:** In the introduction, “positron-emitting nuclides” would be preferred to “positron nuclides” and “single-photon-emitting nuclides” would be preferred to “single photon nuclides”.

*Reply 2:* We thank the reviewer for this suggestion and the corresponding change has been made in the fourth paragraph of the introduction.

**Changes in the text:** “PET relies on **positron-emitting nuclides** for imaging, mainly including  $^{18}\text{F}$ ,  $^{68}\text{Ga}$ , etc., while SPECT relies on **single-photon-emitting nuclides** and  $^{99\text{m}}\text{Tc}$  is mainly used in clinical applications.”

**Comment 3:** In the “Application of ML in PET” section, there are a couple of times that the authors use a present tense verb, e.g. “is proposed” or “are developed”. Please try to consistently use past tense and consider changing to “was proposed” or “were developed”.

*Reply 3:* Sorry for the typos and we have made corresponding revisions as suggested. The changes were listed below.

**Changes in the text:** “ $^{18}\text{F}$ -FET, a specific brain tumor imaging agent, significantly

*reduced* the background of the normal brain, and **improved** the contrast of tumor.” in the second paragraph of the “Application of ML in PET” section.

“Automated PET/CT segmentation trained with CNN **was** also used in the prostate cancer lesion uptake which **was** in association with overall survival.” in the second paragraph of the “Application of ML in PET” section.

“Recent studies based on ML approaches **could** automatically analyze data related to nuclear changes to assist diagnosis decision.” in the second paragraph of the “Application of ML in PET” section.

“Recently a ML model trained only by normal brain PET data was established and it **could** assist experts to identify and locate the abnormal patterns of PET images.” in the third paragraph of the “Application of ML in PET” section.

“A method based on deep convolutional neural network (DCNN) **was** proposed for CS classification.” in the fourth paragraph of the “Application of ML in PET” section.

“By applying CNN to FDG and AV-45 PET, a CNN-based method that **could** successfully predict cognitive decline **was** proposed. Several other in-depth learning algorithms combined with PET imaging **were** developed to predict cognitive performance and AD and it **was** very beneficial to the early treatment of patients.” in the eighth paragraph of the “Application of ML in PET” section.

**Comment 4:** Similar to the previous statement, in the “Application of ML in SPECT” section, there are some instances where the past tense should be used. For example, “patients undergo” should be “patients underwent”, etc.

**Reply 4:** Sorry for the typos and we have made corresponding revisions as suggested. The changes were listed below.

**Changes in the text:** “Usually manual adjustment is required to accurately locate the position of mitral valve plane (VP) in the left ventricle of heart and Julian Betancur et al. **developed** a ML method for fully automatic VP positioning in MPI without the need for expert intervention. One thousand patients **underwent** rest/stress SPECT MPI and the diagnostic performance of AI reporting system that **generated** a structured natural language report **was** comparable to the experts.” in the third paragraph of the “Application of ML in SPECT” section.

“Reza Arsanjani et al. established a ML algorithm to predict early revascularization which **was** comparable to or better than the experienced experts. Trained with 1638 patients (67% males) without known CAD, deep learning with MPI **made** better performance in the prediction of per-patient and per-vessel coronary artery disease (CAD) compared with current clinical methods in 2018. By integrating clinical and imaging data, ML could predict adverse cardiac events (MACE) risk in patients **underwent** SPECT MPI.” in the fourth paragraph of the “Application of ML in SPECT”

*section.*

**Comment 5:** I think some of the references are incomplete. For example, no journal is listed for reference 1 (should be Radiology). There are multiple other missing journals, authors, etc. If the authors could please make sure that all references match the journal recommended format.

**Reply 5:** *Thank you for pointing it out. We have revised the format of the references in accordance with the requirements of ATM.*

**Changes in the text:** *The changes have been marked in the **Reference** Section.*