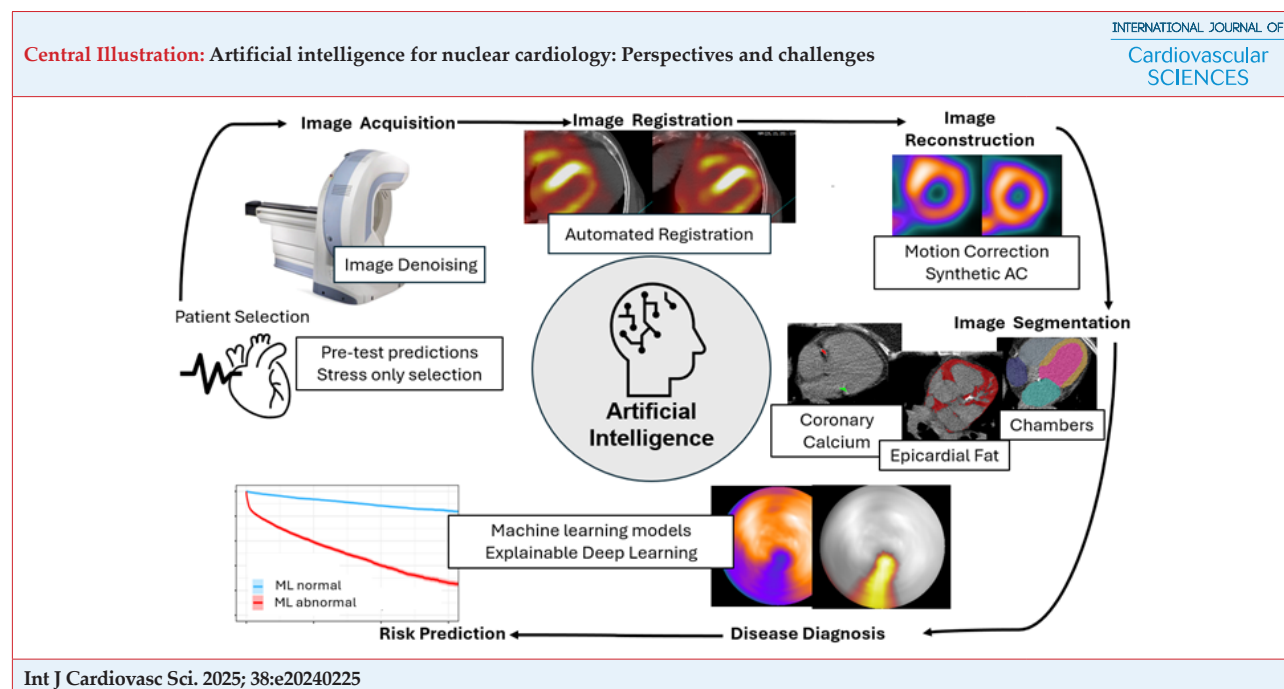


## REVIEW ARTICLE

## Artificial intelligence for nuclear cardiology: Perspectives and challenges

Caitlyn Gilbert,<sup>1,2</sup> Alec Chunta,<sup>1,3</sup> Robert Miller,<sup>1</sup>University of Calgary, Department of Cardiac Sciences,<sup>1</sup> Alberta – Canada

Potential roles for AI in nuclear cardiology. AI has the potential to be applied during every step of a typical scan. AC: attenuation correction; ML: machine learning

## Abstract

Recent advancements in artificial intelligence (AI) have significantly enhanced the efficiency and quality of nuclear cardiology imaging. AI algorithms, such as generative adversarial networks (GAN) and deep learning (DL) models, are improving image acquisition by reducing noise and correcting motion to minimize radiation exposure while maintaining diagnostic accuracy. AI has also demonstrated the potential to

create synthetic attenuation correction (AC) imaging, accounting for soft-tissue attenuation without added computed tomography (CT) imaging. In patients with CT attenuation imaging, AI can automate the segmentation of coronary artery calcification (CAC), epicardial adipose tissue (EAT), and other structures to maximize the clinical information obtained from these added studies. Furthermore, machine learning (ML) models that combine clinical, imaging, and stress test data are advancing risk prediction for coronary artery disease (CAD) and ischemia, assisting clinicians in decision-making and improving patient outcomes. While many of these applications have been developed using myocardial perfusion imaging (MPI), they are increasingly applied to other nuclear cardiology studies. This review explores

## Keywords

Artificial intelligence; Nuclear Medicine; Machine Learning; Deep Learning; Cardiac Imaging Techniques.

## Mailing Address: Robert Miller

University of Calgary. GAA08 Health Research innovation center 3230, Hospital Drive NW Calgary. Postal code: T2N 4Z6. Alberta – Canada.

E-mail: robert.miller@albertahealthservices.ca

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these AI applications and their impact on diagnostic accuracy, workflow efficiency, and risk stratification while also highlighting potential future directions and challenges.

## Introduction

Nuclear cardiology plays a prominent role in the management of patients with known or suspected cardiac disorders.<sup>1</sup> Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) myocardial perfusion imaging (MPI) are two of the most commonly used cardiac imaging tests for coronary artery disease (CAD), with established roles in disease diagnosis and risk prediction.<sup>1</sup> Nuclear cardiology also plays a central role in the diagnosis of other cardiovascular disorders, including cardiac amyloidosis, cardiac sarcoidosis, and microvascular disease.<sup>2</sup> However, to maintain this central role, nuclear cardiology must continue to improve diagnostic accuracy and expand on the information provided to clinicians. In this regard, artificial intelligence (AI) is transforming the field to address these needs.<sup>3</sup>

Highlighting recent advancements, this review aims to provide an updated perspective for clinicians and researchers. Following a brief review of AI terminology, we will highlight how AI algorithms during any time point during a typical nuclear cardiology study as shown in the Central Illustration. In particular, AI has been increasingly used to improve image denoising, motion correction, and attenuation correction (AC). In hybrid imaging, AI can automate the segmentation of important structures, including coronary artery calcification (CAC), epicardial fat, and cardiac chambers. We will then review how machine learning (ML)-based algorithms leverage clinical, stress, and imaging data from typical MPI procedures to predict CAD and cardiovascular risk. Further, we will discuss the role of deep learning (DL) in risk prediction and how clinicians could utilize it to improve disease diagnosis. Finally, we will explore future directions in AI research, outlining the potential advancements and challenges in this transformative field.

## AI Terminology

AI refers to any computer algorithm which performs a task normally characteristic of human intelligence.<sup>4</sup> ML algorithms are an example of AI which utilize input

data (typically tabular variables) to perform a task, without being explicitly programmed to understand the importance of the different features.<sup>5</sup> ML algorithms are well suited to integrate the vast amount of information from nuclear cardiology studies while accounting for non-linearity, collinearity, and interactions.<sup>6</sup> DL is a subset of ML, which refers to algorithms that use a multi-layered learning approach. Convolutional neural networks (CNN) are one common example in which nodes from one layer are only connected to nearby nodes in subsequent layers to maintain the spatial relationships of input images.<sup>7-9</sup> The model architecture (e.g., the number of layers, the number of nodes per layer, and the connectivity between nodes) influences the functionality of DL models. Another common approach is a generative adversarial network (GAN) in which a generator model (such as CNN) is trained in parallel with a discriminator network until the simulated/predicted images are indistinguishable from actual images.

All AI algorithms require data to learn patterns, which can then be applied to predict future outcomes. The process of determining the optimal method for combining parameters to predict the outcome of interest is referred to as training. Hyperparameters are variables that control the learning process, for example, the learning rate or number of iterations. Methods used to optimize the hyperparameters of the model are termed “tuning.” Testing (sometimes called validation) is the process in which an AI model is applied to a new data set to evaluate its performance. Two commonly used procedures are k-fold cross-validation and external testing. In k-fold cross-validation, the population is randomly divided into k-folds (or sets of data), with each fold sequentially held out for testing.<sup>10</sup> Repeated testing decreases the variance in estimating model accuracy and is preferred to testing in a single random sample.<sup>11</sup> In external testing, the patients selected for training are from a different population than was used for training and tuning.<sup>12</sup> External testing provides an estimate of the model performance when it is applied in a new, unrelated population and may also be repeated.<sup>12</sup> Most importantly, the data used for training and tuning the model should not be used in any way during model testing.<sup>13</sup>

## Improving Image Quality Through Denoising

AI algorithms are increasingly being utilized to enhance nuclear cardiology image quality, which can then be used to reduce radiation exposure, shorten acquisition

times, or both. For instance, Sun et al. employed a conditional generative adversarial network (cGAN) to enhance denoising performance and facilitate ultra-low dose SPECT imaging.<sup>14</sup> They demonstrated that a cGAN could generate images more similarly to noise-free images, even at dose levels as low as  $1/20^{\text{th}}$ , compared to conventional post-reconstruction filtering from simulated half-dose images.<sup>14</sup> Similarly, Du et al. applied a 3D integrated attention-guided multi-frequency cGAN, which improved denoising efficiency and performance compared to conventional reconstruction across multiple noise levels.<sup>15</sup> Image denoising is frequently applied as a post-processing step, which means that images can still be reconstructed using camera or vendor-specific algorithms.

While many studies apply denoising as a post-processing step, it may be preferable to integrate denoising into image reconstruction. Yousefzadeh et al. evaluated a GAN (with CNN generator) for denoising images during each iteration of an ordered subset expectation maximization algorithm.<sup>16</sup> In a dataset of 247 SPECT-MPI patients, they demonstrated higher contrast-to-noise ratios for the GAN model (improved by 54.5%) compared to traditional Gaussian filtering.<sup>16</sup> They also demonstrated that denoising after each iteration outperformed post-reconstruction denoising concerning the contrast-to-noise ratio.<sup>16</sup> Wang et al. trained a two-component DL model to first reconstruct PET images from a sinogram and then denoise the same images.<sup>17</sup> This dual approach had a higher structural similarity index compared to U-Net-based denoising in complex images.<sup>17</sup> However, it is important to note that assessing improvements in task-specific outcomes, like defect identification, is essential, as denoising may boost technical quality without translating into better clinical performance.<sup>18</sup>

### Motion Correction

Nuclear cardiology studies are influenced by cardiac, respiratory, and gross patient motion. While these can be addressed with traditional techniques, there is also a potential role for AI. For instance, Zhang et al. assessed the impact of a DL network on cardiac motion correction in SPECT MPI.<sup>19</sup> Quantitative analysis of perfusion from DL motion-corrected images showed the highest prediction performance for abnormal perfusion.<sup>19</sup> Chang et al. developed and used an artificial neural network (ANN) to

provide motion correction directly from sinograms which demonstrated a higher contrast-to-noise ratio compared to traditional methods.<sup>20</sup> DL can also estimate respiratory signals from SPECT projection data to provide respiratory motion correction.<sup>21</sup> Ko et al. developed a CNN-based motion prediction model that accurately predicts respiratory motion amplitude from static MPI.<sup>22</sup> Their model enabled the identification of images with significant motion and predicted potential artifacts affecting total perfection deficit (TPD) results.<sup>22</sup> Builoff et al. have implemented an automatic algorithm for automated motion correction of stress and rest dynamic PET MPI acquisitions.<sup>23</sup> Compared to manual image correction, which took 10 minutes per case, the automatic algorithm completed motion correction in <17 seconds while achieving similar diagnostic accuracy.<sup>23</sup> Motion during PET scans can cause mismatches between frames, often resulting in altered images with lowered quality.<sup>24</sup> Guo et al. also developed a promising model for inter-frame motion correction in dynamic cardiac PET imaging.<sup>25</sup> Any of these methods could be used to significantly reduce the technical time required for motion correction during reconstruction without sacrificing image quality or accuracy.

### Image Registration

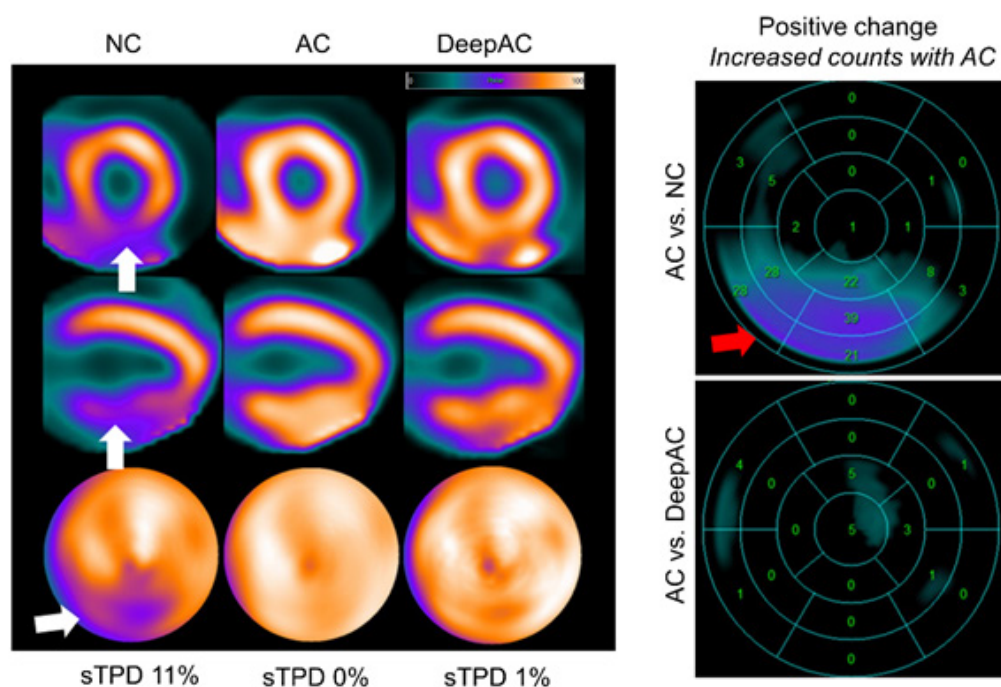
Nuclear cardiology studies are increasingly acquired on hybrid camera systems, which include computed tomography (CT) for AC.<sup>26</sup> While AC imaging enhances the diagnostic accuracy of SPECT, it requires precise image registration to avoid inducing artifacts.<sup>27,28</sup> AI can help minimize image misregistration. For example, Ko et al. trained a CNN to predict the offset between images using 402 cases and demonstrated an average residual misalignment of  $2.38 \pm 2.00$  mm during testing on 100 cases.<sup>29</sup> Another method is to generate synthetic AC maps (which should be perfectly co-registered with the emission images used to generate them). Canalejo et al. found that DL-based synthetic AC maps for SPECT MPI achieved high mean structural similarity (MSSIM = 0.97) and low normalized mean absolute error (NMAE = 3.08%) compared to traditional CT-based AC maps.<sup>30</sup> Chen et al. proposed a Dual-Channel-Squeeze-Fusion-Excitation co-attention module for the registration of cardiac SPECT and CT-derived attenuation maps, demonstrating lower residual misregistration compared to conventional approaches.<sup>31</sup> Synthetic AC maps (generated using a

GAN-based approach) have also been used to enhance the registration of coronary CT angiography with sodium fluoride PET images.<sup>32</sup>

### AI-Derived AC

CT-based AC can account for soft-tissue attenuation on SPECT and PET, but it requires additional radiation exposure and imaging time.<sup>26</sup> AI could address this limitation by generating synthetic AC imaging. Yu et al. developed a DL-based method for generating synthetic AC SPECT images.<sup>33</sup> The synthetic AC images were visually similar to actual AC images in cases without misregistration but more similar to the reference standard in cases with misregistration.<sup>33</sup> Chen et al. developed a DL network (incorporating clinical information with images) to predict AC images that better matched actual images compared to a U-Net model, with a normalized mean square error of 2.01% versus 2.23%.<sup>34</sup> Nguyen et al. utilized a GAN

to simulate AC images from non-AC data, achieving a structural similarity index of 0.946 compared to true AC images, outperforming U-Net alone.<sup>35</sup> Hagio et al. developed a CNN that generated synthetic AC polar maps from non-AC polar map images,<sup>36</sup> with improvement in specificity ranging from 26% (in higher quality studies) to 8% (when considering lower quality studies as well). Shanbhag et al. devised a cGAN strategy for generating synthetic short-axis AC SPECT images from non-attenuation corrected images using a training set of 5000 cases,<sup>37</sup> with representative images in **Figure 1**. In external testing, the area under the receiver operating characteristic curve (AUC) for obstructive CAD of synthetic AC images (0.79) was higher than non-AC images (0.72,  $p < 0.001$ ) and similar to actual AC imaging (0.81,  $p = 0.196$ ).<sup>37</sup> Synthetic AC images can also be generated using images from stand-alone SPECT camera systems, with AUC improving from 0.717 to 0.752.<sup>38</sup> This last study suggests that synthetic AC imaging could be applied broadly to



**Figure 1** – Example of DL AC imaging. Short-axis (top), vertical long-axis (middle), and polar map images (bottom) for non-attenuation corrected (NC), attenuation corrected (AC), and synthetic attenuation corrected (DeepAC) data sets. There was a defect in the inferior wall on NC images (white arrows) which was resolved with AC and DeepAC imaging. The patient had no CAD on coronary CT angiography. Stress total perfusion deficit (sTPD) was abnormal for NC images only. There was a positive change (increased counts with AC) in the inferior wall for AC vs NC (red arrow), but no significant change between AC vs DeepAC images. This research was originally published in the JNM. (From Shanbhag et al.<sup>37</sup>).

NC: non-attenuation corrected; AC: attenuation correction; DeepAC: synthetic attenuation corrected; sTPD: Stress total perfusion deficit

improve diagnostic accuracy without additional cost or radiation exposure.

## AI Applications on Hybrid CT Imaging

### CAC scoring

While the CT acquired for AC on hybrid SPECT/CT and PET/CT camera systems are of low quality (to reduce radiation exposure), they still carry valuable anatomic information. For instance, CAC can be detected on CT AC scans, potentially refining risk stratification<sup>39</sup> or guiding medical therapy initiation.<sup>40</sup> AI can be used to automate the segmentation of these structures, providing similar results to manual segmentation.<sup>41,42</sup> AI-derived CAC scores significantly improve the risk stratification of SPECT MPI, with a continuous net-reclassification index of 0.494.<sup>43</sup> They also provide similar risk reclassification as expert CAC scores in patients undergoing PET MPI.<sup>44</sup> In a separate study, Cho et al. demonstrated that AI-based CAC scores correlate with coronary blood flow capacity and myocardial blood flow.<sup>45</sup> Van Velzen et al. utilized a GAN to generate images with only CAC (to remove the influence of image noise), which can then be scored using standard methods with lower absolute error compared to values from ECG-gated CAC compared to direct scoring.<sup>46</sup> Outside of CAC, AI can also be used to quantify calcium in the thoracic aorta and heart valves to provide clinicians with additional information.<sup>47</sup>

### Epicardial Fat

Though much attention has been given to CAC segmentation, other anatomical features (such as epicardial adipose tissue [EAT]) could also be valuable. EAT serves as a key predictor of cardiovascular risk but has traditionally required labor-intensive manual segmentation.<sup>48,49</sup> DL segmentation of EAT from CCTA images demonstrated a strong agreement with expert manual segmentation, with a median dice score coefficient of 0.916 for 2D slices and 0.896 for 3D volumes.<sup>50</sup> Miller et al. evaluated a DL approach to segment EAT volume and attenuation from low-dose, ungated CT AC scans.<sup>51</sup> The model derived results in less than 2 seconds, with excellent agreement with expert annotated values (Spearman correlation 0.82 to 0.91).<sup>51</sup> Importantly, both EAT volume and density were independently associated with the incidence of death or myocardial infarction.<sup>51</sup> EAT is an intuitive marker to consider because it captures metabolic and

inflammatory information that is complementary to traditional imaging biomarkers.

## Cardiac Chambers and Other Structures

There are other emerging applications of DL to segment a variety of different structures from chest CT. We demonstrated that cardiac chamber measurements obtained through previously validated AI models<sup>52</sup> can enhance risk stratification following SPECT MPI.<sup>53</sup> This analysis enables physicians to utilize the higher spatial resolution of CT to assess left ventricular mass and volume, along with atrial and right ventricular volumes that are not typically evaluated on SPECT MPI. The same segmentation can be used to automate the quantification of cardiac bone scintigraphy images<sup>54</sup> or fluorodeoxyglucose activity.<sup>55</sup> Aortic size can be quantified automatically using AI to provide additional clinical insights into the risk of aortic dissection or aneurysm.<sup>56</sup> Michalowska et al. segmented 33 thoracic structures and then applied radiomics to extract relevant anatomic information.<sup>57</sup> The resulting features were combined using ML to improve the prediction of all-cause mortality.<sup>57</sup> Notably, any of these features can be extracted automatically after image reconstruction, offering physicians anatomical, metabolic, and inflammatory data to support more accurate risk predictions without additional technical time required.

## AI for Disease Diagnosis

### ML

ML can incorporate a multitude of features into predictive models to improve patient selection or disease diagnosis. For instance, ML models have been developed to predict abnormal myocardial perfusion from pre-test features in patients referred for SPECT<sup>58</sup> or PET<sup>59</sup> imaging. ML has also been used to automatically identify abnormal perfusion from polar map images.<sup>60</sup> ML models have also been developed to identify patients with a low likelihood of obstructive CAD who could safely have their rest scan canceled.<sup>61</sup> ML can also predict ischemia from stress-only SPECT, suggesting that it may be possible to utilize stress-only imaging in all patients.<sup>62</sup> ML has also been used to identify patients with obstructive CAD from PET MPI variables, with similar diagnostic accuracy compared to expert image interpretation (89% vs 88%).<sup>63</sup> Lastly, ML can be applied to provide therapeutic decision support. For example, ML may be able to help identify cardiac

resynchronization therapy super-responders from electrocardiography and gated SPECT MPI.<sup>64</sup>

## DL

ML models typically need variables to be coded or quantified, whereas DL algorithms can process images directly to generate predictions. One such DL model utilizes polar maps as the input to predict the likelihood of obstructive CAD, demonstrating significant improvements in prediction performance compared to quantitative perfusion assessment (AUC 0.81 vs 0.78).<sup>8</sup> DL can also be utilized to automate the detection of transthyretin cardiac amyloidosis.<sup>65</sup> In addition to directly predicting the likelihood of disease, DL models may help identify important abnormalities on SPECT or PET images. Kusumoto et al. used SPECT MPI images to develop and validate a DL-based support system to identify perfusion defects with an AUC of 0.91.<sup>66</sup> DL has also been utilized to identify wall motion abnormalities from SPECT MPI.<sup>67</sup>

## AI for Risk Prediction

### ML

MPI has a critical role in estimating cardiovascular risk, an area in which AI may be particularly valuable as the number of features increases. Hu et al. incorporated clinical, stress, and imaging features to identify patients with low risk of major adverse cardiovascular events.<sup>68</sup> The addition of DL-based CAC scores can further improve this risk stratification.<sup>69</sup> Feher et al. incorporated clinical, stress test, and imaging parameters to create an AI model to predict heart failure hospitalizations in patients undergoing SPECT MPI.<sup>70</sup> The combined ML model displayed superior prediction performance in external validation (AUC 0.80) compared to both stress left ventricular ejection fraction (AUC 0.72) and a clinical model (AUC 0.72).<sup>70</sup>

### DL

DL approaches have also demonstrated significant potential in predicting risks in MPI. Singh et al. developed an explainable DL model that used PET-derived relative perfusion, myocardial blood flow, and myocardial flow reserve polar maps to predict mortality. In simulated prospective testing with 1,135 patients, the DL model achieved a higher prediction accuracy (AUC 0.82)

compared to myocardial flow reserve (AUC 0.70) and a comprehensive regression model (AUC 0.75).<sup>71</sup> A similar methodology has been applied to predict death or myocardial infarction using SPECT polar maps, where the DL model outperformed both logistic regression (AUC 0.70) and stress TPD (AUC 0.65) in external testing (n = 9,019).<sup>72</sup>

## Explainable AI: Going Beyond a “Black Box”

Clinical implementation of AI remains challenging, largely due to the limited ability of clinicians and researchers to evaluate and critique the quality of predictions.<sup>73</sup> There have been some attempts at making AI more explainable as this is key to overcoming this notion of a “black box”. Otaki et al. integrated gradient-weighted class activation mapping into a model for identifying obstructive CAD from polar maps, highlighting areas of an image contributing most to predictions.<sup>74</sup> Physician interpretation diagnostic accuracy can be improved with the aid of an explainable DL model.<sup>75</sup> ML models can also incorporate methods to provide patient-specific risk explanations, summarizing the most important features for a prediction,<sup>68</sup> as shown in **Figure 2**. Alternatively, models can incorporate attention-based methods with variable importance to provide a summary of the relative impact of image regions and clinical features.<sup>76</sup>

## Future Directions and Challenges

Nuclear cardiology is an ever-advancing field, and AI is at the forefront of these future changes. One ongoing unmet need is the rigorous evaluation of the prospective implementation of AI solutions. This is critical to ensure that the proposed benefits of the solutions are realized when applied in clinical practice. While explainable AI models help clinicians understand AI predictions, dedicated training on the use of the model is also needed to ensure optimal results. Another relatively unexplored area is unsupervised learning, where models are tasked with understanding data structure instead of classification. Unsupervised learning has significant potential for discovering novel phenotypes and uncovering disease subtypes. Unsupervised learning has been employed to classify patients with normal myocardial perfusion into four distinct clusters, revealing a six-fold difference in risk between the groups,<sup>77</sup> a risk variation greater than that seen with traditional clinical factors like

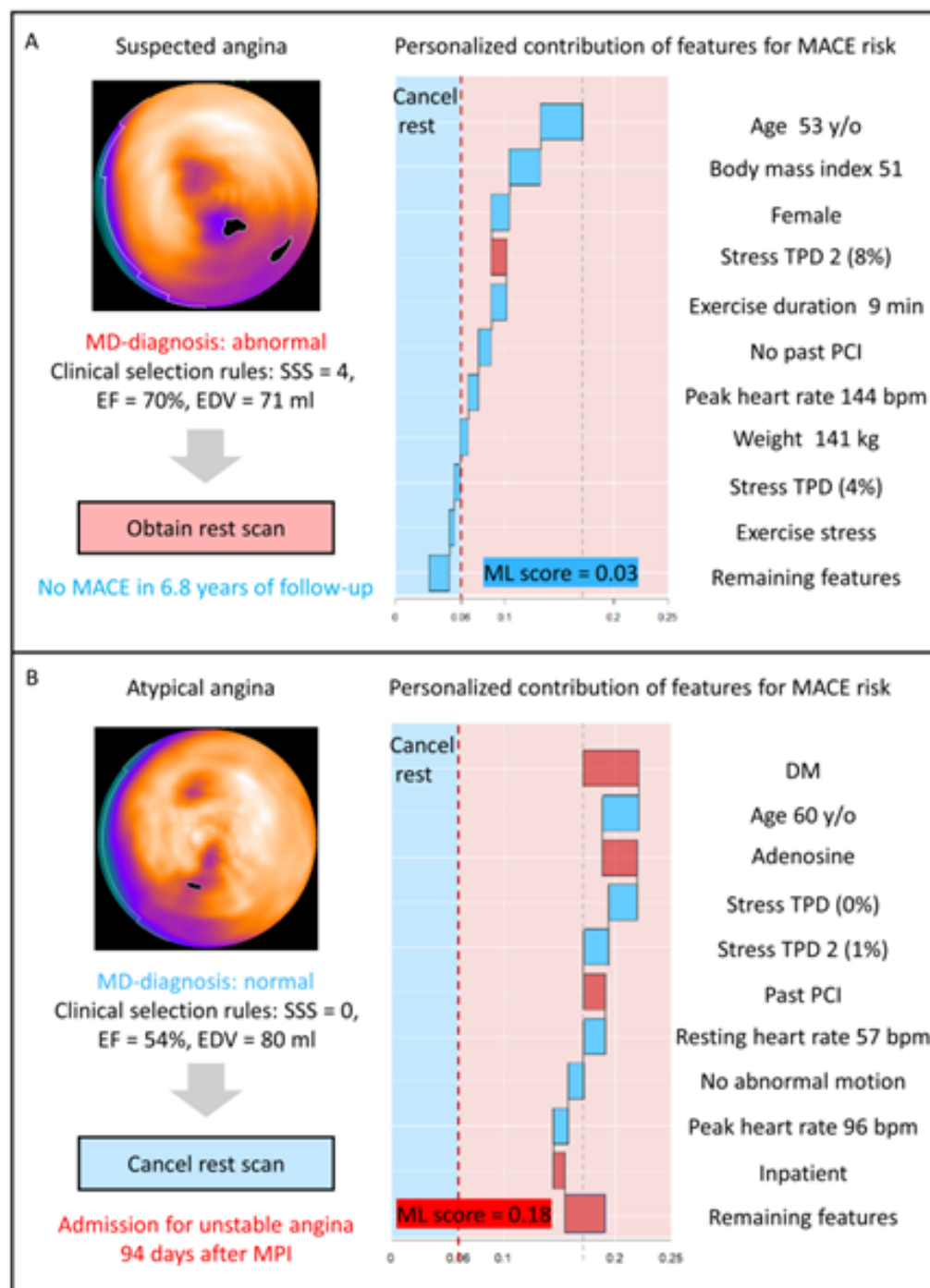


Figure 2 – Examples of personalized explanations of ML recommendations from Hu et al.<sup>68</sup> The individual contributions of the top features to the overall risk for each patient are shown. Figure reproduced from Hu LH, Miller RJH, Sharir T, Commandeur F, Rios R, Einstein AJ, et al. Prognostically Safe Stress-Only Single-Photon Emission CT MPI Guided by ML: Report from REFINE SPECT. Eur Heart J Cardiovasc Imaging. 2021;22(6):705-14, with the permission of Oxford University Press.

ML: machine learning; sTPD: Stress total perfusion deficit; DM: diabetes mellitus; PCI: percutaneous coronary intervention.

a history of diabetes. This technique has also been applied to uncover phenotypes in patients with known CAD.<sup>78</sup> More information is needed to ensure that DL models perform well in under-represented populations. For example, DL models can overestimate the prevalence of obstructive CAD in female patients.<sup>79</sup> Prospective performance monitoring is needed for DL models when deployed in new populations, in the same way that post-marketing efforts for novel therapeutics are needed to avoid unintentional bias. Lastly, the role of large language models in providing clinicians and patients with a source of information is required. Recently it has been demonstrated that these models can answer nuclear cardiology board-style questions with increasing accuracy.<sup>80</sup> Finding the best way to incorporate this potentially incredible source of knowledge into clinical practice requires focused research and guidance from professional societies.

## Summary

AI is establishing key roles in nuclear cardiology. AI-driven methods have shown improvements in denoising performance and image reconstruction for SPECT and PET imaging, facilitating dramatic radiation dose reductions. DL-based motion correction and AI-driven AC have also improved image registration and diagnostic accuracy. Automated segmentation of CT imaging is rapidly expanding the clinical information provided by hybrid MPI studies. For disease diagnosis and risk prediction, AI models combining clinical and imaging data have

outperformed conventional methods. Explainable AI is being developed to help clinicians understand predictions, facilitating implementation. Overall, implementing AI throughout the workflow of nuclear cardiology will help ensure the value of SPECT and PET MPI in the future, securing their ongoing central role in patient care.

## Author Contributions

Conception and design of the research, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Gilbert C, Chunta A, Miller R; acquisition of data: Miller R.

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## Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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