Appendix B: Artificial Intelligence/Machine Learning Steps to CCTA Image Evaluation: The following figures present in graphical detail the stepwise use of artificial intelligence algorithms used for CCTA analysis.

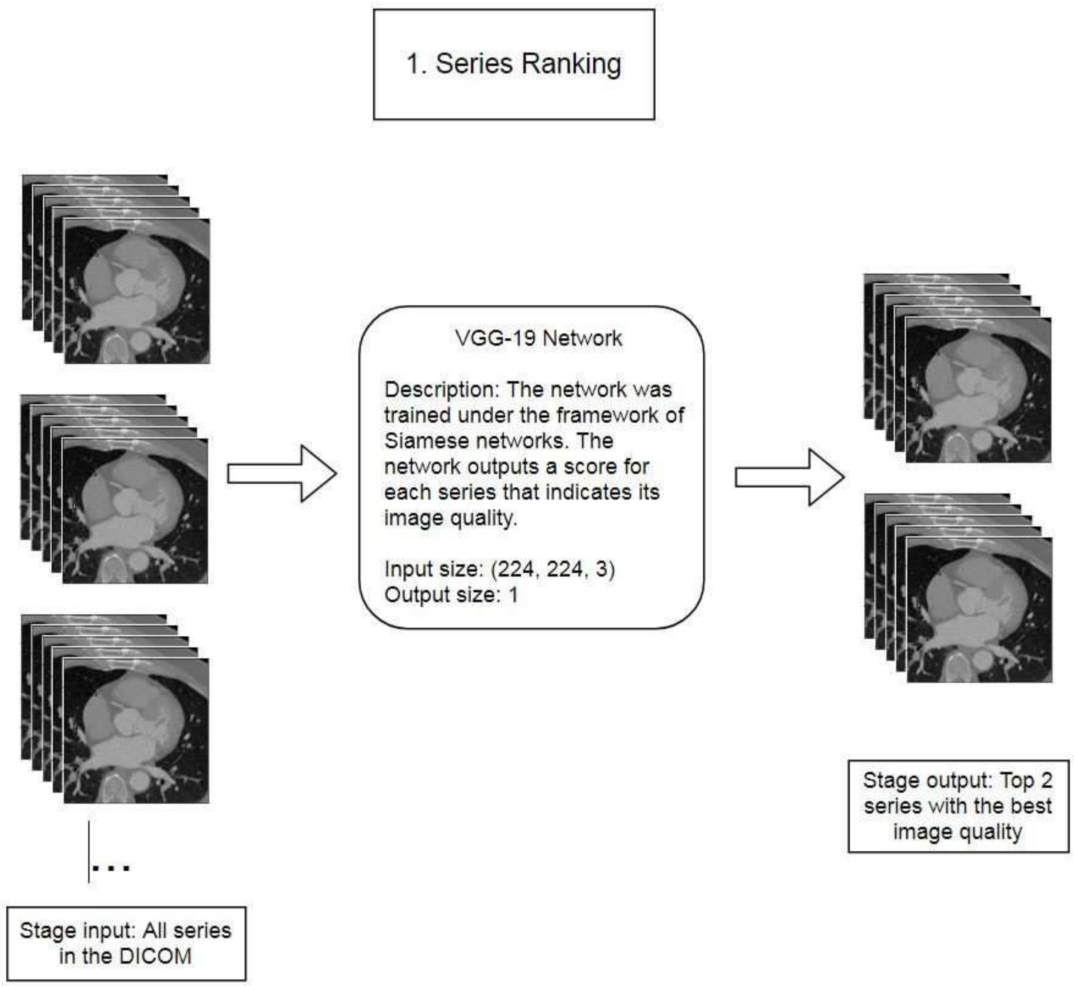
This is an AI-aided approach (Cleerly Inc, New York, NY) that performs an automated analysis of CCTA using a series of validated convolutional neural network models (including VGG 19 network, 3D U-Net and VGG Network Variant) for image quality assessment, coronary segmentation and labeling, lumen wall evaluation and vessel contour determination and plaque characterization(19). No manual interaction is required from the reader. First, the AI-aided approach leverages 2 deep convolutional neural networks (VGG-19 Network and 3D U-Net) to produce a centerline along the length of the vessel, and then for lumen and outer vessel wall contouring. This approach is applied to multiple phases/series of the CCTA examination, if present, and enables phase-specific evaluation at the coronary segment vessel. The algorithm reviewed all series and determined the top 2 optimal series for further analysis including vessel and lumen segmentation, plaque, and stenosis quantification. The algorithm rank-orders all available phases for the segmentation of the arteries. It then uses the top two phases interactively on a per vessel basis, e.g., the right coronary artery (RCA) will be reconstructed from the phase which yields the highest RCA image quality, while the posterior descending artery (PDA) may come from the second phase if the PDA has a higher image quality on that phase. Once coronary artery segmentation is performed, an automated labeling is done to classify arteries by their location as well the proximal, mid and distal portions within a single vessel. The AI further allows for defining of coronary artery lesions (i.e., those areas where plaque is present; VGG Network Variant). Utilizing a normal proximal reference vessel cross-sectional slide, the start and the end of the lesion, and the cross-sectional slice that demonstrates the greatest absolute narrowing, % diameter stenosis severity is automatically calculated. The software determines the start and end of lesions and drops stenosis markers at the region of the highest stenosis. Within coronary artery lesions, plaque is quantified in a similar fashion, and further characterized as low-attenuation non-calcified plaque, non-calcified plaque and calcified plaque based upon Hounsfield unit (HU) densities of <30, -189 to 350, >350, respectively. Positive arterial remodeling was identified as a remodeling index $\geq$1.10 by diameter when compared to a proximal vessel reference. Vessel length, vessel volume, lumen volume, total plaque volume, calcified plaque volume, noncalcified plaque volume, low density noncalcified plaque volume, maximum diameter and area stenosis, and maximum remodeling index are calculated.

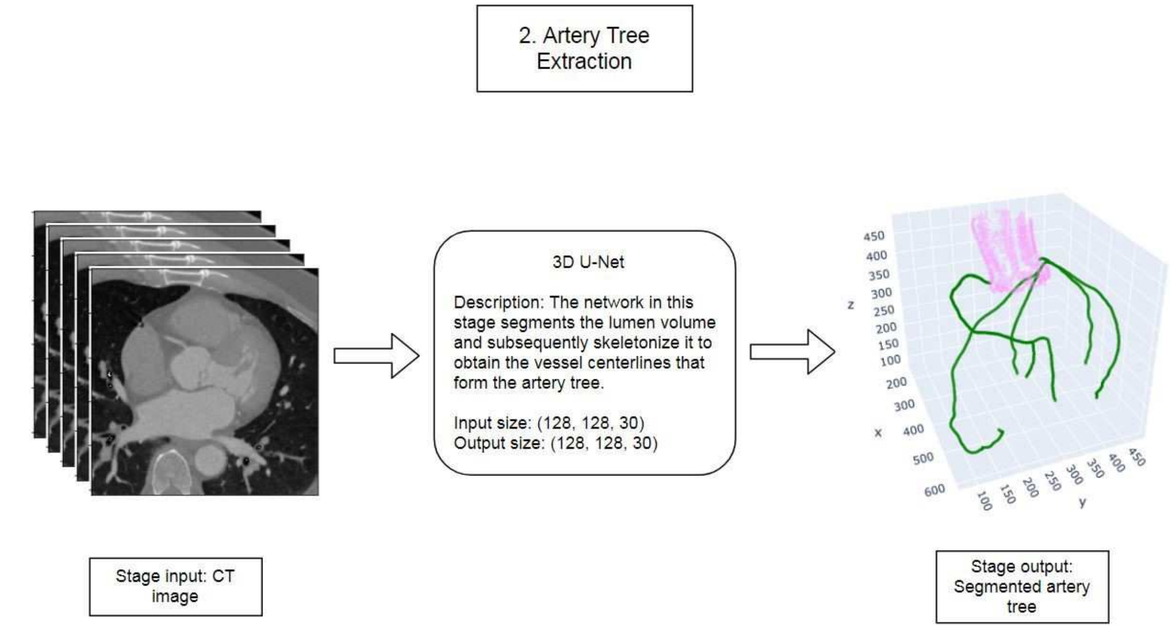
Training and testing were performed on a proprietary database. The centerline algorithm was developed from 1,007,945 images, which comprised 23,068 vessels from 3,671 patients. The lumen and vessel wall algorithms were developed from 1,414,877 images, which comprised 8,555 vessels from 3,676 patients.

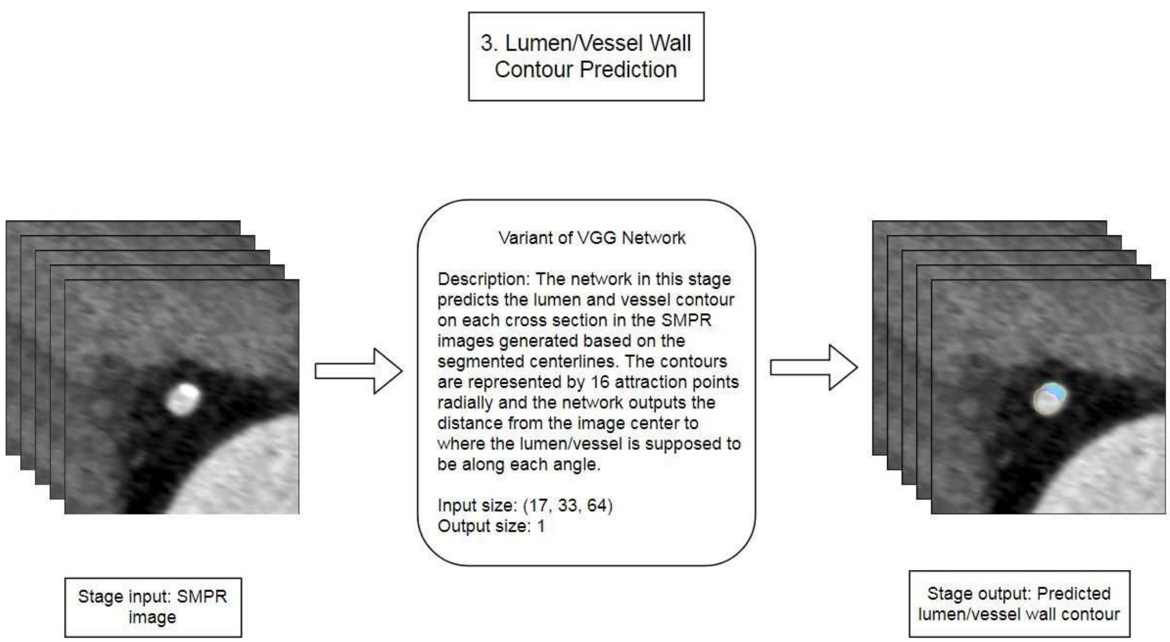
Information and documentation of U.S. Food and Drug Administration (FDA) approval may additionally be found here in the FDA Access document here:

(https://www.accessdata.fda.gov/cdrh_docs/pdf19/K190868.pdf).

Jonas R, *et al. Open Heart* 2021; 8:e001832. doi: 10.1136/openhrt-2021-001832


1. Series Ranking
VGG-19 Network
Description: The network was trained under the framework of Siamese networks. The network outputs a score for each series that indicates its image quality.
Input size: (224, 224, 3)
Output size: 1
Stage input: All series in the DICOM
Stage output: Top 2 series with the best image quality


2. Artery Tree Extraction
3D U-Net
Description: The network in this stage segments the lumen volume and subsequently skeletonize it to obtain the vessel centerlines that form the artery tree.
Input size: (128, 128, 30)
Output size: (128, 128, 30)
Stage input: CT image
Stage output: Segmented artery tree


3. Lumen/Vessel Wall Contour Prediction
Variant of VGG Network
Description: The network in this stage predicts the lumen and vessel contour on each cross section in the SMPR images generated based on the segmented centerlines. The contours are represented by 16 attraction points radially and the network outputs the distance from the image center to where the lumen/vessel is supposed to be along each angle.
Input size: (17, 33, 64)
Output size: 1
Stage input: SMPR image
Stage output: Predicted lumen/vessel wall contour