4DMedical™

CAC Software

Instructions for Use US

This edition is valid for Device release from 3.1.x

CAC Software Instructions for Use US

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1 Introduction

1.1 Scope of Manual

This user manual was written for the 4DMedical CAC Software.

1.2 Product Overview

4DMedical's Coronary Artery Calcification (CAC) software is a set of automated image post-processing algorithms designed to help radiologists and cardiologists determine the location and calculate the amount of calcification within the coronary arteries in patients who have undergone a non-contrast, chest computed tomography (CT), by providing visualization and quantification of abnormal coronary CT densities. The CAC software runs automatically on the input CT series, with no user input or intervention.

The 4DMedical CAC software analyses high resolution CT DICOM images of the heart. The specific input requirements are given in the Scan Protocol section of this document (3.3).

The 4DMedical CAC algorithm provides a DICOM or PDF summary report with the results of the analysis.

2 Symbols

The meaning of the symbols shown on the labeling and/or instructions for use are as follows:



Consult Electronic Instructions for Use



Manufacturer



Date of Manufacture (YYYY-MM-DD)



Medical Device



Unique Device Identifier



Batch Code (Device Version)



Caution: Federal law restricts this Device to sale by or on the order of a physician.

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3 Indications for Use and Requirements

CAC Software is intended for use as a non-invasive post-processing software to evaluate calcified plaques in the coronary arteries, which present a risk for coronary artery disease. CAC Software uses machine learning to analyze non-contrast thoracic CT images and outputs a summary report containing Agatston score, arterial age, and calcified lesion mass and volume metrics of the calcification burden for the whole heart and individual coronary artery level. Additionally, CAC Software outputs annotated images previewing the segmentation of calcifications for informational purposes only. CAC Software is limited to the quantification of detected possible calcifications in adult patients ≥ 29 years of age. It does not diagnose coronary artery disease. The device output will be available to the users as part of the standard DICOM viewing workflow. The CAC Software results are not intended to be used on a stand-alone basis for clinical decision-making or otherwise preclude clinical assessment of CT images.

3.1 Cautions, Warnings, and Contraindications

There are no known contraindications. Known limitations and precautions related to image quality, anatomy, and artefacts are described in Sections 4 and 7.

3.2 Intended Users and Use

The intended users of the CAC software are Radiologists, Cardiologists, imaging technologists under the supervision of a physician, or researchers to aid in their assessment of coronary artery calcifications. The intended use environment is in a radiology department. The target population of the device is adults (patients aged 29 years and older).

3.3 Scan Protocol Requirements

To ensure an optimal quantitative CT analysis, please adhere to the following guidelines. It is important that the patient fully understands the scanning procedure, and that any concerns are addressed prior to performing the CT scan. CAC software's performance on both cardiac-gated (i.e., ECG-gated) and nongated acquisitions along with low and standard dose acquisitions is further described in later within the Standalone Software Performance Study Section of this document (Section 6).

Table 1: Recommended protocol for 4DMedical CAC input images.

	SIEMENS	PHILIPS	TOSHIBA	GE
Standard Kernel Reconstruction	≤B45, ≤145	B, C	≤FC08, FC10-FC18	Standard
Slice Thickness	≤3.0 mm			
Slice Spacing	Consistently spaced, no gaps, and ≤3.0 mm			
Anatomic Coverage	Full coverage of the heart			
Severe Motion Artifact	Absent			
Contrast Enhanced	None			
Patient Age	≥29			

3.3.1 Subject Positioning

The patient should be in the supine position. Arms should be positioned comfortably above the head in a head-arm rest, lower legs supported. Using the laser positioning lights, line up the patient so the chest is at the isocenter of the CT gantry. Move the table so the patient is in the correct position for a chest CT scan.

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3.3.2 Scan Coverage

The scan should, at a minimum, completely cover the entire heart in all directions. Failure to capture the full extent of the heart could result in analysis failure. Chest/lung CT images are highly suitable for analysis by CAC software.

3.4 Product Lifecycle

The software is supported and maintained throughout its active lifecycle. Users will be notified in advance of end-of-support or end-of-life milestones. Use beyond end-of-support is not recommended as performance and cybersecurity cannot be assured.

3.5 Hardware Requirements

Hardware requirements for running CAC are as follows:

- 4 CPU Cores
- 16 GB RAM

The CAC software was validated on Ubuntu 14.04.

4 Quality Assessment

The scan quality and possible artifacts must be assessed before utilizing the results produced by the CAC Software.

This software is designed to run on any input data that satisfies the criteria in Section3.3 and it does not perform any additional quality checking. **It is the responsibility of the medical professional who is using the software (i.e., the cardiologist or radiologist) to ensure that the input data is of adequate quality.** If the input data is not of adequate quality, the application's results should be disregarded.

It is also the responsibility of the medical professional using the software to perform quality assurance on the outputs. Performance degradation is possible in cases of anatomical anomalies, image artifacts, etc. as described further in Section 7.

4DMedical CAC software was designed and validated on adult (patients 29 years of age or older) chest CT images and has not been validated on children.

5 CAC Software

5.1 Input

The CAC Software requires one DICOM format high-resolution CT image series as input. Reference Section 3.3 for more information.

5.2 Outputs

When run with appropriate input data, the CAC Software generates a summary report. More information about this output is provided below. In the event that input data fails the input metadata check process, an input check failure report is generated.

5.2.1 CAC Summary Report

The CAC summary report contains the results from the CAC Software analysis. It can be provided in several formats: PDF file, DICOM encapsulated PDF, or a DICOM Secondary Capture Storage.

The key quantitative measures reported within the CAC summary report include:

- **Agatston Score (AS):** A score for the total coronary artery calcium based on the area and density (Hounsfield units (HU)) of calcified coronary lesions identified from CT images. [1, 2] (Units: arbitrary units (a.u.))
- **Arterial Age:** A patient-digestible form of CAC score in terms of chronological age that is surrogate for atherosclerotic burden. Arterial age is calculated from the total Agatston score using the McClelland et al. method. [3] (Units: years)

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- **#Lesions:** The number of individual calcified arterial lesions detected by the software. (Units: a.u.)
- **Lesion Volume (LV):** The total volume of the arterial lesion(s) detected by the software. (Units: mm^3)
- **Lesion Mass (LM):** An estimation of the total mass of the arterial lesion(s) detected by the software using the McCollough et al. method. [4] A mass calibration factor of 0.743 mg/(HU•cm^3) is used by default but is configurable. The value is rounded to the nearest integer. (Units: mg)

These key metrics are displayed in a table on the report for each of the coronary arteries: right coronary artery + posterior descending artery (RCA+PDA), left main (LM) artery, left anterior descending (LAD) artery, and left circumflex (LCX) artery.

The report includes a graph or graphs of the published risk stratification percentiles, which can be created using published data from the Multi-Ethnic Study of Atherosclerosis (MESA) [5] or Hoff [6] studies. Please contact 4DMedical Support for more information.

MESA Report

The first page of the MESA report includes:

- A table of key quantitative measures.
- Two selected axial slices of the CAC map.
- A 3D graphical image of the detected calcified lesions, color-coded for each coronary artery. The locations of the two axial slices are marked.

The second page of the MESA report includes:

- Four graphs of the published risk stratification percentiles [5] for the Agatston score as a function of chronological age are included for reference only. There is a graph for each Race/Ethnicity category from the MESA [5] study. The risk percentiles are shown for 25th, 50th, 75th and 90th percentiles. If the patient age is known, then their location on the risk chart is marked with a yellow star.
- A table of the published risk categories based on Agatston score[7].

If the patient sex is unknown, the MESA report will include a third page. The second page will include MESA risk stratification charts for one sex and the third page will include MESA risk stratification for the opposite sex.

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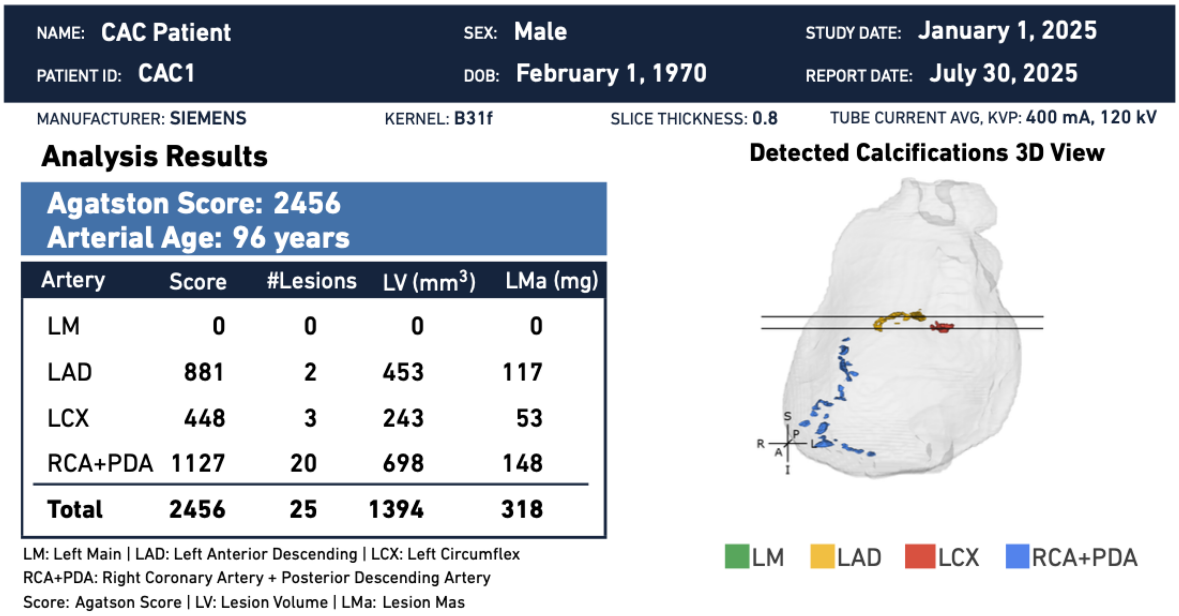
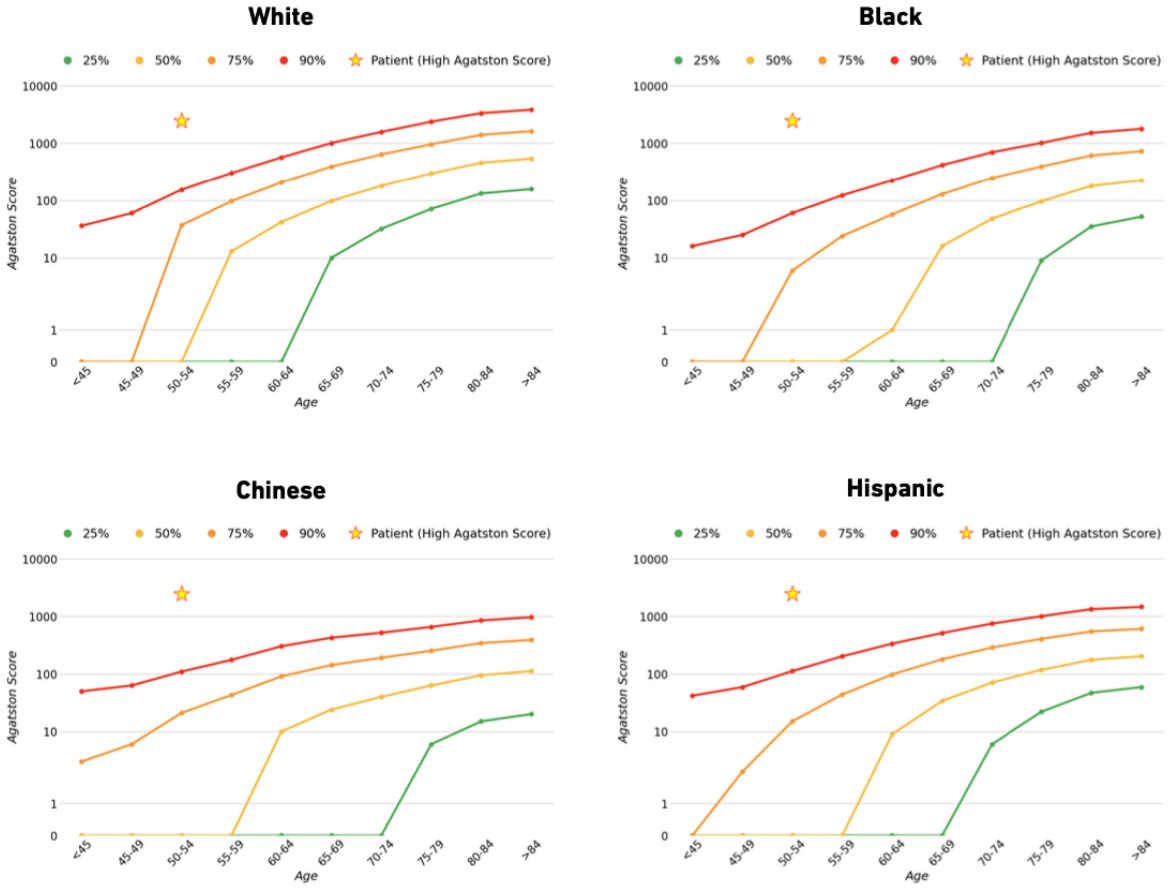


Figure 1: Example MESA report first page.

NAME: **CAC Patient**	SEX: **Male**	STUDY DATE: **January 1, 2025**	
PATIENT ID: **CAC1**	DOB: **February 1, 1970**	REPORT DATE: **July 30, 2025**	
MANUFACTURER: **SIEMENS**	KERNEL: **B31f**	SLICE THICKNESS: **0.8**	TUBE CURRENT AVG, KVP: **400 mA, 120 kV**

MESA Risk Stratification (The information in this section is for reference only)

Circulation. 2006;113(1):30-37 McClelland et al. DOI:10.1161/CIRCULATIONAHA.105.580696



Risk Categories

Category	Agatston Score	Risk of Coronary Artery Disease
None	0	Very low, generally less than 5%.
Minimal	1-10	Very unlikely, generally less than 10%.
Mild	11-100	Mild or minimal coronary narrowings likely.
Moderate	101-400	Mild coronary artery disease highly likely, significant narrowings possible.
Extensive	>400	High likelihood or at least one significant narrowing.

MAYO CLIN PROC. 1999;74:243-252 Rumberger et al. DOI: 10.4065/74.3.243

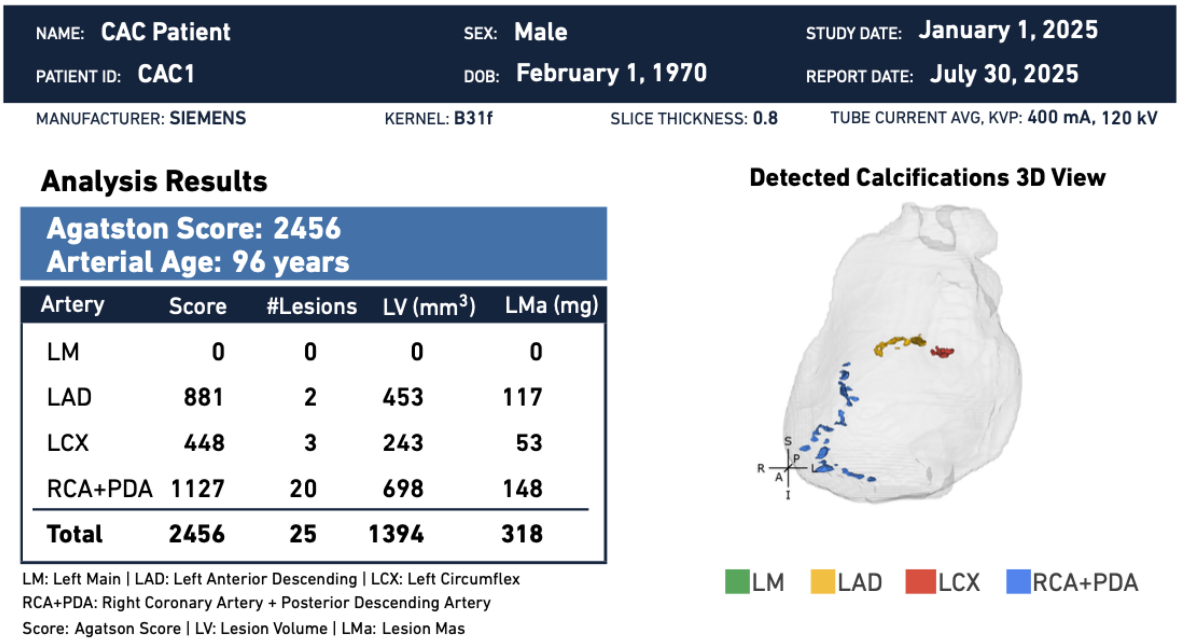
Figure 2: Example MESA report second page.

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Hoff Report

The Hoff report is a single page report that includes:

- A table of key quantitative measures.
- A graph of the published risk stratification percentiles[6] for the Agatston score as a function of chronological age is included for reference only. The risk percentiles are shown for 25th, 50th, 75th and 90th percentiles. If the patient age is known, then their location on the risk chart is marked with a yellow star.
- A 3D graphical image of the detected calcified lesions, color-coded for each coronary artery.
- A table of the published risk categories based on Agatston score[7].



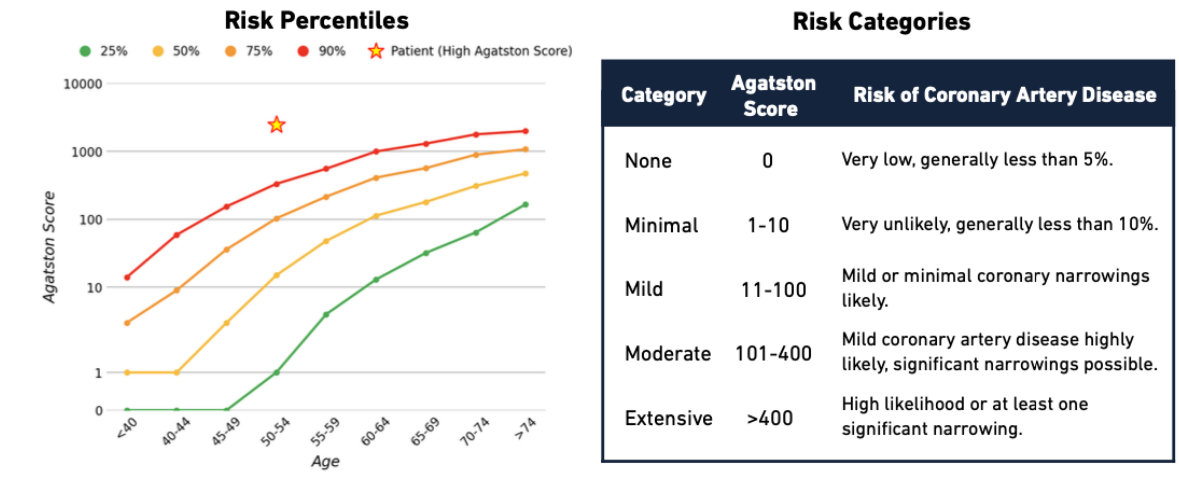


Figure 3: Example Hoff report.

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5.2.2 CAC Map

The CAC Map is a DICOM Secondary Capture Image with voxel data that is the original image with an RGB overlay. The RGB overlay colors each calcified lesion voxel as a color corresponding to the coronary artery.

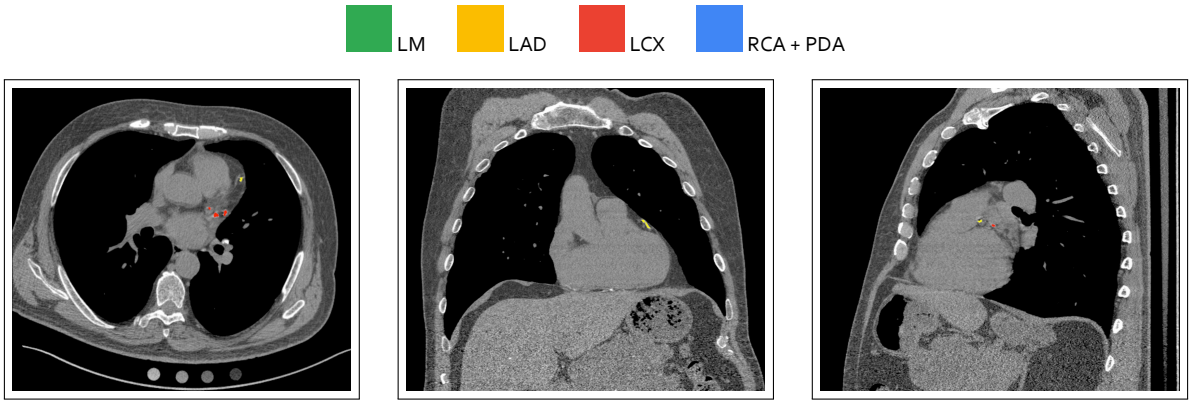


Figure 4: Example images of the RBG overlay series shown in the axial, coronal, and sagittal (L to R) orientations. The gray scale original CT image is overlaid with the coronary calcifications detected by the software and color-coded according to the coronary artery.

5.2.3 Input Check Failure Report

In the event that the input data is determined to not meet the minimum requirements, the algorithm outputs an input check failure report indicating the reason why the input data was deemed unacceptable. An example input check failure report is shown in Figure 5. The cause(s) of the input check failure can be identified by the red 'X' mark in the 'Result' column. In Figure 5, the offending parameters are the modality and the presence of the Contrast Bolus Agent information in the DICOM header, indicating the series was acquired with contrast enhancement. Note the yellow triangle warning signs indicate sub-optimal parameters or parameters that are missing from the input meta data. These warnings do no not result in an input check failure, but should be noted nonetheless.

	Requirement	Value	Result
Series Instance UID	Valid UID	...33396132.5428.4364.2819322250408.4001	✓
Modality	CT	CT	✓
Revolution Time (s)	<= 1.0	Not Present	⚠
Pixel Spacing (mm)	<= [1.0, 1.0]	[0.875, 0.875]	✓
FOV/ImagePositionPatient (mm)	>= (100, 100, 100)	(448, 448, 270)	✓
Image Orientation	(±1,0,0,0,±1,0)	(1.0, 0.0, 0.0, 0.0, 1.0, 0.0)	✓
Slice Spacing (mm)	<= 3.0	0.5	✓
Slice Thickness (mm)	<= 3.0	1.0	✓
Rescale Type	HU	Not Present	⚠
Patient Age (years)	>= 29	34	✓
Convolution Kernel	Non-edge-enhancing	B30f	⚠
Contrast Bolus Agent	Missing	Present	✗
Transfer Syntax UID	Non-Big-Endian	OK	✓
Patient Position	Either	FFS	✓

Figure 5: 4DMedical input check failure report showing the input data is unacceptable for analysis.

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6 Standalone Software Performance Study

6.1 Purpose

The standalone software performance study aimed to demonstrate the effectiveness of the CAC Software compared to a clinically-acceptable, reference standard (i.e., ground truth dataset) to measure the following metrics from a cardiac/chest CT image series:

- CVD Risk Category
- Agatston Score (i.e. CAC score)
- Calcified Volume
- Calcified Mass

in total and within the LAD, LM, LCX, and RCA+PDA coronary arteries.

6.2 Methods

Inclusion/Exclusion Criteria:
Exclusion criteria included the following:

- CTs from patients < 29 years old
- Contrast-enhanced CT scans
- Scans with Significant respiratory motion
- Scans with severe metal artifacts
- Scans containing only non-thoracic anatomy (e.g. head CT)

Inclusion criteria included the following:

- Scanner vendor = GE, Imatorn (now GE), Siemens, Philips, or Toshiba/Canon
- Pixel Spacing ≤2.0 mm
- Slice Spacing ≤3.0 mm
- Slice Thickness ≤3.0 mm
- Field of View = Complete coverage of heart
- Gating = ECG/Cardiac-gated or no-gating
- Dose = Low dose or standard dose

Data Characteristics: A total of N=500 testing chest CT datasets were retrospectively selected that meet the input criteria and equally split between those with ECG-gating (N=250) and no gating (N=250). Data was derived from four CT scanner vendors: GE Medical (N=326, 65.1%), Siemens (N=97, 19.4%), Imatron (N=76, 15.2%), and Philips (N=1, 0.2%)). 389 standard dose and 111 low dose scans were included. Low versus standard dose was determined using a cut-off tube current (mAs) value of 150 mAs with the 265 scans being >250 mAs and 80 scans <110 mAs.

Demographics: From the 422 CT datasets with gender information available, 209 were male and 213 were female. The average and standard deviation of the study's patient age for N=495 subjects with patient's age available was 64.3 +/- 10.0 years with the oldest and youngest subject being 90+ (not listed above 90 years old) and 29 years old.

6.3 Results

All datasets were analyzed by CAC software and compared against ground truth for Agatston score, lesion mass, and lesion volume for each coronary artery.
Performance on overlapping or faint calcium deposits was not analyzed as an independent subgroup during the performance evaluation.

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6.3.1 CVD Risk Categorization Performance

The reliability of 5-scale CVD risk categorization was assessed with Cohen's Kappa (K). Cohen's kappa is a statistic ranging from 0 (no agreement) to 1 (perfect agreement) describing the reliability or agreement between two qualitative measurements by different raters/readers. Cohen's kappa for 5-scale CVD risk categorization between the ground truth and CAC software was 0.936 (0.926, 0.947) across all subjects (N=495) indicating "near perfect" agreement.

Table 2: Reliability (Cohen's kappa) for CVD risk categorization between human readers and CAC device by cohort.

Cohort	Subjects (N)	Cohens Kappa (95% CI)
All	495	0.936 (0.926, 0.947)
Non-Gated	245	0.907 (0.889, 0.925)
ECG-Gated	250	0.966 (0.956, 0.977)
Standard Dose	387	0.958 (0.948, 0.967)
Low Dose	108	0.861 (0.829, 0.893)

Table2 summarizes the Cohen's kappa reliability measurements for the different cohorts.

6.3.2 Total Agatston Score, Total Volume, and Total Mass Performance

All quantitative metrics (e.g. Agatston score, calcified volumes, and calcified mass) were analyzed with the intraclass correlation coefficient (ICC) between the CAC software and ground truth measurements. The ICC is a statistic ranging from 0 (no agreement) to 1 (perfect agreement) describing the reliability or agreement between two or more quantitative measurements by different raters/readers. Across all subjects, the ICC between ground truth and the device for total Agatston, total calcified volume, and total calcified mass was 0.947 (0.94 0.96), 0.954 (0.95 0.96), and 0.948 (0.94 0.96), respectively.

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Table 3: Reliability (ICC) for CAC metrics between human readers and CAC device by cohort in total and by artery.

Cohort	Total	LM	LAD	LCX	RCA
Agatston Score			**ICC (95% CI)**		
All	0.947 (0.94 0.960)	0.793 (0.76 0.82)	0.896 (0.88 0.91)	0.879 (0.86 0.9)	0.862 (0.84 0.88)
ECG-Gated	0.984 (0.98 0.99)	0.747 (0.69 0.8)	0.965 (0.96 0.97)	0.942 (0.93 0.95)	0.963 (0.95 0.97)
Non-Gated	0.934 (0.92 0.95)	0.799 (0.75 0.84)	0.865 (0.83 0.89)	0.864 (0.83 0.89)	0.831 (0.79 0.87)
Low Dose	0.928 (0.9 0.95)	0.785 (0.7 0.85)	0.797 (0.72 0.86)	0.75 (0.65 0.82)	0.937 (0.91 0.96)
Standard Dose	0.951 (0.94 0.96)	0.796 (0.76 0.83)	0.922 (0.91 0.94)	0.906 (0.89 0.92)	0.844 (0.81 0.87)
CAC Volume			**ICC (95% CI)**		
All	0.948 (0.94 0.96)	0.78 (0.74 0.81)	0.897 (0.88 0.91)	0.885 (0.86 0.9)	0.875 (0.85 0.89)
ECG-Gated	0.985 (0.98 0.99)	0.717 (0.65 0.77)	0.966 (0.96 0.97)	0.938 (0.92 0.95)	0.963 (0.95 0.97)
Non-Gated	0.935 (0.92 0.95)	0.792 (0.65 0.77)	0.864 (0.83 0.89)	0.871 (0.84 0.9)	0.847 (0.81 0.88)
Low Dose	0.931 (0.9 0.95)	0.789 (0.71 0.85)	0.857 (0.8 0.91)	0.74 (0.64 0.82)	0.936 (0.91 0.96)
Standard Dose	0.952 (0.94 0.96)	0.772 (0.73 0.81)	0.907 (0.89 0.92)	0.919 (0.9 0.93)	0.857 (0.83 0.88)
CAC Mass			**ICC (95% CI)**		
All	0.954 (0.95 0.96)	0.771 (0.73 0.8)	0.91 (0.89 0.92)	0.871 (0.85 0.89)	0.845 (0.82 0.87)
ECG-Gated	0.985 (0.98 0.99)	0.722 (0.66 0.78)	0.971 (0.96 0.98)	0.936 (0.92 0.95)	0.96 (0.95 0.97)
Non-Gated	0.944 (0.93 0.96)	0.778 (0.72 0.82)	0.887 (0.86 0.91)	0.856 (0.82 0.89)	0.806 (0.76 0.85)
Low Dose	0.925 (0.89 0.95)	0.793 (0.71 0.85)	0.82 (0.75 0.87)	0.688 (0.57 0.78)	0.952 (0.93 0.97)
Standard Dose	0.96 (0.95 0.97)	0.761 (0.72 0.8)	0.928 (0.91 0.94)	0.91 (0.89 0.93)	0.827 (0.79 0.86)

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7 Considerations to Reduce Risk

7.1 Protocol

Users must follow CT protocol as outlined in Section 3.3.

7.2 Algorithm Limitations

The CAC Software uses advanced image processing techniques to identify coronary artery calcifications from chest CT images. The software checks input parameters and notifies users with warnings or error messages when there is a suspected issue. Even so, there are a number of cases where no warning or error is given and the output report is generated with potentially misleading results. Below are examples of possible cases. Users of the software should inspect outputs of the software for these or similar issues. If present, users should proceed with caution. The CAC Software should only be used by intended users.Also note, even when the CAC Software is used correctly according to these instructions, segmentation errors or misclassification may occur due to imaging artefacts, patient motion, or anatomical variation.

Stents Present: Subjects with known (or unknown) metallic implants or stents may produce misleading results. For example, a stent in the coronary artery may cause a false positive for CAC by the software.

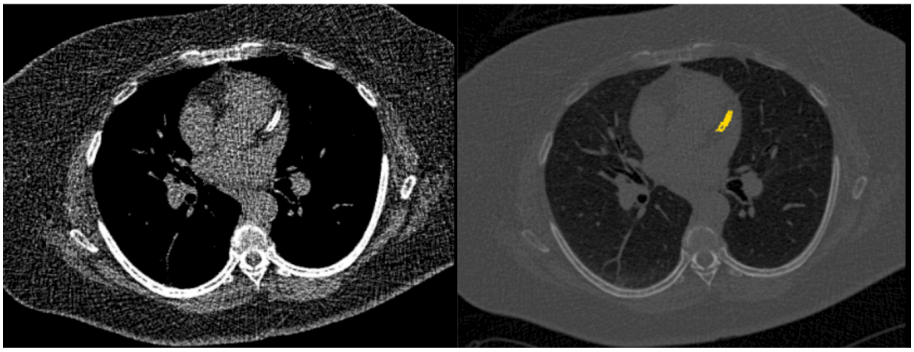


Figure 6: An example demonstrating a false positive calcified region by the CAC software. In this example, a stent is falsely classified as an arterial calcification. The original CT image (left) is displayed next to the RGB-overlay output from the CAC software (right) with the false positive results showing the stent as a calcified region (highlighted in yellow).

Dextrocardia: A significantly, shifted heart anatomy (e.g., dextrocardia) may cause a false negative result where none of the calcified regions within the arteries are highlighted.

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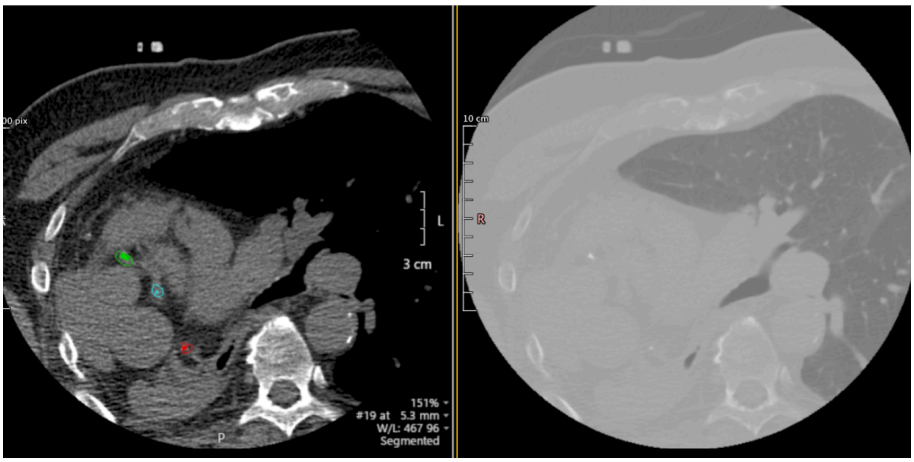


Figure 7: An example demonstrating a false negative for calcified regions by the CAC software. In this unique chest CT example, the heart is located in the right hemithorax and is an example of dextrocardia. On the left, is the ground truth, color-coded calcified regions by a human reader and on the right, RGB-overlay output from the CAC software showing none of the calcified regions highlighted.

7.3 Cybersecurity Recommendations

When deploying systems on which this application will run, please consider the following technical security guidelines:

- Ensure only permitted users are able to sign into the system, using at minimum, a username and strong password.
- Ensure that system firewalls are configured in such a way as to only allow needed traffic to ingress the system.
- Ensure that operating system patches are kept up to date, and monitor operating system vendor communications for security and patching-related announcements.

8 Regulatory Information

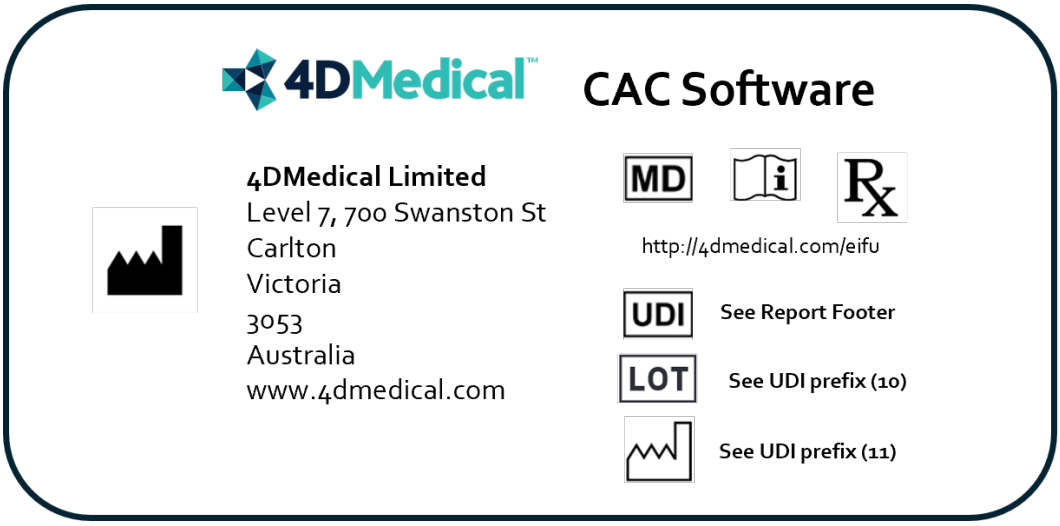
8.1 Contact 4DMedical

For support, contact 4DMedical using the details below during standard business hours.

Phone: +1 833 877 2267
Address: 21255 Burbank Blvd. Suite 120
Woodland Hills, California
91367
U.S.A
Email: support@4DMedical.com | 4DMedical.com/support

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8.2 Software Label



Disclaimer Imbio, Inc is a wholly owned subsidiary of 4DMedical Limited; any references to Imbio within this document refer to 4DMedical.

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