imbio

# CAC

v2.0.0

SOFTWARE USER MANUAL

Imbio Document Number: UM-114 v1.0

THE PRODUCT DESCRIBED IN THIS MANUAL IS INTENDED FOR INVESTIGATIONAL USE ONLY.

# Contents

# 1 Introduction

Caution: This product is for investigational use only.

## 1.1 Scope of Manual

This user manual was written for the Imbio CAC Software (FOR INVESTIGATIONAL USE ONLY).

## 1.2 Product Overview

Imbio'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 Imbio CAC software runs automatically on the input CT series, with no user input or intervention.

The Imbio 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 (Section 2.2).

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

## 1.3 Contact Imbio

Imbio Inc.
1015 Glenwood Avenue Floor 4
Minneapolis, MN 55405
United States
www.imbio.com

# 2 Intended Use and Requirements (For Investigational Use Only)

Caution: This product is for investigational use only.
Imbio 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. Imbio 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, Imbio CAC Software outputs annotated images previewing the segmentation of calcifications for informational purposes only. Imbio 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 Imbio 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.

## 2.1 Intended Users and Use

This product is not for clinical use. Users should use this product for investigational use only.

## 2.2 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. Imbio 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 5).

### 2.2.1 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.

### 2.2.2 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 Imbio CAC software.

| | SIEMENS | PHILIPS | TOSHIBA | GE |
|---|---|---|---|---|
| Standard Kernel Reconstruction | ≤B45, ≤I45 | 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 | | | |

Table 1: Recommended protocol for Imbio CAC input images.

## 2.3 Hardware Requirements

Hardware requirements for running CAC are as follows:

- 4 CPU Cores
- 16 GB RAM

# 3 Quality Assessment

Caution: This product is for investigational use only.

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

## 3.1 Precautions

This software is designed to run on any input data that satisfies the criteria in Section 2.2 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 6.

Imbio 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.

# 4 Imbio CAC Software

Caution: This product is for investigational use only.

## 4.1 Input

The Imbio CAC Software requires one DICOM format high-resolution CT image series as input. Reference Section 2.2 for more information.

## 4.2 Outputs

When run with appropriate input data, the Imbio 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.

### 4.2.1 CAC Summary Report

The Imbio 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 Imbio 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)
- **#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 $mg/(HU \cdot cm^3)$ 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 (RCA), left main (LM) artery, left anterior descending (LAD) artery, and left circumflex (LCX) artery as shown in Figure 1.

| Agatston Score: | 2456 | Arterial Age: | 96 years |
|---|---|---|---|

| Artery | #Lesions | AS | LV ($mm^3$) | LMa (mg) |
|---|---|---|---|---|
| RCA | 20 | 1127 | 698 | 148 |
| LM | 0 | 0 | 0 | 0 |
| LAD | 2 | 881 | 453 | 117 |
| LCX | 3 | 448 | 243 | 53 |
| **Total** | **25** | **2456** | **1394** | **318** |

RCA: Right Coronary Artery | LM: Left Main | LAD: Left Anterior Descending
LCX: Left Circumflex | AS: Agatson Score | LV: Lesion Volume | LMa: Lesion Mass

Figure 1: The CAC scores summary table on the report.

A 3D graphical rendering image of the detected calcified lesions, color-coded for each coronary artery, is include in the report. An example is shown in Figure 2.

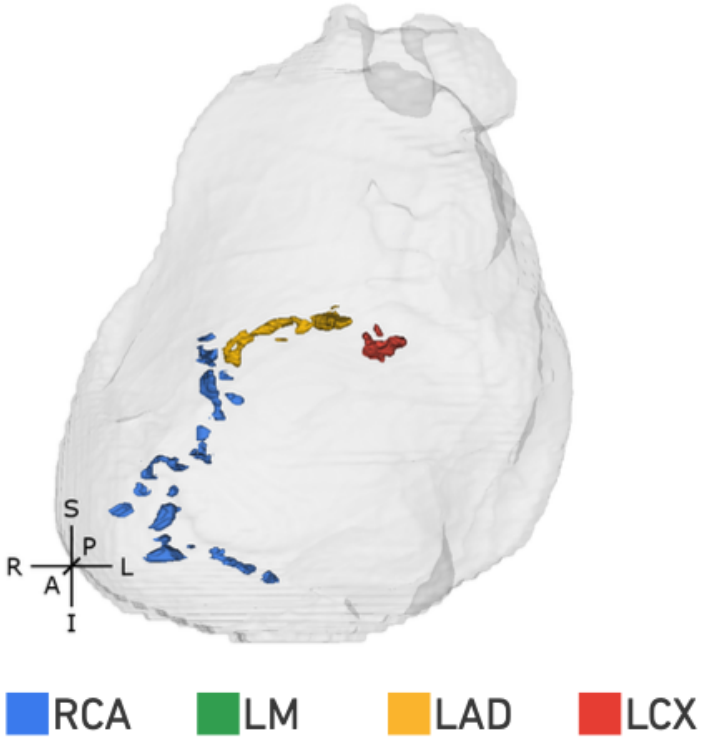



Figure 2: The 3D rendering included on the Imbio CAC summary report.

A graph of the published risk stratification percentiles [5] for the Agatston score as a function

of chronological age is included on the report for references 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.

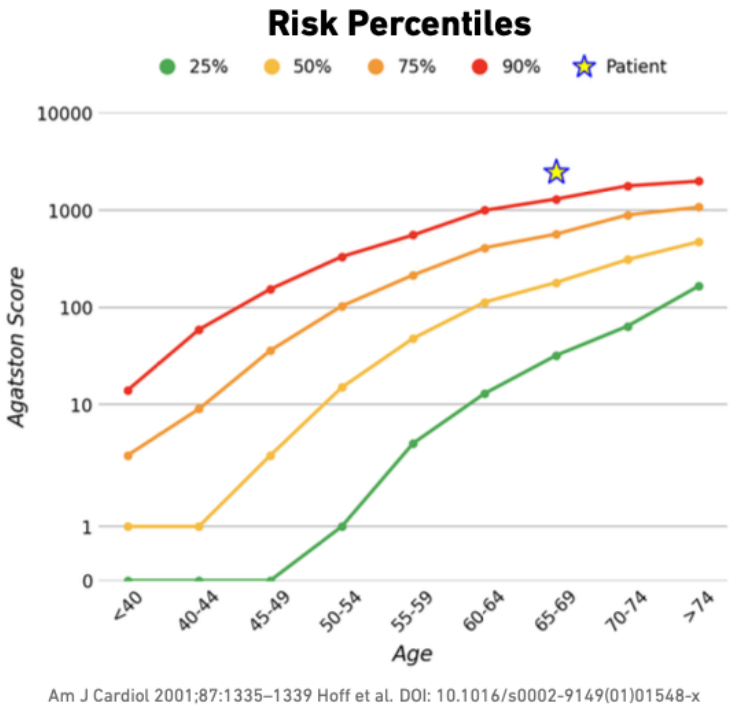



Figure 3: Risk percentiles for Agatston score as a function of age [5].

A table of the published risk categories based on Agatston score [6].

**Risk Categories**

| Category | Agatston Score | Risk of Coronary Artery Disease |
|---|---|---|
| None | 0 | Very low, generally less than 5 percent. |
| Minimal | 1-10 | Very unlikely, generally less than 10 percent. |
| 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 coronary narrowing. |

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

Figure 4: Risk categories based on Agatston score [6].

### 4.2.2 Imbio CAC Map

The Imbio 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.

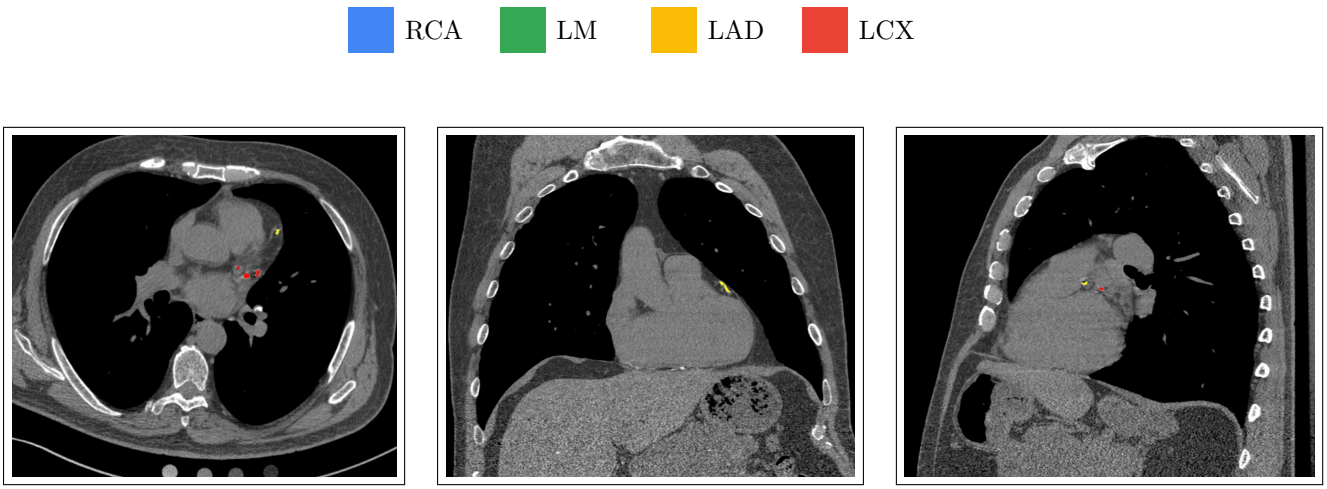
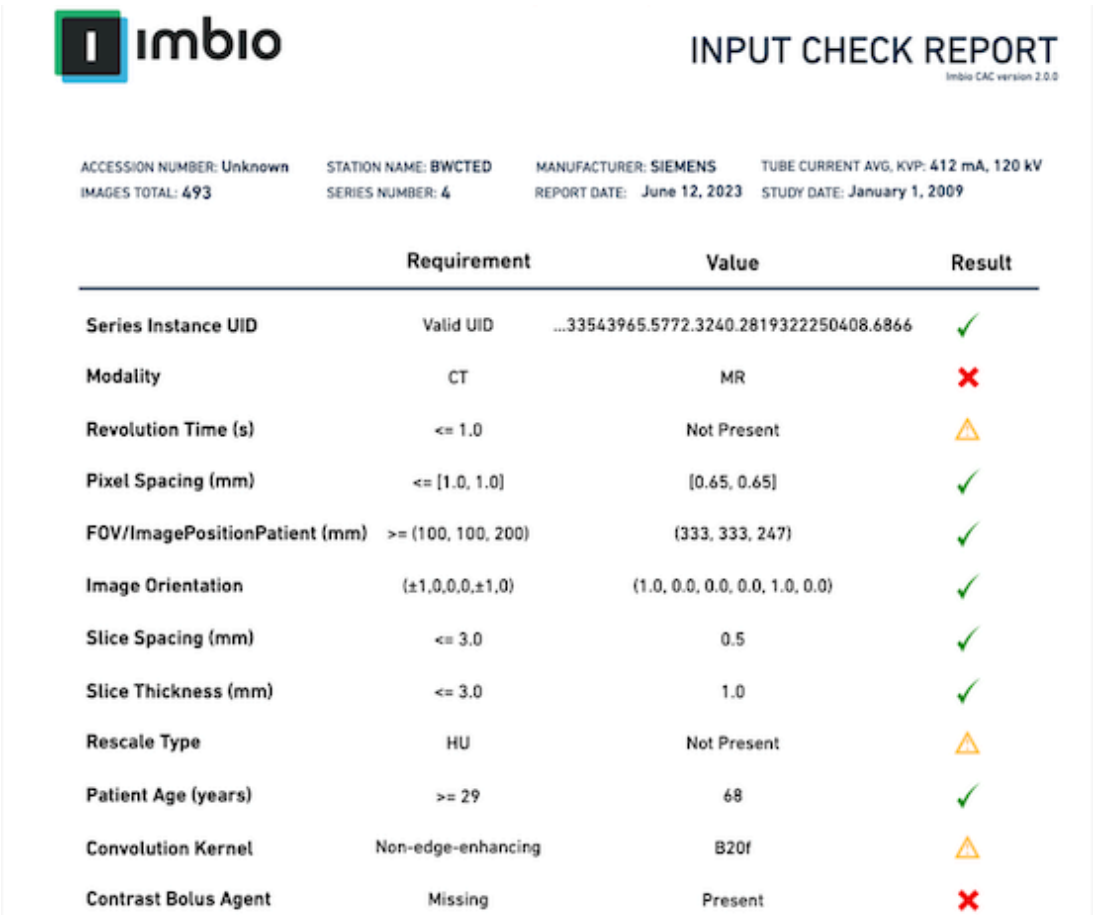



Figure 5: Example images of the RBG overlay series shown in the axial, coronal, and sagittal (L to R) orientations. The gray scale original CT image is overlaid with the coronary calcifications detected by the software and color-coded according to the coronary artery.

### 4.2.3 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 6. The cause(s) of the input check failure can be identified by the red 'X' mark in the 'Result' column. In Figure 6, 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.



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INPUT CHECK REPORT

Imbio CAC version 2.0.0

ACCESSION NUMBER: Unknown
IMAGES TOTAL: 493
STATION NAME: BWCTED
SERIES NUMBER: 4
MANUFACTURER: SIEMENS
REPORT DATE: June 12, 2023
TUBE CURRENT AVG, KVP: 412 mA, 120 kV
STUDY DATE: January 1, 2009

| | Requirement | Value | Result |
|---|---|---|---|
| Series Instance UID | Valid UID | ...33543965.5772.3240.2819322250408.6866 | ✓ |
| Modality | CT | MR | ✗ |
| Revolution Time (s) | <= 1.0 | Not Present | ⚠ |
| Pixel Spacing (mm) | <= [1.0, 1.0] | [0.65, 0.65] | ✓ |
| FOV/ImagePositionPatient (mm) | >= (100, 100, 200) | (333, 333, 247) | ✓ |
| 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 | 68 | ✓ |
| Convolution Kernel | Non-edge-enhancing | B20f | ⚠ |
| Contrast Bolus Agent | Missing | Present | ✗ |

Figure 6: Imbio input check failure report showing the input data is unacceptable for analysis.

# 5 Standalone Software Performance Study

## 5.1 Purpose

The standalone software performance study aimed to demonstrate the effectiveness of the Imbio 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 RCA, LAD, LM, and LCX coronary arteries.

## 5.2 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, Imatron (now GE), Siemens, Philips, or Toshiba/Canon
- Pixel Spacing $\leq$ 2.0 mm
- Slice Spacing $\leq$ 3.0 mm
- Slice Thickness $\leq$ 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.

## 5.3 Results

All datasets were analyzed by Imbio CAC software and compared against ground truth for Agatston score, lesion mass, and lesion volume for each coronary artery.

### 5.3.1 CVD Risk Categorization Performance

The reliability of 5-scale CVD risk categorization, as discussed in Figure 2 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 Imbio CAC software was 0.936 (0.926, 0.947) across all subjects (N=495) indicating "near perfect" agreement.

| Cohort | Subjects (N) | Cohen's 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) |

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

Table 2 summarizes the Cohen's kappa reliability measurements for the different cohorts.

### 5.3.2 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 Imbio 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.

| Cohort | Total | LM | LAD | LCX | RCA |
|---|---|---|---|---|---|
| **Agatston score** | ICC (95% CI) | | | | |
| All | 0.947 (0.94 0.96) | 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 (0.74 0.83) | 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) |

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

# 6 Considerations to Reduce Risk

## 6.1 Protocol

Users must follow CT protocol as outlined in Section 2.2.

## 6.2 Algorithm Limitations

The Imbio CT 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 Imbio CAC Software should only be used by intended users.

**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.

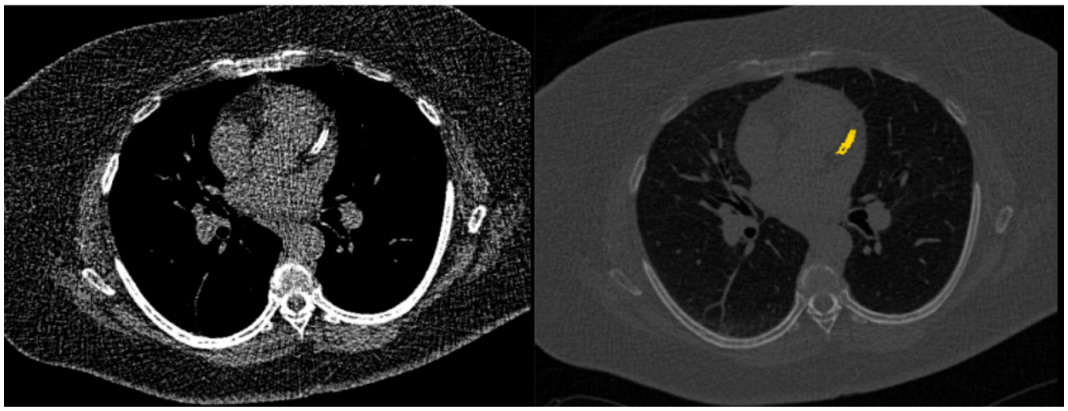


Figure 7: An example demonstrating a false positive calcified region by the Imbio CAC software. In this example, a stent is falsely classified as an arterial calcification. The original CT image (left) is displayed next to the RGB-overlay output from the Imbio CAC software (right) with the false positive 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.

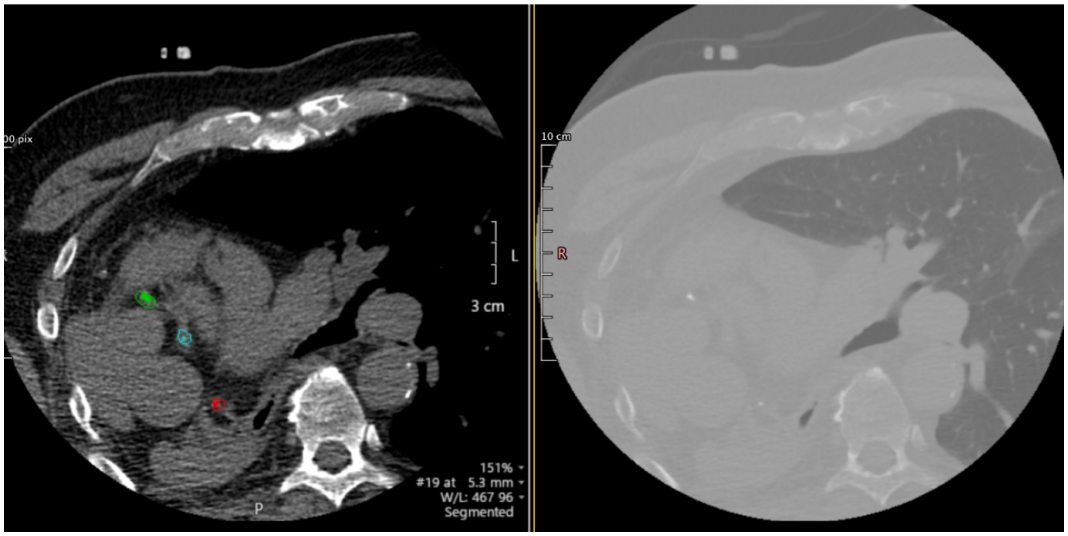


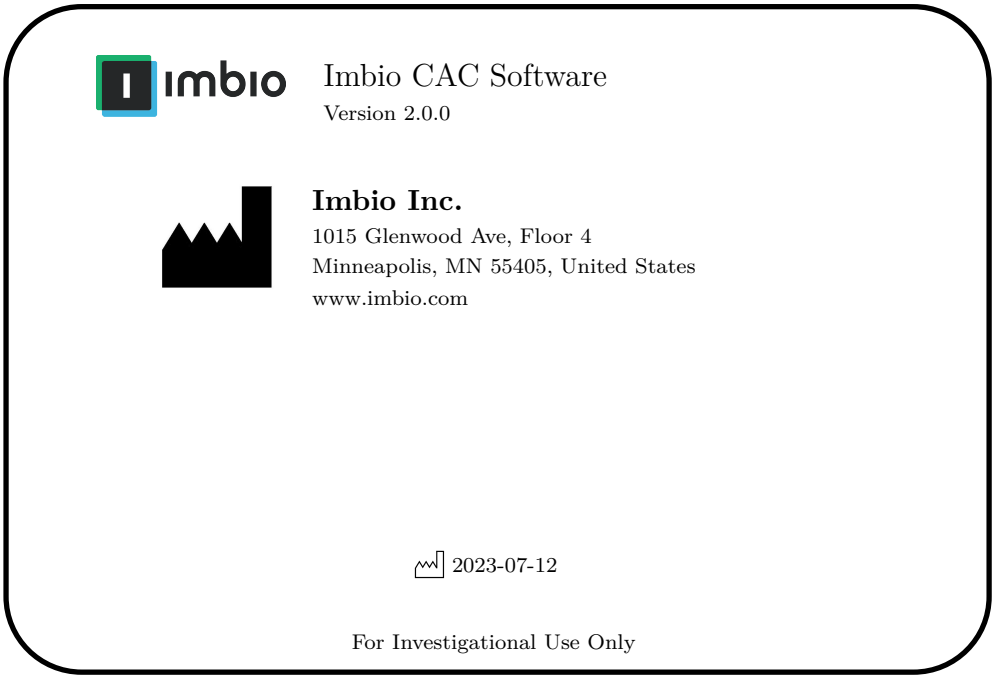

Figure 8: An example demonstrating a false negative for calcified regions by the Imbio CAC software. In this unique chest CT example, the heart is located in the right hemithorax and is an example of dextrocardia. On the left, is the ground truth, color-coded calcified regions by a human reader and on the right, RGB-overlay output from the Imbio CAC software showing none of the calcified regions highlighted.

## 6.3 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.

# 7 Software Label



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