Gender differences in CT calcium scoring: A phantom study

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CDRH/OSEL/DIDSR
U.S. Food and Drug Administration

OUTLINE

- Part 1
  - Quantitative imaging at CDRH
- Part 2
  - Gender differences in calcium scoring
- Summary

Part 1

CDRH and Quantitative Imaging

Center for Device and Radiological Health

- Mission: Protect and promote public health
  - Assuring that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and radiation-emitting products

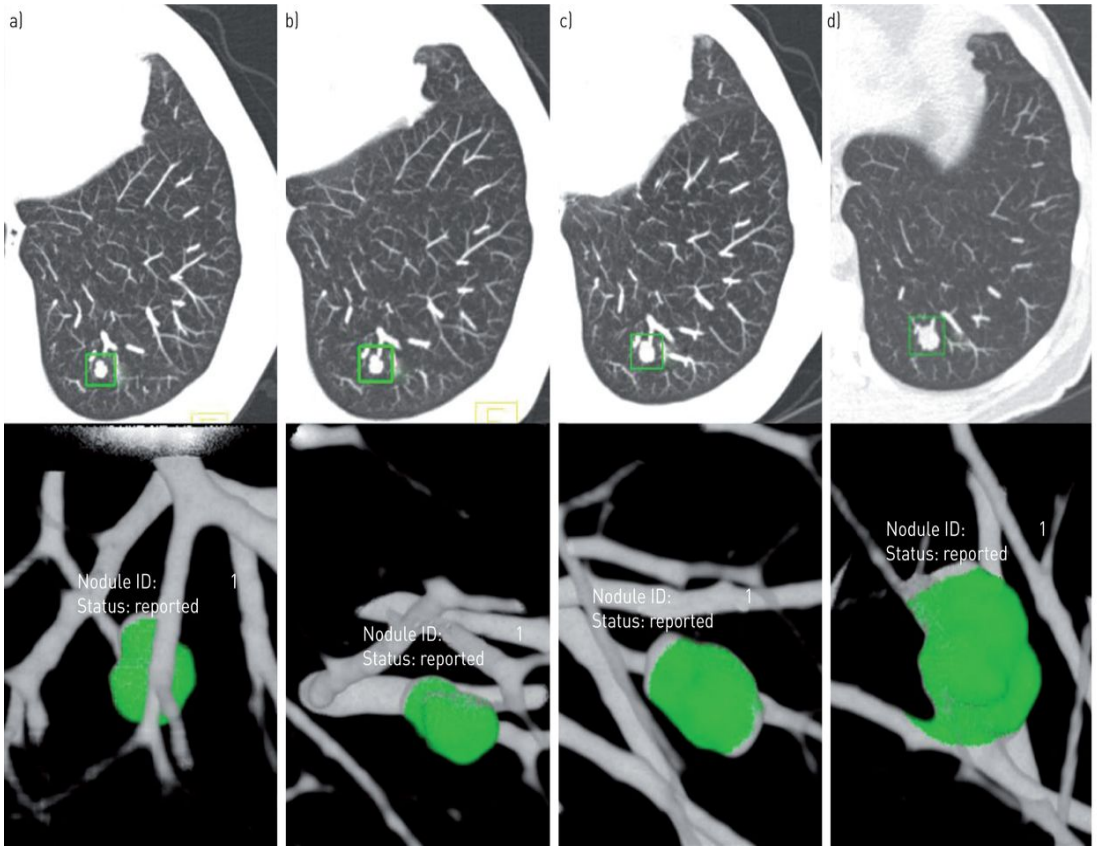
- CDRH regulates:
  - Medical imaging devices
  - Image processing/analysis devices
    - Picture Archive and Commination Systems (PACS)
    - Image processing tools
    - Image-based measurement tools (Quantitative Imaging [QI])
    - Computer-aided diagnosis (CAD)
    - …

CDRH Basics

- Device classifications
  - Class I, Class II, Class III
    - Depends on risk and special controls
- Premarket submission types
  - 510(k), PMA, de novo, HDE, exempt
- CT, PACS, Review workstations, CAD, standalone QI tools generally fall into Class II

DEVICES USING QI

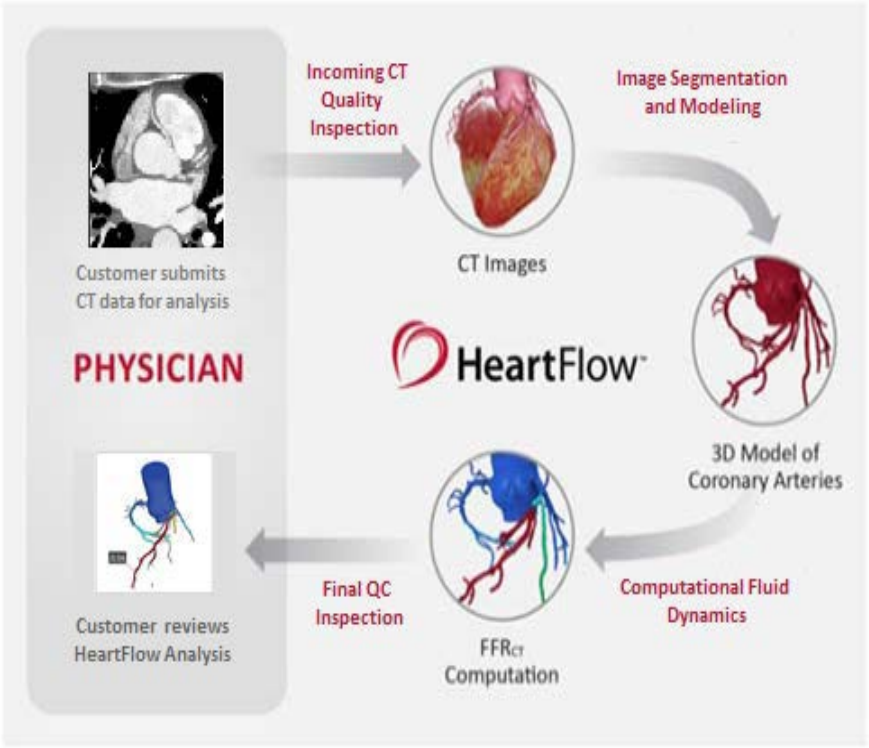
- Direct application
  - Radiological measurement tools



*Infante, M., et al., European Respiratory Journal, 2013.

DEVICES USING QI

- Indirect application
  - HeartFlow FFR_{CT}
    - Personalized 3D flow model of the coronary arteries
    - Impact of CT acquisition on model/analysis?
  - Evaluation:
    - Clinical study comparing FFR_{CT} to cCTA



Current regulatory framework for most QI

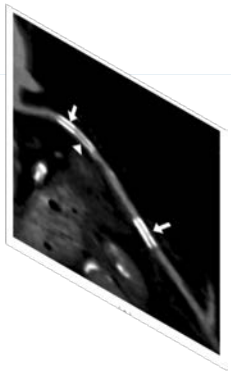
- Most QI devices regulated as tools (or part of PACS/review workstations)
  - No specific performance or utility claims are made
  - Single estimated value is given (no error bars or added context for number)
  - Tool under physician control
  - No specific QI performance data submitted

Future regulatory framework for QI

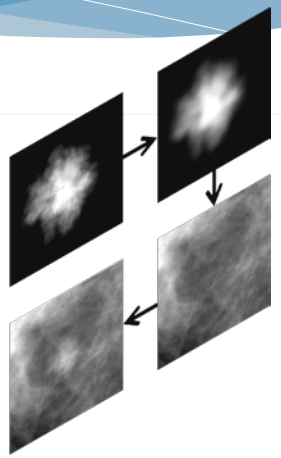
- CDRH sees QI as an area of expected growth

- CDRH interested in:
  - Allowing meaningful error bars to be included with QI measurements
  - Allowing for specific QI device claims

CDRH QI RESEARCH



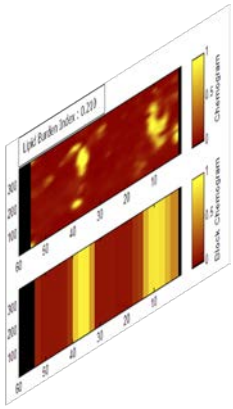
Quantitative Measurements



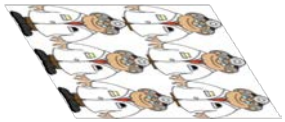
Data Generation

QI/CAD Assessment

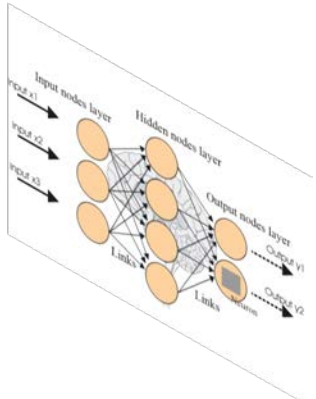
CAD



Reader Studies



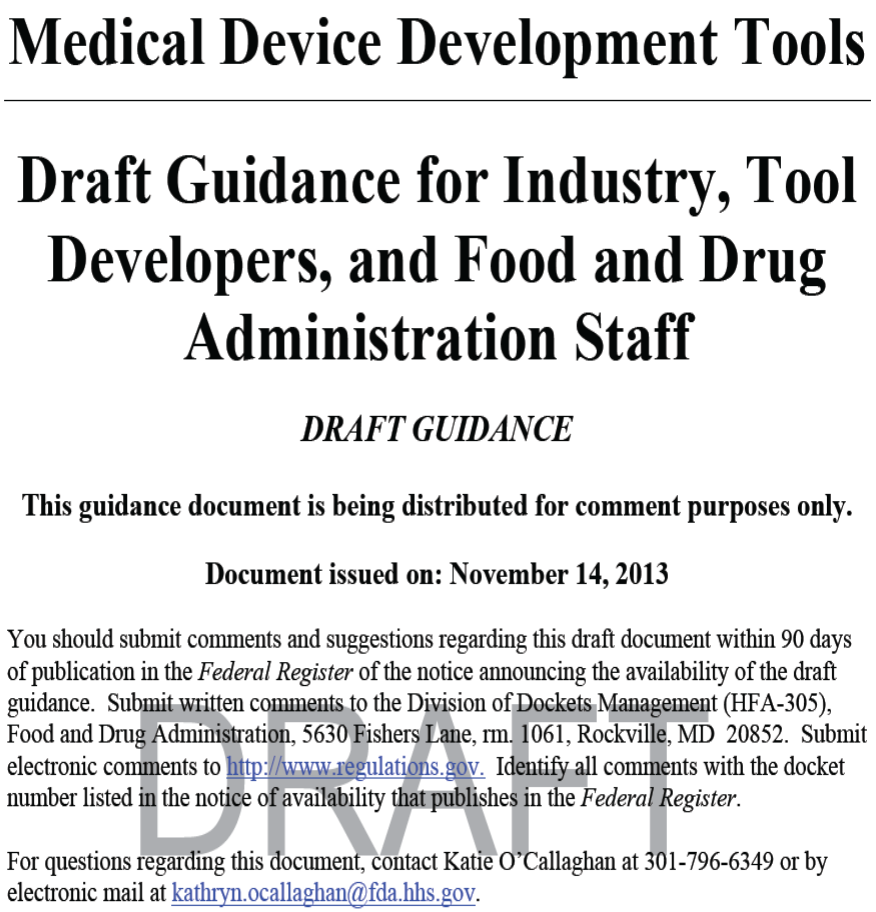
Machine Learning



Scope of CDRH QI Research

- Current CDRH funded QI projects
  - Lesion volume estimation
    - Lung, liver
  - Material characterization
    - Calcium scoring, characterizing vascular plaques
- Goal of CDRH's research is to develop general assessment methods along with task-specific phantoms that allow for least burdensome assessment of QI estimates

CDRH MDDT PROGRAM



Medical Device Development Tools

Draft Guidance for Industry, Tool Developers, and Food and Drug Administration Staff

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Document issued on: November 14, 2013

You should submit comments and suggestions regarding this draft document within 90 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. Identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this document, contact Katie O'Callaghan at 301-796-6349 or by electronic mail at kathryn.ocallaghan@fda.hhs.gov.

DRAFT

- MDDT
  - Scientifically validated tool that aids device development and regulatory evaluation
    - Clinical outcome or test used to detect or measure a biomarker or non-clinical assessment method or model

Part 2

Gender differences in CT calcium scoring

Work from

Qin Li, Ben Berman, Marios Gavrielides

Background

- Common cardiovascular disease screening approach for intermediate risk patients
  - Identification of calcium in the coronary arteries using CT
    - Calcium score used as indicator of coronary health
  - Secondary use
    - Calcium scoring applied to lung cancer screening images

BACKGROUND

- Gender
  - Willemink et al.[1] compared calcium scoring with a smaller 300×200 mm and a larger 400×300 mm chest phantom
    - Calcium scores underestimated in larger chest phantom

- Reconstruction
  - Iterative algorithm ASIR[2], SAFIRE[3] and ADMIRE[4] reduced noise but also decreased Agatston calcium scores comparted to FBP

[1]Willemink et al. J Cardiovasc Comput Tomogr **9** (2015)
[2]Gebhard et al. International journal of cardiology **167** (2013).
[3]Kurata et al. Eur Radiol **23** (2013).
[4]McQuiston et al. Eur J Radiol **85** (2016).

Background

- Differing CT imaging protocols & patient characteristics can impact CT calcium scoring
  - May lead to inconsistent patient treatment recommendations

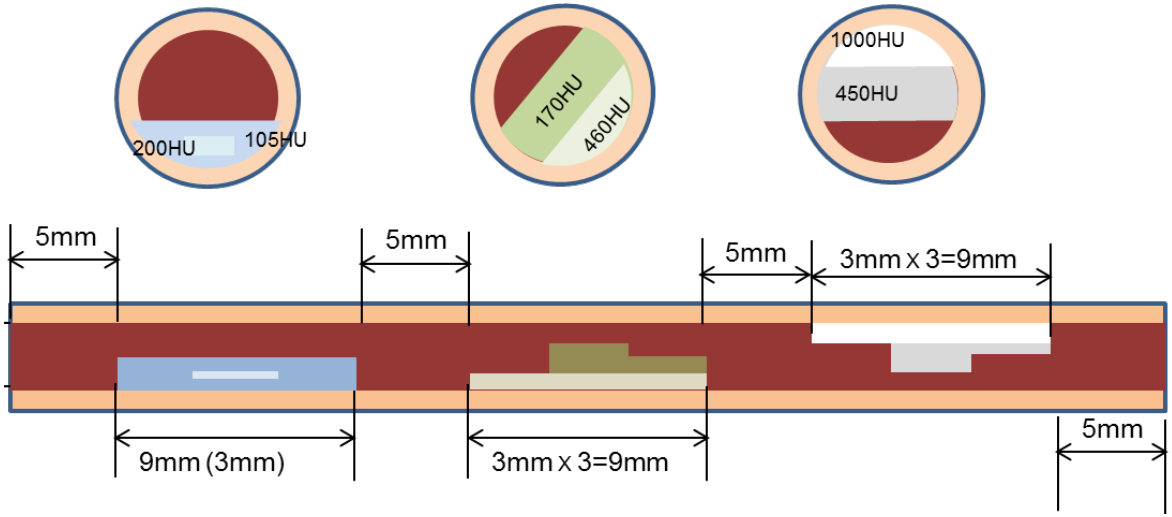
PURPOSE

- None of the previous studies specifically examined gender differences

- Aim is to determine impact of gender on coronary artery calcium scoring
  - Investigate impact of CT recon through imaging gender-specific anthropomorphic phantoms
    - Gender-based breast structure and vessels

GENDER-SPECIFIC VESSELS

- Custom designed 4 synthetic vessels containing stenoses
- Vessel Layout



GENDER-SPECIFIC VESSELS

- Vessel diameters
  - Average diameters for corresponding arteries in women/men*

Diameter of lumen	LM (left main)	LCX (left circumflex artery)
Female	4.0 mm	2.9 mm
Male	4.5 mm	3.4 mm

*Dodge et al. Circulation **86**, 232-246 (1992).

GENDER-SPECIFIC VESSELS

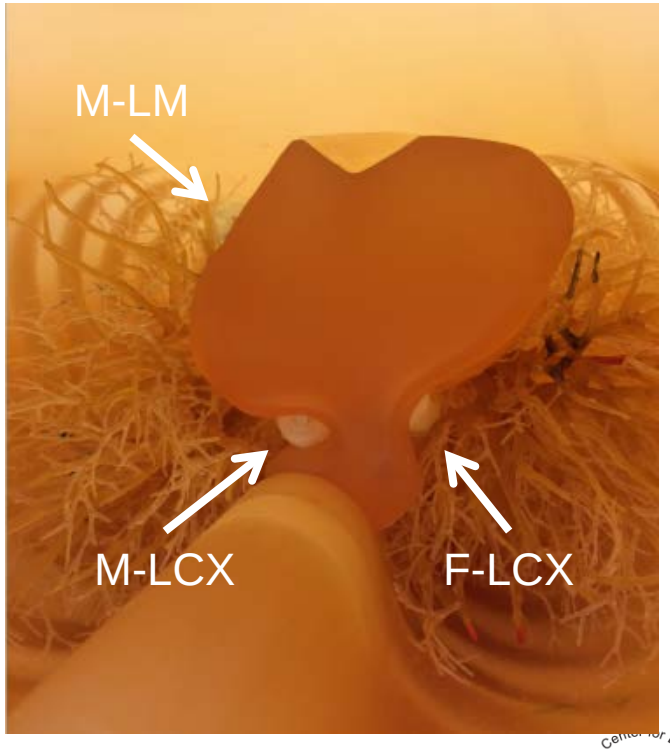
- Vessels wrapped in butter-wax mixture (pericardium) & Styrofoam

F-LM

F-LCX

M-LM

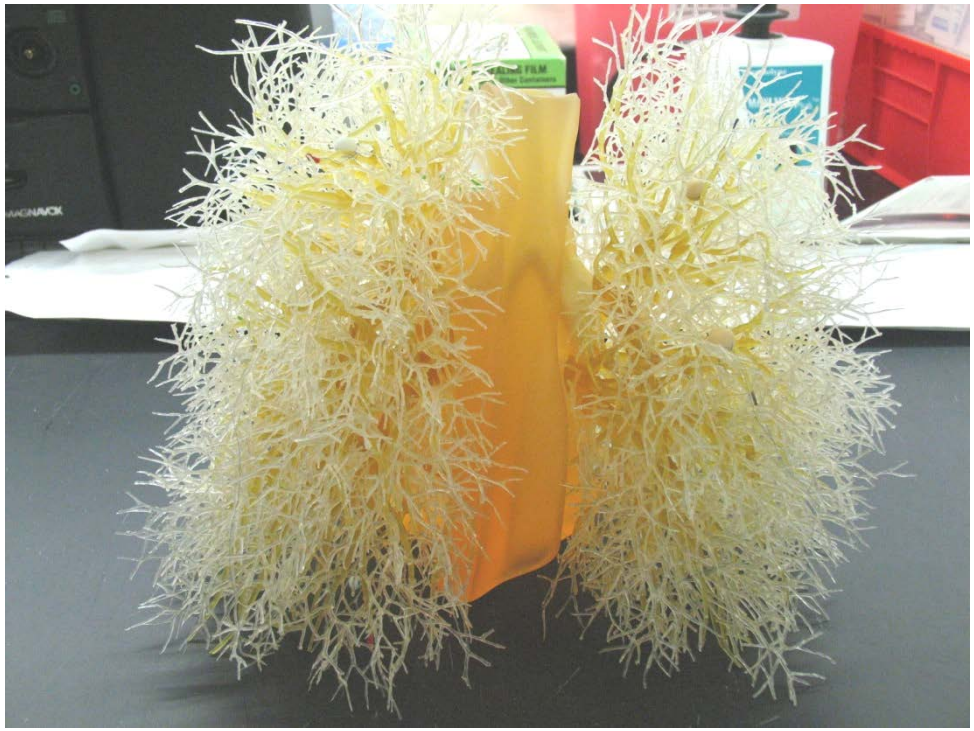
M-LCX



GENDER-SPECIFIC VESSELS

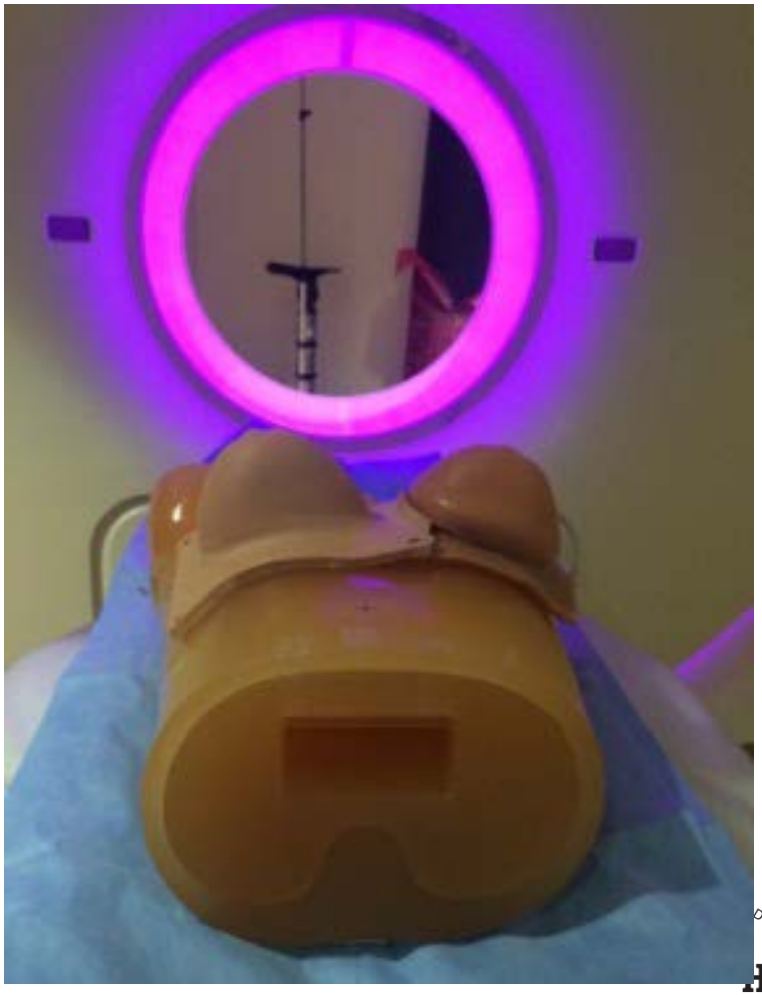
- Reference standard
  - Micro CT for determining true size of calcium

ANTHROPOMORPHIC THORAX PHANTOM



IMAGING PROTOCOL

- Female phantom
  - Imaging with two synthetic breast plates attached to chest
- Male phantom
  - Imaging w/o breast plates



IMAGING PROTOCOL

- Dual-source CT scanner
  - SOMATOM Force, Siemens USA
    - Single-energy mode
      - 120kV, 80 mAs, 192x0.6 mm, 0.2 pitch, 330 ms rotation time
      - $CTDI_{vol}$: 5.98 ± 0.4 mGy
        - Fixed dose for direct comparison between male/female phantoms
    - Retrospective ECG-trigger mode
      - Simulated ECG signal (heart rate = 60 bpm) used as trigger
      - Phantom is static so no lung/heart motion

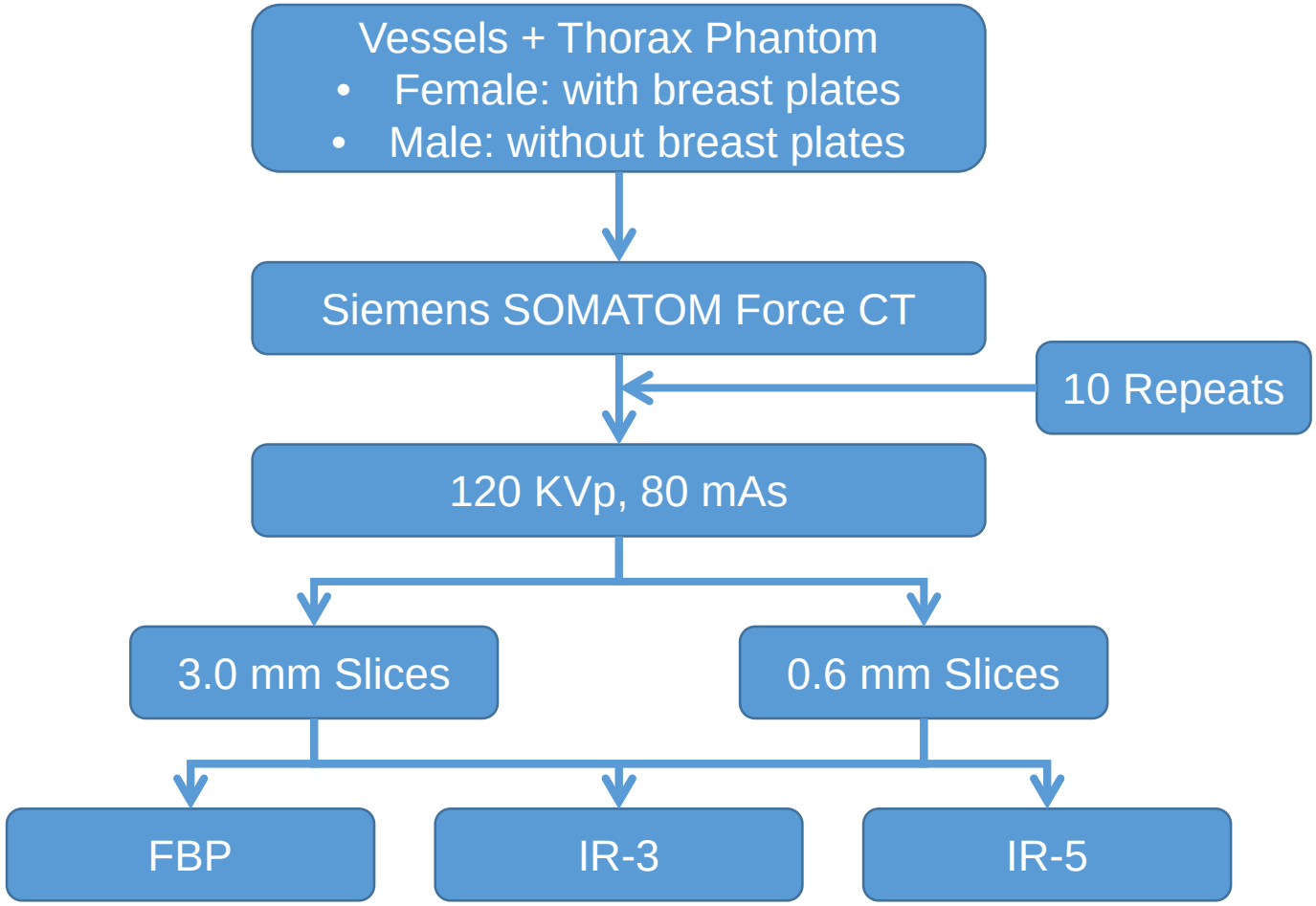
IMAGING PROTOCOL

- Reconstruction
  - Methods
    - Filtered-back projection (FBP)
    - Iterative recon (ADMIRE)
      - IR3: Denoising strength 3
      - IR5: Denoising strength 5
  - Kernel: Br36 (Standard medium-smooth)
  - Slice thicknesses
    - 3.0 mm, 50% overlap (standard calcium scoring)
    - 0.6 mm, 50% overlap

IMAGING PROTOCOL

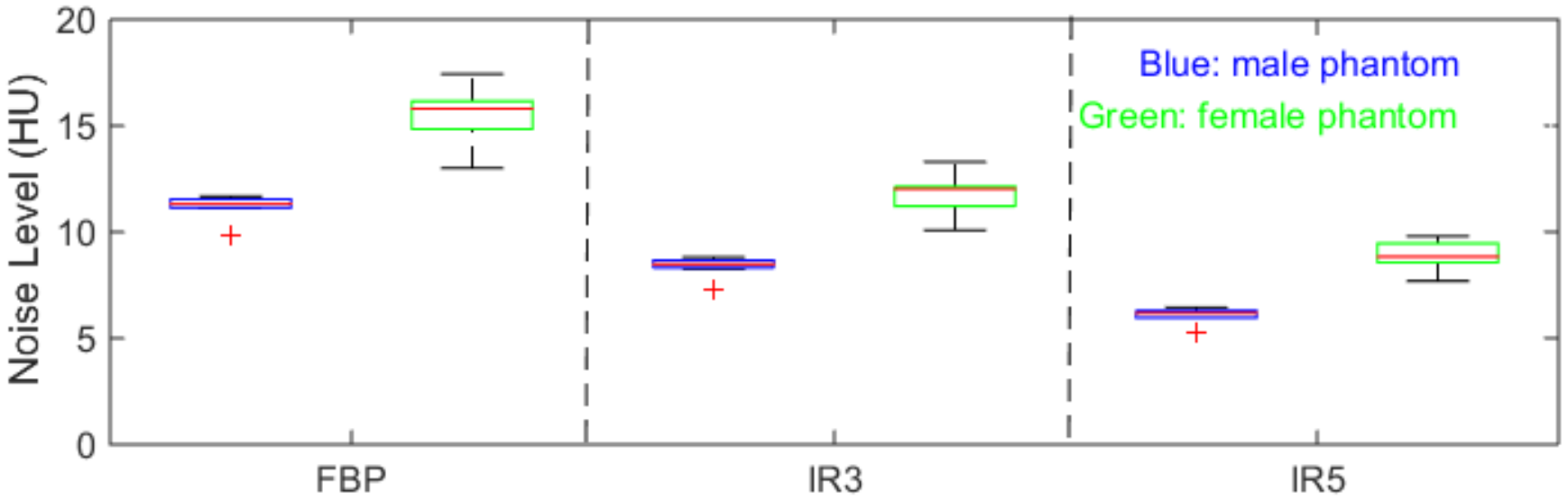
- 10 repeat scans
  - Repositioned phantom between each scan
    - Small random rotation of phantom

IMAGING PROTOCOL



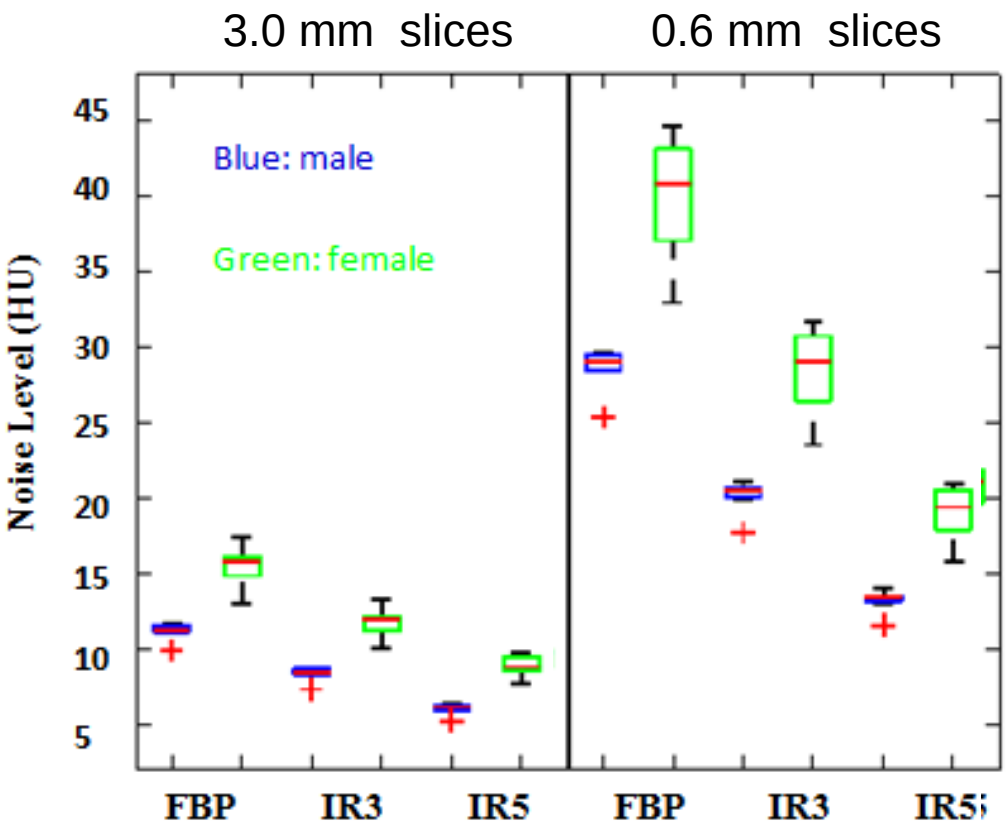
PIXEL NOISE LEVELS

- Female phantom higher noise +4.4, +3.6, +2.9 HU



PIXEL NOISE LEVELS

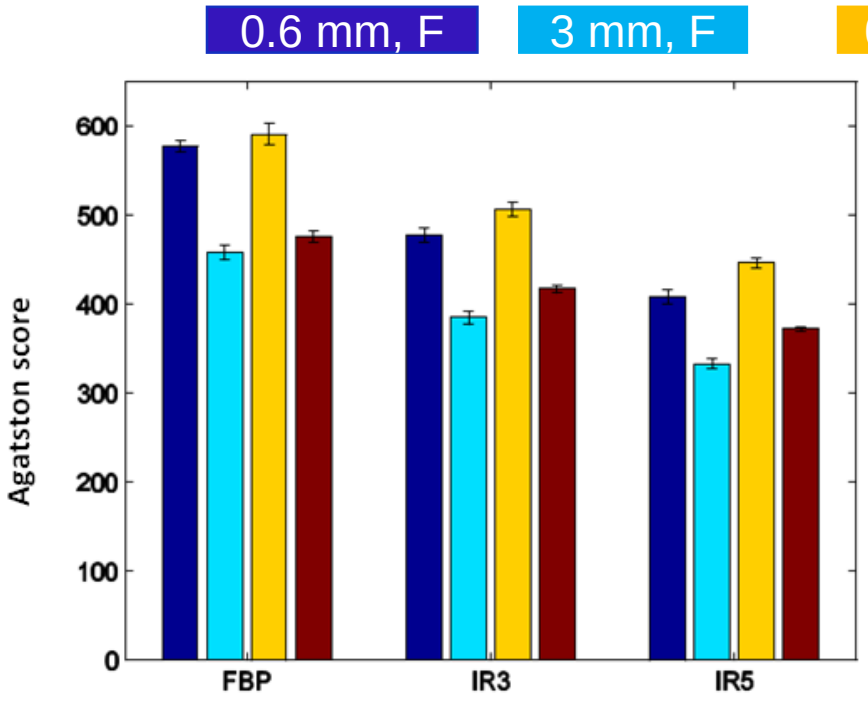
- Higher noise in female phantom/thinner slices as expected

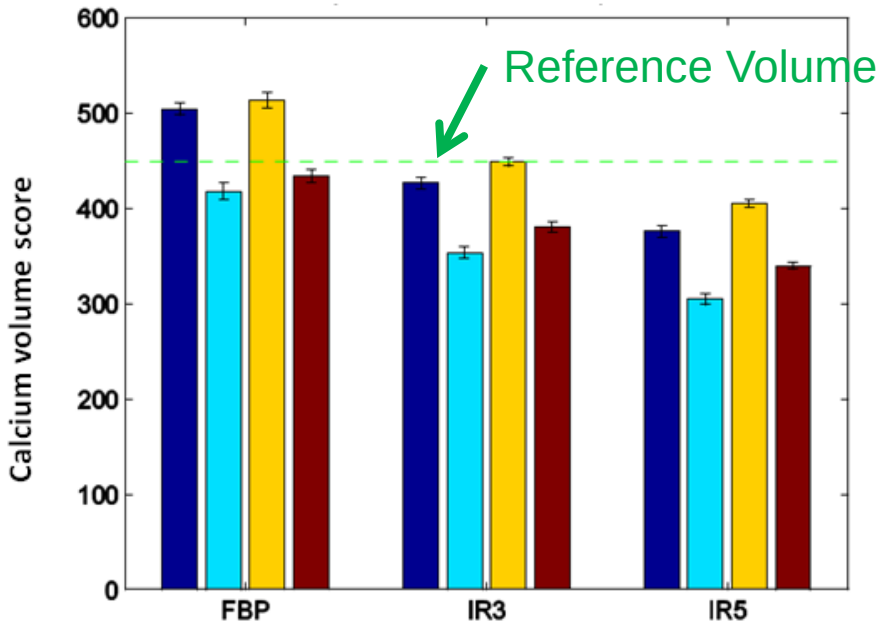


CALCIUM SCORING

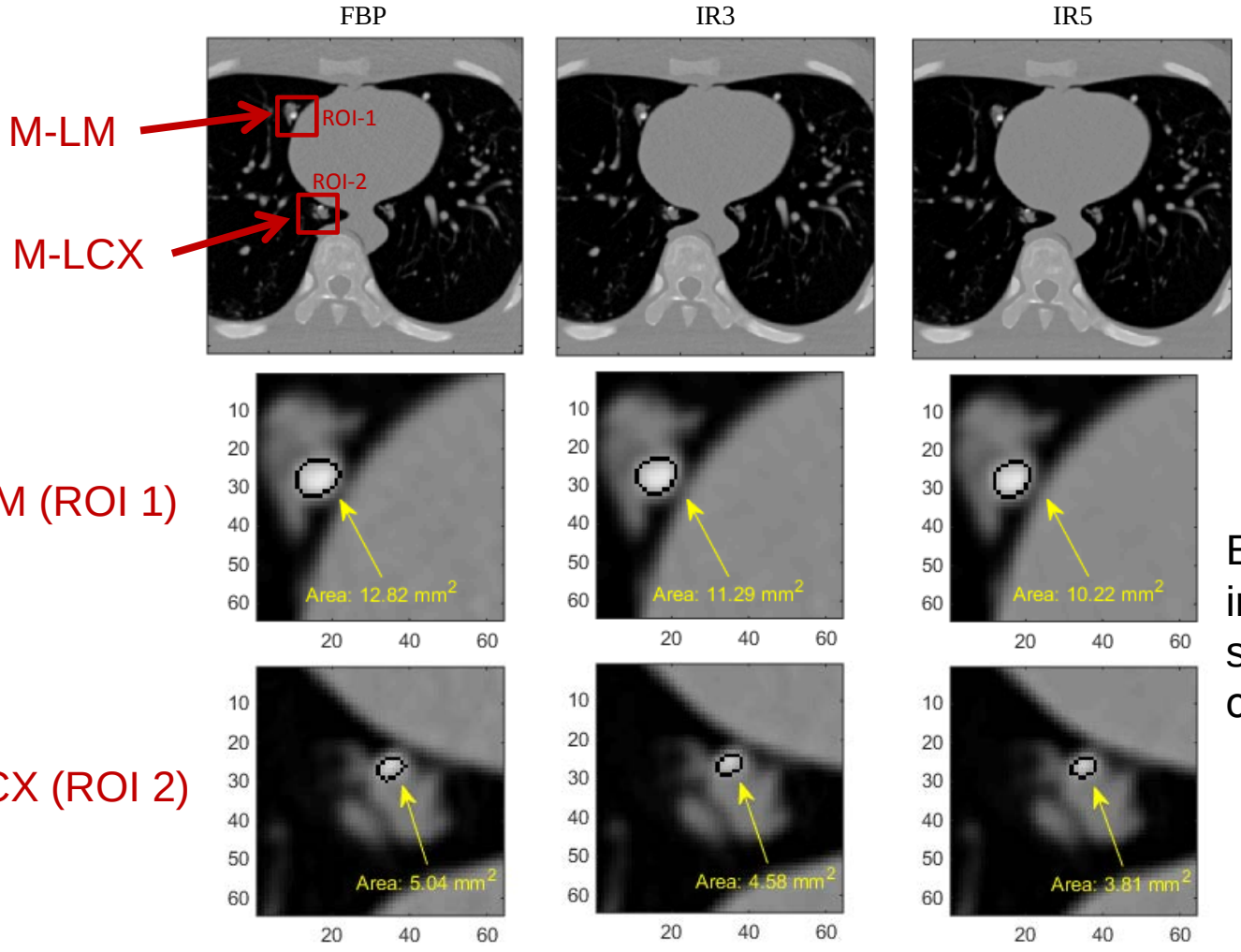
- Total calcium score
  - Sum all four vessels (F-LM, F-LCX, M-LM, M-LCX) in female/male
- Female calcium score
  - F-LM or F-LCX vessel in female phantom
- Male calcium score
  - M-LM or M-LCX vessel in male phantom

TOTAL CALCIUM SCORE RESULTS





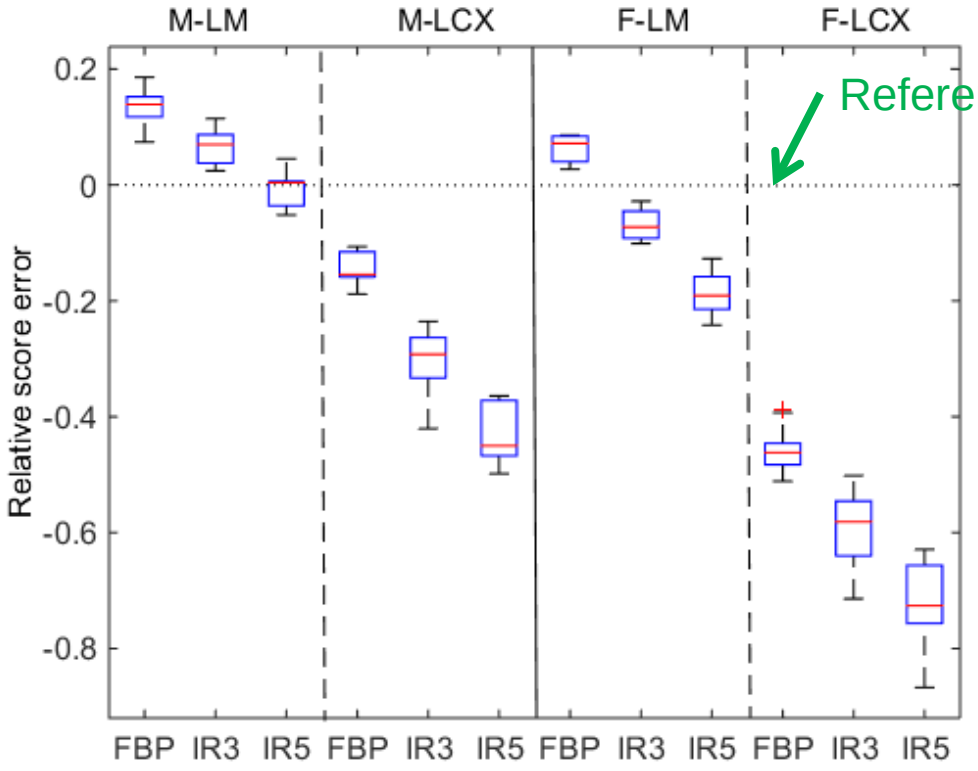
COMPARISON OF FPB AND IR



Black contours indicate segmented calcium (≥130 HU)

GENDER COMPARISON

- Trend to underestimate calcium score when vessel is small & imaged in female phantom

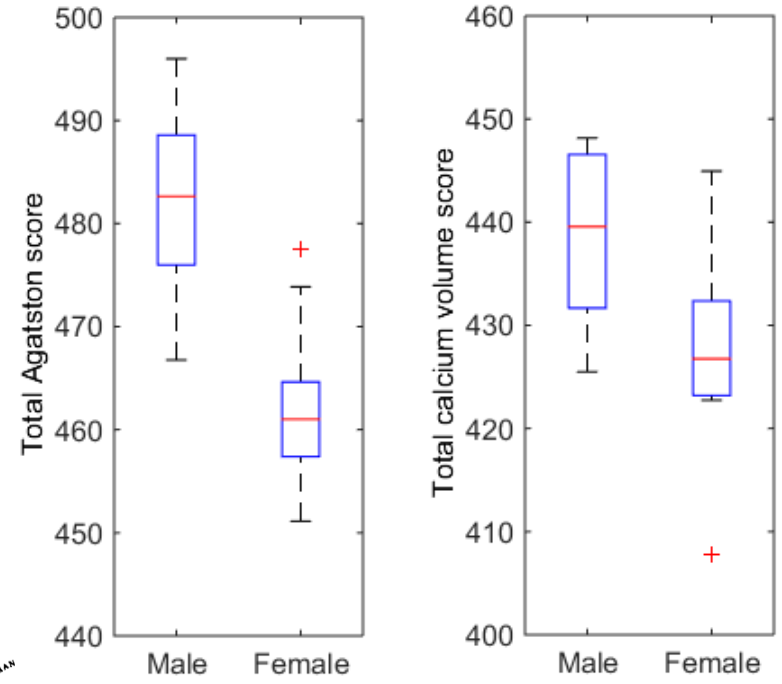


- $Relative\ Error = log\left(\frac{Measurment}{Refernce\ Standard}\right)$
- 3.0 mm slices

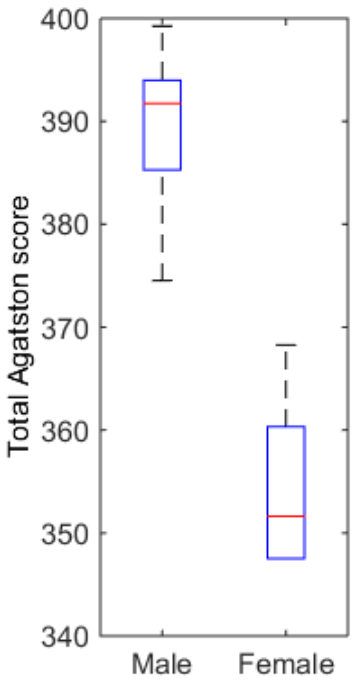
CCS (Agaston)	Risk
0	Non-identified
1-10	Minimal
11-100	Mild
101-400	Moderate
>400	High

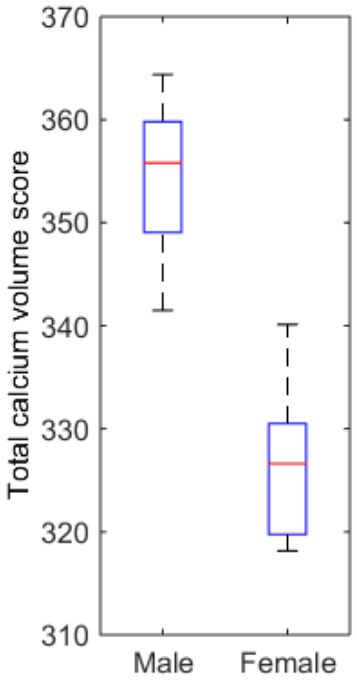
GENDER COMPARISON

- Gender-specific total calcium scores



FBP





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GENDER DIFFERENCES IN CALCIUM SCORING

- Smaller vessels, female breast anatomy and IR significantly decrease calcium scores
- 0.6 mm slice thickness yields higher scores than 3 mm slices
- Imaging protocols & patient characteristics impact calcium score
  - May lead to inconsistent interpretation of patient risk

SUMMARY

- Part 1: Quantitative imaging at CDRH
  - Interested in developing alternate least burdensome pathways for QI for inclusion of enhanced information (e.g., error bars) or claims
- Part 2:
  - Implementation of calcium scoring within a lung cancer screening program requires corrections/modifications for compatibility with current practice

ACKNOWLEDGMENTS

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- The authors thank the assistance of Jiamin Liu (NIH) in supporting data collection