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1 Introduction

The Framingham Heart Study (FHS) is conducting a study of the genetic and environmental determinants of sub-clinical coronary, aortic and cardiac calcification and their relations with clinical CVD. A multi-detector CT scanner is being used (General Electric Lightspeed + 8 detector scanner) in 1200 Offspring Cohort subjects and 1900 selected Generation 3 subjects (plus approximately 400 from the Family Study) to detect and quantify coronary calcification and abdominal aortic calcification. This document is the manual of operation for the CT exam of the Framingham Heart Study, June 2002 through June 2007. Scanning of participants was completed in April 2005. Scoring of the thoracic aorta calcification plus measurement of the phantom was ongoing since 2005. Total completion occurred at the end of June 2007.

1.1 Summary of Updates to Manual of Procedures

Detailed below are the significant developments since the start of the study, including: finalization of our software and reading protocols for calcium scoring; full implementation of procedures for review and reporting of high calcium scores and incidental findings; and complete harmonization of age-criteria of both the Framingham and Family Heart Study CT protocols, including the addition of a 'possibly pregnant' screening questionnaire for all premenopausal women. Collaboration with the Family Heart Study ended in December 2003 at the end of their enrollment period.

a. Scanning Protocol. There have been no modifications to the actual scanning protocol since the start of the study.

b. Summary of Procedures.

1) *Change in calcium scoring software from the General Electric package to TeraRecon in early 2003.* In early 2003, [redacted] and colleagues recommended we conduct our calcium scoring with the Aquarius software package (TeraRecon, Inc), to which the MGH had full access. Among the many distinct advantages offered by the TeraRecon software package over and above the General Electric package: i. ease of use by technicians and physicians; ii. substantially reduced time to conduct scoring per patient; iii. readily available flatfile database of all completed calcium scores, in a format that can be easily transferred to the Framingham database, with variables including vessel-specific data for calcium volume, mass and Agatston score; and iv. ease/ability to modify software to user specifications. In addition to providing the MGH-based workstation, TeraRecon has provided additional copies of its software for use on two workstations sited at the FHS site for the duration of our Framingham CT study. In a

blinded pilot test of the TeraRecon package, our MGH colleagues determined that calcium scores were virtually identical whether conducted using the GE or the TeraRecon software.

2) *Continuation of reporting of high calcium scores.* We have completed training of our initial CT technician [redacted] and her replacement [redacted] Each participant with a calcium score $\geq 90^{th}$ percentile receives a letter notifying her/him to contact her/his physician, who is sent the actual calcium score.

3) *Initiation of incidental findings readings and reporting in early 2003.* The initial scan review protocol called for the reporting of potentially clinically important "incidental findings" for scans undergoing a "quality assurance" review. Under the original protocol, a quality assurance review was conducted on a limited number of scans. However, in early 2003, we modified the review procedure for IFs. Now, a systematic review is conducted by one of four MGH radiologists of every CT scan to identify potentially clinically important IFs. If an IF is identified, a more thorough review of the scan is conducted for other IFs, and an IF report is prepared.

4) *Initiation of additional measures to screen for possible pregnancy.* See new Pregnancy Screening Procedures (below).

c. Incidental Findings.

1) *Reading scans for IFs.* A thorough review and report for potential IFs on all scans began in late winter/early spring. As of August 31, 2003, an IF review was completed for 1110 subjects, or approximately 75% of all subjects scanned. Some unanticipated logistical issues delayed our ability to rapidly reduce the large initial backlog of unread scans, including slow transfer times for uploading scans to the TeraRecon workstation at MGH, availability of only a single workstation for three MGH radiologists (for IF readings) and the FHS CT technologist (for

calcium scoring), and hardware/storage issues leading to delays in transfer of images from the MGH West site to the TeraRecon workstation at MGH. After a collaborative effort by MGH, FHS and TeraRecon staff, these delays have been significantly reduced at the MGH reading center site, and two fully functional workstations (for exclusive use by the Framingham CT technician) have been placed at the FHS site. Also, a fourth radiologist has been added to the IF reading team. By June 2005, all IF's were completely read and reported (scans were completed by April, 2005).

2) *Reporting IFs to each participant and his/her MD.* A report is completed for every IF and the report is sent to [redacted] and his staff for review. Initial IF reports were carefully reviewed by [redacted] and the MGH radiology staff to ensure that style, clarity and clinical recommendation are consistent with reporting of other research tests in the FHS. Within a few days of receipt by [redacted] of the IF report, the report is sent with a cover letter to the participant's MD, and a second letter is sent several days later to the Framingham participant. Additionally, reports and letters are sent early in the week. We implemented this sequence of reporting after we received statements of concern from a few subjects who expressed anxiety related to uncertainty because they received the IF report before their MD. In all such cases, [redacted] discussed the findings with the participants. As of August 31, 2003, an IF report was mailed to the participant's MD for 211 subjects, or 19.0% of all scans reviewed for an IF. When subjects have questions about their IF, they are referred to both their PCP and, if desired, to [redacted] Additionally, a handout of frequently asked questions was drafted to be provided to participants and as a resource. By June 2005, all IF reports were completely read and reported to the participants and their physician.

d. Calcium Scores. As of August 31, 2003, coronary calcium scoring has been completed on 844 subjects, or approximately 57% of all subjects scanned. Our goal is to complete a calcium score on all subjects within 8 weeks of completion of the scan. In August 2003, our first CT technician [redacted] resigned from the FHS (to attend medical school), and she was replaced by one of senior research coordinators, [redacted] Both [redacted] completed extensive training in CT scoring under MGH radiologists working in [redacted] group, and both have completed coronary and aortic calcium reproducibility scoring for 125 FHS participants using the TeraRecon workstation. The inter-reader correlation was excellent between the two FHS technicians and between each FHS technician and two MGH radiologists. All 3500 scans (including the 400 from the Family Study) were completely scored for coronary artery calcium by May, 2005. All scans were scored for thoracic aortic calcification and phantom measurements and were completed by June, 2007.

e. Adverse Events. There were no adverse events.

f. New PG Procedures. In September 2003, we reported to the OSMB an inadvertent exposure of a 38 year old pregnant participant in the Family Heart Study-SCAN/Framingham Heart Study. This incident was reported to the OSMB of the Family Heart Study as well as the Institutional Review Board of the Boston University. Our response to this incidence is summarized in the memorandum of September 9, 2003 to the FHS. Since the writing of that memorandum, we have implemented the following measures: a. obtained Boston University IRB approval for and implemented a supplement to Pregnancy Determination Form to screen for possible pregnancy; b. enforced strict adherence to the age criteria for all FHS participants who are also participating in the CT study, regardless of participation in the Family Heart Study-SCAN; c. continued urine pregnancy testing; and d. trained all coordinators and recruiters regarding proper implementation of the new pregnancy screening measures.

2. CT Exam Protocol Overview

FHS is conducting a multi-detector CT scan using a General Electric Lightspeed +8 detector scanner in 1200 Offspring Cohort subjects and 1900 selected Gen 3 subjects to detect and quantify coronary calcification and abdominal aortic calcification. Due to the anticipated low prevalence in young persons, women < 40 years of age and men < 35 years of age are excluded.

Furthermore, all pre-menopausal women who have not had a hysterectomy or tubal ligation will require a negative screening urine pregnancy test (QuSTICK ™ Pregnancy test, STANBIO Laboratory) conducted by Framingham Heart Study staff within 24 hours prior to the scheduled test. However, urine pregnancy testing with this and other assays cannot detect pregnancies until 6 days after conception. Thus, to minimize the risk of performing a CT scan on a woman whose very early pregnancy might not be detected by the pregnancy test, we have decided it is necessary to administer a brief questionnaire in all pre-menopausal women *in addition to conducting the pregnancy test.*

Eligible subjects are contacted by phone or in the Generation 3 initial clinic visit to schedule the CT test. Subjects are asked to transport themselves to Massachusetts General Hospital West, on Route 128 in Waltham, MA (approximately 20 minutes by automobile from the Framingham Heart Study). The Framingham Heart Study does provide transportation for persons unable or unwilling to drive to the site.

After providing proper informed consent, each subject is escorted to the changing room to remove any clothing that has metal (i.e., pants with zippers, bras, etc) and is given a jonnie top to wear open in the front, and hospital pants if needed. The subject lies down on the imaging couch and has the ECG leads placed on their chest and the couch is then moved within the scanner. One scout image, two coronary images and one abdominal image are obtained during a total session within the scanner that takes no more than 15 minutes and requires three short (<20 seconds/each) breath holds. A QCT phantom is positioned beneath the

participant's heart and abdomen. The total anticipated door-to-door time for the scan is less than or equal to 30 minutes.

Scans are being conducted for research purposes, however, in the event that the research evaluation of the scan uncovers clinically important findings that require medical diagnosis for treatment, this information will be provided to the participant and their doctor. Also, because there is a lack of consensus on the clinical utility of coronary calcium scores, we are not routinely notifying or reporting calcium scores to all subjects. However, we are routinely reporting calcium scores to physicians of subjects with a $>90^{th}$ percentile score for age and sex.

In addition, Quality Assurance readings are ordered on each scan and clinically important incidental findings are identified and reported to physicians of subjects. The General Electric scanner undergoes a daily QC test. In addition, a calcium density phantom is used during each scan and QCT calibration phantoms are imaged every 15 days, in an identical manner to the Family Heart Study-SCAN protocol. An Agatston calcium score for the coronary arteries and aorta is generated for each participant using TeraRecon, which is installed and currently functioning on GE Scanners at the Waltham campus and the main MGH campuses. The study begins by generating coronary calcification scores using TeraRecon. This is the same general analysis algorithm being used by the Multi-Ethnic Study of Atherosclerosis (MESA) study, and the Framingham Heart Study. We have ascertained that the procedures for imaging, reproducibility, quality assurance, and image analysis in the Framingham Heart Study are similar or identical to those being used in the MESA study and the NHLBI Family Heart Study-SCAN study as well as the NHLBI Coronary Artery Disease in Young Adults (CARDIA) study. This allows consistency across ongoing NHLBI studies.

3. Study Personnel

Framingham Heart Study Personnel

Framingham Heart Study
73 Mt. Wayte Avenue
Framingham, MA 01702 / Telephone # (508) 872-6562

Lead Staff	**Study Coordinators and Recruitment Staff**
[redacted] Principal Investigator CT Study, FHS [redacted] FHS [redacted] FHS [redacted] FHS	[redacted] Offspring Study Coordinator [redacted] Third Generation Study Coordinator [redacted]

Statistical and Data Management Staff	**MGHW Liaisons/FHS Research Assistants**
[redacted]	[redacted] (past) **FHS Research Assistant** [redacted] (past)

Family Heart Study Staff

[redacted]
Family Heart Study Coordinator
[redacted]

Massachusetts General West Imaging Center Personnel
40 Second Avenue
The PARC Center Suite 120 (CT/MRI Services)
Waltham, MA 02451 / Telephone#: (800) 697-8296

Supervisor [redacted]
Technical Manager [redacted]
CT Technicians [redacted]

Radiology Staff- MGH Boston
100 Charles River Plaza
Boston, MA 02114 / Telephone #: (617) 726-3033

Head of CIMIT office, MGH Boston [redacted]
Supervising Radiologist [redacted]
Radiologists [redacted]

MGH RADIOLOGIST CONTACT LIST FOR CT STUDY

[redacted]Cardiologist, Head of CIMIT Office
[redacted]
Effective Date: June, 2002

[redacted]Radiologist
[redacted]
Effective Date: June, 2002

[redacted]Radiologist
[redacted]
Effective Date: June, 2002

[redacted]Radiologist
[redacted]
Effectuve Date: May, 2003

[redacted]adiologist
[redacted]
Effective Date: June, 2003

4. Framingham Heart Study CT Examination Protocol and Procedures

4.1 Pre-and post-scan procedures at FHS

a. Eligibility

Women: The CT scan will not be done on women who are pregnant, who may be pregnant, or who have been breast-feeding for less than six months. Women must be age 40 or older.

Men: Must be age 35 or older.

All participants must weigh less than 352 pounds.

b. Scheduling

Prior to calling participants, the calling list is checked for priority needs, i.e. whether a participant is also in the Family Study, and to determine the eligibility of Offspring spouses. The recruiter reviews the Roster Screen for each participant for any pertinent information prior to placing a call. When the appointment is scheduled women are screened for age, and pregnancy or postmenopausal status. If transportation is needed the participant is scheduled in coordination with the Family Study transportation needs.

The appointment is then entered into the CT Booking Screen and the CT scheduling book. The participant is classified according to their participation in the Framingham Heart Study and/or the Family Heart Study and if the participant is a priority for both studies, i.e. age and other factors. If a pregnancy test is needed it is also documented when scheduled. Other factors, such as health issues, are also noted as needed.

Once the **schedule**† for a given day is complete, it is run and printed, proofread and emailed to the facility one week ahead. Appointment letters with directions to MGH-West are sent to the participant two weeks prior to their scheduled appointment. Folders are prepared containing the **Completion Form, Consent**

Forms, Pregnancy Determination Form (for women only), and if needed, **Health History Update Form**[1] along with a Folder checklist. Reminder calls are made one day prior to the appointment.

c. Pre-CT exam instructions for participants

There is no outside preparation that the participant must perform before having a CT scan. The Framingham Heart Study coordinators notify women who are able to become pregnant that they must undergo a pregnancy test at MGH West before having a CT scan. Because the urine pregnancy test cannot detect pregnancies of less than one week, pre-menopausal women are told that they should not have unprotected sexual intercourse for 7 days prior to the CT scan. Study Coordinators also arrange transportation for participants who require or request it.

d. Tracking participant information at MGH and FHS

On the day following appointments, schedules are collected from liaison staffers, the numbers of completed scans are tallied and the schedule is put into a binder. Reports are generated for those participants with a significant incidental finding and/or those participants whose values are above the predetermined threshold. The report is sent to the participant's physician along with a cover letter from the Principal Investigator, [redacted]

[1] To view these forms refer to the following appendices: Schedule-Appendix 17; Completion form-Appendix 18; Consent form-Appendix 8; Pregnancy Determination form-Appendix 14; Addendum to Pregnancy Determination From- Appendix 15; Supplement to Pregnancy Determination Form- Appendix 16; Heath History Update form-Appendix 20; and Thank You Letters-Appendices 22-24.

4.2 Verifying the Identity of the Participant at MGH West Imaging

The liaison asks the participant their full name and has them state their date of birth. This information is matched to the schedule and paperwork to make a positive identification of the participant. The liaison is alert to the fact that there are often relatives with the same name but for Jr. or Sr. If there is any doubt as to the person's identity the liaison uses the address and phone numbers on the schedule as further confirmation. If there is still doubt, the liaison calls the appropriate FHS coordinator for assistance. In addition, the MGHW CT tech introduces her/himself, asks the participant to state his/her name and leads the participant into the CT scanning room. To verify identity, the tech then asks the participant to spell his/her last name, and to state his/her date of birth.

4.3 Obtaining Informed consent

All Framingham Heart Study Participants are required to sign a **Consent form** (Appendix 8) prior to the CT scan. A trained FHS staff member at either the Framingham Heart Study or at Massachusetts General Hospital West administers consent forms. The informed consent is administered in a semi-private area. If further privacy is needed a conference room outside of the CT suite is available. Once the participant has read the form s/he is given the opportunity to ask questions. Once all of the participant's questions and concerns are addressed s/he may sign the consent form and will be given a copy for his/her records.

4.4 Determining Pregnancy Status

A urine pregnancy test is used in the Framingham Heart Study CT Study to screen for pregnancy (QuSTICK ™ Pregnancy test, STANBIO Laboratory). However, urine pregnancy testing with this and other assays cannot detect pregnancies until 6 days after conception. Also, although in most cases we obtain a pregnancy test immediately before the CT exam, we allow up to 24 hours between the urine pregnancy test and the CT scan, so conception (a pregnancy) could theoretically occur during the 24 hour time period between pregnancy testing and the CT scan. Thus, to minimize the risk of performing a CT

scan on a woman whose very early pregnancy might not be detected by the pregnancy test, we have decided it is necessary to administer a brief questionnaire in all women of childbearing potential *in addition to conducting the pregnancy test.*[2]

4.5 Participant Preparation at MGH West

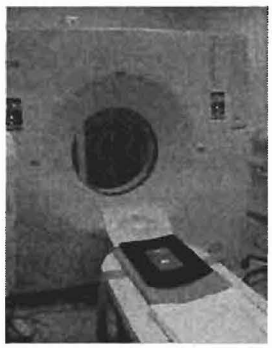
The Framingham Heart Study liaison reviews the CT schedule form provided by the CT coordinator and ensures that all the necessary paperwork is present and filled out correctly. After providing proper informed consent and for female participants, after determining pregnancy status and if necessary administering a pregnancy test, the liaison escorts the participant to the changing room to get changed. The participant is asked to remove any articles of clothing that contain metal (i.e., pants with zippers, bras, etc). If they need to change their pants, hospital pants are provided. The jonnie top must be worn open in the front to facilitate easy access for the placement of electrodes. Participants only have to remove jewelry that hangs below the nape of his/her neck.

Once the participant is changed they are brought into the scan room by the CT technologist, where they will then be asked to spell their last name and state their date of birth. Beginning in September of 2003 the CT technologists ask every non-exempt female participant if there is any possibility that she may be pregnant. After the participant confirms that there is no possibility that she could be pregnant the tech initials the pregnancy field of the Completion Form. The CT technologist then instructs the subject on the importance of breath holding and immobility during scanning. (Preliminary studies by [redacted] suggest that at least 99.5% will be able to hold their breath for more than 15 seconds and 80% will be able to hold their breath for more than 30 seconds.) Only after the technologist is satisfied that the subject understands the importance of breath holding does he/she proceed with the exam. The technologist attaches 4 electrocardiography electrodes under the left and right clavicle and on either side of the thorax near the axilla (to maximize ECG signal).

[2]The Self-Administered Questionnaire was implemented September 15, 2003.

4.6 Positioning of the participant on the QTC Phantom/CT Couch

A feet-first protocol is used for the FHS scan. The rectangular calcium calibration QCT Phantom is placed underneath the chest and abdomen and is included in the field-of-view for both cardiac CT scan series as well as the abdominal scans. A foam cushion and a special gel filled mat is placed between the phantom and the subject to insure appropriate contact is provided with the calibration pad phantom to prevent artifacts and provide for subject comfort. The calibration phantom is placed inside the blue catcher bag with its long axis parallel to the long axis of the scanning table. The phantom is made of tissue equivalent plastic with rods of hydroxyapatite of known radiographic density. For the cardiac and abdominal scans, the QCT Phantom is positioned directly behind the thoracic spine and the heart as well as the abdominal spine. The superior extent is above the carina and extends inferiorly to the sacral spine.

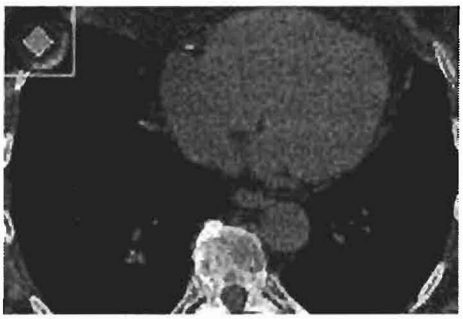


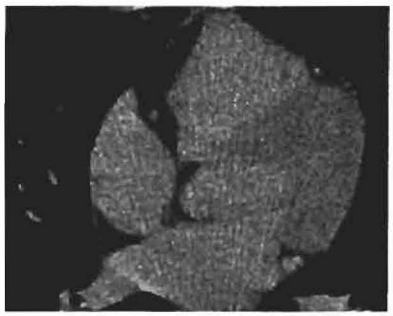
4.7 Coronary and Aortic Imaging

The CT examination is designed to efficiently and accurately provide volumetric CT image data for measuring coronary and abdominal aortic calcium. The examination consists of scout images, 2 cardiac gated series of the heart to measure coronary calcium and a helical (volumetric) acquisition of the abdominal aorta to measure aortic calcium. On average, 20 minutes of participant time is spent within the CT scan suite; this includes instructions, setup and imaging. In rare cases, the examination may require 30 minutes. In many cases, the examination is completed in less than 15 minutes. Participants have ECG

electrodes attached for cardiac gating and are instructed as to standardized breath holding instructions

(Appendix 21).





CT Scans:

Series	Description	No. of images	Scan time	ECG gating
1	Scout of thorax and abdomen[1]	2	7 sec x 2	No
2	Coronary scan 1[2]	40-50	20-40 sec	Yes
3	Coronary scan 2[2]	40-50	20-40 sec	Yes
4	Abd. Aorta scan	60	30	No

[1]Scout images will consist of a frontal and lateral low energy 2D scanogram

[2]Duplicate scans will be obtained of the coronary circulation to improve the precision of the calcium measurement in the first 500 patients

5. Radiation Dose Estimates of the FHS CT Examination and Protocol Adherence for Radiation Exposure

The CT examination uses ionizing radiation (X-rays) to generate images of the participants. The level of exposure utilized in this particular CT examination is on the same magnitude as that typically used in other diagnostic CT imaging. The next section describes the potential risks of exposure to low levels of radiation and where in continuum from the average natural exposure of 3.6 mSv annually the dose for participant in this study is located. The radiation exposure in this CT examination is well below the threshold for any observable direct dose related effects of ionizing radiation. Therefore, the theoretical concerns of low-level radiation exposure for participants of Framingham Heart Study CT Study are the potential for hereditary defects, developmental defects and cancer induction. These potential risks are detailed along with steps that have been taken to further reduce these potential risks.

Radiation induced hereditary defects: "Despite comprehensive studies of the children of the atomic-bomb survivors in Japan, there remains no evidence for heritable effects in humans (UNSCEAR, 1993)."(NCRP Report 124, Mar. 1996, p. 12). To further reduce this potential risk the gonads (testes and ovaries) are not directly irradiated in the CT examination.

Radiation induced developmental defects: "High radiation doses can cause death, malformation, growth retardation and functional impairment. However, low doses (<0.2 Gy) do not appear, in general, to affect the developmental process." (NCRP Report 124, Mar. 1996, p. 12). To further eliminate this potential risk, women who have the potential to be pregnant (i.e. functioning ovaries and uterus) are required to have a pregnancy test prior to being eligible for an Framingham Heart Study CT examination.

Radiation-induced oncogenesis: "Cancers arising in various organs and tissues are the principal late somatic effects of radiation exposure. As a very general guideline, the BEIR V Report (NAS/NRC, 1990) suggests a fatal cancer risk estimate of four cancers per 100 mSv in 1,000 exposed individuals. At the doses of 2.5 to 5 mSv experienced by nuclear medical personnel annually, the cancer risk is small. To place this in perspective, if an unexposed population of 1,000 persons was exposed to doses of 5 mSv y^{-1} for 40 y there could be eight cancers in addition to the 210 cancer deaths that would occur in that population due to the normal incidence of cancer in the population of the United States." (NCRP Report 124, Mar. 1996, p. 13). In this study participants receives a one-time exposure of 5.7 to 6.4 mSv as opposed to the same exposure over 40 years described in the above example. The exposure in this study is also less than the cumulative exposure of the active and approved MESA (3 CT examinations of the heart) and CARDIA (2 CT examinations of the heart) protocols.

This section provides an estimate of the radiation dose that results from the CT scans performed as part of the research study "Framingham Offspring/Generation 3 CT Scan Examination". The calculations in this section were performed by [redacted], and Medical Physicist UCLA Department of Radiological Sciences in conjunction with [redacted] of Wake Forest University Medical Center. These calculations were used for the Family Heart Study-SCAN the revision history of the dose estimates is as follows: The initial dose estimates calculated as part of the grant submission were prepared by [redacted] in conjunction with [redacted] Division of Radiological Sciences Wake Forest Univ. School of Medicine. At the request of the NIH, an external review of the calculations was performed by [redacted] and submitted to NIH in a letter prior to the awarding of the grant in September of 2001. As detailed in this letter, the plan was to finalize the CT scan protocol and equipment to be used at each field center and provide an accurate but conservative estimate of radiation exposure.

As specified in the preceding sections of this MOP, Framingham participants will have a CT examination that consists of the following components:

1. The coronary scans 1 & 2 are identical by design to those currently in the field in both the NHLBI-funded MESA and CARDIA studies as well as the Family Heart Study-SCAN Study. Like these other studies, we conduct 2 coronary scans in our Multi-detector CT (MDCT) protocol in order to maximize the reproducibility of our scans and comparability with other NHLBI studies. However, we do plan to evaluate test-test agreement after approximately 500 scans are scored, and regularly thereafter for reproducibility reporting. After the scoring of the first 500 scans, Framingham Heart Study investigators, and MGH investigators will discuss possible reproducibility criteria that might justify only one coronary scan in consultation with NHLBI staff involved with the Framingham Heart Study MDCT study and other NHLBI CT studies. These data will be reviewed and discussed together by Framingham Heart Study investigators, MGH investigators and NHLBI staff for evidence of reproducibility sufficiently high thresholds to consider omission of one of the 2 coronary scans.

2. The abdominal CT protocol includes a limited scan of the abdominal aorta. Using the same protocol and the rationale of other NHLBI studies that coverage of the entire infrarenal aorta was advantageous, the coverage includes 15 cm of length. This provides complete coverage of the infrarenal aorta and imaging of the lumbar spine and visceral fat for future analysis.

Participants undergoing the MDCT examination will have:

1. Peak radiation dose of approximately 2.5 rad (25 mGy) at the peripheral position (essentially the skin) of the patient.

2. Highest doses to radiosensitive organs are approximately 1.3 rad (13 mGy) to the lungs and approximately 1.4 rad (14 mGy) to the female breast.
3. An estimate of effective dose would be 5.7 to 6.4 mSv per CT examination that is broken down by sequence below.

Summary of Effective Dose Estimates-Table 1

Sequence	Description	Deff [mrem]	Deff [mSv]
1	coronary axial 1	150 to 190	1.5 to 1.9
2	coronary axial 2	150 to 190	1.5 to 1.9
3	Abd. Aorta helical	270	2.7
	Total	570 to 640	5.7 to 6.4

Note: [redacted] stated that the radiation exposure related to the low energy scouts / topograms were inconsequential in dose compared to the above series; as a result they are not detailed in the above table.

These estimates of effective dose can be compared to the annual average effective dose from background radiation, which is 3.6 mSv/year and the annual whole body effective dose that a radiation worker (radiologist, radio logic technologist) is allowed on an annual basis (50 mSv/year). Thus, the patient receives the equivalent of approximately 1.58 to 1.78 years of background radiation from the CT scans. Alternatively, this is 12.8% (6.4 mSv/50 mSv) of the annual allowance of 50 mSv for radiation workers.

5.1 Detailed Discussion of Dose Estimates

Examination description

The CT examination consists of the series of scans described above with repeat series (total of 2) through the coronary arteries using standard techniques and one series through the abdominal aorta.

Technical factors for each series used in the dose estimates

a. Coronary Scans 1 and 2 (which are identical sequences)

Using the GE LightSpeed multidetector scanner, the standard protocol are employed:

4 x 2.5 mm collimation (4i axial) mode with 10 mm table increment (contiguous scans).

Prospective EKG gating; x-ray beam is only on 2/3 of a scan rotation 140 KVp, 150 mA, 0.5 second scans.

Scan Coverage: 2 cm below the carina extending to the base of the heart.

b. Limited Scan of Abdominal Aorta

Using the GE LightSpeed multidetector scanner, the following protocol are employed:

4 x 2.5 mm collimation with Helical HQ mode (table speed of 7.5 mm/rotation)

140 KVp, 250 mA, 0.5 second scans. Scan Coverage: starting 15 cm above S1 vertebra and stopping at the superior endplate of S1.

Peak Radiation Dose

Estimated radiation dose (CTDI) is reported below using the technical factors described above for each sequence. These values were calculated based on measured values using a standard test object (CTDI 32 cm-diameter body phantom) in comparable scanners (GE LightSpeed) at UCLA:

Table 2 – Estimates of Peak dose for each sequence

Scan	Peak Radiation Dose at Center	Peak Radiation Dose at Periphery
Each Coronary Scan	6.3 mGy (.63 rad)	12.5 mGy (1.25 rad)
Abdominal Aorta Scan	7.3 mGy (.73 rad)	15 mGy (1.5 rad)

Because the two coronary scans cover the same anatomy, the peak dose in those two regions add so that the peak dose occurs in the anatomy ranging from the carina to the base of the heart, which receives 25 mGy (2.5 rad).

Effective Dose Calculations

Effective Dose is the sum of the weighted absorbed doses for all irradiated tissues, where the weighting factors represent the different risk of each tissue to mortality from cancer and hereditary effects. These weighting factors are higher for the gonads and lower for less sensitive organs (such as the extremities).

These estimates were obtained by finding the average dose to each radiosensitive organ (based on the phantom radiation dose measurements described above and anatomical coverage for each sequence). The weighting factors were then applied according to the description in the International Council on Radiation

Protection Report 60. These estimates were performed for each sequence and then summed to obtain the results for the entire examination. The results are summarized in table 2 on the previous page.

For each coronary scan, the estimated effective dose is estimated to be 1.5 mSv (150 mrem) for men and 1.9 mSv (190 mrem) for women. The difference is that the breast is irradiated in this scan, and because the breast dose carries a weighting factor of .05 of the total effective dose, the effective dose is higher for women.

For the abdominal aorta scans, the estimated effective dose is 2.7 mSv (270 mrem) for the 15 cm of coverage. The reproductive organs are not irradiated, as the true pelvis is not scanned.

For the entire examination, the estimates of effective dose range 5.7 mSv for men to 6.4 mSv for women. These values would compare with 3.6-mSv annual background radiation and the 50 mSv whole body exposure annual limit for radiation workers. Therefore, the total effective dose from these scans for an average patient is significantly less than that allowed for radiation workers on an annual basis and is equivalent to about 1.6 to 1.8 years of background radiation. However, because these estimates are based on population averages, these estimates should not be taken to provide an estimate of risk for any individual patient.

6. Result Reporting and Tracking for Coronary Calcium Scores and Incidental Findings of Participant CT Examinations

For each subject, a complete output of calcium scoring data for the coronary arteries, and the abdominal aorta, including an Agatston Calcium Score for the coronary arteries are generated and forwarded to the Framingham Heart Study. The physician of each subject with a coronary calcium scores above the upper 10^{th} decile for age are sent a summary of the calcium score with wording indicating that the score is high for age and with references to the most recent ACC/AHA guideline statement on coronary calcium imaging. (The published literature will be reviewed annually.) If deemed appropriate after review of the literature and contact with the other NHLBI population-based studies, and if approved by the Framingham Heart Study Executive Committee and OSMB, reporting may be extended to more or all subjects.

Scans are being conducted for research purposes, however, the entire scan will be screened for clinically important findings and clinically important findings will be reported by a radiologist at Mass General Hospital. Also, because there is a lack of consensus on the clinical utility of coronary calcium scores, we will not routinely notify or report calcium scores to all subjects. However, we will routinely report calcium scores to physicians of subjects with a $>90^{th}$ percentile score for age and sex.

6.1 Protocol for Reporting to Participants and the Participant's Primary Care Physician of Incidental Findings

Participants will receive a letter thanking them for participation in the CT study and indicating, if appropriate, that a letter has been sent to his/her primary care physician for either a high calcium score, an incidental finding, or both. Once both the incidental finding report and the coronary calcium score are received by the Study Coordinator overseeing clinical reports [redacted] the appropriate letter is

prepared to be sent to the participant and his/her physician. Each incidental finding report will be reviewed by a Framingham Heart Study MD [redacted] before being sent by mail to the participant and the participant's MD. The timeline from completion of imaging to mailing of letters and/or physician reports will be no greater than six weeks. At the discretion of the Framingham Heart Study MD [redacted], the MD of participants with serious incidental findings (e.g., a likely cancerous mass) may be contacted directly by phone as well as mail.

Letter to Participant

A thank you letter will be sent to each participant in the CT study. For participants with neither an incidental finding nor a high (>90th percentile) coronary calcium score, a generic thank you letter will be sent (see Thank You Letter, Appendix 20). For participants for whom an incidental finding was noted, a letter regarding the presence of an incidental finding will be sent containing a generic notification about the incidental finding and instructed to speak with his/her physician for more details (see Letter for Incidental Findings, Appendix 22). Participants with a high (>90^{th} percentile) coronary calcium score will be sent a letter containing a notification of the presence of a high calcium score and instructed to speak with his/her physician for more details (see Letter for High Calcium Score, Appendix 21). Participants with both an incidental finding and a high coronary calcium score will receive a single letter notifying him/her of the presence of both abnormalities.

Letter to Physician

The physician for each participant with an incidental finding will be mailed the incidental finding report, electronically signed by the MGH radiologist, with a cover letter from [redacted] (see Physician Letter, Appendix 23). The physician for each participant with a high coronary calcium score will be mailed a

letter signed by [redacted] describing the presence of a high coronary calcium score, (see Physician Letter, Appendix 23). A letter will be sent to physicians of participants with both an incidental finding and a high coronary calcium score (see Physician Letter, Appendix 23). Physicians of participants with neither an incidental finding nor a high calcium score will receive no letter or report unless specifically requested and authorized by the participant.

Tracking of Completed Incidental Findings Reports, Completed Clinical Coronary Calcium Scores, and Completed Letters to Participants and the Participant MD

Copies of all letters/reports are placed in the participant's respective chart, as well as kept in a CT study reports binder. Information regarding completion and notification is also being tracked in a CT study tracking database that records the completion of coronary scoring, completion of quality assurance readings, completion of incidental findings reports, mailing of letters to participants (all participants receive a letter), and mailing of letters to the participant's physician (for those with a high calcium score and/or incidental finding).

7. Participant Safety and Confidentiality Considerations

The Framingham Heart Study CT examination both operationally and scientifically is built on the experience of National Heart Lung and Blood Institute with recent large population-based studies which have incorporated CT measures of sub clinical atherosclerosis. The MESA and CARDIA study and Family Heart Study-SCAN study have successfully implemented an identical protocol for measuring coronary calcium as proposed in the Framingham Heart Study. The Framingham Heart Study CT protocol adds imaging of the abdominal aorta. It should be noted that the current Framingham Heart Study protocol calls for a single examination at baseline as opposed to CARDIA in which CT examinations were obtained at years 10 and 15 and MESA in which 3 examinations are proposed. However, repeat testing has been conducted for many other radiographic and ultrasound imaging modalities in the Framingham Heart Study. We have developed the current MDCT imaging protocol in such a way as to allow the study of vascular calcification progression, should repeat scanning be performed.

The investigators realize the importance of participant safety and informed consent and all have formal training in the various aspects of the ethical conduct required for research with human participants. Specifically, we understand the necessity for reporting deviations, unexpected events, adverse events, serious adverse events, IRB concerns, participant complaints or any other significant issue potentially representing safety concern immediately to the relevant Investigation Review Boards (IRB) and the NHLBI Program Officer. If the IRB determines a situation has occurred in which an unanticipated risks to human subjects has occurred this will be reported by the Institutional Official to the Office of Human Research Protection (OHRP).

7.1 Procedures to detect protocol violations

As described above, a predefined protocol is employed with fixed MA and kV parameters. To ensure that systematic errors in radiation dosing are not propagated to participants, we are recording the following accumulated examination DLP. Additionally, during the CT scoring for coronary calcium, the imaging parameters recorded on the digital CT image are recorded. If there is a protocol violation for any given scan, [redacted] and other relevant Framingham Heart Study and MGH staff will be notified. If protocol violations occur, corrective measures will be immediately undertaken, to include the generation of a report regarding the protocol violation and corrective measures undertaken by the MGH West CT technologist staff. All protocol violations will be reported in the regular QC report to NHLBI.

7.2 Informed consent issues

a. Informing Participants of Radiation Exposure

To provide participants with a concise and understandable explanation of the radiation involved with the CT examination we have chosen to present the effective dose. The effective dose estimates the exposure by organ irradiated and allows the values to be compared directly with the annual exposure to natural sources of radiation (3.6 mSv) and the annual allowance for radiation workers. We believe that the alternatives of (1) simply providing a number out of context or (2) comparing the dose to other medical procedures, while informative to scientists and healthcare professionals, is less informative to the lay public. The following language is recommended to the field centers for informed consent concerning the CT examination. Local requirements or standard language may require modifications as appropriate.

b. Recommended Language for Informed Consent

The CT scan of the heart and abdomen involves low doses of radiation. The total amount of radiation for the scan is 6 mSv or less than 12% of the yearly radiation exposure limit allowed for a radiation worker. Another way of understanding this is that the total amount of radiation is approximately equivalent to the radiation exposure from 2 mammograms. The risk from this amount of radiation (X-rays) is generally recognized to be safe by the Food and Drug Administration (FDA) for such studies. There are no other known risks associated with the procedure. The CT scan is being done for research purposes only to measure calcium in the heart and major arteries. Because a complete clinical evaluation of the CT scan images for all possible abnormalities in the chest and abdomen will not be performed, some clinically important findings may not be discovered.

We believe the above language accurately and conservatively presents the information related to radiation exposure with the Framingham Heart Study CT examination and allows our participants and potential participants to make an informed decision about involvement in this study.

8. CT Imaging and Data Management Procedures

8.1 Imaging Procedures

The FHS-SCAN CT examination is designed to efficiently and accurately provide volumetric CT image data for measuring coronary and abdominal aortic calcium. The exam consists of scout images, 2 cardiac gated series of the heart to measure coronary calcium and a helical (volumetric) acquisition of the abdominal aorta to measure aortic calcium. On average, 20 minutes of participant time is spent within the CT scan suite; this includes instructions, setup and imaging. In rare cases, the exam may require 30 minutes. In many cases, the examination is completed in less than 15 minutes. Participants have ECG electrodes attached for cardiac gating and be instructed as to a standardized breath holding instructions.

Figure 1. FHS-SCAN CT Series:

Series	Description	No. of images	Scan time	ECG gating
1	Scout of thorax and addomen[1]	2	7 sec x 2	No
2	Coronary scan 1[2]	40-50	20-40 sec	Yes
3	Coronary scan 2[2]	40-50	20-40 sec	Yes
4	Abd. Aorta scan	60	30	No

[1]Scout images will consist of a frontal and lateral low energy 2D scanogram

[2]Duplicate scans will be obtained of the coronary circulation to improve the precision of the calcium measurement in the first 500 patients

Scout Image of the Thorax

The technologist instructs the participant using the standard breathing instructions, (at end-inspiration), while acquiring two scout images of the thorax (Frontal and lateral scout images, aka scanograms or topograms). The technologist checks that the participant is centered, and positions the Calcium CT Calibration Phantom. The technologist then chooses the start position for the highest group of four slices just below the carina of the trachea. The end location of the volume acquisition will be beyond the diaphragmatic aspect of the heart so that the entire coronary arterial system will be imaged. The CT couch is moved to the start position. The technologist confirms correct positioning of the Calcium phantom on the scout image and repositions it if necessary.

Heart 1 CT Scan Series

Scanning procedure for cardiac gated CT scans of the coronary arteries is based on the standard protocols currently active in the NHLBI's MESA and CARDIA studies. To ensure complete coverage of the entire heart, a minimum of 10.5 cm of image data in the z direction (head-to-foot) is acquired with each scan. This coverage results in slightly more than 40 slices when using the 4 slices by 2.5 mm sequential (axial) acquisition. The heart scans is reconstructed centered on the heart using a display field-of-view of 35 cm. This includes the Calcium QCT phantom within the images as well as the majority of the lungs.

Figure 2: The CT Technical Settings for Coronary Scan Series using the GE Lightspeed + 8 (Framingham-MGH/WFU):

Mode	FOV	Multi-Slice	Kernel/recon	Time	ECG gating

Axial	35cm	4 slices by 2/5 mm	Std/Partia l	0.5s	Prospective

Heart Scans: Adjusting mA / mAs based on Weight

KVp	**Gantry Speed (s)**	**Exposure Time(s)**	**Weight < 220lbs.**	**Weight => 220lbs**
120	0.50d	0.33 s	320mA 106 mAs	400mA 133 mAs

Participant Weight and the CT exam:

If participants weigh more than 160 kg (352 lbs) they are excluded from the CT exam. As individuals become larger more X-ray photons are stopped or attenuated by their tissue. This means that there are fewer photons making the trip through the participant to make an image. This results in decrease image quality. To compensate**, the tube** current (or mA) are adjusted upwards (25%) for participants who weight more than 100 Kg (220 lbs.) at their clinic visit. This is why clinic personnel must record weight on the CT scheduling form.

This adjustment, although imperfect, maintains a more constant signal-to-noise ratio (or photon flux) across participants of varying weights and result in improved image quality and calcium measurement. Note that this along with all the additional technical and demographic information including individual time stamps for the scan, scan series and individual image is recorded in the DICOM header which is part of each image and is available on the CT image library of all the FHS studies as part of our quality control procedures.

Reconstruction Parameters:

The following technical parameters should be entered into a memorized protocol on each CT system, which should greatly facilitate protocol compliance. All series are performed using the large scan field-of-view. This may also be referred to as the body as opposed to the head scan field-of-view. The technologist reconstructs using a display or reconstruction field-of view of 35 cm (or 350 mm). By reconstructing with a 35 cm fov we insure that the QCT phantom is included in the reconstructed images. The standard reconstruction kernel is used for the two cardiac series and the abdominal aorta scan. For the cardiac series, the 240 degree scan reconstruction algorithm is used (note that this option has various names depending on vendor (segmented, ultrafast). This algorithm reconstructs images using 240 degrees of raw scan data (tube rotation) with an optimized reconstruction technique to provide images of ~250-500 msec temporal resolution depending on the speed of gantry rotation (0.5s or 0.8s). For the abdominal aorta scan temporal resolution is not a critical factor and the full reconstruction (360 degrees) is used. Images have an initial display reconstruction at 350 mm (35 cm) followed by a retrospective reconstruction at 500 mm (50 cm).

Figure 3- Table CT Image Reconstruction Parameters using the GE Lightspeed + 8 (Framingham-MGH/WFU):

Series	Scan FOV	Display FOV	Kernal	Recon Type
Heart 1	**Large/Body/55cm**	**350 mm**	**Standard**	240° (partial)
Heart 2	**Large/Body/55cm**	**350 mm**	**Standard**	240° (partial)
Abd. Aorta	**Large/Body/55cm**	**350 mm** **500mm** **(retro)**	**Standard**	360° (full)

Abdominal Aorta CT series Scanning Procedures for the Aorta

The scanning procedure described below requires less than 2-5 minutes of the participant's time. A single lateral scout image of the chest and abdomen was obtained before the start of coronary CT imaging. The lateral scout image should include the thoracic and lumbar spine and should be similar to a routine chest/abdomen/pelvis scout in coverage. By performing a low energy lateral scout of the entire thoracic and lumbar spine the CT technician is able to accurately determine the vertebral levels and landmarks for the scan. The abdominal aorta protocol requires that the lateral scout image adequately identify the L5-S1 disk space. The stop location for this scan is the top of S1.

Helical Scan Acquisition of the Abdominal Aorta

The abdominal aortic scan is prescribed graphically based on the location of S1 vertebra from the lateral scout image. One may also use information from the coronal scout image to adjust the right-left centering. If this is the case, while looking at the later scout image, the cursor tool and the image at the top of the S1 vertebra is selected. One can then switch to the coronal scout image. A total of 150 mm of volumetric, imaging data in the z direction (head to foot) is prescribed. The start location is toward the head. It is important to scan in the head-to-foot direction. When using 2.5 mm slice collimation, as specified in the protocol, this will result in 60 images for each abdominal scan. When you graphically prescribe you can either:

1) Move the block of slices until the last slice is at the location determined to be the superior endplate of S1

2) **OR**, add 150 mm to the value of the S1 location and use this as your start location

The Lumbosacaral junction is used because it is the most easily identifiable and consistent landmark identified in the abdomen/pelvis. Our objective is for you to start scanning just above the renal arteries so that image the entire infrarenal abdominal aorta and the proximal common iliac arteries. The protocol is

designed to avoid imaging the true pelvis where in females the ovaries are located. We performed a study and have determined that 150 mm superior to S1 is above the renal arteries in all participants in our sample population. Other landmarks like the top of the diaphragm and counting the vertebral levels are variable between people and we believe are less reproducible. The CT scanners are set at the technical parameters specified in the table below.

Figure 4: Technical Parameter for the Abdominal Aorta Scan using the GE Lightspeed + 8 (Framingham-MGH/WFU):

Ct System	Mode	FOV	Pitch[1]	Kernel/recon	KV	mA	Time	mAs
GE LightSpeed Plus (WFU & BU)	Helical	35 & 50cm	4i 3:1 HQ	Std/full	120	400	0.5s	200

1Note pitch on multidetector CT systems have been described with competing conventions by different vendors, thus for the Siemens & Marconi systems the pitch can be explained as 3:1 [7.5 mm table travel per rotation over a 2.5 mm slice collimation] or alternatively as 0.75:1 [7.5 mm table travel per rotation over a beam collimation of 10 mm (i.e. in 4 slice mode 2.5 mm x 4 = 10 mm beam collimation)].

Abdominal Aorta CT scan series is acquired in the helical mode, full or 360° recon mode, four slices at once, with a 2.5 mm slice collimation and a scan pitch of 3:1 or 0.75:1 depending upon the definition of pitch chosen by the CT scanner manufacturer for a particular system. A detailed definition of pitch is provided in the note below the table on technical factors. The CT Reading Center confirms through the quality assurance scans performed on phantom objects that all protocol parameters are set appropriately. Human and software checks each pilot and participant scan for the key technical parameters related to

image quality and radiation exposure to insure protocol compliance. Scans are obtained during suspension of breathing. Technologist should instruct participants and use the same breathing script as used for the heart 1 and heart 2 series.

Abdominal Aorta Reconstruction Parameters

The technologist uses the 35 cm field of view and the standard reconstruction kernel. In addition, a retrospective reconstruction into a 500 mm (50cm) display fov is performed so that we include the entire body in this set of images. The 50 cm reconstructions are performed *using a 5 mm slice thickness.* Because of significantly reduced motion of the abdominal aorta relative to the coronary arteries, the full or 360 degree reconstruction rather than the partial scan reconstruction algorithm are used for the aorta scans.

Recording of Scan Information on Completion Form:

The CT tech records the following scan data on the participant's Completion Form (Appendix 16): the Tech ID#, Exam Number, whether the scan was archived locally, confirmation of 120 Kv, sets MA according to weight by indicating whether the participant is less than 220 lbs (set to 320mA) or equal to/more than 220 lbs (set to 400mA), the series and number of images for the scout, coronary1, coronary2, and abdominal aorta. The CT tech also documents on the completion form the Accumulated Exam DLP and whether the scan was completed. The tech then gives the Completion Form to the liaison. If the participant is scanned during an "off-time" (without a liaison) then the CT tech puts the completion form in a locked cabinet for the liaison to retrieve on another day.

8.2 Data Management

The following procedures describe the data entry/tracking steps for the CT participant schedule, CT Completion Form, Pregnancy Determination Form, Self- Administered Pregnancy Questionnaire and the Consent Form3.

We record the daily CT participant schedule in order to track when and which participants have had a CT scan. At the CT scan site, the liaison indicates on the schedule whether or not each participant was seen. The day following the scans, the schedule is returned to the CT coordinator. The CT coordinator reviews the schedule to ensure it is filled out correctly and completely. Next, the schedule is given to data management. The schedules are data-entered twice by two different people into the Ingres Database. The data is converted from the Ingres system into a SAS data set. Range checks and logic checks are performed to ensure that the data is accurate.

The CT Completion Form, Pregnancy Determination Form and Consent Form are sent directly to data management after being reviewed by the CT coordinator. They are data-entered twice by two different people into the Ingres Database. The data is converted from the Ingres system into a SAS data set. The two keyings are compared to ensure accuracy. Next, range checks and logic checks are performed to further ensure accuracy as well as examined for consistency. The CT completion form, pregnancy form, and consent form are then returned to the participant CT scan folder.

8.3 Database Backup and Image Data Backup

[3] To view these forms refer to the following appendices: Schedule-Appendix 17; Completion Form-Appendix 18; Pregnancy Determination Form-Appendix 14; Self-Administered Pregnancy Questionnaire- Appendix 16; Consent form-Appendix 8.

The CT Reading Center (MGHW) Computer files are secured in several ways. The system configuration file is backed up to a network drive, which has a daily-automated tape back up routine. Image data, raw and process is redundantly written to Magnetic Optical Discs (MODs) on a weekly basis. [redacted] In the event of a system crash or damage to the system or data files, these redundant methods of back up can be easily retrieved, and the system restored in a timely manner.

The CT technologists at MGH West in Waltham "push" (electronic transfer via T1 line) scans that they have generated that day of the Scout, Coronary Arteries 1 (CA1), Coronary Arteries 2 (CA2), and Abdominal Aorta (AA) to the CV Image (CVI) server in the MGH Boston Research Radiology CIMIT office at 100 Charles River Plaza. The technologists keep a back-up copy of the scans on an MOD and store those MODs [redacted] The technologists fax a list of the exams that they pushed that day, containing the following information: the scan-date, the study type, the participant's [redacted] and the participant's date of birth. This faxed list is addressed to [redacted] and is stored in a "Calcium Registry" folder kept [redacted]

The four pushed scans for each participant are all maintained in one folder labeled with the participant's FHS ID # or the GENCAC Acrostic ID. [redacted] The list of participant folders is then allocated in equal numbers into the individual folders of the three MGH radiologists who are reading the scans for incidental findings. Once the scans have been read for incidental findings, the participant folders are placed into a "Read" (i.e., completed review for incidental findings) folder, which is divided into sub folders identified as "Incidental Findings" and "No Incidental Findings".

9. Reading Center Analysis Procedures

9.1 Vascular Calcium Analysis Software

The CT exams of the coronary arteries and abdominal aorta will be analyzed using conventional scoring algorithms similar to those currently implemented in the NHLBI funded MESA and FHS-SCAN studies. On March 1, 2003, the MGH and Framingham Heart Study investigators made the decision to proceed with a rapid assessment and, if approved, implementation of the Aquarius Workstation and software from TeraRecon, Inc. Among the many advantages of this software over the currently available alternative software (General Electric SmartScore) is ease and speed of file management, ease and speed of calcium scoring, which contribute to enhanced reader Quality Assurance, as well as an integrated database and reporting, ability to use the software on a desktop PC, and responsiveness of the vendor to study needs. The software calculates a traditional Agatston, total calcium score, and it has the capability of measuring calcium using newer approaches, such as phantom adjusted score/volume. We are in the process of completing a full review of this software, including an assessment of score comparability with 50 scans that have been read using the General Electric SmartScore system.

9.2 Training of FHS Research Assistant with TeraRecon

Training is performed under the supervision of [redacted] MGH, Radiology and contains the following basic elements for the FHS Research Assistant:

Study cardiac and coronary anatomy

Learn the basic principles of CT techniques and imaging

Get to know the most common sources of measurement errors

Learn to use the Scoring software

Train on a test of 20 subjects that have been scored by [redacted]

Every six to twelve months, repeat the scoring on the test set of 20 subjects

Before beginning to read CT scans, the Massachusetts General Hospital radiologist provides the Framingham Heart Study Research Assistant with two articles to review in order to gain familiarity with coronary calcium scoring and the appearance of coronary anatomy and calcium in a CT scan. Both articles, one entitled Electron Beam CT of the Coronary Arteries: Cross-Sectional Anatomy for Calcium Scoring4, and the second entitled A Pictorial Review of Coronary Artery Anatomy on Spiral CT5, briefly describes the technology and methods involved in quantifying coronary calcium, and provides a pictorial reference of the major coronary vessels and calcium deposits as seen on an EBCT and Spiral CT scan. An anatomy text is also utilized by the FHS Research Assistant to review the anatomy of the heart. The FHS Research Assistant obtains general instructions on the operation of the TeraRecon Calcium Scoring package from the MGH radiologist and assistant and supplements the instructions with information obtained from the TeraRecon operations manual.

During the initial training the FHS Research Assistant reads and scores 20 coronary artery scans that are reviewed by the MGH radiologist and the radiologist's assistant. The FHS Research Assistant is instructed by the MGH radiologist on the appearance of fat, air, calcium, bone, muscle, pericardium, and vessels on a CT, as well as which coronary landmarks to look for, which density patterns are typical for coronary calcium, stents or clips, and which patterns are typical for beam hardening and motion artifact. The MGH radiologist instructs the FHS Research Assistant to score the Left Anterior Descending, the Left Main Artery, the Right Coronary Artery, the Left Circumflex and the Posterior Descending Artery. The MGH radiologist identifies an example of an overweight person with a small heart and the effect that high heart

[redacted] American Journal of Radiology, 177, December 2001
[redacted] MD, FCCP, p. 488-491, Chest, 118, 2, August, 2000.

rate has on motion artifact, as well as other examples of coronary abnormalities. The FHS Research Assistant is periodically asked to identify structures of the heart and chest area at various slice locations.

9.3 Coronary and Aortic Calcium Measurement Procedures

Management of Image Files: The CT technologists at MGH West in Waltham "push" (electronic transfer via T1 line) scans that they have generated that day of the Scout, Coronary Arteries 1 (CA1), Coronary Arteries 2 (CA2), and Abdominal Aorta (AA) to the CV Image (CVI) server in the MGH Boston Research Radiology CIMIT office at 100 Charles River Plaza. [redacted] The technologists fax a list of the exams that they pushed that day, containing the following information: the scan-date, the study type, the participant's [redacted] and the participant's date of birth. This faxed list is addressed to [redacted] and is stored in a "Calcium Registry" folder [redacted]

The four pushed scans for each participant are all maintained in one folder labeled with the participant's [redacted] The list of participant folders is then allocated in equal numbers into the individual folders of the three MGH radiologists who are reading the scans for incidental findings. Once the scans have been read for incidental findings, the participant folders are placed into a "Read" (i.e., completed review for incidental findings) folder, which is divided into sub folders identified as "Incidental Findings" and "No Incidental Findings".

Procedure for Producing a Calcium Score for the Coronary 1, Coronary 2 and Abdominal Aorta Scans:

Initiating a Reading Session: The FHS Research Assistant (RA) who conducts the calcium scoring of the scans obtains the scans to be scored from these "Incidental Findings" or "No Incidental Findings" sub folders, selecting scans *with* incidental findings first. The scans *without* incidental findings are scored within the shortest possible time frame after those with incidental findings have been scored. The RA loads the selected participants folders onto the TeraRecon (TR) Patient List from the CVI.

Once the participant folders are loaded onto the TR Patient List, the RA reviews the participant identifiers that appear on the screen. These include: the MGH West assigned patient ID #, the participant's [redacted] the date and time of scan completion, and the modality (i.e., CT). The participant's folder is opened by highlighting any identifier for that participant. When a participant's folder is opened, all of the scans appear in list format in a window below the Patient List. Each scan is clearly identified as a scout, heart (there are two heart series, coronary artery 1, or CA1 and coronary artery 2, or CA2), or abdominal series. To select a scan for calcium scoring, the RA highlights the desired series and chooses the "Calcium" button from among several options. This step imports the images into the calcium scoring program, enabling the RA to measure the quantity of arterial calcium.

Coronary Artery Calcium Scoring: The RA begins with the first Heart series (CA1). Once the images are imported into the calcium scoring program, the RA first scrolls through the entire series of images to obtain an over view of the heart. Returning to the first image, or "slice", the RA scores any calcium that may be present in the Left Main Artery (LM), the Left Anterior Descending Artery (LAD), the Left Circumflex Artery (LCx), the Posterior Descending Artery (PDA) and the Right Coronary Artery (RCA). Using the mouse to click on, or to draw a circle around, a suspect calcium lesion highlights that lesion. If the lesion falls within the pre-specified Hansfeld Unit range (3 pixels), then a window appears containing colored buttons corresponding to each coronary artery location, i.e. a button for each the LAD, LMA, RCA, LCx, and PDA. The RA selects the appropriate location of the lesion, and the lesion is automatically highlighted

with the predetermined color. For example, all scored calcium in the LAD is highlighted red. Simultaneous to highlighting the calcium, a score for the selected lesion is generated and appears in a "score sheet" that is constantly open on the screen and updated during the scoring session. Information provided on these score sheets include: volume, AJ-130 and mean scores generated for each artery location, as well as a total coronary calcium score for each score type (volume, AJ-130, mean).

At the completion of scoring, the RA generates a report for the completed series (eg CA1) by selecting the "Save and Exit" button. A preliminary report sheet appears and can be edited to include the scorer's name and to identify the series as CA1 (coronary artery series 1), CA2 (coronary artery series 2), and AA (abdominal aorta). Once the editing is complete, the completed score information is saved in an Access database.

Adjudicating Calcium Plaques: During the scoring process the CT Reader will review all potential calcified lesions related to the extract regions around the coronary arteries. The reader will be guided by the program from lesion-to-lesion until the CT Reader has made a determination on each potential lesion. Typical false positive calcified abnormalities are: valvular calcification, calcified mediastinal lymph nodes, pericardial calcification, and metallic artifacts from coronary stents, clips, surgery or penetrating objects.

Abdominal Aortic Calcium Scoring: The procedure for scoring the abdominal aorta (AA) is similar. The AA scan is opened, scored, and reported using the same method used for the CA1, allowing for anatomic differences. The RA first establishes the lowest abdominal slice for scoring. This location in the aorta is predetermined as the first slice that is immediately superior to the aortic bifurcation, where the dividing aortic branches maintain a 50% shared lumen wall. The RA scores calcium from that point upwards, to the final superior-most slice of the AA scan.

For the purposes of avoiding any possible biases in scoring, the RA scores the second Heart series (CA2) after s/he has scored at least 2 – 3 other participants' CA1 and AA scans. This rotating cycle continues until all scans loaded onto the TR Patient List have been calcium scored.

Thoracic Aorta Scoring: The procedure for scoring the thoracic aorta (TAC) is similar to the scoring of the abdominal aorta (AA). The RA scores only the wall calcium from the first slice to the last slice of the scan. Typical false positives are the reflection from vertebrae and vertebrae calcium very close to overlapping the TAC.

Phantom Image Scoring:

For each participant, the phantom will be scored and these data used to adjust the Agatston and volume calcium scores.

Phantom image scoring is done at the completion of CAC soring. Click on the thumbnail corresponding to CA1. Click on "Setup Params" in the center of the screen. This will make a box pop-up that is entitled: Calcium Scoring Parameters. Calibration should be set as:

RO1 #1: 0 (Density)
RO2 #2: 100 (Density)
RO3 #3: 200 (Density)

#RO1s: 3
Target RO1 Area: 2

Once this is set, click on Calibrate Mass. A blue circle (calibration circle) will appear on the scan, movable by the curser. Using the mouse, scroll to an LAD (Left Anterior Descending Artery) slice, preferably a first image or LM (Left Main Artery) and LAD together. Note at the bottom of the screen is the phantom, a rectangle with 3 variations of gray: dark gray, light gray, and white gray. Position the calibration circle in the center of the dark gray square first. Left click. The measurement will appear on the top left part of the screen under Mean HU. Repeat procedure with the middle (light) gray square. Then write down the number on your CT Measurement Sheet. Repeat procedure with the last (white) gray square and the final

measurement result will appear at the top left of the screen: Calibrated: r^2=0.9XXX or 1.0000. Note: the measurement for the third (white) gray will not be shown. Also the final calibrated number should not exceed 1.0000.

Next click on Save Calibration and then Save and Exit (boxes in center of screen, towards the bottom).

Repeat the same procedure for CA2.

Repeat the same procedure for AA. Measurement for AA should be done at the slice immediately superior to the aortic bifurcation.

These measurements are saved on the TR. They can be found by going to: Drive E->AquariusReport->AnalysisData->Calcium. They are stored in FHS ID order. To do FHS data analysis, these files need to be converted into text files. On a drive with disk space (ie D drive) make a Phantom Folder. Under this folder create individual folders (these smaller folders will contain ~ 200 scans, depending on how many are measured before putting them in text files). Open the smaller folder to accept the data. Click on the FHS ID. Check the numbers (CalibrationMeasured 0, 1, and 2 and LsqR2) with those on your CT Measurement Sheet to verify you have the correct numbers measured for CA1, CA2 and AA. If so, highlight from PatientName to (and including) LsqR2). Copy this, close box and paste it into your individual folder. Keeping a double space between entries, continue this until all phantom measurements are in the text file. Keep a separate text file for Offpspring (1-XXXX) and Gen 3 (3-XXXX).

When completed, copy to a flashdrive or disk and give to FHS data staff.

Measures of CT Reader Variability

A set of 50 scans have been selected to as part of the quality control procedures at the MGH. These are being used to measure inter- and intra- reader variability. Interobserver and interscan variabilities will be

calculated (e.g., coefficient of variability, kappa statistics). The subset of scans with large interobserver variability will be re-evaluated to determine, if possible, the source of variability. In addition, 20 scans will be selected to be re-analyzed periodically by the RA to assess for evidence of "temporal drift" in scoring.

Measures of Interscan Variability

Results of the first 500-700 coronary artery scans will be analyzed for interscan variability, with a particular focus on variability across the spectrum of Agatston scores (e.g., low score < 10), HR and BMI. The subset of scans with large interscan variability will be re-evaluated to determine, if possible, the source of variability.

9.4 Data Management of Calcium Measurement Results

Data concerning the CT exam is stored in an Access relational database that is automatically generated and updated by the TeraRecon sofware. Results related to participant safety, protocol adherence, quality control and vascular calcium results will be downloaded from the scoring PC to the coordinating center at least once per week. This will be coordinated and overseen by the Framingham Heart Study RA for the CT study and a designated member of the Framingham Heart Study data management team.

10. Image Reading Quality Reviews Procedures

As per previous arrangements, both the Framingham Heart Study CT scan and the NHLBI FHS-SCAN studies are being performed by the same MGH West Imaging Center using the same technologists and the identical scanning protocol. Therefore, the Quality Review Procedures are identical for both studies. [redacted] for the FHS-SCAN CT Imaging Study, has conducted detailed training and testing of the MGH West CT technologist staff and has conducted one site visit during the fall of 2002. In addition, [redacted] have in parallel conducted training and reviews of the CT imaging procedures by their staff, the MGH West CT Technologists.

10.1 Protocol Adherence – CT Scanner Technical Factors

a. Calibration to Air (Baseline, then daily)

An initial baseline followed by daily scans is obtained. This calibration is part of the daily scanner start-up routine. These procedures follow the manufacturer's recommended procedure.

b. Calibration to Water (Baseline, then bi-weekly)

An initial baseline followed by bi-weekly scans obtain an image analyzed by using a water phantom. These procedures follow the manufacturer's recommended procedure and include zeroing and calibrating the scanner unit.

c. Calibration to Calcium (Baseline, then bi-weekly)

Each CT scanning site is provided a standardized Calcium QCT Calibration Phantom, which includes a Torso QA phantom for scanner calibration (Image Analysis Inc, Lexington, KY).

The center plug of the Torso QA phantom contains a region with a known concentration of calcium hydroxyapatite (100mg/ml). The Calcium QCT Calibration phantom contains four cylindrical rods with the following concentrations of calcium: 0, 50, 100, 200 mg/ml calcium hydroxyapatite. Every two weeks, quality assurance scans of the torso phantom will be performed at the CT scan site. The analysis of these scans by the CT Reading Center allows convenient and quick verification of accuracy and precision of the CT scanner.

d. Positioning the Calibration and Torso Phantoms.

The table height of the CT couch is positioned such that the center of the Torso Calibration phantom is located at isocenter of the scanner field of view.

Place the torso phantom on top of the calibration phantom (positioned in couch pad) and using your laser alignment light; adjust the table height until the torso center insert is at the location of isocenter on the CT scanner. This is the table height you will use for QA scans with your Torso phantom.

e. Scanning the TORSO QA Phantom

After the correct position has been determined, take a vertical axial slice through the center of the TORSO phantom. Use the same parameters as with patient examinations. Each site performs a scout of the phantom followed by an axial scan (identical parameters to the heart series) and helical scan (identical parameters to the abdominal aorta scan). Reconstruction should be done with the same parameters as in scanning study subjects. Then display your axial image on your CT monitor and examine it to ensure that it is free of artifacts, such as air gaps and streaks. Ensure that the calibration phantom is included in the field of view. If

there are significant artifacts over the calibration phantom, you should discard the image and rescan the phantom.

Using your CT software place ROI's on the calibration phantom reference samples (0, 50, 100, 200 mg/cc). The 0 sample will be an apparent blank space on one end of the calibration phantom. Then place an ROI in the TORSO vertebral sample. The ROIs should be as large as practical while remaining completely within the reference cylinder. (We recommend ROIs about 70% of the sample area). Record the five mean CT numbers within these five ROIs. The QA data sheet is then filed in the Framingham Heart Study 3-ring binder for your records.

f. Analysis of the Phantom Results at the CT Reading Center.
Use the QCT software available to the reading center which runs on a standard PC using Microsoft Windows OS, click on the QCT-5000 icon on your desktop. Click the enter QA button on the toolbar. A QA data entry screen pops up. Enter the data from the QA data sheets from the field centers. When all the data is entered, click OK. This will save the data to the QA database and open a window showing the QA report. To discard the entries you have made, click cancel. The QCT 5000 software computes the calibrated calcium density for the Torso phantom. The results are displayed in graphic and tabular format. The software also accesses the database and retrieves any previous data on the Torso phantom. Previous data and calculated changes are displayed in the tabular form. The individual QA torso readings should be maintained at within $\pm$ 3% of the mean value of all the readings. If the values fall out of range, the field site must be notified in order to have the scanner checked by the field engineers.

g. Radiation exposure

A primary concern is protocol adherence with respect to CT technical factors related to radiation exposure. In clinical practice, these are, within certain parameters, adjustable by the technologist for a given exam. CT technical factors are included as a requirement in the DICOM header. This provides the radiology staff of [redacted] and others the means of reviewing the technical parameters of each participant CT exam. Once an exam is received, the following steps will be taken as part of the Quality Assurance readings:

1) Verify participant identity by cross-validating [redacted] entered by the CT technologist with a prepared list of subjects imaged on that particular day, provided by the Framingham Heart Study.
2) Verify each scan series of the exam are within technical parameters for KV and mA for weight.
3) Review image data quality points.
4) Human review of the technical parameters as reported on image data (KV, mA).
5) Determine if each CT exam is adherent to protocol and if not take appropriate action through communication with the MGH West technologist staff.

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Appendix 1: CT Exam Protocol Overview

1. Examination Protocol and Procedures

FHS is conducting a multi-detector CT scanning using a General Electric Lightspeed +8 detector scanner in 1200 Offspring Cohort subjects and 1900 selected Gen 3 subjects to detect and quantify coronary calcification and thoracic and abdominal aortic calcification. Due to the anticipated low prevalence in young persons, women < 40 years of age and men < 35 years of age are excluded. Furthermore, all pre-menopausal women require a negative screening urine pregnancy test (QuSTICK ™ Pregnancy test, STANBIO Laboratory) conducted by Framingham Heart Study staff within 24 hours prior to the scheduled test. However, urine pregnancy testing with this and other assays cannot detect pregnancies until 6 days after conception. Thus, to minimize the risk of performing a CT scan on a woman whose very early pregnancy might not be detected by the pregnancy test, we have decided it is necessary to administer a brief questionnaire in all pre-menopausal women *in addition to conducting the pregnancy test.*

Eligible subjects are contacted by phone or in the Generation 3 initial clinic visit to schedule the CT test. Subjects are asked to transport themselves to Massachusetts General Hospital West, on Route 128 in Waltham, MA (approximately 25 minutes by automobile from the Framingham Heart Study). The Framingham Heart Study does provide transportation for persons unable or unwilling to drive to the site.

After providing proper informed consent, each subject is escorted to the changing room to remove any clothing that has metal (i.e., pants with zippers, bra's, etc) and will be given a jonnie top to leave open in the front, and jonnie pants if needed. The subject lies down on the imaging couch, has the ECG leads placed and the couch is moved within the scanner. One scout image, two coronary images and one abdominal image are obtained during a total session within the scanner that takes no more than 15 minutes and requires three short (<20 seconds/each) breath holds. For the cardiac and abdominal scans, the QCT Phantom is positioned directly behind the thoracic spine and the heart as well as the abdominal spine. The

superior extent is above the carina and extends inferiorly to the sacral spine. The total anticipated door-to-door time for the scan is less than or equal to 30 minutes.

Scans are being conducted for research purposes, however, the entire scan will be screened for clinically important findings and clinically important findings will be reported by a radiologist at Mass General Hospital. Also, because there is a lack of consensus on the clinical utility of coronary calcium scores, we will not routinely notify or report calcium scores to all subjects. However, we will routinely report calcium scores to physicians of subjects with a > 90^{th} percentile score for age and sex.

In addition, Quality Assurance readings are ordered on each scan and clinically important incidental findings are identified and reported to the physician of the subjects. The General Electric scanner undergoes a daily QC test. In addition, a calcium density phantom is used during each scan and QC torso and QCT calibration phantoms are imaged every 15 days, in an identical manner to the Family Heart Study-SCAN protocol. An Agatston calcium score for the coronary arteries and aorta is generated for each participant using TeraRecon, which is installed and currently functioning on GE Scanners at the Waltham campus and the main MGH campuses. The study begins by generating coronary calcification scores using TeraRecon. This is the same general analysis algorithm being used by the Multi-Ethnic Study of Atherosclerosis (MESA) study and the Family Heart Study SCAN. We have ascertained that the procedures for imaging, reproducibility, quality assurance, and image analysis in the Framingham Heart Study are similar or identical to those being used in the MESA study and the NHLBI Family Heart Study-SCAN study as well as the NHLBI Coronary Artery Disease in Young Adults (CARDIA) study. This will allow consistency across ongoing NHLBI studies.

2. Study Rationale

Sub clinical coronary and aortic calcifications commonly occur early in the atherosclerotic plaque, preceding the onset of clinical CVD by years or decades. Abdominal aortic and coronary calcifications on plain radiograph are associated with long-term exposure to established risk factors in FHS subjects. Abdominal and thoracic aortic calcific deposits predict incident CHD and other CVD events, independent of other CVD risk factors. ECG-gated CT imaging of coronary artery calcium is now available and provides a noninvasive modality for detection of the presence and burden of coronary atherosclerosis.

We recently completed a pilot study (1998-2000) of electron beam computed tomography (EBCT) in 327 FHS Offspring Cohort participants, and we found significant associations of coronary calcification with Framingham risk score, long-term (time-averaged 25 years) risk factors, blood CRP level and aortic plaque detected by MRI. These initial findings require confirmation by a much larger study. Although coronary calcium detected by EBCT predicted onset of overt CHD and other CVD in some studies, population-based data are limited regarding the predictive utility of these measures over and above traditional risk factors. There is a substantial genetic (heritable) component to lumbar aortic calcification and to coronary calcification in the FHS. The FHS offers a unique opportunity to conduct a large-scale, family-based epidemiology study to identify genetic determinants and gene-environment interactions leading to sub clinical coronary and aortic calcification. Given the proposed Generation 3 cohort design, heritability and genome scan analyses will be possible using all Offspring Cohort sibling pairs and selected Third Generation subjects undergoing MDCT testing. Association studies of specific candidate gene variants would then be performed using population-based association and transmission disequilibrium testing.

3. Study Design

FHS is conducting a study of the genetic and environmental determinants of sub-clinical coronary, aortic and cardiac calcification and their relations with clinical CVD. FHS is using a multi-detector CT scanner

(General Electric Lightspeed 8 detector scanner) in 1200 Offspring Cohort subjects and 1900 selected Gen 3 subjects to detect and quantify coronary calcification and thoracic and abdominal aortic calcification.

Data from the FHS pilot study and other available databases suggests that the prevalence of coronary calcification will be extremely low (<10%) in men under age 35 and in women under age 40. Thus, we are excluding women < 40 years of age (n~860) and men < 35 years of age (n ~530) from MDCT testing, and we expect that about 10% will refuse to undergo the procedure, yielding an expected number of 1,900 MDCTs on third generation subjects. Accordingly, we expect to conduct coronary calcification testing in 1,200 Offspring Cohort and 1,900 Gen 3 subjects. The family-based design of the Offspring/Gen 3 CT Examination will permit the use of vascular calcification as a quantitative phenotype for genetic studies.

4. CT Examination Protocol

The CT examinations are designed to efficiently and accurately provide volumetric CT image data for measuring coronary and abdominal aortic calcium. The examination consists of 1 scout image, 2 cardiac gated series of the heart to measure coronary calcium, and a helical (volumetric) acquisition of the abdominal aorta to measure aortic calcium. On average, 20 minutes of participant time is spent within the CT scan suite; this includes instructions, setup and imaging. In rare cases, the examination may require 30 minutes. In many cases, the examination is completed in less than 15 minutes. Participants will have ECG electrodes attached for cardiac gating and be instructed as to a standardized breath holding instructions (Appendix 19).

CT Scans:

Series	Description	No. of images	Scan time	ECG gating
1	Scout of thorax and	2	7 sec x 2	No

	abdomen[1]			
2	Coronary scan 1[2]	40-50	20-40 sec	Yes
3	Coronary scan 2[2]	40-50	20-40 sec	Yes
4	Abd. Aorta scan	60	30	No

[1]Scout images will consist of a frontal and lateral low energy 2D scanogram

[2]Duplicate scans will be obtained of the coronary circulation to improve the precision of the calcium measurement in the first 500 patients

5. Reconstruction Parameters

The following technical parameters are entered into a memorized protocol on each CT system, which should greatly facilitate protocol compliance. Each series is performed using the large scan field-of-view. This may also be referred to as the body as opposed to the head scan field-of-view. The technologist reconstructs the image using a display or reconstruction field-of-view of 35 cm (or 350 mm). By reconstructing with a 35 cm fov we insure that the QCT phantom is included in the reconstructed images. It is very important when prescribing the scan to make sure that the anterior-posterior center is such that the entire phantom is included in the image. The AP must be centered behind the heart on individuals with very large chest. If while reviewing images it is seen that the phantom is partially clipped off. Reconstruct the series with the appropriate AP offset. Be sure to check this on the first heart scan. The standard reconstruction kernel is used for the two cardiac series and the abdominal aorta scans. For the cardiac series, the 240 degree (scan reconstruction algorithm is used (note that this option has various names depending on vendor (segmented, ultra fast). This algorithm reconstructs images using 240 degrees of raw scan data (tube rotation) with an optimized reconstruction technique to provide images of ~250-500 msec temporal resolution depending on the speed of gantry rotation (0.5s or 0.8s). For the abdominal aorta scan temporal resolution is not a critical factor and the full reconstruction (360 degrees) will be used. Images have an initial display reconstruction at 350 mm (35 cm) followed by a retrospective reconstruction at 500 mm (50 cm).

Table CT Image Reconstruction Parameters

Series	Scan FOV	Display FOV	Kernel	Recon. Type
Heart 1	Large / Body / 55 cm	350 mm	standard	240° (partial)
Heart 2	Large / Body / 55 cm	350 mm	standard	240° (partial)
Abd. Aorta	Large / Body / 55 cm	350 mm 500 mm (retro)	standard	360° (full)

6. Radiation Dose Estimates for the Framingham Heart Study CT Examination

The CT examination involves the use of ionizing radiation (X-rays) to generate images of the participants. The level of exposure utilized in this particular CT examination is on the same magnitude as that typically used in other diagnostic CT imaging. The next section describes the potential risks of exposure to low levels of radiation and where in continuum from the average natural exposure of 3.6 mSv annually the dose for participant in this study is located. The radiation exposure in this CT examination is well below the threshold for any observable direct dose related effects of ionizing radiation. Therefore, the theoretical concerns of low-level radiation exposure for participants of Framingham Heart Study CT Study are the potential for hereditary defects, developmental defects and cancer induction. These potential risks are detailed along with steps that have been taken to further reduce these potential risks.

Radiation induced hereditary defects: "Despite comprehensive studies of the children of the atomic-bomb survivors in Japan, there remains no evidence for heritable effects in humans (UNSCEAR, 1993)."(NCRP

Report 124, Mar. 1996, p. 12). To further reduce this potential risk the gonads (testes and ovaries) are not directly irradiated in the CT examination.

Radiation induced developmental defects: "High radiation doses can cause death, malformation, growth retardation and functional impairment. However, low doses (<0.2 Gy) do not appear, in general, to affect the developmental process." (NCRP Report 124, Mar. 1996, p. 12). To further eliminate this potential risk, women who have the potential to be pregnant (i.e. functioning ovaries and uterus) are required to have a pregnancy test prior to being eligible for an Framingham Heart Study CT examination.

Radiation-induced oncogenesis: "Cancers arising in various organs and tissues are the principal late somatic effects of radiation exposure. As a very general guideline, the BEIR V Report (NAS/NRC, 1990) suggests a fatal cancer risk estimate of four cancers per 100 mSv in 1,000 exposed individuals. At the doses of 2.5 to 5 mSv experienced by nuclear medical personnel annually, the cancer risk is small. To place this in perspective, if an unexposed population of 1,000 persons was exposed to doses of 5 mSv y^{-1} for 40 y there could be eight cancers in addition to the 210 cancer deaths that would occur in that population due to the normal incidence of cancer in the population of the United States." (NCRP Report 124, Mar. 1996, p. 13). In this study participants receive a one-time exposure of 5.7 to 6.4 mSv as opposed to the same exposure over 40 years described in the above example. The exposure in this study is also less than the cumulative exposure of the active and approved MESA (3 CT examinations of the heart) and CARDIA (2 CT examinations of the heart) protocols.

This section provides an estimate of the radiation dose that results from the CT scans performed as part of the research study "Framingham Offspring/Generation 3 CT Scan Examination". The calculations in this section were performed by [redacted] and Medical Physicist UCLA

Department of Radiological Sciences in conjunction with [redacted], MS of Wake Forest University Medical Center. These calculations were used for the Family Heart Study-SCAN The revision history of the dose estimates is as follows: The initial dose estimates calculated as part of the grant submission were prepared by [redacted] in conjunction with [redacted] Division of Radio logic Sciences Wake Forest Univ. School of Medicine. At the request of the NIH, an external review of the calculations was performed by [redacted] and submitted to NIH in a letter prior to the awarding of the grant in September of 2001. As detailed in this letter, the plan was to finalize the CT scan protocol and equipment to be used at each field center and provide an accurate but conservative estimate of radiation exposure.

As specified in the preceding sections of this MOP, Framingham participants will have a CT examination that consists of the following components:

a. The coronary scans 1 & 2 are identical by design to those currently in the field in both the NHLBI-funded MESA and CARDIA studies as well as the Family Heart Study-SCAN Study. Like these other studies, we will conduct 2 coronary scans in our MDCT protocol in order to maximize the reproducibility of our scans and comparability with other NHLBI studies. However, we plan to evaluate test-test agreement after approximately 500 scans have been scored. After the conduct of scoring the first 500 scans Framingham Heart Study investigators, and MGH investigators will discuss possible reproducibility criteria that might justify only one coronary scan in consultation with NHLBI staff involved with the Framingham Heart Study MDCT study and other NHLBI CT studies. These data will be reviewed and discussed together by Framingham Heart Study investigators, MGH investigators and NHLBI staff for evidence of reproducibility sufficiently high to consider omission of one of the 2 coronary scans.

b. The abdominal CT protocol includes a limited scan of the abdominal aorta. Using the same protocol and the rationale of other NHLBI studies that coverage of the entire infrarenal aorta was advantageous, the coverage includes 15 cm of length. This provides complete coverage of the infrarenal aorta and imaging of the lumbar spine and visceral fat for future analysis.

Participants undergoing the MDCT examination will have:

a. Peak radiation dose of approximately 2.5 rad (25 mGy) at the peripheral position (essentially the skin) of the patient.
b. Highest doses to radiosensitive organs are approximately 1.3 rad (13 mGy) to the lungs and approximately 1.4 rad (14 mGy) to the female breast.
c. An estimate of effective dose would be 5.7 to 6.4 mSv per CT examination that is broken down by sequence below.

Summary of Effective Dose Estimates-Table 1

Sequence	Description	Deff [mrem]	Deff [mSv]
1	coronary axial 1	150 to 190	1.5 to 1.9
2	coronary axial 2	150 to 190	1.5 to 1.9
3	Abd. Aorta helical	270	2.7
	Total	570 to 640	5.7 to 6.4

Note: [redacted] stated that the radiation exposure related to the low energy scouts / topograms were inconsequential in dose compared to the above series; as a result they are not detailed in the above table.

These estimates of effective dose can be compared to the annual average effective dose from background radiation, which is 3.6 mSv/year and the annual whole body effective dose that a radiation worker (radiologist, radio logic technologist) is allowed on an annual basis (50 mSv/year). Thus, the patient receives the equivalent of approximately 1.58 to 1.78 years of background radiation from the CT scans. Alternatively, this is 12.8% (6.4 mSv/50 mSv) of the annual allowance of 50 mSv for radiation workers.

Detailed Discussion of Dose Estimates

1. Examination description

The CT examination consists of the series of scans described previously with repeat series (total of 2) through the coronary arteries using standard techniques and one series through the abdominal aorta.

2. Technical factors for each series used in the dose estimates

a. Coronary Scans 1 and 2 (which are identical sequences)

Using the GE LightSpeed multidetector scanner, the standard protocol will be employed:

4 x 2.5 mm collimation (4i axial) mode with 10 mm table increment (contiguous scans)

Prospective EKG gating; x-ray beam is only on 2/3 of a scan rotation

140 KVp, 150 mA, 0.5 second scans

Scan Coverage: 2 cm below the carina extending to the base of the heart.

Limited Scan of Abdominal Aorta

Using the GE LightSpeed multidetector scanner, the following protocols are employed:

4 x 2.5 mm collimation with Helical HQ mode (table speed of 7.5 mm/rotation)

140 KVp, 250 mA, 0.5 second scans

Scan Coverage: starting 15 cm above S1 vertebra and stopping at the superior endplate of S1.

7. Peak Radiation Dose

Estimated radiation dose (CTDI) is reported below using the technical factors described above for each sequence. These values were calculated based on measured values using a standard test object (CTDI 32 cm-diameter body phantom) in comparable scanners (GE LightSpeed) at UCLA:

Table 2 – Estimates of Peak dose for each sequence

Scan	Peak Radiation Dose at Center	Peak Radiation Dose at Periphery
Each Coronary Scan	6.3 mGy (.63 rad)	12.5 mGy (1.25 rad)
Abdominal Aorta Scan	7.3 mGy (.73 rad)	15 mGy (1.5 rad)

Because the two coronary scans cover the same anatomy, the peak dose in those two regions add so that the peak dose occurs in the anatomy ranging from the carina to the base of the heart, which receives 25 mGy (2.5 rad).

Effective Dose Calculations

Effective Dose is the sum of the weighted absorbed doses for all irradiated tissues, where the weighting factors represent the different risk of each tissue to mortality from cancer and hereditary effects. These weighting factors are higher for the gonads and lower for less sensitive organs (such as the extremities).

These estimates were obtained by finding the average dose to each radiosensitive organ (based on the phantom radiation dose measurements described above and anatomical coverage for each sequence). The weighting factors were then applied according to the description in the International Council on Radiation Protection Report 60. These estimates were performed for each sequence and then summed to obtain the results for the entire examination. The results are summarized in table 2 on page 59.

For each coronary scan, the estimated effective dose is estimated to be 1.5 mSv (150 mrem) for men and 1.9 mSv (190 mrem) for women. The difference is that the breast is irradiated in this scan, and because the breast dose carries a weighting factor of .05 of the total effective dose, the effective dose is higher for women.

For the abdominal aorta scans, the estimated effective dose is 2.7 mSv (270 mrem) for the 15 cm of coverage. The reproductive organs are not irradiated, as the true pelvis is not scanned.

For the entire examination, the estimates of effective dose range 5.7 mSv for men to 6.4 mSv for women. These values would compare with 3.6 mSv annual background radiation and the 50 mSv whole body exposure annual limit for radiation workers.

Therefore, the total effective dose from these scans for an average patient is significantly less than that allowed for radiation workers on an annual basis and is equivalent to about 1.6 to 1.8 years of background

radiation. However, because these estimates are based on population averages, these estimates should not be taken to provide an estimate of risk for any individual patient.

Informing Participants of Radiation Exposure

To provide participants with a concise and understandable explanation of the radiation involved with the CT examination we have chosen to present the effective dose. The effective dose estimates the exposure by organ irradiated and allows the values to be compared directly with the annual exposure to natural sources of radiation (3.6 mSv) and the annual allowance for radiation workers. We believe that the alternatives of (1) simply providing a number out of context or (2) comparing the dose to other medical procedures, while informative to scientists and healthcare professionals, is less informative to the lay public. The following language is recommended to the field centers for informed consent concerning the CT examination. Local requirements or standard language may require modifications as appropriate.

10. Recommended Language for Informed Consent

The estimated amount of radiation (effective dose) the average participant in this study receives is 6 mSv. This amount of radiation exposure can be compared to the amount of radiation exposure you get each year from natural sources which is 3.6 mSv (average annual background exposure). The actual amount the participant receives for the whole CT examination depends on several factors such as how big the participant is and if they are a man or women; however, the range of these values is between 1.5 and 2 times the annual background exposure is received each year from natural sources. People who have jobs in which they work with radiation have a yearly limit of 50 mSv. The amount of radiation you will receive by participating in this study is approximately 13% of this annual limit for radiation workers.

We believe the above language accurately and conservatively presents the information related to radiation exposure with the Framingham Heart Study CT examination and allows our participants and potential participants to make an informed decision about involvement in this study.

The investigators of the study are aware that local review and approval of the CT protocol, as for other aspects of the study, must be made through the appropriate IRB. In some cases additional review by radiation safety committees may be required. The CT Reading Center will provide assistance and the material contained in the manual of operation to the local principal investigator and imaging investigator to facilitate and enhance the process.

11. Participant Safety and Confidentiality Considerations Related to the CT Examination

The Framingham Heart Study CT examination both operationally and scientifically builds on the experience of National Heart Lung and Blood Institute with recent large population-based studies which have incorporated CT measures of sub clinical atherosclerosis. The MESA and CARDIA study and Family Heart Study-SCAN study have successfully implemented an identical protocol for measuring coronary calcium as proposed in the Framingham Heart Study. The Framingham Heart Study CT protocol adds imaging of the abdominal aorta. It should be noted that the current Framingham Heart Study protocol calls for a single examination at baseline as opposed to CARDIA in which CT examinations were obtained at years 10 and 15 and MESA in which 3 examinations are proposed. However, repeat testing has been conducted for many other radiographic and ultrasound imaging modalities in the Framingham Heart Study, and we have developed the current MDCT imaging protocol in such a way as to allow the study of vascular calcification progression should repeat scanning be performed.

The investigators realize the importance of participant safety and informed consent and all have formal training in the various aspects of the ethical conduct required for research with human participants.

Specifically, we understand the necessity for reporting deviations, unexpected events, adverse events, serious adverse events, IRB concerns, participant complaints or any other significant issue potentially representing safety concern immediately to the relevant Investigation Review Boards (IRB) and the NHLBI Program Officer. If the IRB determines a situation has occurred in which an unanticipated risks to human subjects has occurred this will be reported by the Institutional Official to the Office of Human Research Protection (OHRP). In the Framingham Heart Study CT study, active oversight is provided for the CT examination components.

12. Coronary Calcium Measurement Procedures

The following is an abbreviated overview of the Calcium scoring software and procedures for the Image Analysis Software. The final analysis procedures section will be completed once the software version to be utilized is determined.

Boxing a Study: The next step of the process isolates the four regions of interest corresponding to the phantom cylinders underneath the participant containing 0, 50, 100 and 200 mg/ml Calcium. This step allows the program to calculate pixel regression values based on the known calcium concentrations of each slice within the examination. Following this step the heart is extracted from the thorax a process termed "Boxing".

a. Trace Arteries: The region of the coronary arteries (Left main, anterior descending, circumflex and right) is seeded by the CT Reader on each slice with each vessel color-coded. The seeding process allows the program to extract sub-regions for each coronary vessel.

b. Adjudicating Calcium Plaques: During the scoring process the CT Reader reviews all potential calcified lesions related to the extract regions around the coronary arteries. The reader is guided by the program from lesion-to-lesion until the CT Reader has made a determination on each potential lesion.

Typical false positive calcified abnormalities are: valvular calcification, calcified mediastinal lymph nodes, pericardial calcification, and metallic artifacts from surgery or penetrating object.

c. Quality Assurance Menu: The CT Reader rates each study on the following quality assessment factors: artifacts, phantom positioning, mis-registration of slices, image noise level, centering of the coronary vessels within the field of view, and coverage of the entire coronary circulation. These variables are graded on a three-point scale (unacceptable, average, and excellent).

d. Integrated Archiving: The processed CT studies are saved and placed into a special archive folder. The program is currently configured to archive to a CDRW drive/mastering system. In the Framingham Heart Study, will change to a DVD ram system secondary to improved reliability, data integrity and decreased overall cost. Although the current cost for CD is ~$3/GB compared with ~$8/GB with DVD, the logistics of tracking and storing 664 CD's verses only 80 DVD's for each copy of the Framingham Heart Study CT library makes DVD the logical choice. A primary advantage of DVD is the format was designed for storing multi-session digital data, as opposed to the CD format, which was originally designed for recording music, which complicates the "authoring/burning" of CD's. We have not experienced any difficulty in copying DICOM files to our DVD ram drive and have been impressed at the dramatically improved throughput when compared with our CD systems.

e. Measures of CT Reader Variability: 3% of all participant studies are selected as part of the quality control procedures at the Reading Center. These are used to measure inter- and intra- reader variability. The software allows replicated readings to determine inter and intra-reader variability. The randomly selected studies will be placed within the appropriate CT Reader's queue for scoring. Equally important, by using separate login accounts, the type of reading (primary or QA) can be determined unambiguously.

Aortic Calcium Measurement Procedures

The procedure is identical for measuring abdominal aortic calcium except for the designation of the arterial segments. During the "Trace Arteries" subroutine the reader designates the segments to be measured in the

abdominal aorta (abdominal aorta, right common iliac, left common iliac). The regions of the abdominal aorta are seeded by the CT Reader on each slice with each vessel color-coded as for the coronary arteries. The seeding process allows the program to extract sub-regions for each vessel.

14. CT Scanner Quality Assurance

a. Calibration to Air (Baseline, then daily)

An initial baseline and daily scans are obtained. This calibration is part of the daily scanner start-up routine. These procedures follow the manufacturer's recommended procedure.

b. Calibration to Water (Baseline, then bi-weekly)

An initial baseline followed by bi-weekly scans is obtained and analyzed using a water phantom. These procedures follow the manufacturer's recommended procedure and include zeroing and calibrating the scanner unit.

c. Calibration to Calcium (Baseline, then bi-weekly)

Each CT scanning site is provided a standardized Calcium QCT Calibration Phantom, which includes a Torso QA phantom for scanner calibration (Image Analysis Inc, Lexington, KY). The center plug of the Torso QA phantom contains a region with a known concentration of calcium hydroxyapatite (100mg/ml). The Calcium QCT Calibration phantom contains four cylindrical rods with the following concentrations of calcium: 0, 50, 100, 200 mg/ml calcium hydroxyapatite. Every two weeks, quality assurance scans of the torso phantom will be performed at the CT scan site. The analysis of these scans by the CT Reading Center allows convenient and quick verification of accuracy and precision of the CT scanner.

Positioning the Calibration and Torso Phantoms.

The table height of the CT couch is positioned such that the center of the Torso Calibration phantom is located at isocenter of the scanner field of view.

Place the torso phantom is on top of the calibration phantom (positioned in couch pad) and using the laser alignment light; adjust the table height until the torso center insert is at the location of isocenter on the CT scanner. This is the table height being used for QA scans with the Torso phantom.

Scanning the TORSO QA Phantom

After the correct position has been determined, take a vertical axial slice through the center of the TORSO phantom. Use the same parameters as with patient examinations. Each site performs a scout of the phantom followed by an axial scan (identical parameters to the heart series) and helical scan (identical parameters to the abdominal aorta scan). Reconstruction should be done with the same parameters as in scanning study subjects. Then display the axial image on your CT monitor and examine it to ensure that it is free of artifacts, such as air gaps and streaks. Ensure that the calibration phantom is included in the field of view. If there are significant artifacts over the calibration phantom, discard the image and rescan the phantom.

Phantom Imaging Scoring:

Phantom image scoring is done at the completion of CAC soring. Click on the thumbnail corresponding to CA1. Click on "Setup Params" in the center of the screen. This will make a box pop-up that is entitled: Calcium Scoring Parameters. Calibration should be set as:

RO1 #1: 0 (Density)
RO2 #2: 100 (Density)
RO3 #3: 200 (Density)

#RO1s: 3
Target RO1 Area: 2

Once this is set, click on Calibrate Mass. A blue circle (calibration circle) will appear on the scan, movable by the curser. Using the mouse, scroll to an LAD (Left Anterior Descending Artery) slice, preferably a first image or LM (Left Main Artery) and LAD together. Note at the bottom of the screen is the phantom, a

rectangle with 3 variations of gray: dark gray, light gray, and white gray. Position the calibration circle in the center of the dark gray square first. Left click. The measurement will appear on the top left part of the screen under Mean HU. Repeat procedure with the middle (light) gray square. Then write down the number on your CT Measurement Sheet. Repeat procedure with the last (white) gray square and the final measurement result will appear at the top left of the screen: Calibrated: r^2=0.9XXX or 1.0000. Note: the measurement for the third (white) gray will not be shown. Also the final calibrated number should not exceed 1.0000.
Next click on Save Calibration and then Save and Exit (boxes in center of screen, towards the bottom).

Repeat the same procedure for CA2.
Repeat the same procedure for AA. Measurement for AA should be done at the slice immediately superior to the aortic bifurcation.

These measurements are saved on the TR. They can be found by going to: Drive E->AquariusReport->AnalysisData->Calcium. They are stored in FHS ID order. To do FHS data analysis, these files need to be converted into text files. On a drive with disk space (ie D drive) make a Phantom Folder. Under this folder create individual folders (these smaller folders will contain ~ 200 scans, depending on how many are measured before putting them in text files). Open the smaller folder to accept the data. Click on the FHS ID. Check the numbers (CalibrationMeasured 0, 1, and 2 and LsqR2) with those on your CT Measurement Sheet to verify you have the correct numbers measured for CA1, CA2 and AA. If so, highlight from PatientName to (and including) LsqR2). Copy this, close box and paste it into your individual folder. Keeping a double space between entries, continue this until all phantom measurements are in the text file. Keep a separate text file for Offpspring [redacted] and Gen 3 [redacted]
When completed, copy to a flashdrive or CD and give to FHS data staff.

15. Analysis of the Phantom Results at the CT Reading Center

Use the QCT software available to the reading center which runs on a standard PC using Microsoft Windows OS, click on the QCT-5000 icon on your desktop. Click the enter QA button on the toolbar. A QA data entry screen pops up. Enter the data from the QA data sheets from the field centers. When all the data is entered, click OK. This will save the data to the QA database and open a window showing the QA report. To discard the entries you have made, click cancel. The QCT 5000 software computes the calibrated calcium density for the Torso phantom. The results are displayed in graphic and tabular format. The software also accesses the database and retrieves any previous data on the Torso phantom. Previous data and calculated changes are displayed in the tabular form. The individual QA torso readings should be maintained at within $\pm$ 3% of the mean value of all the readings. If the values fall out of range, the field site must be notified in order to have the scanner checked by the field engineers.

16. Procedures for Participant Notification

For each subject, a complete output of calcium scoring data for the coronary arteries, the thoracic aorta and the abdominal aorta, including an Agatston calcium score for the coronary arteries, will be generated and forwarded to the Framingham Heart Study. The physician of each subject with a coronary calcium scores above the upper 10^{th} decile for age is sent a summary of the calcium score with wording indicating that the score is high for age and with references to the most recent ACC/AHA guideline statement on coronary calcium imaging. The published literature will be reviewed annually. If deemed appropriate after review of the literature and contact with the other NHLBI population-based studies, and if approved by the Framingham Heart Study Executive Committee and OSMB, reporting may be extended to more or all subjects.

Scans are being conducted for research purposes, however, the entire scan will be screened for clinically important findings and clinically important findings will be reported by a radiologist at Mass General Hospital. It is possible that a non-subtle abnormality will be apparent upon review of the coronary arteries and the abdominal aorta (e.g., a large mass or lymph node, a large abdominal aortic aneurysm). In these cases, the subject's physician will be notified with the caveat that the scan was not performed to detect the stated abnormality or to exclude other abnormalities.

17. Procedure for Monitoring of Participant Radiation Exposure

As described previously, a predefined protocol is employed with fixed MA and kV parameters. To ensure that systematic errors in radiation dosing are not propagated to participants, we record the following radiation exposure data for each participant scanned: Accumulated examination DLP, projected series DLP, dose efficiency and CTDWi. If there is a protocol violation for any given scan, [redacted] and other relevant Framingham Heart Study and MGH staff will be notified. If protocol violations

occur, corrective measures are immediately undertaken, to include the generation of a report regarding the protocol violation and corrective measures undertaken by the MGH West CT technologist staff. All protocol violations are reported in the regular QC report to NHLBI.

18. Eligibility and Pregnancy Testing

1200 participants from the Framingham Heart Study Offspring cohort and 1900 participants in the Generation III cohort will be recruited for CT scanning. Offspring cohort members will be selected for recruitment according to the following priorities: members of families that have participated in the genome scan; members of the largest families for whom family members are available for recruitment in the Generation III cohort; live within the New England region; men $\geq$ 35 years of age; women $\geq$ 40 years of age; premenopausal women who are not pregnant (confirmed by a negative pregnancy test and by screening for unprotected sexual intercourse within the seven days prior to the CT scan). Generation III subjects are recruited from among Generation III subjects who have completed the initial clinic examination and according to the following criteria: men $\geq$ 35 years of age; women $\geq$ 40 years of age; premenopausal women who are not pregnant (confirmed by a negative pregnancy test and by screening for unprotected sexual intercourse within the seven days prior to the CT scan). Postmenopausal women are also scanned. Participants must weigh less than 352 pounds.

Appendix 2: RFP Response-Coronary Calcium Imaging

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Principal Investigator/Program Director (Last, first, middle): [redacted]

N.B. Follow-up for morbidity and mortality in all three generations will be performed according to standardized protocol (See Appendix 2.11)

LABORATORY TESTING (Please refer to Appendix 2.3 for details)

The FHS has extensively studied the contributions of cholesterol and HDL-cholesterol to cardiovascular risk. [redacted] The underpinnings of these lipoprotein cholesterol levels have also been investigated, and factors such as age, weight gain, menopause, and diabetes mellitus are important determinants of lipid levels.(Siegel et al, 1996; Niedzwiecki et al, 1997) Newer measurements on the Gen3 sample and continued measurements on the first and second generation participants will provide high quality laboratory determinations that are scientifically comparable to past analytic techniques; this will allow us to test the hypotheses that a) lipoprotein cholesterol levels are heritable, b) secular trends over time in lipids are demonstrable, and c) time-averaged risk factor levels are associated with subclinical and clinical CVD. These analyses will take into account age, calendar year, and environmental effects such as physical activity and diet.

More recent FHS investigations, confined to the Offspring cohort, have investigated endothelial and hematologic markers and their relation to CVD risk factors. Not enough follow up has occurred to effectively relate these biomarkers to the incidence of CVD, investigate their heritability across generations, or gauge their role after consideration of conventional CVD risk factors. Hypotheses to test related to these laboratory measures are how fibrinogen, C-reactive protein, homocysteine, tPA antigen, and plasminogen activator inhibitor are related to subclinical and clinical CVD.

Diabetes mellitus is a well-recognized CVD risk factor, but few population studies have had the opportunity to investiga prospectively how the insulin resistance syndrome is related to cardiovascular sequelae. The Offspring cohort has been well characterized with regard to diabetes and borderline diabetes status, and oral glucose tolerance tests were performed the early 1990's on all Offspring participants. Oral glucose tolerance tests with fasting insulin levels will be performed Gen3 participants. This information will allow us to test the heritability and expression of insulin resistance traits across two generations, bearing in mind that body mass index, abdominal adiposity, and blood pressure levels are high related to expression of the phenotype, as previously shown from the FHS experience. [redacted] These investigatic will also facilitate the study of the determinants of risk factor clustering associated with adiposity and insulin resistance considering a variety of conventional and novel CVD risk factors. The latter will include assessment of microalbuminu and triglyceride rich lipoprotein determinations.

EBCT: Background and Rationale

Subclinical coronary and aortic calcifications commonly occur early in the development of atherosclerotic plaque, preceding the onset of clinical CVD by years or decades. Abdominal aortic and coronary calcifications on plain radiogr are associated with long-term exposure to established risk factors in FHS subjects [redacted] Abdominal thoracic aortic calcific deposits predict incident CHD and other CVD events, independent of other CVD risk factors [redacted] ECG-gated CT imaging of coronary artery calcium is now available and provides a noninvasive modality for detection of the presence and burden of coronary atherosclerosis.

We recently completed a pilot study of electron beam computed tomography (EBCT) in 327 FHS Offspring cohort participants, and we found significant associations of coronary calcification with Framingham risk score, long-term (ti averaged 25 year) risk factors [redacted], blood CRP level [redacted] and aortic plaque dete by MRI. These initial findings require confirmation by a much larger study. Although coronary calcium detected by EBCT predicted onset of overt CHD and other CVD in some studies (O'Malley et al, 2001; Arad et al 1996), populatio based data are limited regarding the predictive utility of these measures over and above traditional risk factors (Wexler et al, 1996; O'Rourke et al 2000). There is a substantial genetic (heritable) component to lumbar aortic calcification [redacted] nd to coronary calcification (Lange et al 2001) in the FHS. The FHS offers a unique opportu to conduct a large-scale, family-based epidemiology study to identify genetic determinants and gene-environment interactions leading to subclinical coronary and aortic calcification. Given the proposed Gen3 design, heritability and genome scan analyses will be possible using all Offspring cohort sibling pairs and selected Third Generation subjects undergoing EBCT testing. Association studies of specific candidate gene variants would then be performed using population-based association and transmission disequilibrium testing.

Proposed Design: We will conduct a study of the genetic and environmental determinants of subclinical coronary, ao and cardiac calcification and their relations with clinical CVD. We propose to use EBCT scanning in 2800 Offspring cohort subjects and 1900 selected Gen3 subjects to detect and quantify coronary calcification and thoracic and abdomi aortic calcification

CONTINUATION PAGE: STAY WITHIN MARGINS INDICATED

Principal Investigator/Program Director (Last, first, middle) [redacted]

Our proposed design differs from the RFP, which calls for coronary calcification testing in a subsample of 1,200 Offspring and 3,500 Gen3 subjects for reasons outlined below. Data from the FHS EBCT pilot study and other available databases demonstrate that there is a broad distribution of coronary calcification in middle age and older persons, such as the Offspring cohort subjects (mean age 65 years). We propose a more appropriate study design would be to conduct EBCT tests on all available Offspring cohort subjects except those who have already completed the pilot study (n=327). Given an anticipated attendance of 3,364 Offspring participants during the callback examination between Cycles 7 and 8, we estimate 2,800 subjects will undergo EBCT testing. Data from the proposed Offspring cohort EBCT tests will be extremely valuable for testing both genetic (in siblings) and non-genetic hypotheses.

Regarding plans to conduct testing in Third Generation participants, data from the FHS pilot study and other available databases suggests that the prevalence of coronary calcification will be extremely low (<<10%) in men under age 35 and in women under age 40 (see Appendix 2.4). Thus, we propose to exclude women < 40 years of age (n~860) and men <35 years of age (n ~530) from EBCT testing, and we expect that about 10% will refuse to undergo the procedure, yielding an expected number of 1,900 EBCTs on third generation subjects. Accordingly, we propose to conduct coronary calcification testing in 2,800 Offspring cohort and 1,900 Gen3 subjects. The design of the Gen3 EBCT study will permit the use of vascular calcification as a quantitative phenotype for genetic studies.

ASSESSMENT OF PULMONARY DISEASE

Asthma and chronic obstructive pulmonary disease (COPD) are the two most common chronic pulmonary diseases, affecting 5% and 6%, respectively, of the US adult population.(Petty, 2000) Both are complex phenotypes, likely determined by the interaction of multiple genes and environmental factors. The three-generation families of the FHS offer a unique opportunity to study the genetic basis of these disorders in the general population, but such analyses require that phenotypic classification be as precise as possible.

In the past, objective pulmonary function measurement at FHS has been limited to spirometry, and questionnaire assessment of lung disease has been limited to less standardized questions included in the physician interview. We propose an expanded battery of objective pulmonary function testing along with the administration of standardized respiratory disease questionnaires. For details of the pulmonary protocol, please see Appendix 2.8. Briefly, the following components are proposed:

- **ATS-DLD Respiratory Disease Questionnaire** (Ferris, 1978) This instrument is currently being revised in an effo funded by NHLBI and ATS and co-chaired by [redacted]. It is anticipated that the revised instrument will be ready for use by the time that Gen3 examinations begin (2002).
- **Spirometry** will be done in accordance with the current spirometry protocol at FHS, which was adapted from the Lung Health Study and is more stringent than ATS standards.(Enright et al, 1991) Up to eight attempts will be mac in an effort to obtain three acceptable spirograms for which the highest two values of FVC and the highest two valu of FEV1 are within 2% of each other.
- **Single-Breath Carbon Monoxide Diffusing Capacity (DLCO) and Carbon Monoxide Diffusing Capacity Per Unit of Alveolar Volume (D_L/V_A).** This test will enhance our ability to distinguish obstructive ventilatory impairment related to emphysema from that related principally to airways disease.(Gelb et al, 1973) In accordance with ATS guidelines,(American Thoracic Society, 1995) we will perform this maneuver at least twice, waiting fou minutes between maneuvers, with a goal of obtaining two results within 10% range.

ECHOCARDIOGRAPHY

The power of echocardiography as an epidemiological tool is reflected in the enormous research productivity of the FH echocardiography laboratory (see bibliography in Appendix 2.5). The noninvasive nature, the brief study time require the lack of X-ray irradiation, and the high subject acceptability make it well suited to community-based examinations the heart. The good reproducibility of echocardiography makes it well suited for studying change in heart structure a function through serial examinations.(Savage et al, 1987; Devereux, Liebson, Horan 1987) An additional advantage echocardiography is that it is the most widely used cardiac imaging modality; hence it is of direct relevance to clinicians

Echocardiography is the investigation of choice for the noninvasive assessment of cardiac structure and function. Echocardiographic LV systolic dysfunction and LV dilation herald the progression to overt CHF[redacted] Framingham investigators have produced widely used reference values for LV mass[redacted]) have documentec that LV mass is heritable, (Post et al, 1997) and have established LV mass as a key risk factor for CVD and mortality.[redacted] In addition, echocardiography in observational studie can lend critical understanding of the prevalence and prognosis of a variety of cardiac conditions, such as mitral valve prolapse[redacted] which have been traditionally overstated in hospital-based studies.

Principal Investigator/Program Director: [redacted]

Appendix 2.4 Framingham Heart Study Calcification Imaging

Appendix 2.4 Framingham Heart Study Calcification Imaging

Feasibility Pilot Imaging Study: Summary and Preliminary Results

We examined the feasibility of subclinical disease testing in the Framingham Heart Study Pilot Imaging Study. We performed electron beam computed tomography (EBCT) of the coronary arteries and thoracic aorta in 327 participants in the FHS, stratified by age, gender and coronary risk profile. In addition, each subject underwent MRI imaging of the thoracic and abdominal aorta to evaluate the presence and degree of atherosclerosis, as well as MRI imaging of the heart to evaluate left ventricular structure and function. Subjects were recruited over a twelve month period from July 1998 through June 1999. The primary scientific hypothesis was that EBCT accurately detects subclinical coronary and aortic atherosclerosis and target organ disease in a population free of clinically apparent cardiovascular disease. Among the primary feasibility criteria for evaluating the broader use of EBCT in the FHS were:

- **Validity:** EBCT provides a valid measure of subclinical atherosclerosis and target organ disease in the FHS
- **Reproducibility and cost:** EBCT is a reproducible method for detection of subclinical disease in the FHS
- **Prevalence:** the prevalence of coronary and aortic atherosclerosis is at least twice as great as the prevalence of clinically manifest CHD in the FHS
- **Acceptability:** EBCT is highly acceptable to FHS participants

We estimated a priori that the study had at least 80% power to detect a two-fold increment in prevalence of subclinical atherosclerosis across quintiles of the FHS coronary risk score.

Selection Criteria for the Framingham Heart Study Pilot Imaging Study Cohort

After excluding those with clinically apparent CVD and sampling from prespecified strata of gender, age, and Framingham coronary risk score [redacted] 327 subjects were selected. The objective of this scheme was to select a cohort that represented the entire spectrum of atherosclerosis risk in the current Offspring Cohort. We sampled one third of subjects from the highest age- and sex-specific quintile of Framingham coronary risk score; one-third from the combined third and fourth quintiles of risk; and one-third from the combined first and second quintiles of risk (see Table 1). The mean ages (standard deviation), in years, in the four age quartiles were 45.4 (4.1), 53.6 (1.7), 60.5 (2.3) and 70.1 (3.9), respectively, for men; and 46.2 (3.4), 54.0 (1.9), 61.5 (2.4), and 70.7 (3.7), respectively, for women.

EBCT Measures

All consenting subjects underwent EBCT imaging of both the coronaries and the entire thoracic aorta under the direction of [redacted] (Beth Israel Deaconess Medical Center). Using standard imaging software, data were generated for each of four coronary artery segments (left anterior descending, left circumflex, right and left main) and for the total of all coronary segments as follows:

- Number of calcifications
- Weight equivalent of calcification
- Volume of calcification
- Volume/(weight equivalent) of calcification
- Agatston score

Similar data were derived for each of four thoracic aortic segments (ascending, arch, proximal descending, distal descending) and for the total of all aortic segments.

ppendix 2.4 Framingham Heart Study Calcification Imaging

Table 1. Sampling Scheme for the Pilot Study of EBCT/MRI in the Framingham Heart Study

			Women	Men
Age Quartile 1 (35-50 years)	*Quintile of Framingham Coronary Heart Disease Risk Score*	1	n=13	n=13
		2		
		3	n=13	n=15
		4		
		5	n=13	n=14
Age Quartile 2 (51-57 years)	*Quintile of Framingham Coronary Heart Disease Risk Score*	1	n=15	n=14
		2		
		3	n=13	n=15
		4		
		5	n=13	n=14
Age Quartile 3 (58-65 years)	*Quintile of Framingham Coronary Heart Disease Risk Score*	1	n=13	n=13
		2		
		3	n=13	n=14
		4		
		5	n=13	n=13
Age Quartile 4 (65-77 years)	*Quintile of Framingham Coronary Heart Disease Risk Score*	1	n=14	n=15
		2		
		3	n=13	n=13
		4		
		5	n=14	n=14

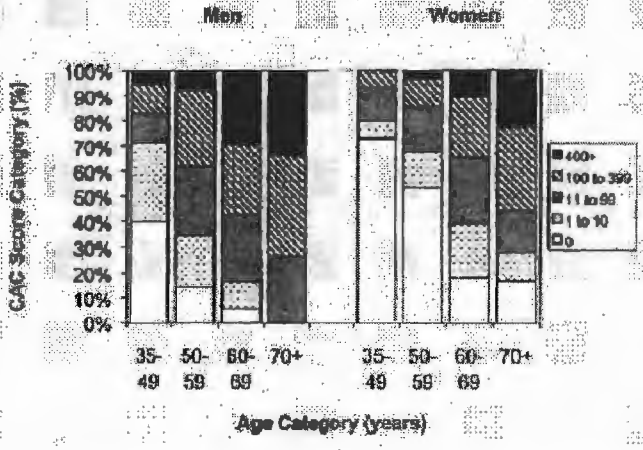
Total Sample N = 327

Appendix 2.4 Framingham Heart Study Calcification Imaging

Results of Imaging Study: Prevalence of calcification

The prevalence of coronary calcification and the Agatston score increased markedly across age categories in both men and women (Figure 1); as expected, the prevalence of any calcification and of calcification scores greater than 100 were substantial even in younger age ranges when CHD is rare.

Figure 1



Distributions of coronary and aortic calcification quantiles were as follows (Table 1):

Table 1

Ca^{++}	Coronary Artery Ca^{++}			Thoracic Aortic Ca^{++}		
Quartile	N	Range	Agatston Score, Mean	N	Range	Agatston Score, Mean
First	80	0	0	75	0-1	1
Second	95	1-3	7	95	2-4	20
Third	67	4-7	86	73	5-9	117
Fourth	85	8-32	691	82	10-119	2485

Principal Investigator/Program Director: [redacted]

Appendix 2.4 Framingham Heart Study Calcification Imaging

Results of Imaging Study: Associations with Established Risk Factors

Coronary calcification were associated with contemporary measurements of established risk factors (i.e., measured at the time of EBCT testing) and Framingham risk score derived from contemporary risk factors, as follows (Table 2):

Table 2a

Risk factor, exam 6	Men CAC Score ≥ 100	Men CAC Score < 100	P-value
N of subjects	72	95	
Age (years)	63	57	0.0001
BMI (kg/m²)	30	28	0.07
Total chol (mg/dL)	203	199	0.43
HDL chol (mg/dL)	44	43	0.80
Total/HDL Ratio	5	5	0.60
Systolic BP (mmHg)	133	125	0.0001
Diabetes (%)	13	7	0.23
Smoker (%)	16	12	0.55
Lipid lowering therapy (%)	13	8	0.44
HTN therapy (%)	39	17	0.002
FHS Point Score	8	6	0.0001

Table 2b

Risk factor, exam 6	Women CAC Score ≥ 100	Women CAC Score < 100	P-value
N of subjects	40	120	
Age (years)	69	59	0.0001
BMI (kg/m²)	28	27	0.30
Total chol (mg/dL)	220	212	0.20
HDL chol (mg/dL)	55	57	0.46
Total/HDL Ratio	4	4	0.35
Systolic BP (mmHg)	136	123	0.0001
Diabetes (%)	15	3	0.01
Smoker (%)	11	8	0.56
Lipid lowering therapy (%)	20	10	0.10
HTN therapy (%)	34	18	0.04
FHS Point Score	10	6	0.0001

There were also associations of coronary calcification with long-term risk factors, measured over 25 years prior to EBCT testing, as follows (Table 3):

Table 3a

Mean risk factor level, examinations 1-6	Men CAC Score ≥ 100	Men CAC Score < 100	P-value
N of subjects	72	95	
Age (years)	51	44	0.0001
BMI (kg/m²)	28	27	0.03
Total chol (mg/dL)	210	196	0.004
HDL chol (mg/dL)	43	44	0.61
Total/HDL Ratio	5	5	0.02
Systolic BP (mmHg)	128	122	0.003
Diastolic BP (mmHg)	80	79	0.16
Diabetes (%)	6	3	0.25
Smoker (%)	28	23	0.42
Lipid lowering therapy (%)	4	3	0.18
HTN therapy (%)	19	8	0.0005
FHS Point Score	6	3	0.0001

Table 3b

Mean risk factor level, examinations 1-6	Women CAC Score ≥ 100	Women CAC Score < 100	P-value
N of subjects	38	118	
Age (years)	60	49	0.0001
BMI (kg/m²)	27	25	0.19
Total chol (mg/dL)	237	202	0.0001
HDL chol (mg/dL)	56	55	0.96
Total/HDL Ratio	4	4	0.03
Systolic BP (mmHg)	129	116	0.0001
Diastolic BP (mmHg)	77	74	0.01
Diabetes (%)	7	1	0.01
Smoker (%)	19	21	0.92
Lipid lowering therapy (%)	5	2	0.02
HTN therapy (%)	16	8	0.08
FHS Point Score	7	0.5	0.0001

Appendix 2.4 Framingham Heart Study Calcification Imaging

In stepwise, multivariable models adjusting for the long-term risk factor measures, we found that the Framingham coronary risk score and long-term total cholesterol and HDL cholesterol remained significant predictors of calcification score in men and women [redacted]

We have also found statistically significant associations of coronary calcification with C-reactive protein [redacted], insulin resistance and hyperglycemia [redacted]; with other subclinical disease measures such as aortic plaque by magnetic resonance imaging; and with osteoporosis in women determined by bone densitometry [redacted].

Results of Imaging Study: Feasibility Study Objectives

- **Validity:** EBCT provides a valid measure of subclinical atherosclerosis and target organ disease in the FHS.

Given the scientific results of our feasibility study and the hundreds of papers on use of EBCT in clinical and population research, we believe there are now substantial data to support the validity of EBCT as a measure of subclinical atherosclerosis and target organ disease.

- **Reproducibility and cost:** EBCT is a reproducible method for detection of subclinical disease in the FHS

There is a substantial literature showing the high test-test reproducibility of EBCT. Although we did not perform intra-subject reproducibility testing (to avoid unnecessary additional radiation exposure), we did perform reader-reader reproducibility and found very high (>90%) rates of inter-reader comparability. There are also a number of studies suggesting that change in EBCT calcium can be accurately quantified and is associated with coronary risk factors.

- **Prevalence:** the prevalence of coronary and aortic atherosclerosis is at least twice as great as the prevalence of clinically manifest CHD in the FHS

The results of our pilot study support the contention that subclinical coronary atherosclerosis detected by EBCT is common in the middle age subjects in FHS and exceeds by at least twofold the prevalence of clinically apparent CHD and other cardiovascular disease in this age group.

- **Acceptability:** EBCT is highly acceptable to FHS participants

We conducted a satisfaction survey of all subjects undergoing the EBCT testing. All tests were prescheduled, and the duration of EBCT testing was approximately 15 minutes. A single CT technician performed most of the tests. Study participants were very satisfied with the speed, ease and comfort of the EBCT test. No participant refused to complete the test and no participant stated unwillingness to undergo a repeat EBCT test in the future. Because EBCT tests were conducted at the Beth Israel Deaconess Medical Center in Boston, we provided a driver for transportation between the FHS and the Boston. Participants were very satisfied with this form of transportation. During the same visit, pilot study participants also underwent cardiac MRI. Overall levels of satisfaction were high (>90%) for the cardiac MRI, and for both EBCT and MRI testing, although a small percentage of subjects were unable to complete the MRI due to claustrophobia. Total time for travel and for conduct of both tests was approximately 2 to 2 ½ hours.

Principal Investigator/Program Director: [redacted]

Appendix 2.4 Framingham Heart Study Calcification Imaging

Expanded Justification for Study of Genetic and Environmental Determinants of Coronary and Aortic Calcification

Proposed Study Design

1) Measure coronary and aortic calcifications in 2800 Offspring Cohort using methods comparable to the previous Offspring Cohort pilot imaging study. We will invite back all living participants in the previous Offspring pilot imaging study.
2) Measure coronary and aortic calcifications in 1900 Third Generation Cohort subjects selected for age and family size/informativeness using methods comparable to the previous Offspring Cohort pilot imaging study.

Hypotheses

1) Coronary and aortic calcifications are valid markers of the burden of atherosclerosis and are associated with cross-sectional and long-term (time-averaged) levels of traditional risk factors as well as novel risk factors such as CRP and other markers of inflammation, fibrinogen and other hemostatic factors, insulin resistance measures, and hyperhomocysteinemia.
2) Gene variants associated with coronary and aortic calcification can be identified by both genome screen and candidate gene approaches. Candidate gene variants include variants that are associated with serum levels of factors listed in Hypothesis 1) above as well as variants associated with atherosclerosis and its risk factors (e.g., hyperlipidemia, hypertension, hyperglycemia/diabetes and atherosclerosis).
3) Coronary and aortic calcification independently predicts the onset of CHD, cerebrovascular disease and peripheral vascular disease independently of traditional CHD risk factors.
4) The development of coronary and aortic calcification occurs via processes similar to bone formation and includes a range of novel risk markers including factors involved in calcification and bone metabolism.

Brief Background and Rationale

Subclinical vascular calcification is associated with the progression of atherosclerosis and often precedes the development of clinical coronary and cerebrovascular events by decades. In the original cohort study, subclinical aortic calcification identified by plain radiographs of the lumbar aorta or of the chest (thoracic arch) is associated with the incidence of CHD, CHF, CVD and CVD death independent of all traditional risk factors [redacted]. Further, in the FHS Original Cohort, longitudinal (time-averaged) exposure to traditional risk factors appears to be an even stronger and more reliable indicator of risk for subclinical aortic calcification than cross-sectional exposure [redacted] Coronary artery calcium is detected and quantitated by EBCT (Agatston, 1990), correlates with the presence and extent of angiographic atherosclerosis (Guerci, 1997; Haberl, 2001), and is associated with coronary risk factors. (Taylor, 2001). In the available studies of subclinical coronary calcification detected by EBCT, coronary calcium predicts the onset of overt myocardial infarction and other CVD (Arad, 1996; Detrano, 1996; O'Malley, 2000); however, there currently little or no population-based data regarding the utility of these measures over and above traditional risk factors (Wexler, 1996; O'Rourke, 2000; Detrano, 1999). A description of the design and initial findings of the FHS Feasibility Pilot Imaging Study is found in the first section of the Appendix above.

Appendix 2.4 Framingham Heart Study Calcification Imaging

The FHS offers a unique opportunity to conduct a large-scale family-based study to assess the heritability and genetic determinants and gene-environment interactions leading to subclinical coronary and aortic calcification. There is a substantial genetic (heritable) component to lumbar aortic calcification in the FHS [redacted] and to coronary calcification (Lange, 2001). Both family-based and association studies can be performed. In particular, heritability and genome screening can be performed using all Offspring Cohort sibling pairs and selected Gen 3 subjects who undergo calcification imaging. Further, association studies of specific candidate gene variants will be performed using both population-based association and transmission disequilibrium testing. The availability of single nucleotide polymorphism genotype information for hundreds or thousands of vascular candidate genes via ongoing collaborations and activities of the FHS genotyping laboratory provides the opportunity to examine not only for single gene associations but also for gene-gene and gene-environment interactions using vascular calcification phenotypes.

Proposed Scientific Content

1) We will conduct a study of the genetic and environmental determinants of subclinical coronary and aortic calcification. We propose to use EBCT scanning in both the Offspring and Third Generation cohorts to quantify the following:
   - Coronary calcification
   - Aortic calcification
2) For coronary and aortic calcification, we propose to determine the prevalence and distribution by age and sex of calcification scores; associations with long-term (in the Offspring Cohort) as well as contemporary measures of established risk factors (blood pressure, total and HDL cholesterol, cigarette smoking, and overt diabetes); associations with novel vascular risk markers—including recent and contemporary measures of CRP (and other measures of inflammation), insulin resistance and hemostatic factors including fibrinogen and plasminogen activator inhibitor 1; and prospective associations with CHD, CHF, stroke, peripheral arterial disease and other CVD outcomes.
3) For the phenotypes of coronary and aortic calcification, we will:
   - Estimate heritability using sibling and family-based methods
   - Identify new genetic variants by fine mapping calcification loci identified by linkage analyses
   - Examine associations with the large number of vascular candidate gene variants already being genotyped in the Offspring Cohort as well as new candidate gene variants using both population association and transmission disequilibrium methods
   - Conduct an extensive study of gene-gene and gene-environment interactions for all genotyped variants
   - Conduct similar analyses of heritability, association and linkage using secondary plaque index phenotypes derived by combining coronary, aortic and carotid plaque measures from available imaging modalities
4) The availability of previously collected subclinical disease measures using carotid ultrasound (IMT/atherosclerosis), brain MRI (white matter hyperintensities and brain volume), brachial artery reactivity/tonometry (vascular reactivity and stiffness), and cardiac ultrasound (LV function and mass) will allow the unique opportunity to examine the interrelations of subclinical disease measures, to derive clinically relevant atherosclerosis index of the coronary, aortic and carotid beds and to examine prospective associations with CHD, CHF, stroke, peripheral arterial disease and other CVD outcomes.

Appendix 2.4 Framingham Heart Study Calcification Imaging

5) We propose to examine associations of vascular and cardiac calcification with bone mineral density determined already in the Offspring Cohort and with serum markers of factors involved in inflammation, calcification and bone metabolism
   - CRP and pro-inflammatory cytokines
   - Hemostatic factors, including fibrinogen and PAI-1, and platelet aggregability
   - Separate funding may be sought to conduct test for additional markers of bone metabolism, such as osteopontin, matrix Gla protein, vitamin K dependent hormones, parathyroid hormone and its analogues, 25-OH vitamin D, estradiol, testosterone, and sex hormone binding globulin

Justification for Sampling Scheme Proposed for Offspring and Third Generation Cohorts

The RFP proposes coronary calcification testing in a subsample of 1200 Offspring Cohort and 3500 Gen 3 Cohort subjects in order to maximize the use of vascular calcification as a quantitative phenotype for genetic studies. In the Gen 3 Cohort, the mean anticipated participant age is 35 years, and data from our pilot imaging study and other available databases suggests that the prevalence of coronary calcification will be extremely low in men under age 35 years and in women under age 40 years (see Figure 1 and Tables 4 and 5). Thus, we propose to exclude women < 40 years of age (n~860) and men < 35 years of age (n~530) from EBCT testing, and we expect that about 10% will refuse to undergo the procedure, yielding an expected number of 1900 EBCTs on Third Generation subjects. Conversely, in the Offspring Cohort, there is a moderate to high prevalence and a broad spread of coronary calcification scores in both men and women. Thus, EBCT testing in the Offspring Cohort will be highly informative, and there will be a substantial proportion of subjects with high calcification scores conferring a high risk for near term events. Accordingly, we propose to conduct coronary calcification testing in 2800 Offspring Cohort and 1900 Gen 3 Cohort subjects. The design of the Gen 3 Cohort EBCT study will permit the use of vascular calcification as a quantitative phenotype for genetic studies.

Table 4. Age distribution of EBCT scores from 9,728 asymptomatic persons drawn from patients selected for EBCT scanning (Raggi, 2001).

Men (n=5433)	Age in Years						
	35-39 (n=479)	40-44 (n=859)	45-49 (n=1066)	50-54 (n=1085)	55-59 (n=853)	60-64 (n=613)	65-69 (n=478)
25th percentile	0	0	0	0	3	14	28
50th percentile	0	0	3	16	41	118	151
75th percentile	2	11	44	101	187	434	569
90th percentile	21	64	176	320	502	804	1178
Women (n=4297)	**Age in Years**						
	35-39 (n=288)	40-44 (n=589)	45-49 (n=822)	50-54 (n=903)	55-59 (n=693)	60-64 (n=515)	65-69 (n=485)
25th percentile	0	0	0	0	0	0	0
50th percentile	0	0	0	0	0	4	24
75th percentile	0	0	0	10	33	87	123
90th percentile	4	9	23	66	140	310	362

Appendix 2.4 Framingham Heart Study Calcification Imaging

Table 5. Age distribution of EBCT scores in 1898 asymptomatic men and women (Janowitz 1993).

Prevalence of coronary calcium per Janowitz et al. [Janowitz, 1993]		
Age (years)	Men	Women
0-29	11%	6 %
30-39	21 %	11 %
40-49	44 %	23 %
50-59	72 %	35 %
60-69	85 %	67 %
70-79	94 %	89 %

Justification for use of EBCT technology

The totality of evidence for vascular calcification testing derives from EBCT technology. EBCT is simple, well-validated, well-established, reproducible, flexible technology, for which there is extensive published data consisting of well over 300 papers that support its utility in determining the presence and extent of coronary atherosclerosis. EBCT tests are well tolerated, including our experience with our own participants, in whom well over 95% of tests were completed with interpretable data using a single center with two technicians and a single physician overreader. We have received a commitment for use of an EBCT scanner for the duration of the imaging study sited within a few miles of the FHS at a highly competitive cost. Spiral (also called helical) CT technology for detection and quantitation of vascular calcification is another widely available calcium test that can be conducted after an upgrade to widely available CT scanners. Compared to EBCT, presently available spiral CT scanners offer spatial resolution as good or superior, temporal resolution that is currently inferior, and somewhat greater radiation doses, and uncertain utility to determine progression of calcification scores. We have contacted [redacted] of the MESA reading center, and we plan to conduct EBCT tests in a manner, including use of a calcium density phantom, which would allow future comparison to scores with spiral CT scores and maximize the potential generalizability of our data.

Appendix 2.4 Framingham Heart Study Calcification Imaging

Imaging Protocol

EBCT uses an electron gun and a stationary tungsten target to allow rapid scanning times of 50-100 milliseconds. The subject is required to perform simple breath-holding maneuvers. Rapid image acquisition and gating of the scan at 80-90% of the R-R interval by ECG results in minimal-to-no motion artifact. EBCT is then performed from the aortic root to the diaphragm, as well as obtaining slices of the coronary arteries. The presence of coronary artery calcification is easily identified, because it is markedly more dense than tissues or blood. The technique is reproducible and sensitive and has been validated in symptomatic patients or high risk patient populations in the past. Application to an asymptomatic general population as proposed here has not been performed.

IMAGE ACQUISITION

General Procedure for Detection of Coronary Artery and Thoracic Aortic Calcification

The technique for coronary calcification detection using EBCT has been validated in subjects with known or suspected coronary artery disease and is standard (Janowitz, 1993; Agatston, 1990). The present investigation will use existing techniques and protocols for evaluation of coronary artery calcification. These techniques will also be used to evaluate aortic calcification.

Patient Preparation

After written informed consent is obtained the subject will be attached to an ECG monitor that is used to gate image acquisition. Subjects will lie supine on the imaging couch.

Ascending, Arch and Proximal Descending Thoracic Aortic Acquisition

Following acquisition of a scout image the subject will be positioned to acquire images from the apex of the aortic arch to the aortic root. Image acquisition uses 512 x 512 matrix with a field of view centered on the heart. After explanation to the subject and practice breath-holds, 20-25 ECG gated continuous 3 mm thick slices are acquired during a single breath-hold. If a subject is unable to hold his/her breath for a full 40 seconds, he is asked to slowly let his breath out over this period. This maneuver does not have significant impact on image quality.

Coronary Artery and Distal Thoracic Aortic Acquisition

Following acquisition of aortic calcification images, the subject is kept in the same position using the same scout view of the upper thorax to extend from the aortic root through the heart to its base (i.e., the level at which the descending thoracic aorta crosses the diaphragm). Image acquisition uses 512 x 512 matrix with a field of view centered on the heart. 40 - 45 ECG gated continuous 3 mm thick slices are acquired during a single breath-hold. If a subject is unable to hold his/her breath for a full 40 seconds, he is asked to slowly let his breath out over this period. This coronary imaging will begin at the same level as the lowest superior thoracic aortic image; therefore, the two sets of images will provide both standard coronary artery calcification images test as well as a complete set of 3 mm images of the thoracic aorta from just above the apex of the arch through the point of passage through the diaphragm.

Appendix 2.4 Framingham Heart Study Calcification Imaging

Examination Duration

Total subject set-up time should be no greater than five minutes. Each set of images will be acquired in approximately 40 seconds, depending upon the heart rate. The completed EBCT examination requires no longer than 15 minutes. ECG electrodes will be kept in place.

Subject Exclusion/Contraindications

EBCT technique uses radiation, and therefore any subject who might be pregnant must be excluded from the protocol. There are no other significant contraindications.

IMAGE ANALYSIS

Coronary Calcification Scoring

Calcification scoring will use existing software available on the EBCT scanner. Using currently accepted protocols (Agatston, 1990), regions of interest will be drawn around all areas of coronary vascular calcification with an attenuation > 130 Hounsfield units. The threshold for calcific lesions is set at a computed tomographic density of 130 Hounsfield units, having an area of greater or equal to 1 mm^2. This eliminates single pixels with a computed tomographic density of greater than 130 Hounsfield units due to noise. An area of calcification will be regarded as four or more contiguous voxels with the attenuation of >130 Hounsfield units. Each image will be analyzed separately with individual regions of interest around areas of calcification seen in each of the three coronary arteries and in the ascending aorta. Using dedicated software for coronary calcifications scoring, the number of individual lesions, voxels exceeding 130 Hounsfield units and vessels affected by calcification will be determined. The coronary calcium score will be calculated and recorded for each vessel. The total coronary calcium score will be calculated by adding the areas of calcification in each artery according to the method of Agatston.

Aortic Calcification Score

Aortic calcification will be scored adopting the method of Agatston (for coronary artery calcification) to analysis of thoracic aortic calcification. A circle will be drawn around each area of calcification with a density of >130 Hounsfield units and larger than 1mm^2. The score will be calculated separately for the ascending aorta, the arch, the proximal descending thoracic aorta and the distal descending thoracic aorta to the level of the diaphragm. The ascending aorta is defined to include all tomograms of the ascending aorta from the aortic valve to the aortic arch. The proximal descending aorta is defined to include all slices of the descending aorta from the aortic arch to the plane of aortic valve. The distal descending aorta is defined to include all slices from the plane of the aortic valve to the arch to the level at which the descending thoracic aorta crosses the diaphragm. The total calcium core in all four segments of the aorta will be calculated by adding the areas of calcification in each of the four segments according to the same method used for the coronary total score.

The time required for scoring the EBCT study will be dependent on the extent of calcification present. In subjects without calcification or minimal calcification, the scoring will take less than 15

minutes. In subjects with calcification seen on every image the score may take up to or more than one hour.

Reproducibility Testing

Image analysis will be performed following acquisition. A replica set of 20 studies will be blindly reanalyzed on a periodic basis by the same operator(s). Kappa scores for intra-rater reliability will be calculated for both the coronary and aortic calcification scores. A physician reader will supervise all technician readings. Additionally, a 3-5% sample will be randomly selected for intra-rater and inter-rater reproducibility. The time required for scoring the EBCT study will be dependent on the extent of calcification present. In subjects without calcification or minimal calcification, the scoring will take less than 15 minutes. In subjects with calcification seen on every image the score may take up to or more than one hour to quantify.

Image Analysis Duration

Image analysis will be performed following patient examination. The time required for scoring the EBCT study will be dependent on the density and the extent of the calcifications present. In patients with no calcification or minimal calcification, scoring may take less than 15 minutes. In patients with calcification seen on every image, scoring may take up to one hour.

Risks and Safety

No problems related to this examination are expected. In particular, subjects will not be at risk for any drug reactions, or exposed to any other potentially harmful affects, except for the extremely low theoretical possibility of radiation related affects. The incremental effect of any radiation involved during this examination is so small as to be unmeasurable. The entrance skin dose is 0.54 cGy per image, less than 1/2 the dose of conventional CT. Sensitive areas such as breast and thyroid receive about 17% of the posterior entrance skin dose.

Sensitive areas such as breast and thyroid receive about 17% of the posterior entrance skin dose. The scanner geometry is such that the bulk of the radiation enters through the back. Any subject who might be pregnant will be excluded from the protocol.

Subjects will be identified by name to the principle investigators who will hold the data in a secure database. Data will be accessible only to the principle investigators and to the study sponsor. No control groups are required.

It is not anticipated that the subjects will undergo any significant stresses as a result of this investigation, but if any patient appears unwilling to enter the ultrafast CT scanner after enrolling in the study they will be at liberty to discontinue the examination at any time. The principle investigators have had considerable experience in the evaluation of CVD and in the assessment of particularly asymptomatic CVD as part of the Framingham Heart Study.

Appendix 3: CT Brochure

Directions

40 Second Avenue
The PARC Center

Suite 120 (CT/MRI Services)
Waltham, MA 02451

Exit 27B off Route 95/128
Telephone: [redacted]

From Route 95/128 Northbound:

Take Exit 27B (Winter St. Waltham) passing the brick and white P.A.R.C. Building on the left of the highway. Bear right off the exit, then right over the highway. Stay in the middle lane. Proceed straight through the first lights. Bear left (from the middle lane) at the sign: Second Ave/Bear Hill Road. The DoubleTree Hotel should now be on your right. Stay in the right lane and follow the signs that state: Second Ave/Bear Hill Rd. Turn right and then left into the parking lot of the P.A.R.C. Building.

From Route 95/128 Southbound:

Take Exit 27B (Winter St. Waltham) and bear right off the exit. Get into the middle lane. Proceed straight through the first lights. Bear left at the sign: Second Ave/Bear Hill Road. The DoubleTree Hotel should now be on your right. Stay in the right lane and follow the signs that state: Second Ave/ Bear Hill Rd. Turn right and then left into the parking lot of the P.A.R.C. Building.

CT

What is a CT scan?

A CT (Computed Tomography) or CAT (Computed Axial Tomography) scan is a type of X-ray that uses a computer to produce detailed cross-sectional images, or "slices," of parts of the body. In this particular scan we will be obtaining pictures of the heart and the aorta (the main artery that carries blood from the heart to the rest of the body). The goal of this test is to measure how much hardened or calcified plaque has built up in these arteries. This hardened plaque could represent the degree of "hardening of the arteries" (atherosclerosis) is present in the coronary arteries of the heart and in the aorta.

Who is eligible to have a CT scan?

Men aged 35 and older and women aged 40 and older who are enrolled in either the Third Generation or Offspring study groups are eligible to participate. Because our recruitment is limited to about half the study participants some participants will not be chosen to have a CT scan.

Is it safe?

A CT scan is a painless type of X-ray. For your safety the radiation is kept to the minimum needed to do the test. Because x-rays might harm a developing fetus, premenopausal women will be asked to take a pregnancy test prior to the scan. Because this test will be used for research purposes, CT scans will not be performed on women who are pregnant, planning to become pregnant within the next year, or nursing.

Where is the CT scan done?

All CT scans will be performed at Massachusetts General Hospital West Imaging Center in Waltham, MA.

How long will it take?

The actual scan takes less than 15 minutes. However, we do ask that you arrive 15 minutes prior to the test to register and complete the necessary forms.

How do I prepare for a CT scan? How is a CT scan done?

No outside preparation is necessary before your CT scan. When you arrive you will be asked to change into a hospital gown and lie down on a scanner bed. Special wires, called electrodes, will be placed on your skin to monitor your heartbeat. Once the scan begins you will be asked to hold your breath several times while pictures of your heart and aorta are being taken. The scan is very rapid and the actual image-taking time may take only one or two minutes to complete.

What happens after I have my CT scan?

Once finished with your CT scan you may go home and resume you normal daily activities without restriction.

[redacted] my CT scan?

This test is being performed for research purpo es only and the clinical significance of this test not yet known. Therefore, your doctor will on receive a report if you have a highly elevated ca dium score. Because this is a research study, complete clinical evaluation of the CT sca images for all possible abnormalities in the che and abdomen will not be performed. It is poss ble that some clinically important findings ma not be discovered.

Contacts

Offspring Study [redacted]

Third Generation [redacted]

Family Heart Study [redacted]

Appendix 4: Recruitment Strategies

Offspring CT Recruitment Strategy

Looking at those offspring cohort members who were currently alive, attended a recent exam (exam 6 or 7), and met the age requirements (men 35 and older and women 40 and older by 12/31/2004), there were 3639 offspring who were eligible for the Cardiac CT scan. From these, 321 were ineligible since they had already participated in the pilot EBCT study. To be able to recruit 1200 offspring from the 3318 who remained, we concentrated on the following groups of subjects: (1) those who have genome† scan information (1046); (2) those who have no genome scan information, but have at least one sibling in the offspring study and also have at least one offspring who met the age requirements and were being targeted for the 3rd generation cohort (202); and (3) those who have no genome scan information, but have at least one sibling in the offspring study (186). This gave us a target group of 1248 offspring to recruit for the CT study. This recruitment strategy also maximized the informative subjects in conjunction with other studies, such as the brain MRI and Cardiac MRI.

† From 1996 to 1998 DNA from approximately 1490 offspring subjects were genotyped by the NHLBI Mammalian Genotyping service for approximately 400micro-satellite markers. These subjects comprise the "genome scan" subjects.

3rd Generation CT Recruitment Strategy

Of the 5317 known potential 3rd generation subjects, 1900 is the recruitment goal for the Cardiac CT study. The recruitment strategy for the 3rd generation utilized the recruitment strategy for exam 1. Using the

offspring and the potential 3rd generation subjects, 879 families were created. These families are sorted in descending order by the following 5 criteria: (1) the number of 3rd generation subjects in each family, (2) the number of 3rd generation subjects who were willing to participate in each family, (3) the proportion of offspring parents with DNA (as of 12/31/2001), (4) the average number of exams the offspring parents attended, and (5) the number of new spouses (of the offspring). Since approximately 3500 3rd generation subjects will be recruited to exam 1, we took the top 4000 potential 3rd generation subjects from this priority list. Of these 4000, 2575 met the age criteria (men 35 and older and women 40 and older by 12/31/2004). This became our pool of 3rd generation subjects to target for the Cardiac CT scan.

Appendix 5: Protocol for Scheduling CT Scans

Prior to calling participants, the calling list is checked for priority needs, i.e. whether participant is also in the Family Study, and to determine the eligibility of the participant's spouse. The roster screen for each participant is also reviewed by the recruiter for any pertinent information prior to placing a call. When the appointment is scheduled, women are screened for age, pregnancy or postmenopausal status. If transportation is needed they are scheduled in coordination with the Family Study transportation needs.

Offspring

Some eligible Offspring participants received an invitational mailing along with the mailing for Health Updates describing the CT Study. This generated a CT eligible call list, as well as participants calling directly to the Recruitment staff, requesting to have their CT scheduled. If a participant is also eligible for the Cardiac MRI, then it takes coordination to make sure both tests are done within a six-month time period.

3rd Generation

Once a participant is booked for their core clinic exam, the following can/will occur. If they are age eligible (Male 35, Women 40) and are traveling from out of state, or have more than 1 hr. travel distance time, the recruitment staff phones the participant to discuss their having a CT Scan for the same day, approximately 6 hours from their scheduled clinic time. Otherwise, the recruitment staff notifies the clinic that they wish to speak to the participant while they are here in the clinic. We explain to the participant that they are eligible for a CT Scan, which takes pictures of their heart and aorta to measure how much calcified plaque has built up in these arteries.

Once an appointment is made with either an Offspring or a 3rd Generation participant, it is then entered into the CT Booking Screen and into the CT scheduling book. The participant is classified according to their

participation in the Framingham Heart Study and/or the Family Heart Study and if the participant is a priority for both studies, i.e. age and other factors. If a pregnancy test is needed it is also documented when scheduled. Other factors i.e. health issues are also noted as needed.

Once the schedule for a given day is complete, the schedule is run and printed, proofed and emailed to the facility one week ahead. Appointment letters with directions to the MGH-West are sent to participants two weeks prior to the scheduled appointment. Folders are prepared containing the Completion Form, Consent Forms, Pregnancy Determination Form (for women only) and Self-Administered Pregnancy Questionnaire, and if needed, Health History Update Form along with a Folder checklist.

Reminder calls are made one day prior to appointment. On day following the appointment, schedules are collected from liaison staffers, the number of completed scans is tallied and the schedule is put into a binder. Reports are generated for those participants whose values are above the predetermined threshold. The report is sent to the participant's physician along with a letter from [redacted] A thank you letter is sent to the participant. The report and the thank you letter will be filed in the participant's file and also with the Participant Coordinator's records. Finally, the monthly numbers are tallied and a report is distributed.

Appendix 6: Cardiac CT Scheduling Forms

The Framingham Heart Study Cardiac CT Scheduling Form

Participant Name: _____

Phone Number: _____

Your CT Scan has been scheduled at:

Mass General West Imaging Center

40 Second Ave.

The PARC Center

Suite 120

Waltham, MA 02451

Your appointment is scheduled for:

_____

Please arrive 15 minutes before your scheduled appointment.

Enclosed are directions and map

Any questions or problems, please call [redacted]

Appendix 7: CT Booking

% abf heart ct booking

To go in by date press "1"

Enter date and press "DO"
F11 – back 1 week
F12 – back 1day
F13 – forward 1 week
F14 – forward 1 day

To book new appointment by date:

"F17" (brings up ID prompt)
Enter Framingham ID and press "F11" OR Family ID and "F12"
Enter info and save with "F10"

To modify appointment by date:

"F18" enter info and save

To go in by Framingham ID press "2"

Enter ID and "DO"
"F11" for new appointment
"F12" to modify appointment

To go in by Family ID press "3"

(Same as "by Framingham ID")

Helpful Hints

"Control P"- go back line
Exam Type (see codes)
Exam Cycle **75** for Offspring
1 for 3rd Gen
Location **3** (offsite)
Exam Status **0** appt is on
2 appt. Canceled
3 call back

Codes for "Exam Type"

61 Framingham Offspring (F)
62 Combined Family and Framingham Offspring I
63 Framingham 3rd Generation (F_3)
64 Combined Family and Framingham 3rd Generation I
65 Family Study only- GENCAC (G)
66 Family Study & low priority Framingham Offspring I
67 Family Study & low priority Framingham 3rd Generation I

Codes for "Exam Type" for CT Booking

61 Framingham Offspring (F)

62 Combined Family and Framingham Offspring I

63 Framingham 3rd Generation (F_3)

64 Combined Family and Framingham 3rd Generation I

65 Family Study only- GENCAC (G)

66 Family Study & low priority Framingham Offspring I

67 Family Study & low priority Framingham 3rd Generation I

*Codes in parenthesis appears on schedule

Appendix 8: Boston University Consent Forms

I. CTADD1.3

Effective date: September 16, 2002-July 24, 2003

(All versions of BU Consent Forms are kept onsite at the Framingham Heart Study)

BOSTON MEDICAL
Boston University School of Medicine
The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910 Title: THE FRAMINGHAM HEART STUDY
I. PRINCIPAL INVESTIGATOR
II. OTHER INVESTIGATORS

Offspring/Generation III Ct Scan
Exam CTADD1.3 Page 1 of 3

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries

(One copy for participant, one copy for chart)

III. INTRODUCTION: You are asked to participate in a study of calcium deposits in the coronary arteries and heart disease and other health conditions.

IV. PURPOSE: The purpose of this supplemental exam is to investigate the role of calcium deposits in the aorta and coronary arteries in the development of 1) heart, lung and blood diseases, stroke, memory loss, joint disease, bone loss, blood vessel diseases and other health conditions; and 2) to examine the role of inherited factors (genes) in calcification of the aorta and coronary arteries. This exam will take approximately 30 minutes. If you decide to participate, you will be asked to undergo a CT scan of your chest and abdomen at a special imaging center.

V. WHAT HAPPENS IN THIS RESEARCH STUDY:
A Computed Tomography (CT) scan will be performed. This is a new type of x-ray done to measure the amount of calcium in the arteries of your heart. For these scans, you will lie on a table with just the upper portion of your body and abdomen inside the CT scanner. You will need to remain still and hold your breath for about 20-30 seconds during the test. The CT procedure should take no more than 20 minutes. This test will not be done on women who are pregnant or breast feeding. Women who have not reached menopause will be asked to provide a urine sample for a pregnancy test before the CT scan. Women who are not pregnant after undergoing the pregnancy test will proceed with the CT test.

This CT scan is being conducted for research purposes. At present, it is the opinion of experts that coronary calcium scores detected by CT scanning are not recommended to be used to make clinical decisions. Therefore, the results of the calcium tests or of genetic research that results from the CT scanning test will not routinely be reported to your physician. However, markedly abnormal levels of calcium deposits in your arteries will be reported to your physician. If you don't have a doctor, you can be referred if you so desire.

VI. RISKS, DISCOMFORTS, AND RESEARCH-RELATED INJURY: The CT scan of the heart involves low doses of radiation. The total amount of radiation for the scan is 6 msv or less than 25% of the yearly radiation exposure limit allowed for a radiation worker. Another way of understanding this is that the total amount of radiation is approximately equivalent to the radiation exposure from 2 mammograms. The risk from this amount of radiation (X-rays) is generally recognized to be safe by the Food and Drug Administration (FDA) for such studies. There are no other known risks associated with the procedure. The CT scan is being done for research purposes only to measure calcium in the heart and major arteries. Because a complete clinical evaluation of the CT scan images for all possible abnormalities in the chest and abdomen will not be performed, some clinically important findings may not be discovered.

More

IRB# 1910
VALID THRU: 7-24-03
PER IRB: ADB
9-16-02 AUTH. INIT.

BOSTON MEDICAL | Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910 Title: THE FRAMINGHAM HEART STUDY
I. Principal Investigator: Philip A. Wolf, M.D.
II. Other Investigators:

Offspring/Generation III Ct Scan
Exam CTADD1.3 Page 2 of 3

NAME: _____

The test procedure and its risks and discomforts have been listed and all of your questions concerning these procedures will be answered. We do not expect an unusual risk or injury to occur as a result of participation. In the unlikely event that, during examination procedures, you should require medical care, first aid will be available.

You should not participate if you are pregnant or breast feeding.

VII. BENEFITS: Although you may not receive any direct benefit from this research, individuals who develop heart, vascular and other diseases in the future and their families, as well as future generations of your family, may benefit if we can identify the causes of these illnesses. These studies may lead to the development of new methods of prevention and treatment of these diseases.

VIII. POSSIBLE COST TO YOU FOR PARTICIPATING: No charge will be made for the test. A complete clinical evaluation of the CT scan image for abnormalities in the chest and abdomen will not be performed for clinically important findings. However, in the event that the research evaluation of the CT scan examination uncovers markedly abnormal levels of calcium deposits in your arteries or any medical problems that require medical diagnosis or treatment, you will be so advised and that information will be provided to the physician or clinic that you choose. In that case, payment must be provided by you and your third party payor, if any (for example, health insurance or Medicare). No special arrangements will be made for compensation or for payment of treatment solely because of your participation in this study. You understand that this paragraph does not waive any of your legal rights.

IX. PAYMENT TO YOU FOR PARTICIPATING: You will not receive payment for your participation. However, if necessary, we will provide transportation to the clinic and your return home.

X. ALTERNATIVE TO PARTICIPATION: Your choice is not to participate.

XI. CONFIDENTIALITY: Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you and any other potentially identifying information will not be used on any information you provide. When study results based on your information are published, your name and any other potentially identifying information will not be revealed. Only the code numbers will be provided to qualified investigators studying the information. To assure that the investigators are following institutional and federal guidelines, the Institutional Review Board of Boston Medical Center may choose to review all study records at any time.

You will not be informed of the results of the research including the genetic research that may arise from the CT test, although genetic tests may be developed as a result of the combined analysis of data

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IRB# 1910
VALID
THRU: 7-24-03
PER IRB: ATB
9/6 02 AUTH. INIT.

BOSTON MEDICAL CENTER
Boston University School of Medicine
The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910 Title: THE FRAMINGHAM HEART STUDY
Principal Investigator: Philip A. Wolf, M.D.
Co-Investigators:
Emelia J. Benjamin, M.D.
Ralph B. D'Agostino, Ph.D.
Peter W. Wilson, M.D.

Offspring/Generation III Ct Scan
Exam CTADD1.3 Page 3 of 3

NAME: _____

In the Framingham Heart Study. You will be kept informed through periodic publications from the Framingham Heart Study of any new information of findings about CT testing or genetic findings related to CT testing for cardiovascular disease or other health conditions, which may be of importance to you or your family.

XII. COMPENSATION FOR RESEARCH RELATED INJURY: In the unlikely event of injury from your participation in the research, emergency medical treatment will be provided at no cost to you. However, no additional medical care or compensation is offered to participants in this study. While you are at the Framingham Heart Study premises, someone who is capable of dealing with emergencies will be escorting you at all times.

If this explanation leaves you with any unanswered questions, please ask and obtain answers before signing below. In addition, you are welcome to ask any questions at any time throughout the course of the study. If you have any questions concerning the research and procedures of this study or if a research-related injury occurs, you can contact [redacted]

and that any questions you have regarding your rights as a research subject can be directed to the Office of the Institutional Review Board for Boston Medical Center at (617) 638-7207. The Framingham Study is a medical research project sponsored by the National Institutes of Health. It is authorized under 42USC 285b-3. The system of records which applies to the Framingham Study is documented in the Federal Register, Vol. 60, No. 13, Friday, January 20, 1995, pages 4264-4266 (OMB 0925-0216).

XIII. YOUR RIGHTS TO PARTICIPATE, NOT PARTICIPATE, OR TO WITHDRAW FROM THE STUDY:
Participating in this Framingham Heart Study CT Scan Study is voluntary. I am free to withdraw my consent and to discontinue participation for any of the procedures in the Framingham Study at any time. Refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled, and I may discontinue participation at any time without penalty or loss of such benefits. A signed copy of this form will be given to you.

Participation is voluntary. Refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled, and I may discontinue participation at any time without penalty or loss of such benefits. A signed copy of this form will be given to you.

_____ _____ _____
DATE SIGNATURE PRINTED NAME

IRB# 1910
VALID
THRU 9-24-03
PER IRB: AJDB
9-16-03 AUTH. INIT.

Offspring/Generation III Ct Scan (Boston) (June 27, 2003)

II. CTADD1.4

Effective date: April 29, 2003-July 24, 2003

BOSTON MEDICAL CENTER

Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G Title: THE FRAMINGHAM HEART STUDY
I. PRINCIPAL INVESTIGATOR: Philip A. Wolf, M.D.
II. OTHER INVESTIGATORS:

Offspring/Generation III Ct Scan
Exam CTADD1.4 Page 1 of 3

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries

(One copy for participant, one copy for chart)

III. INTRODUCTION: You are asked to participate in a study of calcium deposits in the coronary arteries and heart disease and other health conditions.

IV. PURPOSE: The purpose of this supplemental exam is to investigate the role of calcium deposits in the aorta and coronary arteries in the development of 1) heart, lung and blood diseases, stroke, memory loss, joint disease, bone loss, blood vessel diseases and other health conditions; and 2) to examine the role of inherited factors (genes) in calcification of the aorta and coronary arteries. This exam will take approximately 30 minutes. If you decide to participate, you will be asked to undergo a CT scan of your chest and abdomen at a special imaging center.

V. WHAT HAPPENS IN THIS RESEARCH STUDY:
A Computed Tomography (CT) scan will be performed. This is a new type of x-ray done to measure the amount of calcium in the arteries of your heart and abdomen. For these scans, you will lie on a table with just the upper portion of your body and abdomen inside the CT scanner. You will be asked to remain still and hold your breath for about 20-30 seconds during the test. Two scans of your coronary arteries and one scan of your abdominal aorta will be performed. The CT procedure should take no more than 20 minutes. This test will not be done on women who are pregnant or who have been breast feeding for less than six months. Women who have not reached menopause will be asked to provide a urine sample for a pregnancy test within 24 hours before the CT scan. Women who are not pregnant after undergoing the pregnancy test will proceed with the CT scan.

This CT scan is being conducted for research purposes. At present, it is the opinion of experts that coronary calcium scores detected by CT scanning are not usually used to make clinical decisions. Therefore, the results of the calcium tests or of genetic research that results from the CT scanning test will not routinely be reported to your physician. However, markedly abnormal levels of calcium deposits in your arteries will be reported to your physician. If you don't have a doctor, you can be referred to one if you so desire.

Incidental Findings: In the event that the research evaluation of the scan uncovers medical problems that require medical diagnosis for treatment, you will be told and the information will be provided to the physician or clinic that you choose.

VI. RISKS, DISCOMFORTS, AND RESEARCH-RELATED INJURY: The CT scan of the heart and abdomen involves low doses of radiation. The total amount of radiation for the scan is 6 msv or less than12% of the yearly radiation exposure limit allowed for a radiation worker. Another way of understanding this is that the total amount of radiation is approximately equivalent to the radiation exposure from 2

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IRB# 1910 h
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THRU: 7/24/03
PER IRB: PL
4/24/03 AUTH. INIT.

BOSTON MEDICAL CENTER
Boston University School of Medicine
The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G Title: THE FRAMINGHAM HEART STUDY
I. PRINCIPAL INVESTIGATOR: Philip A. Wolf, M.D.
II. OTHER INVESTIGATORS:

Offspring/Generation III Ct Scan
Exam CTADD1.4 Page 2 of 3

NAME: _____

mammograms. The risk from this amount of radiation (X-rays) is generally recognized to be safe by the Food and Drug Administration (FDA) for such studies. There are no other known risks associated with the procedure. The CT scan is being done for research purposes only to measure calcium in the heart and major arteries. Because a complete clinical evaluation of the CT scan images for all possible abnormalities in the chest and abdomen will not be performed, some clinically important findings may not be discovered.

The test procedure and its risks and discomforts have been listed and all of your questions concerning these procedures will be answered. We do not expect an unusual risk or injury to occur as a result of participation. In the unlikely event that, during examination procedures, you should require medical care, first aid will be available.

You should not participate if you are pregnant or have been breast feeding for less than six months .

VII. BENEFITS: Although you may not receive any direct benefit from this research, individuals who develop heart, vascular and other diseases in the future and their families, as well as future generations of your family, may benefit if we can identify the causes of these illnesses. These studies may lead to the development of new methods of prevention and treatment of these diseases.

VIII. POSSIBLE COST TO YOU FOR PARTICIPATING: No charge will be made for the scan. A complete clinical evaluation of the CT scan image for abnormalities in the chest and abdomen will not be performed for clinically important findings. However, in the event that the research evaluation of the CT scan examination uncovers markedly abnormal levels of calcium deposits in your arteries or any medical problems that require medical diagnosis or treatment, you will be so advised and that information will be provided to the physician or clinic that you choose. In the event that clinical tests or treatments for finding are necessary, payment must be provided by you and your third party payor, if applicable (for example, health insurance or Medicare). No special arrangements will be made by the Framingham Heart Study for compensation or for payment of treatment solely because of your participation in this study. You understand that this paragraph does not waive any of your legal rights.

IX. PAYMENT TO YOU FOR PARTICIPATING: You will not receive payment for your participation. However, if necessary, we will provide transportation to the clinic and your return home.

X. ALTERNATIVE TO PARTICIPATION: Your choice is not to participate.

XI. CONFIDENTIALITY: Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will

More

IRB# 1910G
VALID
THRU: 7/24/03
PER IRB: MC
4/29/03 AUTH. INIT.

BOSTON MEDICAL CENTER
Boston University School of Medicine
The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G Title: THE FRAMINGHAM HEART STUDY
I. PRINCIPAL INVESTIGATOR: Philip A. Wolf, M.D.
II. OTHER INVESTIGATORS:

Offspring/Generation III Ct Scan
Exam CTADD1.4 Page 3 of 3

NAME: _____

be assigned to you and any other potentially identifying information will not be used on any information you provide. When study results based on your information are published, your name and any other potentially identifying information will not be revealed. Only the code numbers will be provided to qualified investigators studying the information. To assure that the investigators are following institutional and federal guidelines, the Institutional Review Board of Boston Medical Center may choose to review all study records at any time.

You will not be informed of the results of the research including the genetic research that may arise from the CT scan, although genetic tests may be developed as a result of the combined analysis of data in the Framingham Heart Study. You will be kept informed through periodic publications from the Framingham Heart Study of any new information of findings about CT testing or genetic findings related to CT testing for cardiovascular disease or other health conditions, which may be of importance to you or your family.

XII. COMPENSATION FOR RESEARCH RELATED INJURY: In the unlikely event of injury from your participation in the research, emergency medical treatment will be provided at no cost to you. However, no additional medical care or compensation is offered to participants in this study. While you are at the Framingham Heart Study premises, someone who is capable of dealing with emergencies will be escorting you at all times.

If this explanation leaves you with any unanswered questions, please ask and obtain answers before signing below. In addition, you are welcome to ask any questions at any time throughout the course of the study. If you have any questions concerning the research and procedures of this study or if a research-related injury occurs, you can contact [redacted]

Questions about the CT scan may also be directed to [redacted], Massachusetts General Hospital [redacted] If you have any questions regarding your rights as a research subject, they can be directed to the Office of the Institutional Review Board for Boston Medical Center at (617) 638-7207. The Framingham Study is a medical research project sponsored by the National Institutes of Health. It is authorized under 42USC 285b-3. The system of records which applies to the Framingham Study is documented in the Federal Register, Vol. 60, No. 13, Friday, January 20, 1995, pages 4264-4266 (OMB 0925-0216).

XIII. YOUR RIGHTS TO PARTICIPATE, NOT PARTICIPATE, OR TO WITHDRAW FROM THE STUDY:
Participating in this Framingham Heart Study CT Scan Study is voluntary. I am free to withdraw my consent and to discontinue participation for any of the procedures in the Framingham Study at any time. Refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled, and I may discontinue participation at any time without penalty or loss of such benefits. A signed copy of this form will be given to you.

DATE	SIGNATURE	PRINTED NAME

IRB# 1910G
VALID THRU: 7/24/03
PER IRB: pc 4/24/03 AUTH. INIT.

III. CTADD1.5

Effective date June 24, 2003 to June 22, 2004

BOSTON MEDICAL CENTER

Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G
Title: THE FRAMINGHAM HEART STUDY

Offspring/Generation III Ct Scan
Exam CTADD1.5 Page 1 of 5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

I. PRINCIPAL INVESTIGATOR:

[redacted]

II. OTHER INVESTIGATORS:

[redacted]

III. INTRODUCTION:
The Computed Tomography (CT) Study is an observational research sub-study designed to identify the relationship between calcium deposits in the coronary arteries and other health conditions. You are being asked to participate in this study because you are a woman over the age of 40 or a male over the age of 35 and are enrolled in the Framingham Heart Study. We hope to examine 2900 participants.

IV. PURPOSE:
The purpose of this study is to investigate the role of calcium deposits in the aorta and coronary arteries in the development of 1) heart, lung and blood diseases, stroke, memory loss, joint disease, bone loss, blood vessel diseases and other health conditions; and 2) to examine the role of inherited factors (genes) in calcification of the aorta and coronary arteries.

V. WHAT HAPPENS IN THIS RESEARCH STUDY:
It is expected that your total participation time will be 30 minutes. The Computed Tomography scan takes about 20 minutes and will include the following:

1) **The CT Scan**
A Computed Tomography (CT) scan will be performed for research purposes at Mass General Hospital West (MGHW) Medical Center in Waltham, MA. This is a new type of x-ray done to measure the amount of calcium in the arteries of your heart and abdomen.

For this scan, you will lie on a table with just your torso (not your head) inside the doughnut shaped CT scanner. You will be asked to remain still and hold your breath for about 20-30 seconds several times during the scan.

Two scans of your coronary arteries and one scan of your abdominal aorta will be performed.

2) **Pregnancy Test (for some women only)**
Most women will be asked to provide a urine sample for a pregnancy test within 24 hours before the CT scan. Women who are not pregnant after undergoing the pregnancy test will proceed with the CT scan. If the pregnancy test is positive you will be referred to your physician for follow up and the scan will not be performed.

IRB# 1910G
VALID THRU: 6/22/04
PER IRB: [illegible]
6/22/03 AUTH. INIT.

BOSTON MEDICAL CENTER · Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G
Title: THE FRAMINGHAM HEART STUDY

Offspring/Generation III Ct Scan
Exam CTADD1.5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

This CT scan will not be done on women who are pregnant or who have been breast feeding for less than six months.

3) **Results**
When the CT scan is read the amount of calcium in your arteries is given a score. At present, it is the opinion of experts that the results scores of the amount of coronary calcium detected by CT scanner are not usually used to make clinical decisions. Therefore, the results of the calcium tests or of genetic research that results from the CT scanning tests will not routinely be reported to your physician. However, markedly abnormal levels of calcium deposits in your arteries will be reported to your physician.

A complete clinical evaluation of the CT scan image for abnormalities in the chest and abdomen will not be performed for clinically important findings.

Incidental Findings: In the event that the research evaluation of the scan does uncover medical problems that require medical diagnosis for treatment, you will be told and the information will be provided to the physician or clinic that you choose.

This CT scan is being conducted for research purposes. The CT scan is being done only to measure calcium in the heart and major arteries. Because a complete clinical evaluation of the CT scan images for all possible abnormalities in the chest and abdomen will not be performed, some clinically important findings may not be discovered.

You will be asked to sign an additional medical release form giving permission to MGHW to release your CT information to the Framingham Heart Study Investigators.

VI. RISKS, DISCOMFORTS, AND RESEARCH-RELATED INJURY:
The CT scan of the heart and abdomen involves low doses of radiation. The total amount of radiation for the scan is 6 msv or less than 12% of the yearly radiation exposure limit allowed for a radiation worker. Another way of understanding this is that the total amount of radiation is approximately equivalent to the radiation exposure from 2 mammograms.

The risk from this amount of radiation (X-rays) is generally recognized to be safe by the Food and Drug Administration (FDA) for such studies.

We do not expect an unusual risk or injury to occur as a result of your participation. In the unlikely event that during examination procedures you should require medical care, first aid will be available. There may also be some risks that are unforeseeable. Framingham Heart Study Investigators will tell you if new information becomes available that may affect your willingness to participate.

IRB# 1910G
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THRU: 6/22/04
PER IRB: Au
6/25/03 AUTH INIT

BOSTON MEDICAL CENTER

Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G
Title: THE FRAMINGHAM HEART STUDY

Offspring/Generation III Ct Scan
Exam CTADD1.5 Page 3 of 5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

VII. BENEFITS:
Although you may not receive any direct benefit from this research, individuals who develop heart, vascular and other diseases in the future and their families, as well as future generations of your family, may benefit if we can identify the causes of these illnesses. These studies may lead to the development of new methods of prevention and treatment of these diseases.

VIII. POSSIBLE COST TO YOU FOR PARTICIPATING:
No charge will be made for the scan.

In the event that the research evaluation of the CT scan examination uncovers markedly abnormal levels of calcium deposits in your arteries or any medical problems that require medical diagnosis or treatment, you will be so advised and that information will be provided to the physician or clinic that you choose.

In the event that your physician decides that follow up clinical tests or treatments are necessary, payment must be provided by you and your third party payer, if applicable (for example, health insurance or Medicare). No special arrangements will be made by the Framingham Heart Study for compensation or for payment of treatment solely because of your participation in this study. This does not waive any of your legal rights.

Costs that you might incur the day of your participation include, but are not limited to, loss of work, and transportation (gas, tolls, etc.).

IX. PAYMENT TO YOU FOR PARTICIPATING:
You will not receive payment for your participation. However, if necessary, we will provide transportation from FHS to and from the center at no cost.

X. ALTERNATIVE TO PARTICIPATION:
Your choice is not to participate. If at any point during the testing you feel uncomfortable and would like to terminate any of the tests, please tell the study staff.

XI. CONFIDENTIALITY:
Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you and any other potentially identifying information you provide. When study results based on your information are published, your name and any other potentially identifying information will not be revealed. Only the code numbers will be provided to qualified investigators studying the information. To assure that the investigators are following institutional and federal guidelines, the Institutional Review Board of Boston Medical Center may choose to review all study records at any time.

IRB# 1910G
VALID
THRU: 6/22/04
PER IRB: [illegible]
6/22/03 AUTH. INIT.

BOSTON MEDICAL CENTER | Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G
Title: THE FRAMINGHAM HEART STUDY

Offspring/Generation III Ct Scan
Exam CTADD1.5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

You will not be informed of the results of the research including the genetic research that may arise from the CT scan, although genetic tests may be developed as a result of the combined analysis of data in the Framingham Heart Study. You will be kept informed through periodic publications from the Framingham Heart Study of any new information of findings about CT testing or genetic findings related to CT testing for cardiovascular disease or other health conditions, which may be of importance to you or your family.

XII. COMPENSATION FOR RESEARCH-RELATED INJURY:
In the unlikely event of an injury occurring from your participation in the research, emergency medical treatment will be provided at no cost to you. If an emergency occurs while you are at the MGHW in Waltham, someone who is capable of dealing with emergencies will stay with you.

However, no additional medical care or compensation is offered to participants in this study.

XIII. YOUR RIGHTS TO PARTICIPATE, NOT PARTICIPATE, OR TO WITHDRAW FROM THE STUDY:
Taking part in this study is voluntary. You have the right to refuse to take part in all of the study. If you choose to take part, you have the right to stop at any time. Refusal to participate will involve no penalty and you may also choose to discontinue participation at any time without penalty.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them as soon as possible.

The investigators may decide to discontinue your participation without your permission in the event that future funding is not obtained.

You are welcome to ask questions at any time during the examination and throughout the course of the Study. If you have any questions concerning the research and procedures of this study or if a research-related injury occurs, you may contact [redacted] Questions about the CT scan may also be directed to [redacted] Massachusetts General Hospital [redacted]

Any questions you have regarding your rights as a research subject may be directed to the Office of the Institutional Review Board for Boston Medical Center at (617) 638-7207. The Framingham Heart Study is a medical research project sponsored by the National Institutes of Health. It is authorized under 42USC 285b-3. The system of records which applies to the Framingham Heart Study is documented in the Federal Register, Vol. 60, No. 13, Friday, January 20, 1995, pages 4264-4266.

IRB# 19104
VALID THRU: 6/22/04
PER IRB: [illegible]
6/22/03 AUTH. INIT.

BOSTON MEDICAL CENTER

Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol # 1910G
Title: THE FRAMINGHAM HEART STUDY

Offspring/Generation III Ct Scan
Exam CTADD1.5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

If you have any unanswered questions, please ask and obtain answers before signing this form. A signed copy of this form will be given to you.

PARTICIPANT AUTHORIZATION

YES ☐ NO ☐ I authorize (give my permission) the Framingham Heart Study to release the results of this scan to:

_____

_____

(List the name(s) of your current physician(s)

_____ _____ _____

DATE PARTICIPANT SIGNATURE PRINTED NAME

I have explained this research study to the participant. I am available to answer any questions now or in the future regarding the study and the participant's rights. You may call me at (508) 872-6562.

_____ _____ _____

DATE SIGNATURE OF PERSON OBTAINING CONSENT / PRINTED NAME

IRB# 1910G
VALID
THRU: 6/22/04
PER IRB: Re
6/23/03 AUTH. INIT.

IV. CTADD1.6

Effective date: December 23, 2003-June 22, 2004

Boston Medical Center | Boston University School of Medicine
The Framingham Heart Study, Framingham, MA

IRB Protocol#1910G
Title: THE FRAMINGHAM HEART STUDY [redacted]
EXAM CTADD 1.6 Page 1 of 5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

I. PRINCIPAL INVESTIGATOR: [redacted]

II. OTHER INVESTIGATORS: [redacted]

III. INTRODUCTION:
The Computed Tomography (CT) Study is an observational research sub-study designed to identify the relationship between calcium deposits in the coronary arteries and other health conditions. You are being asked to participate in this study because you are a woman over the age of 40 or a male over the age of 35 and are enrolled in the Framingham Heart Study. We hope to examine 2900 participants.

IV. PURPOSE:
The purpose of this research study is to investigate the role of calcium deposits in the aorta and coronary arteries in the development of 1) heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, joint disease, bone loss, deafness, cancer, and other major diseases and health conditions; and 2) to examine the role of inherited factors (genes) in calcification of the aorta and coronary arteries.

V. WHAT HAPPENS IN THIS RESEARCH STUDY:
It is expected that your total participation time will be 30 minutes. The Computed Tomography scan takes about 20 minutes and will include the following:

1) **The CT Scan**
A Computed Tomography (CT) scan will be performed **for research purposes** at Mass General Hospital West (MGHW) Medical Center in Waltham, MA. This is a new type of x-ray done to measure the amount of calcium in the arteries of your heart and abdomen.

For this scan, you will lie on a table with just your torso (not your head) inside the doughnut shaped CT scanner. You will be asked to remain still and hold your breath for about 20-30 seconds several times during the scan.

Two scans of your coronary arteries and one scan of your abdominal aorta will be performed.

2) **Pregnancy Test (for some women only)**
Most women will be asked to provide a urine sample for a pregnancy test within 24 hours before the CT scan. Women who are not pregnant after undergoing the pregnancy test will proceed with the CT scan. If the pregnancy test is positive you will be referred to your physician for follow up and the scan will not be performed.

IRB# 1910G
VALID
THRU: 6-2204
PER IRB: ALTB
12-23-03 AUTH. INIT.
Valid from

Boston Medical Center
Boston University School of Medicine
The Framingham Heart Study
Framingham, MA

IRB Protocol#1910G
Title: THE FRAMINGHAM HEART STUDY [redacted]
EXAM CT ADD 1.6 Page 2 of 5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

This CT scan will not be done on women who are pregnant or who have been breast feeding for less than six months.

3) **Results**
When the CT scan is read the amount of calcium in your arteries is given a score. At present, it is the opinion of experts that the results scores of the amount of coronary calcium detected by CT scanner are not usually used to make clinical decisions. Therefore, the results of the calcium tests or of genetic research that results from the CT scanning tests will not routinely be reported to your physician. However, markedly abnormal levels of calcium deposits in your arteries will be reported to your physician.

A complete clinical evaluation of the CT scan image for abnormalities in the chest and abdomen will not be performed for clinically important findings.

Incidental Findings: In the event that the research evaluation of the scan does uncover medical problems that require medical diagnosis for treatment, you will be told and the information will be provided to the physician or clinic that you choose.

This CT scan is being conducted for research purposes. The CT scan is being done only to measure calcium in the heart and major arteries. Because a complete clinical evaluation of the CT scan images for all possible abnormalities in the chest and abdomen will not be performed, some clinically important findings may not be discovered.

You will be asked to sign an additional medical release form giving permission to MGHW to release your CT information to the Framingham Heart Study Investigators.

VI. RISKS, DISCOMFORTS, AND RESEARCH-RELATED INJURY:
The CT scan of the heart and abdomen involves low doses of radiation. The total amount of radiation per scan is 1 msv or less than 8% of the yearly radiation exposure limit allowed for a radiation worker. Another way of understanding this is that the total amount of radiation is approximately equivalent to the radiation exposure from 2 mammograms.

The risk from this amount of radiation (X-rays) is generally recognized to be safe by the Food and Drug Administration (FDA) for such studies.

We do not expect an unusual risk or injury to occur as a result of your participation. In the unlikely event that during examination procedures you should require medical care, first aid will be available. There may also be some risks that are unforeseeable. Framingham Heart Study Investigators will tell you if new information becomes available that may affect your willingness to participate.

IRB# 1910G
VALID
THRU: 6.22.04
PER IRB: NSB
Valid From 6.22.03 AUTH. INIT.

Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol#1910G
Title: THE FRAMINGHAM HEART STUDY [redacted]
EXAM CTADD 1.6 Page 3 of 5

IRB# 1910G VALID THRU: 6.2004

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

VII. BENEFITS:
Although you may not receive any direct benefit from this research, individuals who develop heart, vascular, and other diseases in the future and their families, as well as future generations of your family, may benefit if we can identify the causes of these illnesses. These studies may lead to the development of new methods of prevention and treatment of these diseases.

VIII. POSSIBLE COST TO YOU FOR PARTICIPATING:
You will not be charged for the scan. If the research evaluation of the CT scan examination uncovers markedly abnormal levels of calcium deposits in your arteries or any medical problems that require medical diagnosis or treatment, you will be so advised and that information will be provided to the physician or clinic that you choose.

In the event that your physician decides that follow up clinical tests or treatments are necessary, payment must be provided by you or your third party payer, if applicable (for example, health insurance or Medicare). No special arrangements will be made by the Framingham Heart Study for compensation or for payment of treatment solely because of your participation in this study. This does not waive any of your legal rights.

Costs that you might incur the day of your participation include, but are not limited to, loss of work, and transportation (gas, tolls, etc.).

IX. PAYMENT TO YOU FOR PARTICIPATING:
You will not receive payment for your participation. However, if necessary, we will provide transportation from FHS to and from the center at no cost.

X. ALTERNATIVE TO PARTICIPATION:
You may choose not to participate. If at any point during the testing you feel uncomfortable and would like to terminate any of the tests, please tell the study staff.

XI. CONFIDENTIALITY:
Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you and any of your potentially identifying information. The code numbers will be provided only to qualified investigators.

You will not be informed of the results of the research including the genetic research that may arise from the CT scan, although genetic tests may be developed as a result of the combined analysis of data in the Framingham Heart Study.

When study results based on your information are published, your name and any other potentially identifying information (i.e. code numbers) will not be revealed. You will be kept informed through periodic publications from the Framingham Heart Study of any new information of findings about CT testing or genetic findings related to CT testing for cardiovascular disease or other health conditions,

Boston University School of Medicine

The Framingham Heart Study
Framingham, MA

IRB Protocol#1910G
Title: THE FRAMINGHAM HEART STUDY
[redacted]
EXAM CTADD 1.6 Page 4 of 5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

which may be of importance to you and/or your family.

The Boston University Medical Center Institutional Review Board and, if appropriate, the U.S. Food and Drug Administration may examine the study records to assure adherence to regulations and protocol.

XII. COMPENSATION FOR RESEARCH-RELATED INJURY:
In the unlikely event of injury occurring from your participation in the research, emergency medical treatment will be provided at no cost to you. If an emergency occurs while you are at the MGHW in Waltham, someone who is capable of dealing with emergencies will stay with you.

However, no additional medical care or compensation is offered to participants in this study.

XIII. YOUR RIGHTS TO PARTICIPATE, NOT PARTICIPATE, OR TO WITHDRAW FROM THE STUDY:
Taking part in this study is voluntary. You have the right to refuse to take part in the study. If you choose to take part, you have the right to stop at any time. Refusal to participate will involve no penalty and you may also choose to discontinue participation at any time without penalty.

If there are any new findings during the study that may affect whether you want to continue to take part, you will be told about them as soon as possible.

The investigators may decide to discontinue your participation without your permission in the event that future funding is not obtained.

You are welcome to ask questions at any time during the examination and throughout the course of the Study. If you have any questions concerning the research and procedures of this study or if a research-related injury occurs, please contact [redacted] Questions about the CT scan may also be directed to [redacted], Massachusetts General Hospital at [redacted]

Any questions you have regarding your rights as a research subject may be directed to the Office of the Institutional Review Board for Boston Medical Center at (617) 638-7207. The Framingham Heart Study is a medical research project sponsored by the National Institutes of Health. It is authorized under 42USC 285b-3. The system of records which applies to the Framingham Heart Study is documented in the Federal Register, Vol. 60, No. 13, Friday, January 20, 1995, pages 4264-4266.

IRB# 1910G
VALID
THRU: 6-22-04
PER IRB: NB
12/23/03 AUTH. INIT.
Valid From

BOSTON MEDICAL CENTER
Boston University School of Medicine
The Framingham Heart Study
Framingham, MA

IRB Protocol#1910G
Title: THE FRAMINGHAM HEART STUDY
[redacted]
EXAM CTADO 1.6 Page 5 of 5

NAME: _____

Permission for CT Scan for Calcium Deposits in Aorta and Coronary Arteries
(One signed copy for participant, one signed copy for chart)

If you have any unanswered questions, please ask and obtain answers before signing this form. A signed copy of this form will be given to you.

Please check the appropriate box beside the statement:

YES	NO	
☐	☐	I agree to allow the Framingham Heart Study to release the findings from tests and examinations to my physician, clinic, or hospital.

PARTICIPANT AUTHORIZATION

_____ _____ / _____
DATE PARTICIPANT SIGNATURE / PRINTED NAME

I have explained this research study to the participant. I am available to answer any questions now or in the future regarding the study and participant's rights. If you have further questions, you may call [redacted]

_____ _____ / _____
DATE SIGNATURE OF PERSON OBTAINING CONSENT / PRINTED NAME

IRB# 19106
VALID THRU: 6-22-04
PER IRB: DSB
12/23/03 AUTH. INIT.
Valid From

FHS Offspring/Generation III Ct Scan 1.6 *(Rev. December 12, 2003)*

V. CTADD1.7

Effective date: December 27, 2004-June 22, 2005

BOSTON UNIVERSITY SCHOOLS OF MEDICINE, PUBLIC HEALTH, DENTAL MEDICINE AND THE BOSTON MEDICAL CENTER

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RESEARCH CONSENT FORM
CTADD Exam 1 - Offsite

H-22762- THE FRAMINGHAM HEART STUDY N01-HC-25195 1910G

Background
The Computed Tomography (CT) Study is an observational research study designed to identify the relationship between calcium deposits in the coronary arteries and other health conditions. You are being asked to participate in this study because you are a woman over the age of 40 or a male over the age of 35 and are enrolled in the Framingham Heart Study.

Purpose
The purpose of this research study is to investigate the role of calcium deposits in the aorta and coronary arteries in the development of 1) heart and blood vessel diseases, lung and blood diseases, stroke, memory loss, joint disease, bone loss, deafness, cancer, and other major diseases and health conditions; and 2) to examine the role of inherited factors (genes) in calcification of the aorta and coronary arteries.

What Happens In This Research Study
You will be one of approximately 2900 subjects to be asked to participate in this study.

The research will take place at the following location(s): Boston University Medical Center.
Your research examination will take place at the PARC Center, located at 40 Second Avenue, Suite 120 (CT/MRI Services) in Waltham, MA at Massachusetts General Hospital West. The examination will take approximately 30 minutes and will include the following Computed Tomography scan taking about 20 minutes:

1) The CT Scan
A Computed Tomography (CT) scan will be performed for research purposes at Mass General Hospital West (MGHW) Medical Center in Waltham, MA. This is a new type of x-ray done to measure the amount of calcium in the arteries of your heart and abdomen.

For this scan, you will lie on a table with just your torso (not your head) inside the doughnut shaped CT scanner. You will be asked to remain still and hold your breath for about 20-30 seconds several times during the scan.

Two scans of your coronary arteries and one scan of your abdominal aorta will be performed.

2) Pregnancy Test (for some women only)
Most women will be asked to provide a urine sample for a pregnancy test within 24 hours before the CT scan. Women who are not pregnant after undergoing the pregnancy test will proceed with the CT scan. If the pregnancy test is positive you will be referred to your physician for follow up and the scan will not be performed.

This CT scan will not be done on women who are pregnant or who have been breast feeding for less than six months.

3) Results
When the CT scan is read the amount of calcium in your arteries is given a score. At present, it is the opinion of experts that the results scores of the amount of coronary calcium detected by CT scanner are not usually used to make clinical decisions. Therefore, the results of the calcium tests or of genetic

RESEARCH CONSENT FORM
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research that results from the CT scanning tests will not routinely be reported to your physician. However, markedly abnormal levels of calcium deposits in your arteries will be reported to your physician.

A complete clinical evaluation of the CT scan image for abnormalities in the chest and abdomen will not be performed for clinically important findings.

Incidental Findings: In the event that the research evaluation of the scan does uncover medical problems that require medical diagnosis for treatment, you will be told and the information will be provided to the physician or clinic that you choose.

This CT scan is being conducted for research purposes. The CT scan is being done only to measure calcium in the heart and major arteries. Because a complete clinical evaluation of the CT scan images for all possible abnormalities in the chest and abdomen will not be performed, some clinically important findings may not be discovered.

You will be asked to sign an additional medical release form giving permission to MGHW to release your CT information to the Framingham Heart Study Investigators.

Any questions you have regarding your rights as a research subject may be directed to the Office of the Institutional Review Board for Boston Medical Center at (617) 638-7207. The Framingham Heart Study is a medical research project sponsored by the National Institutes of Health. It is authorized under 42USC 285b-3. The system of records which applies to the Framingham Heart Study is documented in the Federal Register: September 26, 2002 (Vol. 67, No. 1879) pages 60776-60780.

Risks and Discomforts

The CT scan of the heart and abdomen involves low doses of radiation. The total amount of radiation per scan is 1 msv or less than 8% of the yearly radiation exposure limit allowed for a radiation worker. Another way of understanding this is that the total amount of radiation is approximately equivalent to the radiation exposure from 2 mammograms.

The risk from this amount of radiation (X-rays) is generally recognized to be safe by the Food and Drug Administration (FDA) for such studies.

We do not expect an unusual risk or injury to occur as a result of your participation. In the unlikely event that during examination procedures you should require medical care, first aid will be available.

There may be unknown risks/discomforts involved. Study staff will update you in a timely way on any new information that may affect your health, welfare, or decision to stay in this study

Potential Benefits

You will receive no direct benefit from your participation in this study. However, your participation may help the investigators better understand the precursors, etiology, and prevention of cardiovascular disease and other medical conditions involving the heart, including th epossibility of genetic linkages .

Alternatives

Your alternative is to not participate in the study.

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Subject Costs and Payments
You will not be charged for the scan. If the research evaluation of the CT scan examination uncovers markedly abnormal levels of calcium deposits in your arteries or any medical problems that require medical diagnosis or treatment, you will be so advised and that information will be provided to the physician or clinic that you choose.

In the event that your physician decides that follow up clinical tests or treatments are necessary, payment must be provided by you or your third party payer, if applicable (for example, health insurance or Medicare). No special arrangements will be made by the Framingham Heart Study for compensation or for payment of treatment solely because of your participation in this study. This does not waive any of your legal rights.

Costs that you might incur the day of your participation include, but are not limited to, loss of work, and transportation (gas, tolls, etc.).

You will not receive payment for your participation. However, if necessary, we will provide transportation from FHS to and from the center at no cost.

Confidentiality
Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you and any of your potentially identifying information. The code numbers will be provided only to qualified investigators.

You will not be informed of the results of the research including the genetic research that may arise from the CT scan, although genetic tests may be developed as a result of the combined analysis of data in the Framingham Heart Study.

When study results based on your information are published, your name and any other potentially identifying information (i.e. code numbers) will not be revealed. You will be kept informed through periodic publications from the Framingham Heart Study of any new information of findings about CT testing or genetic findings related to CT testing for cardiovascular disease or other health conditions, which may be of importance to you and/or your family.

Information from this study and from your medical record may be reviewed and photocopied by the Food and Drug Administration (FDA) and/or state and federal regulatory agencies such as the Office of Human Research Protection as applicable, and the Institutional Review Board of Boston University Medical Center.

Please check the appropriate box that you agree with:

I___IYES I___INO
I agree to allow the Framingham Heart Study to release the findings from tests and examinations to my physician, clinic, or hospital.

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RESEARCH CONSENT FORM
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Subject's Rights

By consenting to participate in this study you do not waive any of your legal rights. Giving consent means that you have heard or read the information about this study and that you agree to participate. You will be given a copy of this form to keep.

If at any time you withdraw from this study you will not suffer any penalty or lose any benefits to which you are entitled.

You may obtain further information about your rights as a research subject by calling the Office of the Institutional Review Board of Boston University Medical Center at 617-638-7207. If this study is being done outside the United States you can ask the investigator for contact information for the local Ethics Board.

The investigator or a member of the research team will try to answer all of your questions. If you have questions or concerns at any time, or if you need to report an injury while participating in this research, contact [redacted]

Compensation for Research Related Injury

If you think that you have been injured by being in this study, please let the investigator know right away. If your part in this study takes place at Boston Medical Center, you can get treatment for the injury at Boston Medical Center. If your part in the study is not at Boston Medical Center, ask the investigator where treatment for injury would be available locally. You and your insurance company will be billed for this treatment. Some research sponsors may offer a program to cover some of the treatment costs which are not covered by your insurance. You should ask the research team if such a program is available.

Right to Refuse or Withdraw

Taking part in this study is voluntary. You have the right to refuse to take part in this study. If you decide to be in the study and then change your mind, you can withdraw from the research. Your participation is completely up to you. Your decision will not affect your being able to get health care at this institution or payment for your health care. It will not affect your enrollment in any health plan or benefits you can get.

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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form.

Subject (Signature and Printed Name) Date

Person Obtaining Consent (Signature and Printed Name) Date

Appendix 9: Family Heart Study-SCAN consent form

Boston University School of Medicine

BOSTON MEDICAL CENTER

Participant's Name: _____
Study ID number: _____

Family Heart Study SCAN
Consent Form
Boston University Medical Center

BACKGROUND INFORMATION

It is now well known that heart disease and stroke are often caused by hardening of the arteries (atherosclerosis). The causes of atherosclerosis, however, are not well understood. We are conducting a research study on several factors that may have a major effect on the development of atherosclerosis in the arteries to the heart (the coronary arteries) and in the aorta (the largest blood vessel coming from the heart).

PURPOSE

In this study we will be looking at how your genetic make-up and your body's inflammation defense system relate to any atherosclerosis that may be present in your arteries. To do this, the amount of calcium in the arteries, a new way to judge the degree of atherosclerosis a person has, will be measured by a CT scan, a procedure similar to an X-ray that uses radiation to evaluate calcium within arteries. Whereas most risk factors such as blood cholesterol and blood pressure provide only indirect estimates of risk, this new test provides direct evidence of the amount of calcium (caused by atherosclerosis) in the arteries. Information obtained from the CT scan would be related to the genetic and other information that has previously been collected from you as part of the Family Heart Study.

You are one of approximately 600 subjects, all from families seen previously in the Family Study clinics in Framingham, who are being invited to participate in this new project. You have been chosen because you are from a family that has supplied enough family data and genetic information to be particularly helpful in this endeavor to discover the factors that relate to heart disease and coronary and aortic calcification. It is hoped that this study will provide leads for the prevention of such disease.

HOW THE STUDY WORKS

If you agree to be in this study, a clinical examination will be performed at the Family Heart Study Clinic in Framingham. The examination will consist of a brief medical history; questions about your family structure, use of alcohol, smoking, physical exercise, weight, socio-economic status, and reproductive history (only for women); and measurement of your height, weight, and blood pressure. Also, the following interviews and tests will be carried out:

1. Family Data: You will be asked about the biological relationships of members of your family. Your responses will be kept confidential, even from other members of your family. You may decline to answer certain questions without jeopardizing your participation in this study.

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2. Blood Tests: You will be asked to provide a blood sample (approximately 4 tablespoons) which will be taken from a vein in your arm. The levels of certain substances that may relate to the development of atherosclerosis, heart disease, or calcification in your aorta or coronary arteries will be measured; these will include assessments of lipids (fats and cholesterol), blood sugar, and some new measures that judge how your body has responded to past inflammation. Some of the blood may also be used to extract additional DNA to supplement the DNA you may have supplied at a previous clinic visit in the Family Heart Study. If additional DNA is required, it will be used for the creation of a living tissue sample (cell line) from which an unlimited supply of DNA can be obtained in the future without the need to obtain more blood from you. Cell lines will be stored at a central site (repository). Neither your name nor Family Study identification number will appear on the sample. A new security bar code number and the date the specimen is drawn will be the only information on the label.

   Data and DNA will be distributed to researchers conducting the Family Heart Study, the Framingham Heart Study, and other qualified researchers interested in the genetics of heart, lung and blood diseases and other diseases and health conditions. The scientists from these laboratories will be given the DNA without any potentially identifying information. Information gained from research on your DNA may be used for the development of diagnostic procedures or new treatments for major diseases. Your DNA will not be sold to anyone or to institutions or companies for financial gain or commercial profit without your consent. However, neither you nor your heirs will gain financially from discoveries made using the information and/or specimens that you provide.

3. C-T Scan: At a separate near-by facility you will be asked to have Sequential Computed Tomography (CT) to measure the calcification in the arteries of the heart and in the main artery of the body (the aorta). The test will be done at a new imaging center near Framingham established by the Massachusetts General Hospital; transportation to and from the facility will be offered. During the procedure, you will be positioned on your back on a special table that is part of the CT scanner. [Electrocardiogram (ECG) leads will be attached.] The table will move into the CT scanner, which is about 4 feet in diameter and shaped like a large donut. During the scanning process, your body will be in the "donut shaped" portion, but your head will be free of the apparatus. You will be asked to remain still and momentarily hold your breath three times, each time for 10 to 15 seconds in order to get good quality pictures. Two scans of your coronary arteries (to increase accuracy) and one scan of your abdominal aorta will be done. You will not need to take any drugs or contrast agents by mouth or by injection for this procedure. Women who are pregnant or are breast feeding, people who weigh more than 352 pounds, and individuals who have undergone radiation therapy within the past year are not eligible to have a CT scan. Women who have not reached menopause will be given a pregnancy test within 24 hours before undergoing the CT scan. The scan is being done specifically to evaluate calcium in your arteries, and does not serve as a "clinical" CT scan that may detect other health conditions. If your scan shows high levels of calcium, you and your doctor will be notified.

All of the above information will be related to self-reported data, laboratory results, and genetic information that were collected from you previously in the Family Heart Study or are being collected now to help us determine how such factors relate to the risk of atherosclerosis and heart disease.

The CT scan is being conducted for research purposes. A complete clinical evaluation of the CT scan images will not be performed. However, in the event that the research evaluation of the scan uncovers medical problems that require medical diagnosis for possible treatment, you will be told and the information will be provided to a physician or clinic that you choose. Results from genetic testing will not be released or placed in your medical record, nor shared in any way with your relatives, personal physician, insurance companies, or any other third party unless you authorize Family Heart Study - SCAN staff, in writing, to do so.

Your cholesterol, blood pressure, and any markedly abnormal findings from your CT scan will be shared with you and, with your permission, with your doctor. If a health condition is detected during this examination, your doctor or clinic will be notified, if you authorize the study staff to do so. However, the Family Heart Study – SCAN is not intended to provide medical care or to interfere with your relationship with your own doctor. You will be referred to your doctor for follow up of all medical information obtained by this study. If you don't have a doctor, you can be referred if you so desire.

LENGTH OF STUDY

You will be in the study for a one-time clinical exam that will take less than 2 hours. Your CT scan will be scheduled at that time, and you will be offered transportation to the CT center on the same day or on another day for your scan. The CT scan will take less than 15 minutes to complete, but you should plan to be there about 30 minutes.

RISKS

The most common side effect of blood drawing is the possibility of pain or a bruise at the site of the needle stick. The bruise may remain for 3 to 4 days and can, in most cases, be prevented by applying pressure directly over the area once the needle has been removed. There is the remote risk of an infection at the site of the needle stick, but this is very small because sterile, disposable needles are used.

This research study involves exposure to radiation from the CT scan to be done as part of the Family Heart Study – SCAN study. As described above, this is being done to measure the calcification in the arteries of your heart and aorta. Since this involves some X-rays, you will be exposed to a small amount of radiation from the procedure. The total radiation dosage for this test is 1.5 to 2.0 times the background radiation for people in the United States and about 12% of the yearly exposure limit for radiation workers. The risk from this level of radiation is not known for sure. The risk from this radiation exposure ranges from no effect to a larger risk of developing a cancer. There is a time delay between exposure to radiation and getting a cancer. This time can be ten years or more. Your chance of getting a cancer from participating in this study is similar to your risk of getting a cancer from natural radiation exposure. There is also an increased risk of genetic effects as demonstrated by animal studies. These are effects which can be

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passed along to your children. Pregnant women and women who are breast feeding may not participate in this research. There may be risks of CT scans that are not yet known.

POTENTIAL BENEFITS
There are no known personal benefits to you from your participation. However, your participation in this study may help others in the future by showing whether this new test is as good as preliminary studies suggest. We may be able to replace more risky tests with this new test if it is shown to be able to provide fast, accurate diagnostic answers. As stated, the CT scan focuses only on calcium in the arteries, and is not the same as a "clinical" CT designed to look for other disease processes.

ALTERNATIVE
You may choose not to participate in this study, and still participate in the Framingham Study and the NHLBI Family Heart Study. If at any time in the future you wish to have the data collected from you in this study removed or destroyed, including blood and DNA samples, you may notify us of this and it will be done.

CONFIDENTIALITY
Any information we obtain about you during this study will be treated as strictly confidential to the full extent permitted by applicable law. To ensure confidentiality, a code number will be assigned to you and any potentially identifying information will not be used on any samples you provide. When study results based on your information are published, your name and any other potentially identifying information will not be revealed. Only the code numbers will be provided to qualified investigators studying the DNA samples.

The coded specimens will be stored securely, separated from files which link your name to the code numbers. Files linking names to samples will be kept locked and accessible only to the Framingham Study data manager. Your sample may be kept until it is no longer of scientific value.

You will not be informed of the results of the research performed upon your genetic blood sample, although genetic tests may be developed as a result of the combined analysis of samples in the Family Heart Study. No other individual, including your spouse, parents, children, physician or employer will have access to the stored sample or information gained from your stored sample. Because no information will be provided to you or to others from the analysis of this sample, the risk for providing this sample is minimal. You will be kept informed through periodic publications from the Family Heart Study of any new information about genetics or genetic testing for cardiovascular disease or other health conditions generated from the DNA analyses which may be of importance to you or your family.

All the information about you from this research, including history, the clinical exam, laboratory data or findings of the DNA testing, will be kept confidential and will not be disclosed to anyone but the researchers conducting this study, except as otherwise required by law. This means that your research records, just like your hospital records, can be subpoenaed by a court of law. Study results will be published so that the information is anonymous and/or disguised, and that identification of any individual cannot be made. Your information will be used for statistical purposes only. To assure that the

investigators are following institutional and federal guidelines, the Institutional Review Board of Boston University Medical Center may choose to review all study records at any time and, if appropriate, this may be done by the US Food & Drug Administration.

Blood samples will be stored by the Family Heart Study – SCAN study for future investigations. These may include medical research projects on other medical conditions. Your name or other information that could identify your family or you will not be released.

COSTS
There are no costs to you for taking part in this study. All examinations, including the CT scan and laboratory tests, will be performed without charge. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

PAYMENTS
You will not be paid for your participation in this study; if you request it, you may be reimbursed for travel expenses associated with your participation in the study.

COMPENSATION FOR ILLNESS OR INJURY
In the unlikely event that during the examination procedures you should require medical care, first aid will be available. If you think you have been injured by being in this study, let Dr Ellison (508 935-3418) know right away. If the examinations uncover any medical problems that require medical diagnosis or treatment, you will be so advised and, if you agree, that information will be provided to the physician or clinic of your choice. In that case, payment must be provided by you or your third party payer, if any (for example, health insurance or Medicare).

PARTICIPANT'S RIGHTS
Taking part in this study is voluntary. You may choose not to take part and you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. You will be given a signed copy of this consent form.

FAMILY HEART STUDY SCAN
Consent Form

VOLUNTARY CONSENT

I am asked to participate in the FAMILY HEART STUDY -- SCAN Study. If I sign this form, I confirm that I have read the preceding (or it has been read to me). To the best of my knowledge, I am not pregnant; further, I have not undergone radiation therapy within the past year. Any questions I have about the research have been answered by the Project Coordinator, [redacted] the Clinic Coordinator, [redacted] or the Principal Investigator, [redacted] all of whom can be reached at [redacted] Questions about the CT scan may also be directed to [redacted] I may obtain further information about my rights as a research subject by calling the Office of the Institutional Review Board for Human Research of Boston University Medical Center at (617) 638-7207. If any problems arise as a result of my participation in this research, I shall call [redacted] immediately.

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VALID THRU: 7/2/04
PER IRB: [redacted]
7/3/03 AUTH. INIT.

A signed copy of this consent form will be given to me. By signing this consent form, I am granting permission to the FAMILY HEART STUDY SCAN investigators to carry out the following:

Please check the appropriate box beside each statement:

YES ☐ NO ☐ I agree to participate in the Physical Examination and Genetic Studies of factors contributing to coronary artery calcification and other heart, lung and blood diseases, stroke, dementia, osteoporosis, cancer, and other major diseases and health conditions. I also agree to undergo a CT scan to assess my heart and aorta for calcification, and relate the findings from this test to genetic and other data collected from me. If I am a pre-menopausal female, I will undergo a pregnancy test to assure that I am not pregnant before the CT scan is done

YES ☐ NO ☐ I agree to provide a blood sample from which DNA can be extracted. The DNA will be made available to researchers studying the diseases listed above.

YES ☐ NO ☐ I agree to allow the creation of a cell line from my blood sample.

YES ☐ NO ☐ I agree to allow researchers from private companies to have access to my DNA and genetic data which may be of use to develop diagnostic lab tests or pharmaceutical therapies that could benefit many people. (Note: you or your heirs will not benefit financially from this, nor will your DNA be sold to anyone.)

The Family Heart Study – SCAN investigators and the scientists with whom they are collaborating will use the information and samples collected on me now, as well as such information collected previously in the Family Heart Study (including results of questionnaires, clinic examination, blood and genetic tests), for research purposes only. Blood samples will be stored by Family Heart Study – SCAN investigators for future studies. These may include medical research projects on all medical conditions, including coronary heart disease, hypertension, other cardiovascular diseases, obesity, diabetes, cancer, etc. My name or other information that could identify me or my family will not be released.

My signature below means that I have freely agreed to the conditions for participation in this study. By signing this consent, I do not waive any of my legal rights.

_____ _____
Signature of Participant Date

_____
Printed Name of Participant

IRB# 2001-2834
VALID THRU: 7/2/04
PER IRB: [illegible]
7/2/03 AUTH. INIT.

Signature of Investigator/Designee

Printed Name of Investigator/Designee

****

RELEASE OF STUDY DATA AND MEDICAL INFORMATION

I do ____ do not____ authorize Family Heart Study – SCAN to release the findings from tests and examinations to my physician, clinic or hospital.

Signature

Date

****

IRB# 2001-2834
VALID THRU: 7/2/04
PER IRB: K
7/3/03 AUTH. INIT.

d:\docs\grant\GENCAP\InfConRevFinalRev.717

Appendix 10: Research Privacy Aurthorization (HIPAA)

Specific description of information we will collect may include:

- •Face Sheet
- •Discharge Summary
- •ER Report
- •Admission Notes
- •Progress Notes
- •Operative Report
- •Pathology report
- •Chest X-Rays
- •EKGs (All)
- •CT Scan (Head)
- •MRI/MRA (Head/Neck)
- •Lab Reports - Cardiac Enzymes
- •Consults (Cardiology & Neurology)
- •Cardiac Catheterization
- •Exercise Tolerance Test
- •Nursing Home Notes
- •Notes near time of death
- •Other: (for example: Echocardiogram, Arteriography, Venous Ultrasound, V/Q Scan, PA gram, etc.)

Section C: General

(1) **Expiration:**
This authorization expires at the end of the study.

(2) **Right To Revoke:**
You may revoke (take back) this authorization at any time. To do this, you must ask the Framingham Heart Study for the names of the Privacy Officers at the institutions where we got your health information. You must then notify those Privacy Officers in writing that you want to take back your Authorization. If you do, we will still be permitted to use the information that we obtained before you revoked your authorization but we will only use your information the way the Informed Consent Form says. If it is easier for you, please contact [redacted] head of Medical Records, and she will help you take back your authorization.

(3) **Your Access to the Information:**
You have the right to see your medical records, but you will not be allowed to review medical records in your research records until after the study is completed.

I have read this information, and I will receive a signed copy of this form.

Signature of research subject or personal representative **Date**

Printed name of personal representative: _____

Relationship to research subject: _____

Please describe the personal representative's authority to act on behalf of the subject:

_____

ACCEPTED
Date: 4/14/03
Sig: [signature]
Research Privacy Advocate

Appendix 11: Informed Consent Procedures

With a liaison:

Consent forms are presented to the participant in a location that is private or semi-private. Currently the liaisons use the chairs by the changing rooms. If further privacy is necessary, the conference room down the hall is usually available. The liaison has access to a private room near the CT scanning room if privacy is not possible at the above locations.

The liaison encourages the participant to read the entire consent form and asks the participant if they have any questions before signing. A copy of the consent form is given to the participant at this time.

Without a liaison:

Participants may come to the Heart Study before going to MGHW in order to ask questions and sign the consent form. If a participant requests an off-time CT appointment (when no liaison is available) and prefers not to come into the Heart Study before going to MGHW in Waltham we will fax a consent form and have the participant fax back to us the last page with their signature.

Appendix 12: Protocol at MGH West

I. Overview of Liaison Duties

The liaison presents the Consent form and answers any questions the participant may have before they sign the Consent form. The liaison fills out a Pregnancy Determination form (Appendix 14) with every female participant. If determined necessary the liaison provides the Self Administered Pregnancy to the participant (Appendix 16) and administers pregnancy tests as needed. Occasionally the liaison completes a Health History Update with the participant (Appendix 18). The liaison handles all questions or concerns the participant has while at MGH West.

The liaison is responsible for bringing the traveling files that carry each participant's paperwork back and forth between Framingham and MGH West. The traveling files are carried in a plastic file holder ("Traveling Folder") that contains extra forms and FHS contact phone numbers.

Supplies that the liaison may need such as extra forms, pregnancy tests, plastic gloves, etc. are kept in a small black suitcase (like a flight attendant's) that is kept in the back right corner of the mechanical room at MGH West. The liaison may use the pens and clipboards on the counter of the front desk.

1. Liaison Obtains Schedule

The day the Liaison goes to Massachusetts General West Imaging Center (MGHW) the Liaison receives that day's schedule from the CT coordinator. The liaison informs the MGH receptionists of any changes in the schedule and provides the CT techs with a copy of the schedule for that day.

2. Traveling Folder:

The "traveling folder" contains the "traveling file" for each participant that is scheduled that day, and is prepared by the CT coordinator. Each "traveling file" contains that participant's Informed Consent, HIPAA form, CT Completion Form, and for women, the Pregnancy Determination Form and, if necessary, the Supplemental Self-Administered Questionnaire. The "traveling file" also includes Health Updates if necessary.

3. Travel:

Liaison drives own car to MGHW and arrives approximately 15 minutes before the first appointment.

II. MGH reception procedure for FHS participants

1. Scheduling

The MGH receptionists and techs are provided with an up-to-date schedule that is emailed from the FHS coordinators either one or two days prior to the date of scan. This schedule includes the participant's name, date of birth, arrival time, and scan time.

The FHS schedule includes a comment line for each participant. Information on this comment line details the status of each participant's FHS paperwork for those with "off-time" appointments (when a FHS liaison is not scheduled).

FHS liaisons are always present at MGH West on Mondays, Tuesdays, and Wednesdays from 3:00 pm to 7:00 pm. There is sometimes a liaison scheduled one Friday morning and one Saturday morning per month from 9:00 am – 11:00 am (to be determined by FHS CT coordinators and MGH technical manager).

2. Reception

When a participant from the Framingham Heart Study arrives at the MGH West Imaging Center the participant checks in with the MGHW receptionists:

a) When a FHS liaison is present at MGHW

The MGH receptionist notes that the participant has arrived, informs the liaison of their arrival, and provides the liaison with the MGH tracking form.

b) When a liaison is scheduled but has not yet arrived

The MGH receptionist notes that the participant has arrived and has them sit in the main waiting area.

c) When a liaison is not scheduled ("off-time" appointments)

the MGH receptionist checks the schedule to see whether the participant should have their FHS paperwork with them or whether the paperwork was previously dropped off or faxed. The receptionist informs the CT tech of the participant's arrival and provides the tech with the participant's FHS paperwork and MGH tracking form if the tech does not already have them.

3. Liaison Arrival at MGHW

When the liaison arrives at MGHW, she gives the MGHW receptionist one copy of the schedule to cross check against the schedule that was e-mailed to her the day before by the Family Study Clinic Recruiter and Tech. In the event that differences exist between the two schedules the receptionist updates her schedule to coincide with the one brought by the liaison. The copy that the liaison brought for MGHW is then given to the CT techs for reference through the evening. The CT techs shred this schedule after the last appointment.

4. Greeting the participant

The liaison greets the participant by reading the participant's full name off of the FHS schedule, introduces him/herself by name and states that s/he is from the Framingham Heart Study.

If the liaison expects that the participant will be waiting long, the liaison explains the situation (the participant may have arrived very early, the schedule may be backed up, the machines may be down, etc.) and informs the participant of the period of time they are expected to wait and of the option to reschedule if necessary. Should the participant wish to reschedule, a coordinator contacts the participant the next day.

III. Verification of Participant's Identity:

The liaison then leads the participant to seating by the changing area (semi-private). The liaison asks the participant to state her/his full name and date of birth to verify that the participant is the correct person. For further identification the participant's address and phone numbers may also be used. A conference room is available if more privacy is needed.

IV. Review and Signing of Informed Consent Form:

Upon confirmation of correct identity, the liaison gives the participant the Informed Consent Form and requests that the participant reads through the entire document. The participant is asked whether s/he has any questions and is asked to sign and date on the third page if s/he is comfortable with the agreement.

V. Health History Update for Offspring Participants:

Once the Informed Consent Form is signed, Offspring participants who have not had a recent Health History Update will be further interviewed to obtain the information needed to complete the Health History Update form (Appendix 20).

VI. Specific Procedures for FEMALE participants

1. Completion Form

A self-reported height and weight are obtained in order to prepare the Completion Form for the MGHW CT tech. A scale is available for participants who do not know their weight.

2. Pregnancy Determination Form and Self-Administered Pregnancy Questionnaire

a. Pregnancy Determination Form

The liaison completes the Pregnancy Determination Form with every female. Female participants who have had a tubal ligation or hysterectomy, or are over 55 years old or older and have not had their period for at least six months, are considered "Exempt" from the pregnancy test. Female

participants under 55 who have not had a tubal ligation or a hysterectomy, and participants 55 and older who have had a period within the last six months are required to have a pregnancy test.

b. Supplement to Pregnancy Determination Form: Self-Administered Pregnancy Questionnaire

A urine pregnancy test is used in the Framingham Heart Study CT Study to screen for pregnancy (QuSTICK ™ Pregnancy Test, STANBIO Laboratory). However, urine pregnancy testing with this and other assays cannot detect pregnancies until 6 days after conception. Also, although in most cases we obtain a pregnancy test immediately before the CT exam, we allow up to 24 hours between the urine pregnancy test and the CT scan, so conception (a pregnancy) could theoretically occur during the 24 hour time period between pregnancy testing and the CT scan. Thus, to minimize the risk of performing a CT scan on a woman whose very early pregnancy might not be detected by the pregnancy test, we have decided it is necessary to administer a brief self administered questionnaire in all women of childbearing potential *in addition to conducting the pregnancy test*,

3. Pregnancy Test

a) Liaison certification

All liaisons become certified to perform pregnancy tests by an FHS laboratory technician. The certification process consists of 1) watching as the tech performs and explains how the QuSTICK Pregnancy Tests are used, and 2) performing the pregnancy test in the same manner with an actual urine sample as the tech supervises. The liaison and tech both sign and date a certificate of completion for pregnancy testing (see Appendix 14).

b) Performing the pregnancy test at MGHW

The liaison prepares the Ladies Room for a pregnancy test by placing a plastic specimen cup with a screw-top lid on a dry paper towel on the sink. The participant is then asked to leave at least a 1-2 oz (10-20 cc, approximately a quarter cup) urine sample in the plastic cup and to return it to the paper towel on the sink. After the participant has left the urine sample on the sink, she returns to the changing area and waits for the results of the test. She does not proceed until the liaison informs her of the results. At this point the liaison has not yet given the CT techs the participant's completion form to insure that the participant is not brought into the scanning room.

The liaison then performs the test using a pregnancy test strip as follows: the liaison adorns latex gloves, sets a timer to 3 minutes and 15 seconds, unscrews the lid and places the lid on another dry paper towel, opens the individually packaged test strip, dips the strip into the urine sample up to the specified line and starts the timer. The test strip is held in that position for 15 seconds, removes the strip from the urine and sets the strip horizontally on top of the dry side of the lid. After waiting for 3 minutes, the liaison stops the timer and examines the strip. One red line above the portion of the strip dipped in urine indicates a negative result (NOT pregnant), and two red lines in that area indicate a positive result (PREGNANT). Participants with a negative result are eligible to proceed, while those with a positive result are not and cannot undergo the scan. Once the liaison has determined a negative result, s/he empties the urine from the cup into the toilet, places the test strip into the toilet and flushes. S/he then discards the paper towels that were on the sink into the Ladies Room garbage can, wipes down the entire top surface of the sink with a Clorox Wipe, discards the wipe into the garbage can, and removes the gloves, also discarding them into the garbage can.

A positive result requires that the liaison take the participant to the conference room for privacy, where the liaison explains that the test came back positive but that the participant should go to her

doctor for a blood test. The liaison further explains that because the test came back positive the CT scan cannot be completed at this time.

c) Completion Form

A negative pregnancy test result is indicated on the Completion Form by circling 'Yes' in response to the statement: "Pregnancy Test Negative". A negative pregnancy test is considered valid for 24 hours from the time of testing. The date 24 hours from the time of testing is written beside the statement: "Pregnancy Test Valid Until". The liaison certifies the pregnancy test on the Completion Form by writing her/his initials beside the above information. The liaison then obtains a self-reported height and weight from the participant in order to prepare the Completion Form for the MGHW CT tech. The liaison gives the MGHW appointment card and the Completion Form to the tech performing the scan.

VII. Participant Changes Clothes

Each day the liaison asks the CT and MRI techs which changing room FHS should use and then proceeds to use only that room for the remainder of the day.

A participant may wear their own pants/skirt if there is no metal on them and if they empty their pockets of any metal. Otherwise participants are asked to change into hospital pants. Participants will be given a jonnie or robe to wear with the opening in the front (for EKG leads). Participants may not wear a bra or undershirt.

Sometimes a participant will strongly prefer not to change but will have metal on their clothing. The MGHW CT techs state that it is OK for a participant to just pull their pants/skirt down enough to bare their

abdomen, and remove any metal from their pockets. It is OK for participants to wear their own shirt if it opens all the way in the front and has no metal on it.

VIII. Participant brought into CT scanning room

Once the participant is changed, s/he sits in the changing room waiting area for the MGHW CT tech to come get her/him for the scan. The tech introduces her/himself, asks the participant to state his/her name and leads the participant into the CT scanning room. To verify identity, the tech then asks the participant to spell his/her last name, and to state his/her date of birth.

IV. Participant Departure

After the scan is complete, the participant changes back into his/ her clothes and is free to leave MGHW.

X. Completion of Documentation for Scan

1. Retrieval of Completion Form

The liaison retrieves the Completion Form from the tech and returns it to the participant's folder.

2. Checklist

The liaison fills in the participant's Checklist, which is stapled to the left inside cover of the participant's folder, indicating that all forms are present, or making any notes explaining why the folder may not be complete or why the scan was not done/finished. Special requests made at the time of the consent (e.g. change of address) are noted in the comment space of the Checklist.

3. Confirming Completed Scan on Schedule

The liaison checks the appropriate box on the schedule, indicating whether the scan was completed or not.

4. Drop Off/Pick-Up Completion Forms

If any Completion Forms need to be dropped off for up-coming "off-time" appointments, the liaison gives those Completion Forms to the techs to put into their lock-box. Likewise, if any Completion Forms need to be picked-up that were left there for previous "off-time" appointments, then the liaison gets those from the tech.

a) "Travel Folder" Returned

The liaison drives the Travel Folder containing all of the participants' folders back to FHS that evening if s/he is not returning to FHS the following morning. The Traveling Folder is given to the CT Coordinator. The CT Coordinator, maintains a central folder and spreadsheet of any special requests.

b) Folders to Data Management

After the Family Study Clinic Recruiter & Technician has removed any Family Study folders, the CT Coordinator gives all FHS-only and Combined folders to the CT project Data Manager, who stores the folders in a file cabinet[redacted]The Data Manager organizes double keying of the folder contents, and cleaning of the data sets.

Framingham Study/MGH West Imaging
CT Scan Flow Sheet

RECEPTION

Participant Arrives

Check emailed FHS schedule

Liaison is scheduled

Wait for the liaison to arrive

(Why? Because the participant may not have signed our consent form, and/or other reasons.)

Tell the liaison & provide the MGH tracking form

Liaison is NOT scheduled

Has the participant brought his/her own paperwork?

Or has the paperwork been faxed or dropped off?

CT TECHNICIAN

Before Scanning

Have participant state his/her full name

Have participant state his/her Date of Birth

Check the completion form of <u>every</u> female for an exempt or negative pregnancy status

If you have any questions please call Barbara at 508-935-3451 Thank you!

FHS Liaison Procedure Checklist

□ **Before Arriving at MGH West**

- Obtain the "Traveling Files" from the CT Coordinator
- Each folder should contain:
  - CT completion form (Appendix 16)
  - Pregnancy determination form (all females) (Appendix 14)
  - Self-Administered Pregnancy questionnaire (all non-exempt females) (Appendix 16)
  - CT scan checklist (Appendix 13)
  - CONSENT FORM (S)-- (Appendix 8, Appendix 9)

□ **At MGH West Imaging**

- Confirm with the receptionist that all the scheduled participants are expected
- Get the materials suitcase from the far right corner of the mechanical room

Check in the participants as they arrive

- Greet participant and note on the daily schedule that the participant arrived
- Obtain Informed Consent
- Health history update if necessary

For Females only:

- Pregnancy determination form and Self-Administered Pregnancy Questionnaire
- Pregnancy test (if necessary)
- Note results on CT completion form and pregnancy determination form

Preparing for the CT scan

- The participant changes into hospital pants and a jonnie (open in front)
  - no bras, pants/shorts/skirts without zippers may remain on, underwear remains on, shoes and socks may remain on, and jewelry (except necklaces) may remain on
- Obtain participant's height and weight (the scale is under the stretcher across from the techs)
- When the participant is almost ready, hand the CT completion form to the CT tech
- Once the first participant has entered the scanning room, the changing area is available for the next participant.

Repeat the process so that when one participant is through with his/her scan, the next participant is out of the changing room and is ready for his/her scan.

Note for the liaison

A letter code must be on the lower right corner of each completion form to help the CT tech identify whether the participant is in the Framingham Heart Study "F", the Family Heart Study "G" (GENCAC), or both "C". All scans are archived locally.

a. GENCAC "G" scans go to [redacted]
b. FHS "F" scans go to [redacted]
c. Combined "C" scans go to [redacted]

□ **COMPLETION OF SCAN:**

1. Once the scan is completed get the CT completion form from the technologist, note on the completion form that the scan was done and put it back in the participant's file.
2. See the participant out and thank them for their time.
3. The next day, bring the files back to the CT coordinator.

Appendix 13: CT Scan Checklist form

CT SCAN CHECKLIST

NAME OF PARTICIAPANT: **Date of Scan:** _____

1. **Signed Consent Form:**

   FHS CONSENT FORM:
   Signed in Waltham _____ Signed in clinic _____ N/A _____

   GENCAC CONSENT FORM:
   Signed in Waltham _____ Signed in clinic _____ N/A _____

2. **PREGNANCY DETERMINATION FORM:** Completed_____ N/A____

   PREGNANCY TEST: **Positive / Negative / Exempt** **(circle one)**
   (If the pregnancy test is **positive**, photocopy this form and give it to the appropriate Coordinator.)

   The person performing the pregnancy test must initial the box on the Completion Form directly under "FHS-Staff Completing Pregnancy Test".

3. **SUPPLEMENT TO PREGNANCY DETERMINATION FORM:** Yes___ N/A____

4. **CT COMPLETION FORM:** _____

5. **HEALTH HISTORY UPDATE FORM:** **N/A:** _____
   To complete in Waltham: Yes _____ Completed _____
   No _____

6. **IF RADIATION LIMIT IS EXCEEDED, SPECIFY #:** _____

COMMENTS:
(In the event of any significant problem please describe briefly then photocopy this form and give a copy to the appropriate coordinator)

CODES: (circle one)
G = GENCAC
F = Framingham Offspring
F3 = Framingham 3rd Generation
C = Combined G and Offspring LIAISON NAME:
C3 = Combined G and 3rd Gen

_____

Appendix 14: Pregnancy Determination Procedure and Form

Pregnancy Determination Procedure

Supplies

(1) Pregnancy Test

(1) Plastic cups with lid

(1) 3 minute & second timer

Plastic Gloves

Cleanser wipes

Pregnancy Test Brand:

QuStick

Catalog # 1210-425

Stanbio Laboratory

Boerne, Texas

**Prior to participants arrival the liaison retrieves the suitcase containing the supplies from the far right corner of the mechanical room. If a pregnancy test is required, direct the participant into the bathroom and ask them to give a urine sample in the cup that is provided by FHS. Let them know that they can leave the sample in the bathroom, and once they are done ask them to sit in the changing area. Proceed to the bathroom, open a new pregnancy test and dip the top section into the sample for 15 seconds. Set the timer to 3 minutes and start it once the 15 seconds is over. Place the stick on top of the cap and wait 3 minutes. Once the 3 minutes has been completed check the pregnancy test. If it is negative proceed with the test (one line), if it was positive (two lines) the CT scan cannot be performed, and you must take the participant into a private area and discuss the findings.

The Framingham Heart Study
Pregnancy Determination Form
[Required for all Women]

FHS I.D. Number:

Last Name: First Name: Middle Name:

---

1. Are you Pregnant? ☐ Yes → Participant is disqualified from the study

☐ No

☐ Don't Know

2. For women < 55 years old:

2.a Have you had a hysterectomy [removal of the uterus] or tubal ligation [tubes tied]?

☐ Yes → Pregnancy test NOT required

☐ NO → Pregnancy test REQUIRED

3. For women > 55 years old:

3.a Have you had a hysterectomy [removal of the uterus] or tubal ligation [tubes tied]?

☐ Yes → Pregnancy test NOT required

☐ NO

↓

3.b When was your last menstrual period?
☐ > 6 months ago → Pregnancy test NOT required
☐ Within 6 months → Pregnancy test REQUIRED

4. Pregnancy Test Required? ☐ Yes → Result ☐ Positive ☐ Negative
☐ NO

5. Supplement to Pregnancy Form ☐ Yes ☐ No

6. Date of pregnancy interview and pregnancy test [if required]:
☐☐/☐☐/☐☐☐☐
m m d d y y y y

7 . ID number of the person completing this form ☐☐☐☐

The Framingham Heart Study

hCG Pregnancy Testing Certification

1. I have reviewed the written protocol with an authorized FHS laboratory staff member.
2. I have reviewed the kit insert with an authorized FHS laboratory staff member.
3. I have received copies of both documents.
3. I have performed the assay on a negative and a positive control while being observed by an authorized FHS laboratory staff member.

Name:_____

Certified by:_____

Date:_____

August 8, 2003

73 Mt. Wayte Avenue • Framingham, MA 01702 • 508.872.6562 tel • 508.626.1262 fax

Appendix 15: Certification of Staff Performing Off-site Pregnancy Testing

FHS staff members who are performing off-site pregnancy testing are required to be certified in the test by an authorized staff member of the Framingham Heart Study Laboratory (Lab manager or Lab coordinator).

Certification process includes;

1. Review of the written protocol with the laboratory staff.
2. Review of the kit package insert with the laboratory staff.
3. Receipt of copies of both documents.
4. Certification form signed by off-site tester and laboratory staff member.

Records of the signed certification forms are maintained by the FHS lab manager.

Rationale

A urine pregnancy test is used in the Framingham Heart Study CT Study to screen for pregnancy (QuSTICK ™ Pregnancy Test, STANBIO Laboratory). However, urine pregnancy testing with this and other assays cannot detect pregnancies until 6 days after conception. Also, although in most cases we obtain a pregnancy test immediately before the CT exam, we allow up to 24 hours between the urine pregnancy test and the CT scan, so conception (a pregnancy) could theoretically occur during the 24 hour time period between pregnancy testing and the CT scan. Thus, to minimize the risk of performing a CT scan on a woman whose very early pregnancy might not be detected by the pregnancy test, we have decided it is necessary to administer a brief questionnaire in all women of childbearing potential *in addition to conducting the pregnancy test*,

Procedure

1. The following script is used when scheduling women of childbearing potential and at the time of a reminder phone call.

> *"Because a pregnant woman should not have a CT scan, we have an additional set of questions we will ask you before authorizing you to have the CT test. These questions are provided on a "CT Study Pregnancy Questionnaire" we have given you. In that questionnaire, we will ask you whether you have used an effective method of birth control each time you have sexual intercourse for the seven days prior to your CT scan. We will also conduct a urine pregnancy test at the time of your CT scan. If you have not used an effective method of birth control in the seven days prior to the CT scan, we will need to reschedule your CT scan."*

[If the participant asks you to name the "effective methods of birth control", read the list from the **SUPPLEMENT TO PREGNANCY DETERMINATION FORM].**

2. The **SUPPLEMENT TO PREGNANCY DETERMINATION FORM** should be self-administered in private at the time of the pregnancy test to all women of childbearing potential. Women who have had sexual intercourse without effective birth control in the previous seven days should not be scheduled for a CT scan.

Appendix 16: Supplement to Pregnancy Determination Form

SELF-ADMINISTERED PREGNANCY QUESTIONNAIRE

Introduction: The Framingham Heart Study CT Study will provide important information about women's cardiovascular health. However, women should not have a CT scan if they are pregnant or even if they could possibly be pregnant, to avoid any potential risk to the fetus. Because the urine pregnancy test cannot detect pregnancies of less than one week, we must ask about your sexual activity in the past seven days. Identifying the chances of a possible pregnancy is done for your safety. If there is a possibility that you are now pregnant, please tell us so that we may re-schedule your CT scan.

1. *Have you had sexual intercourse in the past seven days?*

   - *Yes* ____ *If Yes, proceed to #2.*
   - *No* ____ *If No, proceed to #3.*

2. *Did you use one of the following forms of birth control each time you had sexual intercourse in the past seven days? (Birth control methods not found on this list are not considered effective in preventing pregnancies by our study physicians.)*

   Oral contraceptives (the pill)
   Male condom
   Female condom
   Injection (Depo-Provera, Lunelle)
   Diaphragm with spermicide
   Cervical cap with spermicide
   Contraceptive Patch
   Vaginal contraceptive ring
   Post-coital contraceptives, taken within 72 hours of intercourse (Preven, Plan B)
   Implant (Norplant)
   IUD (Intrauterine Device)
   Male surgical sterilization

- *Yes* ____ *If Yes, proceed to #3.*

- *No* ____ *If No, stop here.* YOU WILL BE RESCHEDULED FOR A PREGNANCY TEST AND A CT SCAN AT A TIME AFTER ONE WEEK FROM TODAY.

3. PLEASE READ: *When you report for your CT scan, the Framingham Heart Study coordinator will repeat questions 1 and 2 above regarding whether there is any reason to believe you are pregnant. If you have sexual intercourse between now and the CT scan, and you do not use one of these forms of birth control, you should tell the technician, "Yes, I may be pregnant". In this case, you will not be permitted to have a CT scan due to the radiation risk to a possible fetus, and we will work with you to reschedule your CT scan.*

Appendix 17: Example of Schedule & MGHW Appointment Card

MGH WEST APPOINTMENT CARD

The MGH West Appointment card is given to the liaison upon arrival of the participant to the CT center.

This tracking form is given to the CT technologist along with the participant's completion form.

EXAMINATION FORM
NAME: CALCIUM, FRAMINGHAM
MRN: XXXXXXX DOB: XX-XX-XXXX Sex: x

Date: xx-xx-xxx Transport: AMBULATORY (w/ Chart)
Comments:

History: cardiac research study
Participant Name & FHS ID# DOB
This is a research study, please do not read gal26
Requesting MD: [redacted] P/B: [redacted]
Physician: UNKNOWN, UNKNOWN P/B:

EXAM FORM (cont.)

NAME: CALCIUM
Prec/Allergies:

CODE: (MG) CTCDFR/0980WACT
Patient Loc: P Phone: Time: Room:
Insurance Carrier:
Technologist: _____ Time Exam Performed: _____
MIXC 8X10 10X12 11X14 14X7 9X9 14X14 CAMERA
! ! ! ! ! ! !

|||||||||||||||| (Barcode)
XXXXXXXX

Appendix 18: CT Scan Completion Form

The Framingham Heart Study CT Scan Completion Form

Date of Birth: Weight (lbs.): _____
Gender: FHS ID: ___-_____

FHS Staff Certifying Pregnancy Test

Pregnancy Test Negative? Yes / No / Exempt (Circle One)
Pregnancy Test Valid Until: _____

Date of Scan: _____ Tech ID: _____
CT Scanner: _____ Exam Number: _____
Archived Locally: **Y / N (Circle One)**

CT Exam Technical Settings
Kv: 120 □ (confirm)

MA: Set according to weight (circle) **<220 lbs 320mA** **220 lbs or more 400 mA**

	Series #	#Images	FOV
Scout	_____	_____	**NA**
Coronary 1	_____	_____	**35 cm**
Coronary 2	_____	_____	**35 cm**
Scout	_____	_____	**NA**
Abd. Aorta	_____	_____	**35 cm (recon 50)** Scan Comments:

Projected Series DLP	Accumulated Exam DLP	Dose Efficiency	CTDWi
_____	_____	_____	_____

Scan completed: □ Yes, complete □ Yes, partial □ No

If "Yes, partial" or "No" (scan not performed) indicate reason below:
□ Equipment failure (specify: _____)
□ Participant refusal (specify: _____)
□ Participant unable to complete protocol (specify: _____
_____)
□ Participant did not arrive
□ Other (specify: _____)

Please fax to The Framingham Heart Study: [redacted]

Appendix 19: CT Data Tracking Form

(abf heart ct if)

CT_TRACK
INCIDENTAL FINDINGS / 90% CALCIUM SCORES

Name:

Framingham Id: -
Gencacid:

Scan Comp:
Comp Date:
Study Type:

Thank You Letter:
Thank You Date:

Finding: Rad. Init.: Rad. Date:
Finding Comment:

Percent90: Tech Score:
Score Date:

90% Comment:

Finding letter sent:
Finding letter date:

Md Call:
Md Date:
Caller's init:

Comm1:

Call Form:
Form Date:

Dentry:
Keyer:

Mod:

No Scan Comm:

Score Comp:

Read Comp:
Read Date: Qa Comp:
Qa Date: Final Score:
Score Letter:
Part Call: Part Date:

Comm2:

Comm3:

Comm4:

Appendix 20: Health History Form

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

For Office Use Only

TYPE |___| 1=TELEPHONE 2=MAILER 3=ONSITE BONE STUDY 4=ONSITE EBCT 88=OTHER

INTERVIEWER |___|___|___| DATA ENTRY |___|___|___| 1 |___|___|___| 2

ID |__|-|__|__|__|__| DATE OF LAST EXAM OR UPDATE |__|__|-|__|__|-|__|__|

EXAM CYCLE |__|__|

LAST NAME _____ FIRST NAME _____ M.I. ____

Address (if changed since last exam/update) _____

SOCIAL SECURITY NUMBER |__|__|__|-|__|__|-|__|__|__|__|

DATE COMPLETED |___|-|___|-|___|

1. a. First, please tell us who is completing this form:

- ☐ Framingham Heart Study (FHS) participant whose name is above **(Go to question 3)**
- ☐ Spouse
- ☐ Family member other than spouse
  Relationship _____
- ☐ Friend
- ☐ Health care provider for FHS participant → **Go to 1.b.**
- ☐ Other ___ _____
  (Specify)

If other than participant, please answer the following questions.

b. Name _____

c. How long have you known the participant?

|___| years |___| months

d. Are you currently living in the same household with the participant?

☐ yes ☐ no

ID |__|-|__|__|__|__|

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

e. How often did you talk with the participant during the prior 11 months? Check one.

☐ Almost every day

☐ Several times a week

☐ Once a week

☐ 1 to 3 times per month

☐ less than once a month

☐ unknown/N/A

2. Have you noticed that he/she has had any memory problems or change in personality?
☐ yes ☐ no

Specifically: _____

If response to #2 "yes":

Has there been a diagnosis of dementia or Alzheimer's Disease made by a doctor?

☐ yes ☐ no

TO WHOM SHOULD WE SEND A CONSENT FORM TO BE SIGNED SO THAT WE CAN OBTAIN MEDICAL RECORDS?

NAME: _____

ADDRESS: _____

RELATIONSHIP: _____

Please go on to the next page

ID |__|-|__|__|__|__|

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

3. Since the date of the last Framingham Heart Study exam or update on the top of Page 1, have you seen a doctor or been hospitalized?

☐ **Yes** ☐ **No** If yes, did you have any of the following problems?

a. Heart Problems, such as:

Yes	No	(Mark yes or no for each question)
☐	☐	Chest pain, angina or angina pectoris
☐	☐	Heart attack or myocardial infarction or MI
☐	☐	Heart failure or congestive heart failure or CHF
☐	☐	Heart catheterization or cardiac catheterization
☐	☐	Heart bypass operation or coronary bypass surgery or CABG
☐	☐	Procedure to unblock narrowed blood vessels to your heart muscles (PTCA, coronary angioplasty, or coronary stent)
☐	☐	Other heart problem (pacemaker, valve problem, aorta surgery, rhythm problem, atrial fibrillation, ventricular tachycardia). (Specify) _____

b. Circulatory Problems, such as:

Yes	No	(Mark yes or no for each question)
☐	☐	Stroke, TIA (transient ischemic attack), sudden paralysis, vision loss, inability to speak
☐	☐	Procedure to unblock narrowed blood vessels in your neck (carotid endarectomy, carotid angioplasty).
☐	☐	Poor blood circulation or blocked or narrowed blood vessels to the legs or feet, (claudication, peripheral arterial disease, gangrene)
☐	☐	Amputation of part of a leg or toes, because of poor circulation or gangrene.
☐	☐	Blood clot or embolism in leg or lung.
☐	☐	Other circulatory problem (Specify) _____

ID |__|-|__|__|__|__|

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

c. **Other Neurological Problems**

Yes	No	(Mark yes or no for each question)
☐	☐	Memory problems
☐	☐	Other neurological problems such as Parkinson's, multiple sclerosis, seizures, head injury Specify problem _____
☐	☐	Have you had an MRI scan of your head other than for the Framingham Heart Study? Name of MRI Facility: _____ Date of MRI: _____

d. **Other Problems**

Yes	No	(Mark yes or no for each question)
☐	☐	Cancer (Specify type) _____ Physician _____ Place where biopsy performed _____ _____ _____
☐	☐	Fracture, broken bone (Specify including hip, back, arm, leg, pelvis, collarbone, foot, toe and others) _____
☐	☐	Other (Specify problem) _____

Please go on to the next page

ID |__|-|__|__|__|__|

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

4. Since the date of your last Framingham Heart Study exam or update on the top of page 1, have you been admitted to a **HOSPITAL** or gone to an **EMERGENCY ROOM** or seen a **PHYSICIAN** for other than a routine examination?

☐ yes (if yes, please give details) ☐ no (go to question 5 on the next page)

Date |__|__|-|__|__|-|__|__|

Type* _____

Reason** _____

Hospital Name _____ Doctor's Name _____

Address _____ Address _____

_____

Date |__|__|-|__|__|-|__|__|

Type* _____

Reason** _____

Hospital Name _____ Doctor's Name _____

Address _____ Address _____

_____

Date |__|__|-|__|__|-|__|__|

Type* _____

Reason** _____

Hospital Name _____ Doctor's Name _____

Address _____ Address _____

_____

*Type

1. Overnight admission
2. Emergency room visit
3. Day Surgery/Procedure
4. M.D. visit

** Reason

1. Heart problems
2. Stroke or transient ischemic attack (TIA), sudden paralysis, vision loss, inability to speak
3. Broken, crushed or fractured bones
4. Cancer or malignant tumor
5. Circulation problem, or blood clots
6. Other reasons (Please specify)

FHS Update Version 5: 12/18/02

OMB No: 0925-0216

ID |__|-|__|__|__|__|

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

Nursing Home/Rehabilitation Admissions.

5. Have you stayed overnight as a patient in a nursing home, rehabilitation center or transitional care unit (TCU) since the date of your last Framingham Heart Study exam or update on the top of page 1?

☐ yes ☐ no If no, go to Question 8.

6. Please list the name and location of the nursing home or rehabilitation center and the date you were admitted.

Nursing home/Rehab Center/TCU name: _____

Street address: _____

City/State/Zip Code _____

Date you entered the nursing home/rehabilitation center |__ __|-|__ __|-|__ __ __ __|
Month Day Year

7. Were you an overnight patient in a nursing home, rehabilitation center or transitional care unit (TCU) at any **other** time since your last exam?

☐ yes ☐ no

Nursing home/Rehab Center/TCU name: _____

Street address: _____

City/State/Zip Code _____

Date you entered the nursing home/rehabilitation center |__ __|-|__ __|-|__ __ __ __|
Month Day Year

Marital Status.

8. What is your **current** marital status? Check one

☐ married ☐ widowed ☐ divorced

☐ separated ☐ single, never married

ID |__|-|__|__|__|__|

FRAMINGHAM STUDY MEDICAL HISTORY UPDATE

Health Status. (Questions 9 and 10 to be filled out only by the participant.)

9. In general, how is your health now:

☐ excellent ☐ fair

☐ poor ☐ good

☐ don't know

10. Compare your health to most people your own age. Would you say your health is:

☐ better ☐ worse than most people

☐ about the same ☐ don't know

Primary Care Physician

11. Please list the name and address of your primary care physician.

Name _____

Address _____

_____

YOU MIGHT BE SENT A CONSENT FORM TO SIGN SO THAT WE MAY OBTAIN YOUR MEDICAL RECORDS.

Appendix 21: Standardized Breath Holding Instructions

Breathing Instructions

Standardized Script for breathing instructions:

a) For Heart Scans:

"Take a deep breath in… <5 sec. pause>

"Blow it all the way out… <5 sec. pause>

"Take a deep breath in… <5 sec. pause>

"Blow it all the way out… <5 sec. pause>

"Take a deep breath in and hold your breath...

<15-40 scan acquisition>

"Breath and relax"

Though total imaging time is approximately 30 to 40 seconds, performing the repeated measure of the heart (Heart 2) requires about 5 to 7 minutes to complete. The technologist first acquires one entire series of image slices. The technologist instructs the subject to relax on the table while he/she reconstructs and assesses the adequacy of positioning, ECG gating and lack of respiratory motion. There is a 45 to 60 second recovery period for the participants in between the repeated scan series of the heart.

b) For Abdominal Scans:

"Breathe in, hold your breath…"

<15-25 sec scan acquisition>

"Breathe."

Heart 2 CT Scan Series

The procedures for the heart 2 CT scan series are identical to heart 1. Prior to performing this series the technologist reviews the images of Heart 1 CT scan series during the participant's 2-minute recovery period. If these are acceptable as to participant positioning and scan coverage, the technologist immediately

acquires another series of image slices while the subject remains immobile and in an identical position. If adjustments to the prescription are needed, these are made on the Heart 2 scan series. *A repeat of Heart 1 CT series is not required and should not be performed. If an unrecoverable error is made (i.e. cannot be fixed through a retrospective reconstruction) the study relies on one measurement of coronary calcium to reduce participant radiation exposure.*

Appendix 22: Thank you Letter, No Abnormalities Noted

Date

Mr. John Smith

XXXXXXXX

Framingham, MA 01702

Dear Mr. Smith:

Thank you for taking part in the CT scan examination at MGH West in Waltham, Ma.
This study would not be possible if it were not for your willingness to participate. Your involvement has taken us one step closer to finding answers regarding cardiovascular health.

Your coronary calcium score did not indicate any significant findings. This CT scan is designed for research purposes only, and as such, it may not detect clinically important abnormalities. Therefore, this scan should not be used instead of a clinical CT scan.

If you have any questions regarding this study, please do not hesitate to contact [redacted]

Sincerely,

[redacted]

Director, CT Study
Framingham Heart Study

Appendix 23: Thank You Letter, High Calcium Score Noted

Date

Mr. John Smith

XXXXXXXX

Framingham, MA 01702

Dear Mr. Smith:

Thank you for taking part in the CT scan examination at MGH West in Waltham, Ma.

We are sending the report of your CT scan to your physician. This CT scan is designed for research purposes only and is not as complete as a scan used for medical diagnosis. Therefore, this scan should not be used in place of a clinical CT scan. Because the Framingham Heart Study does not provide any clinical diagnosis or treatment, we recommend that you follow-up with your physician regarding the results of this report.

Again, thank-you for your participation. This study would not be possible if it were not for your willingness to participate. Your involvement has taken us one step closer to finding answers regarding cardiovascular health.

If you have any questions regarding this study, please do not hesitate to contact [redacted]

Sincerely,

[redacted]

Director, CT Study
Framingham Heart Study

Appendix 24: Thank You Letter, Incidental Finding Noted

Date

Mr. John Smith
XXXXXXXX
Framingham, MA 01702

Dear Mr. Smith:

Thank you for taking part in the CT scan examination at MGH West in Waltham, Ma.

A radiologist has reviewed your scan and has encountered a finding that may be important to you and your physician. We are sending the report of your CT scan to your physician. This CT scan is designed for research purposes only and is not as complete as a scan used for medical diagnosis. Therefore, this scan should not be used in place of a clinical CT scan. Because the Framingham Heart Study does not provide any clinical diagnosis or treatment, we recommend that you follow-up with your physician regarding the results of this report.

Again, thank-you for your participation. This study would not be possible if it were not for your willingness to participate. Your involvement has taken us one step closer to finding answers regarding cardiovascular health.

If you have any questions regarding this study, please do not hesitate to contact [redacted]

Sincerely,

[redacted]

Director, CT Study
Framingham Heart Study

Appendix 25: Letter to Physician

February 27, 2003

John Doe, M.D.
73 Mt. Wayte Avenue
Framingham, MA 01701

Dear Dr. Doe:

Jane Doe, a patient of yours, is a participant at the Framingham Heart Study and recently underwent a test to screen for coronary calcium using a MultiDetector (spiral) Computed Tomography (CT) scanner at Massachusetts General Hospital West, Waltham, MA. This test was performed as part of a research study. Limited scans of the chest and abdomen were obtained. This letter is being sent to notify you of the coronary calcium score and of any clinically important incidental findings.

Your patient has an Agatston coronary calcium score of 51. Compared to available age and sex-adjusted distribution of coronary calcium, this score is considered:

[ ] High (greater than 90th percentile)
[X] Not High (less than 90th percentile)

A high calcium score might be helpful in determining whether a patient is at an increased risk for coronary heart disease; conversely, a low calcium score might be helpful in determining whether a patient is a low risk for coronary heart disease. However, there is currently lack of consensus regarding the utility of the coronary calcium score, and it is not known whether the calcium score adds to the information provided by other measurements such as cholesterol and blood pressure in predicting future heart disease risk. More information regarding the most recent consensus guidelines for the use of this test can be found at: http://www.acc.org/clinical/consensus/electron/dirIndex.htm.

In the event that potentially important incidental findings were subsequently identified during a partial review of the CT scan, a report will be enclosed describing these findings.

Report Enclosed: [NO:] **[YES: X]** if yes, please review the enclosed report

The Framingham Heart Study is designed exclusively for epidemiologic research. However, we routinely send letters to a participant's physician if he/she has a high calcium score or an important incidental finding, or if the participant requests that the results be sent. If you have any questions about this test, please direct inquiries to me via our CT Study Coordinator, [redacted]. We greatly appreciate your support of the Framingham Heart Study.

Sincerely,

[redacted]
Director, CT Study
Framingham Heart Study

Cc: [redacted]
Massachusetts General Hospital

Appendix 26: Incidental Findings Report for study subjects undergoing coronary and aortic calcium scoring for the Framingham Heart Study, GENCAC Study

Scan Date	Fram	Id	Gencac Id	DOB
7/31/2002	1	xxx		11/17/1940

	YES	NO
Pulmonary nodules of indeterminate or suspicious morphology		X
Cardiac or paracardiac masses, pericardial effusion		X
Aneurysms of the thoracic or abdominal aorta > 4cm		X
Indeterminate or suspicious abdominal masses (renal, liver, etc.)	X	
Large left renal cyst, 7.6 x 6.4 cm, that look uncomplicated		
Indeterminate or suspicious bone lesions		X

Please note that this CT scan was conducted for research purposes only in order to identify and quantify calcium deposits in the coronary arteries and the abdominal aorta. Because of limited coverage of the chest and the abdomen clinically important findings may not be identified on this scan.

Study Contact for Emergencies
Framingham Heart Study
[redacted]

[redacted]
Radiologist

(Signature)

Incidental Findings Report for study subjects undergoing coronary and aortic calcium scoring for the Framingham Heart and GENCAC Study

Scan Date	Study ID number	DOB

This CT scan was conducted for research purposes only in order to identify and quantify calcium deposits in the coronary arteries and the abdominal aorta. Because of the specific technique, limited coverage of parts of the thorax and abdomen, and blinding of the interpreting radiologist to the patient history and other imaging studies, clinically important incidental findings may not be identified on this scan.

The following potentially significant incidental findings were identified:

Radiologist

1

Framingham Heart/GENCAC Study Contacts [redacted]

Appendix 27: Coronary Calcium Score Percentiles

	Age (years)								
	<40	40-44	45-49	50-54	55-59	60-64	65-69	70-74	>74
Men									
25th Percentile	0	0	0	1	4	13	32	64	166
50th Percentile	1	1	3	15	48	113	180	310	473
75th Percentile	3	9	36	103	215	410	566	892	1071
90th Percentile	14	59	154	332	554	994	1299	1774	1982
Women									
25th Percentile	0	0	0	0	0	0	1	3	9
50th Percentile	0	0	0	0	1	3	24	52	75
75th Percentile	1	1	2	5	23	57	145	210	241
90th Percentile	3	4	22	55	121	193	410	631	709

Age and Gender Distributions of Coronary Artery Calcium Detected by Electron Beam Tomography in 35,246 Adults

Julie Anne Hoff, PhD, RN, Eva V. Chomka, MD, Andrew J. Krainik, MPH, Martha Daviglus, MD, PhD, Stuart Rich, MD, and George T. Kondos, MD

Electron beam tomography (EBT) is a noninvasive method used to detect coronary artery calcium (CAC). Due to the age-associated increase in incidence and magnitude of CAC, interpretation of results can be difficult. The purpose of this study was to develop a set of age- and gender-stratified CAC distributions to serve as standards for the clinical interpretation of EBT scans. Between 1993 and 1999, 35,246 asymptomatic subjects, 30 to 90 years of age, were self-referred for CAC screening using an Imatron EBT scanner. CAC score was calculated based on the number, areas, and peak computed tomographic density for each detected calcific lesion. CAC score in each coronary artery was equal to the sum of all lesions for that artery and the total CAC score was equal to the sum of the score of each artery. Total CAC scores were assigned to a percentile according to age and gender. CAC scores were reported at the 10th, 25th, 50th, 75th, and 90th percentiles for 16 age and/or gender groups. The prevalence of CAC increased with age for men and women. The extent of CAC differed significantly between men and women in the same age group. In summary, this study reports the distribution of CAC score by age and gender. Knowledge of the distribution of CAC, the effect of age on the total CAC score as well as the differences in total CAC scores that exist between men and women of similar age will assist the clinician in interpreting EBT CAC results. ©2001 by Excerpta Medica, Inc.

(Am J Cardiol 2001;87:1335–1339)

Electron beam tomography (EBT) is a sensitive, noninvasive method for quantifying coronary artery calcium (CAC).[1–4] A positive EBT scan confirms the presence of coronary atherosclerotic plaque.[5,6] Among men and women, the prevalence of CAC increases with age.[7] The amount of CAC correlates with both the extent and severity of angiographically documented coronary artery disease (CAD).[6,8] It has also been demonstrated that the amount of CAC detected by EBT correlates with histologic plaque volume.[9,10] Other studies have shown that the total CAC score can predict an increased risk of subsequent cardiovascular events in patients with and without CAD symptoms.[11–14] The extent of CAC is affected by age, gender, and traditional CAD risk factors.[15,16] One of the limitations of utilizing EBT technology in CAD risk factor assessment is the absence of a set of CAC distributions that represent the general population by age and gender.[17] The objective of this study is to report age- and gender-stratified CAC distributions in a healthy, asymptomatic cohort of 35,246 self-referred adults to serve as guidelines for the clinical interpretation of EBT scans.

METHODS

Study subjects: Between January 1993 and September 1999, 41,021 subjects, ages 30 to 90 years, underwent EBT CAC screening. Subjects who reported (≥1 of the following conditions) medical history of angina, coronary angiography, catheter-based intervention, coronary artery bypass surgery, and/or myocardial infarction were not included in this analysis (n = 5,775). Thus, the study sample consisted of 25,251 men and 9,995 women who were free of known CAD at the time of CAC screening.

CAC screening was performed at either the University of Illinois at Chicago (UIC) Medical Center or the UIC Physicians Group in Arlington Heights, Illinois. Immediately before undergoing EBT screening, all subjects were asked to complete a questionnaire that solicited information regarding demographics, CAD risk factors, and medical history. CAD risk factors included history of smoking, family history of CAD, history of diabetes, hypercholesterolemia, and hypertension. History of smoking was defined as either past or current use of cigarettes. A family history of CAD was defined as a history of myocardial infarction in a parent, grandparent, or sibling at <65 years of age. Subjects reporting a history of physician-diagnosed diabetes or the use of hypoglycemic medications were considered diabetic. Patients reporting a total cholesterol level >200 mg/dl or the use of medications to lower cholesterol were considered hyper-

From the Department of Medicine, Section of Cardiology, University of Illinois at Chicago College of Medicine, Department of Preventive Medicine, Northwestern University Medical School, and Rush Heart Institute, Chicago, Illinois. This study was supported with internal funding from the Department of Medicine, Section of Cardiology, University of Illinois, Chicago, Illinois. Manuscript received and accepted November 24, 2000; revised manuscript received January 16, 2001.

Address for reprints: George T. Kondos, MD, Department of Medicine, Section of Cardiology, 840 South Wood Street (m/c 787), Chicago, Illinois 60612. E-mail: gkondos@uic.edu.

cholesterolemic. Patients reporting a history of physician-diagnosed high blood pressure or the use of medication to lower blood pressure were classified as hypertensive. To assess the cardiovascular health status of the study sample, the prevalence of cigarette use, diabetes, hypercholesterolemia, and hypertension was compared with the prevalence rates reported for the general population. The UIC Internal Review Board approved the study protocol as well as the questionnaires used to obtain data for this study.

Electron beam tomographic imaging procedures: The EBT scanning procedure was performed with an Imatron scanner (Imatron, South San Francisco, California). Up to 40 transaxial 3-mm thick slices were obtained during 1 to 2 breath holding sequences to cover the entire coronary tree. The acquisition time for each slice was 100 ms and the electrocardiogram was gated to diastole. To ensure identification of CAC in the proximal coronary arteries, an overlap scan consisting of an additional set of 20 images starting at the base of the heart was obtained in the same manner. Images were reconstructed to a 512 × 512 matrix with a 26-cm field-of-view, using sharp kernel.

EBT software allowed quantification of calcium area and density.[18] A calcified plaque was considered present if ≥3 adjacent pixels with a signal density of ≥130 Hounsfield units were identified. An attenuation factor for each lesion was determined by peak density. The calcium score for each lesion is the product of the attenuation factor multiplied by the area of the lesion in square millimeters. The total CAC score reported is the sum of all the lesions scored within the left main, left anterior descending, left circumflex, and right coronary arteries. The overlap scan of the proximal coronary arteries was then scored using the same protocol. On an artery by artery basis, the higher of the 2 scores was used to calculate the total CAC score. Reproducibility of the CAC results is considered moderate to excellent depending on the EBT screening laboratory (technician and/or physician experience) and the magnitude of calcium present.[19] In this study, all EBT CAC screening studies were performed and analyzed by 1 of 2 experienced technicians.

Percentile rank: To determine the percentile rank for men and women, the sample was divided by gender and then into 9 exclusive age groups (<40, 40 to 44, 45 to 49, 50 to 54, 55 to 59, 60 to 64, 65 to 69, 70 to 74, and >74 years old). The number of subjects in each age group ranged from 235 to 4,940 among men and 174 to 2,184 among women. Independent sample *t* tests and multiple pair-wise nonparametric tests were used to compare the sex and/or age strata. Percentiles and statistics were determined using SPSS 9.0 for Windows (SPSS, Inc., Chicago, Illinois).

RESULTS

Sample characteristics: The study sample consisted primarily of white (80%) men and women who were 30 to 90 years of age. All subjects were self-referred for the CAC screening procedure. Demographic characteristics are summarized in Table 1. Education and income levels in our population were higher compared with national averages reported for the United States population.[20]

TABLE 1 Baseline Demographic Characteristics of Men and Women Who Underwent Electron Beam Tomographic Coronary Artery Calcium Screening

Characteristics	Men (n = 25,251)	Women (n = 9,995)
Mean age (yrs)	50 ± 10	54 ± 10
Education >12 yrs	98%	96%
Annual household income >$50,000	79%	64%

CAD risk factors, including age, smoking, CAD in other family members, history of hypercholesterolemia, diabetes mellitus, systemic hypertension, and body mass index (>30 kg/m^2), were elicited by a self-administered questionnaire. The prevalence of CAD risk factors in our study sample were compared with CAD risk factors reported for the US population and are listed in Table 2. With the exception of hypercholesterolemia, the UIC sample had a lower prevalence of all CAD risk factors compared with those subjects from the National Health and Nutrition Survey (NHANES)[21] as well as the Atherosclerosis Risk in Communities (ARIC) study.[22] Hypercholesterolemia was more prevalent among the UIC sample participants compared with the ARIC study participants.

Coronary artery calcium distribution in asymptomatic men and women: CAC is not normally distributed and the amount of calcium varies greatly among subjects of similar ages. Table 3 provides the mean, SD, and median scores observed in this study for each age strata of men and women. For men and women, higher average and median total CAC scores were associated with increasing age. Table 4 provides the sample size and the percentile cut-point of the total CAC scores for the 10th, 25th, 50th, 75th, and 90th percentiles in men and women, respectively. The total CAC score in all percentiles increased with age.

Results of multiple pair-wise nonparametric tests (data not shown) show that most of the median total CAC scores in each of the male strata were significantly different from the corresponding female age strata. The p values were >0.05 when comparing men <40 years versus women 50 to 54 years (p = 0.82); men 40 to 44 years versus women 55 to 59 years (p = 0.47); men 45 to 49 versus women 60 to 64 (p = 0.35); men 50 to 54 versus women 65 to 69 (p = 0.25); and men 55 to 59 versus women 70 to 74 years (p = 0.82).

DISCUSSION

A major impediment to the use of EBT screening is the unavailability of a set of population-based standards against which scans can be compared.[17] The use of large databases of patients screened by EBT allows for the construction of tables of age–sex percentiles. The percentiles reported rank subjects against matched populations, suggesting an "anatomic age"

TABLE 2 Coronary Artery Disease (CAD) Risk Factors in the US Population Compared With Men and Women Who Underwent Electron Beam Tomographic Coronary Artery Calcium Screening

Risk Factors	UIC (n = 35,246)	NHANES (n = 1,838 of 14,407)	ARIC (n = 15,800)
Age (yrs) (mean)	51	66	54
Smoking (ever/current) (%)	53/15	70/34	55/27
CAD in other family members (%)	62	n/a	n/a
Hypercholesterolemia (history) (%)	36	37	19
Diabetes mellitus (history) (%)	3	7	3
Systemic hypertension (history)	20	24	33
Body mass index (>30 kg/m^2)	24	25	28

for their coronary arteries. An age–sex nomogram would be useful in classifying subjects based on the extent of their atherosclerotic disease compared with the expected norm in the population.[23]

The total CAC score follows a nonuniform distribution and varies with age and gender. To our knowledge this is the first study to report the distribution of CAC as a function of age and gender in a very large sample of 35,246 subjects. Previously, 2 studies have reported CAC prevalence. The first study reported the prevalence and extent of CAC in 1,396 men and 502 women, aged 14 to 88 years, who underwent EBT imaging at Mount Sinai Medical Center, Miami Beach, Florida.[24] The source of subjects for this study were physician referred, self-referred, or followed in an industrial medicine clinic. All study subjects were considered asymptomatic for CAD. The second study reported age- and sex-adjusted CAC scores for 5,433 men and 4,297 women, aged 35 to 70 years, who underwent EBT imaging at the EBT Research Foundation, Nashville, Tennessee.[25] The prevalence of CAD risk factors, the referral source for the study subjects, and the CAD disease status was not reported. The distribution of total CAC scores was compared for men and women using 5-year age groups.

The prevalence of CAC reported in these 2 studies compares favorably to one another as well as to the present study when examining the percentile cut-points for the different age and gender strata. To illustrate this observation, we compared the data reported by Callister and Raggi[23] to the data reported in this study along the 75th percentile. The differences in the total CAC scores set as the 75th percentile cut-point increased with age and ranged from 2 to 28 among men and 1 to 30 for women.

One limitation of this study is the reliance on data obtained from self-referred subjects. Volunteers for clinical research are believed to represent the extremes of the population: the most healthy and those that self-refer for personal reasons.[2] Nevertheless, the sample used in this study compared closely to the general population relative to the prevalence of CAD risk factors. Therefore, the potential bias due to the nonrandom method of sample selection might have only minimal adverse effects on the validity of these results and can be applied to the United States population.

A second limitation is that the education and income levels (indicators of socioeconomic status) of the subjects described in this sample are above the national average.[19] Thus, the subjects in this sample might be different in terms of their use of preventive health care, screening procedures, and other preventive measures compared with the general population. The forthcoming National Institutes of Health/National Heart, Lung, and Blood Institute Multiethnic Study of Atherosclerosis (MESA) will evaluate the use of EBT in a multiethnic, population-based cohort of asymptomatic subjects representing all socioeconomic strata. However, data from this study regarding the prevalence of CAC as measured by EBT will not be available for at least 4 to 5 years.

A third limitation of this study pertains to the applicability of the CAC data presented relative to other technologies that may be used to detect CAC. Because the Imatron Electron Beam Computed Tomographic Scanner was the only technology employed to detect CAC in this study, extrapolation of this data to CAC studies performed with other technologies, such as a helical or spiral computed tomographic scanner, may not be appropriate.

These results demonstrate age- and gender-related CAC values as determined by EBT-CAC screening. It was uncommon for men <40 years of age and women <50 years of age to have EBT-detected CAC. Total CAC scores were higher in men than in women across all age groups. Men consistently demonstrated CAC scores equal to women who were 15 years older, suggesting that subclinical CAD is detected earlier in men compared with women.

Previous studies have assigned a threshold value of 400 as the cut-point for high risk for obstructive CAD,[25,26] yet in this study we have found that such scores are very rare in men <60 years old and almost nonexistent in women <65 years old. Among symptomatic subjects who underwent angiography for clinical indications, Rumberger et al[26] reported a total EBT CAC threshold score of 371 that was associated with ≥70% angiographic luminal stenosis in ≥1 coronary artery. In screening for a disease as prevalent as CAD, such stringent criteria for a positive scan may not be appropriate when screening asymptomatic individuals.

The percentile rank stratifies individual total CAC scores, allowing flexible thresholds to be set that account for the independent effects of age and gender. The percentile rank is particularly useful among younger individuals with low scores who would otherwise be overlooked on the basis of total CAC score. Conventional CAD risk factors fail to predict <½ of future cardiovascular events[27,28]; the percentile rank as opposed to the total CAC score may provide a better indication of CAD risk in asymptomatic men and women when combined with the Framingham

TABLE 3 Descriptive Characteristics of the Total Electron Beam Tomographic Coronary Artery Calcium Scores in Asymptomatic Men and Women

	Men				Women			
		Total CAC Score				Total CAC Score		
Age (yrs)	n	Mean	SD	Median	n	Mean	SD	Median
<40	3,504	12	70	0.5	641	2	14	0
40–44	4,238	27	120	1	1,024	8	97	0
45–49	4,940	57	175	3	1,634	18	186	0
50–54	4,825	121	305	16	2,184	29	135	0.5
55–59	3,472	203	411	49	1,835	54	189	1
60–64	2,288	350	972	113	1,334	78	250	3
65–69	1,209	464	731	180	731	142	338	24
70–74	540	665	921	309	438	225	515	53
>74	235	836	1053	473	174	258	507	75

TABLE 4 Electron Beam Tomographic Coronary Artery Calcium Score Percentiles for Men and Women Within Each Age Strata

	Age (yrs)								
	<40	40–44	45–49	50–54	55–59	60–64	65–69	70–74	>74
Men (25,251)	3,504	4,238	4,940	4,825	3,472	2,288	1,209	540	235
25th percentile	0	0	0	1	4	13	32	64	166
50th percentile	1	1	3	15	48	113	180	310	473
75th percentile	3	9	36	109	215	410	566	892	1,071
90th percentile	14	59	154	332	554	994	1,299	1,774	1,982
Women (9,995)	641	1,024	1,634	2,184	1,835	1,334	731	438	174
25th percentile	0	0	0	0	0	0	1	3	9
50th percentile	0	0	0	0	1	3	24	52	75
75th percentile	1	1	2	5	23	57	145	210	241
90th percentile	3	4	22	55	121	193	410	631	709

Risk Score. Preliminary follow-up data on this population for cardiovascular events suggest that the 75th percentile is a very sensitive cut-point for identifying subjects at greatest risk. Thus, the age- and gender-stratified CAC distributions we report in conjunction with published clinical guidelines should improve the interpretation and application of EBT CAC screening results in clinical practice.

Acknowledgment: We are indebted to Bruce Friedman, MBA, Daniel B. Garside, MS, Vladimir Jelnin, MD, Alex Sevrukov, MD, and Shu-Pi Chen, PhD, for their assistance in the preparation of this manuscript.

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Appendix 28: MGH West Directions

Mass General West Imaging

40 Second Avenue

The PARC Center

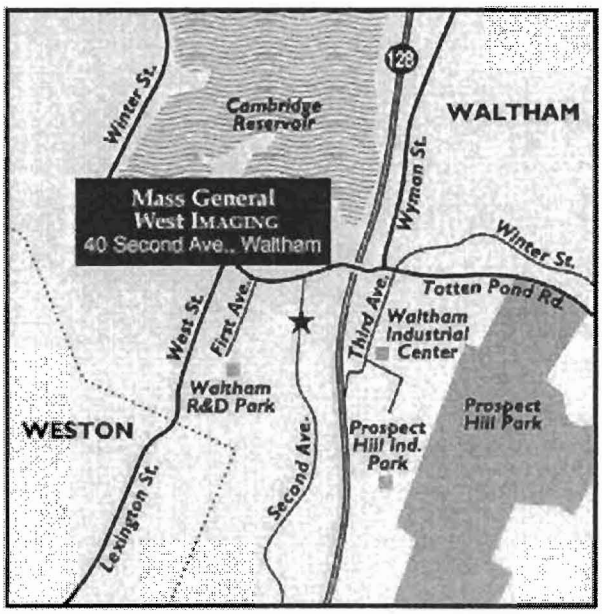
Suite 120 (CT/MRI Services)

Waltham, MA 02451

Exit 27B off Route 95/128

Telephone: 800-697-8296

Directions



From Mass Pike West (From Boston):
Take Exit 15 and follow instructions below for Route 95/128 Northbound.

From Mass Pike East (From Framingham / Natick):
Take Exit 14 and follow instructions below for Route 95/128 Northbound.

From Route 93 North or South:
Take the Route 95/128 south exit and take Exit 27B – Winter Street

From the parking lot:

From Route 95/128 Northbound:

Take Exit 27B (Winter St. Waltham) passing the brick and white P.A.R.C. Building on the left of the highway. Bear right off the exit, then right over the highway. Stay in the middle lane. Proceed straight through the first lights. Bear left (from the middle lane) at the sign: Second Ave/Bear Hill Road. The DoubleTree Hotel should now be on your right. Stay in the right lane and follow the signs that state: Second Ave/Bear Hill Rd. Turn right and then left into the parking garage of the P.A.R.C. Building.

From Route 95/128 Southbound:

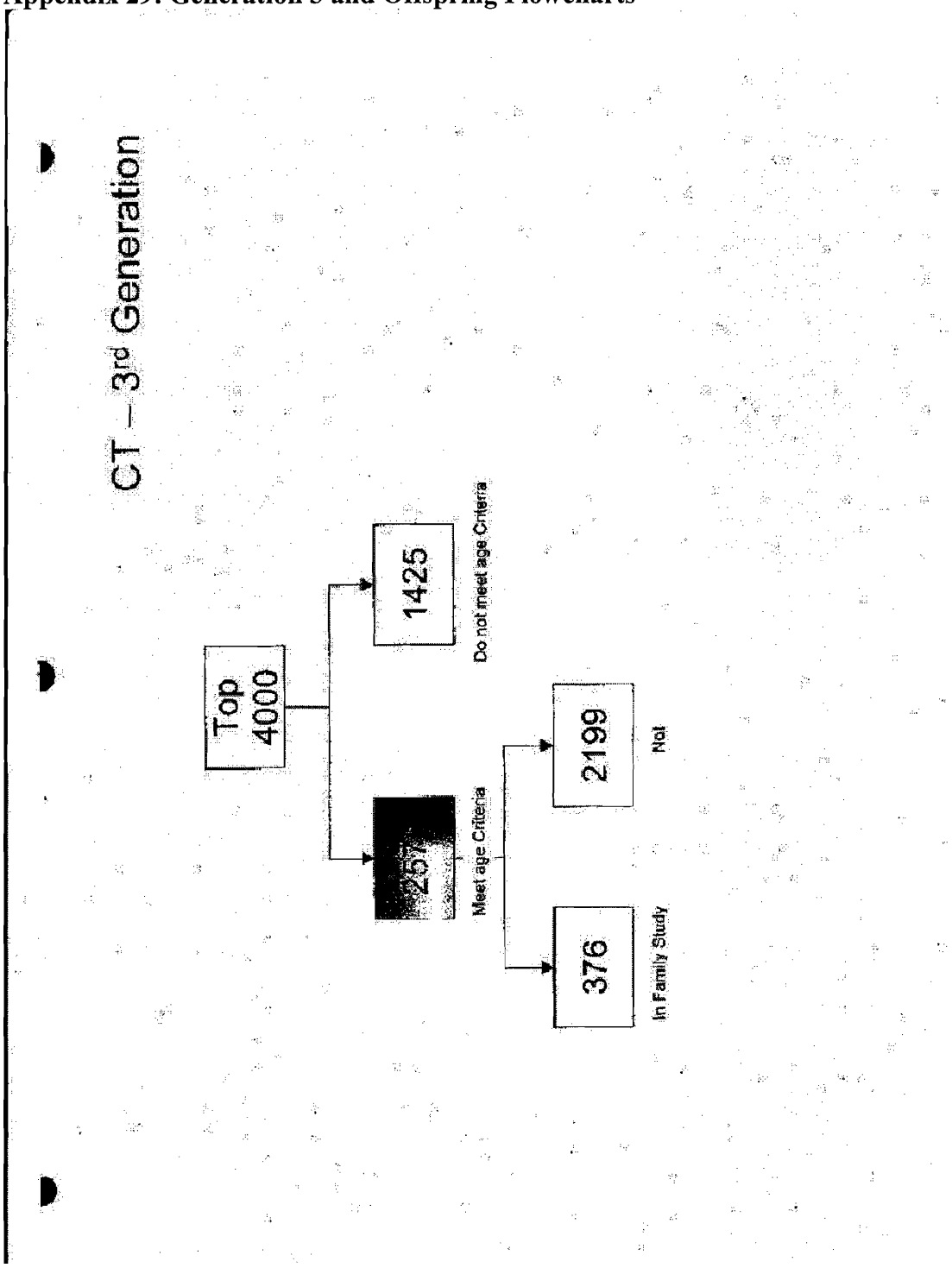
Take Exit 27B (Winter St. Waltham) and bear right off the exit. Get into the middle lane. Proceed straight through the first lights. Bear left at the sign: Second Ave/Bear Hill Road. The DoubleTree Hotel should now be on your right. Stay in the right lane and follow the signs that state: Second Ave/ Bear Hill Rd. Turn right and then left into the parking lot of the P.A.R.C. Building.

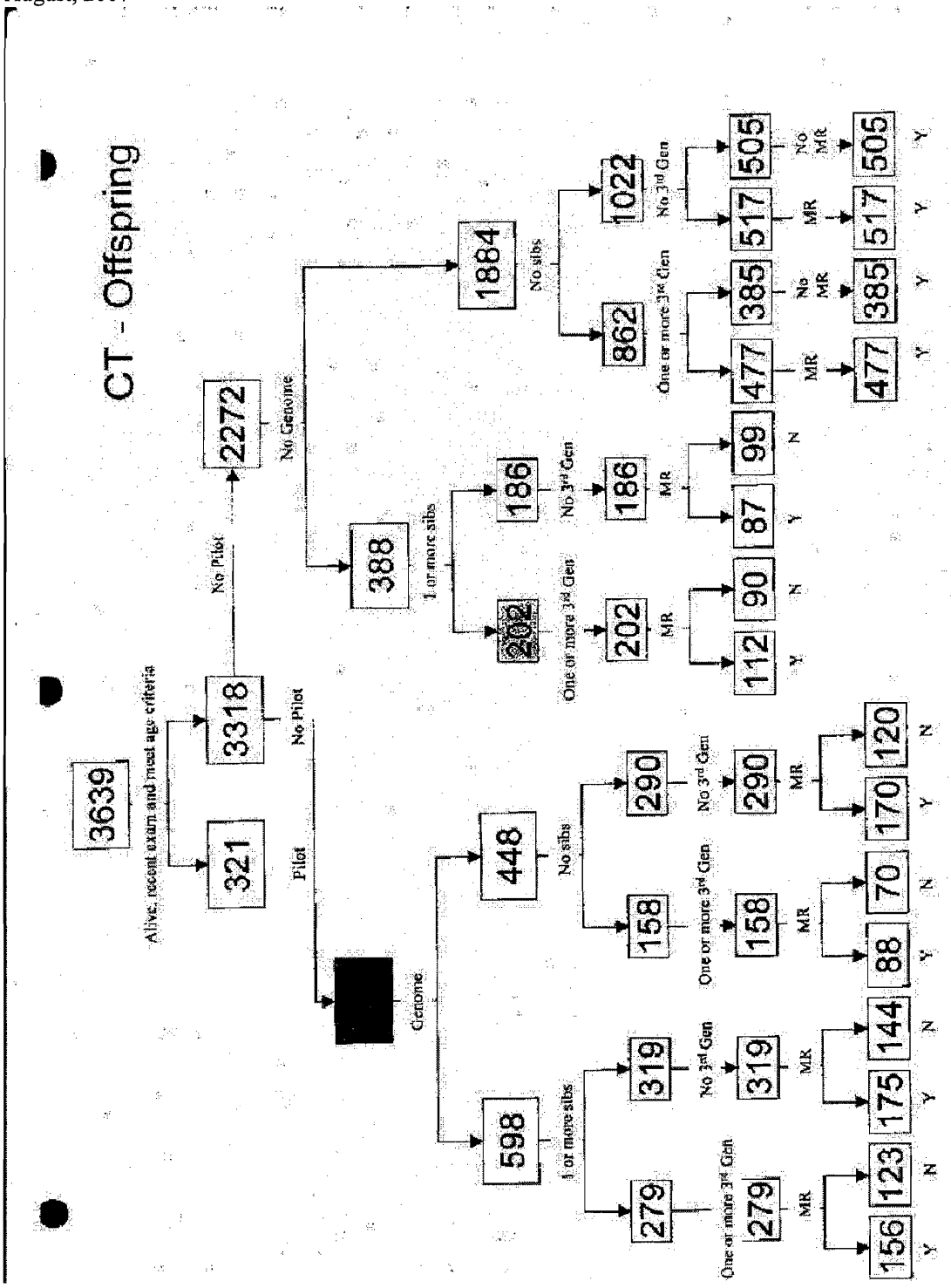
Take the elevator to Floor 1. Make a left out of the elevator and go through the glass door (to Suite 120). Make an immediate right (do not go outside!) and enter the Imaging Center. Please check in with the receptionist.

From the Handicap Drop-off:

Go in the glass door and immediately turn left (do not go through the second glass door). Enter the Imaging Center. Please check in with the receptionist.

Appendix 29: Generation 3 and Offspring Flowcharts




CT - Offspring
3639
Alive, recent exam and meet age criteria
321
3318
No Pilot
2272
Pilot
No Pilot
Genome
No Genome
598
448
388
1884
1 or more sibs
No sibs
279
319
158
290
202
186
862
1022
One or more 3rd Gen
No 3rd Gen
MR
156
123
175
144
88
70
170
120
112
90
87
99
202
186
477
385
517
505
Y
N

Appendix 30: Frequently Asked Questions

The Framingham Heart Study
73 Mount Wayte Avenue
Framingham, MA 01702

Coronary Calcium Testing
Frequently Asked Questions
Version 1.0

Coronary Calcium and Other Findings on Your Computed Tomography (CT) Scan
Frequently Asked Questions

My doctor and I were informed that I have a "high calcium score." What does that mean and should I be concerned?
The CT scan is being conducted to help us determine whether a high calcium score could be a "risk factor" for heart attacks and other heart diseases. If you have a high calcium score, it is currently unclear whether any additional measures should be undertaken beyond the usual treatment of high cholesterol, high blood pressure, and other heart disease risk factors. For example, the American Heart Association and the American College of Cardiology most recent guidelines did not recommend CT scanning for calcium in otherwise healthy persons. We have provided the score because some primary care physicians and/or participants want to know this information as a basis for further testing or further treatment to prevent heart disease.

Why was my scan reviewed for additional "incidental" findings?
Your CT Scan was performed to identify and measure calcium deposits in the heart arteries and the aorta. However, after the CT Scan Study began, several scientific papers were published describing additional findings with possible medical importance that were seen on patient CT scans measuring calcium in the arteries. Since January 2003 the Massachusetts General Hospital radiologists affiliated with the MGH West Imaging Center began reviewing CT scans for the presence of additional, possibly important, findings.

If my scan does not have an additional finding, does this mean I am completely healthy?
The CT scan and Framingham Heart Study examinations are not meant to replace regular check-ups with your physician. Your research CT scan was not designed to diagnose all possible additional findings or health problems in the chest and abdomen. Therefore, while it may be reassuring when no additional findings are detected, you should still consult your physician about medical care.

How likely is it that my scan will have an additional "incidental" finding?
The large majority of scans will not have an additional finding. About 15-20% of scans will have an additional finding.

If my scan has an additional "incidental" finding, should I be concerned?
Most of the additional findings will not require further testing or treatment as they are not significant. Therefore, for most of the findings there is no reason for concern. In some cases, you and your doctor may already be aware of them. It is possible that some of these additional findings might be medically important and will require more definitive testing. For example, in a few subjects we have found a very enlarged aorta or a "spot on the lung." Because your physician knows your entire medical history, he/she is in the best position to decide whether further testing is necessary.

If I receive a report of an additional "incidental" finding, who should I contact?
Contact your primary care physician, to whom we have sent the report. If you have any questions regarding the study, please do not hesitate to call [redacted]

Appendix 31: Presentation to the FHS OSMB on reproducibility and progress

Slide 1

Framingham Heart Study Cardiac CT Study

Report to the Framingham Heart Study OSMB

December 12, 2003

Slide 2

OSMB 2002 Recommendation #2. *"The Board discussed concerns regarding radiation exposure from the CT scans... The Board reminded program staff and investigators to consult them in the future when protocol changes potentially involving participant safety are being considered."*

- There have been no protocol changes involving changes in the scanning protocol.
- There have been no protocol violations.
- Inadvertent exposure of a pregnant participant has led to a number of additional pregnancy screening measures.
- A proportion of the radiation exposure results from the conduct of two coronary scans rather than one, a scanning protocol designed to address the considerable scan-scan variability that has been documented in a number of other studies. The study investigators plan to conduct an interim analysis to examine the extent of interscan variability using calcium scoring data collected to date.

Slide 3

FHS Cardiac CT Study

- Recruitment and scanning
- Calcium scoring
- Coronary calcium reproducibility
- Incidental finding reporting
- Pregnancy screening measures

Slide 4

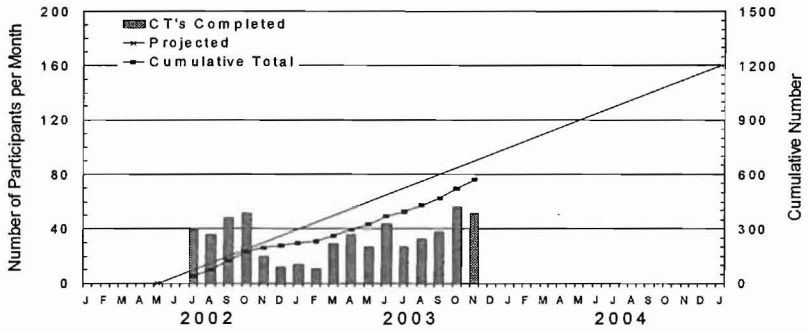
FHS Cardiac CT Study

- Recruitment and scanning
- Calcium scoring
- Coronary calcium reproducibility
- Incidental finding reporting
- Pregnancy screening measures

Slide 5

Number of Participants, Offspring Cardiac CT

(Not Including CT's Done on Offspring by Family Heart Study)



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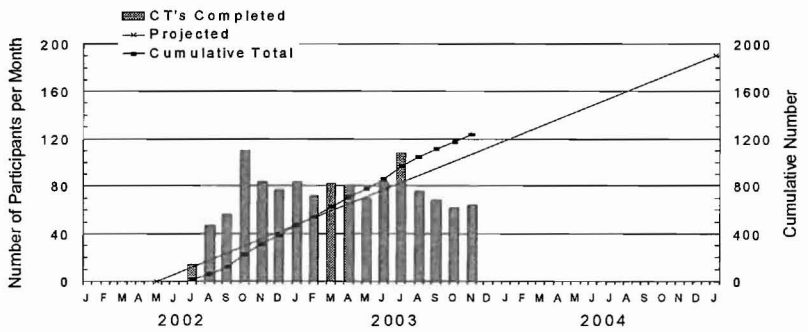
Slide 6

Number of Participants, Generation III Cardiac CT

(Not Including CT's Done on Generation III by Family Heart Study)



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Slide 7

Eligible Participants Who Have Not Had a Cardiac CT Exam as of 11/30/03

Study	CT Exam Completed	CT Scan Scheduled	Refused CT (%)
Gen 3	1239	17	80 (6.0%)
Offspring	573	29	105 (14.9%)

Notes:
CT Eligibility:
- Gen 3 eligibility is based on attending Exam 1 and current age (women age ≥ 40, men age ≥ 35).
- Offspring eligibility is based on prioritization by recent exam attendance, age, genome scan information, and sibling exam participation.
- Initially, 1248 Offspring participants were eligible for the CT exam.

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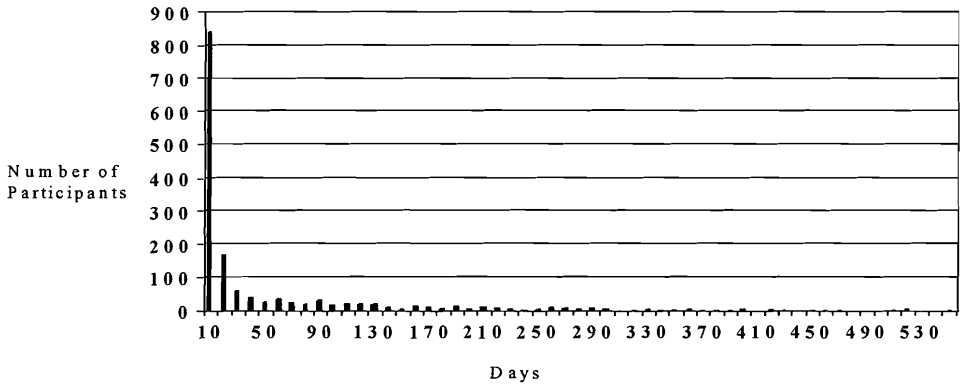
Slide 8

Number of Days Between Gen 3 Exam 1 and Cardiac CT Exam as of 11/30/2003



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Slide 9

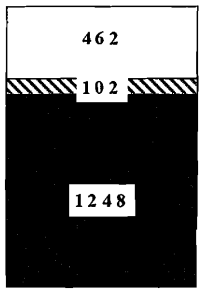
FHS Cardiac CT Study

- Recruitment and scanning
- Calcium scoring
- Coronary calcium reproducibility
- Incidental finding reporting
- Pregnancy screening measures

Slide 10

Cardiac CT Scans Through November 30, 2003

CALCIUM SCORING (CS)



Based upon n=1350 scans scored for CS, 7.6% were positive and 92.4% were negative

Slide 11

Coronary Calcium Score, N=632 Subjects

Cohort	Age	Men			Women		
		N	Mean (SD) CAC Score	Median CAC Score	N	Mean (SD) CAC Score	Median CAC Score
Offspring	35-49	5	0.1 (0.3)	0.0	6	0.0 (0.0)	0.0
	50-59	30	105.7 (214.2)	6.5	27	27.0 (69.1)	0.0
	60-69	34	862.5 (1527.7)	173.5	32	41.0 (112.5)	0.7
	70+	17	819.4 (984.5)	305.3	24	138.3 (190.1)	62.0
GIII	35-49	184	72.0 (368.5)	0.0	156	4.64 (30.7)	0.0
	50-59	45	170.7 (378.1)	7.8	57	21.4 (73.5)	0.0
	60-69	2	1339.9 (1756.7)	1339.9	7	37.3 (58.7)	0.0
	70+	1	1232.5 (-)	1232.5	1	156.5 (-)	156.5

Slide 12

Mean Differences in Agatston Score Between CAC Scan 1 and Scan 2

Group	Scan 1 Mean (SD) Score	Scan 2 Mean (SD) Score	Mean Diff Scan 1 - 2
Overall	126.3 (519.0)	123.7 (505.5)	2.6 (61.0)
Men	223.1 (708.9)	219.6 (690.9)	3.5 (81.6)
Women	25.7 (90.7)	24.1 (80.6)	1.7 (25.7)
Age 35-49 y	41.4 (282.1)	38.2 (258.6)	3.2 (51.6)
Age 50-59 y	81.7 (237.1)	79.4 (233.6)	2.3 (33.0)
Age 60-69 y	447.5 (1135.8)	447.8 (1125.6)	-0.3 (99.4)
Age 70+ y	435.8 (740.3)	431.1 (700.1)	4.7 (109.9)

Slide 13

Concordance and Discordance Agatston Score=0 Between Scan 1 and Scan 2

Group	N (%) Yes: Yes	N (%) Yes: No	N (%) No: No
Overall	390/632 (62%)	47/632 (7%)	195/632 (31%)
Men	163/332 (51%)	26/322 (8%)	133/322 (41%)
Women	227/310 (73%)	21/310 (7%)	62/310 (20%)
Age 35-49 y	274/351 (78%)	25/351 (7%)	52/351 (15%)
Age 50-59 y	86/159 (54%)	15/159 (9%)	58/159 (36%)
Age 60-69 y	25/75 (33%)	2/75 (3%)	48/75 (64%)
Age 70+ y	2/43 (5%)	4/43 (9%)	37/43 (86%)

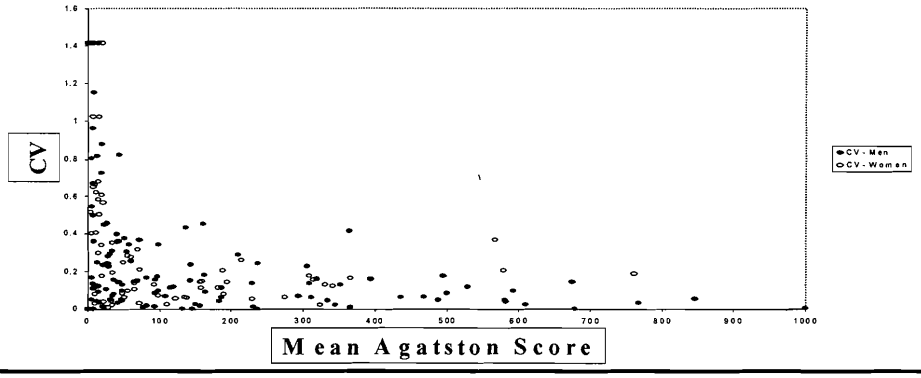
Slide 14

Concordance and Discordance Agatston Score < 10 Between Scan 1 and Scan 2

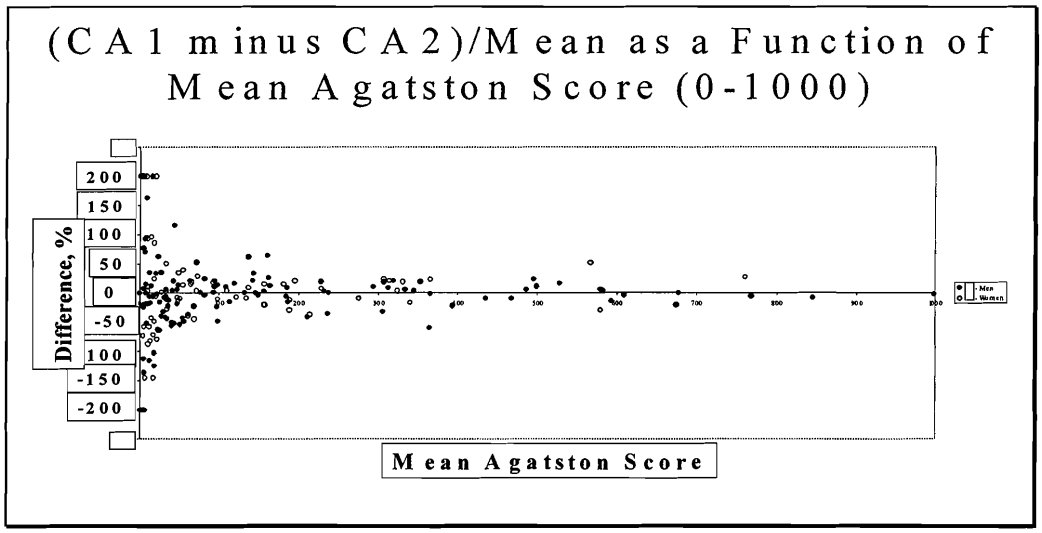
Group	N (%) Yes: Yes	N (%) Yes: No	N (%) No: No
Overall	442/632 (70%)	23/632 (4%)	167/632 (26%)
Men	195/322 (61%)	10/322 (3%)	117/322 (36%)
Women	247/310 (80%)	13/310 (4%)	50/310 (16%)
Age 35-49 y	302/351 (86%)	8/351 (2%)	41/351 (12%)
Age 50-59 y	102/159 (64%)	9/159 (6%)	48/159 (30%)
Age 60-69 y	30/75 (40%)	3/75 (4%)	42/75 (56%)
Age 70+ y	4/43 (9%)	3/43 (7%)	36/43 (84%)

Slide 15

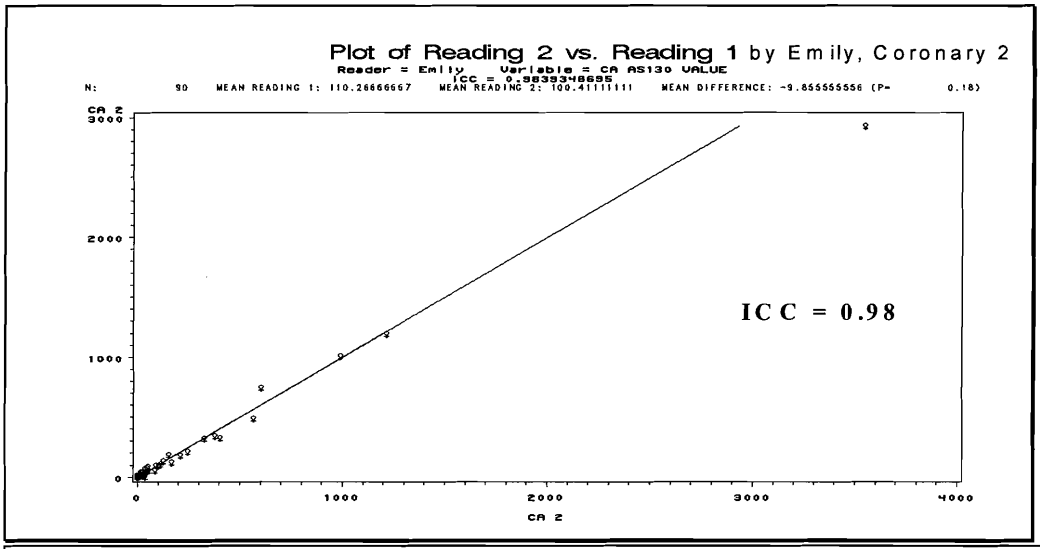
Coefficient of Variation as a Function of Mean Agatston Score (0-1000)



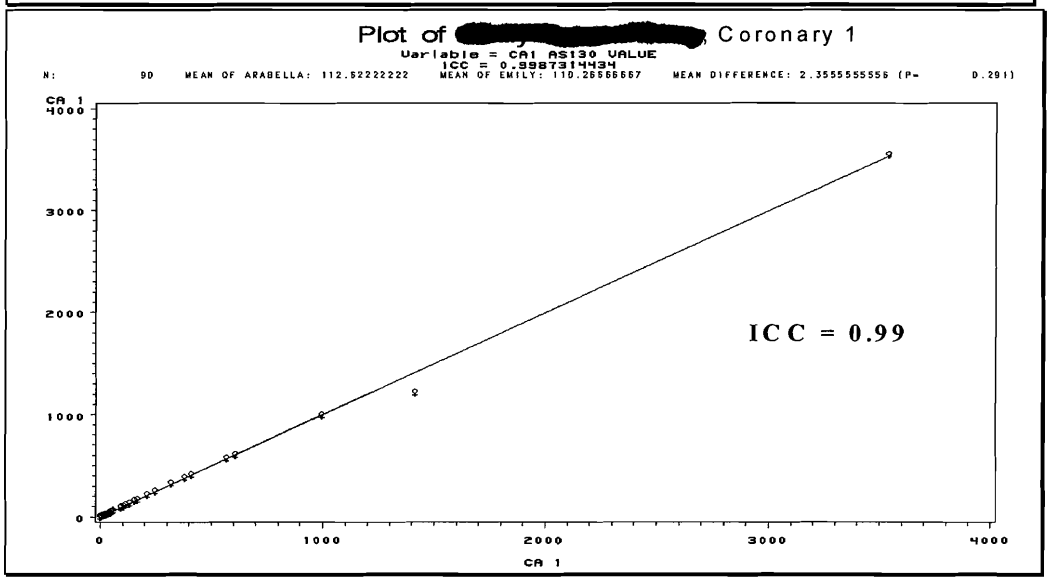
Slide 16



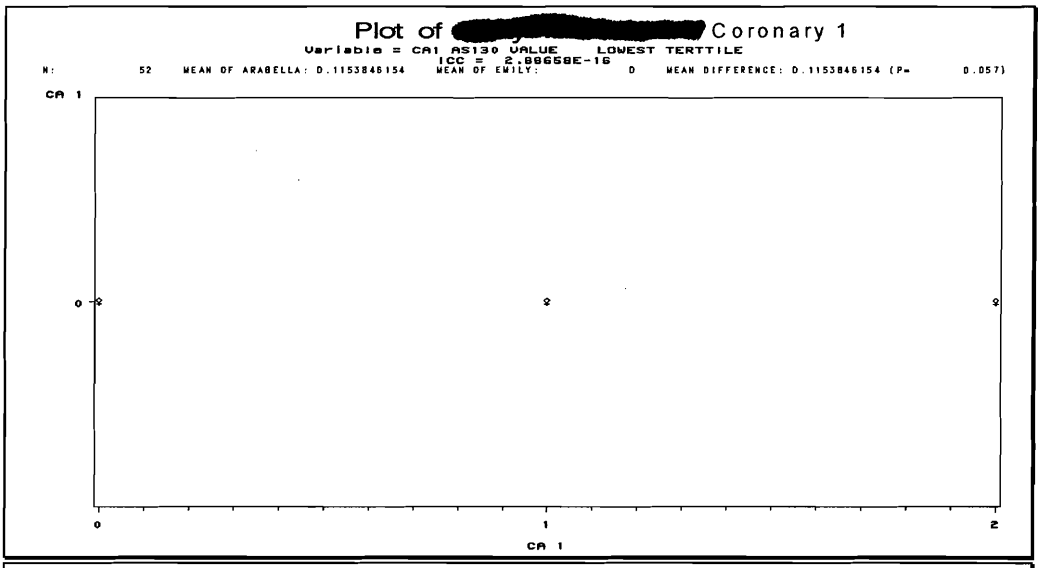
Slide 17



Slide 18



Slide 19



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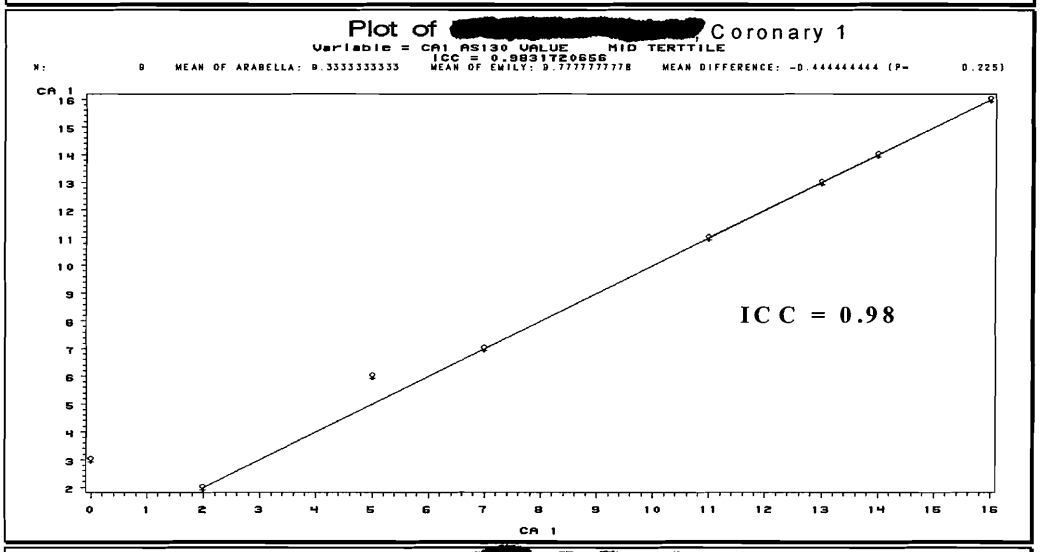

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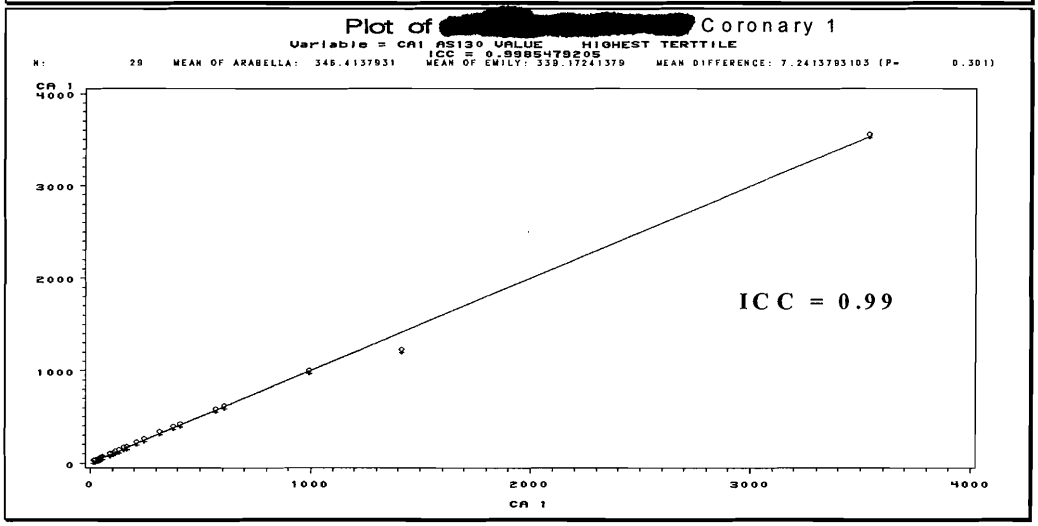
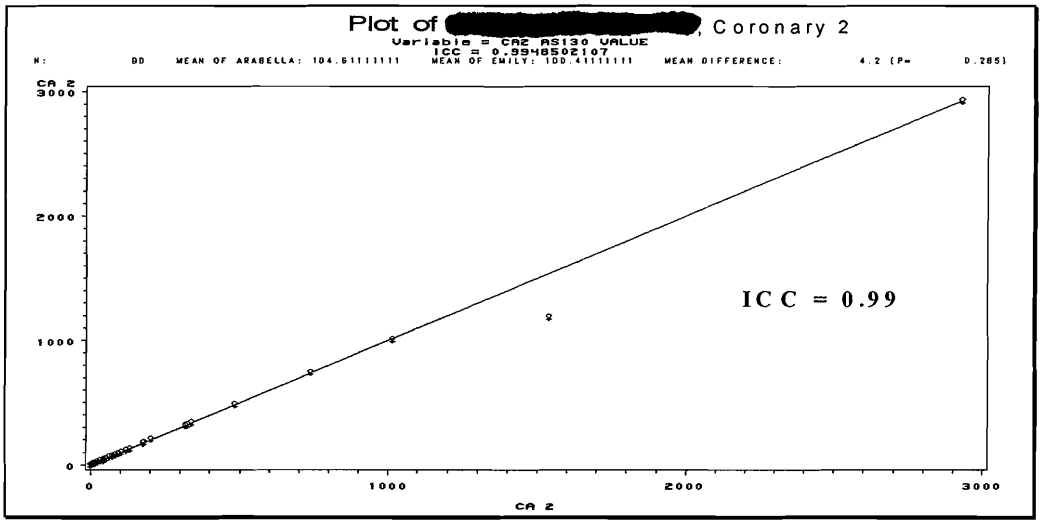
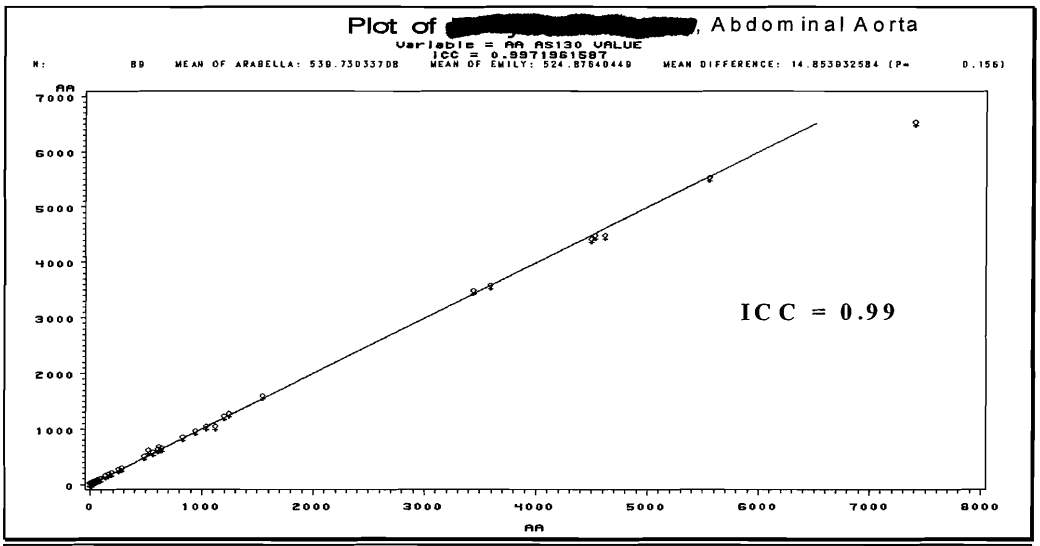


Slide 22



Slide 23



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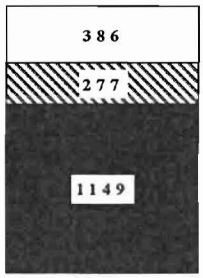
FHS Cardiac CT Study

- Recruitment and scanning
- Calcium scoring
- Coronary calcium reproducibility
- Incidental finding reporting
- Pregnancy screening measures

Slide 25

Cardiac CT Scans Through November 30, 2003

INCIDENTAL FINDINGS (IF)



NOT READ
POSITIVE IF
NEGATIVE IF

Based upon n=1426 scans read for IF, 19.4% were positive and 80.6% were negative

Slide 26

Incidental Findings: Definitions and Notification Rules— FHS CT Study

Recommendation by radiologist	Type of finding: examples	Notification procedure by FHS
Immediate or emergent action	Malignant pulm. nodule, Ao aneurysm with hemorrhage	Refer to PCP immediately or within 1 week + phone call to PCP and participant
Follow-up recommended	Probably benign pulmonary nodule— 6 month f/u CT	Refer to PCP within 1 month
Clinical follow-up at discretion of PCP	Kidney stones, large hiatal hernia, horseshoe kidney	Communicate finding to PCP within 2 months

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Summary of IF's, 227 Scans as of 11/31/03

Location of Finding	Recommended Action		
	Immediate Action	Follow-Up	Incidental Finding
Abdominal Aorta	0	1	3
Adrenal	0	2	0
Bone	0	2	4
Breast	1	3	1
Esoph/Stomach	1	0	0
Gastrointestinal	0	0	21
Gall Bladder	0	0	8
Heart	0	6	6
Liver	0	29	4
Lung	0	58	11
Mediastinum	0	4	1
Renal	0	51	32
Retroperitoneal	0	2	0
Thoracic Aorta	0	11	8
Other	0	7	11
Total	3	175	110

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Summary of Findings Requiring Immediate Action

- Breast Mass: Known breast CA, s/p mastectomy
  - Phone Call with PCP: Lesion already known, no further follow-up planned
- Esophageal Tumor: Not previously known
  - Phone Call with PCP: Subject had been undergoing work-up for "not feeling well", further follow-up was underway

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FHS Cardiac CT Study

- Recruitment and scanning
- Calcium scoring
- Coronary calcium reproducibility
- Incidental finding reporting
- Pregnancy screening measures

Slide 30

Summary of Measures Taken in Response to Pregnancy Test Incident

- Strict adherence to FHS age cutpoints by FHS-SCAN study
- Continuation of Pregnancy Testing--Recertification of Coordinators
- Implementation of Questionnaire Screening for Recent Sexual Activity

Slide 31

Participant Response to Questionnaire Screening for Recent Sexual Activity

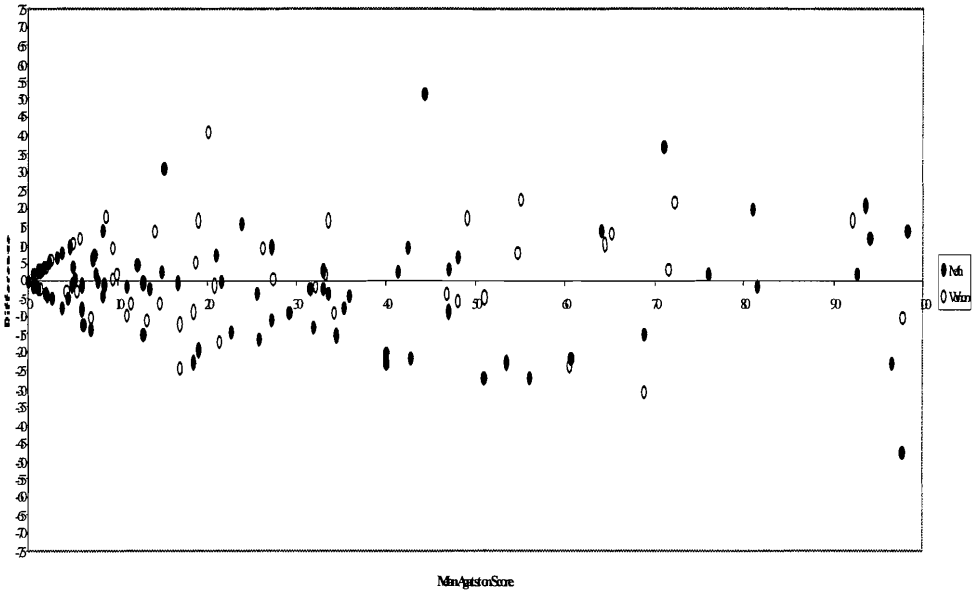
- No significant privacy concerns or other significant complaints
- As of November 31, 2003
  - 61 questionnaires administered
  - 2 subjects were not allowed to undergo CT due to responses on questionnaire
  - 59 subjects proceeded with CT

Slide 32

blank

Slide 33

Figure: (CA1 minus CA2) as a Function of Mean Agatston Score (0-100)



Slide 34

Entire November Report
SlideShow

Updated through November 30, 2003

Slide 35

*Total Number of CT Scans Completed Through November 30, 2003

PART 1 – THROUGH DECEMBER 31, 2002

Month 2002	Offspring		Gen 3		Total
	Framingham	Combined	Framingham	Combined	
June		6		1	7
July	39	16	14	6	75
August	36	21	47	14	118
September	48	22	56	13	139
October	52	24	110	17	203
November	20	18	84	15	137
December	12	5	77	6	100
Total	**207**	**112**	**388**	**72**	**779**

*Includes both eligible and non-eligible scans based on Framingham Heart Study criteria. Also include partial scans.

Notes: Framingham - Framingham Heart Study Participants
Combined - Framingham Heart Study and Family Heart Study Participants

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***Total Number of CT Scans Completed Through November 30, 2003** (part II)

Month 2003	Offspring		Gen 3		Total
	Framingham	Combined	Framingham	Combined	
January	14	8	84	13	119
February	11	8	72	16	107
March	29	10	82	14	135
April	36	20	81	7	144
May	27	13	70	16	126
June	44	14	84	26	168
July	27	10	108	16	161
August	33	6	76	8	123
September	38	14	68	15	135
October	56	4	62	8	130
November	51	0	64	1	116
Total 2002	207	112	388	72	779
Grand Total	573	219	1239	212	2243

*Includes both eligible and non-eligible scans based on Framingham Heart Study criteria. Also include partial scans.

Notes: Framingham - Framingham Heart Study Participants
Combined - Framingham Heart Study and Family Heart Study Participants

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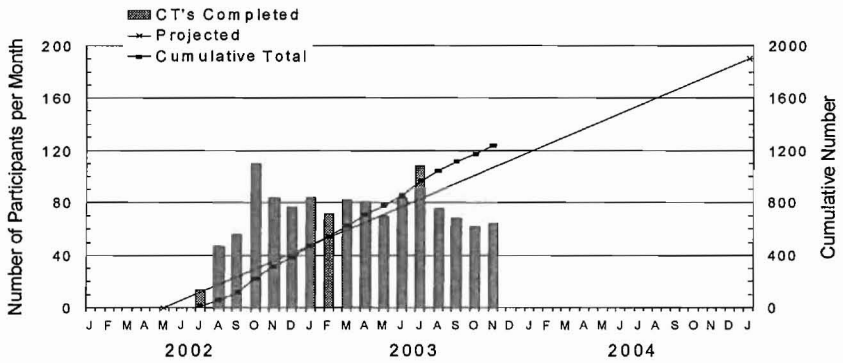
Number of Participants, Generation III Cardiac CT

(Not Including CT's Done on Generation III by Family Heart Study)



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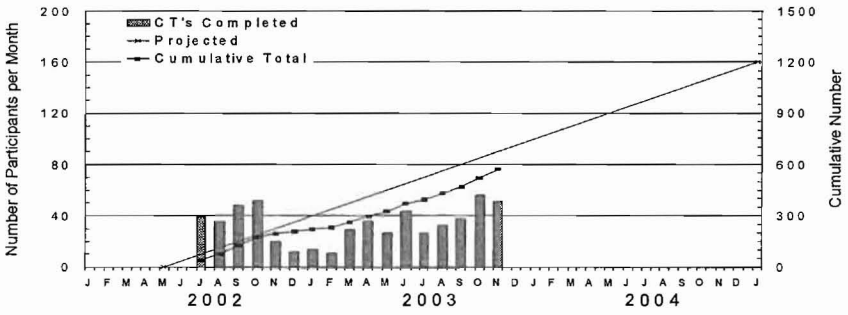
Number of Participants, Offspring Cardiac CT

(Not Including CT's Done on Offspring by Family Heart Study)



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Eligible Participants Who Have Not Had a Cardiac CT Exam as of 11/30/03

Study	CT Exam Scheduled	CT Eligible, not yet scheduled	Refused CT
Gen 3	17	190	80
Offspring	29	458	105

Notes:
1. Some of these participants belong to both the Framingham Heart Study and Family Heart Study.

2. CT Eligibility:
   - Gen 3 eligibility is based on attending Exam 1 and current age (women age ≥ 40, men age ≥ 35).
   - Offspring eligibility is based on prioritization by recent exam attendance, age, genome scan information, and sibling exam participation.
   - Initially, 1248 Offspring participants were eligible for the CT exam.

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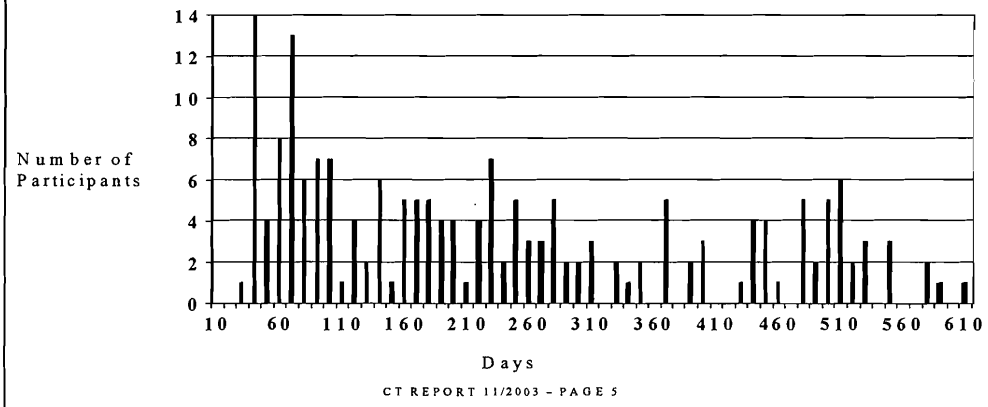
Number of Days Between Gen 3 Exam 1 and 11/30/03 for Participants Who Have Not Had a CT and are Eligible



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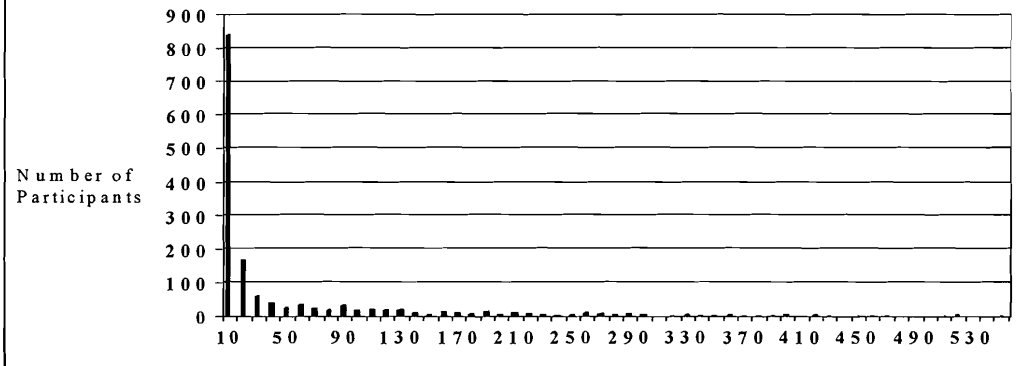
Number of Days Between Gen 3 Exam 1 and Cardiac CT Exam as of 11/30/2003



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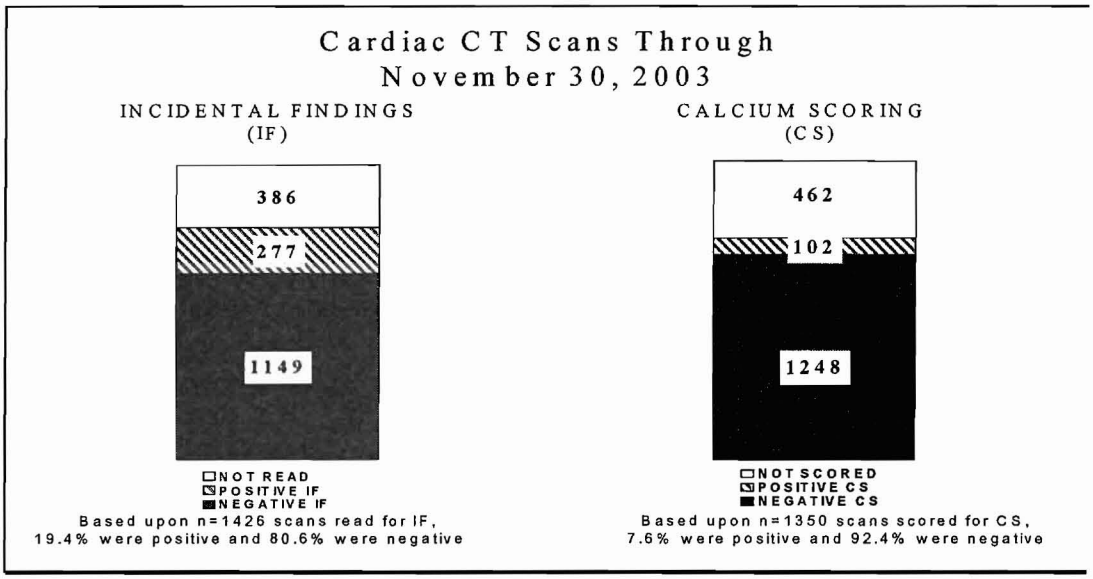

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CT Scans Not Read for Incidental Findings

Year	Month	Not Read for IF
2002	July	0
	August	0
	September	0
	October	0
	November	0
	December	0
2003	January	0
	February	0
	March	0
	April	1
	May	19
	June	9
	July	1
	August	38
	September	85
	October	118
	November	115
Total		386

Of unread IFs:

82% scanned after Sept 1 (ie in Past 3 months)

18% scanned in Past 4-8 months

Backlog will be Reduced to ≤ 2 Months by Jan 1

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Figure: Coefficient of Variation as a Function of Mean Agatston Score

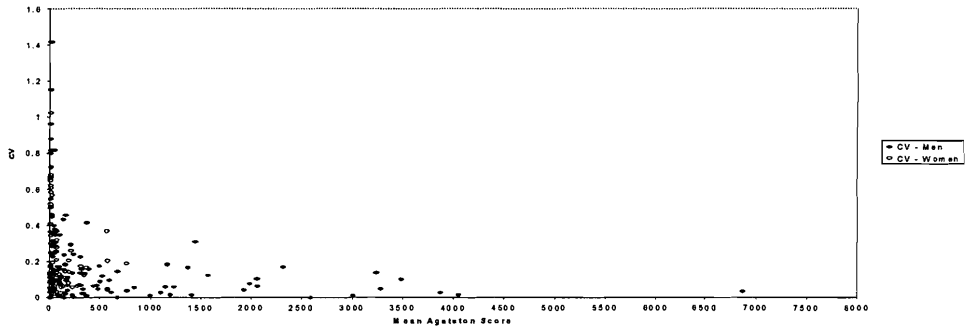

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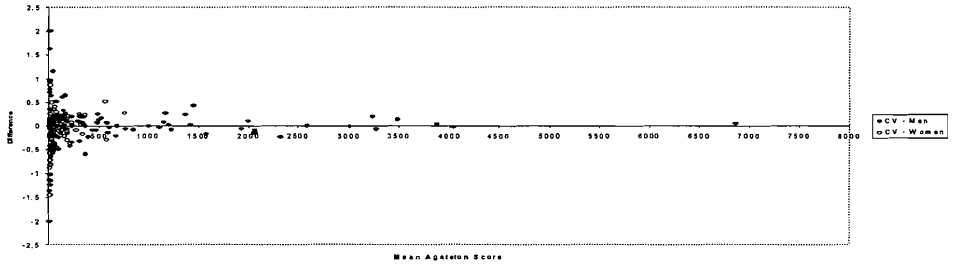
Figure: (CA1 minus CA2)/Mean as a Function of Mean Agatston Score



Appendix 32: Protocol for Incidental Finding Follow-up Procedures And Survey Questionnaire

Protocol for Incidental Finding Follow-up Procedures

The participant was called via telephone 6 months after the incidental finding letter was mailed to both participant and their physician(s) informing them that an incidental finding (IF) was found during a CT scan of the coronary arteries.

The person conducting the phone call survey followed a series of questions from the FHS CT Scan Incidental Finding Follow-up Questionnaire. Each Questionnaire had the participants [redacted] and date of call. Survey answers were recorded on the Questionnaire.

Upon completion, the Questionnaire results were data entered into the FHS database.

Date of call ___/___/_____

Framingham Heart Study CT Scan Incidental Finding Follow-up Questionnaire

«scan_date» **Date of CT Scan**
«letter_date» **Date of IF letter**

«percent90»

|__|__|__| **Interviewer ID.**

Introductory script:

On _____ you underwent a CT scan examination for the Framingham Heart Study at MGH West in Waltham, MA. The Heart Study sent you and your physician a letter regarding a finding on the CT scan identified by a radiologist as part of the normal review of your scan. Most such findings were not dangerous however in some cases your doctor may have recommended additional testing. We are conducting a brief follow-up survey to determine the type of medical testing you may have undergone. We would also like to ask you a few questions about the letter you and your doctor received regarding the CT scan to better understand what difficulties you may have encountered as a result of participating in this study.

Is this a good time? if no, when would be a good time to call back?
Date: ___-___-____ Time: ___:___ am/pm

«C01»
«C02»
«C03»
«C04»
«C05»
«C06»
«C07»
«C08»
«C09»
«C10»
«C11»
«C12»
«C13»
«C14»
«C15»
«C16»
«C17»
«C18»
«C19»
«C20»
«C21»
«C22»
«C23»

«C24»
«C25»

1. Who is completing this form?

- ☐ Participant
- ☐ Spouse
- ☐ Other relative
- ☐ Other (write in relation to participant)

2. Do you remember receiving a letter after the scan?

- ☐ Yes
- ☐ No
- ☐ Unknown

If no or unknown, skip question 3.

3. When you received the letter regarding the CT scan findings, did you feel anxious or worried? (read all responses)

- ☐ Not at all
- ☐ Mildly but it didn't bother me much
- ☐ Moderately, it wasn't pleasant
- ☐ Severely, it bothered me a lot

4. Did you and your doctor discuss the findings on the CT scan? (check all that apply)

- ☐ No
- ☐ Yes, phone contact
- ☐ Yes, office visit

If yes, please specify the following:

Name of physician _____
Address of physician _____
Phone number of physician _____

5. Do you know the type of finding and its location (eg, "spot" or "abnormality" on the lung, liver, kidney)?

- ☐ No
- ☐ Yes, specify the type of finding and its location briefly:

_____

If yes, did you know previously that the finding existed?

- ☐ No
- ☐ Yes

6. Were you referred to a specialist?

☐ No
☐ Yes

If yes, please specify for each specialist:

Type of specialist
Name of specialist
Address of specialist
Phone number of specialist

Type of specialist	
Name of specialist	
Address of specialist	
Phone number of specialist	

Type of specialist	
Name of specialist	
Address of specialist	
Phone number of specialist	

7. Please estimate the total number of office visits to any physician (primary care physician and specialists) to address the finding(s) on the CT Scan examination?

☐ No physician visits
☐ One visit
☐ More than one visit

8. Did you undergo any of the following tests for the finding on your CT scan? (read each test)

If yes obtain name and address of facility where testing was performed and date of test

YES	NO	PROCEDURE	DATE	FACILITY
☐	☐	Ultrasound	__-__-____	_____
☐	☐	CT scan	__-__-____	_____
☐	☐	MRI scan	__-__-____	_____
☐	☐	Endoscopy (look into GI tract)	__-__-____	_____
☐	☐	Bronchoscopy (look into lungs)	__-__-____	_____
☐	☐	Biopsy Specify site _____	__-__-____	_____
☐	☐	Angiogram (put "dye"/contrast in blood vessels) Specify site _____	__-__-____	_____
☐	☐	Other Write in name of test _____	__-__-____	_____

9. What special treatments did you undergo as a result of the finding on your CT scan?

a)

YES	NO
☐	☐

Surgery

if yes, Specify each specific surgery, surgery date, and hospital

SURGERY	DATE	HOSPITAL
1.		
2.		
3.		

b)

YES	NO
☐	☐

Medication

if yes list all medications

LIST OF MEDICATIONS
1.
2.
3.
4.

10. If you discussed the CT scan findings further with your doctor and/or if your doctor recommended further testing, did you feel anxious or worried? (read all responses)

- ☐ Not at all
- ☐ Mildly but it didn't bother me much
- ☐ Moderately, it wasn't pleasant
- ☐ Severely, it bothered me a lot

11. Did the discovery of the CT scan finding and the evaluation by your physician require you to miss any of your full-time responsibilities (eg, work or care of your children)?

- ☐ No
- ☐ Yes, less than one day (0-8 hours) total
- ☐ Yes, 1-2 days
- ☐ Yes, > 2 days

12. Did you incur any financial costs related to the CT scan finding?

- ☐ No
- ☐ Yes

13. If you had further testing for the finding on the CT scan examination, please tell us the final medical diagnosis for the finding

write in _____

14. Do you have any comments about the CT examination you would like to share with the study investigators?

- ☐ No
- ☐ Yes

If yes write in

_____

_____

_____

_____

_____

Thank you for completing this survey.

Appendix 33: Exporting, Importing and Transferring CT Scans from the Terarecon

EXPORTING CT SCANS FROM TERARECON TO EXTERNAL HARD DRIVE
(Western Digital)

- Plug in the Western Digital (WD) with either the USB port or Fire Wire to the Terarecon computer
- Power on the WD
- Under My Computer, the WD will be seen under "Hard Disk Drives" called WD Combo (G:)
- First check that the WD has enough space to accept the files you will be exporting
- Double click on WD Combo
- Under File, create a New Folder and name it
- Copy (Ctrl C) the name on the Address line (ie:G:\xxxx)
- Click on Export
- Click on Add and a box will appear in the center of the screen
- Paste (Ctrl V) the new folder on the line that is called Path
- On line of Setting Name, give a name (use a letter, 2 letters or a name)
- Click OK
- This "folder" will now appear on the small box on the left of the screen
- Highlight this "folder" and using the tabs below the box, click on Initialize Media
- The "folder" line will now read Online (instead of No Media) under the Status column. It is ready to accept scans
- Highlight what scan(s) you want to export to the WD. To highlight more than 1 scan, hold down the Ctrl key while mouse clicking on designated scans
- Right click one of the highlighted scans.
- Left click on Export
- A blue box will appear in the middle of the screen
- On the Destination line should be the Setting name (of the folder where the scans are going)
- Source should be Local Database (faint writing)
- Click on OK at the bottom of the blue box
- To see the scan list as it is copied to the destination (WD), click on Export, after the "hourglass" cursor disappears
- A white box will appear with the list of scans being exported. Under Status, you will see the number of files moving over
- When the white box is empty, the files have all been copied to the WD
- Go to My Computer, open WD Combo, and then the folder just made to check if the scans were exported successfully.
- Remember files that have been exported are COPIED to that destination. There are now the same files on both the Terarecon and WD.
- To remove WD:
    - Close open files, including the Aquarius Workstation
    - Turn off WD
    - Press the Windows key to bring up the bottom toolbar
    - Click on the green left pointing arrow

- Click on Safely remove WD
- When it says Safe to remove Hardware, unplug the WD from the computer

Exporting Scans from Lacie to Terarecon:

- Before you start, make sure your destination has enough room to accept the files you are sending
- Go to Target (top of screen) and using the down arrow select Lacie
- Lacie scans will then appear on scan list underneath
- Highlight what scan(s) you want to export to the Terarecon (=Local Database): to highlight more than 1 scan, hold down the Ctrl key while mouse clicking on designated scans
- Right click on one of the highlighted (blue) scans
- Left click on Export
- A blue box will appear in the middle of the screen
- On Destination, click on the down arrow and click on Local Database (which is the Terarecon)
- Click on OK at the bottom of the blue box
- To see your scan list as it is copied to the destination, click on Export, after "hourglass" cursor disappears (in the middle of the screen)
- A white box will appear with your list. Under Status you will see the number of files moving over
- When the white box is empty, your files have all been copied to the Local Database or Terarecon
- Go back to Target (top of screen) and click on the down arrow and select Local Database
- Your files will be there but in either ID or Study Date order, which ever you have selected to use (by either clicking on Patient Name=ID or Study Date, Time=scan date)
- Files you have exported are COPIED to that destination. You now have the same files on the Lacie and Terarecon.

Exporting Scans from Terarecon to Lacie:

- Before you start, make sure your destination has enough room to accept the files you are sending
- Go to Target (top of screen) and using the down arrow select Local Database
- Local Database (or Terarecon) scans will then appear on scan list underneath
- Highlight what scan(s) you want to export to the Lacie: to highlight more than 1 scan, hold down the Ctrl key while mouse clicking on designated scans
- Right click on one of the highlighted (blue) scans
- Left click on Export
- A blue box will appear in the middle of the screen
- On Destination, click on the down arrow and click on Lacie
- Click on OK at the bottom of the blue box
- To see your scan list as it is copied to the destination, click on Export, after "hourglass" cursor disappears (in the middle of the screen)
- A white box will appear with your list. Under Status you will see the number of files moving over
- When the white box is empty, your files have all been copied to the Lacie
- Go back to Target (top of screen) and click on the down arrow and select Lacie
- Your files will be there but in either ID or Study Date order, which ever you have selected to use (by either clicking on Patient Name=ID or Study Date, Time=scan date)
- Files you have exported are COPIED to that destination. You now have the same files on the Terarecon and Lacie.

Burn DVD From Terarecon

- Put DVD in F: drive (white drive)
- Start
- Programs
- Roxio Easy CD Creator
    - Project Selector
    - Make a Data CD
    - Direct CD
        - Should show: 4488 MB
        - Select CD: (F:)
    - Format CD
    - Label: as date or name
    - Start Format

Once Formatted:

- Close small box (F:)
- CD Ready: click OK
- Close Direct CD box
- On Aquarius Workstation, click on Export
- Small box on left, highlight DVD-R (F:)
- Click on Initialize Media (tabs under small box)
- Highlight scans being sent to DVD **(appox. 35 scans/DVD)**
- Right click on a highlighted scan
- Left click on Export
- Blue box should appear in center of screen
    - Source: Local database (very faint writing)
    - Destination: DVD-R
    - Click: OK

Under Status in the white box in the lower half of the screen, shows the scans being exported to the DVD. When the white box is empty, the exporting is done.

After scans are burned to DVD:

- Go back to Direct CD
- Click: Eject
- Click on Close to Read on Any Computer
- Click OK
- Click Yes on next little box that pops up
- Wait for DVD drive to open itself to be totally done

To Look at Scans on DVD

- Put DVD into white F: drive
- Wait for the scan IDs to appear on the right side of screen
- Click on My Computer
- Right click on DVD/F: drive
- Click on Explore
- If list of files in F: drive do not appear, click on View→Details

- Write down the Study ID numbers of the scans: [redacted]
- Close screen
- Go back to Aquarius Workstation. It already may be running. Click on the * on the bottom toolbar (accessed by pressing the Windows key)
- Click on Import (directly under Patient List IDs)
- Click on + of F: drive (study ID of scans will appear)
- Highlight scan (can only highlight one/time)
- Click on (to check) Scan Sub Directories (directly above letter A: drive)
- Click on Import (directly above Scan Sub Directories, not the previous Import tab)
- Import to Local Database of Terarecon is done when the right side of screen says DB update done.

To eject DVD:

- Press Windows key to show bottom toolbar
- Click on white highlighted *
- Click on Exit, bottom left box on screen
- Manually open CD drive and remove DVD