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# Development and Application of a Longitudinal ECG Repository: the Framingham Heart Study

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## Abstract

The electrocardiogram (ECG) has wide-spread use in clinical care and research. Despite its extensive use and study, important gaps remain in examining prospective, repeated longitudinal ECG measures and their association with cardiovascular outcomes. The Framingham Heart Study (FHS) is a community-based study designed to examine risk factors and outcomes associated with cardiovascular disease. Here we describe a novel effort in the FHS to develop a unique resource: serial ECGs conducted on three generations of study participants spanning multiple decades (1986 to the present). We describe the FHS and the role the ECG has had in conducting cardiovascular epidemiology in the FHS. We then describe potential applications for a longitudinal ECG repository. We expect the Framingham ECG repository to enhance cardiovascular research and epidemiologic study. Such a resource will complement the FHS' phenotypic and genotypic characterization, facilitating novel investigations of cardiovascular epidemiology.

### Keywords

electrocardiography; epidemiology; repository; Framingham

The electrocardiogram (ECG) has a long-standing and extensive history with regard to clinical care and research. Despite over a century of such applications, important gaps remain in the application and utilization of the ECG. The U.S. Preventive Task Force has recently reported that the ECG literature lacks classification metrics to evaluate risk for cardiovascular events.[1] Furthermore, there is limited literature assessing and integrating prospective, repeated longitudinal ECG measures. Addressing these challenges requires repeated collection of ECGs across adulthood in conjunction with measuring anthropometric



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and clinical characteristics, evaluating cardiovascular risk factors, and active surveillance for cardiovascular or other outcomes. A prospective, community-based study encompassing 3 generations of participants, the Framingham Heart Study (FHS) has the potential to address important research gaps by including the ECG as a routine component of a standardized participant examination. Here we describe a novel initiative to develop and implement a digitized ECG repository in the FHS and introduce potential applications and future directions

## The Framingham Heart Study

The FHS is a prospective, community-based study that was initiated in 1948 to examine risk factors and outcomes associated with cardiovascular disease.[2] The study's original cohort consisted of 5,209 men and women who underwent examinations every 2 years. Of the original cohort, 91 surviving participants with mean age 92 years attended their 31$^{st}$ examination in 2008–2011. In 1971, the offspring cohort was enrolled, consisting of 5,124 men and women and comprised of the children or spouses of children of the original cohort.[3] The offspring cohort completed its 8$^{th}$ examination in 2008 (mean age 67 years) and included 3,021 participants. In 2002, 4,095 grandchildren and spouses of grandchildren (Third Generation cohort) of the original cohort were enrolled.[4] In 2011, 3,411 Third Generation cohort participants completed their second examination. Examinations in each of the 3 generational cohorts have included a standardized interview and physical examination, ECG, laboratory evaluations, and diverse functional, cardiac, pulmonary, and neurologic assessments. Cardiovascular outcomes are adjudicated by three Framingham Heart Study physicians and include coronary heart disease (coronary insufficiency, angina, myocardial infarction), heart failure, atrial fibrillation, and sudden cardiac death.

## Electrocardiography in the Framingham Heart Study

The ECG has been integral to FHS examinations since its initiation. Analyses of standard 12-lead ECGs acquired at the original cohort's initial examination contributed towards heart disease detection algorithms and development of the epidemiology of left ventricular hypertrophy.[5–7] In the following decades, FHS investigators integrated the standard 12-lead ECG from subsequent examinations into early analyses of atrial fibrillation,[8,9] heart failure,[10,11] coronary disease,[12] and sudden cardiac death.[13]

Initial ECG tracings were obtained on Hewlett-Packard 1500-B and Sanborn 100 platforms. In 1985, the FHS adopted the Marquette MAC/PC followed by the Marquette (now General Electric) MAC 5000, which allowed for digital storage of the ECG. Regardless of the electrocardiograph used, all paper recordings have uniformly been printed on lined paper at 25 mm/sec and 0.1 mv/mm. Recently, investigators at the Study have purchased the MUSE 8 ECG Management System (General Electric) for development of an ECG repository. With the assistance of GE Healthcare, older digital data has been transformed for contemporary analysis on the MUSE 8. The Framingham Heart Study MUSE system now contains all ECGs recorded since the switch to the digital electrocardiographs in 1986.

## Contents of the Framingham Heart Study ECG Repository

Specific examinations included in the repository, the number of participants, and their dates are summarized in Table 1. In total there have been 13 examinations of the original cohort, 7 of the offspring and 2 of the Third Generation participants from which digital ECGs were incorporated into the repository. The tracings included in the repository amount to over 30,000 unique ECGs.

## Application of the Framingham ECG Repository

Development of an ECG repository and storage in the MUSE 8 provides the FHS with an unparalleled opportunity for combining the phenotypic and genotypic characterization and clinical outcomes of the FHS with ECG analyses. In Table 2 are summarized selected phenotypic and genotypic assessments conducted during the FHS examinations since 1986.

Presently, FHS investigators have 4 principal objectives in applying the ECG data:

1. *To integrate and utilize a database of repeat ECG measures.* Serial ECGs permit repeated measurements of interval duration, voltage, and axis across FHS examinations. Longitudinal, prospectively ascertained assessments of ECG measures will facilitate evaluating changes as the cohorts proceed from mid-to-older adulthood. Examples for applying prospective, serial measures include establishing the progression in voltages to assess ECG left ventricular hypertrophy and mass; evaluating the changes in standard measures such as the PR, QRS and QT intervals across the adult life-course; and determining changes in P, QRS, and T axes.

2. *To determine the association of anthropometric and clinical measures with ECG data.* The comprehensive phenotyping of FHS participants will facilitate examining an array of covariates related to ECG measures. Such investigations may be conducted by using repeated cross-sectional assessments of anthropometry or clinical measures with ECG intervals; examining how changing anthropometry or clinical measures impact ECG traits; or examining ECG factors as an intermediate phenotype demonstrating the progression of a clinical exposure towards a cardiovascular outcome. An example for such a series of investigations include examining the relation of obesity and body mass index to precordial voltages, establishing how prospective changes in obesity measures relate to voltage magnitude, and assessing the association of such changes with heart failure, an outcome that has been related to obesity by FHS investigators. A second example entails relating successive determinations of blood pressure and hypertension status to P wave indices and changing atrial electrical function, followed by determining how such changes relate to risk of atrial fibrillation.

3. *To integrate novel and repeated ECG measures into risk assessment and modeling.* The FHS has produced an extensive literature on risk by identifying diverse risk factors associated with adverse cardiovascular outcomes that include coronary heart disease, atrial fibrillation, heart failure, and stroke. Such assessments have yielded risk scores accessible throughout the world for enhancing clinical practice and prevention by utilizing risk stratification (www.framinghamheartstudy.org/risk/index.html). Examples for application of the ECG repository data include adding novel ECG measures to established risk scores to enhance the scores by integrating contemporary assessments of model discrimination, calibration, and risk reclassification. The repository may be used for determining the relation of prospective changes in ECG intervals or voltages to outcomes, e.g. determining how changes in QT interval relate to cardiovascular and all-cause mortality, the contribution of serial P wave indices towards atrial fibrillation risk, or the prospective association of various indices for left ventricular hypertrophy and heart failure.

4. *To integrate ECG measures into the catalog of Framingham Heart Study genetic and genomic investigations.* The FHS has conducted extensive genetic characterization of participants as described in Table 2. The ECG repository will facilitate the participation of the FHS in multi-cohort genome wide association

studies with other cohorts. Data generated from the MUSE ECG repository will be available worldwide for approved investigators via the database of Genotypes and Phenotypes (dbGaP, http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v17.p6) sponsored by the National Center for Biotechnology Information. Second, the repository will result in novel studies to describe the relations between ECG measures and clinical and genetic assessments. An example of such an application is the undertaking of pharmacogenomics to examine the longitudinal association between genomic variants, time-varying use of medications, and the change in ECG intervals. An example of such an approach, extending from the integration of outcomes described above, would examine the use of various medications on QT interval and its association with mortality.

## Conclusion

The FHS ECG repository has only recently been developed and its application has yet to be realized. In the next 2–3 years, FHS investigators expect to implement the repository and apply it towards the applications described here. Members of the scientific community will have access to this unique resource and to participate in such efforts. We expect the Framingham ECG repository to contribute to numerous clinical applications of the ECG. We ultimately intend to apply the ECG repository towards improving public health by guiding prevention strategies and enhancing risk assessment and management.

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**Table 1**

Contents of the Framingham Heart Study ECG Repository

| Cohort | Examination | Dates | No. of Attendees |
|---|---|---|---|
| Original | 19* | 1985–1988 | 1045 |
| | 20 | 1986 – 1990 | 1203 |
| | 21 | 1988 – 1992 | 1319 |
| | 22 | 1990 – 1994 | 1166 |
| | 23 | 1992 – 1996 | 1026 |
| | 24 | 1995 – 1998 | 831 |
| | 25 | 1997 – 1999 | 703 |
| | 26 | 1999 – 2001 | 558 |
| | 27 | 2002 – 2003 | 414 |
| | 28 | 2004 – 2005 | 303 |
| | 29 | 2006 – 2007 | 218 |
| | 30 | 2008 – 2010 | 141 |
| | 31 | 2010 – 2012 | 91 |
| Offspring | 3* | 1983–1987 | 1010 |
| | 4 | 1987 – 1991 | 4019 |
| | 5 | 1991 – 1995 | 3799 |
| | 6 | 1995 – 1998 | 3532 |
| | 7 | 1998 – 2001 | 3539 |
| | 8 | 2005 – 2008 | 3021 |
| | 9 | 2011 - | (Exam on-going) |
| Third Generation | 1 | 2003 – 2005 | 4095 |
| | 2 | 2008 – 2011 | 3411 |

*Digital electrocardiograms partially available for this examination.

## Table 2

Selected* phenotypic and genotypic assessments of Framingham Heart Study participants for integration with data from the ECG Repository.

| Assessment | Participating Cohorts and Exams |
|---|---|
| Echocardiography – cardiac structure and function | Original – 20<br>Offspring – 4, 5, 6<br>Third Generation – 1 |
| Computed tomography, cardiac and chest | Offspring – 7<br>Third Generation – 1 |
| Pulmonary function testing | Offspring – 3, 5, 6, 7, 8<br>Third Generation – 1 |
| Biomarkers (BNP, CRP, IL-6, IL-18) | Offspring – 2, 6, 7<br>Third Generation – 1 |
| Cardiac and non-cardiac outcomes (Cardiovascular disease, atrial fibrillation, revascularization procedures) | Through 2010 |
| Arterial tonometry | Original – 26<br>Offspring – 7<br>Third Generation – 1 |
| Genetic sequencing | All participants |
| Genomics, metabolomics, proteomics | Offspring – 6<br>Third Generation – 1 |

*Selected as representative assessments from the comprehensive Framingham Heart Study evaluations described at www.framingham.org. Of note, all participants did not undergo the studies described. All examinations include standardized physical exam, anthropometry, interview, clinical history, medication inventory, and laboratory studies.

**Original, Original Cohort; Offspring, Offspring Cohort;