**CRC IRB proposal**
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**The Effect Genetic Testing for Hypertrophic Cardiomyopathy Has on Communication of Disease Diagnosis within Families and Surveillance Measures for Asymptomatic Family Members**

## A. Study Purpose and Rationale

Cardiomyopathy is a chronic and progressive cardiac disease in which the myocardium is abnormally enlarged, thickened or stiffened. Eventually, the weakened heart loses the ability to pump blood effectively and heart failure or arrhythmias may occur. The World Health Organization (WHO) recognizes four subtypes of cardiomyopathy: hypertrophic (HCM), dilated, restrictive and arrhythmogenic right ventricular. Although not formally categorized by the WHO, left ventricular non-compaction cardiomyopathy is increasingly being recognized.[1] HCM which is characterized by increased thickness of the myocardium is considered the most common cardiomyopathy seen in pediatric patients. HCM is associated with sudden cardiac death in young people (especially athletes), but it is also seen as an important cause of heart failure at a later age.[2]

HCM is also the most common genetic cardiovascular disease.[2] HCM is a genetic disease primarily of the cardiac sarcomere due to mutations in genes encoding the contractile proteins. Thirteen genes and more than 900 mutations implicated in HCM have been identified. Contractile proteins affected by gene mutations in HCM patients include cardiac troponin T, cardiac troponin I, cardiac beta-myosin heavy chain, myosin essential light chain, alpha tropomyosin, and titin. There are also additional genes implicated in HCM which do not encode contractile proteins such as the gene for the muscle LIM protein (a regulator of myogenic differentiation), the gene encoding AMP-activated protein kinase gamma2 (PRKAG2), and the gene encoding the protein titin-cap (which partially comprises the Z-disc).[3] HCM is inherited in an autosomal dominant Mendelian pattern with variable expressivity and age-related penetrance.[4]

For patients with hypertrophic cardiomyopathy, genetic testing is beginning to be more widely used in clinical practice as opposed to being solely confined to the research laboratory. In the US, Correlagen Diagnositics, GeneDx, Partners, and Transgenomic/FAMILION are 4 clinical laboratories approved under the Clinical Laboratory Improvement Amendments that offer fee-based clinical genetic testing for cardiomyopathies. These laboratories use a variety of technologies, including oligonucleotide hybridization chip–based methodology, traditional direct dideoxy DNA sequencing, and high-throughput “next-generation” or “massively parallel” sequencing. The analytic sensitivity of these tests is typically 95% to 100% for the detection of nucleotide substitutions and small insertion/deletion mutations. Some laboratories also currently offer multiple-ligation probe analysis or oligo array hybridization for the detection of large gene rearrangements that would escape detection when standard DNA sequencing methodologies are used.[5]

Developments in genetic knowledge, the decreasing costs of technologies, and the approval of legislative acts prohibiting discrimination in health coverage and employment on the basis of genetic information, have all contributed to the increasing clinical application of genetic testing. There are many potential benefits associated with genetic testing including the possibility of prevention of SCD. Currently there is no cure for HCM, but following lifestyle advice, echocardiographic monitoring, implanting a cardioverter defibrillator (ICD), or taking medications may help to prevent SCD.[2]

Another potential benefit is the resolution of question about diagnosis either in symptomatic patients with unclear electrocardiography or echocardiogram results or in family members of probands found to have a genetic mutation. The latter case raises several potential concerns for testing in asymptomatic family members of probands, especially for the pediatric population.[6] It was long argued that the testing of children should be postponed until they were able to give their own consent but new professional guidelines recommend that genetic testing should be framed in terms of ‘‘the best interests of the child.” This concept allows more room for testing at a younger age. However the little literature that does exist on genetic testing of children for HCM emphasizes its controversial nature. [2]

Further complicating the decision, many newly developed tests only provide risk estimates as the correlation between genotype and phenotype is sometimes unclear. The genetic defects of hypertrophic cardiomyopathy are very variable in their expression, even among people with the same mutation within the same family. Therefore, a fixed predictable genotype-phenotype correlation for a particular mutation has not proved clinically reliable in some cases.[6] In addition to incomplete penetrance, the fact that many families have adult-onset disease, complicates the decision of when genetic testing should be pursued in an otherwise asymptomatic patient. Little is known about the psychological impact genetic testing has on the pediatric patient or what potential effect genetic testing has on family dynamic.

It has not been studied whether genetic test results influence the dissemination of diagnosis information within a family. The way in which a genetic test result influences the surveillance approach of asymptomatic family members has also not been studied. Although, the 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy does recommend individuals with pathogenic mutations who do not express the HCM phenotype to have serial EKGs, echocardiograms and clinical assessment every 12 to 18 months (Class I recommendation), but it is unknown if this is advice is followed or if family members of a proband with negative genetic testing follow the same surveillance measures.[7]

As genetic testing becomes more readily available, it is helpful for clinicians to understand what is done with this information in order to formulate practical clinical guidelines to help counsel their patients and to understand the implications this has for extended family. As the psychological impact of genetic testing on HCM families has not been studied, if positive genetic test results significantly alter the surveillance approach of asymptomatic patients, perhaps recommendation of genetic testing in this population is warranted.

We hypothesize that positive genetic testing will increase the communication of disease status within a family. We also hypothesize that asymptomatic family members of a proband that test positive for a genetic mutation will undergo more frequent surveillance measures than asymptomatic family members of a proband with a gene mutation with negative testing.

## B. Study Design and Statistical Analysis

We propose to do a retrospective cohort study using questionnaires to evaluate the effect positive genetic testing has on the dissemination of disease knowledge within a family and on the long-term surveillance measures of asymptomatic patients.

Primary Outcome Measure: Communication vs. lack of communication of disease status to extended family (second-degree relatives).

Secondary Outcome Measure: Pursuit of serial echocardiograms, EKGs, clinical assessment annually

For the primary outcome study arms will be:

- HCM probands with positive genetic testing
- HCM probands with negative testing

For the secondary outcome study arms will be:

- Asymptomatic, genotype-positive/phenotype-negative first-degree relatives of probands with positive genetic testing, less than 18 years of age
- Asymptomatic first-degree relatives of probands with negative genetic testing, less than 18 years of age

Number of subjects:
Statistical analysis for the primary outcome will be performed by means of a chi-squared test for the categorical outcome of communication or lack of communication of disease diagnosis information. The database provides 320 probands. Of those, approximately 150 probands have positive genetic testing and 170 probands will have negative testing. For power analysis, the assumption was made that 90% of probands with positive genetic testing will communicate the diagnosis information. We will be able to detect an effect size as small as 12% between groups with 80% power and a p of 0.05.

Statistical analysis for the secondary outcome will also be performed by means of a chi-squared test for the categorical outcome of pursuit of annual echocardiograms, EKGs and clinical assessment vs. surveillance at a less frequent time interval. Again, the database provides 320 probands. For the 150 probands with positive genetic testing, there were approximately 120 probands with first-degree family members under the age of 18 that tested positive for the mutation. We will assume that 60% of these patients are asymptomatic and without echocardiogram findings, leaving approximately 72 probands with genotype-positive, phenotype-negative family members. Of the 170 probands with negative testing, there are approximately 135 probands with first-degree relatives under the age of 18. We again assumed a 40% penetrance. For power analysis, we also made the assumption that 95% of asymptomatic

genotype-positive, phenotype-negative would pursue annual screening. We will be able to detect an effect size as small as 13% between groups with 80% power and a p of 0.05.

**C. Study Procedure**
Not applicable

**D. Study drugs**
Not applicable

**E. Medical Device**
Not applicable

**F. Study questionnaires**
Questionnaires need to be constructed. For the primary outcome, the questionnaire will ask both probands with positive genetic testing or negative genetic testing if the HCM diagnosis and/or genetic testing result were conveyed to extended family. For the secondary outcome, the questionnaire will confirm each family's approach to surveillance in clinically asymptomatic family members with negative echocardiogram, EKG, clinical assessment findings. It will be determined if the family plans to do annual surveillance or surveillance at a less frequent time interval.

**G. Study subjects**
The study participants will be drawn from a comprehensive cardiomyopathy database, which includes data on all HCM probands who have been diagnosed in the last 10 years and have been seen at CUMC. Immediate family members' genetic testing results if performed are also included in this database. Inclusion criteria for primary outcome analysis include patients diagnosed with HCM from day of birth through 50 years of age and unexplained LV hypertrophy associated with non-dilated ventricular chambers with LV hypertrophy (defined as LV wall thickness > 15 mm for adults and a LV wall thickness > 2 standard deviations above the mean for age, sex or body size for children). Exclusion criteria for primary outcome analysis include presence of another cardiac (in addition to LV hypertrophy) or systemic disease that would be capable of producing hypertrophy, lack of genetic testing and genetic testing finding a variant of unknown significance. For the secondary outcome, inclusion criteria also include, presence of an asymptomatic first-degree relative, less than 18 years of age. For those in the first study arm, inclusion criteria also include that these aforementioned relatives also must have positive genetic testing.

**H. Recruitment of Subjects**
Subjects will be recruited either through email, letter or telephone. Patients with scheduled clinic appointments will also be recruited during their visit.

**I. Confidentiality of Study Data**
Participants in this study will be given a unique identifier. Identifying information will be coded and safeguarded to protect confidentiality. Data will be stored on a secure network database, accessible only to investigators.

**J. Potential conflict of interest**
No conflict of interest.

**K. Location of the Study**
Data analysis will take base in Russ Berrie Medical Science Pavilion, CUMC.

**L. Potential Risks**
There are no potential risks associated with this study.

**M. Potential Benefits**
There are no potential benefits associated with this study.

**N. Alternative Therapies**
Not applicable

**O. Compensation to Subjects**
A small grant will be applied for in order to give a small monetary compensation to study participants.

**P. Costs to Subjects**
There are no additional costs to subjects.

**Q. Minors as Research Subjects**
Approval from the Department of Pediatrics Committee on Human Investigation will be received prior to initiation of the study.

**R. Radiation or Radioactive Substances**
Not applicable

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