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The return of first-degree relatives of hypertrophic cardiomyopathy patients for HCM-related follow-up

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THE RETURN OF FIRST-DEGREE RELATIVES OF HYPERTROPHIC CARDIOMYOPATHY PATIENTS FOR HCM-RELATED FOLLOW-UP

by

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2013
DEDICATION

I would like to dedicate this thesis to my mother. Without her strength, guidance, and memory, I would never have started or finished it.
Hypertrophic cardiomyopathy is an inherited heart disease characterized by unexplained thickening of the left ventricle. Given its autosomal dominant method of inheritance, all first-degree family members of an HCM patient have a 50% risk of inheriting the disease. Since family members are at high risk for disease, we consider HCM a disease of not just a single patient, but of a whole family. Medical guidelines propose that all first-degree family members seek HCM-related follow-up. In most cases the follow-up involves longitudinal clinical screening. In some cases genetic testing is also indicated for relatives.

In an observational study of 361 HCM patients and family members, who were seen at a specialized HCM clinic in the Cardiovascular Genomics Center at Brigham and Women’s Hospital in Boston, MA, we show that only 39% of relatives pursued any HCM-related follow-up. In general, children of HCM patients were more likely to seek follow-up than siblings or parents of HCM patients. In cases where genetic testing was indicated for family members,
relatives were more likely to seek clinical than genetic screening. Yet, a large proportion did seek both types of testing.

Genetic testing results seemed to influence the return by relatives for clinical follow-up. When a disease-causing genetic variant was identified in one individual, family members were more likely to have HCM-related follow-up than when no genetic variant was identified or no genetic testing was performed.

This study provides initial insights into the causes for the low overall rate of familial follow-up for an inherited disorder. We recognize that relatives are lost to follow-up at the stage when the initial patient must transmit information about follow-up to his relatives. Of greater concern, our data suggests that patients may be misinterpreting negative genetic test results, which may reflect a mutation in a gene that has yet to be discovered, despite appropriate genetic counseling.

Determining what factors influence familial follow-up allows us to reassess current processes, so as to ensure that more at-risk family members receive evaluations. Providing clinical care to the entire HCM population is important for treatment of symptoms and prevention of sudden cardiac death, the most devastating outcome caused by HCM. With the use of genetic testing we are also able to identify HCM patients before any symptoms arise. Studying this asymptomatic population allows us to learn more about disease biology and progression with the end goal of finding a medical therapy to reverse or prevent HCM.
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<tr>
<td>CVGC</td>
<td>Cardiovascular Genetics Center</td>
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<td>DNA</td>
<td>Deoxyribonucleic Acid</td>
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<tr>
<td>ECG</td>
<td>Electrocardiogram</td>
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<tr>
<td>ICD</td>
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<td>LMM</td>
<td>Laboratory for Molecular Medicine</td>
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<tr>
<td>LVH</td>
<td>Left Ventricular Hypertrophy</td>
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<tr>
<td>SCD</td>
<td>Sudden Cardiac Death</td>
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<tr>
<td>VUS</td>
<td>Variant of Unknown Significance</td>
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INTRODUCTION

Hypertrophic Cardiomyopathy

Hypertrophic Cardiomyopathy is a disease of the heart muscle characterized by left ventricular wall thickening or hypertrophy (LVH) that cannot be explained by an existing cause, such as pressure overload or metabolic abnormalities (Gersh, et al., 2011). At the cellular level, myocyte disarray and increased amounts of cardiac fibrosis occur with hypertrophy (Gersh, et al., 2011). HCM affects about 1 in 500 people in the general population, and it is the most common cause of sudden cardiac death in young people (Maron, 1995).

Clinical manifestations of HCM vary widely, with a broad range of disease severity and age of onset. Common symptoms include shortness of breath, especially upon exertion, chest pain, palpitations, orthostasis, presyncope, and syncope (Cirino & Ho, 1993). HCM patients can have any variety of these symptoms ranging from asymptomatic to progressive heart failure (Cirino & Ho, 1993). Importantly, there is not always a correlation between the severity of symptoms that are experienced by a patient and the patient’s risk for life-threatening ventricular arrhythmias or sudden cardiac death (SCD). Risk for arrhythmias or SCD may be high even in patients with very mild cardiac symptoms. There are even rare cases when the first presentation of disease is sudden cardiac death (Maron, 2000). For these reasons there is a great need for a method of screening that can detect the disease in the absence of symptoms. Normally left ventricular hypertrophy, the hallmark of HCM, presents at
adolescence or young adulthood, which is potentially related to pubertal development changes (Cirino & Ho, 1993). There are cases, however, of LVH presenting as early as infancy or childhood and also much later in life (Cirino & Ho, 1993).

Figure 1. Gross and Histological Anatomy of HCM. Figure 1 shows a comparison between a normal heart and an HCM heart. On a gross level, the left ventricle of an HCM heart has visible hypertrophy. Note the resultant changes in chamber size. Microscopically, myocytes in a normal heart have regular order, and there is minimal fibrosis. In an HCM heart there is myocyte disarray. The regular order of the cells is lost. The light pink areas are diffuse fibrosis. (Arad, Seidman, & Seidman, 2002)

Genetic Basis for HCM

Hypertrophic cardiomyopathy was first recognized as a familial disease inherited in an autosomal dominant pattern over 50 years ago (Hollman, 1960). Through linkage studies twenty years ago we discovered that HCM is caused by
mutations in genes coding for cardiac sarcomeric proteins (Ho, 2012). For this reason HCM is often referred to as the “disease of the sarcomere” (Thierfelder, et al., 1994). Over 1,000 HCM causing mutations have been discovered in at least 8 genes either within or associated with the sarcomere, including beta-myosin heavy chain, cardiac myosin-binding protein C, cardiac troponin T, cardiac troponin I, essential myosin light chain, regulatory myosin light chain, alpha-tropomyosin, cardiac actin, and titin (Gersh, et al., 2011). The majority of mutations, about 80%, are in genes coding for myosin heavy chain and myosin binding protein C (Richard, et al., 2003).

Figure 2. Model of Sarcomeric Proteins. Figure 2 shows the protein components of the sarcomere. These proteins are coded for by the genes that when mutated cause HCM. Myosin heavy chain and myosin binding protein C are the genes that are most commonly mutated in HCM patients. (Arad, Seidman, & Seidman, 2002)

The number of mutations causing disease is constantly growing. Currently genetic testing can identify a mutation in approximately 40-50% of HCM patients.
Patients who have a family history of HCM have a higher mutation detection rate of up to 70%. Patients with no family history of disease, where the mutation may have arisen de novo, have a lower rate of detection at approximately 30-40% (Ho, 2012). Most of the discovered mutations are unique to a family. There are few instances of a single mutation explaining disease in unrelated patients (Ho, 2012).

**Diagnosis of HCM**

Clinical diagnosis of HCM occurs when unexplained LVH is identified, most often by a two-dimensional echocardiograph or more recently by magnetic resonance imaging (Maron, Seidman, & Seidman, 2004). Patients are most commonly diagnosed with HCM when they present with cardiac symptoms, have a murmur upon physical exam, have an abnormal electrocardiogram (ECG), or come to the doctor for family screening (Maron, Seidman, & Seidman, 2004). Sometimes a diagnosis may only occur after a patient has experienced an adverse event.

The diagnosis of HCM can be difficult, as other conditions that cause LVH, including hypertensive heart disease, disorders of cardiac valves, athlete’s heart, or storage disease must be ruled out. The clinical management of these conditions is considerably different than that for HCM. Genetic testing can resolve an ambiguous diagnosis, because the identification of a disease-causing sarcomere mutation definitively differentiates HCM from other conditions where hypertrophy is present.
Management of HCM

There is currently no treatment that can prevent or reverse HCM. There is, however, a three-pronged strategy to manage disease that includes treatment of symptoms, assessment of SCD risk, and counseling and screening. The counseling and screening aspect of management includes lifestyle recommendations, family screening, and genetic counseling (Ho, 2012a).

The two most common symptoms of HCM are dyspnea upon exertion and chest pain. These symptoms are likely caused by diastolic dysfunction, or incomplete cardiac relaxation (Olivotto, et al., 2006). Beta-blockers or L-type calcium channel blockers are used to treat these symptoms as these medications prolong diastolic fill time (Ho, 2012a).

Palpitations are common in HCM, a symptom that can indicate an underlying cardiac arrhythmia. Atrial fibrillation, the most common HCM arrhythmia, prevents complete emptying of the cardiac atria, which can result in stagnant blood that can clot and lead to thromboembolism. Anticoagulants are prescribed to these patients with atrial fibrillation to address this risk (Ho, 2012).

In about two thirds of HCM patients, disease is complicated by obstruction due to either hypertrophy that impinges into the outflow tract of blood or due to another HCM hemodynamic abnormality. The obstruction may either be at rest or only under provocation by exercise or tachycardic arrhythmias (Maron, et al., 2006). Vasodilators, typically used to treat symptoms in other cardiovascular diseases, can exacerbate the obstructive physiology and are contra-indicated in
HCM patients with obstructive disease (Ho, 2012). If patients become limited by symptoms relating to obstruction they can be treated with disopyramide. Patients with severely symptomatic obstructive HCM may consider having invasive septal reduction (Gersh, et al., 2011). Options for reduction include surgical myectomy and alcohol septal ablation, procedures that respectively excise or produce an infarct in the hypertrophied obstructive segment. Although these procedures improve blood flow through the heart and, in turn, cardiac symptomology they are not proven to increase lifespan or decrease SCD risk (Ho, 2012).

In addition to managing symptoms we assess for sudden cardiac death risk. SCD risk is clinically assessed on the following five factors: personal history of resuscitated cardiac arrest, family history of SCD, becoming hypotensive upon exercising, discovery of ventricular ectopy, and a history of unexplained syncope (Cirino & Ho, 1993).

Any patient with a personal history of sudden cardiac arrest will be advised to have an implantable cardioverter-defibrillator placed. Patients who have two or more of these risk factors have an increased risk for SCD, and may be advised to have an ICD placed to prevent SCD (Elliott, et al., 2000). There are, however, additional complications associated with ICDs, so the decision to implant a device should be assessed on a case-by-case basis (Czosek, et al., 2012).

There are a number of clinical measures used to identify and characterize additional risk factors for SCD. Physicians compile complete family histories of
SCD in affected family members. Exercise testing is used to monitor blood pressure response in a controlled clinical environment. Holter monitoring is used to detect ventricular ectopy over a longer time period than that which occurs in the clinical setting. These risk factors tests are repeated every 12 to 24 months, depending on the findings and symptoms, to identify the patient’s SCD risk throughout life and as disease progresses.

Physicians devote considerable time to counseling HCM patients. Patients with HCM, dependent on the extent of disease, may be advised to avoid certain activities or situations, including competitive or endurance training, burst exertion, dehydration, and hypovolemia. These scenarios can be particularly dangerous to patients with obstructive HCM (Cirino & Ho, 1993). Although SCD has been documented in competitive athletes with HCM, (Maron, 2003) moderate aerobic exercise (that allows conversation) is recommended for HCM patients with minimal symptomology (Gersh, et al., 2011).

The other arm of counseling involves family screening, because sarcomeric HCM is an inherited disease. In genetic disease, like HCM, physicians have the unique opportunity to treat not only the patient, but also the patient’s entire family. By identifying disease in family members early we can prevent future complications and assess for SCD risk (Ho, 2012). The clinical and genetic aspects and recommendations of screening family members will be discussed in the sections to follow.
Clinical Screening for Family Members

Since HCM is a familial disease that follows an autosomal dominant inheritance pattern, it is recommended that first-degree family members of an HCM patient undergo clinical screening. Proper clinical screening includes a physical, family history, two-dimensional echocardiogram and 12-lead ECG (Maron, Seidman, & Seidman, 2004). Clinical screening is focused on family members aged 12 to 18, because this is the most common time for disease to develop (Maron, Seidman, & Seidman, 2004). Patients in this age group should be seen every 12-18 months (Maron, Seidman, & Seidman, 2004). Historically, after reaching age 21 with a negative evaluation for HCM patients were thought not to carry the gene for disease, and they were deemed unaffected (Maron, Seidman, & Seidman, 2004). However recent information indicates the potential for late onset disease, and a negative evaluation at 21 years of age cannot rule out the future development of HCM. As such, continued clinical screening for patients older than 21 is recommended approximately every five years (Maron, Seidman, & Seidman, 2004). It is generally reasonable to defer screening in family members younger than 12 years old, because LVH is infrequent in this age group (Maron, Seidman, & Seidman, 2004).

Genetic Testing

Ten years ago genetic testing for HCM moved from research laboratories to clinically available tests (Ho, 2012). There are two types of genetic tests, diagnostic and predictive. Diagnostic testing uses a candidate-gene approach
where a panel of sarcomere genes is sequenced. In addition to the sarcomere genes, a few genes associated with diseases that have similar clinical presentations, but can be explained by metabolic, storage, or mitochondrial disorders, are included (Arad, et al., 2005). This comprehensive test tries to identify the mutation that causes disease in an HCM patient.

If a diagnostic test identifies a disease causing mutation there is an opportunity for predictive testing in the patient’s family members. Predictive testing is the targeted sequencing of the region of the gene where the previously identified mutation is located. Predictive testing only has the power to confirm or deny the presence of a known mutation. A predictive test cannot find any additional mutations (Ho, 2012).

**Interpreting Genetic Test Results**

Proper interpretation of genetic test results is key to using genetic information clinically. Genetic test results yield probabilities instead of quantitative outcomes like other clinical tests (Ho, 2012). Once a DNA variant has been found in a gene coding for a sarcomeric protein, the laboratory attempts to determine the probability that the variant is pathogenic or disease causing (Ho, 2012). The probability a variant is pathogenic increases when family studies are performed. We look for segregation of the variant with clinical affection status in a large number of relatives. Other considerations that increase the likelihood that a variant is pathogenic include the absence of the variant from
large numbers of healthy normal individuals, and evidence that the variant alters a gene region that is highly conserved over evolutionary time.

**Classification of Variants**

Several criteria are used to support the classification of a variant as pathogenic. These criteria were developed by the Laboratory for Molecular Medicine (LMM), which is the preferred genetic testing facility of the CVGC clinic. First, when there is significant data showing the variant segregating with disease in one or multiple families. Second, we call a variant pathogenic when there is moderate segregation data, and the variant is absent from a large number of controls, and the region of the genome where the variant occurs is evolutionarily conserved. Third, a variant can be called pathogenic in the absence of segregation data if it does not occur in a large, race-matched group of controls and we have convincing functional data about the variant, such as evidence that the variant causes HCM in an experimental model. A DNA variant is designated as pathogenic if it causes a loss of function in a protein that is known to have a critical role in disease. Finally, if a variant arises *de novo* in a gene implicated in the disease, and genetic analyses confirm biologic parentage, it will be classified as pathogenic. In each of these cases we have confidence that the variant explains why the patient developed disease (Laboratory of Molecular Medicine, 2011).

When we still believe the variant is disease causing, but we have less definitive information about the variant, the variant is called likely pathogenic. The
The most ambiguous variant classification is unknown significance. When we find a variant of unknown significance (VUS) we do not have sufficient data to determine if it is disease causing or if it is a benign polymorphism. A variant that is absent in a large group of controls but has no other information available is a variant of unknown significance. A novel variant that has been predicted to cause disease by computational assessment only is a VUS. Also, any variant that has conflicting information about whether or not it is disease causing will be called a VUS. Detecting variants of unknown significance does not give us any additional information for clinical use (Laboratory of Molecular Medicine, 2011).
Possible Clinical Outcomes from Genetic Test Results

There are a number of possible outcomes for genetic test results that impact how clinical follow-up for family members should proceed. In the absence of any genetic test results all first-degree relatives should be longitudinally clinically followed by a cardiologist as outlined in the section on clinical screening. The following will explain in which cases genetic testing can narrow the focus of clinical screening to just those family members who are at-risk to develop inherited disease.

When diagnostic testing can identify a variant that is classified as pathogenic or likely pathogenic, all first-degree family members can pursue predictive genetic testing with a level of confidence that their risk for disease will be ascertained. Those who are negative for the mutation are not at-risk to develop HCM. Those who are positive for the mutation are at-risk, need to be longitudinally screened by a cardiologist, and should have all of their first-degree relatives tested as well. This initiates a process termed cascade screening.

When diagnostic testing identifies a variant of unknown significance, there is ambiguity as to whether or not the variant causes disease. Defining whether or not additional clinically affected family members carry the variant of unknown significance can be helpful. If the variant segregates with disease in the family the classification can be updated to pathogenic or likely pathogenic. If it does not segregate with disease in the family, the variant can be re-classified as likely benign. This is useful not only for the family, but also for our general knowledge.
of disease-causing mutations and their classifications. As long as uncertainty exists, all family members need longitudinal clinical screening.

Last, if a diagnostic test fails to identify a variant we call this a negative genetic test result. The proband’s HCM may still be familial in nature, but there is no clear genetic marker to help focus further clinical screening of family members. All first-degree relatives should continue their longitudinal screening. Importantly, a negative genetic test result means only that we failed to identify a disease-causing variant in the small panel of HCM genes we sequenced. Currently we do not know all of the genes involved in causing or modifying HCM. Until we have discovered all of them a negative genetic test result can still imply familial disease. In time, with the discovery of more genes that modify and cause HCM and the development of more comprehensive sequencing techniques, we may be able to re-test this group of patients to find novel disease-causing mutations.

**Clinical Genetics**

Clinically genetic testing in HCM patients has limited utility in impacting patient management. While the identification of a mutation clarifies the patient’s diagnosis of HCM, genetic test results are not likely to directly change the patient’s care. HCM is a heterogeneous disease. Symptoms, age of onset, the pattern and amount of left ventricle hypertrophy, existence of obstruction, and the patient’s risk for sudden cardiac death vary not only among patients, but also across family members who share a disease mutation (Ho, 2012). Therefore, a
specific mutation cannot normally predict anything additional about disease progression or severity.

Genetic testing’s greatest current practical value lies in helping to guide the management of the family. Once a disease-causing family mutation has been identified in the proband all first-degree relatives of the patient can and should be tested for the mutation. First-degree relatives are any children, siblings, or parents of the proband. They each have a 50% chance of carrying the disease mutation due to HCM’s autosomal dominant inheritance pattern. If they carry the mutation they are at risk to develop HCM and should undergo serial clinical screening. Those who do not carry the mutation are not at risk to develop HCM.

A mutation carrier who wishes to have children can consider pre-implantation genetic diagnosis. Using in vitro fertilization, early stage embryos can be tested for the HCM causing mutation. Then only embryos that do not carry the mutation will be implanted in an attempt to start pregnancy (Ho, 2012). Pre-implantation diagnosis can be especially useful in families where the mutation is associated with severe disease phenotypes. When many HCM patients with well-managed disease lead relatively normal, full lives, the majority of family members do not pursue this invasive technique.

**Preclinical HCM patients**

The increased use of clinical genetic testing has created a new group of patients termed preclinical. Preclinical patients are genotype positive, carrying a disease-causing mutation, but phenotypically negative, meaning they have no
evidence of LVH on cardiac imaging. All preclinical HCM patients are asymptomatic. They may, however, show signs of HCM such as ECG abnormalities, or alterations on their echocardiograms (McKenna, et al., 1997).

We have also identified other markers that are associated with preclinical HCM. When Doppler tissue imaging is performed as part of an echocardiogram, we have seen diastolic dysfunction in the preclinical cohort. Diastolic function measurements in combination with ejection fraction, another measurement from an echocardiograph, were found to be a good predictor of preclinical disease (Ho, et al., 2002). In another study, impaired cardiac energetics seemed linked to preclinical HCM. This study looked at the relationship between levels of ATP and cardiac phosphocreatine and found it similar in HCM mutation carriers with and without LVH (Crilley, et al., 2003). A third study found an association between preclinical HCM and increased collagen synthesis. High levels of a serum protein that marks collagen turn-over were found in both preclinical and overt HCM patient cohorts (Ho, et al, 2010).

The discovery and characterization of cardiac changes that occur before hypertrophy are a big step forward in our understanding of HCM. This new group of patients is an exciting population to study. We have the ability to identify an at-risk population before we are even able to clinically diagnose these patients. This ability is a rare phenomenon in medicine. The more short-term good news for future patients is that we are becoming increasingly better at identifying HCM early. In families where genetic testing fails to find a disease-causing mutation
there are still research-based ways to look for disease in at-risk patients. More importantly, our ability to study mutation carriers gives us the unique opportunity to study early disease. Finding and studying changes in the preclinical patients, who have yet to develop disease, helps us learn more about HCM disease biology. We hope to ultimately develop a disease-modifying therapy based on these findings.
CURRENT STUDY

We are investigating the rate of return of family members for clinical follow-up when their first-degree relative has a diagnosis of HCM. Since HCM is an autosomal dominant disease all first-degree family members of an HCM patient have a 50% chance of carrying the genetic information that makes them at-risk to develop disease. For this reason we consider disease management in terms of a family and not just the individual patient. In clinic, we advise each patient to have all of his or her children, siblings, and parents clinically evaluated for HCM.

Maintaining longitudinal clinical care of this high-risk population is one of the most proactive parts of managing HCM. With adequate clinical care and follow-up most HCM patients live full lives with their day to day lifestyles only minimally limited by disease. The key to this type of disease management is identifying at-risk patients early. Then we can optimize the care an entire family receives. We are able to follow patients more closely when any symptoms change or present and when they are at an age when disease is most likely to develop.

To determine the extent to which families are pursuing clinical follow-up for HCM, we are looking at a cohort of HCM patients seen at the Cardiovascular Genetics Clinic at Brigham and Women’s hospital who have clearly documented family information available. We want to determine what fraction of the patients’ family members return for follow-up of disease. There are many factors that may
influence who returns or does not return to clinic for evaluations. In this study we are looking for trends involving relationship to the proband, the presence or absence of genetic test results, and in cases where genetic testing has occurred, the classification of the identified mutations.

We hope that learning more about what makes family members more likely to return will allow us to increase the percentage of family members who pursue follow-up for HCM in the future. Increasing the number of family members we test will both help us learn more about HCM and allow patients to take maximum advantage of the clinical treatment and management of HCM currently available.
METHODS

We reviewed the records of all HCM patients who were evaluated at the Cardiovascular Genetic Center at Brigham and Women’s Hospital between 1998 and 2012 and had pedigrees providing complete information about their first-degree family members. These patients were seen in the HCM clinic, which is a subspecialty of the CVGC. We obtained information on the patients and their family members by querying the CVGC database of longitudinal patient records and supplementing with information from a review of their medical records.

All new patients visiting the HCM clinic at the CVGC are provided full genetic counseling. They are also provided printed educational material describing HCM as an inherited disease, recommendations for clinical follow-up, and the genetic testing process. At each patient’s return visit they are reminded to seek screening for family members if they have not already done so.

There were 361 patients who eligible for this study. The 361 patients have a total of 1,761 living first-degree relatives. We investigated the family history of each proband to determine which first-degree relatives, if any, pursued any type of follow-up, either clinical or genetic screening, through the clinic. We separated the first-degree relatives into categories based on their relationship to the proband: children, siblings, and parents. Each family has only one designated proband to facilitate classification of relationship and to ensure that no large families are counted multiple times in the study. The designated proband is either
the first family member to be evaluated in clinic or, in the case of genetic testing, the patient who underwent large-scale genetic screening first within the family.

We divided the cohort based on genetic testing status, including a genotype positive group, genotype negative group, and not genetically tested group. Each proband in the genotype positive group has a disease-causing mutation identified. The genotype positive group can be further broken down by variant classification status as determined by the Laboratory for Molecular Medicine at the time the genetic testing was performed. The categories for variants that are considered mutation positive are pathogenic, likely pathogenic, and variant of unknown significance or VUS. The members of the genotype negative group underwent diagnostic genetic testing, but did not have a disease-causing variant identified. In five probands, variants were classified as likely benign, and these patients were included in the genotype negative group. The third group contains all of the probands who did not pursue genetic testing.

We performed hypothesis testing comparing proportions in different sized populations with significance set at 95%.
RESULTS

A general profile of the 361 probands included in this study, grouped by genetic testing status, is presented in the table below.

**Table 1. Clinical Summary of HCM Probands**.

<table>
<thead>
<tr>
<th>Genotype Positive</th>
<th>Genotype Negative</th>
<th>Not Genetically Tested</th>
<th>All probands</th>
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<td>139</td>
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<td>range</td>
<td>(16,80)</td>
<td>(19,83)</td>
<td>(15,85)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of males</td>
<td>81</td>
<td>56</td>
<td>89</td>
</tr>
<tr>
<td>Number of females</td>
<td>63</td>
<td>22</td>
<td>50</td>
</tr>
<tr>
<td>Number of probands with positive family history of HCM</td>
<td>86</td>
<td>14</td>
<td>51</td>
</tr>
<tr>
<td>Number of probands with positive family history of SCD</td>
<td>56</td>
<td>18</td>
<td>40</td>
</tr>
</tbody>
</table>

** Average age and gender breakdown of the probands are included. Additionally the presence or absence of both a family history of HCM and a family history of SCD were recorded in each proband.

In the study of 361 HCM patients seen in our clinic who had comprehensive family information recorded, the patients had a total of 1,761 first-degree relatives. We grouped the family members by the genetic testing status of
the proband they are related to. Information about the first-degree relatives of the probands in each of the three groups is in the table below.

**Table 2. Summary of HCM Probands' First-Degree Relatives**.

<table>
<thead>
<tr>
<th></th>
<th>Genotype Positive</th>
<th>Genotype Negative</th>
<th>Not Genetically Tested</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Probands</strong></td>
<td>144</td>
<td>78</td>
<td>139</td>
<td>361</td>
</tr>
<tr>
<td>Number of Children</td>
<td>258</td>
<td>127</td>
<td>224</td>
<td>609</td>
</tr>
<tr>
<td>Number of Siblings</td>
<td>328</td>
<td>148</td>
<td>320</td>
<td>796</td>
</tr>
<tr>
<td>Number of Parents</td>
<td>151</td>
<td>67</td>
<td>138</td>
<td>356</td>
</tr>
<tr>
<td><strong>Total number of relatives</strong></td>
<td>737</td>
<td>342</td>
<td>682</td>
<td>1761</td>
</tr>
</tbody>
</table>

**The first row of this table shows how many probands fall into each of the genetic testing status groups. The rest of the table divides the probands' relatives by both relationship to proband and genetic testing status as further described. The genotype positive group contains all family members related to a HCM patient who has a pathogenic, likely pathogenic, or VUS identified. The genotype negative group contains all family members related to an HCM patient who underwent genetic testing, but had no variant identified. The not genetically testing group includes the family members of HCM patients who did not opt to have genetic testing.

Out of all 1,761 family members, we looked first to see who came back for any type of HCM-related follow-up including clinical evaluation only, genetic testing only, and both clinical and genetic testing. Overall, 39% of the family members pursued any type of follow-up. Children of probands sought follow-up at a rate of 46% returning, which is a slightly higher rate than the 35% of both
siblings and parents returning to clinic. The rate of children returning is also higher than the total percentage of relatives returning.

Table 3. Overall Relatives Seeking Follow-up for HCM**.

<table>
<thead>
<tr>
<th>Overall Relatives Seeking Follow-up for HCM</th>
<th>% Returning for Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>*46%</td>
</tr>
<tr>
<td>Siblings</td>
<td>35%</td>
</tr>
<tr>
<td>Parents</td>
<td>35%</td>
</tr>
<tr>
<td>Total</td>
<td>39%</td>
</tr>
</tbody>
</table>

** Values are listed as percentages to account for patients’ ability to have multiple children and sibling, but only two biological parents.
*Statistically significantly different from both % of siblings and % of parents returning for follow-up at a 95% confidence interval.

After looking at the percentages of all patients’ family members returning for any type of HCM examination, we divided the relatives by the genetic testing status of the proband. First we looked at genotype negative and not genetically tested probands’ families. Afterwards, we examined the slightly more complex genotype positive probands’ relatives. For these relatives, there are some cases where genetic testing is implicated, and we can compare rates of genetic and clinical follow-up.

Genotype negative proband’s family members pursued follow-up for HCM at 31% overall. Fewer children received evaluations for HCM, only 27%. More siblings, about 32%, and parents, about 36%, returned to the clinic for HCM evaluations. See data for genotype negative family members in the table below.
Table 4. Relatives of Genotype Negative Probands Seeking Follow-up for HCM**.

<table>
<thead>
<tr>
<th></th>
<th>% Returning for Follow-Up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>27%</td>
</tr>
<tr>
<td>Siblings</td>
<td>32%</td>
</tr>
<tr>
<td>Parents</td>
<td>36%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>31%</strong></td>
</tr>
</tbody>
</table>

** Percentages of family members seeking clinical HCM screening, who are related to a proband who underwent genetic testing, but did not have a disease-causing mutation identified. All percentages are not significantly different at a 95% confidence interval.

When probands did not opt for HCM genetic testing, 32% of their relatives overall returned for HCM follow-up. This value is not statistically different from the 31% of relatives who had follow-up in the genotype negative group. Among those who did not have genetic testing, 36% of children were clinically evaluated for HCM. This is higher than the overall percent return in this group. 29% of both siblings and parents return to clinic. This is not significantly lower than overall relatives seeking evaluations for HCM. A summary of this group’s data follows.
Table 5. Relatives of Not Genetically Tested Probands Seeking Follow-up for HCM**.

<table>
<thead>
<tr>
<th>Relatives of Not Genetically Tested Probands Seeking Follow-up for HCM</th>
<th>% Returning for Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>36%</td>
</tr>
<tr>
<td>Siblings</td>
<td>29%</td>
</tr>
<tr>
<td>Parents</td>
<td>29%</td>
</tr>
<tr>
<td>Total</td>
<td>32%</td>
</tr>
</tbody>
</table>

** Percentages are separated by the family members’ relationship to the patient. All percentages are not significantly different at a 95% confidence interval.

Last, we have the follow-up data for the relatives of HCM patients who have had disease-causing mutations identified upon genetic testing. The majority of these relatives are advised to have both genetic and clinical follow-up for HCM. Our data, as summarized in Table 6 shows how many of each type of relative pursued genetic testing, clinical HCM testing, or any follow-up for HCM at all.

Table 6. Relatives of Genotype Positive Probands Seeking Follow-up for HCM**.

<table>
<thead>
<tr>
<th>Relatives of Genotype Positive Probands Seeking Follow-up for HCM</th>
<th>% Returning for genetic testing</th>
<th>% Returning for clinical evaluations</th>
<th>% Returning for any type of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>44%</td>
<td>43%</td>
<td>*64%</td>
</tr>
<tr>
<td>Siblings</td>
<td>13%</td>
<td>40%</td>
<td>41%</td>
</tr>
<tr>
<td>Parents</td>
<td>18%</td>
<td>32%</td>
<td>39%</td>
</tr>
<tr>
<td>Total</td>
<td>25%</td>
<td>38%</td>
<td>48%</td>
</tr>
</tbody>
</table>

** Percentages are separated by the family members’ relationship to the patient. Siblings, parents, and total relatives return for clinical evaluation at a higher percentage than genetic testing at a 95% confidence interval. *Statistically significantly different from both % of siblings and % of parents returning for any type of follow-up at a 95% confidence interval.
Overall trends show that more relatives pursue clinical than genetic testing. Children, however, pursue clinical and genetic testing at approximately equal rates. Children of mutation positive probands are followed up for HCM at 64%. This is the highest rate of any group we studied. Siblings and parents seek follow-up at only 41% and 39% respectively. The Venn diagram below shows that while the highest proportion of relatives did not pursue any type of HCM follow-up, the majority of people tested had both clinical evaluations and genetic testing done. There are only a small amount of family members who had genetic testing, but were never screened clinically.
Figure 3. Proportional Venn Diagram of Genotype Positive Probands’ Relatives Pursuing Testing for HCM. Figure 3 groups the relatives related to a genotype positive proband by what type of HCM testing they pursued. 380 relatives did not seek any HCM-related testing. 21 relatives had genetic testing only. 130 family members had clinical evaluations only. The remaining 206 relatives had both genetic testing and clinical evaluations.

In the genotype positive cohort we separated the group further by variant classification of the mutation identified in the proband. Figure 4 shows how each of the subdivisions of the genotype positive group compare to the genotype negative and not genetically tested groups. Relatives of a proband with a pathogenic or likely pathogenic variant seek HCM-related follow-up about 50% of the time. Relatives of a proband with a variant of unknown significance seek follow-up significantly less with about 38% returning (significant at 95%
confidence interval). Family of probands who had genetic testing, but did not have a disease-causing mutation identified, returned at the lowest rate of 31%. However, a similar amount, 32%, of relatives of not genetically tested probands returned for HCM-related follow-up.

**Figure 4. Proportion of relatives screened by probands' genetic testing status.** The y-axis denotes the percentage of probands' relatives who sought any type of HCM-related follow-up. The x-axis groups the relatives by the genetic testing status of the proband who the relative is related to. The genotype positive group is separated into three variant classification categories: pathogenic, likely pathogenic, and variant of unknown significance. The graph allows a comparison between the different subgroups of the genotype positive cohort and both the genotype negative and not genetically tested groups. The last bar is the total return rate, which includes all of the family members in the first 5 groups.
DISCUSSION

Overall, only 39% of the first-degree relatives of HCM patients treated in the CVGC clinic pursue HCM-related follow-up. This is a disappointingly low percentage. We advise 100% of first-degree relatives of HCM patients to seek clinical evaluations as this group has a 50% risk of inheriting HCM. When relatives are being screened at a rate lower than 50% there are certainly family members who have or will develop HCM that are not receiving proactive clinical care and management.

The CVGC HCM clinic is a highly specialized clinic. The team at the CVGC provides family counseling at every patient visit. They believe the best way to treat HCM is not only treating the patient, but treating the entire family. Each member of the team is actively involved in spearheading the latest HCM research. If return for family members is low for patients seen in this ideal clinic, it must be even lower for patients seen in less specialized cardiology clinics.

There are many reasons why family members may not pursue HCM-related follow-up. First, it is inconvenient to schedule and take time to visit a doctor’s office. Just as people do not always visit their primary care physician for a yearly physical, people may not come to the cardiologist for HCM evaluation.

Second, family members may be afraid to learn about a medical illness. When a family member has witnessed the medical problems related to HCM in his relative, he may prefer not to discover whether or not he too has HCM. He
may also fear discrimination from family, friends, work, or insurance companies if he is diagnosed with HCM.

Third, parents of an HCM patient may not want to be evaluated for HCM because they would feel guilty for passing the disease onto their child. In autosomal dominant disease only one parent needs to transmit the disease. Discovering which parent is responsible for carrying and passing on the disease may introduce problems in the family dynamic.

One of the reasons preventing family members from seeking HCM-related follow-up is lack of understanding in the proband, the family member, or both people. This factor is important, because we have the most influence over it. Every HCM patient is advised to bring his first-degree relatives to clinic for screening, and we provide referrals and resources to help. We, however, have no way of knowing how much the patient understood about the familial nature of HCM and its pattern of inheritance. Even when we believe the patient understands our message, we do not have control over how or if the patient transmits the message to his relatives. We also do not know how, in turn, the relative interprets the information. Some of our results suggest that patients may not be interpreting genetic test results properly. If this is true, we will have to rethink how to explain this information in the clinical setting.

Another overall trend in our data is that children of probands return for HCM-related follow-up in the highest relative numbers. This is not surprising, because in any cases where children are under 18, their parent, the proband,
ultimately manages their health care. More generally, we expect that healthcare decisions by adult children are influenced by parental input. This trend suggests that the transmittal of advice, regarding HCM follow-up, between proband and relative may be where we lose relatives to return. We can interpret the data to mean that probands understand the message heard in clinic, but they have more success convincing their children that it is important to seek follow-up than they do convincing their siblings or parents.

Interestingly, when looking at groups of relatives separated by proband genetic testing status, both genotype positive and not genetically tested groups have the highest return for follow-up in children. In the genotype negative group children are the least likely to return for HCM-related follow-up. The low levels of child follow-up in the genotype negative group is concerning, especially when children have the highest levels of follow-up in all other groups. When a proband is genotype negative, we advise him and his family to seek the same clinical care that they would have if they had not pursued genetic testing at all.

These data suggest that parents are misinterpreting negative genetic test results. When we perform diagnostic genetic testing on a proband, we only sequence and analyze a subset of genes. There are many more genes that may contain HCM-causing mutations that are not included on this panel, because they have not yet been discovered. There are also certain genetic changes that may cause disease, but cannot be detected by this sequencing method. Current genetic testing only identifies a disease-causing mutation in 40-50% of HCM
patients (Ho, 2012). Negative genetic test results do not rule out a familial cause of HCM. If anything, family members of patients who are genotype negative should be coming to clinic more often than people in genotype positive families, because no family member can be ruled disease-free via genetic testing.

**How to Group Patients with a VUS Identified**

When grouping probands by their genotype status it is difficult to decide how to interpret the data on patients with variants of unknown significance. From the clinician’s point of view these patients are treated as genotype negative. When a variant of unknown significance is identified, advice for screening family members follows the same guidelines as if the patient either had negative genetic test results or never had genetic testing done. All first-degree family members are recommended for longitudinal clinical evaluations. Clinically, we treat the identification of a VUS as unhelpful information. We do not know anything more than we did before the genetic testing was ordered.

However, when patients with a VUS receive the results of their genetic testing, we do inform them that they carry a variant. We also explain that we are uncertain of whether or not the variant explains their disease. We can never be sure of how the patient interprets the information. For the purposes of this study, we have included patients with a VUS identified as genotype positive. We did this because a truly genotype negative patient receives no information about variants identified, while a patient with a VUS does receive information about a variant in the results of their genetic testing. Looking at the group of patients with a VUS
separately from both the genotype positive group and the genotype negative group will help us see if the patients truly understand the genetic counseling that accompanies their genetic test results.

38% of relatives with a VUS identified in their proband seek follow-up. This is roughly halfway between the approximate 50% of relatives in the genotype positive group and around 31-2% of the relatives in the genotype negative or not genetically tested groups. Families of patients with a VUS act differently from any of the other groups. While we advise probands with a VUS, negative genetic test results, and no genetic testing performed to seek family follow up the same way, patients with a VUS are more likely to seek family follow up. This suggests that genetic counseling’s emphasis on the ambiguity of a VUS and the importance of familial screening is better understood by these patients.

Genotype negative and VUS identified probands are similarly engaged in their HCM medical care, because both groups sought genetic testing initially. It is more difficult to compare these groups to the not genetically tested group, because there are many reasons patients do not pursue genetic testing. Our data still suggests that patients understand the familial nature of disease and the need for family screening better when an ambiguous variant is found than when no variant is found during genetic testing. Understandably, patients do not recognize the similar ambiguity that exists in a negative genetic test result. Until we know all possible genetic causes of HCM, a genetic test can never rule out familial
disease. This confusion underscores the need for genetic counseling when any genetic testing is done.

In the advent of whole genome sequencing becoming widely clinically available there will be genome reports with many VUS identified. Proper interpretation of these results is one of the largest problems with making whole genome sequencing available to the public.

**Reasons to Pursue Clinical Testing Only**

There are many reasons why a patient may return for clinical evaluation but be uninterested in genetic testing. An important reason is the expense. Insurance companies will cover the cost of most clinic visits, but may require patients to pay out-of-pocket for genetic testing. It is not always possible to be absolutely sure that the insurance company will pay the cost of genetic testing at the time when the patient is in the clinic and available to give blood for the test. Extra time and energy is required to look into insurance policies and schedule an additional visit for genetic testing.

Additionally, there are emotional and psychological issues with genetic testing. Some people prefer not to know they carry a disease variant, because then they will worry about getting sick. Genetic test results can cause stress, feelings of guilt, and strain on family relationships.

Finally, while there are laws in place to protect patients from being discriminated against because of genetic test results, discrimination can still take place. Employers and health insurance companies have not been allowed to
treat patients differently because of their genetic information since the Genetic Information Nondiscrimination Act was passed in 2008. Life insurance companies, however, are not limited by this law. Patients interested in obtaining life insurance in the future may or may not face difficulties if they have genetic test results in their medical records.

Limitations

There are a few major limitations of this study. First, this is an observational study. Groups were not systematically gathered or standardized. All of the data comes from observing and reviewing real world practice in the CVGC HCM clinic.

Second, we were unable to capture information about familial follow-up that may be affected by geographic location. If any family members were evaluated remotely we are unlikely to have this data. The only means of capturing data on this group is if the proband reported the family information to the physician during his scheduled clinic visit and it was recorded in the patient’s family history.

Third, age plays a large role in which relatives are recommended or likely to return for disease evaluation. Very young children or very elderly parents are less likely to come into the clinic for evaluation. Children are often not advised to come in for clinical evaluations until they are closer to puberty when LVH is more likely to develop (Maron, Seidman, & Seidman, 2004).
Fourth, this review occurred at a single point in time looking at past information. Patients who have had their first clinic visit more recently may not have had time to order and receive genetic test results. In turn, their family members may not yet have time to schedule and come in for either clinical or genetic testing. Additionally, families grow and change in size. Information to construct family histories is collected on or near each patient’s first visit. Changes and updates since the first visit are potentially unrecorded.

Fifth, in this study we have only collected binary data. The relative either came to the clinic for follow-up at least one time or the relative did not come in for follow-up. We suggest that patients who are at-risk for HCM come in for longitudinal screening. If a patient has one normal clinical evaluation at a relatively young age, he is still at-risk for HCM and may develop it in the future. This review does not capture any data regarding whether family members have had multiple clinical encounters over an extended period of time as clinically advised.

Sixth, in this study we only included living family members in our total counts of probands’ relatives. We did this because only living family members are able to return for follow-up. Including deceased family members would dilute the percentages of family members returning for HCM follow-up. However, there are families with severe disease phenotype and early onset disease where most affected family members were deceased at the time of this study. In these families we are not capturing a full record of which family members sought
clinical follow-up for HCM. The majority of probands in this study do not have this severe familial disease phenotype. Yet, there are many cases where one of the proband’s parents is deceased with a clear diagnosis of HCM. We are reasonably confident that the proband’s disease was inherited from this parent. The other living parent is then most likely not at-risk for HCM, and does not need a clinical evaluation for the disease. This may partially account for the low percentage of follow-up in parents of probands.

Future Directions

One way to increase the numbers of HCM patients’ relatives returning for follow-up is to have a family clinic. A family clinic embodies our belief that the HCM patient is an entire family. The family clinic can increase convenience by scheduling a whole family to come into clinic together. The level of awareness of HCM within the family increases when a large clinic visit is being planned. The clinic will also help family members understand HCM and inheritance better. More people will listen to the physician at the same time. Individuals will feel more comfortable asking the physician questions, and there is built-in opportunity for open discussion.

Family based practices may also make better use of time, as they can enable general (not personal or confidential) information to be provided to a group instead of repeated discussions at each individual’s appointment. Additionally, with more family members the physician is better able to collect an accurate and complete family history of disease.
However, family clinics are only helpful when the patient has gone so far as to schedule a clinic appointment. The family clinic cannot help the many more people who have not made an initial appointment. In the future we need to find a way to target this unaided population for evaluations.
REFERENCES


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Year of Birth: 1988

Education: Boston University, Boston, MA
Bachelor of Arts in Mathematics and Mathematics Education, May 2010
Magna Cum Laude
Completed Boston University Honors program, May 2007

Boston University School of Medicine, Boston, MA
Candidate for Master of Arts of Medical Science, May 2013
Coursework: Biochemistry and Cell Biology, Cellular Organization of Tissues, Advanced Human Physiology, Pathology, Biostatistics

Research Experience:

11/12 to present Brigham and Women’s Hospital
- Boston, MA
- Working as Research Coordinator in the Cardiovascular Medicine Division helping recruit, contact and enroll study subjects, and design and manage ongoing study protocols

09/10 to 08/11 Harvard Medical School
- Boston, MA
- Worked as Research Technician I constructing genomic libraries for in house samples, The Cancer Genome Atlas, and Pediatric Cardiac Genomic Consortium, innovating our lab protocol, and collaborating with other researchers to teach our methods of library generation

06/10 to 08/10 Harvard Medical School
- Boston, MA
• Worked on identification of new heart disease causing mutations in the titin gene. Involved verification of new mutation calls, DNA extraction and sequencing of family members, drawing family pedigrees to look for segregation, and extensive PCR troubleshooting.

06/09 to 08/09 Harvard Medical School
• Boston, MA
• Worked genotyping patients with known genetic mutations causing heart disease, while training new summer student. Includes DNA extraction from saliva, lymphocytes, and whole blood, DNA quantification, PCR, gels, restriction digests, and sequencing. Constructed a lab manual detailing my specific protocols of all above procedures.

06/08 to 08/08 Harvard Medical School
• Boston, MA
• Screened family members of hypertrophic cardiomyopathy patients with known genetic mutations. Includes DNA extraction from saliva samples, PCR, designing enzyme restriction digests, making and running gels.

06/06 to 08/07 Harvard Medical School
• Boston, MA
• Summer Student
• Introduced to DNA extraction from saliva and whole blood, genotyping, and making laboratory solutions. Worked entering data, organizing patient consent forms, drawing pedigrees, and facilitating the receipt of patient samples.

Employment:

01/10 to 06/10 North Quincy High School
• Quincy, MA
• Student Teacher
• Assumed full responsibility for teaching high school algebra and discrete mathematics at varying ability levels. Includes creating innovative lessons, drawing from various resources, determining methods of
student assessment, working with IEPs, classroom management, and collaboration with colleagues.

01/08 to 12/09  
**Boston University Educational Resource Center**
- Boston, MA
- Tutoring Fellow
- Tutored college-level science and math courses, worked as a liaison between professors and peer tutors, developed and implemented training workshops for tutors.

Volunteer Work:

01/07 to 12/09  
**Student Studio Volunteer**
- Boston, MA
- Peer Leader
- Planned art lessons for elementary-aged, inner city students at after school programs. Coordinated and led volunteers to teach weekly art lessons, and facilitated communication between community service center and volunteer sites.

09/07 to 05/08  
**High School Tutor**
- Fenway High School, Boston, MA
- Tutor and College Advisor

09/07 to 12/09  
**Honors Program Peer Mentor**
- Boston University, Boston, MA

01/06 to 05/06  
**Admissions Volunteer**
- Boston University, Boston, MA
- Day and Overnight Host