

Cardiovascular Genetics: Getting a “Pulse” on How Cardiologists Assess and Act on Cardiogenetic findings that May Lead to Sudden Cardiac Death

Study Investigators: Tamar Ailenberg¹, Anna (Schon) Levy¹, and Samone Schneider¹

Faculty Advisors: Laura Hercher¹ and ²Samantha Freeze

¹Joan H. Marks Graduate Program in Human Genetics, Sarah Lawrence College, ²Indiana University School of Medicine

Samone Schneider
2 Consulate Drive Apt. 1J
Tuckahoe, NY 10707
Phone: (802)578-1764
Email: VT.Samone@gmail.com

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Abstract:

Sudden cardiac death (SCD), defined as an unexpected death due to cardiac causes is the leading cause of non-random death in young athletes (Harmon et al., 2011). Current statistics suggest that 1 in 200,000 competitors experience SCD (Firoozi et al., 2003). Early detection of individuals with cardiac disease, such as Hypertrophic Cardiomyopathy (HCM) and Long QT syndrome (LQTS), can help prevent SCD, however, the heterogeneous presentation of heritable cardiovascular conditions makes them difficult to diagnose and prognose (O'Mahony et al., 2014). Thus, it is difficult to create universal activity restriction guidelines for at-risk athletes. This study examines practice variation among cardiologists with regard to genetic testing of competitive athletes for risk of SCD and subsequent activity restriction recommendations. To our knowledge, there are no previous studies that examine these specific clinical practices among cardiology providers. A survey was sent out through the ACC Sports and Exercise Section email list and a University of Vermont Medical Center listserv. In total, the listservs were comprised of ~1800 cardiologists. The survey received 73 responses, 68 of which were completed in entirety. Four knowledge-based questions were asked to create a rating scale. A significant proportion of cardiologists answered the knowledge question regarding variants of uncertain significance (VUS's) incorrectly (~25%). These results suggest that physicians have some sense of uncertainty associated with VUS's compounded with an unfamiliarity with practice guidelines as they relate to VUS's. Regarding activity restriction, there is no single answer regarding recommendations that all cardiologists chose for either LQTS scenario, a clinical diagnosis compared to diagnosis-causing mutation and no clinical diagnosis. If a patient had a clinical diagnosis of HCM, only half of respondents chose to strongly recommend activity restriction; we anticipated the proportion being closer to 100%. The results indicate that there is a lack of

knowledge pertaining to VUS's as well as a lack of consensus with regards to activity restriction recommendations pertaining to HCM/LQTS.

Introduction:

Sudden cardiac death (SCD) is the most common cause of non-traumatic death in athletes, accounting for 16% of deaths in this population (Harmon et al., 2011). SCD often occurs with no prior warning, and can appear in patients who have no other clinical cardiac findings or previous symptoms (Zheng et al., 2001). The lack of any warning signs, coupled with low rates of revival, contributes to the high death rate of cardiac events (Zheng et al., 2001). Startling and often unanticipated, but with a relatively high incidence rate, SCD is a major enigma for cardiologists, emergency medicine personnel, and public health officials, not to mention the victims and their relatives.

Competitive athletes may be particularly vulnerable to SCD due to the immense pressure placed on them to perform during both competition and training; they may not be able to recognize when symptoms of cardiac conditions warrant medical attention or when to end physical activity (Barry J Maron, Zipes, & Kovacs, 2015).

The incidence of SCD in U.S. competitive college athletes ranges in report from 0.0012% to 0.0023% (Harmon et al., 2011; Maron, Haas, Murphy, Ahluwalia, & Rutten-ramos, 2014). However, 75% of sudden deaths during exertion were shown to be attributed to underlying cardiac disease (Harmon et al., 2011).

In a study analyzing 1866 SCDs in young competitive athletes by Maron et al. (2009), SCD was found to occur during or just after physical exertion 80% of the time. The other 20% of athletes died suddenly in situations not associated with sports. The overall risk of SCD in an NCAA student-athlete during or soon after exertion is estimated at 1 in 54,000 athletes/year

(0.0019%). The exertion-related risk of SCD in male athletes (0.0026%) is higher than the risk for female athletes (0.00082%). African-American athlete SCD risk (0.0045%) is 3x higher than the risk in Caucasian athletes (0.0015%) (Hainline et al., 2016; Harmon, Asif, et al., 2011).

Participation in certain sports confer higher risks than others. In order of frequency, SCD events are most likely to occur in: basketball, football, soccer, track and field, baseball, wrestling, swimming, and cross country (Barry J. Maron et al., 2009).

SCD is generally defined as an unexpected natural death within a relatively short time period (usually under an hour from the onset of symptoms in an individual without any prior lethal conditions) that is cardiac in nature (Zheng et al., 2001). Despite the fact that SCD is, by definition, a unexpected event, there are findings, both clinical and pathologic, which suggest that certain patients might have a predisposition for sudden cardiac events. The vast majority of SCD events are due to malignant tachyarrhythmias, usually ventricular fibrillation (VF) or ventricular tachycardia (VT) which devolves to VF. These tachyarrhythmias occur in individuals with arrhythmogenic disorders, most commonly hypertrophic cardiomyopathy (HCM) and Long QT syndrome (LQTS) (Mont et al., 2017). Although competitive athletes with HCM or LQTS may have considerable risk with sports participation, activity restriction can cause physical and psychological harm. Therefore, a balance must be struck between providing medical clearance and activity restriction (Barry J Maron, Zipes, et al., 2015).

There is sizable phenotypic heterogeneity and reduced expressivity with both HCM and LQTS, which can make diagnosing these conditions difficult. Their heterogeneous presentation may be partially attributed to the dozens of genes and hundreds to thousands of associated genetic variants (Caleshu & Ashley, 2017). There is debate in the literature as to the most accurate screening method to use in order to identify true cases of LQTS and HCM, to minimize

both false positives and false negatives. For example, the use of an electrocardiography (ECG) during preparticipation physical evaluation. The current recommendations are adequate for detecting individuals with major symptoms of HCM and LQTS, but many patients at risk of SCD will not experience significant symptoms. The use of an ECG during pre-participation evaluation (PPE) would detect 75-95% of HCM cases and the majority of LQTS cases (Johnson & Ackerman 2009; Maron & Maron, 2013). There is also debate as to what degree of athletic participation is appropriate for individuals diagnosed with these conditions.

Given the broad and conflicting guidelines from leading cardiovascular associations, it is not surprising that the recommendations cardiologists make for their athlete patients in practice vary.

Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is a disease characterized by left ventricular hypertrophy (LVH) and has broad clinical, genotypic, and phenotypic manifestations. It is a frequent cause of SCD (Maron et al., 1995). HCM accounts for 36% of SCD in young athletes, with a population incidence of 1/500 (Maron et al., 2009).

Risk factors for individuals with suspected or diagnosed HCM include a family history of SCD and/or premature SCD, unexplained syncope, non-sustained ventricular tachycardia, and abnormal blood pressure during exercise (Gollob et al., 2011). According to American College of Cardiology/American Heart Association (ACC/AHA) guidelines, LVH that is ≥ 15 mm is considered diagnostic, while 13-14mm is considered borderline (Gersh et al., 2011). Medical management for these high-risk individuals usually includes use of an ICD (Implantable Cardioverter Defibrillator) as well as exercise restriction, which is designed to minimize an inducement of arrhythmia (Gollob et al., 2011).

HCM can result from genetic factors, or a combination of both. Genetically HCM is a heterogeneous, autosomal dominant disease with thousands of mutations reported in 34+ genes. These genes encode thick and thin contractile myofilament proteins in the sarcomere or Z-disc. The vast majority of HCM-associated mutations occur in β -myosin heavy chain (*MYH7*) and myosin-binding protein C (*MYBPC3*) (Barry J. Maron & Maron, 2013). However, other genes have been implicated (Caleshu & Ashley, 2017). HCM mutations tend to be family-specific (Barry J. Maron & Maron, 2013), but there is phenotypic variation between (Brito et al., 2003) and within families (Menon et al., 2008). This suggests that the sarcomere mutation alone does not determine HCM phenotype.

Long QT Syndrome (LQTS)

LQTS is a disorder that is characterized by an increased period of ventricular repolarization, identified by a prolonged QT interval on ECG, that cannot be explained by drugs, electrolyte imbalance, other cardiac conditions, or other factors. It includes a predisposition to developing ventricular arrhythmias, characteristically *torsades de pointes* arrhythmias that can manifest as palpitations, presyncope, syncope, seizures, or sudden cardiac arrest (Mont et al., 2017). The 10-year mortality rate for untreated, symptomatic patients is ~ 50% (Ackerman et al., 2011). LQTS has an estimated prevalence of 1/2000 people (Schwartz et al., 2009).

A corrected QT (QTc) interval of ≥ 470 ms in men and ≥ 480 ms in women are considered above the 99th percentile and should prompt evaluation for LQTS (Drezner, Ackerman, Cannon, et al., 2013). High risk patients are characterized by QTc >500 ms (Gomez, Prutkin, & Rao, 2016). Diagnosis should take into account ECG findings, clinical history, and family history (Schwartz & Crotti, 2011). A family history of sudden death, especially <30 years, unexplained drowning, vehicle accidents when the individual is driving, seizures, or sudden infant death can raise suspicion of LQTS (Gomez et al., 2016). Despite established diagnostic

criteria, there is significant variability between heart rhythm specialists in diagnosis of LQTS. In one study, when LQTS patients received a second opinion, 40% were reclassified as normal (Taggart, Haglund, Tester, & Ackerman, 2007).

The mutations associated with LQTS are ones that lead to defective cardiac K⁺ and Na⁺ channels, resulting in the prolonged repolarization (Pelliccia et al., 2005). The clinical presentation of LQTS as well as triggers of a cardiac events are gene specific (Priori et al., 2013). There are three genes whose autosomal dominant mutations account for 70-85% of LQTS, and are each associated with an LQTS subtype (Napolitano et al., 2005, Taggart et al., 2007).

LQTS1 (*KCNQ1*) patients are more likely to have an event during exercise, emotional stress, or elevated sympathetic activity. Particular triggers for those with LQTS1 are swimming and diving. Individuals with LQTS2 (*KCNH2*) tend to have events both in exercise and at rest, with auditory stimuli being particularly triggering. Those with LQTS3 (*SCN5A*) are more likely to have events during rest or sleep because their QT-interval tends to prolong at slower heart rates. (Baars & van der Heijden, 2011; Caleshu & Ashley, 2017; Schwartz, Priori, Spazzolini, & Moss, 2001)

The incidence of cardiac arrest/SCD was found to be 20% in LQTS2 patients, 16.4% in LQTS3 locus patients, and 10% in LQT1 patients. The pattern was similar for any cardiac event or syncope. However, age at first event and gender did not differ between groups (Priori et al., 2013). Interestingly, while a prolonged QT interval is a hallmark of LQTS, it is not always present. Approximately 10-36% of patients with LQTS1-3 pathogenic mutations have normal QTc intervals at rest (Ackerman et al. 2011; Priori et al. 2013).

Genetic Testing for LQTS and HCM

Genetic Testing is recommended for anyone with a clinical diagnosis of LQTS and HCM,

but identifying a pathogenic mutation can be very challenging (Kumar and Elliott, 2010). While the genes associated with LQTS and HCM have been identified, there can be many different pathogenic mutations within these genes (Löllgen and Löllgen, 2012). Even when a mutation is reported, it is possible that this is the first time this specific variant has been identified in a gene associated with LQTS or HCM, in effect a family specific mutation, so it is difficult to determine whether the variant is pathogenic or benign, especially in a phenotypically negative individual (someone showing no clinical features) (Kumar and Elliott, 2010).

While using through rapid, automated, DNA sequencing to look for pathogenic mutations for HCM and LQTS is possible, it is not very practical as fewer than 50% of clinically affected patients test positive for a known pathogenic mutation due to the heterogeneity. This means that the results of DNA-based testing frequently result in a VUS, which would provide virtually no clinical utility to the patient or the patient's family. (Maron and Maron, 2013) Furthermore, even if a patient is genotype positive, the majority (HCM) or nearly half (LQTS) of patients will be asymptomatic due to reduced penetrance. In fact, in the case of HCM, if a patient is genotype positive, phenotype negative, and lacks a significant family history of SCD; then it appears the risk of SCD for that patient is extremely low and is likely no different from the risk in the general population. (Maron et al., 2015)

If a pathogenic mutation is identified in a phenotype positive patient, it can be used as a "predictive" gene test for other members of that family (Kumar and Elliott, 2010). That being said, a negative result for this mutation can also lead to uncertain results. It is common, in both LQTS and HCM, for there to be more than one disease causing mutation present within one family (Kumar and Elliott, 2010). For example, it is possible for a sibling to have a different pathogenic mutation in the same or another gene after testing negative for the pathogenic

mutation identified in the affected sibling.

For these reasons, genetic testing may not act as a reliable method to screen individuals for HCM and LQTS. Nevertheless, the conditions are genetically linked and are passed in an autosomal dominant fashion, and so a detailed family history can act as a key tool for identifying at risk individuals. An ECG and an echocardiography should be performed regularly on individuals believed to be at risk and on family members of affected individuals (Enriquez and Goldman, 2014).

Return to Play and Activity Restriction Guidelines

The 2015 *Eligibility and Disqualification Criteria for Athletes With Cardiovascular Abnormalities* guideline from the AHA/ACC informs the competitive athlete cardiovascular sports participation landscape (Barry J Maron, Zipes, et al., 2015; Pelliccia et al., 2005). The document cautions that it is a general guideline aimed to aid physicians with activity restriction decisions; it is not precise advice for individual cases and should therefore help inform but not replace the judgment of the physician (Mitten, Zipes, Maron, Bryant, & Heart, 2015; Pelliccia et al., 2005). The guideline aims to balance the risks and benefits of participation in competitive sports, and to not simply restrict all activity in at-risk athletes.

AHA/ACC guideline provides recommendations for HCM and LQTS. For HCM, the ACC/AHA recommends that probable or unequivocally symptomatic athletes (i.e. manifesting LVH) should not participate in competitive sports, except low-intensity sports. This recommendation is independent of age, sex, magnitude of LV hypertrophy, particular sarcomere affected by the mutation, presence or absence of LV outflow obstruction (at rest or with physiological exercise), absence of prior cardiac symptoms, presence or absence of late gadolinium enhancement (fibrosis) on CMR, and whether or not major interventions such as surgery have been performed previously. The ACC/AHA guideline states that for athletes who

are G+/P-, participation in competitive athletics is reasonable, especially if there is no family history of HCM-related SCD. The ACC/AHA also advises that pharmacological agents and ICDs should not be administered or placed in athletes for the sole purpose of allowing them to participate in high-intensity sports (Barry J Maron, Udelson, et al., 2015).

With regard to LQTS, the AHA/ACC recommends that athletes who are suspected to have or who are diagnosed with LQTS undergo a comprehensive evaluation by a heart rhythm specialist or genetic cardiologist with sufficient experience and expertise. When symptomatic athletes are suspected to have or are diagnosed with LQTS, it is recommended that they be restricted from all competitive sports until a comprehensive evaluation has been completed, the athlete and his/her family are well-informed, treatment has been initiated, and the athlete has been asymptomatic for 3 months. For an athlete with either symptomatic LQTS or electrocardiographically manifest LQTS (corrected QT interval >470 ms in males or >480 ms in females), competitive sports participation (except competitive swimming in a previously symptomatic LQT1 individual) may be considered after treatment, given appropriate precautionary measures, and assuming that the athlete has been asymptomatic on treatment for at least 3 months. The AHA/ACC guideline states that it is reasonable for a G+/P- LQTS athlete to participate in competitive sports if they avoid QT-prolonging drugs, ensure electrolyte/hydration replenishment, avoid dehydration, avoid or treat hyperthermia from febrile illnesses or training-related heat exhaustion or heat stroke, acquire a personal automatic external defibrillator as part of the athlete's personal sports safety gear, and establish an emergency action plan with the school or team officials (Ackerman et al., 2015).

The ultimate decision on activity restriction is a complex balance of the athlete's individual liberties, physician's legal liabilities, and third-party (coaches, schools) interests.

Although the ultimate goal is to prevent SCD, it is unfair to unnecessarily prevent athletes from competitive sports or a healthy lifestyle (Barry J Maron, Zipes, et al., 2015). According to a consensus statement from the ACC and NCAA, the NCAA holds each individual school/institution responsible for protecting the health and safety of the athletes. Further, the management of cardiac disorders and all sport eligibility decisions or RP/AR are ultimately the responsibility of team's health care providers in conjunction with cardiology specialists (Hainline et al., 2016).

Recommendations for handling athletes with confirmed or suspected HCM or LQTS are complex and sometimes contradictory. This study examines practice among cardiologists with regard to genetic testing of competitive athletes for risk of SCD, and how cardiologists handle issues of return to play among competitive athletes who are at risk based on clinical examination and/or genetic testing. To our knowledge, there are no previous studies looking at either of these questions.

Methods:

Participants

Participants in this study were practicing cardiologists working both in general practice and specialty settings. Cardiologists were contacted through The ACC Sports and Exercise Section listserv and a University of Vermont Medical Center listserv. In total, the listservs are comprised of ~1800 cardiologists. Two e-mails were sent to each listserv: an initial e-mail and one reminder e-mail. Interested participants gave informed consent online prior to the beginning of the survey. The survey received 73 responses, 68 of which were completed in entirety. This study received IRB approval on 1/23/18 prior to the survey distribution.

Procedures

A voluntary and confidential survey was developed on [surveymonkey.com](https://www.surveymonkey.com). Participants were asked to answer general demographics questions and rate their opinions on a variety of topics relating to knowledge of genetics, recommendations, and their experiences in practice.

Data Analysis

Frequency statistics were generated for demographics and Likert scales questions. Chi-square tests were conducted to determine statistically significant relationships between genetics knowledge and working with genetics professionals, ordering testing, results disclosure, and demographics. Practices with regard to use of pedigree construction were also analyzed. We examined the course of action participants would take in 4 clinical scenarios (clinical manifestation of HCM, genotype positive-phenotype negative for HCM, clinical manifestation of LQTS, and genotype positive-phenotype negative for LQTS) and the relationship between NCAA employment and results communication, hesitation to perform genetic testing, and course of action.

All qualitative data and open-ended questions were downloaded from [surveymonkey.com](https://www.surveymonkey.com). The data was loaded into Statistical Package for the Social Sciences (SPSS) Statistics, a software program used for statistical analysis. An independent experienced qualitative analyst reviewed the data to determine appropriateness and significance. Crosstabs, chi-square tests, and one-way ANOVA assessed differences in mean scores, and correlations of two continuous variables. A p-value of less than 0.05 was considered significant.

Results:

Demographics

The survey was distributed to over 1800 cardiologists from multiple specialties and locations throughout the United States). From this cohort, 73 cardiologists completed the survey. The majority of respondents were general practice cardiologists (39.73%, n=29). A similar

proportion of the cardiologists surveyed were specialists in electrophysiology (19.28%, n = 14), sports cardiology (15.07% n=11), or other (17.81%, n=13). Of the other category, the majority were pediatric cardiologists (n=7). The final category was specialist in heart failure/cardiomyopathy, which consisted of 8.22% (n=6) of the subset. (Figure 1)

The majority of the individuals sampled worked at an academic medical center (63.89%, n=46). A similar proportion of the cardiologist's reported working in a private practice (16.67%, n=12), or a community hospital (13.89%, n=10). The remaining 4 cardiologists (5.56%) selected the other category. (Figure 1)

When asked how often the cardiologist sees competitive athletes under the age of 25, over 78% of respondents replied either regularly (38.36%, n=28), or occasionally (39.73%, n=29). A similar proportion of the cardiologists reported seeing this set of patients frequently (9.59%, n=7), compared to rarely/never (12.33%, n=9).

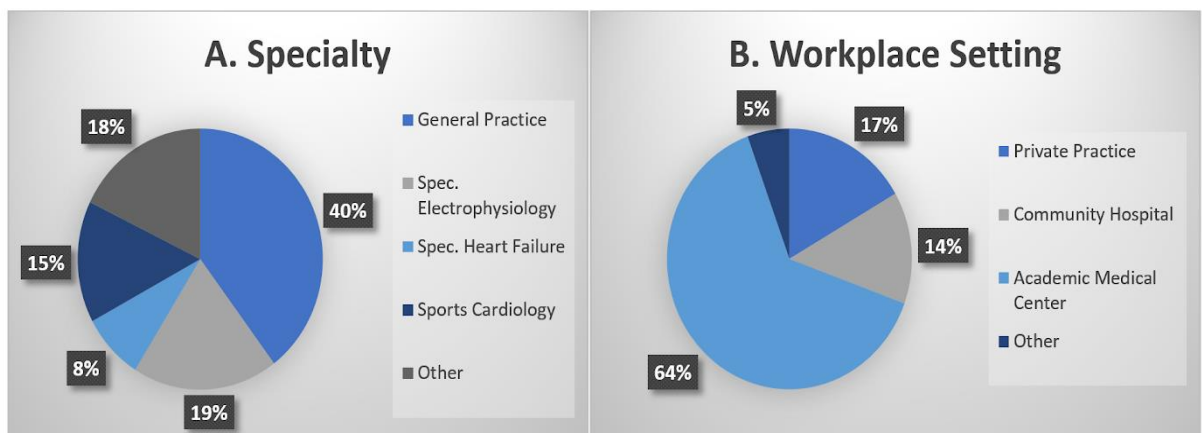


Figure 1:

- A. A pie chart of the specialties of the cardiologist's survey where the majority were general practice cardiologist.
- B. A pie chart of the workplace settings of the cardiologist's survey where the majority of the individuals sampled worked at an academic medical center.

Knowledge of Cardiovascular Genetics

Four knowledge-based questions were asked to create a rating scale. All 73 cardiologists that participated in the survey responded to these questions in entirety. Most, 94.5% (n=69) knew that patients with hereditary cardiovascular conditions may have a completely negative family history for the same condition. In comparison, 75.3% (n=18) of cardiologists knew that a variant of uncertain significance (VUS) found by genetic testing for hereditary cardiovascular conditions cannot be used to make medical management decisions. Almost everyone, 91.8% (n = 67) knew that a VUS found by genetic testing for hereditary cardiovascular disease should not be treated as pathogenic (disease-causing) until otherwise specified (question 7). Likewise, 93.2% knew that negative genetic testing in a patient with a suspected hereditary cardiovascular condition rules out a diagnosis for that specific condition. (Figure 2)

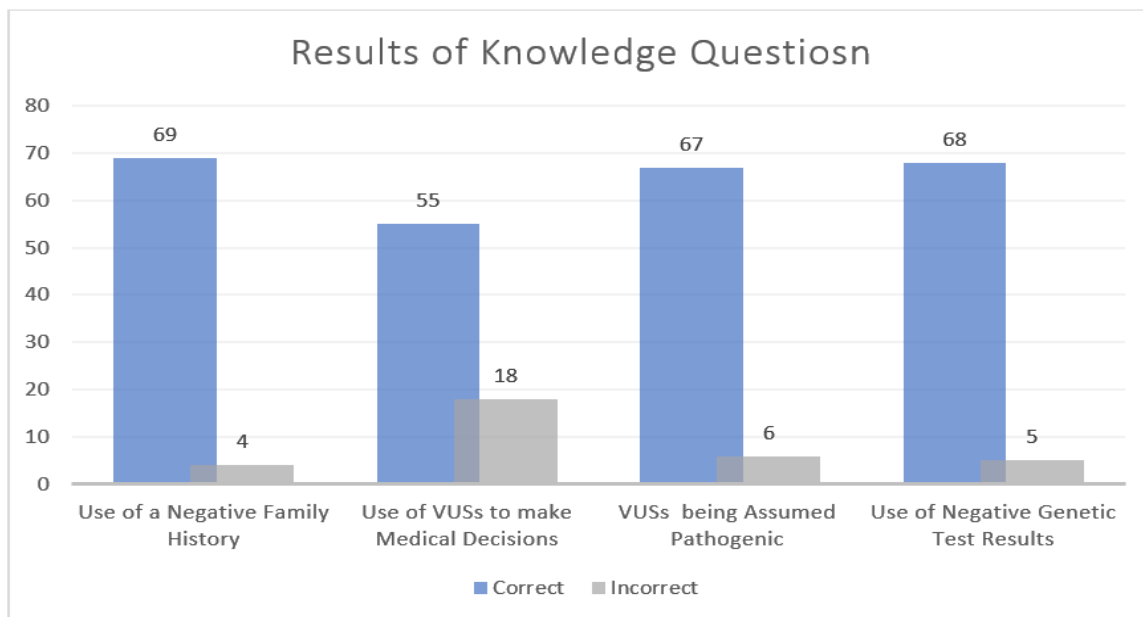


Figure 2: Bar graph showing the results of the knowledge based questions.
VUS: Variant of Uncertain Significant. Use of Negative Family History: Patients with hereditary cardiovascular conditions may have a completely negative family history for the same condition. Use of VUSs to make Medical Decisions: A VUS found by genetic testing for hereditary cardiovascular conditions can be used to make medical management decisions. VUSs being Assumed Pathogenic: A VUS found by genetic testing for hereditary cardiovascular conditions should be treated as pathogenic (disease-causing) until otherwise specified. Use of Negative Genetic Test Results: Negative genetic testing in a patient with suspected hereditary cardiovascular condition rules out a diagnosis for that specific condition.

Based on the responses to the four questions, a knowledge score was created where a score of one was given for each correct answer. The total score is reported below:

| Number of Cardiologists | Score (out of 4) |
|-------------------------|------------------|
| 67.1% (49) | 4 |
| 23.3% (17) | 3 |
| 8.2% (6) | 2 |
| 1.4% (1) | 0 |

The mean score was 3.55 (Std. Dev. = .76), and the median and mode were 4.0.

Respondents were separated into 2 categories: those who answered all questions correctly, 67.1% (n=49), and those who answered less than 4 questions correctly 32.9% (n=24). This was done due to the limited sample size of this study.

When asked, “A VUS is best presumed...” 95.59% of respondents answered “Inconclusive – report to the patient with an explanation of inconclusive results.” There were 3 outliers. Of these, one cardiologist said that a VUS is presumed to be disease-causing and two said “inconclusive-do not report to patients.” None of the three were specialist cardiologists. Two of the three were general cardiologists and one was working in research and evaluation.

Working with Genetics Professionals

Genetic counselors and/or geneticists are the genetics providers physicians tend to refer patients to regarding genetic conditions and/or genetic testing. 19.44% (n=14) of cardiologists report working with or referring to a genetic counselor frequently, 30.56% (n=22) reported regularly, 27.78% (n=20) reported occasionally, and 22.22% (n=16) reported rarely/never working with or referring to a genetic counselor.

There was a significant difference in the knowledge score between cardiologists who ordered the initial genetic testing themselves and those who referred patients to genetic counselors, geneticists, or a genetic nurse for initial testing (Chi-square = 5.03, (df=1) $p < .05$). 44.44% (n=32) refer their patients to genetic counselors, 1.39% (n=1) refer their patients to genetic nurses, 15.28% (n=11) refer their patients to geneticists, while 30.56% (n=22) order the genetic testing themselves.

There was also a relationship between how often the cardiologist works with or refer to a genetic counselor and knowledge ($t(70) = 3.93, p < .001$). Cardiologists who answered all 4 questions correctly tended work with genetic counselors frequently, while those who answered less than 4 questions correctly tended to work with genetic counselors occasionally.

Knowledge of Who Orders Initial Genetic Testing

86.4% (n=19) of those who ordered genetic testing themselves answered all questions correctly, while 59.1% (n=26) of those who referred the patients to genetics for testing answered all questions correctly. (Figure 3)

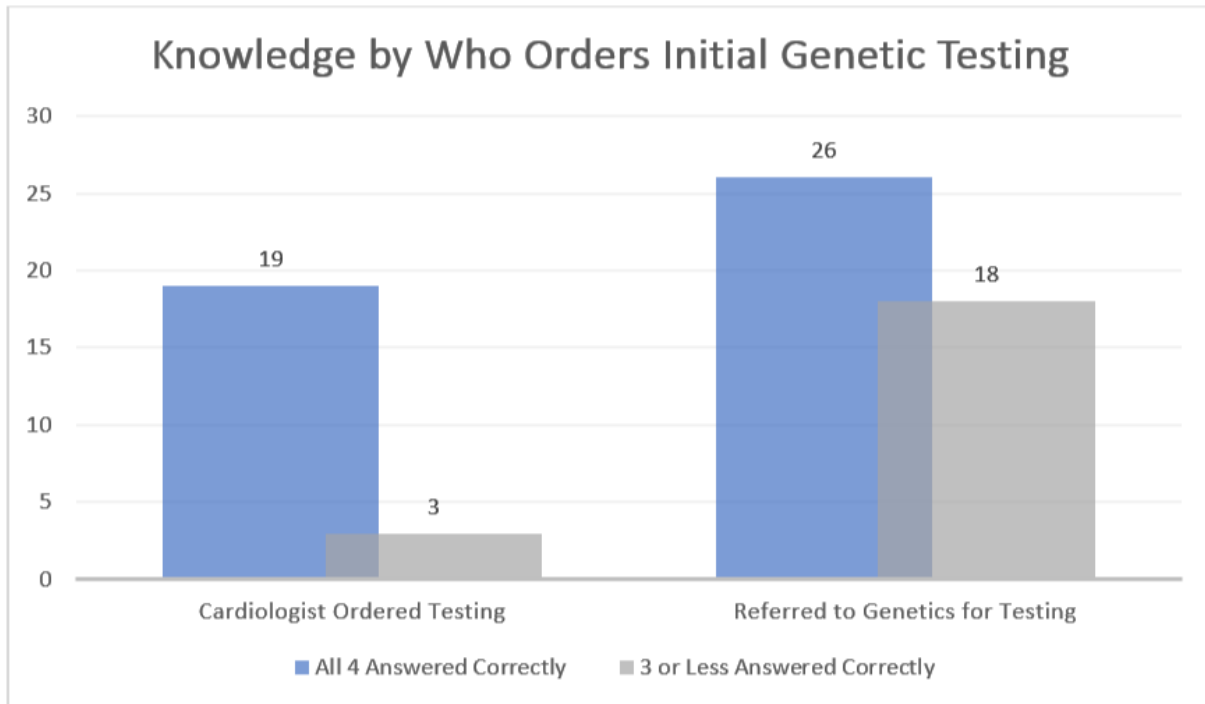


Figure 3: Bar graph showing the difference in number of correct answers of cardiologist who ordering genetic testing themselves compared to cardiologists who refer to genetics to order genetic testing.

Knowledge and Disclosing results

Answering all questions correctly was not associated with practice in terms of disclosing the results of the testing to patients (Chi-square = .07, (df=1), $p=.79$, n.s.). Almost the same number of cardiologists who disclosed the results themselves (64.5%) and those who referred the patient to a genetic counselor, a geneticist or a genetic nurse (67.6%), answered all the questions correctly.

Cardiologists who order the genetic testing themselves also tend to disclose the results to patients (Chi-square = 11.81 (df=1), $p<.01$). 80.0% (n=16) of those who order the testing themselves also disclose results to patients, while only 33.3% of those who refer to genetics for testing disclose the results to patients. In total, 45.2% (n=28) refer to genetics for testing and refer to genetics for results; 25.7% (n=16) order the testing and disclose the results themselves;

22.6% (n=14) refer for testing but disclose the results themselves, and 6.5% (n=4) order the testing but refer the patients to genetics for results. (Figure 4)

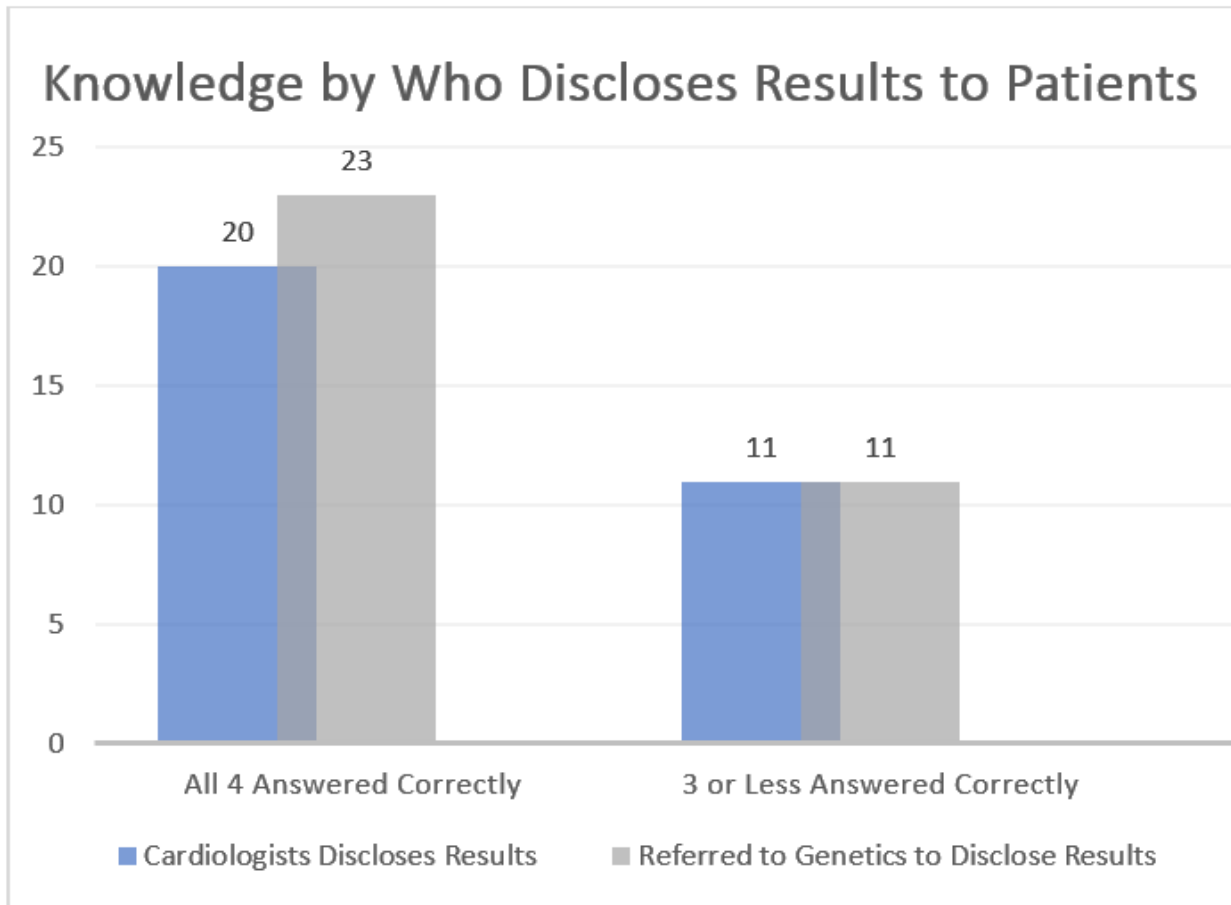


Figure 4: Bar graph showing the difference in number of correct answers of cardiologist who disclose results themselves compared to cardiologists who refer to genetics to disclose results.

Knowledge and Demographics

The knowledge category was not related to workplace setting, whether or not the cardiologist was employed in an NCAA school, or how often the cardiologist saw competitive athletes under the age of 25.

Family History

With regard to construction of pedigrees, 16.6% of respondents indicated that they always construct a pedigree, 31.94% construct a pedigree frequently on a case-specific basis, 37.5% rarely construct a pedigree on a case-specific basis, and 13.89% never construct a pedigree. Of the respondents who do construct pedigrees, 9.84% only ask about parents and siblings, 49.18% ask about siblings, parents, aunts, uncles and grandparents, and 40.98% also ask about cousins.

There was a significant positive correlation between how often cardiologists construct a pedigree when asking about a family medical history and how often they work with or refer to a genetic counselor ($r(71) = .31, p < .01$)

| Parents and Siblings Only | Parents and Siblings, Aunts, Uncles, and Grandparents | Parents and Siblings, Aunts, Uncles, Grandparents, and Cousins | F, p level |
|---------------------------|---|--|-------------------------|
| Mean (s.d) | Mean (s.d) | Mean (s.d) | F = 2.51 P=0.09, n.s |
| 2.67 (.82) | 2.70 (.99) | 2.12 (1.01) | |

Table 1: One-way ANOVA: Frequency of Cardiologist Working with a Genetic Counselor by How Many Generations They Ask About When Constructing a Pedigree. Index on Working With a Genetic Counselor: 1= frequently 2 = regularly 3 = occasionally 4 = never. A significant difference was not found between the 3 categories ($F = 2.51, p = .09, n.s.$).

The frequency of working with a genetic counselor was not related to how many generations the cardiologist asks about when constructing a pedigree (Table 1, $F = 2.51, p = .09, n.s.$) Those who asked about parents, siblings, aunts, uncles, grandparents and cousins had slightly more contact with genetic counselors than those that asked about fewer family members with a mean score of 2.12, the equivalent of regularly. However, the difference was not statistically significant.

Course of Action

For a clinical diagnosis of LQTS, 38.24% (n=26) of respondents would strongly recommend activity restriction (no competitive athletics), 35.29% (n=24) would suggest activity restriction (no competitive athletics) but support the athlete's decision if they choose to participate, none of the respondents would make no recommendation as to competitive athletics and 26.47% (n=18) would choose other courses of action. Some of the other courses of action included: referring the patient to an electrophysiologist, allowing participation if precautionary measures are met, requiring more information about LQTS subtype and history, utilizing joint decision making, and referring to guidelines. (Figure 4)

If a patient does not have a clinical diagnosis of LQTS but does have a pathogenic mutation, 7.35% (n=5) of respondents strongly recommend activity restriction, 44.12% (n=30) suggest activity restriction but support the athlete's decision if they choose to participate, 16.18% (n=11) make no recommendation as to competitive athletics, and 32.35% (n=22) would take another course of action. Some of the other courses of action include: taking into account LQTS subtype, further testing to identify intermittent LQTS, and allow the patient to play if on beta blockers and an emergency action plan is in place, referring to guidelines, and referring the patient to an electrophysiologist. (Figure 4)

Because many respondents answered that they would refer to an electrophysiologist for the LQTS recommendation questions, we also examined the answers from electrophysiologists exclusively. Electrophysiologists (25.87%, n=14) strongly recommend activity restriction, 42.86% Suggest activity restriction (no competitive athletics) but support the athlete's decision if they choose to participate, none chose to make no recommendations, and 28.57% would chose "other". Their explanations of their course of action include: following guideline recommendations, discussing ramifications/guidelines and doing joint decision making, depends

on LQTS subtype and clinical history, and allow to play assuming emergency action plan, takes beta blockers, and receives ICD if the patient meets clinical criteria.

Of the electrophysiologists, if a patient does not have a clinical diagnosis of LQTS but does have a pathogenic mutation, 7.14% (n=1) strongly recommend activity restriction, 28.57% (n=4) suggest activity restriction but support the athlete's decision if they choose to participate, 28.57% (n=4) make no recommendation as to competitive athletics, and 35.71% (n=5) would take another course of action. Some of the other courses of action include: taking into account LQTS subtype, further testing to identify intermittent LQTS, and allow the patient to play if on beta blockers and an emergency action plan is in place.

If a patient has a clinical diagnosis of HCM, 52.24% (n=35) of respondents would strongly recommend activity restriction (no competitive athletics), 34.32% (n=23) would suggest activity restriction (no competitive athletics) but support the athlete's decision if they choose to participate, 2.99% (n=2) would make no recommendations as to competitive athletics, 10.44% (n=7) would choose other courses of action. Some of the other courses of action include: their recommendations depend on HCM phenotype, said they would allow [the athlete] to play assuming emergency action plans, stays well hydrated, receives ICD if meets clinical criteria, and follows guidelines. (Figure 4)

If a patient does not have a clinical diagnosis of HCM but does have a pathogenic mutation, 7.46% (n=5) strongly recommend activity restriction, 32.84% (n=22) suggest activity restriction but support the athlete's decision if they choose to participate, 31.34% (n=21) make no recommendation as to competitive athletics, and 28.36% (n=19) would take another course of action. Some of the other courses of action include: stratifying risk, close follow-up, allow

participation with close surveillance, and further determining risk based on specific mutations.

(Figure 5)

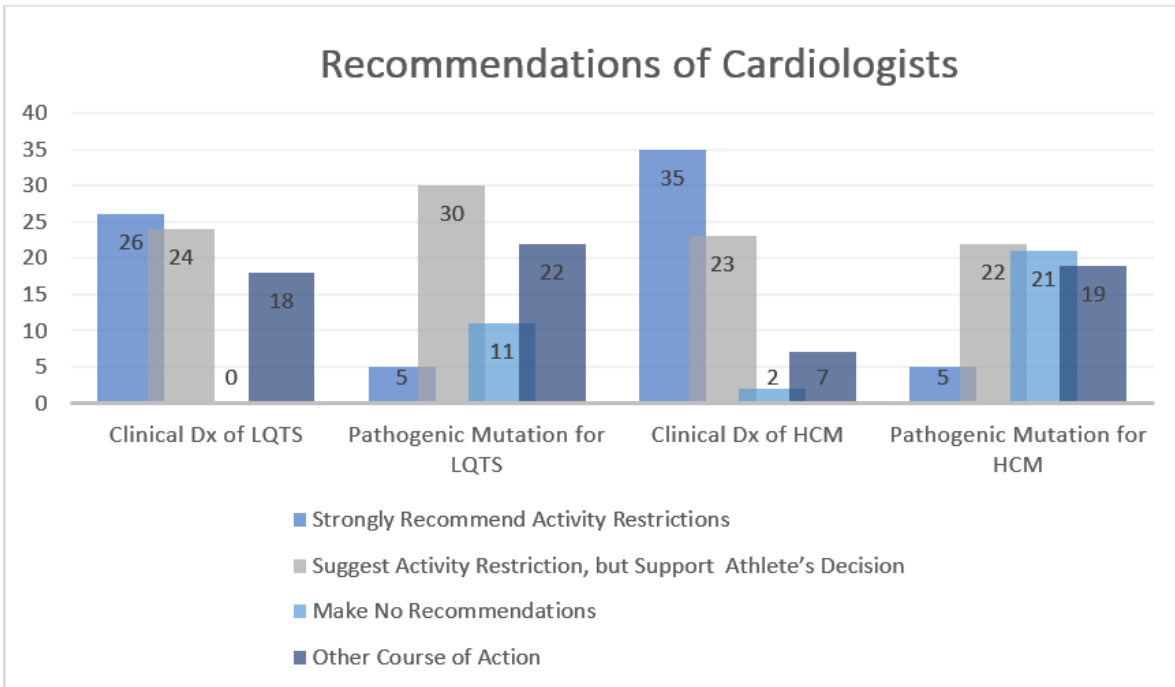


Figure 5: Bar graph showing the differences in the recommendations of cardiologists in four unique scenarios. These scenarios include: a patient with a clinical diagnosis of LQTS, a patient with no clinical diagnosis, but a pathogenic mutation for LQTS, a patient with a clinical diagnosis of HCM, a patient with no clinical diagnosis, but a pathogenic mutation for HCM.

Generalist vs. Specialist

There were no significant differences between generalist and specialist cardiologists and the recommendations they would give with a clinical diagnosis of LQTS, a disease-causing mutation of LQTS, a clinical diagnosis of HCM, or a disease-causing mutation of HCM. There were no significant differences between generalist and specialist cardiologists and what the cardiologist thought was sufficient to merit ordering genetic testing for LQTS or HCM.

Likewise, there were no significant differences between how frequently the cardiologist referred

to a genetic counselor and what they thought was sufficient to order genetic testing for LQTS or HCM.

There was a significant difference between the knowledge category of general practice cardiologists and specialist cardiologists (Figure 4) (Chi-square = 4.49 (df=1), $p < .05$). While 80.6% (25) of specialists answered all 4 questions correctly, only 55.2% (n=16) of general practice cardiologists answered all 4 questions correctly. While 44.8% (n=13) of general practice cardiologists answered all 4 questions correctly. While 44.8% (n=13) of general practice cardiologists answered only 0-3 questions correctly, only 19.4% (n=6) of the specialists answered less than 4 questions correctly. (Figure 6)

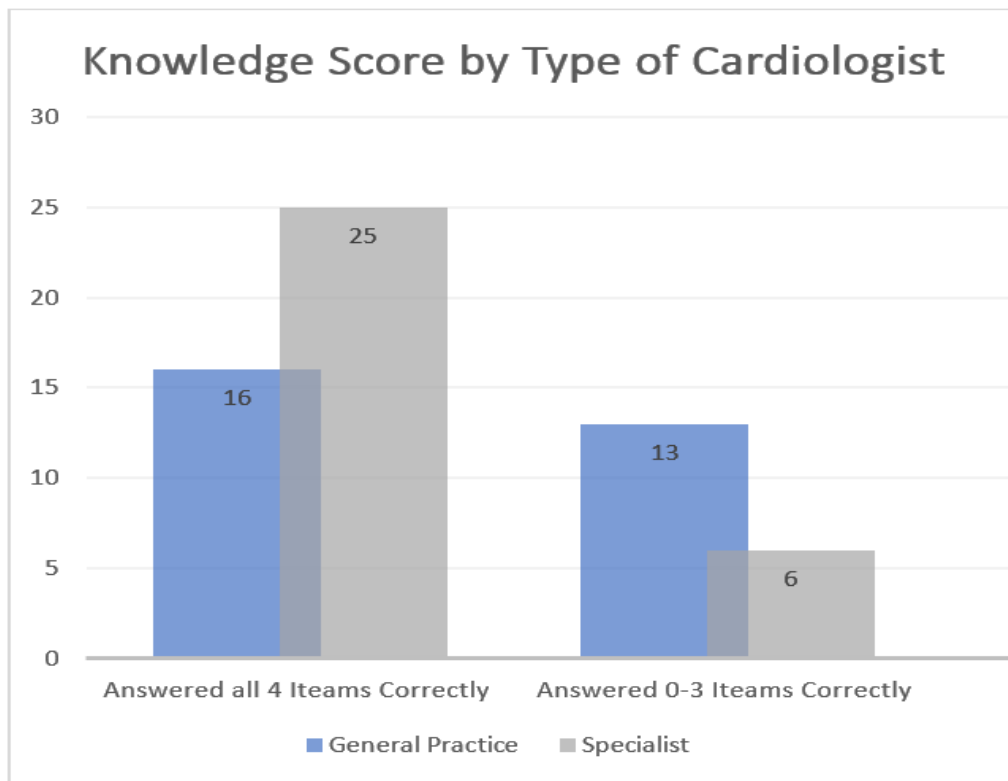


Figure 6: Bar graph showing the difference in number of correct answers of general practice cardiologist compared to specialists in an area of cardiology.

Being Employed by an NCAA School

23.61% (n=17) of respondents reported being employed in some capacity by an NCAA school. Being employed by an NCAA school was not associated with any significant difference in respondents' reported practices in terms of giving results to coaches, parents or other parties when there is a clinical diagnosis of LQTS or HCM. 64.7% (n=11), of those with an NCAA affiliation would communicate results directly back to the referring physician, while 54.5% (n=30) of those without an NCAA affiliation would communicate results directly to the referring physician. (Figure 7)

Being employed by an NCAA school was associated with no significant difference in how people, other than the patient, would be informed if a disease-causing mutation was identified for LQTS or HCM, but no clinical features were present. (Figure 7)

There were no significant differences between whether or not the cardiologist would hesitate to perform genetic testing for LQTS or HCM due to potential consequences of having this information in their medical records and their affiliation with an NCAA school. In addition, there was no significant difference between the respondent's reported course of action in the event of a diagnosis or positive genetic testing results and their affiliation with an NCAA school.

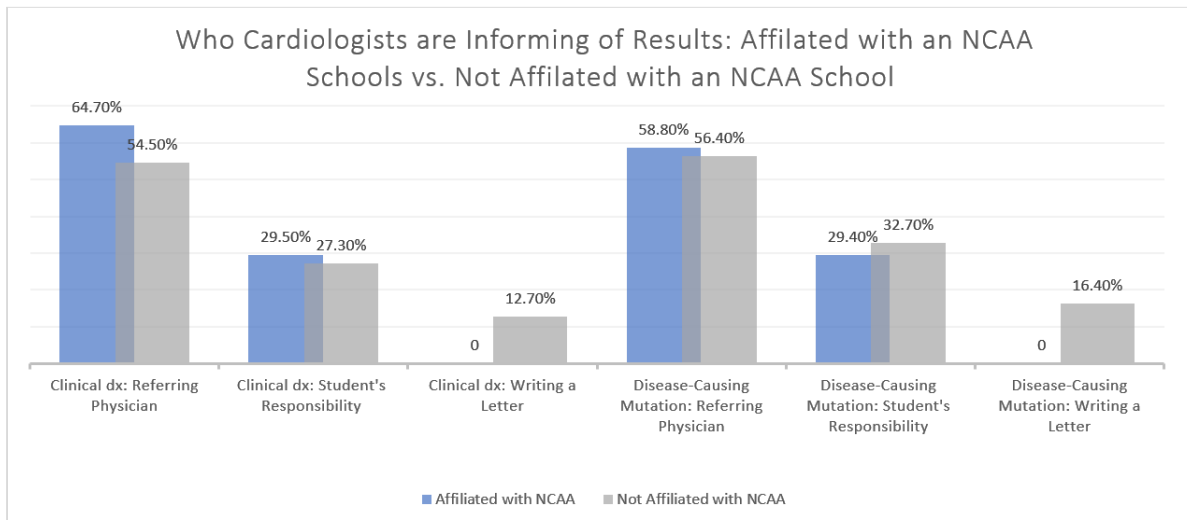


Figure 7: A bar graph showing who Cardiologists are informing of results and how it differs for cardiologists affiliated with an NCAA school compared to cardiologists not affiliated with an NCAA. Clinical dx: A clinical diagnosis of HCM or LQTS. Disease-Causing: disease-causing mutation was identified for LQTS or HCM, but no clinical features were present.

Discussion:

Misapprehensions Regarding Variants of Uncertain Significance (VUS)

Four knowledge based questions were asked in order to assess the underlying genetics knowledge of our cohort as it pertains to understanding the intricacies involved in interpreting pathogenicity of genetic variants for HCM and LQTS. As expected, the majority of cardiologists knew that patients with hereditary cardiovascular conditions may have a completely negative family history for the same condition. The question requires respondents to demonstrate an understanding of the concept of reduced/age dependent penetrance in cardiovascular conditions, and/or the possibility of a *de novo* mutation that would not present in the family history. The four individuals who answered incorrectly were statistical outliers; three of these cardiologists were general practitioners and one was a cardiology fellow.

While the majority of cardiologists understood the relationship between family history and HCM/LQTS (94.52%, n=69), fewer understood that a VUS found by genetic testing for hereditary cardiovascular conditions could not be used to make medical management decisions (75.34%, n = 55). One possible explanation is that cardiologists simply do not have adequate

training in genetics and therefore do not fully understand the limitations of clinical application of an identified VUS.

Previous studies have shown that genetics education is a limited part of the medical school curriculum (Burke, Stone, Bedward, Thomas, & Farndon, 2006). Burke specifically looked at four medical specialties: family practice, neurology, cardiology, and dermatology and found that training in genetics was insufficient according to student reports. Alarmingly, 12 students out of the cohort reported that they only received a few hours of instruction with regard to genetics. Another study found a significant lack of genetics preparation for the provider community. The study cites a recent survey by the American Medical Association and Medco, which found that the majority of medical schools have only just begun to institute genetics training curriculum for their students. They also indicated that only 29% of current practicing physicians report any training in genetics (Marchant, G.E., Lindor, R.A., 2013).

Although genetics is making its way into mainstream practice (Marchant, G.E., Lindor, R.A., 2013), given this background it is not surprising that there is a gap in the knowledge of our cohort of cardiologists, especially when it comes to complex genetic concepts such as the VUS. At first glance, such a response would indicate that these physicians do not adequately understand the nuances of a VUS, due to their lack of training and/or underlying knowledge of variant analysis. Though concern over liability is feasible, it seems less likely that this concern informed the physician response in this hypothetical scenario.

Although 24.7% (n=18) of cardiologists said that medical management decisions can be made based on a VUS, of that group, only 6 cardiologists did not know that a VUS found by genetic testing for a hereditary cardiovascular disease should not be treated as pathogenic. This discrepancy further strengthens the argument that perhaps most of the cardiologists actually do

understand the limitations of clinical application of a genetic variant with uncertain pathogenicity. However, medical management decisions do not necessarily correlate with knowledge, as there are outside forces that influence cardiologists to make other decisions that are not necessarily supported by scientific evidence.

It is interesting to note that all three of the cardiologists with incorrect answers to question 19, the fill-in statement “A VUS is best presumed...”, had correct answers to the question indicating that it was false that ‘a VUS found by genetic testing for hereditary cardiovascular conditions, can be used to make medical decisions’. One of the three who said that a VUS is best presumed to be disease causing also had an incorrect answer to the question saying that it was false that a VUS found by genetic testing for hereditary cardiovascular disease conditions should be treated as pathogenic until otherwise specified. The two cardiologists who said a VUS is presumed to be “inconclusive - do not report to the patients” answered correctly that treating the VUS as pathogenic was false.” Since these cardiologists are outliers, no statistical conclusions can be drawn from their statements.

Cardiologists’ Recommendations: Inconsistencies in Practice

For athletes with a clinical diagnosis of LQTS, a similar proportion of cardiologists chose the options of strongly recommending activity restriction or suggesting activity restriction, but also supporting the athlete’s decision if they choose to participate. The lack of consensus regarding activity restriction recommendations for LQTS is also reflected in the literature.

Among athletes with phenotypic LQTS who continued to play in competitive sports, only 1/60 of them experienced a sentinel event (Johnson & Ackerman, 2013). Additionally, data indicates that athletes with ICDs can continue to play with negligible mortality (0 deaths within 31 months follow-up) (Lampert et al., 2013).

According to the 2015 AHA/ACC guidelines, athletes who are suspected to have or who are diagnosed with LQTS should undergo a comprehensive evaluation by a heart rhythm specialist or genetic cardiologist with sufficient experience and expertise. The AHA/ACC guidelines further state that competitive sports participation (except competitive swimming in a previously symptomatic LQT1 individual) may be considered after treatment, given appropriate precautionary measures, and assuming that the athlete has been asymptomatic on treatment for at least 3 months (Ackerman et al. 2015). Therefore, cardiologists who chose the “other” option and recommended referring to an electrophysiologist or would likely allow participation if precautionary measures are met are within the bounds of the guideline recommendations. To add, although one could go even further and infer that perhaps it is inappropriate for cardiologists to make any activity restrictions at all if the patient has been asymptomatic for an adequate amount of time with appropriate precautionary measures in place.

If a patient does not have a clinical diagnosis of LQTS but does have a pathogenic mutation, the majority of respondents suggest activity restriction but ultimately support the athlete if they chose to play. The least popular answer was strong recommendation of activity restriction. The AHA/ACC guideline states that it is reasonable for a genotype-positive/phenotype-negative LQTS athlete to participate in competitive sports if they take the recommended precautionary measures (Ackerman et al., 2015). Therefore, our finding that strongly recommending activity restriction is the least preferred choice among cardiologists for athletes with an LQTS pathogenic mutation but no clinical diagnosis is not surprising; a strong recommendation to discontinue competitive sports is likely unwarranted in this setting. Further, in a study following 70 athletes with genotype-positive, phenotype-negative LQTS who participated in competitive sports, none of them had a sentinel event during play (Johnson & Ackerman, 2013). Our finding that supporting the athlete if they choose to participate makes sense

in the context of the literature. In general, there is a lack of data regarding the risk of an athlete with a LQTS has by competing in competitive sports (Ackerman et al. 2015). Therefore, genotype-positive, phenotype-negative athletes introduce even more uncertainty. If SCD or sentinel events are unlikely for genotype-positive, phenotype-negative LQTS athletes, then it makes sense to support an athlete if they choose to play. It is also in line with expectation that many cardiologists chose to elaborate on their thoughts by choosing “other”, as there are many different considerations and nuances to an athlete’s fitness to play in this scenario.

In athletes with a clinical diagnosis of HCM, the majority of respondents would strongly recommend activity restriction (52.24%), with a smaller proportion opting to suggest activity restriction (32.84%) but support the athlete if they choose to participate. The ACC/AHA recommends that symptomatic athletes should not participate in competitive sports, except low-intensity sports. This recommendation is independent of age, sex, magnitude of LV hypertrophy, particular sarcomere affected by the mutation, presence or absence of LV outflow obstruction (at rest or with physiological exercise), absence of prior cardiac symptoms, presence or absence of late gadolinium enhancement (fibrosis) on CMR, and whether or not major interventions such as surgery have been performed previously (Maron et al. 2015). Given the explicit recommendation that athletes with a clinical diagnosis of HCM should not participate in competitive sports, it is not surprising that the vast majority of cardiologists strongly recommend activity restriction. However, it is surprising that with such definitive guidelines, only half of respondents chose to strongly recommend activity restriction; we anticipated the proportion being closer to 100%. To add, 2.99% of cardiologists make no recommendation with regards to competitive sports participation. This is surprising because the guideline is quite unambiguous. Furthermore, respondents seem less certain of their response here than they did with LQTS, although

guidelines for LQTS provide more room for clinical judgment. Although risk-stratification is encouraged in order to determine HCM SCD probability and treatment plan (Gersh et al. 2011), it is not part of ACC/AHA Eligibility and Disqualification Recommendations for Competitive Athletes in order to determine return to play eligibility. These responses are in contrast with ACC/AHA guidelines as particular sarcomere affected by the mutation, absence of LV outflow obstruction, absence of prior cardiac symptoms, absence of fibrosis, and interventions should not impact competitive athletic recommendation if a patient has unequivocal or probable HCM (Maron et al. 2015).

In patients with a clinical diagnosis of HCM without a pathogenic mutation, most cardiologists in this sample would support of the athlete's decision if they choose to participate or offer no recommendation regarding competitive athletics. The ACC/AHA guideline states that for athletes who are genotype-positive, phenotype-negative, participation in competitive athletics is reasonable especially if there is no family history of HCM-related SCD (Maron et al. 2015). Therefore, our finding that strongly recommending activity restriction for these athletes is the least likely course of action for cardiologists, is in line with expectation. Interestingly, although ACC/AHA guidelines specifically mention evaluating the family history in this situation, none of the respondents commented on examining family history for SCD and incorporating that into their activity restriction decision-making. However, we found that 48.54% of respondents indicated they always or frequently construct pedigrees. Therefore, it is possible that the cardiologists examine family history in the initial work-up in order to determine if a genetics evaluation or testing is warranted, but do not revisit family history information when providing activity restriction recommendations. One respondent stated that they would "[a]llow [the athlete] to play assuming emergency action plan [is in place] and [the athlete] stays well

hydrated.” This response was unexpected as environmental factors are not commented on in the ACC/AHA 2015 guidelines for HCM.

Limitations:

A recurrent limitation in this study was the small sample size. Specifically, when considering our two knowledge categories (all 4 correct vs. 3 or less correct). Originally, we wanted this to be a knowledge score, but this became illogical as only 7 cardiologists answered 2-0 questions correctly. Additionally, when comparing cardiologists affiliated with an NCAA school and cardiologists not affiliated with an NCAA school, we had a very small sample of cardiologists affiliated with an NCAA school. Final, our findings regarding family history was almost significant. With a larger sample size, it is possible these differences could be found significant.

We also believe that using specific case scenarios would have helped us better understand the intricacies of how a given cardiologist might make decisions about treatment, diagnosis, and recommendations with regards to HCM and LQTS. We observed that some cardiologists were not able to answer the survey questions properly because there were not enough details in the questions. For example, many cardiologists chose to elaborate on their thoughts by choosing “other”, because there are many different considerations and nuances to an athlete’s fitness to play in any given scenario.

Conclusion:

The majority of cardiologists have some understanding of the nuances of genetic testing for inherited cardiovascular conditions however, this study suggests that cardiologists are uncertain of the clinical application of a VUS associated with an inherited cardiovascular condition and vary considerably in how VUS is used in clinical practice to make medical

management recommendations. Reported practice by this cohort of cardiologists demonstrates significant variability in recommended activity restriction in individuals with a diagnosis of LQTS and individuals with an inherited predisposition to LQTS but without definitive phenotypic disease which reflects the lack of consensus in the available literature regarding best practices for individuals with LQTS. Although HCM activity restriction guidelines definitively state that athletes with a clinical diagnosis of HCM should not participate in competitive athletics, only half of respondents chose to strongly recommend activity restriction. For athletes with genotype-positive, phenotype-negative HCM, our finding that strongly recommending activity restriction for these athletes is the least likely course of action for cardiologists, is in line with expectation.

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Conflict of Interest

Tamar Ailenberg, Samone Schneider and Anna Schon Levy declare that they have no conflict of interest.

Informed Consent

Professors Claire Davis and Elizabeth Johnston of the Sarah Lawrence College IRB, approved this study prior to any recruitment. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national)

and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

References

- Ackerman, M. J., Priori, S. G., Willems, S., Berul, C., Brugada, R., Calkins, H., ... Olson, S. (2011). HRS/EHRA expert consensus statement on the state of genetic testing for the channelopathies and cardiomyopathies. *Europace*, 13(8), 1077–1109. <https://doi.org/10.1093/europace/eur245>
- Ackerman, M. J., Zipes, D. P., Kovacs, R. J., & Maron, B. J. (2015). Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities : Task Force 10 : The Cardiac Channelopathies and American College of Cardiology. *Circulation*, 132(22), 326–330. <https://doi.org/10.1161/CIR.0000000000000246>
- Baars, H. F., & van der Heijden, J. F. (2011). Congenital Long QT-Syndrome. In H. F. Baars, P. A. F. M. Doevendans, & J. J. van der Smagt (Eds.), *Clinical Cardiogenetics* (pp. 143–164). London: Springer-Verlag.
- Brito, D., Richard, P., Isnard, R., Pipa, J., Komajda, M., & Madeira, H. (2003). Miocardiopatia Hipertrófica Familiar : INTRODUCTION. *Revista Portuguesa de Cardiologia*, 22(12), 1445–1461.
- Burke, S., Stone, A., Bedward, J., Thomas, H., & Fardon, P. (2006). A “neglected part of the curriculum” or “of limited use”? Views on genetics training by nongenetics medical trainees and implications for delivery. *Genetics In Medicine*, 8, 109. Retrieved from <http://dx.doi.org/10.1097/01.gim.0000200159.19920.b5>
- Caleshu, C., & Ashley, E. (2017). 17 Genetic Testing for Cardiovascular Conditions Predisposing to Sudden Death, 175–186.
- Christiaans, I., Leakane dit Deprez, R. H., van Langen, I. M., & Wilde, A. A. M. (2009). Ventricular fibrillation in MYH7-related hypertrophic cardiomyopathy before onset of ventricular hypertrophy. *Heart Rhythm*, 6(9), 1366–1369. <https://doi.org/http://dx.doi.org/10.1016/j.hrthm.2009.04.029>
- Enriquez, A. D., & Goldman, M. E. (2014). Management of hypertrophic cardiomyopathy. *Annals of global health*, 80(1), 35-45.
- Firoozi, S., Sharma, S., & McKenna, W. J. (2003). Risk of competitive sport in young athletes with heart disease. *Heart*, 89(7), 710-714. <http://dx.doi.org/10.1136/heart.89.7.710>
- Gersh, B. J., Maron, B. J., Bonow, R. O., Dearani, J. A., Fifer, M. A., Link, M. S., ... Yancy, C. W. (2011). 2011 ACCF/AHA guideline for the diagnosis and treatment of hypertrophic cardiomyopathy: A report of the American College of cardiology foundation/American heart association task force on practice guidelines. *Circulation*, 124(24). <https://doi.org/10.1161/CIR.0b013e318223e2bd>
- Gollob, M. H., Blier, L., Brugada, R., Champagne, J., Chauhan, V., Connors, S., ... & Harris, L. (2011). Recommendations for the use of genetic testing in the clinical evaluation of inherited cardiac arrhythmias associated with sudden cardiac death: Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper. *Canadian Journal of Cardiology*, 27(2), 232-245. <https://doi.org/10.1016/j.cjca.2010.12.078>
- Gomez, A. T., Prutkin, J. M., & Rao, A. L. (2016). Evaluation and Management of Athletes With Long QT Syndrome. *Sports Health*, 8(6), 527–535. <https://doi.org/10.1177/1941738116660294>
- Hainline, B., Drezner, J. A., Baggish, A., Harmon, K. G., Emery, M. S., Myerburg, R. J., ... Thompson, P. D. (2016). Interassociation Consensus Statement on Cardiovascular Care of College Student-Athletes. *Journal of the American College of Cardiology*, 67(25), 2981–2995. <https://doi.org/http://dx.doi.org/10.1016/j.jacc.2016.03.527>

- Harmon, K. G., Asif, I. M., Klossner, D., & Drezner, J. A. (2011). Incidence of sudden cardiac death in national collegiate athletic association athletes. *Circulation*, *123*(15), 1594–1600. <https://doi.org/10.1161/CIRCULATIONAHA.110.004622>
- Johnson, J. N., & Ackerman, M. J. (2009). QTc: how long is too long?. *British journal of sports medicine*, *43*(9), 657–662. <http://dx.doi.org/10.1136/bjsm.2008.054734>
- Johnson, J. N., & Ackerman, M. J. (2013). Return to play? Athletes with congenital long QT syndrome. *Br J Sports Med*, *47*(1), 28–33. <http://dx.doi.org/10.1136/bjsports-2012-091751>
- Kumar, D., & Elliott, P. (2010). *Principles and practice of clinical cardiovascular genetics*. Oxford University Press, USA.
- Lampert, R., Olshansky, B., Heidbuchel, H., Lawless, C., Saarel, E., Ackerman, M., ... Cannom, D. (2013). Safety of Sports for Athletes With Implantable Cardioverter-Defibrillators, 2021–2031. <https://doi.org/10.1161/CIRCULATIONAHA.112.000447>
- Löllgen, H., & Löllgen, R. (2012). Genetics, genetic testing and sports: Aspects from sports cardiology. *Genomics, Society and Policy*, *8*(1), 1–16. <https://doi.org/10.1186/1746-5354-8-1-32>
- Marchant, G. E., & Lindor, R. A. (2013). Personalized Medicine and Genetic Malpractice. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, *15*(12), 921–922. <http://doi.org/10.1038/gim.2013.142>
- Maron, B., Haas, T., Ahluwalia, A., & Rutten-Ramos, S. (2013). Incidence of cardiovascular sudden deaths in Minnesota high school athletes. *Heart Rhythm*, *10*(3), 374–377. <https://doi.org/10.1016/j.hrthm.2012.11.024>
- Maron, B., Haas, T., Doerer, J., Thompson, P., & Hodges, J. (2009). Comparison of U.S. and Italian experiences with sudden cardiac deaths in young competitive athletes and implications for preparticipation screening strategies. *American Journal of Cardiology*, *104*(2), 276–280. <https://doi.org/10.1016/j.amjcard.2009.03.037>
- Maron, B. J., Doerer, J. J., Haas, T. S., Tierney, D. M., & Mueller, F. O. (2009). Sudden deaths in young competitive athletes analysis of 1866 deaths in the united states, 1980–2006. *Circulation*, *119*(8), 1085–1092. <https://doi.org/10.1161/CIRCULATIONAHA.108.804617>
- Maron, B. J., Gardin, J. M., Flack, J. M., Gidding, S. S., Kurosaki, T. T., & Bild, D. E. (1995). Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults. *Circulation*, *92*(4), 785–9. <https://doi.org/10.1161/01.cir.92.4.785>
- Maron, B. J., Haas, T. S., Murphy, C. J., Ahluwalia, A., & Rutten-ramos, S. (2014). Incidence and Causes of Sudden Death in U . S . College Athletes. *Journal of the American College of Cardiology*, *63*(16), 1636–1643. <https://doi.org/10.1016/j.jacc.2014.01.041>
- Maron, B. J., & Maron, M. S. (2013). Hypertrophic cardiomyopathy. *The Lancet*, *381*(9862), 242–255. [https://doi.org/10.1016/S0140-6736\(12\)60397-3](https://doi.org/10.1016/S0140-6736(12)60397-3)
- Maron, B. J., Udelson, J. E., Bonow, R. O., Nishimura, R. A., Ackerman, M. J., Estes, M., ... Maron, M. S. (2015). AHA / ACC Scientific Statement Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities : and Other Cardiomyopathies , and Myocarditis and American College of Cardiology. *Circulation*, *132*(22), 273–281. <https://doi.org/https://doi.org/10.1161/CIR.0000000000000239>
- Maron, B. J., Zipes, D. P., & Kovacs, R. J. (2015). AHA/ACC Scientific Statement: Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities. *Circulation*, *132*(22), e256–61. <https://doi.org/10.1161/CIR.0000000000000236>

- Mitten, M. J., Zipes, D. P., Maron, B. J., Bryant, W. J., & Heart, A. (2015). Eligibility and Disqualification Recommendations for Competitive Athletes With Cardiovascular Abnormalities : Task Force 15 : Legal Aspects of Medical Eligibility and Disqualification Recommendations and American College of Cardiology. *Circulation*, *132*(22), 346–350. <https://doi.org/10.1161/CIR.0000000000000251>
- Mont, L., Pelliccia, A., Sharma, S., Biffi, A., Borjesson, M., Brugada Terradellas, J., ... Domenico, C. (2017). Pre-participation cardiovascular evaluation for athletic participants to prevent sudden death : Position paper from the EHRA and the EACPR , branches of the ESC . Endorsed by APHRS , HRS , and. *European Journal of Preventive Cardiology*, *24*(1), 41–69. <https://doi.org/10.1177/2047487316676042>
- Napolitano, C., Priori, S.G., Schwartz, P.J. et al. (2005). Genetic testing in the long QT syndrome: development and validation of an efficient approach to genotyping in clinical practice. *JAMA*, *294*: 2975–2980.
- O'Mahony, C., Jichi, F., Pavlou, M., Monserrat, L., Anastasakis, A., Rapezzi, C., ... & Omar, R. Z. (2014). A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). *European heart journal*, *35*(30), 2010-2020. <https://doi.org/10.1093/eurheartj/eh439>
- Pelliccia, A., Fagard, R., Bjørnstad, H. H., Anastassakis, A., Arbustini, E., Assanelli, D., ... Thiene, G. (2005). Recommendations for competitive sports participation in athletes with cardiovascular disease : A consensus document from the Study Group of Sports Cardiology of the Working Group of Cardiac Rehabilitation and Exercise Physiology and the Working Group of M. *European Heart Journal*, *26*(14), 1422–1445. <https://doi.org/https://doi.org/10.1093/eurheartj/ehi325>
- Priori, S. G., Chairperson, H. R. S., Wilde, A. A., Chairperson, E., Horie, M., Chairperson, A., ... Kannankeril, P. (2013). HRS / EHRA / APHRS Expert Consensus Statement on the Diagnosis and Management of Patients with Inherited Primary Arrhythmia Syndromes. *Heart Rhythm*, *10*(12), 1932–1963. <https://doi.org/10.1016/j.hrthm.2013.05.014>
- Schwartz, P. J., & Crotti, L. (2011). QTc behavior during exercise and genetic testing for the long-qt syndrome. *Circulation*, *124*(20), 2181–2184. <https://doi.org/10.1161/CIRCULATIONAHA.111.062182>
- Schwartz, P. J., Priori, S. G., Spazzolini, C., & Moss, A. J. (2001). Genotype-phenotype correlation in the {long-QT} syndrome. *Circulation*.
- Schwartz, P. J., Stramba-Badiale, M., Crotti, L., Pedrazzini, M., Besana, A., Bosi, G., ... Spazzolini, C. (2009). Prevalence of the Congenital long-QT Syndrome. *Circulation*, *120*(18), 1761–1767. <https://doi.org/10.1161/CIRCULATIONAHA.109.863209>
- Taggart, N. W., Haglund, C. M., Tester, D. J., & Ackerman, M. J. (2007). Diagnostic miscues in congenital long-QT syndrome. *Circulation*, *115*(20), 2613–2620. <https://doi.org/10.1161/CIRCULATIONAHA.106.661082>
- Zheng, Z., Croft, J. B., Giles, W. H., & Mensah, G. a. (2001). Clinical Investigation and Reports Sudden Cardiac Death in the United States , 1989 to 1998. *Circulation*, *2158–2163*. <https://www.ncbi.nlm.nih.gov/pubmed/11684624>