The *At Risk* Child:
An exploration of the journey of children *at risk* of an inherited arrhythmia or cardiomyopathy and an examination of how age at diagnosis impacts well-being.

by

Susan Christian

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Medical Sciences- Medical Genetics

University of Alberta

ABSTRACT

Background: There are currently knowledge gaps in our understanding of factors that influence a child's journey through diagnosis and management of an inherited arrhythmia or cardiomyopathy. It is also unclear how age at diagnosis for one of these conditions impacts the physical, psychological and social well-being of a child. This dissertation explores these knowledge gaps and evaluates the role of family values and healthcare providers practice characteristics on the patient's experience.

Method: Focusing on long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy, we used mixed methods to (1) assess the current state of predictive genetic testing and management in a pediatric population (2) explore perspectives on the optimal timing of predictive genetic testing and (3) evaluate the downstream effects of diagnosis and management on well-being. We reviewed medical genetics and pediatric cardiology charts to assess current practice; we surveyed pediatric electrophysiologists, genetics counsellors, and families to better understand their perspectives; and we recorded physical activity and measured HRQL in a cohort of children diagnosed with one of these conditions to evaluate the physical and psychosocial well-being of this population.

Results: With regard to current practice, we learned that two thirds of families chose to pursue genetic testing for their *at risk* child(ren) and that three quarters of children underwent cardiac screening when it was indicated. Uptake of predictive genetic testing was significantly associated with genetic specialist recommendation and the gender of the carrier parent in the absence of symptoms. Cardiac evaluation was significantly associated with uptake of genetic testing.

We further learned that the majority of pediatric cardiologists recommended some level of physical activity restriction for phenotype positive children but less commonly restricted phenotype negative children. Physical activity recommendations varied based on the type of physical activity, guidelines referenced and physicians' own level of physical activity. Beta blocker therapy was prescribed for the majority of symptomatic patients and a significant number of asymptomatic patients.

When we surveyed genetic counsellors and families we discovered varied opinions with regard to the optimal time to offer predictive genetic testing. Although, the majority felt that testing should be offered prior to 5 years of age for long QT syndrome and catecholaminergic polymorphic ventricular tachycardia, and before 10 years of age for hypertrophic cardiomyopathy and arrhythmogenic right ventricular cardiomyopathy. Rationale for when to offer predictive genetic testing could be described by the ethical principles of beneficence, non- maleficence, autonomy, and informed consent.

We then explored the well-being of this patient population and investigated the impact of age at diagnosis. We found that children diagnosed with an inherited arrhythmia or cardiomyopathy were involved in less moderate- to vigorous-intensity physical activity per day and had lower health related quality of life scores compared to normative data. Although many children adjusted well to their diagnosis, obesity and having to change one's physical activity were negatively associated with physical and psychosocial well-being. Children diagnosed at a younger age adapted better to physical activity recommendations supporting the idea that predictive genetic testing should be offered at a young age.

Discussion: Overall we discovered that the journey of children *at risk* of an inherited arrhythmia or cardiomyopathy is influenced by personal and family attributes as well as characteristics of the medical team caring for them. These results have several implications for clinical practice. Screening tools should be in place to identify children *at risk* for poor physical and psychosocial outcomes and care should be personalized based on the needs of each child. These results also highlight the need for more research in the areas as clinical practice is variable due to inconsistent published guidelines which are based mainly on expert opinion. In conclusion, it is important that the medical team stays abreast of the latest evidence, listens to the family's perspective, works with families to develop the best care plan for each child and closely monitors the well-being of children overtime.

PREFACE

Chapter 2i of this dissertation has been published as S. Christian, J. Atallah, R. Clegg, M. Giuffre, C. Huculak, T. Dzwiniel, J. Parboosingh, S. Taylor, and M. Somerville, "Uptake of Predictive Genetic Testing and Cardiac Evaluation for Children at Risk for an Inherited Arrhythmia or Cardiomyopathy," in the Journal of Genetic Counseling. 2018 Feb; 27(1): 127-130**.** I was responsible for concept formation, data collection and analysis as well as the manuscript composition. R. Clegg, M. Giuffre, C. Huculak, T. Dzwiniel and J. Parboosingh were involved in data collection and manuscript edits. S. Taylor and M. Somerville were involved in concept formation and manuscript edits. J. Atallah, was involved in concept formation, data collection and manuscript edits. The project received research ethics approval from the University of Alberta Research Ethics Board, Project Name: "Impact of exercise restriction for children, adolescents and young adults with LQTS, CPVT, HCM and ARVC with regard to weight status and exercise capacity." No. Pro00052201, November 18, 2014 and the University of Calgary Ethics Board, Project Name: "Impact of exercise restriction for children, adolescents and young adults with LQTS, CPVT, HCM and ARVC with regard to weight status and exercise capacity." No. REB14-2500_MOD1, November 19, 2015.

Chapter 2ii has been published as S. Christian, M. Somerville, S. Taylor, J. Atallah, "Exercise and beta blocker therapy recommendations in inherited arrhythmogenic conditions," in Cardiology in the Young. 2016 Aug;26(6):1123-9. I was responsible for concept formation, data collection and analysis as well as the manuscript composition. J. Atallah, S. and M. Somerville were involved in concept formation, data analysis and manuscript edits. The project received research ethics approval from the University of Alberta Research Ethics Board, Project Name: "Diagnosis and Management of Familial Arrhythmias and Cardiomyopathy Survey," No. Pro00044218, February 19, 2014.

Chapter 3i has been published as S. Christian, C. Huculak, M. Somerville, and J. Atallah, "Practice variation among an international group of genetic counselors on when to offer predictive genetic testing to children at risk of an inherited arrhythmia or cardiomyopathy," in the Journal of Genetic Counseling. Epub 2018 Aug 21. I was responsible for concept formation, data collection and analysis as well as the manuscript composition. C. Huculak was involved in data analysis and manuscript edits. J. Atallah, and M. Somerville were involved in concept formation and manuscript edits. The project received research ethics approval from the University of Alberta Research Ethics

Board, Project Name: “Presymptomatic genetic testing for children at risk for an inherited arrhythmia or cardiomyopathy”, No. Pro00065194, June 30, 2016.

Chapter 3ii has been published as S. Christian, M. Somerville, S. Taylor, and J. Atallah, “When to Offer Predictive Genetic Testing to Children at Risk of an Inherited Arrhythmia or Cardiomyopathy: The Family Perspective,” in Circulation: Genomics and Precision Medicine. 2018 Aug;11(8):e002300. I was responsible for concept formation, data collection and analysis as well as the manuscript composition. J. Atallah, S. Taylor and M. Somerville were involved in concept formation and manuscript edits. The project received research ethics approval from the University of Alberta Research Ethics Board, Project Name: “Predictive genetic testing for children at risk for an inherited arrhythmiaor cardiomyopathy- What do families think?” No. Pro000705845, March 28, 2017.

Chapter 4 has been published as S. Christian, M. Somerville, M. Giuffre, J. Atallah. “Physical activity restriction for children and adolescents diagnosed with an inherited arrhythmia or cardiomyopathy and its impact on body mass index,” in the Journal of Cardiovascular Electrophysiology. 2018 Dec;29(12):1648-1653. I was responsible for concept formation, data collection and analysis as well as the manuscript composition. M. Giuffre, was involved in data collection and manuscript edits. J. Atallah, was involved in concept formation, data analysis and manuscript edits and M. Somerville was involved in concept formation and manuscript edits. The project received research ethics approval from the University of Alberta Research Ethics Board, Project Name: “Impact of exercise restriction for children, adolescents and young adults with LQTS, CPVT, HCM and ARVC with regard to weight status and exercise capacity,” No. Pro00052201, November 18, 2014 and the University of Calgary Research Ethics Board, Project Name: “Impact of exercise restriction for children, adolescents and young adults with LQTS, CPVT, HCM and ARVC with regard to weight status and exercise capacity,” No. REB14-2500_MOD1, November 19, 2015.

Chapter 5 has been submitted for publication as S. Christian, M. Somerville, S. Taylor, J. C. Spence, M. Giuffre, J. Atallah **“**The impact of age at diagnosis on physical activity modification and health related quality of life in a cohort of children with an inherited arrhythmia or cardiomyopathy” in the Journal of September 10, 2019. I was responsible for concept formation, data collection and analysis as well as the manuscript composition. M. Giuffre, was involved in data collection and manuscript edits. J.C. Spence was involved in data analysis and manuscript edits. J. Atallah, was involved in

concept formation, data analysis and manuscript edits and M. Somerville was involved in concept formation and manuscript edits. The project received research ethics approval from the University of Alberta Research Ethics Board, Project Name: “Does age at diagnosis impact health related quality of life and adherence to physical activity restriction in a group of children and adolescents diagnosed with an inherited arrhythmia or cardiomyopathy?” No. Pro00060362, November 28, 2016 and the University of Calgary Research Ethics Board, Project Name: “Does age at diagnosis impact health related quality of life and adherence to physical activity restriction in a group of children and adolescents diagnosed with an inherited arrhythmia or cardiomyopathy?” No. REB17-0070_REN1, June 23, 2017.

ACKNOWLEDGMENTS

I am most appreciative for the altruistic contribution of the children, families and healthcare professionals who participated in my studies. The gift of their precious time and thoughtful responses are greatly valued. Patient organizations such as the Sudden Arrhythmia Death Syndrome (SADS) Foundations, the Hypertrophic Cardiomyopathy Association and the ARVD Heart for Hope group provide an instrumental service connecting individuals in a meaningful way and supporting the exchange of knowledge between individuals living with an inherited heart conditions and the healthcare professionals caring for them. Professional organizations such as the Canadian Association of Genetic Counsellors, the National Society of Genetic Counselors, the Australasian Society of Genetic Counsellors, the Association of Genetic Counsellors and Nurses in the United Kingdom and the Pediatric and Congenital Electrophysiology Society allow us to learn from one another and work towards improved patient care. I am very grateful for the support of all of these organizations as their assistance was crucial in understanding the international practice and perspectives of healthcare professionals.

My PhD experience has also given me a great appreciation of the value of collaboration. We can achieve much more by sharing expertise and working together to recruit participants with rare conditions. I am thankful for the opportunity to work with Dr.'s Robin Clegg, Michael Guiffre, Valerie Carson, and John Spence. I am also grateful for the additional supports provided by the REDCap staff, SPOR knowledge translation group, the WCHRI staff and the professors who taught me about study design, biostatistics, and health related quality of life measures.

I am enormously grateful for the time and energy provided by my supervisors over the 6 years of my PhD studies. I appreciate the challenges of supervising a PhD student among all the clinical demands on their time and attention. Their insight and support was instrumental in helping me achieve this goal.

Finally, a PhD cannot be achieved without significant support and sacrifice from family and friends. The support I received through the many highs and lows from my husband, children, colleagues and friends was priceless. I feel both joy and a little sadness as I come to the end of this chapter in my life but also look forward to where this experience may lead me.

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LIST OF ABBREVIATIONS

AED	Automated external defibrillators
AGCN	Association of Genetic Counsellors and Nurses
ARVC	Arrhythmogenic right ventricular cardiomyopathy
ASGC	Australasian Society of Genetic Counsellors
BMI	Body mass index
CAGC	Canadian Association of Genetic Counsellors
CCS/CHRS	Canadian Society/ Canadian Heart Rhythm Society-
CI	Confidence interval
CPR	Cardiopulmonary resuscitation
CPVT	Catecholaminergic polymorphic ventricular tachycardia
CSANZ	Cardiac Society of Australia and New Zealand
ECG	Electrocardiography
ESC	European Society of Cardiology
FAP	Familial adenomatous polyposis
HCM	Hypertrophic cardiomyopathy
HFSA/ACMG	Heart Failure Society of American/American Society of Medical Genetics
HRQL	Health related quality of life
HRS/EHRA	Heart Rhythm Society/ European Heart Rhythm Association
ICD	Implantable cardioverter defibrillator
LQTS	Long QT syndrome
LQTS1	Long QT syndrome type 1
LQTS2	Long QT syndrome type 2
LQTS3	Long QT syndrome type 3
MVPA	Moderate- to vigorous-intensity physical activity
NF2	neurofibromatosis type 2
NGS	Next generation sequencing
NSGC	National Society of Genetics Counselors
OR	Odds ratio
SADS	Sudden Arrhythmia Death Syndrome
SCA	Sudden cardiac arrest
SCD	Sudden cardiac death

SD	Standard deviation
WCCHN	Western Canadian Children's Heart Network

Chapter 1: INTRODUCTION AND LITERATURE REVIEW

Sudden cardiac death (SCD) tragically steals years from its victims and creates significant grief and sorrow for family and friends. It is even more perplexing when the victim is a young athlete as this population is perceived as particularly healthy. As a result, the medical community has placed much emphasis on accurately diagnosing cardiac conditions that predispose to SCD, and on implementing management to prevent such a catastrophic outcome. Predictive genetic testing is now clinically available as a strategy towards early diagnosis, as more than a third of these deaths have been attributed to an inherited arrhythmia or cardiomyopathy (Maron et al, 2009). This testing approach permits the identification of *at risk* individuals, providing an opportunity to intervene prior to SCD.

While predictive genetic testing is well accepted in adult populations, there has been greater ethical debate when testing involves children (Tozzo et al, 2012; Botkin et al, 2015). Children are viewed as a vulnerable population as they lack the maturity to understand the potential implications of testing, which would allow them to provide informed consent. In an effort to protect a child's autonomy, predictive genetic testing has historically only been considered when testing leads to clear and immediate medical benefit (Borry et al, 2006). Consequently, age at disease onset and the availability of prophylactic therapy have played a critical role in defining when predictive genetic testing should be considered during childhood.

Predictive genetic testing is currently offered to minors *at risk* of an inherited arrhythmia or cardiomyopathy such as long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), hypertrophic cardiomyopathy (HCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC), as these conditions may present during childhood. Testing permits early diagnosis and initiation of preventative management, both protecting children from arrhythmogenic events and improving their long term cardiac function. Unnecessary cardiac screening may also be eliminated for children who do not inherit the familial genetic variant. However, there are currently knowledge gaps in our understanding of factors influencing the pathway to diagnosis and the impact of diagnosis and management on the physical, psychological and social well-being of children. This dissertation explores these knowledge gaps and evaluates the impact of age at diagnosis, family values, and healthcare providers practice characteristics on the patient's journey.

1.1 Diagnoses of Interest

A pediatric population diagnosed with LQTS, CPVT, HCM or ARVC was examined as each condition carries a risk of SCD which can be associated with vigorous-intensity physical activity. These conditions are most commonly inherited in an autosomal dominant manner placing offspring at 50% risk of inheriting the condition and leaving parents in a position to decide if or when their child(ren) should have predictive genetic testing. Management of all four conditions may include physical activity restriction, beta blocker therapy, and/or placement of an implantable cardioverter defibrillator (ICD). Each condition is described in more detail below and in Table 1.1.

1.1.1 Long QT Syndrome (LQTS)

Long QT syndrome (LQTS) is an inherited arrhythmia caused by abnormal cardiac ion channels with onset commonly occurring between 9-20 years of age (Figure 1.1) (Alders et al, 2015). Disruption of ion channels result in a prolonged QT interval and delayed repolarization (Figure 1.2) (Abriel and Zaklyazminskaya, 2013). Diagnosis can be challenging with approximately 25% of genotype positive individuals presenting with a QT interval within the normal range (Goldenberg et al, 2011). Exercise electrocardiography (ECG) and intravenous pharmacologic provocation testing may help clarify a diagnosis (Krahn et al, 2012).

The majority of pathogenic variants occur in genes causing LQTS 1-3 (*KCNQ1*: 30-35%, *KCNH2*: 25-30%, and *SCN5A*: 5-10%, respectively) (Alders et al, 2015). Distinct differences in ECG pattern, clinical presentation and risk factors have been identified between these 3 types of LQTS (Schwartz et al, 2001; Alders et al, 2015). LQTS1 presents with a broad T wave on ECG and is highly responsive to beta blocker therapy. Cardiac events more commonly occur during intense physical activity. Missense variants within the cytoplasmic loop domain of *KCNQ1* are associated with the greatest response to beta blocker therapy (Barsheshet et al, 2012). LQTS2 presents with a flat, notched T wave on ECG and response to beta blocker therapy is variable (Kim et al, 2010). Cardiac events generally occur in response to emotion or surprise. Individuals with LQTS3 often have a long ST segment with a narrow T wave on ECG and are also less responsive to beta blocker therapy than individuals with LQTS1. Cardiac events tend to occur during rest or sleep. Because of the differences in presentation and response to treatment, identification of the specific type of LQTS can be useful in management.

The majority of LQTS is inherited in an autosomal dominant manner, however, a condition known as Jervell and Lange-Nielson syndrome is inherited in an autosomal recessive manner. This condition is caused by pathogenic variants in *KCNQ1* and/or *KCNE1* and presents with arrhythmia and hearing loss. LQTS4, LQTS7 and LQTS8 are autosomal dominant but also present with additional features such as autism, periodic paralysis and syndactyly, respectively (Alders et al, 2015). Patients with a syndromic form of LQTS were excluded from our studies.

1.1.2. Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an arrhythmia caused by calcium dysregulation in the cardiomyocyte (Figure 1.1). Approximately 35% of individuals present by 10 years of age and 75% by 20 years of age (Pflaumer and Davis, 2012). Overall penetrance for the condition is thought to range between 60-70% (van der Werf et al, 2012). The resting ECG for most individuals affected with CPVT is normal. Therefore an exercise ECG, 24 hour Holter monitor, and/or intravenous pharmacologic provocation may be required to confirm a diagnosis (Krahn et al, 2012; Roston et al, 2015).

CPVT is autosomal dominant in the majority of families. Pathogenic variants occur in genes involved in calcium regulation within cardiomyocytes. Fifty five percent of cases are caused by a pathogenic variant in the *RYR2* gene and a small percent by pathogenic variants in the *KCNJ2* gene (Napolitano, 2016). CPVT can also be inherited in an autosomal recessive manner as a result of pathogenic variants in the *CASQ2* gene (3-5% of families) (Faggioni et al, 2012). More recently, pathogenic variants have been identified in two calmodulin genes (*CALM1* and *CALM2*) (Crotti et al, 2013).

1.1.3 Hypertrophic Cardiomyopathy (HCM)

Hypertrophic cardiomyopathy (HCM) is characterized by left ventricular hypertrophy in the absence of a predisposing cardiac condition such as systemic hypertension or aortic stenosis. Age of onset is variable and some individuals with a genetic predisposition remain asymptomatic throughout their lifetime.

HCM often occurs as a result of pathogenic variants within genes that encode sarcomere proteins or proteins that regulate sarcomere proteins (Figure 1.1). The sarcomere is the architectural structure within cardiomyoctyes that allows the cells to contract. The most common genes linked to HCM are *MYH7* (40%) and *MYBPC3*

(40%) (Cirino, 2014). All pathogenic variants classified to-date are inherited in an autosomal dominant manner. Some individuals have been identified to carry two pathogenic variants and generally present with a more severe phenotype (Ingles et al, 2005). No other clear genotype-phenotype associations have been found.

1.1.4 Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a heart condition characterized by progressive replacement of right ventricular muscle cells with fibrous tissue and fat. Onset generally occurs between the second and fifth decade of life (Calkins, 2015). The condition is more prevalent in specific geographical locations such as Italy, Greece and Newfoundland (McNally, 2014). Alberta also has a sizeable population affected with ARVC due to an influx of individuals of Newfoundland ancestry to the northern part of the province.

The vast majority of ARVC is inherited in an autosomal dominant fashion with some rare cases being inherited in an autosomal recessive manner. The most common pathogenic variants present in genes involved in the desmosome which is a structure that mechanically connects cardiomyocytes (Figure 1.1). Variants in these genes disrupt electrical coupling between neighbouring cardiomyocytes (Cruz et al, 2015). Pathogenic variants are most common in the *PKP2* (Plakophilin-2) gene (34%-74%) and are thought to predispose to earlier disease and a higher risk of arrhythmias compared to other implicated genes (Iyer and Chin, 2013; McNally, 2014). A variant in the non-desmosomal gene *TMEM43* is a founder mutation in Newfoundland. This variant has a higher penetrance in males than females and results in a more pathogenic form of ARVC with a high risk of SCA (Hodgkinson et al, 2013). Two rare recessive forms of the condition involve the *DSC2* and *JUP* genes. Both conditions present with multisystem involvement including woolly hair and palmoplantar keratoderma (McNally, 2014).

Table 1.1: Characteristics of LQTS, CPVT, HCM and ARVC

Characteristic	LQTS	CPVT	HCM	ARVC
Incidence	1/2000	1/10 000	1/500	1/100- 1/5000
Average age of onset	Preteens- Young adults	Childhood- Preteens	Adulthood	Adulthood
Possible symptoms	syncope, palpitations, SCA	syncope, palpitations, SCA	chest pain, shortness of breath, syncope, palpitations, SCA	syncope, palpitations, SCA
Potential interventions	physical activity restriction, beta blocker therapy, avoidance of QT prolonging medications, electrolyte imbalances, dehydration and drastic increases in core body temperature, left cardiac sympathetic denervation surgery, ICD placement	physical activity restriction, beta blocker therapy, calcium blockers, and/or antiarrhythmic drugs, left sympathetic denervation surgery, ICD placement	physical activity restriction, beta blocker therapy, calcium blockers and/or antiarrhythmic drugs, myectomy, alcohol septal ablation, heart transplant, ICD placement	physical activity restriction, beta blocker therapy, antiarrhythmic drugs, catheter ablation, heart transplant, ICD placement
Number of associated genes	15+	4+	16+	13+
Detection rate of genetic testing	75-80%	55-65%	30-60%*	~50%

SCA- sudden cardiac arrest; ICD- implantable cardioverter defibrillator
(Van Driest et al, 2005; Cirino 2014; McNally 2014; Alfares et al, 2015; Alders et al, 2015; Napolitano 2016;)

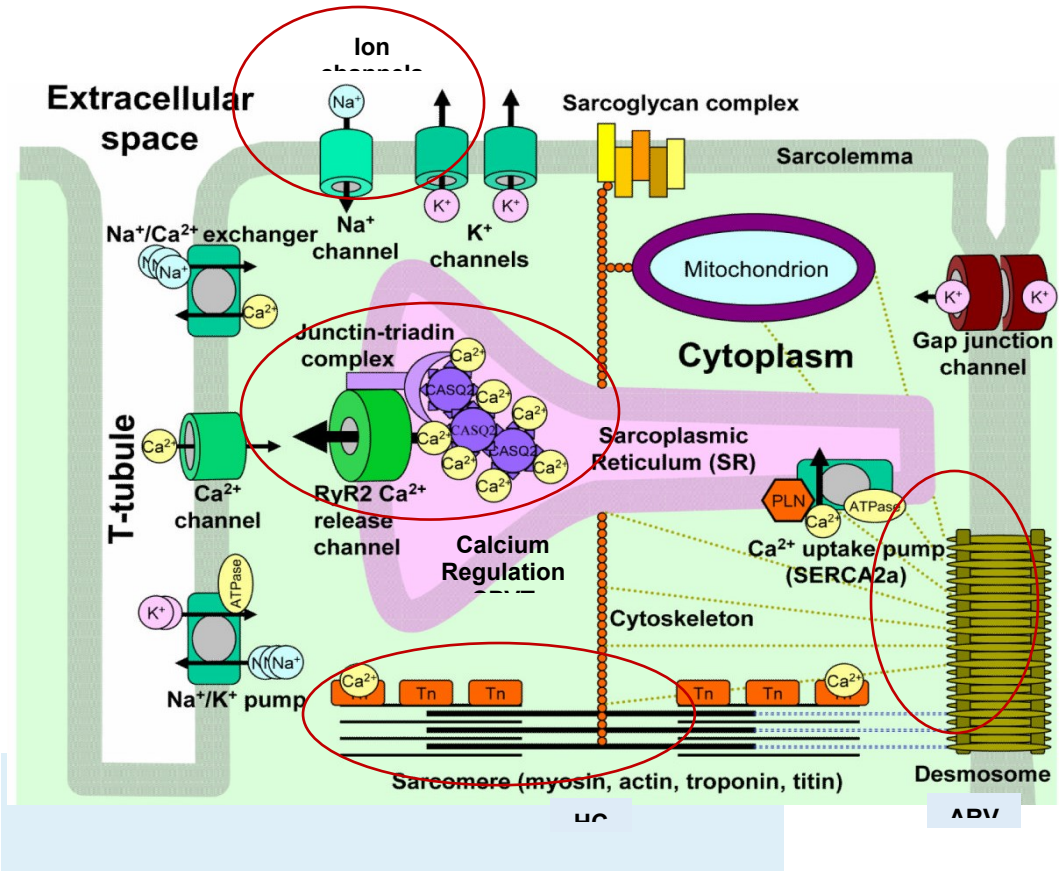


Figure 1.1: Cellular impact of pathogenic variants for LQTS, CPVT, HCM and ARVC

Long QT syndrome (LQTS) results from abnormal cell membrane ion channel function. Catecholaminergic polymorphic ventricular tachychardia (CPVT) is caused by disruption of intra-cellular calcium homeostasis. Hypertrophic cardiomyopathy (HCM) is related to abnormalities in sarcomere proteins. Arrhythmogenic right ventricular cardiomyopathy (ARVC) often develops as a result of disruption of the desmosome. Adapted from Figure 1 by Faggioni et al (2012) Pediatr Cardiol. August;33(6): 959–967.

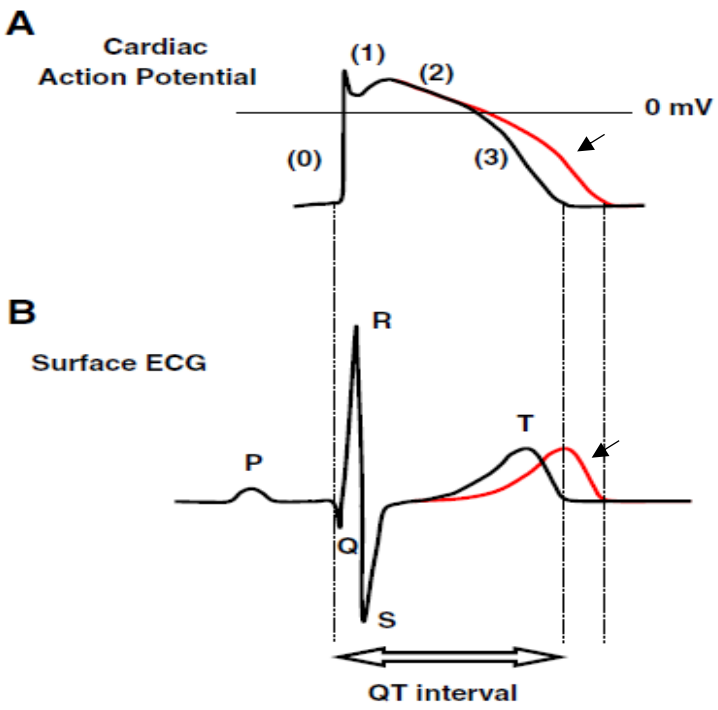


Figure 1.2: Long QT interval

A- The black tracing represents a normal cardiac action potential. The red tracing illustrates the delayed repolarization that occurs in patients with long QT syndrome.

B- The black tracing represents a normal EGC pattern. The red tracing illustrates the prolonged QT interval seen in patients with long QT syndrome.

Adapted from Figure 2 by Abriel et al *(2013)* Gene March(1): 1-11.

1.2 Published Recommendations

In an effort to standardize care, several professional bodies have published guidelines or position/consensus statements pertaining to the diagnosis and management of LQTS, CPVT, HCM and ARVC. Recommendations address the utility of genetic testing, physical activity restriction and other common interventions (i.e. beta blocker therapy, antiarrhythmic drugs, ICD placement, and surgery) for these patient populations.

1.2.1 Genetic testing recommendations

Due to the heterogeneity of LQTS, CPVT, HCM and ARVC, genetic testing was initially limited to targeting the most common gene(s) or to research testing. However, the introduction of next generation sequencing (NGS) has provided the opportunity to sequence many genes in parallel at a reasonable cost. NGS cardiac gene panels became clinically available in Alberta in 2008. The number of genes included in each gene panel has expanded over time with the discovery of new genes, although the detection rates have only marginally improved as the most prevalent genes associated with these conditions have remained constant.

The utility of genetic testing varies between diagnoses depending on the detection rate, genotype-phenotype associations, and the penetrance and age of onset of the condition. Recommendations consider the utility of genetic testing for the purpose of diagnosis, risk stratification, guiding therapy and cascade family screening. A review of published guidelines is presented in Table 1.2.

The potential for cascade predictive genetics testing is currently perceived as having the greatest utility with regard to these conditions and is therefore discussed in detail in each guideline or position/consensus statement (Ackerman et al, 2011; Gollob et al, 2011; Ingles et al, 2011; Charron et al, 2014). Cascade screening within a family has the potential to improve outcomes and has been shown to be cost-effective to the overall healthcare system (Phillips et al, 2005; Ingles et al, 2012). Consequently, much work has been done to increase the uptake of predictive genetic testing by relatives including providing patients with tools such as family letters and communication aids (van der Roest et al, 2009; Smagarinsky et al, 2017).

Although each guideline supports genetic testing for the purpose of cascade family screening, there is less consistency regarding the age at which predictive genetic testing is recommended. The European Society of Cardiology and the Cardiac Genetic

Diseases Council Writing Group in Australia/New Zealand suggest deferring predictive genetic testing for HCM and ARVC until after 10 years of age (Ingles et al, 2011; Charron et al, 2014). This is consistent with historical screening recommendations that propose the first cardiac evaluation occur between 10 and 12 years of age. In contrast, the more recently published guidelines by the Heart Failure Society of America/ American College of Medical Genetics (HFSA/ACMG) recommend at least one cardiac evaluation before 5 years of age for children who have a first-degree relative diagnosed with HCM or ARVC (Hershberger et al, 2018). This suggests that there may be utility in offering predictive genetic testing at an early age. In comparison, there has been general agreement that predictive genetic testing be offered at a young age for LQTS and CPVT (Ackerman et al, 2011).

In summary, the greatest utility of genetic testing is in providing an opportunity for early diagnosis using cascade predictive genetic testing within a family. Significant improvement in detection rates are necessary to advance the utility of testing for diagnostic purposes. Although some genotype-phenotype associations have been identified, further research is required to support the utility of testing for the purpose of risk stratification or guiding therapy.

Table 1.2: Review of genetic testing guidelines

(√- recommended*, X*- not recommended*)*

Condition	Utility	CCS/CHRS 2011	HRS/EHRA 2011	ESC 2010	CSANZ 2011	HFSA/ ACMG 2018
LQTS	Diagnosis	*X*	√	-	-	-
	Risk stratification	√	√	-	*X*	-
	Therapy	√	√	-	*X*	-
	Family screening	√	√	-	√	-
CPVT	Diagnosis	*X*	√	-	-	-
	Risk stratification	*X*	*X*	-	*X*	-
	Therapy	*X*	*X*	-	*X*	-

	Family screening	√	√	-	√	-
HCM	Diagnosis	*X*	√	*Recommended for rare diagnosis Not recommended for borderline diagnosis*	-	-
	Risk stratification	*X*	*X*	*X*	*X*	√
	Therapy	*X*	*X*	*X*	*X*	√
	Family screening	√	√	√	√	√
ARVC	Diagnosis	*Recommended if diagnosis borderline*	*May consider if diagnosis borderline*	*Recommended for rare diagnosis Not recommended for borderline diagnosis*	-	-
	Risk stratification	*X*	*X*	*X*	*X*	√
	Therapy	*X*	*X*	*X*	*X*	√
	Family screening	√	√	√	√	√

LQTS- long QT syndrome, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy

CCS/CHRS- Canadian Society/ Canadian Heart Rhythm Society- Joint Position Paper (Gollob et al, 2011)

HRS/EHRA- Heart Rhythm Society/ European Heart Rhythm Association- Consensus Statement (Ackerman et al, 2011)

ESC- European Society of Cardiology- Position Statement (Charron et al, 2014)

CSANZ- Cardiac Society of Australia and New Zealand- Guidelines (Ingles et al, 2011)

HFSA/ ACMG- Heart Failure Society of American/American College of Medical Genetics- Practice Guideline (Hershberger et al, 2018)

1.2.2 Physical activity recommendations

In the early 1980s, Italy introduced mandatory ECG screening for all competitive athletes in an effort to detect inherited arrhythmias and cardiomyopathies and decrease the number of athlete deaths (Corrado et al, 2006). In the time period between when this screening program was implemented in 1982, and 2000, the incidence of SCD in athletes (12-35 years of age) in the Veneto region of Italy was reported to dramatically decrease from 3.6/100 000/year to 0.4/100 000/year. Over this same time period, the incidence of SCD in the general population remained constant at 0.79/100 000/year. This study provided significant support for the prescription of physical activity restriction for individuals diagnosed with LQTS, CPVT, HCM and ARVC.

A follow up study in the United States revealed that inherited cardiomyopathies represent the largest proportion of sudden cardiac death in athletes with HCM and ARVC accounting for 29% and 3%, respectively (Maron et al, 2009). A significant proportion (2-10%) of deaths have also been attributed to arrhythmias such as LQTS and CPVT (Schmied and Borjesson, 2014).

The connection between vigorous-intensity physical activity and sudden cardiac arrest (SCA) is thought to relate to the increased production of epinephrine which is recognized by the beta adrenergic receptors on the cell surface of cardiomyocytes (Thomas et al, 2004). These receptors interact with specific proteins involved in the production of cAMP which initiates a cascade of events that leads to the release of additional calcium from the sarcoplasmic reticulum. Disruption of calcium concentrations within the cardiomyocytes leads to premature electrical activity and the induction of life threatening ventricular arrhythmias. In contrast, ARVC pathogenic variants are thought to disturb the connection between cardiomyocytes, interrupting the electrical impulses which pass from one cell to another, resulting in syncope or SCA (Cruz et al, 2015). It has also been postulated that repeated endurance activities further disrupt the connection between cardiomyocytes, advancing disease progression for individuals with ARVC (James et al, 2013; Saberniak et al, 2014).

Consequently, in an effort to prevent SCA, several professional bodies have recommended restriction from vigorous-intensity physical activity for these patient populations. The recommendations vary based on cardiac diagnosis, phenotype and therapeutic intervention. Many of the guidelines focus on participation in competitive

sport which is defined as individual or team sport participation that involves “regular competition against others as a central component, places a high premium on excellence and achievement, and requires some form of systematic (and usually intense) training” (Maron and Zipes, 2005). The recommendations also vary based on how the professional bodies interpret the published data and expert opinion.

Published guidelines and position/consensus statements describing physical activity recommendations for each diagnosis are reviewed in Table 1.3. The table highlights the discrepancies between guidelines and reflects an ongoing debate between the risks associated with sport participation and the health benefits provided by involvement in regular moderate- to vigorous-intensity physical activity. Physical activity has been shown to reduce the risk of type 2 diabetes, hypertension, depression, coronary heart disease and all-cause mortality (Barker et al, 2002; Engeland et al, 2003; Eriksson et al, 2003; Field et al, 2005; Nocon et al, 2008; Al Mamun et al, 2009; Andersen et al, 2010; Mammen and Faulkner 2013). Therefore, it is important to better define a “safe” level of physical activity for these patient populations. In addition, large collaborative studies are required to clarify the risks and better inform management recommendations.

Table 1.3: Physical activity recommendation based on diagnosis and phenotype

Genotype	Phenotype	#36BC 2005	ESC 2005	HRS/EHRA /APHRA 2013	AHA/ACC 2015
LQTS	Positive	No competitive sport*	No competitive sport*	No direct recommendations	Competitive sport may be considered after 3 months of beta blocker therapy. Exception -no competitive swimming
	Negative	Unrestricted Except LQTS1-no competitive swimming	Competitive sport discouraged	Not addressed	Unrestricted
CPVT	Positive	No competitive sport*	No competitive sport*	No competitive sport*	No competitive sport*

	Negative	Unrestricted	No competitive sport*	Not addressed	Unrestricted
HCM	Positive	No competitive sport*	No competitive sport*	N/A	No competitive sport*
	Negative	Unrestricted	No competitive sport*	N/A	Unrestricted
ARVC	Positive	No competitive sport*	No competitive sport*	N/A	No competitive sport*
	Negative	Not addressed	Not addressed	N/A	No direct recommendation

* Exception- Low intensity/low dynamic sports

LQTS- long QT syndrome, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy

#36BC- #36 Bethesda Conference consensus recommendations (Maron and Zipes 2005)

ESC- European Society of Cardiology consensus document (Pelliccia et al, 2005)

HRS/EHRA/AAPHA- Heart Rhythm Society/ European Heart Rhythm Association/Asian-Pacific Heart Rhythm Society expert consensus statement (Priori et al, 2013b)

AHA/ACC- American Heart Association/ American College of Cardiology scientific statement (Maron et al, 2015)

1.2.3 Recommendations for other common interventions

Other common interventions for LQTS, CPVT, HCM and ARVC include beta blocker therapy, antiarrhythmic drugs, ICD placement and occasionally surgery (i.e. left cardiac sympathetic denervation, myectomy, alcohol septal ablation, heart transplant). The treatment approach is dependent on diagnosis, cardiovascular findings, clinical symptoms and risk stratification for an arrhythmogenic event.

Research has shown that beta blocker therapy lowers mortality rates for individuals with LQTS and CPVT who are phenotype positive and phenotype negative at presentation, although no randomized trials have been conducted in these populations (Villain et al, 2004; Postma et al, 2005; Goldenberg et al, 2008; Hayashi et al, 2009; Vincent et al, 2009). Mortality rates are also decreased for phenotype positive individuals with HCM, whereas, there is currently no evidence that beta blocker therapy improves survival for ARVC patients in the absence of non-sustained ventricular arrhythmia (Ostman-Smith et

al, 1999; Marcus et al, 2009). Based on this data, guidelines generally recommend beta blocker therapy for individuals who are phenotype positive for LQTS and CPVT and indicate that therapy be considered for phenotype negative carriers of these conditions (Pflaumer and Davis, 2012; Priori et al, 2013b; Waddell-Smith and Skinner, 2016). Beta blocker therapy is recommended for treating some symptoms (ie. angina or dyspnea) associated with HCM and for managing ARVC patients with specific cardiac findings (ie. frequent premature ventricular beats or non-sustained ventricular arrhythmia) (Gersh et al, 2011; Corrado et al, 2015). They are not recommended for phenotype negative carriers of HCM or ARVC.

Antiarrhythmic drugs may be prescribed as adjunct therapy in situations where arrhythmia cannot be controlled by beta blocker therapy alone. ICD placement is informed by risk stratification based on cardiac function and history of arrhythmogenic events. Medical management may be further influenced by gender, age of onset and family history of SCA. In addition, evidence is building regarding associations between specific genetic variants and a higher risk of cardiac arrest. For example, ICD placement as a primary prevention has been shown to improve survival rates for males and females with a clinical diagnosis of ARVC who carry the founder *TMEM43* variant (c.1073C>T) (Hodgkinson et al, 2016). Finally, surgery may be considered for symptomatic patients to improve heart function and/or quality of life. Management with antiarrhythmic drugs, ICD placement and surgery is outside the scope of this dissertation and therefore specific recommendations are not reviewed.

1.3 Impact of Diagnosis and Management on Well-being

The benefits of early diagnosis of LQTS, CPVT, HCM and ARVC related to predictive genetic testing are well accepted. However, potential harms that accompany diagnosis and management are less understood. The current literature is reviewed evaluating how well-being is impacted by predictive genetic testing, a clinical or genetic diagnosis and common interventions.

1.3.1 Impact of predictive genetic testing on well-being

Learning that one has an increased chance of developing a life threatening heart condition has the potential to negatively impact their psychological well-being. Many adults describe health anxiety following disclosure of a predictive genetic result and express concern and/or guilt of passing the condition on to their offspring (Smart, 2010;

Etchegary et al, 2015). Feelings of uncertainty are also depicted - what does the result actually mean for their health (Bonner et al, 2018).

The perceived significance of a test result is related to an individual's interpretation of their disease risk and whether or not testing leads to behavioral change (Ormondroyd et al, 2014; Bonner et al, 2018). For example, a predictive diagnosis could alter the career path of an individual employed as, or striving to be, a pilot, truck driver, police officer, or engaged in military service. In addition, a greater psychological impact is reported for individuals involved in high dynamic competitive sport at the time of their diagnosis due possible disqualification (Ormondroyd et al, 2014; Asif et al, 2015;).

Much of the research in this area has focused on how adults interpret and react to a predictive diagnosis. It is likely that children and adolescents translate this information differently depending on their age and experience with the specific condition. Qualitative research for pediatric populations mainly focuses on how parents perceive predictive genetic testing to impact their child's well-being. Parents relay that testing provides clarification regarding the risk status of the child and improves the care they, as parents, can offer, but may also create worry, negatively impact how the child is treated by friends and family, remove opportunity for the child and disregards the child's autonomy (Geelen et al, 2011).

Issues raised through qualitative research have not been supported by health related quality of life (HRQL) research. HRQL scores measured before and after a group of adults underwent predictive genetic testing for LQTS, HCM, ARVC or dilated cardiomyopathy found no significant change between baseline, and 1-3 months, 6 months and 12 months post disclosure of their result (Ingles et al, 2012). Similar conclusions have been drawn from three systematic reviews looking at the impact of predictive genetic testing in children and young adults at risk of a variety of inherited conditions (Wade et al, 2010; Godino et al, 2016; Wakefield et al, 2016). They conclude that although the research in this area is limited, predictive genetic testing does not appear to negatively impact the emotional state, self-perception or social well-being of children, adolescents, and young adults.

Uptake of predictive genetic testing

Approximately 40% and 60% of adult 1st degree relatives reportedly undergo cascade genetic testing in HCM and LQTS families, respectively (Christiaans et al, 2008; Miller et

al, 2013). Uptake of predictive genetic testing is similar to what is reported in other inherited conditions such as familial breast and ovarian cancer (Brooks et al, 2004). Predictive genetic testing for children *at risk* of HCM and LQTS has been estimated at approximately 56% by 2 small studies (Christiaans et al, 2008; Ormondroyd et al, 2014). This is slightly lower than uptake for inherited cancer syndromes that can present during childhood such Li-Fraumeni syndrome where uptake was reported at 79% (Alderfer et al, 2015). Uptake of cardiovascular screening is greater in families with a known genetic cause and is higher overall compared to predictive genetic testing among relatives (Miller et al, 2013).

1.3.2 Impact of diagnosis on well-being

Individuals with a clinical diagnosis of an inherited arrhythmia or cardiomyopathy report heightened feelings of anxiety and fear of dying as a result of having an increased risk of SCA (Andersen et al, 2008). As described above, alterations to behaviour can lead to additional feelings of loss of freedom of choice concerning career and sport participation (Subasic, 2013). Quality of life may be further impacted by disease symptoms such as palpitations, chest pain, shortness of breath and fatigue.

Although parents describe more negative consequences when children receive a clinical diagnosis during adolescence, they also express concerns that a child may be stigmatized and overprotected when they are diagnosed at a younger age (Farnsworth et al, 2006; Andersen et al, 2008; Bratt et al, 2011). Parents suffer the greatest anxiety and worry concerning SCA for their children even though they may possess the same diagnosis.

HRQL has been evaluated in pediatric and adult LQTS, CPVT, HCM and ARVC patient populations. Although there are some conflicting results, the majority of studies have found that clinically affected children and adults diagnosed with one of these conditions have decreased HRQL scores compared to normative data (Cox et al, 1997; Ingles et al, 2008; Smets et al, 2008; Christiaans et al, 2009; Hamang et al, 2010; Bratt et al, 2013; Czosek et al, 2015; Friess et al, 2015; Spanaki et al, 2015; Sleeper et al, 2016). Some of the discrepancies can be explained by the populations used for comparison, small sample size and the sensitivity of the instruments used. Higher prevalence of anxiety and depression have also been reported for adults with LQTS, CPVT and HCM (Ingles et al, 2008; Wesolowska et al, 2017).

Results are inconsistent with regard to the HRQL for genotype positive/ phenotype negative individuals and *at risk* family members. Friess et al, (2015) found that children *at risk* of a cardiomyopathy based on family history had significantly lower total PedsQL scores compared to healthy controls but similar to their clinically affected group. Further, Bratt et al, (2012) measured the effect of cardiac screening on HRQL, comparing the scores of *at risk* children before and after a clinical diagnosis and found that HRQL scores did not change following clinical diagnosis. In contrast, Ingles et al, (2008) and Spanaki et al, (2015) report similar HRQL scores for their *at risk* groups when compared to normative adult and pediatric data, respectively.

1.3.3 Impact of common interventions on well-being

As discussed previously, common interventions for LQTS, CPVT, HCM, and ARVC include physical activity restriction, beta blocker therapy, and ICD placement. Other treatments include antiarrhythmic medication and surgery. The impact of the common interventions on well-being are described.

1.3.3.1 Physical activity restriction and well-being

Psychological impact

When high school and college athletes were disqualified from sport due to a diagnosis of LQTS or HCM, they reported significant and prolonged psychological morbidity (Asif et al, 2015). Disqualification reportedly threatened the athlete's self-identity, interfered with their social network and eliminated a coping mechanism for dealing with stress. Disruption of their structured environment also led to feelings of isolation during an already emotionally vulnerable period of time.

A subset of adults diagnosed with LQTS and HCM relate that learning of their genetic diagnosis earlier in life may have influenced their choice of activities growing up (Ormondroyd et al, 2014). Similarly, parents of children diagnosed with LQTS expressed that when children grew up with physical activity restriction from a young age they had more time to adjust their behaviour, potentially improving psychological outcomes (Andersen et al, 2008). However, limiting physical activity from a young age may also reduce the potential benefits associated with involvement in moderate- to vigorous-intensity physical activity such as reduced risk of cardiovascular mortality, cancer, all-cause mortality and diabetes, as well as improved mental health outcomes (DiLorenzo et al, 1999; Engeland et al, 2003; Nocon et al, 2008; Andersen et al, 2010; Mammen and Faulkner, 2013).

Impact on weight

An additional concern linked to physical activity restriction relates to the increased risk of obesity due to an imbalance of caloric intake and energy expenditure. Obesity is associated with an increased risk of type 2 diabetes, hypertension, coronary heart disease and all-cause mortality (Irvine et al, 2002; Engeland et al, 2003; Eriksson et al, 2003; Field et al, 2005; Al Mamun et al, 2009; Andersen et al, 2010). Physical activity restriction may decrease the risk of arrhythmias and improve cardiac function related to an inherited arrhythmia or cardiomyopathy but lead to other health concerns over an individual's lifetime.

Concerns relating to obesity are raised in a study by Reineck et al (2013) who found that adult HCM patients had higher body mass index (BMI) scores compared to the general population. It is unclear, however, if the higher BMI scores were the result of decreased physical activity related to disease symptoms, physical activity restriction or if obesity is a predisposing factor for disease presentation. This study highlights the need for more research in this area.

There is currently a knowledge gap with regard to the consequence of restriction of vigorous-intensity physical activity on weight status for children with an inherited arrhythmia or cardiomyopathy. Looking at a cohort of children with a congenital heart defect, physical activity restriction was significantly associated with greater increases in BMI scores and being overweight or obese. However, the overall overweight (17.3%) and obesity (15.4%) rates did not significantly differ when compared to the general Canadian population (Stefane et al, 2005). In addition, Elias et al (2017) did not find an association been physical activity restriction and BMI scores overtime in a group of children with anomalous aortic origin of a coronary artery. The overweight and obesity rates and exercise capacity did not differ based on physical activity recommendation.

Compliance with physical activity restriction

In general, people are resistant to changing their behavior, even when there is strong evidence that change would lead to improved health outcomes such as smoking cessation (Hollands et al, 2016). Behavioral change has added challenges when the evidence linked with improved health outcomes is less clear. It has been shown that only a small proportion of athletes chose to discontinue sport participation following a diagnosis of LQTS after being counselled about the associated risks with SCA (Johnson and Ackerman, 2013) This finding is further supported by Gow et al (2013) who found

that a significant proportion of adolescents diagnosed with an inherited arrhythmia continue to perform vigorous- and very vigorous-intensity physical activity regardless of the prescription of physical activity restriction. A greater understanding of patients' interpretation of physical activity restriction and their motivation to comply with recommendations is needed in addition to clarifying the risks associated with different forms of physical activity.

1.3.3.2 Beta blocker therapy and well-being

Side effects

Although beta blocker therapy provides protection against arrhythmogenic events, it can also produce side effects. Side effects related to significant morbidity and mortality are rare, however, minor side effects are common and may impact long-term HRQL and compliance with treatment (Koponen et al, 2015). A group of adults treated with beta blockers for heart disease reported symptoms including: dyspnea (9.8%), fatigue (5.3%), dizziness (4.9%), sleep disturbances (2.6%) and bronchospasms (0.7%) (Kalra et al, 2013). Additional side effects include: tired legs, cold extremities, loss of overall well-being and weight gain (Lewis et al, 1985; Maggioni et al, 2005; Taylor 2008; Merlo et al, 2013).

Almost a quarter of children with LQTS on beta blocker therapy report concerns such as nightmares and parasomnias, coldness of extremities, tiredness, dizziness and impaired physical condition (Koponen et al, 2015). More serious side effects have also been reported including asthma, postural hypotension, hypoglycemia, and Raynaud phenomenon (Villain et al, 2004). Medication use has been linked to lower HRQL scores for children with an inherited arrhythmia or cardiomyopathy and side effects have been associated with lower parent proxy scores (Czosek et al, 2015; Friess et al, 2015). For this reason, beta blocker therapy is assessed as a potential confounder in our studies.

Compliance with beta blocker therapy

Medication side effects have been shown to reduce compliance with treatment (Mohr et al, 1998; Fitzgerald et al, 2008). In a group of adults with heart disease, 27% had discontinued beta blocker therapy by 1 year of age, increasing to 34% by 2 years and 50% by 3 years (Kalra et al, 2013). Individuals were more likely to discontinue treatment if they had suffered side effects such as bronchospasm, sleep disturbances and fatigue.

In a study by Koponen et al (2015), 28% of children diagnosed with LQTS report forgetting at least 1 beta blocker dose per month and 4% discontinued treatment. They found that compliance was lower for LQTS2 patients compared to LQTS1 patients and hypothesize that lower compliance rates may be related to a belief that beta blocker therapy is less effective in preventing cardiac arrest for the former genotype. They did not find an association between compliance and side effects.

Beta receptors are transiently up-regulated immediately after termination of beta blocker therapy which leads to an increased risk of a SCA (Waddell-Smith et al, 2015). Because of this, cardiac events have repeatedly been reported following non-compliance with beta blocker therapy (Chatrath et al, 2004; Vincent et al, 2009; Johnson and Ackerman 2013). This emphasises the importance of good compliance with treatment.

1.3.3.3 Impact of ICD on well-being

ICDs may be used for both primary and secondary prevention of cardiac events for individuals with an inherited arrhythmia or cardiomyopathy. Although they can be lifesaving, they sometimes produce inappropriate shocks which may lead to anxiety and post-traumatic stress syndrome (Ingles et al, 2013). Being female, having had inappropriate shocks and being younger at the time of implantation are associated with a greater risk of psychological consequences (Passman et al, 2007; von Kanel et al, 2011; Ingles et al, 2013a). Having an ICD has also been linked to lower HRQL scores among children with the largest impact on physical health (Sears et al, 2011). Qualitative research has identified concerns regarding the impact of the device on appearance, implications for sport participation and fear of an inappropriate shock, which can result in behaviour avoidance. Although ICDs are less common among children, because of these associated concerns, it is important to control for ICD placement in any study evaluating HRQL.

1.4 Goals and Objectives of Dissertation

The ultimate goal is to offer predictive genetic testing at the optimal age to protect children with an inherited arrhythmia or cardiomyopathy from cardiac events while maximizing health and minimizing potential harms. Focusing on LQTS, CPVT, HCM and ARVC, mixed methods were used to assess the current state of predictive genetic testing and management in a pediatric population, explore perspectives on the optimal timing of predictive genetic testing and evaluate the downstream effects of diagnosis and management on well-being.

The following questions were specifically addressed:

1. What are the current practices of pediatric cardiologists on the topic of prescription of beta blockers and physical activity restriction?
2. What proportion of *at risk* children undergo predictive genetic testing and/or cardiovascular screening?
3. What is the optimal time to perform predictive genetic testing?
4. How do diagnosis and management for these conditions impact the well-being of children/adolescents with regard to body mass index (BMI), physical activity level, sport participation and health related quality of life (HRQL). How does age of diagnosis impact these outcomes?

These questions were evaluated by surveying pediatric electrophysiologists, genetics counsellors, and families; by reviewing medical genetics and pediatric cardiology charts; and by measuring physical activity and HRQL in a cohort of children/adolescents diagnosed with LQTS, CPVT, HCM or ARVC. New insight was gained through both quantitative and qualitative analysis. An overview of the experience of *at risk* children and the key points assessed in this dissertation are described in Figure 1.3.

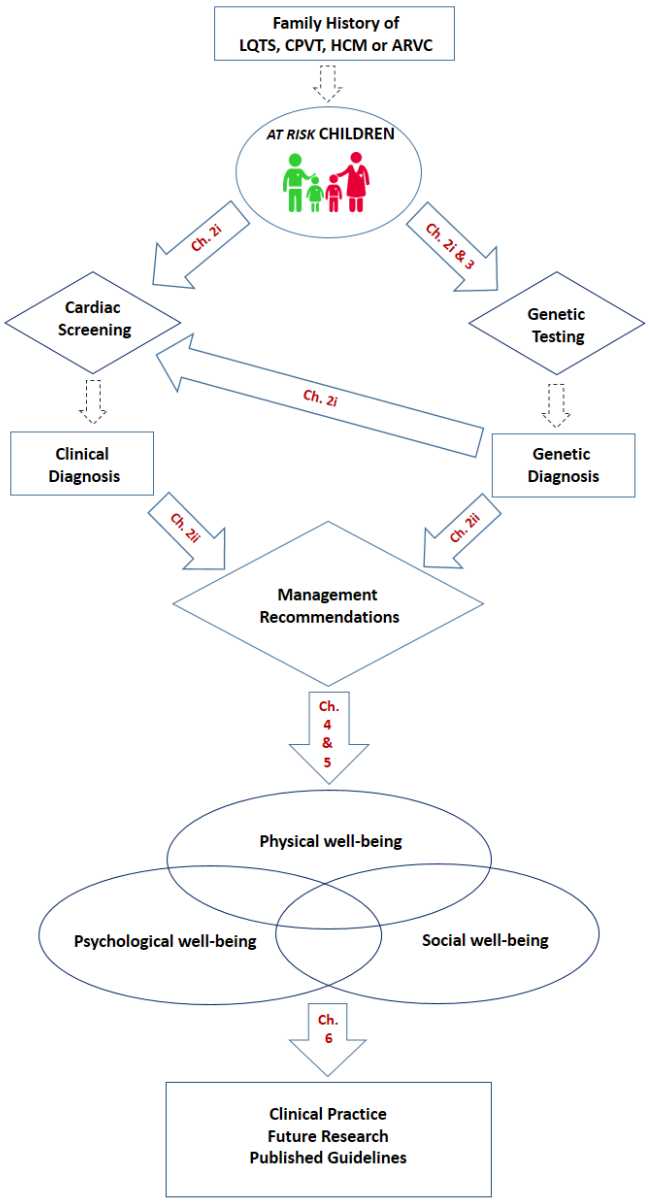
This dissertation is organized as follows:

CHAPTER 2: Data is presented from 2 studies looking at uptake of predictive genetic testing and cardiovascular screening, and current management practices.

CHAPTER 3: Various perspectives relating to the timing of offering predictive genetic testing are explored.

CHAPTER 4 and 5: The impact of diagnosis and management recommendations on the well-being of children is examined.

CHAPTER 6: Conclusions are drawn from review of all our studies and results are discussed in terms of their impact on clinical practice, future research and possible review and revision of current guidelines.



Investigated Outcome	Identified Associated Factors
Genetic Testing Uptake	- Healthcare worker recommendation - Asymptomatic carrier farther
Time of Genetic Testing	- Family history - Country - Clinical setting - Experience of genetic counsellor - Age & education - Ethical principles
Cardiac Screening	- Genetic testing
Management	- Phenotype - Type of activity - Guidelines referenced - Physician activity level
Well-being	- Age - Gender - Obesity - Sport participation - Change to physical activity

Legend

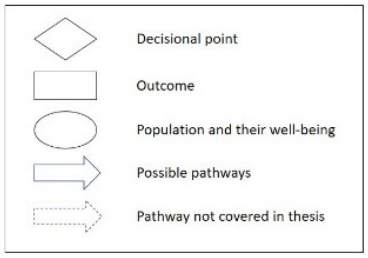


Figure 1.3 The experience of *at risk* children

This figure describes the experience of *at risk* children as they journey to diagnosis and management of LQTS, CPVT, HCM or ARVC.

Chapter 2: CURRENT PRACTICE

Professional guidelines are currently inconsistent regarding when to offer predictive genetic testing to children *at risk* of an inherited cardiomyopathy. They are also inconsistent regarding physical activity recommendations for individuals who are genotype positive/phenotype negative for an inherited arrhythmia or cardiomyopathy. This dissertation therefore starts by examining current practice relating to predictive genetic testing and clinical management for children with or *at risk* of LQTS, CPVT, HCM or ARVC. Through a chart review, we assessed the proportion of *at risk* children who underwent predictive genetic testing and cardiovascular evaluation. We searched further for factors influencing uptake, and assessed the interplay between genetic testing and cardiovascular screening. In addition, management practices were examined by surveying an international group of pediatric electrophysiologists. We assessed potential factors influencing physical activity recommendation. This data set the stage for subsequent work.

2.1. Uptake of predictive genetic testing and cardiac evaluation for children *at risk* for an inherited arrhythmia or cardiomyopathy

2.1.1 Introduction

Family members of individuals who carry a pathogenic variant for an inherited arrhythmia or cardiomyopathy are at increased risk of heart disease and/or cardiac arrest. This includes conditions such as LQTS, CPVT, HCM and ARVC. Cascade genetic testing has been recommended by various professional bodies in an effort to identify and monitor *at risk* individuals and in some situations implement lifestyle modifications and/or prophylactic therapy (Charron et al, 2010; Ackerman et al, 2011; Gollob et al, 2011).

Although penetrance is incomplete and age of onset is variable for all four conditions, each can present during childhood. Nonetheless, recommendations regarding predictive genetic testing in children are less defined. Guidelines by the American Society of Human Genetics indicate that predictive genetic testing may be appropriate in minors for conditions where clinical intervention is available (Botkin et al, 2015). The European Society of Cardiology's position statement regarding predictive genetic testing for cardiomyopathies recommends that genetic testing be considered for children between 10 and 12 years of age (Charron et al, 2010). The Heart Rhythm Society and the European Heart Rhythm Society's consensus statement recommends offering genetic testing as early as infancy for inherited arrhythmias but suggests only cardiac surveillance during childhood for other inherited heart conditions (Ackerman et al, 2011).

As far as we are aware, only two studies have specifically assessed uptake of predictive genetic testing for inherited arrhythmias and cardiomyopathies in children. Christiaans et al (2008) found that approximately 56% of children between 10-18 years of age with a first degree relative found to carry a pathogenic variant for HCM had genetic testing. No specific family characteristics were associated with uptake of predictive genetic testing. In a qualitative study, Ormondroyd et al, (2014) found that five out of nine pathogenic variant carriers for LQTS or HCM reported having tested their children. Parents described being motivated to test their children to ensure appropriate physical activity involvement and understand when they should further investigate clinical symptoms. The four parents who chose not to test their children raised concerns regarding a fear of overprotecting their children, insurance and psychological concerns, and possible adverse effects on marriageability.

The objective of this study was to examine factors associated with uptake of genetic testing and cardiac evaluation for children in families identified to carry a pathogenic variant for LQTS, CPVT, HCM or ARVC.

2.1.2 Methods

Clinical Services

Within the province of Alberta, genetic counselling is required prior to undergoing genetic testing for LQTS, CPVT, HCM, or ARVC. Families are counselled by a genetic counsellor or clinical geneticist, and genetic testing is publically funded through the Genetic & Genomics Division of Alberta Public Laboratories. The two main medical genetics groups in Alberta offer either genetic testing and/ or cardiac evaluation for children *at risk* for LQTS and CPVT regardless of age. With regard to predictive genetic testing for children *at risk* for HCM or ARVC, one medical genetics group offers genetic testing and/or cardiac evaluation for *at risk* children over 10 years of age in accordance with the ESC guidelines. The other medical genetics group offers genetic testing and/ or cardiac evaluation regardless of age.

In Alberta, pediatric cardiac evaluation is performed through pediatric cardiology at the Stollery Children's Hospital in Edmonton, the Alberta Children's Hospital in Calgary, or a private pediatric cardiology clinic in Calgary.

Data Collection

The study was approved by the Research Ethics Board at the University of Alberta and was conducted as part of a larger chart review. Genetic & Genomics databases were queried to generate a list of adults (>21 years) found to carry a pathogenic variant for LQTS, CPVT, HCM or ARVC between January 1, 2005 and December 31, 2014. Medical genetics clinic charts at the University of Alberta Hospital and the Alberta Children's Hospital were reviewed a minimum of 1 year post genetic diagnosis to identify individuals with *at risk* children (<18 years) at the time of disclosure of their results.

A "family" was defined as the carrier parent(s) and their biological children. Data collected from the medical genetics charts for each family included genetic diagnosis, presence of any clinical symptoms for the carrier parent, number of children under 18 years of age, the first and last name of the children and their date of birth, family history of sudden cardiac arrest/death, uptake of genetic testing and outcome of testing for each child.

If available, the names of *at risk* children were then cross referenced with the two hospital pediatric cardiology departments and the one private pediatric cardiology clinic in the province to identify which children had undergone a cardiac evaluation related to the familial cardiac diagnosis. Phenotype for each child was recorded based on review of the pediatric cardiology charts. Phenotype positive was defined as the presence of diagnostic electrophysiological findings with or without clinical symptoms. Children identified as the proband in the family were excluded.

Data Analysis

Categorical data is presented as counts and percentages. Diagnoses were categorized as an arrhythmia (LQTS) or a cardiomyopathy (HCM or ARVC) for statistical analysis. Wald's chi square test, Fisher's exact test, and logistic regression were used to assess the significance of associations. Stata Statistical Software: Release 13 (College Station, TX: StataCorp LP) was used for statistical analysis.

2.1.3 Results

In total, 216 adults were found to carry a pathogenic variant for LQTS, CPVT, HCM, or ARVC between January 1, 2005 and December 31, 2014. Families were excluded if they had no children under 18 years of age at the time of disclosure of their genetic result (n=106), they carried a syndromic founder variant (n=44), or if the medical genetic

chart could not be located (n=7). There were no children (<18 years) identified at 50% risk of inheriting CPVT. Upon reviewing the medical genetics charts, 97 *at risk* children (< 18 years) were identified from 58 families. Overall, predictive genetic testing was performed for the children in 38 (66%) of the families after parental results were disclosed. Of the 58 families, all children tested negative in nine (16%) families, at least one child tested positive in 29 (50%) families, and 20 (34%) families have not yet presented for genetic testing. Characteristics of the families are described in Table 2.1. A summary of genetic testing and cardiac evaluation is shown in Figure 2.1.

Table 2.1: Description of families

Characteristics	Total sample (n=58)	Sub Sample (n=51)[a]
Diagnosis		
LQTS	26 (45%)	26 (51%)
HCM	21 (36%)	19 (37%)
ARVC	11 (19%)	6 (12%)
Sex of the carrier parent		
Male	25 (43%)	22 (43%)
Female	32 (55%)	28 (54%)
Both parents carriers	1 (2%)	1 (2%)
Symptoms for the carrier parent		
Asymptomatic	26 (45%)	23 (45%)
Symptomatic	32 (55%)	28 (55%)
Number of children	Median=2 Range (1-4)	Median=2 Range (1-4)
Family history of SCA/D		
Any relation	30 (52%)	27 (53%)
1st degree relative	10 (17%)	10 (20%)
Diagnosed first in sibling	7 (13%)	7 (14%)
Genetic testing performed	38 (66%)	38 (75%)

[a]Sub Sample excludes families where the genetic specialist recommended deferring genetic testing/cardiac evaluation until >10 years of age. ARVC-arrhythmogenic right ventricular cardiomyopathy, HCM- hypertrophic cardiomyopathy, LQTS- long QT syndrome, SCA/D- sudden cardiac arrest/death

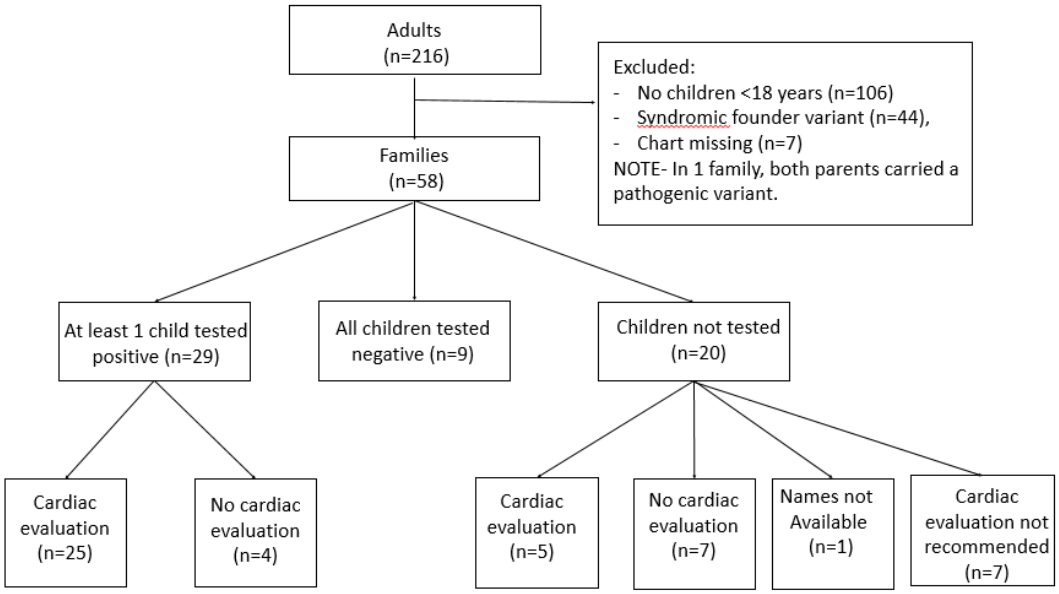


Figure 2.1: Summary of uptake of genetic testing and cardiac evaluation

Uptake of genetic testing

As described above, one of the medical genetics groups recommended deferring genetic testing for children *at risk* for HCM or ARVC until after 10 years of age. Seven of the 20 families who did not test their children did so at the recommendation of the genetic specialist based on the age of their child(ren). One additional family with a pathogenic variant for ARVC had four children; two were under 10 years of age and two were over 10 years of age. The family requested testing only for the two older children. Recommendation of the genetic specialist was significantly associated with uptake of genetic testing ($p<0.001$). Because it was 100% predictive of not pursuing genetic testing, the seven families who did not test any of their children at the recommendation of the genetic specialist were excluded from further analysis.

A significant interaction was identified between the gender of the carrier parent and the presence of clinical symptoms for the carrier parent with regard to uptake of genetic testing ($p=0.035$). Families with an asymptomatic carrier father were significantly less likely to pursue genetic testing compared to families with an asymptomatic carrier mother (30% vs. 92%) in the sub sample of 51 families (OR= 0.04, CI [0.0008, 0.6], $p=0.006$) (Figure 2.2). This same association between genetic testing and gender of the carrier parent was not observed when symptoms were present in the carrier parent (83% vs 81%) (OR=1.2, CI [0.1, 16.2], $p=1.00$).

Family history of sudden cardiac arrest/death (SCA/D) was not significantly associated with uptake of genetic testing regardless of the relationship of the affected individual (Table 2.2). Diagnosis, age of the oldest child, number of children, diagnosis initiating in a sibling and year of testing were also not associated with uptake of testing for children.

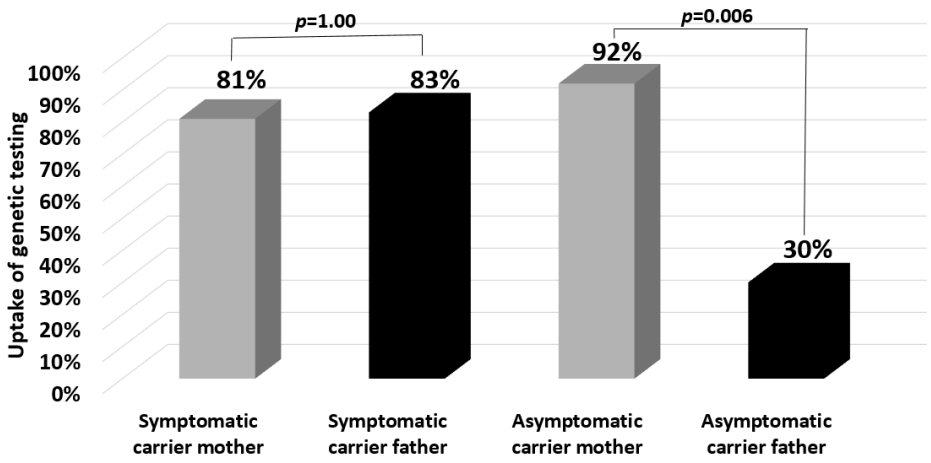


Figure 2.2: Association between gender and presence of symptoms in the carrier and uptake of genetic testing

Table 2.2: **Associations between uptake of genetic testing and family characteristics (n=51)**

Characteristics	Odds Ratio	95% Confidence Interval	*p* value
Univariate Analyses			
Age of oldest child	1.1	1.0, 1.2	0.22
Number of children	2.4	0.8, 7.0	0.11
Diagnosis (cardiomyopathy versus arrhythmia)	0.5	0.1, 1.8	0.30
Diagnosis initiating in a sibling	*	*	0.17
Family history- SCA in any relative	1.0	0.3, 3.4	0.94
Family history- SCA in 1st degree relative	1.5	0.2, 16.2	1.00
Year tested	1.0	0.8, 1.4	0.85
Interaction Analyses			
Carrier mother vs carrier father	4.2	0.9, 21.6	0.05
Symptomatic carrier parent vs asymptomatic carrier parent	2.5	0.7, 8.9	0.17
Asymptomatic carrier fathers compared to asymptomatic carrier mothers	**0.04**	**0.0008, 0.6**	**0.006****
Symptomatic carrier fathers compared to symptomatic carrier mothers	1.2	0.1, 16.2	1.0

*Odds ratio not possible based on a cell count of 0, SCA= Sudden cardiac arrest **Significant at p<0.05

Uptake of cardiac evaluation

The need for a cardiac evaluation was discussed with 29 families based on at least one of the children being identified to carry the familial pathogenic variant. A cardiac referral was recommended for an additional 13 families based on the parent's genetic result and the age of the child(ren). The remaining seven families had young children (<10 years of age) and were counselled that the child(ren) should be referred for a cardiac evaluation when they are older. Finally, the names of the children in one family were not available. In total, when cardiac evaluation was recommended, the children in 73% (n=30/41) of the families were seen in one of the pediatric cardiology clinics in Alberta. Families

were significantly more likely to undergo a cardiac evaluation if they had pursued genetic testing (OR = 8.8, CI [1.5, 55.5], *p*=0.007). Eighty six percent (n=25/29) of families had been seen in pediatric cardiology when a pathogenic variant was identified for at least one child compared to 42% (n=5/12) of families when predictive genetic testing was not performed. No other factors were associated with uptake of cardiac evaluation (Table 2.3).

Table 2.3: Associations between uptake of cardiac screening and family characteristics (n=51)

Characteristics	**Odds Ratio**	**95% Confidence Interval**	***p* value**
Age of oldest child	1.1	0.9, 1.2	0.33
Number of children	2.4	0.7, 7.7	0.14
Carrier mother vs carrier father	2.5	0.5, 14.0	0.29
Symptomatic carrier parent vs asymptomatic carrier parent	2.6	0.5, 14.7	0.29
Cardiomyopathy versus arrhythmia	0.3	0.04, 1.4	0.09
Diagnosis initiating in a sibling	*	*	0.16
Family history- SCA in any relative	1.8	0.5, 7.3	0.41
Family history- SCA in 1st degree relative	3.0	0.3, 150.7	0.41
Genetic testing performed*	**8.8**	**1.5, 55.5**	**0.007***

* Odds ratio not possible based on a cell count of 0, SCA-sudden cardiac arrest, **Significant at p<0.05

Of 41 *at risk* children assessed through pediatric cardiology, 54% (n=22) were found to be phenotype positive and two were found to have borderline findings. Electrophysiological findings with or without clinical symptoms were significantly more common in children *at risk* of LQTS (73%, n=16/22) compared to children *at risk* of a cardiomyopathy (32%, n=6/19) (*p*=0.004).

2.1.4 Discussion

This study assessed uptake of genetic testing and cardiac evaluation for children in families identified to carry a pathogenic variant for LQTS, HCM or ARVC. Overall, 66% of families chose to test their children and 73% of families underwent cardiac evaluation when it was recommended.

Uptake of Genetic Testing

Uptake of predictive genetic testing for children in this study is slightly higher than that reported in the previously published studies (Christiaans et al, 2008; Ormondroyd et al, 2014). This difference may be partially related to two factors: First, the carrier parent in our study had already chosen to have genetic testing themselves, and second, our sample includes both inherited arrhythmias and cardiomyopathies.

Predictive genetic testing for other genetic conditions is not common during childhood and therefore limited data are available for comparison. Inherited cancers such as familial adenomatous polyposis (FAP), von Hippel-Lindau, neurofibromatosis type 2 (NF2) and Li-Fraumeni syndrome can present during adolescence, and predictive genetic testing may therefore be considered. Evans et al (1997) evaluated uptake of genetic testing for each of these conditions. Uptake of genetic testing ranged from 33% (n=6/18) in 5-9 year olds *at risk* for von Hippel-Lindau to 100% (n=14/14) in 10-16 year olds *at risk* for NF2. In another study, uptake of predictive genetic testing in minors for Li-Fraumeni syndrome was reported in 79% (n=22/28) of families (Alderfer et al, 2015). Genetic testing for both inherited cancer syndromes and inherited cardiac conditions provide clarification regarding who should undergo screening. The conditions differ with regard to penetrance and screening method which may influence families' motivation to pursue testing.

Recommendation of genetic specialist

Recommendation of the genetic specialist had a large impact on uptake of genetic testing for children. Seven of the 20 families who did not test their children did so at the recommendation of the genetic specialist. In a study by Khouzam et al (2015), 60% of individuals with or *at risk* for HCM reported that they chose to have genetic testing at the recommendation of a health care provider. Similarly, Levine et al (2010) found that genetic testing was positively correlated with health care provider recommendations among a group of families *at risk* for FAP. These finding highlight the importance of clear, evidence-based guidelines to standardize care.

The ESC guidelines recommend waiting to pursue genetic testing for cardiomyopathies until the age at which cardiac evaluation is recommended (>10 years of age) (Charron et al, 2010). This allows the child to potentially take part in the decision making process (Hein et al, 2015). There is, however, uncertainty regarding a 10 year old child's ability to understand potential harms such as insurance and employment discrimination. The child may place greater emphasis on harms associated with a blood draw. In addition, it may be more challenging to implement lifestyle modifications such as physical activity restriction after 10 years of age at which point the child's self-identify and many of her or his social relationships have potentially formed around these activities. Conversely, children diagnosed at a younger age may be restricted from competitive sport based on their genetic diagnosis and then remain asymptomatic through childhood and adolescence. Overall, the decision to pursue genetic testing for children is family-specific and requires an in-depth discussion with specialists. More research on the impact of genetic testing at different time periods throughout childhood and adolescence would be helpful for this decision making process.

Sex of the Carrier Parent in the Absence of Symptoms

Families with an asymptomatic carrier father were significantly less likely to pursue genetic testing for their children compared to families with an asymptomatic carrier mother (30% vs. 92%). Women have been reported to place greater value on risk based genetic information compared to men (Taylor, 2011). It is possible that in the absence of symptoms for themselves, carrier fathers do not perceive a significant risk for their children; although, it is unclear how this translates to uptake of genetic testing for children in a joint decision model. Marital status may be a significant factor; however, this information was not available from the medical genetics charts. In a qualitative study by Geelen et al (2011), gender of the carrier parent was not reported as a significant factor in the uptake of testing children; however, they commented that the carrier parent took the lead on the decision, and that this was not questioned by the other parent. Christiaans et al (2008) did not find an association between uptake of cascade testing and the gender of the proband or the relative; however, the proband would have been symptomatic.

Family history of sudden cardiac arrest/death

Qualitative research has suggested that a family history of SCA/D is a motivator for individuals in pursuing both genetic testing and cardiac evaluation (Manuel and Brunger

2014; van der Werf et al, 2014). Our study did not find a significant association between family history of SCA/D and uptake of genetic testing, regardless of the relationship with the proband. These results are consistent with Christiaans et al's (2008) findings in relation to cascade genetic testing.

Uptake of cardiac screening

We found that, approximately 27% of families with at least one child *at risk* for LQTS, HCM or ARVC in Alberta had not undergone a cardiac evaluation when it was recommended. This is concerning as these children are at increased risk of associated cardiac events including SCA/D. Seventy three percent of children evaluated for LQTS and 32% for HCM or ARVC were phenotype positive. This highlights that although these conditions have incomplete penetrance in childhood, cardiac screening is important. Further research is needed to develop strategies to encourage compliance with cardiac evaluation.

Study Limitations

The study may be biased in that the sample comprises families where a parent chose to undergo genetic testing for themselves. These findings may, therefore, not represent uptake of predictive genetic testing in all families. Additional limitations include the fact that data were not available for all potentially significant demographic variables (i.e. parental age, education and socioeconomic status), the sample size is small, and follow-up was limited in some families to one year post disclosure of parental results. Families may pursue genetic testing and/or cardiac screening at a later date, particularly in the families with young children. It is also possible that some families may have moved out of province and sought genetic testing and/or cardiac screening through another institution. Finally, names were not available for all *at risk* children which limited the ability to assess their uptake of cardiac evaluation.

2.1.5 Conclusion

This study assessed factors associated with uptake of predictive genetic testing and cardiac evaluation for children *at risk* for LQTS, HCM, or ARVC. Declining predictive genetic testing was significantly associated with genetic specialist recommendation and the absence of symptoms in carrier fathers. The study also found that cardiac evaluation was associated with uptake of genetic testing. This study highlights the impact of inconsistent professional guidelines and the need to educate families about the importance of cardiac evaluation even in the absence of genetic testing.

2.2 Physical activity and beta blocker therapy recommendations in inherited arrhythmogenic conditions.

2.2.1 Introduction

Advances in the field of genetics have led to the identification of numerous genes involved in LQTS, CPVT, HCM, and ARVC. Genetic testing can provide confirmation of a diagnosis and genetic screening for *at risk* family members. Penetrance of disease is variable both between and within families and is condition and gene dependent. The advances in cardiac genetic testing have resulted in the identification of various populations including individuals who are genotype positive/phenotype positive (symptomatic carriers of a pathogenic variant) and individuals who are genotype positive/phenotype negative (asymptomatic carriers of a pathogenic variant).

Vigorous-intensity physical activity has been implicated as a trigger for life threatening cardiac arrhythmias in LQTS, CPVT, HCM and ARVC. As a result, guidelines have been published regarding physical activity restrictions for both phenotype positive and phenotype negative carriers of a pathogenic variant (Pelliccia et al, 2005; Vaseghi et al, 2012; Priori et al, 2013a; Maron et al, 2015). Beta blocker therapy can provide some protection from SCA for individuals with these conditions (Ostman-Smith et al, 1999; Villain et al, 2004; Postma et al, 2005; Iyer and Chin 2013). Management recommendations are challenging as clinicians must weigh the benefits against the implications of decreased physical activity and possible side effects of medications.

The objective of this study was to assess the practices of a group of pediatric electrophysiologists regarding physical activity recommendations and prescription of beta blockers for genotype positive/phenotype positive and genotype positive/phenotype negative individuals with LQTS, CPVT, HCM and ARVC. A second objective was to assess factors that influence recommendations including physician physical activity level.

2.2.2 Methods

The study involved a cross sectional assessment of the practices of an international group of pediatric electrophysiologists regarding management of genotype positive/ phenotype positive and genotype positive/phenotype negative individuals with LQTS, CPVT, HCM and ARVC. LQTS was subdivided into the 3 most common types, type 1 (LQTS1), type 2 (LQTS2), and type 3 (LQTS3). An online survey was developed using SurveyMonkey Inc (Palo Alto, California, USA) and was composed of 20 multiple choice

and matrix of choice questions (Appendix 1). The survey included questions regarding demographic information, physical activity recommendations and beta blocker therapy. The survey could be completed in 5-10 minutes. With executive approval, the survey was circulated to members of the Pediatric and Congenital Electrophysiology Society (PACES) (~150 cardiologists) in April 2014. The study was approved by the Research Ethics Board at the University of Alberta.

Collected demographic data is detailed in Table 2.4. Assessment of the level of physician physical activity was recorded using Godin et al's "simple self-report question" (Godin et al, 1986). Respondents were asked to describe 'how often they participated in active sport or vigorous physical activity long enough to get sweaty, during leisure time within the past four months' and during their adolescence (12-17 years of age).

Physical activity recommendations were reported for different activities, for phenotype positive and phenotype negative carriers of a pathogenic variant and are detailed in Figure 2.4 and Figure 2.5. The activity categories were modelled after a survey developed by Roston et al (2013) with permission from the authors. Respondents were asked to indicate which guidelines they base their physical activity recommendations on and who should be responsible for disqualifying an athlete from sport (the cardiologist, the athlete or the sporting organization). The frequency of body mass index assessment and dietary counselling was also evaluated. Finally, respondents were asked to describe the use of beta blocker therapy, in their practice, for phenotype positive and negative carriers.

Statistical analysis

Categorical data is presented as counts with percentages. Physician activity level was categorized as 'more active' (exercising 3 or more times per week) and less active (exercising less than 3 times per week). *Stata Statistical Software: Release 13* (College Station, TX: StataCorp LP) was used to calculate Fisher exact odds ratios to assess the relationships between management recommendations and respondents level of physical activity, guidelines referenced, years of practice and country of practice. Odds ratios were adjusted using the Mantel-Haenszel test. Cell counts were too small to assess the impact of gender or subspecialty in relation to management recommendations.

2.2.3 Results

In total 53 individuals initiated the survey and 45 completed all sections resulting in an estimated response rate of 30%. Only data from respondents that completed the survey are included in the analysis. Demographic data is described in Table 2.4.

Physical Activity Recommendations

Restriction from competitive sport was the most consistent recommendation for phenotype positive carriers for all conditions (Figure 2.3). Approximately half of respondents restrict phenotype negative carriers from this level of sport (Figure 2.4). Recreational sport is less commonly restricted for any of the conditions regardless of clinical symptoms.

Just over a quarter of respondents (28%) do not restrict physical activity for phenotype positive LQTS3 carriers. This compares to 5% and 12% for LQTS1 and LQTS2 carriers, respectively. Fifty three percent (n=24) of respondents follow the 36th Bethesda Conference guidelines, 4% (n=2) follow the European Society of Cardiology guidelines and 18% (n=8) indicated that they reference both. Additional resources referenced include the American Heart Association, Australian guidelines, literature reviews and personal experience. Respondents who reference the European Society of Cardiology guidelines alone or in addition to the 36th Bethesda Conference guidelines were more likely to recommend physical activity restrictions for phenotype negative carriers compared to respondents that indicated that they only reference the 36th Bethesda Conference guidelines. This association reached statistical significance for HCM. Respondents who referenced the European Society of Cardiology guidelines had 15.2 times the odds of prescribing physical activity restrictions for phenotype negative HCM carriers compared to respondents that did not reference these guidelines (95% CI [1.3, 734.4], p=0.01). After adjusting for physician activity level, the odds ratio increased to 22.8 (95% CI [1.5, 336.8], p=0.01). The same association was not seen for phenotype positive patients as the majority of respondents recommend some level of restriction for all conditions.

Table 2.4: Physicians' demographics and exercise habits (n(%))

Demoraphics	Categories	n (%)
Gender	Males	37 (82%)
Years of practice		
	1-5	11 (24%)
	5-10	8 (18%)
	>10	26 (58%)
Sub specialty	Pediatric electrophysiologist	40 (89%)
	Pediatric General Cardiology	3 (7%)
	Adult and pediatric electrophysiologist	2 (4%)
Country of practice	United States	31 (69%)
	Canada	8 (18%)
	Other	6 (13%)
Number of patients seen per month with these conditions		
	1-5	9 (20%)
	5-10	15 (33%)
	>10	21 (47%)
Current level of physical activity	Not at all	2 (4%)
	<1/month	1 (2%)
	~1/month	3 (7%)
	~2-3 X/month	4 (9%)
	~1-2 X/week	14 (31%)
	3 or more X/week	21 (47%)
Level of physical activity in adolescence (12-17 years)	Not at all	1 (2%)
	<1/month	2 (4%)
	~1/month	0 (0%)
	~2-3 X/month	1 (2%)
	~1-2 X/week	12 (27%)
	3 or more X/week	29 (64%)

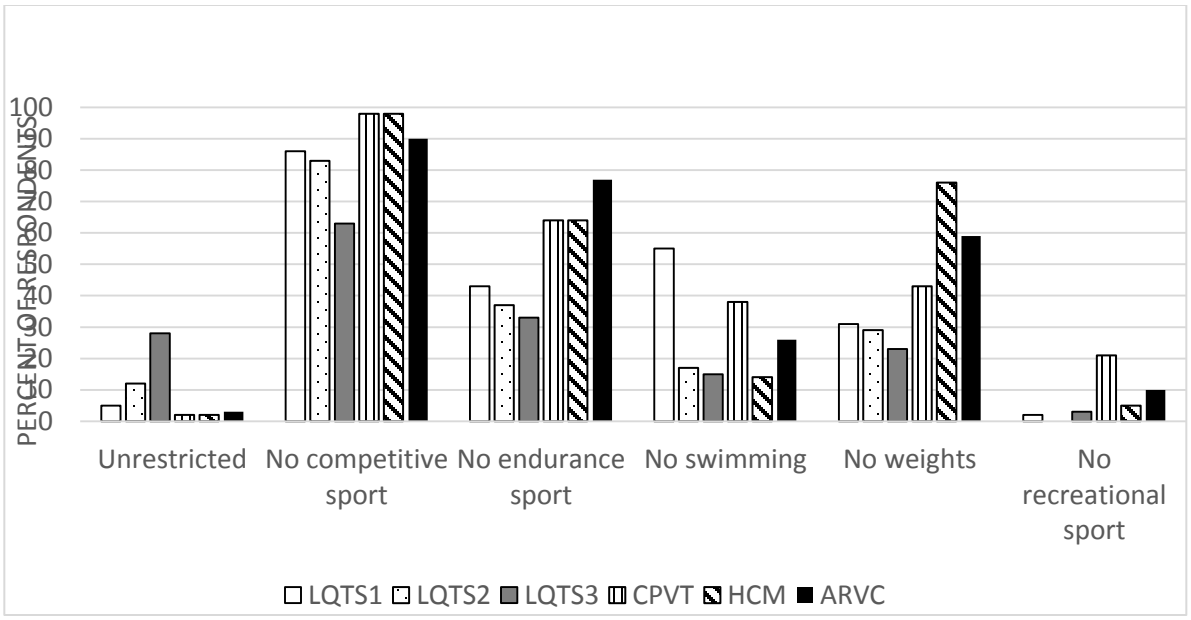


Figure 2.3: Physical activity recommendations for individuals who are genotype positive/ phenotype positive (n (%))

LQTS1- long QT syndrome type 1, LQTS2- long QT syndrome type 2, LQTS3- long QT syndrome type 3, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy

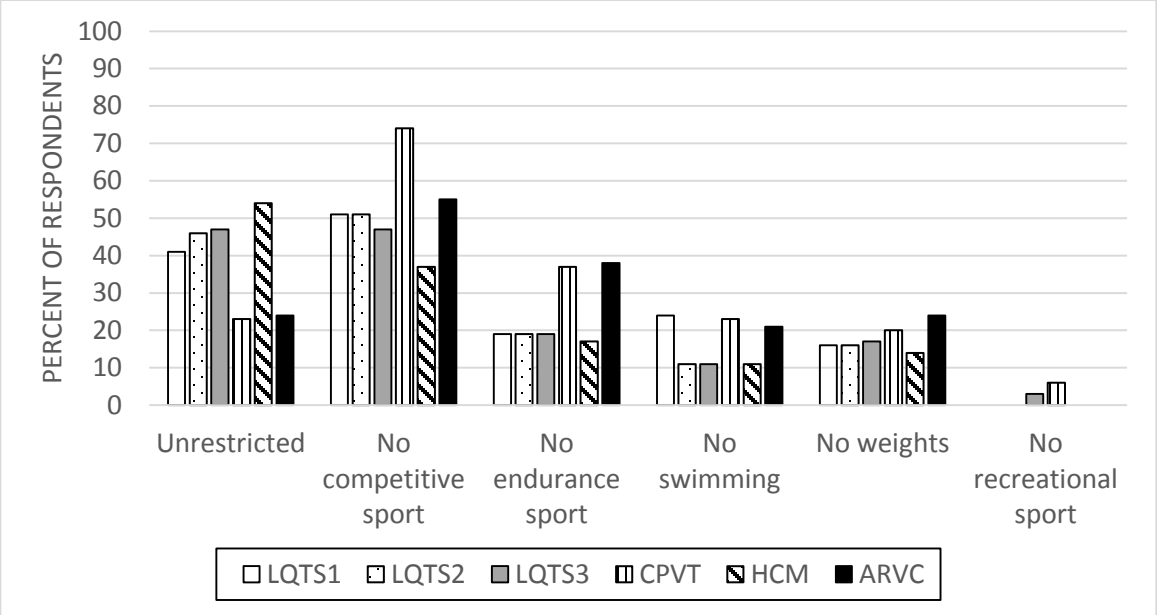


Figure 2.4: Physical activity recommendations for individuals who are genotype positive/ phenotype negative (n(%))

LQTS1- long QT syndrome type 1, LQTS2- long QT syndrome type 2, LQTS3- long QT syndrome type 3, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy

When asked who should be responsible for disqualifying an athlete from sport, 54% of respondents reported that it should be the cardiologist, 5% the sporting organization and 41% the athlete (or parent). Approximately a quarter (n=11) of respondents added a comment suggesting that sport participation should be a shared decision between the athlete, their parents and the cardiologist.

Body mass index was rarely or never assessed by 22% of respondents and 42% rarely or never discuss the option of dietary counselling.

A trend was identified regarding respondents' current level of physical activity and physical activity recommendations for phenotype negative carriers (Table 2.5). The trend reached significance for ARVC. Less active respondents (exercise less than 3 times a week) had 10.5 times the odds of restricting physical activity for phenotype negative ARVC carriers compared to more active respondent (exercise 3 or more times a week) (p=0.02). A similar, but not statistically significant, trend was seen for CPVT and LQTS2. Physical activity recommendations did not differ based on years of practice or country of practice.

Beta-Blocker Therapy Recommendations

The majority of respondents discuss the option of beta blocker therapy with some or all patients who are phenotype positive and phenotype negative (Table 2.6 and Table 2.7). Less respondents discuss beta blockers as an option for phenotype negative ARVC and HCM carriers (47% and 64% respectively). No significant associations were identified between discussion of beta blocker therapy and the demographic information collected.

Table 2.5: Odds of prescribing physical activity restrictions based on physician level of physical activity (exercise 3 or more times/week vs <3 times/week) for genotype positive/phenotype negative patients.

Condition	Odds Ratio	95% Confidence Intervals	*p* value
LQTS1	2.2	0.5, 10.2	0.32
LQTS2	3.4	0.7, 16.4	0.07
LQTS3	1.25	0.3, 5.9	1.0
CPVT	4.4	0.6, 49.9	0.09
HCM	1.43	0.3, 6.7	0.60
ARVC*	**10.5**	**0.9, 516.5**	**0.02**

*Significant at p<0.05

Table 2.6: Beta blocker therapy for individuals who are genotype positive/phenotype positive (n (%))

Discuss beta blocker therapy	LQTS1	LQTS2	LQTS3	CPVT	HCM	ARVC
Never	1 (2%)	1 (2%)	3 (7%)	1 (2%)	2 (5%)	12 (30%)
Some patients	1 (2%)	1 (2%)	12 (27%)	1 (2%)	17 (40%)	15 (38%)
All patients	43 (96%)	43 (96%)	29 (66%)	42 (95%)	24 (56%)	13 33%)

Table 2.7: Beta blocker therapy for individuals who are genotype positive/phenotype negative (n (%))

Discuss beta blocker therapy	LQTS1	LQTS2	LQTS3	CPVT	HCM	ARVC
Never	2 (4%)	2 (4%)	8 (21%)	1 (2%)	15 (36%)	18 (53%)
Some patients	15 (33%)	17 (38%)	14 (36%)	10 (24%)	17 (40%)	11 (32%)
All patients	28 (62%)	26 (58%)	17 (44%)	30 (73%)	10 (24%)	5 (15%)

2.2.4 Discussion

Physical Activity Recommendations

This survey evaluated the practices of pediatric electrophysiologists with regard to management of individuals with LQTS, CPVT, HCM and ARVC. The majority of respondents in this study restrict phenotype positive individuals with LQTS, CPVT, HCM and ARVC from competitive sport, which is consistent with published North American and European guidelines. Conflicting guidelines regarding participation in competitive sport for phenotype negative individuals are reflected by varying recommendations across all conditions. The survey showed that respondents referencing the European Society of Cardiology guidelines are more likely to restrict phenotype negative individuals from competitive sport. This is not surprising considering that the European Society of Cardiology guidelines, in contrast with the 36th Bethesda Conference guidelines, recommend physical activity restrictions for this patient population. Recommendations varied regarding other physical activities for phenotype positive and phenotype negative individuals.

Although limited, a few studies have been published regarding physical activity and condition specific cardiac risks. Data suggest that vigorous-intensity physical activity is a trigger for cardiac events for LQTS1 whereas emotion is the primary trigger for LQTS2 and sleep or rest for LQTS3 (Schwartz et al, 2001). This study found that respondents recommend fewer restrictions for phenotype positive individuals with LQTS3 compared to LQTS1, however, only a slight difference was seen in physical activity recommendations between phenotype negative LQTS1, LQTS2 and LQTS3 carriers (Figures 2.3 and Figure 2.4). A greater number of respondents restrict swimming for individuals with LQTS1 compared to LQTS2 and LQTS3 (phenotype positive- 55% vs 17% & 15% and phenotype negative- 24% vs. 11% & 11%, respectively).

Recent evidence has also identified an association between vigorous-intensity physical activity and ventricular arrhythmias and development of heart failure for ARVC carriers (James et al, 2013; Saberniak et al, 2014). Although the majority of respondents in our study recommend some physical activity restrictions for phenotype positive ARVC carriers, almost a quarter recommend no restrictions for phenotype negative carriers.

Weight Assessment and Dietary Counselling

A significant proportion of respondents recommend physical activity restrictions for at least some of their patients. Decreased physical activity makes this population susceptible to weight gain and other risks associated with a sedentary lifestyle. Nevertheless, 22% of respondents rarely or never assess body mass index and 42% rarely or never discuss the option of dietary counselling. A comprehensive approach could help reduce the risk of obesity and related morbidity for this population.

Disqualification from Sport

Approximately half of respondents in this survey feel that disqualification from sport is the responsibility of the cardiologist. However, additional comments emphasized the importance of a shared decision making model. Several lawsuits have been filed against physicians over the years relating to sport restrictions as well as lack of restrictions ("Harris-Lewis v. Mudge" 2004; Vaseghi et al, 2012). In the absence of clear guidelines, a shared decision making approach supports personalized patient care and may decrease medical legal vulnerability (Bisognano and Schummers, 2014).

Physician Activity Level

Previous research has identified an association between physicians' activity level and the amount of counselling provided to patients regarding the importance of physical activity, with more active physicians providing more counselling (Abramson et al, 2000; Howe et al, 2010). This suggests that patient care may be influenced by physician lifestyle. Our study found evidence to suggest that respondents that exercise less often were more likely to restrict physical activity for phenotype negative carriers compared to their more active colleagues. A more consistent management approach was seen for phenotype positive patients, suggesting that when established guidelines exist, physician specific factors may be less likely to influence patient care.

Beta Blocker Therapy Recommendations

Beta blocker therapy has been shown to reduce the risk of sudden cardiac death for phenotype positive and phenotype negative individuals with LQTS and CPVT (Priori et al, 2013b). This is reflected in our study with the majority of respondents discussing this treatment as an option for some or all patients with these diagnoses. Individuals with obstructive HCM have also been shown to benefit from treatment. In contrast, beta blocker therapy does not have an established benefit for phenotype negative individuals with HCM (Gersh et al, 2011). However, 64% of respondents in our study report

discussing this as an option for some or all of their phenotype negative HCM patients. There is also limited data to support the benefit of beta blocker therapy for phenotype positive or phenotype negative individuals with ARVC whereas 71% and 47% of respondents discuss this treatment with some or all patients respectively (Smith et al, 2011). It is evident that clinical experience and practice patterns can significantly defer from published guidelines.

Limitations:

The greatest limitation of the study is the low response rate, which is unfortunately common with such surveys (VanGeest et al, 2007). It is unclear what proportion of PACES members are active and are involved in managing patients with these conditions which may partially explain the low response rate. As respondents are self-selected, it is difficult to know if the practices reported accurately reflect the practices of most pediatric electrophysiologists.

The study is also limited by the survey format in that all concepts could not be completely defined. Specifically, a detailed definition of criteria for genotype positive/phenotype positive and genotype positive/phenotype negative was not provided in the survey. Genotype positive/phenotype positive was intended to describe individuals with evidence of structural and/or electrical abnormality associated with the disease. Whereas genotype positive/phenotype negative was intended to describe asymptomatic individuals with no evidence of structural and/or electrical abnormality associated with disease.

This is a cross sectional study and describes management practices at the time of the survey which may change over time. Finally, physician activity level was self-reported and due to the small sample size, we were unable to obtain statistically significant associations between physician activity level and management recommendations for each condition.

2.2.5 Conclusions

In pediatric LQTS, CPVT, HCM and ARVC, congruence and discrepancy among different physical activity restriction guidelines were reflected in the clinical practice patterns. Recommendation for phenotype negative individuals was additionally influenced by physicians' personal physical activity habits, adding to the complex dimensions of clinical decision making. Beta-blocker therapy recommendation was

relatively common including for the majority of phenotype negative patients. The varied approaches reported from this study regarding physical activity recommendations and beta blocker therapy illustrate the need for more research in the area. The value of beta blocker therapy and physical activity restriction in certain scenarios must be weighed against potential detrimental consequences of the morbidity associated with treatment side effects and a sedentary lifestyle. Regular assessment of body mass index and dietary counselling may help reduce some of these potential harms.

Chapter 3: WHEN TO OFFER PREDICTIVE GENETIC TESTING TO MINORS

In Chapter 2, practice variation was identified between the two main medical genetics departments in Alberta with regard to when to offer predictive genetic testing to minors *at risk* of an inherited cardiomyopathy. This led to the question- what is the optimal time to offer predictive genetic testing to children? Online surveys were used to assess the perspectives of an international group of genetic counsellors and families regarding when predictive genetic testing should be offered to children at 50% risk of LQTS, CPVT, HCM or ARVC. They were also asked to identify factors that influence their point of view. Results from the genetic counsellor survey were used to design the family survey. Potential benefits and harms of performing genetic testing at different points in childhood reported from these surveys were further evaluated in later studies.

3.1 Practice variation among an international group of genetic counsellors on when to offer predictive genetic testing to children *at risk* of an inherited arrhythmia or cardiomyopathy.

3.1.1 Introduction

With advances in the field of cardiac genetics, cascade predictive genetic testing is now available in many families as a means to identify children *at risk* of an inherited arrhythmia or cardiomyopathy, such as LQTS, CPVT, HCM, and ARVC. Each condition carries a risk of SCA which can present at any time between infancy and old age. Arrhythmic events are more common between the preteen years and the early 20s for LQTS and between 7 and 12 years of age for CPVT (Alders et al, 2015; Napolitano, 2016). The risk is greatest during adolescence for HCM and during adulthood for ARVC (Cirino, 2014; McNally, 2014). Variable expression and incomplete penetrance are common for all four conditions and electrocardiographic abnormalities can be concealed for LQTS and CPVT, complicating diagnosis.

Mixed opinions currently exist regarding the optimal age to initiate predictive cardiac genetic testing for children. Early identification and intervention could potentially be lifesaving. Prophylactic beta blocker therapy has been shown to reduce the risk of cardiac events in individuals diagnosed with LQTS or CPVT (Alders et al, 2015; Napolitano, 2016). Individuals with LQTS, CPVT, HCM or ARVC may also be restricted from vigorous-intensity competitive sport, based on an association with life threatening cardiac arrhythmias (Maron et al, 2004; Pelliccia et al, 2008; Dunbar et al, 2012; Maron et al, 2015). The prescription of physical activity restriction is more common for individuals who are phenotype positive although may be considered for some individuals

who are phenotype negative (Christian et al, 2016). For example, recent studies have shown a positive correlation between intensity and amount of physical activity with severity of disease for individuals *at risk* of ARVC which may support limiting physical activity in phenotype negative individuals (Kirchhof et al, 2006; James et al, 2013; Saberniak et al, 2014).

On the other hand, testing young children removes their autonomy and their ability to provide informed consent (Hein et al, 2015). In addition, concerns have been raised regarding positive cardiac genetic test results potentially leading to negative psychological effects, causing overprotection and stigmatization, and resulting in discrimination later in life with regard to insurance and employability (Meulenkamp et al, 2008; Geelen et al, 2011; Bratt et al, 2012; Mohammed et al, 2017; Bonner et al, 2018).

A consensus statement by the Heart Rhythm Society and the European Heart Rhythm Association recommends that predictive genetic testing be offered as early as infancy for LQTS and CPVT to assist with medical management (Ackerman et al, 2011). On the other hand, for cardiomyopathies, the European Society of Cardiology's position statement and the Australian/New Zealand guideline suggest that predictive genetic testing be deferred until 10 to 12 years of age (Charron et al, 2010; Ingles et al, 2011). Older guidelines recommend that cardiac screening begin around 10 to 12 years of age whereas the more recently published guidelines by the Heart Failure Society of America suggest at least one cardiac evaluation for children under 5 years of age who have a first-degree relative diagnosed with HCM or ARVC (Gersh et al, 2011; Charron et al, 2014; Corrado et al, 2015; Hershberger et al, 2018).

This study assessed the current practices of cardiac genetic counsellors regarding when to offer predictive genetic testing for asymptomatic children at 50% risk of LQTS, CPVT, HCM or ARVC. The study also describes genetic counsellors' rationale for when to offer predictive genetic testing.

3.1.2 Methods

Data Collection

An online questionnaire was circulated to the Canadian Association of Genetic Counsellors (CAGC), the National Society of Genetics Counselors (NSGC), the Australasian Society of Genetic Counsellors (ASGC) and the Association of Genetic Counsellors and Nurses (AGCN) in the United Kingdom between July and October

2016. The questionnaire was developed by the research group based on clinical experience as a validated tool was not available (Appendix 2). Cardiac genetic counsellors were asked to indicate the youngest age at which they felt that predictive genetic testing should be offered to asymptomatic children at 50% risk of LQTS, CPVT, HCM, or ARVC. An assumption was made that genetic counsellor's views were consistent with their practice. The following age categories were included: 0-5 years, 6-9 years, 10-15 years, 16-18 years and >18 years. These age categories were selected to allow for comparison of the recommended age of predictive genetic testing with published consensus and position statements (before 5 years for LQTS and CPVT and after 10 years of age for HCM and ARVC). If more than one age range was selected, the youngest age category was used. An open ended question was included to assess the genetic counsellor's rationale for choosing the specific age range for predictive genetic testing. Demographic information was also collected.

The survey was created using Survey Monkey Inc (Palo Alto, California, USA). An email invitation and reminder with a web link were circulated to the memberships of the above groups through their respective list servers. The sole inclusion criterion was self-identifying as a cardiac genetic counsellor. Submitted surveys were excluded if the respondent was not a practicing genetic counsellor or if less than 2 questions were completed. The survey took approximately 5 to 10 minutes to complete. Approval was obtained from the University of Alberta Research Ethics Office.

Data Analysis

The proportion of genetic counsellors who selected each age range to offer predictive genetic testing is described for each condition and compared to published consensus and positions statements. Chi square analysis, Fisher exact test, and univariate logistic regression were used to assess the relationship between when to offer predictive genetic testing and the independent variables including country of practice, years of experience as a cardiac genetic counsellor, clinical setting (medical genetics, cardiology, multidisciplinary), and respondent's gender. Data on country of practice was grouped to reflect genetic counsellors practicing within North American (Canada and United States) and those practicing outside of North America (United Kingdom, Australia, and New Zealand).

The open ended question was reviewed by 2 independent coders to identify key themes provided to justify the youngest age to offer predictive genetic testing. Consensus was reached between the coders.

3.1.3 Results

A total of 102 responses were received. Four responses were excluded: 3 completed only the first question on the survey and 1 was completed by a genetic counselling student. It is not possible to calculate a response rate as the total number of genetic counsellors involved in providing cardiac genetic counselling in all associations is unknown and many counsellors are members of multiple associations. NSGC 2016 Professional Status Survey reported that 152 members provide genetic counselling to cardiac patients, with the majority of these counsellors working in the United States and Canada (NSGC 2016). This would suggest a response rate of roughly 47% (n=71/152) for North American genetic counsellors. Characteristics of the respondents are shown in Table 3.1.

Predictive genetic testing

The majority of respondents practice in accordance with published guidelines for LQTS (n=81/98, 83%) and CPVT (n=73/96, 75%), offering predictive genetic testing to children before 5 years of age. Practice was less consistent with published guidelines with regard to offering testing to children after 10 years of age *at risk* of HCM (n=33/98, 34%) and ARVC (n=29/97, 30%) (Figure 3.1). The vast majority (96-99%) reported that they offer testing for all four conditions at some point during childhood (<18 years of age).

Country of practice was significantly associated with whether respondents offer predictive genetics testing for *at-risk* children before or after 10 years of age for HCM and ARVC (Figure 3.2). Respondents practicing within North America had 16.6 times the odds (95% CI [5.0, 59.5, p<0.001) and 9.0 times the odds (95% CI [2.9, 28.3], p<0.001) of offering predictive genetic testing to children before 10 years of age for HCM and ARVC, respectively, compared to genetic counsellors practicing outside of North America. Overall, 22% (n=6/27) of genetic counsellors practicing outside of North America offer predictive genetic testing before 10 years of age for HCM and 33% (n=9/27) offer testing this early for ARVC.

Table 3.1: Characteristics of respondents

Characteristic	n (%)
Gender – Female (n=94)	87 (92.6%)
Country of practice (n=96)	
Canada	20 (21%)
United States	49 (51%)
Australia/ New Zealand	20 (21%)
England/United Kingdom	7 (7%)
Years of experience as a cardiac genetic counsellor (n=96)	
0-2 years	30 (31%)
3-5 years	28 (29%)
6-10 years	24 (25%)
>10 years	14 (15%)
Clinical setting* (n=91)	
Medical Genetics	41 (45%)
Cardiology	42 (46%)
Multidisciplinary Clinic	21 (23%)
Molecular Diagnostic Lab	8 (9%)
Other	2 (2%)

*Some respondents practice in more than one setting

Years of experience proved to be significantly associated with offering predictive genetic testing before 5 years of age for LQTS with more experienced cardiac counsellors offering testing to children under 5 years (p= 0.02). This same association was not seen for the other cardiac conditions. Whereas, respondents working within medical genetics or a multidisciplinary clinic were less likely to offer predictive genetic testing prior to 10 years of age for HCM and ARVC compared to those working solely within Cardiology (p=0.02/p=0.06, p=0.008/p=0.02, respectively) (Table 3.2).

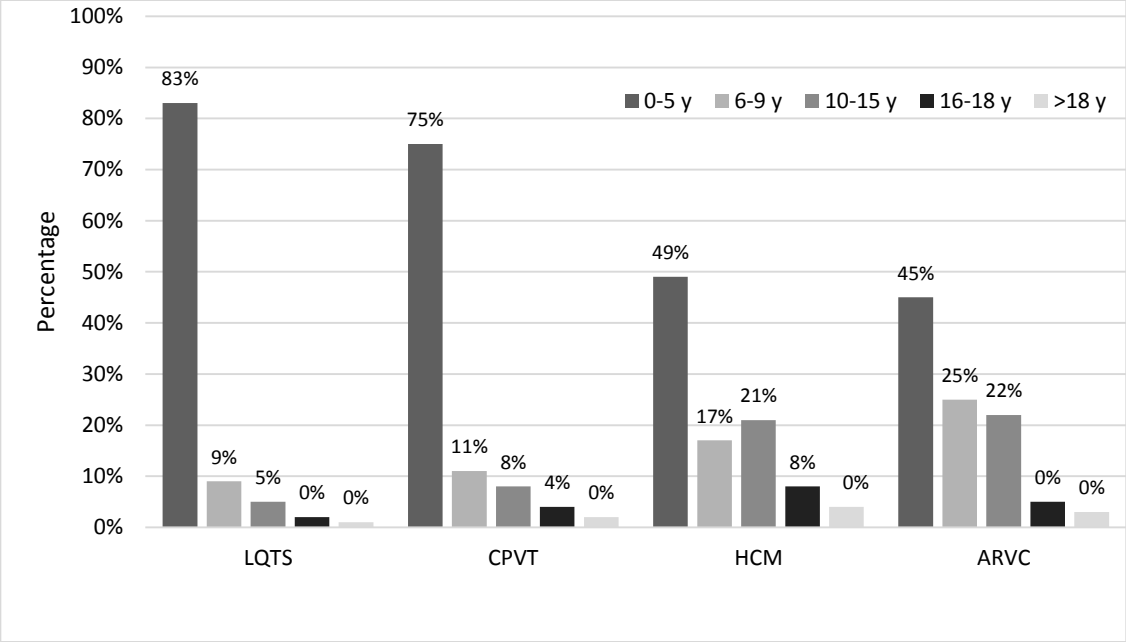
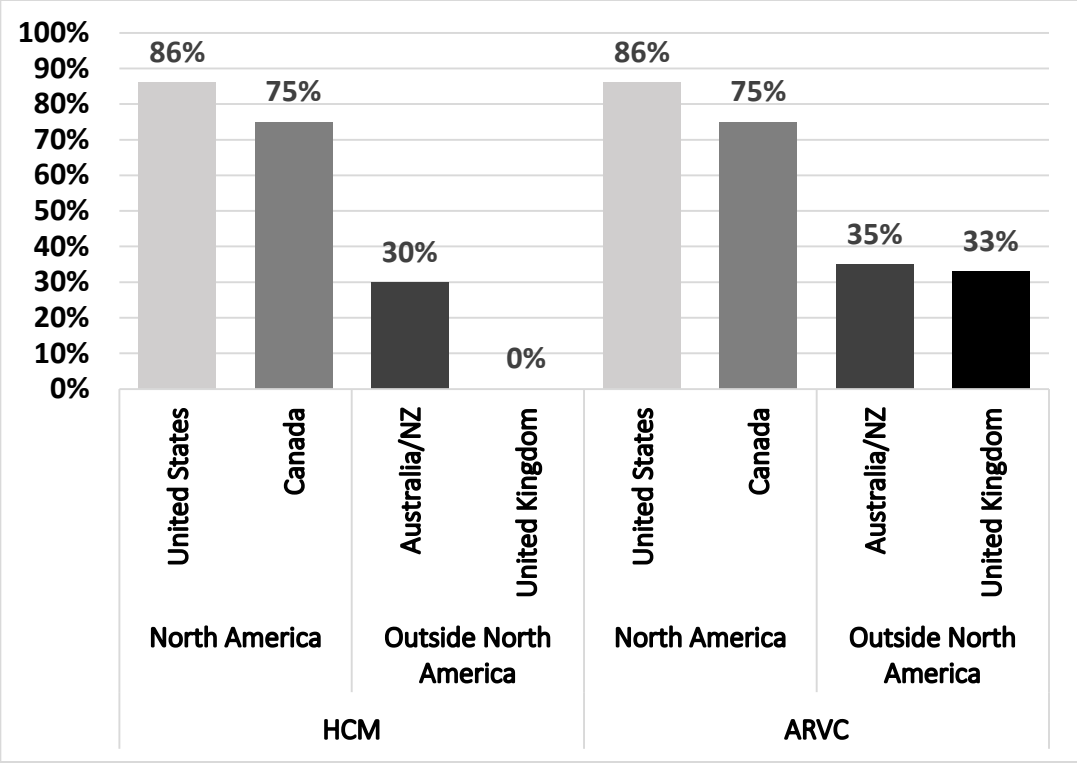


Figure 3.1: When should predictive genetic testing be offered to children *at risk* for LQTS, CPVT, HCM and ARVC



HCM- hypertrophic cardiomyopathy, ARVC-arrhythmogenic right ventricular cardiomyopathy

Figure 3.2: Proportion of respondents that would offer predictive genetic testing before 10 years of age for HCM and ARVC based on country of practice

Table 3.2: Association between genetic counsellor characteristics and offering predictive genetic testing before versus after 5 years of age for LQTS and CPVT and before versus after 10 years of age for HCM and ARVC

Characteristics	Odds Ratio	95% Confidence Interval	*p* value
Gender (male vs female)			
LQTS	0.5	0.1, 5.6	0.34
CPVT	0.7	0.1, 8.2	0.66
HCM	0.7	0.1, 4.9	0.69
ARVC	1.1	0.2, 12.5	1.00
Increasing year of practice			
LQTS*	**2.2**	**1.2, 4.0**	**0.02**
CPVT	1.3	0.8, 2.1	0.28
HCM	0.9	0.6, 1.4	0.75
ARVC	1.2	0.8, 1.8	0.39
Country of practice (NA vs outside NA)			
LQTS	2.8	0.8, 9.4	0.06
CPVT	2.4	0.8, 7.4	0.08
HCM*	**16.6**	**5.0, 59.5**	**<0.001**
ARVC*	**9.0**	**2.9, 28.3**	**<0.001**
Clinic setting (Reference group: cardiology)			
LQTS			
Medical genetics	0.6	0.2, 2.6	0.53
Multidisciplinary	0.6	0.16, 2.6	0.53
CPVT			
Medical genetics	0.5	0.1, 1.6	0.22
Multidisciplinary	0.8	0.2, 3.0	0.74
HCM			
Medical genetics*	**0.2**	**0.1, 0.8**	**0.02**
Multidisciplinary	0.3	0.1, 1.0	0.06
ARVC			
Medical genetics*	**0.2**	**0.04, 0.6**	**0.008**
Multidisciplinary*	**0.2**	**0.1, 0.8**	**0.02**

LQTS- long QT syndrome, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy, NA- North America, *Significant at p<0.05

Rationale for when to offer predictive genetic testing

Eighty one respondents provided rationale for when to offer predictive genetic testing. The most common theme was natural history of the disease (n=46/81, 57%) with 13 respondents specifically commenting on age of presentation within a family. This was followed by the opportunity to initiate management (n=39/81, 48%) and screening (n=30/81, 37%). Additional themes included lifestyle modification (i.e. physical activity) (n=16/81, 20%), psychological benefits or harms (n=14/81, 17%), and autonomy (n=7/81, 9%). Thirteen respondents (16%) indicated that parents should decide when it is in the "best interest" of their child to perform predictive genetic testing and 6 respondents (7%) specifically referred to following published professional guidelines. Many responses included a combination of reasoning. Table 3.3 describes the breakdown of rationale for when to offer testing based on country of practice.

Table 3.3: Rationale for when to offer testing by country of practice

Rationale for When to Offer	N n=80	United States n=42	Canada n=14	Australia n=17	United Kingdom n=7
Natural history	46	23	11	8	4
Presentation within family	13	6	1	4	2
Management	39*	12	8	11	7
Screening	30	15	8	6	1
Lifestyle modifications (ie. physical activity)	16	8	5	2	1
Psychological impact (benefits and harms)	14	8	4	2	0
Autonomy	7	3	0	1	3
Parental autonomy	13	9	3	1	0
Following guidelines	6	3	0	2	1

***** Country Practice not reported by 1 respondent

The following are examples of statements provided to justify offering predictive genetic testing to children at an earlier age (i.e. <5 years of age):

- "Psychosocially we prefer to test before kids start participating in organized sports, as many of the conditions have exercise restrictions. Some of our families find it easier to steer them away from certain athletics from a young age if they're positive, rather than let them play and start to really love a sport and want to play competitively and then have that taken away from them when they test positive at a later age." *United States*
- "Screening is more expensive and anxiety provoking than genetic testing for most families." *United States*
- "Limit unnecessary screening; make appropriate management recommendations, i.e. meds (LQTS, CPVT) or exercise restrictions (LQTS, CPVT); ease parental anxiety." *Canada*
- "To assist families with treatment and guide the safe vocational interests of *at risk* children." *Australia*

Examples of statements justifying access to genetic testing at an older age (i.e. >10 years of age) for HCM and ARVC include:

- "It depends on the typical onset of the condition and the onset seen in the specific family." *United States*
- "[Predictive genetic] testing should be done at a time when evidence-based guidelines suggest screening should start." *Australia*
- "[My preference is] for children to be clinically screened until they are at age of consent for predictive testing." *Australia*
- "Children should be able to make an informed decision where there is no invasive management, in HCM ARVC." *United Kingdom*

3.1.4 Discussion

The identification of a pathogenic variant for an inherited arrhythmia or cardiomyopathy such as LQTS, CPVT, HCM and ARVC permits cascade genetic testing within a family to identify *at risk* individuals. Families with young children may be provided with two options: perform predictive genetic testing to clarify genetic status and appropriate management or perform regular cardiac screening and consider predictive genetic testing when the child is older (i.e. >10 years of age). This study aimed to summarize

current practices and the justification for those practices among an international group of genetic counsellors.

When to offer predictive genetic testing

This study found that 83% and 76% of respondents would offer predictive genetic testing before 5 years of age for children *at risk* of LQTS or CPVT. One might have expected an even greater number to offer predictive genetic testing at this young age based on the association with sudden infant death syndrome (Napolitano, 2016). Genetic counsellors' years of experience was associated with offering predictive genetic testing at an earlier age for LQTS. This may reflect the impact of years of experience on clinical knowledge or exposure to the variable onset of this condition. It may also reflect changing personal and/or family circumstances and values. It is unclear why this finding was only seen with regard to LQTS.

We also found that genetic counsellors practicing within Cardiology were more likely to offer testing before 10 years of age for HCM and ARVC compared to those working within medical genetics or a multidisciplinary clinic. This may be explained by cardiology genetic counsellors being more specialized and having a greater appreciation for the phenotypic variability of these conditions. It may also be due to genetic counsellors being influenced by cardiologists aiming to eliminate unnecessary cardiac screening for children.

Respondents were less likely to offer predictive genetic testing before 5 years for HCM and ARVC compared to LQTS and CPVT, although the vast majority offer testing at some point in childhood. These findings likely reflect an older average phenotypic age of onset for these conditions and are consistent with professional guidelines (Charron et al, 2010; Ingles et al, 2011; Iyer and Chin, 2013; Cirino 2014; Alders et al, 2015; Napolitano, 2016).

Country of practice significantly influenced whether or not respondents followed published guidelines with regard to HCM and ARVC. Respondents practicing in North America more commonly offer testing earlier in childhood compared to respondents practicing outside of North America. Although North American cardiac genetic testing guidelines do not specifically address the issue of predictive genetic testing in minors for cardiomyopathies, practice may be influenced by more general position statements such as the American Society of Human Genetics which emphasizes the importance of

parental involvement with regard to predictive genetic testing in minors in the presence of clinical uncertainty (Botkin et al, 2015).

A policy statement published by the American College of Medical Genetics on reporting of secondary findings causes further re-evaluation of genetic testing in children (Kalia et al, 2017). The identification of a cardiac pathogenic variant, in this context, takes a bottom up approach and allows for the testing and/or screening of relatives who would have otherwise not been aware of the condition. Wynn et al (2018) found that a group of adults did not show increased anxiety, depression or health worry following the finding of a secondary genetic finding. They concede that "the experience of receiving secondary results may differ from the results of focused clinical testing because in the latter case patients are likely to have greater familiarity with the condition, have deliberately sought specific genetic information, and have the opportunity to prepare psychologically for the findings." It should be noted that this study evaluated the perspective of adults and the impact of secondary findings for children remains unclear. Regardless, with an increasing number of cardiac secondary findings being reported from exome and genome sequencing, North American genetic counsellors may be becoming more relaxed in their views around predictive genetic testing in minors (Kalia et al, 2017). Debate remains among European, Australian and Canadian professional groups regarding the reporting of secondary findings and a more targeted approach to testing is currently recommended (Boycott et al, 2015; Hehir-Kwa et al, 2015; RCPA, 2015).

Finally, medical malpractice rates have historically been higher in North America compared to Australia and the United Kingdom (Danzon, 1990). The North American approach is consistent with a shared decision-making model which may be influenced by concerns of medical liability (Monico et al, 2008).

In contrast, the European and Australia/ New Zealand guidelines suggest deferring predictive genetic testing until after 10 years of age for children *at risk* of a cardiomyopathy (Charron et al, 2010; Ingles et al, 2011). In addition, more general statements by the European Society of Human Genetics and Human Genetics Society of Australasia specifically emphasize that predictive genetic testing should only be offered to children at the age at which a condition is expected to present and when there is medical benefit (Borry et al, 2006; HGSA 2017). In the absence of specific guidelines in North America, some American and Canadian genetic counsellors may also be drawn to these European practice recommendations.

Overall, variability in practice was observed among genetic counsellors practicing in countries with and without clear published guidelines. Variability in professional guidelines highlight that they were created based on expert opinion rather than empiric evidence. An assessment of the impact of age of predictive genetic testing on the modified natural history of these conditions and quality of life is needed for these populations.

In general, predictive genetic testing is not common during childhood and as a result there are limited appropriate conditions for comparison. A few inherited cancer syndromes including familial adenomatous polyposis (FAP) and Li-Fraumeni syndrome can present during adolescence and as such, predictive genetic testing may be considered. Published guidelines recommend predictive genetic testing for childhood cancer syndromes when a child reaches the age at which the cancer predominately presents and screening is generally initiated (ASCO, 2003). Although there are inherent differences with regard to penetrance and invasiveness of screening methods for childhood cancer syndromes compared to inherited arrhythmias and cardiomyopathies, a study by Douma et al (2010) reported that the majority of parents feel that the most suitable time to perform predictive genetic testing for children *at risk* for FAP is after 12 years of age. In contrast, Gjone et al (2011) noted a trend towards better health and psychosocial functioning for children tested for FAP at birth as part of a research study compared to those tested at an older age. In addition, 11 of 12 adolescents and young adults who underwent predictive genetic testing for Li-Fraumeni syndrome during childhood did not feel that parents should delay testing until a child is old enough to take part in the decision making process (Alderfer et al, 2017).

Rationale for when to offer predictive genetic testing

Rationale for when to offer predictive genetic testing included the natural history of the disease, clarification of who requires ongoing cardiac screening, implementation of treatment, lifestyle modifications, psychological benefits and harms, the child's autonomy, parents' autonomy, and following published guidelines. These factors are considered further in the context of the ethical principles of beneficence, non-maleficence, autonomy and informed consent.

Beneficence: With respect to when to offer predictive genetic testing for LQTS, CPVT, HCM or ARVC, respondents in this study reported the following potential benefits: cardiac screening, beta blocker therapy, lifestyle modification and reduced anxiety.

Respondent's rationale was also influenced by their interpretation of the natural history of the conditions.

Cardiac screening- Genetic testing has the ability to clarify who requires ongoing cardiac screening. This eliminates unnecessary cardiac assessments for children who do not carry the familial pathogenic variant resulting in decreased burden for the family and the healthcare system.

Beta blocker therapy- Prophylactic beta blocker therapy has been shown to reduce the risk of cardiac events for individuals diagnosed with LQTS and CPVT (Villain et al, 2004; Postma et al, 2005; Goldenberg et al, 2008; Koponen et al, 2015). As a result, professional guidelines recommend beta blocker therapy even for genotype positive, phenotype negative individuals (Priori et al, 2015).

Lifestyle modification- Historically, professional guidelines have recommended that phenotype positive individuals with LQTS, CPVT, HCM or ARVC avoid vigorous-intensity competitive sport (Maron et al, 2005; Pelliccia et al, 2005). Clarification of genetic status at a young age may lead parents to guide their child towards lower intensity activities. This averts the need for the child to be disqualified from sport at a point when their self-identity and social relationships are strongly linked to these activities.

Reduce anxiety- Genetic testing performed early in childhood has the potential to significantly reduce anxiety for the families of children found not to carry a familial pathogenic variant. This is supported by a prospective assessment of children who tested negative for a familial FAP variant who were found to have reduced anxiety, worry and distress following testing (Michie et al, 2001).

Natural history- Consideration of the natural history of each cardiac condition could lead one to offer predictive genetic testing earlier, if the youngest possible age of onset is considered, or later if the more common age of onset is considered.

Non-maleficence: Potential harms relating to when to offer predictive genetic testing for LQTS, CPVT, HCM and ARVC included: unnecessary restriction of physical activity and anxiety.

Unnecessary physical activity restriction- Although physical activity restriction based on genetic status may be seen as a benefit to a child, this could also be considered a potential harm. Participation in sport has many physical, psychological and social

benefits (Helmrich et al, 1991; DiLorenzo et al, 1999; Nocon et al, 2008; Mammen and Faulkner 2013). Recent guidelines suggest that participation in competitive sport may be acceptable for individuals diagnosed with LQTS following a period of stability on beta blocker therapy (Ackerman et al, 2015). In addition, the penetrance of HCM is variable and more commonly presents during adulthood. Testing a child at a young age may eliminate their chance to benefit from sport participation unnecessarily.

Increase anxiety- Predictive genetic testing may increase psychological distress for children and their parents when a pathogenic variant is identified (Bratt et al, 2011; Geelen et al, 2011). Two systematic reviews looking at the impact of predictive genetic testing for a variety of genetic conditions, for children and young adults, did not find a negative effect on emotional state, self-perception or social wellbeing although research in the area was reported as limited (Wade et al, 2010; Wakefield et al, 2016). Whereas qualitative research in cardiac genetics has identified some potential concerns (Meulenkamp et al, 2008; Bratt et al, 2011; Geelen et al, 2011; Bratt et al, 2012; Bonner et al, 2018). Bratt et al, (2012) interviewed a group of children and adolescents who tested positive for a HCM variant and described a transition from perceiving themselves as being healthy to having a serious heart condition. The greatest impact on daily life was related to participants' interest in sport and physical activity restrictions associated with their diagnosis. Bonner et al (2018) postulate that psychological impact may be associated with the individual's motivations for testing, understanding of their result, perception of their risk and the need for behaviour change related to the result. This highlights the importance of an in-depth conversation with families around these key issues to reduce the psychological impact of testing. Finally, parents have raised concerns that predictive genetic testing at a young age may also lead to additional years of stigmatization and overprotection (Geelen et al, 2011). The validity of these concerns have yet to be investigated.

Autonomy/ Informed Consent: Autonomy describes the ability of an individual to make informed choices about their own health. Young children lack the capacity to comprehend the potential benefits and harms of predictive genetic testing. The age at which a child develops this ability is likely variable. Hein et al (2015) suggest that children under 10 years of age are unlikely to have the competence required for involvement in the consenting process whereas children over 12 years of age are likely to be competent. The European and Australian/New Zealand guidelines suggest

consideration of predictive genetic testing for cardiomyopathies between 10 and 12 years of age (Charron et al, 2010; Ingles et al, 2011).

Thirteen responses suggested that the ultimate decision regarding when to perform predictive genetic testing should be left to the discretion of the family. Geelen et al (2011) effectively illustrated that families can weigh the potential benefits and harms differently and come to opposite conclusions. Parents have a greater understanding of the child and family situation and are likely in a better position to appreciate the true impact of predictive genetic testing. Parental anxiety may also be considered and a negative genetic result may provide significant reassurance for the parents.

Study limitations

This study reports the opinions of genetic counsellors practicing in the field of cardiac genetics. We were unable to determine an accurate response rate and it is therefore difficult to generalize these results to all cardiac genetic counsellors. We were also unable to consistently link the rationale provided by respondents to the specific conditions based on the structure of the survey.

3.1.5 Conclusions

Variation in practice was observed among an international group of genetic counsellors regarding when to offer predictive genetic testing for children *at risk* of an inherited cardiomyopathy. Country of practice and clinical setting were significantly associated with when respondents offer predictive genetic testing for HCM and ARVC which likely reflects published guidelines. In addition, years of experience impacted the age at testing for LQTS. This study highlights the complex issues surrounding predictive genetic testing in minors and the importance of genetic counselling to assist families' in reaching a personalized decision around testing. It also illustrates the impact of evolving views in genetics and supports the need for more research in the area to assist with the development of congruent and evidence-based guidelines grounded on ethical principles, with recognition of the parental role in decision-making.

3.2 When to offer predictive genetic testing to children *at risk* of an inherited arrhythmia or cardiomyopathy: The family perspective

3.2.1 Introduction

Individuals found to carry a pathogenic variant for a dominantly inherited arrhythmia or cardiomyopathy have a 50% likelihood of passing the variant on to their children, placing them at increased risk to develop the potentially life threatening condition. A chart review performed by our group revealed that, between 2005 and 2015, 66% (38/58) of Alberta families with a genetic diagnosis of long QT syndrome (LQTS), hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC) performed predictive genetic testing for their *at-risk* children at some point during childhood or adolescence (Christian et al, 2018).

Determining the optimal time to perform predictive genetic testing in minors is complex and involves balancing the ethical principles of beneficence, non-maleficence, autonomy and informed consent. Qualitative research has highlighted parental concerns regarding stigmatization, discrimination and psychological harm for children who test positive for a familial genetic variant (Geelen et al, 2011). In contrast, potential benefits have also been described including the ability of genetic testing to clarify which children require ongoing cardiac care, guide sport participation and decrease worry for children who test negative for a familial genetic variant.

A consensus statement by the Heart Rhythm Society and the European Heart Rhythm Association recommends offering predictive genetic testing as early as infancy for children *at risk* of LQTS due to possible early onset of the condition and because the result may directly impact medical management with the initiation of beta blocker therapy (Ackerman et al, 2011). In comparison, North American guidelines do not directly address the issue of predictive genetic testing for minors *at-risk* of a cardiomyopathy such as HCM or ARVC. Whereas the European Society of Cardiology's position statement and the Australian and New Zealand guideline recommend deferring predictive genetic testing until after 10 years of age for these conditions when the likelihood of onset is higher, cardiac screening is recommended and assent may be possible (Charron et al, 2010; Ingles et al, 2011).

The objective of this study was to assess families' perspectives regarding when predictive genetic testing should be offered to children at 50% risk of LQTS, HCM or ARVC as well as identify factors that influence their point of view.

3.2.2 Methods

Data collection

An online survey composed of 16 questions was created by the research group based on clinical experience and a review of the literature (Appendix 3). Individuals over 18 years of age with a genetic diagnosis or who have a partner with a genetic diagnosis of LQTS, HCM or ARVC were invited to complete the survey. LQTS was used as a comparison group as there is consistent guidelines supporting offering predictive genetic testing at an early age. We did not include individuals diagnosed with CPVT as we predicted limited responses due to the rarity of the condition. An invitation was circulated by email to members of the Sudden Arrhythmia Death Syndrome (SADS) Foundations in the United States and Canada and the Hypertrophic Cardiomyopathy Association in the United States between May 2017 and November 2017. Membership is composed of patients with LQTS, HCM, ARVC and other heart conditions as well as family members and healthcare professionals. The available data from each foundation or association did not allow us to ascertain the proportion of members with a genetically confirmed diagnosis of interest. An invitation with a link to the survey was also posted to these organization's Facebook groups and the ARVDHeart for Hope Facebook group.

The primary question addressed the youngest age at which predictive genetic testing should be offered to children at 50% risk of these conditions. Age categories were described as 0-5 years, 6-9 years, 10-14 years, 15-17 years and over 18 years. These categories were selected to allow for comparison with published position statements/guidelines. A response to this question was required for the survey to be included in the study.

A matrix of choice question was included to assess the importance, on a scale of 1 to 5 (1= not important, 5= very important), of eight factors in deciding when predictive genetic testing should be offered. The eight factors included: (1) Clarifying if a child needs to be followed by cardiology; (2) Identifying if a child should be started on medication (only LQTS families were asked to respond to this question); (3) Guiding sport participation; (4) Decreasing worry for a child who tests negative; (5) Allowing a child to take part in the decision about genetic testing; (6) Allowing a child time to adjust to their diagnosis

before their health is affected; (7) Creating worry for a child who tests positive; and (8) Impacting a child's ability to get insurance when they are older if they test positive. An open ended question followed asking respondents to identify other factors that influence when testing should be offered. Additional information collected is described in Table 3.4.

The survey was created and managed using the REDCap electronic data capture tool hosted at the University of Alberta and took approximately 10-15 minutes to complete (Harris et al, 2009). Approval was obtained from the University of Alberta Research Ethics Board.

Data Analysis

Continuous variables are presented as mean with standard deviation. Categorical variables are presented as counts with percentages. The proportion of respondents who selected each age range to offer predictive genetic testing is described. Chi squared analysis, Fisher exact test, or simple logistic regression were used to evaluate the relationship between when to offer predictive genetic testing (categorized as before or after 5 years of age for LQTS and before or after 10 years of age for HCM/ARVC) and independent variables. Diagnosis was categorized as LQTS or cardiomyopathy (HCM or ARVC). Simple logistic regression was used to evaluate the relationship between the 8 factors and when to offer predictive genetic testing. *Stata Statistical Software: Release 13* (College Station, TX: StataCorp LP) was used for statistical analysis.

3.2.3 Results

A total of 231 responses were included in the study with 210 (91%) surveys being completed in full. It is difficult to estimate a response rate as the number of eligible members within each organization is unknown. Characteristics of respondents are described in Table 3.4. HCM was the most common diagnosis (n=133, 58%) followed by LQTS (n=83, 36%) and ARVC (n=15, 6%). Most respondents were female (n=173, 82%), over 40 years of age (n=135, 64%), had post-secondary education (n=181, 86%) and resided in the United States (n=160, 76%). The earliest age of onset in a family was on average 7.9 +/- 9.9 years for LQTS, 22.6 +/-15.2 years for HCM, and 23.8+/- 9.3 years for ARVC.

Overall, 92% (n=76/83) of respondents reported that predictive genetic testing should be offered before 5 years of age for children *at risk* of LQTS and 77% (n=114/148) indicated

that it should be offered before 10 years of age for children *at risk* of HCM or ARVC (Figure 3.3).

Table 3.4: Characteristics of respondents

Characteristics (Total # of responses)	n (%)
Female (n=210)	173 (82%)
Age (n=213)	
<20 years	6 (3%)
21-30 years	25 (12%)
31-40 years	47 (22%)
41-50 years	70 (33%)
51-60 years	39 (18%)
>60 years	26 (12%)
Diagnosis (n=231)	
LQTS	83 (36%)
HCM	133 (58%)
ARVC	15 (6%)
Self-report	201 (87%)
Spouse-report	30 (13%)
Diagnosed <30 years of age (n=226)	108 (48%)
Presence of symptoms (n=231)	190 (82%)
Biological children (n=230)	183 (80%)
Tested children during childhood	111 (61%)
Country (n=211)	
Canada	32 (15%)
United States	160 (76%)
Other	19 (9%)
Education (n=213)	
No post-secondary	32 (15%)
Post-secondary	181 (85%)
Annual net income (n=210)	
< $100 000/ year	100 (48%)
≥ $100 000/ year	80 (38%)
Prefer not to answer	30 (14%)
Family history of SCA (n=212)	133 (63%)

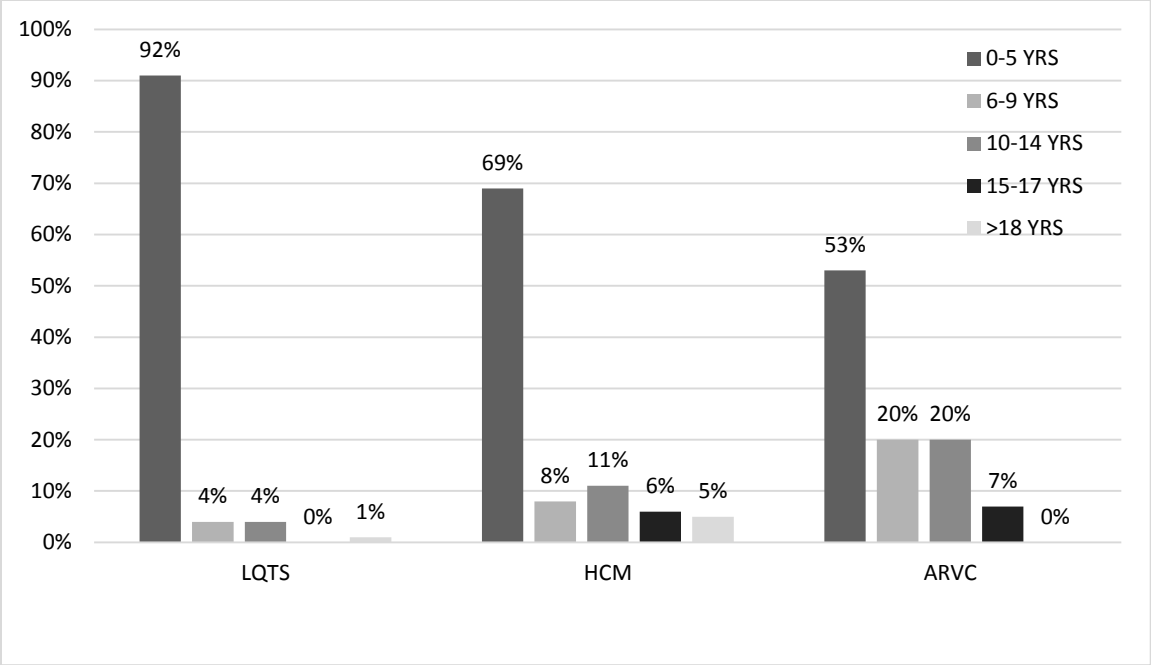


Figure 3.3: When to offer predictive genetic testing to children *at risk* of LQTS, HCM or ARVC

On univariate analysis, post-secondary education was significantly associated with respondents reporting that predictive genetic testing should be offered before 5 years of age for children *at risk* of LQTS (OR= 21.7, 95%CI [3.3, 143.7], *p*=0.001). On the other hand, offering testing before 10 years of age for HCM and ARVC was associated with female gender (OR=2.4, 95%CI [0.98, 5.8], *p*=0.05), younger age of the respondent (OR= 0.7 per 10 year increase; 95%CI [0.5, 0.97], *p*=0.03) and earlier disease onset in the family (OR=0.97 per one year increase; 95% CI [0.94, 0.99], *p*=0.03). Odds ratios are described in Table 3.5 and Table 3.6

Table 3.5: Association between testing before 5 years for LQTS and respondent characteristics

Characteristic	**Odds Ratio**	**95% Confidence Interval**	***p* value**
Female[+]	-	-	1.00
Per age category (10 years)	1.5	0.7, 2.9	0.28
Spouse versus Self-report	0.8	0.1, 7.5	0.85
Age of diagnosis (per year)	0.7	0.3, 1.4	0.28
Presence of symptoms	2.6	0.3, 22.9	0.39
Biological children	2.1	0.4, 12.3	0.40
Country (reference Canada) United States[+] Other[+]	 - -	 - -	 0.58 0.26
Post-secondary education*	**21.7**	**3.3, 143.7**	**0.001**
Income	1.4	0.9, 2.1	0.18
Earliest onset in family (per year)	1.0	0.9, 1.1	0.63
Family history of SCA/D	1.0	0.2, 6.0	0.98

[+]Cell count too small to calculate odds ratio *Significant at p<0.05, SCA/D= sudden cardiac arrest/death

Table 3.6: Association between testing before 10 years for HCM/ARVC and respondent characteristics

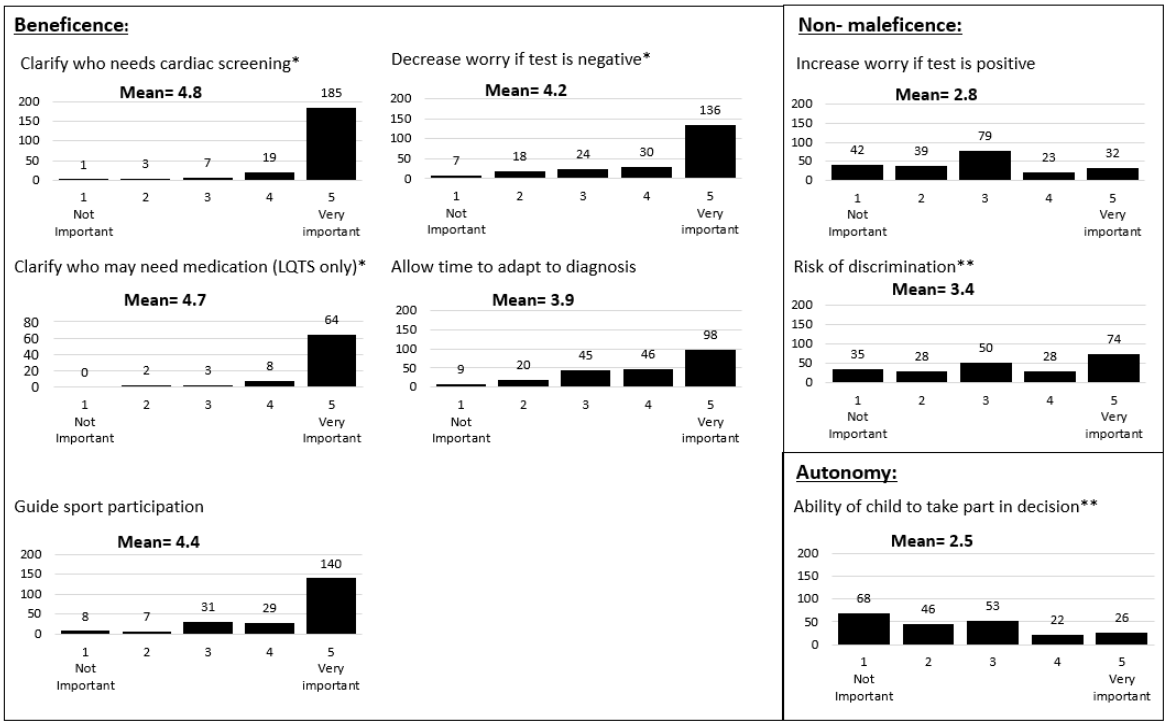
Characteristic	Odds Ratio	95% Confidence Interval	*p* value
Female*	**2.4**	**0.98, 5.8**	**0.05**
Per age category (10 years)*	**0.7**	**0.5, 0.97**	**0.03**
ARVC vs HCM	0.8	0.2, 2.6	0.68
Spouse versus Self-report	6.7	0.8, 49.7	0.08
Age at diagnosis (per year)	0.8	0.6, 1.0	0.08
Symptoms	1.4	0.4, 5.2	0.62
Biological children	1.2	0.5, 3.1	0.65
Country (reference: Canada)			
United States	2.2	0.7, 6.6	0.16
Other	1.1	0.2, 5.2	0.88
Post-secondary	0.3	0.1, 1.4	0.13
Income	1.0	0.8, 1.3	0.88
Earliest disease onset in family (per year)*	**0.97**	**0.94, 0.99**	**0.03**
Family history of SCA	1.8	0.8, 4.2	0.15

*Significant at p<0.05, SCA/D= sudden cardiac arrest/death

Clarifying who requires ongoing cardiac screening was given the highest rating of importance in deciding when predictive genetic testing should be offered overall (4.8/5) followed by who may need medication specifically for LQTS families (4.7/5) (Figure 3.4). Scores ranged from 1 to 5 for all eight factors with the exception of clarifying who may need medication where scores ranged from 2 to 5. Indicating that predictive genetic testing should be offered before 5 years of age was associated with higher scores for clarifying cardiac screening (OR=2.2, 95% CI [1.3, 3.5], *p*=0.002), who may require medication (LQTS only) (OR= 2.4, 95% CI [1.0, 5.6], *p*=0.05) and decreasing worry for children who test negative (OR= 4.5, 95% CI [1.2, 1.9], *p*=0.003). Guiding sport participation was also marginally associated with offering testing before 5 years of age (OR=1.3, 95% CI [0.99, 1.7], *p*=0.06). In contrast, higher scores relating to concerns about discrimination (OR=1.5, 95% CI [1.1, 2.0], *p*=0.005) and allowing a child to take part in the decision making process (OR=1.9, 95% CI [1.4, 2.6], *p*<0.001) were

associated with deferring offering testing until after 10 years of age. The importance of each factor did not differ significantly based on the diagnosis.

Two additional factors were reported to influence when predictive genetic testing should be offered including assisting with parenting (n=16) and decisions around placement of an ICD (n=5).



*Significantly associated with offering predictive genetic testing before 5 years of age
** Significantly association with offering predictive genetic testing after 10 years of age

Figure 3.4: Rating of importance of eight factors with regard to deciding when to offer predictive genetic testing for a child *at risk* for LQTS, HCM or ARVC

3.2.4 Discussion

The identification of a disease causing variant for LQTS, HCM and ARVC provides an opportunity for cascade predictive genetic testing. This study assessed the perspectives of a large number of families regarding when predictive genetic testing should be offered and the importance of various factors in determining the optimal age to initiate testing.

Optimal Age to Offer Predictive Genetic Testing

Ninety two percent of respondents reported that testing should be offered prior to 5 years of age for children *at risk* of LQTS. This is consistent with published guidelines which recommend testing as early as possible (Ackerman et al, 2011). Early diagnosis has the potential to be lifesaving based on variable onset of the condition and initiation of prophylactic beta blocker therapy (Alders et al, 2015). Respondents with post-secondary education were significantly more likely to report that predictive genetic testing should be offered before 5 years of age compared to those without post-secondary education. Although education has previously been inconsistently associated with interest in genetic testing, this finding may highlight an educational opportunity to help families better understand the spectrum of disease presentation and treatment options (Sweeny et al, 2014).

The majority (77%) of respondents reported that predictive genetic testing should be offered prior to 10 years of age for children *at risk* of HCM or ARVC. This is contrary to the European and Australian/New Zealand position statement and guideline which recommend deferring testing until after 10 years of age (Charron et al, 2010; Ingles et al, 2011). Whereas, these results supports the more recent American Society of Human Genetics guideline which recommends leaving the decision around predictive genetic testing in minors to the parents in situations where the risks and benefits are less clear (Botkin et al, 2015).

Offering testing to children *at risk* of HCM or ARVC before 10 years of age was associated with female gender and younger age of the respondent. In a previous chart review, our group found that for phenotype negative carrier parents, female gender was associated with significantly greater uptake of genetic testing for children during childhood (Christian et al, 2018). Younger age has also been reported as a significant factor associated with parental interest in genetic testing for children affected with HCM in a study by Fitzgerald-Butt et al (2010). Gender and age were not, however,

significantly associated with when to offer predictive genetic testing for LQTS in our study.

Earlier presentation of the condition in the family was also associated with when to offer predictive genetic testing for HCM and ARVC. Earlier onset within a family may increase the perceived risk of onset during childhood and increase parental worry related to the disease. Earlier onset may also influence the recommendation made by a healthcare professional regarding the timing of predictive genetic testing which in turn could impact uptake of testing (Khouzam et al, 2015; Christian et al, 2018).

Factors Influencing When to Offer Testing

Regardless of diagnosis, respondents ranked factors relating to beneficence (clarify cardiac screening and beta blocker therapy, guiding sport participation, decreasing worry and adaptation) higher than factors relating to non-maleficence (increasing worry and risk of discrimination) and autonomy/informed consent (child assent).

The impact of a positive genetic result on medical management may empower families to be proactive and potentially improve the outcome for their child(ren). The impact on sport participation is less clear. Although there is a growing body of evidence linking physical activity with onset and severity of ARVC, the published guidelines are inconsistent with regard to physical activity recommendations for phenotype negative carriers of a pathogenic variant for LQTS and HCM (Maron et al, 2005; Pelliccia et al, 2005; Kirchhof et al, 2006; James et al, 2013; Saberniak et al, 2014). The European Society of Cardiology recommends avoiding vigorous-intensity competitive sport whereas the Heart Rhythm Society indicates that there is insufficient evidence at this time for restriction. It is unclear if parents would consider discouraging participation in vigorous-intensity competitive sport, in the absence of a recommendation of restriction, in an effort to avoid psychological distress relating to possible later disqualification from sport. A qualitative study interviewing adults who underwent predictive genetic testing for HCM postulated that the psychological impact of testing is linked to risk perception and the need for behaviour change related to the result (Bonner et al, 2018).

Decreasing worry for children that test negative for a familial variant had an average rating of importance of 4.3 out of 5 compared to an average score of 2.8 out of 5 for the possibility of increasing worry for children that test positive. Two systematic reviews on predictive genetic testing in minors concluded that, although the research is limited,

testing does not appear to negatively impact the emotional state, self-perception or social wellbeing of a child (Wade et al, 2010; Wakefield et al, 2016). In addition, the health related quality of life scores were similar between children diagnosed with a cardiomyopathy and those *at risk* of developing a cardiomyopathy based on family history (Friess et al, 2015). This suggests that children *at risk* of a cardiomyopathy may already be negatively impacted by their family history and further support the families' perception that the ability of testing to decrease worry is more important than the possibility of increasing worry. This is further supported by a study by Michie et al (2001) that found that predictive genetic testing significantly reduced worry, anxiety and distress for children who tested negative for a familial variant for familial adenomatous polyposis (FAP).

Many families acknowledged the risks associated with insurance discrimination however most appear to feel that the potential benefits of testing outweigh the risks related to discrimination. Similar concerns were expressed regarding employment and insurance discrimination by a group of adults with or *at risk* of HCM, however, the majority still chose to pursue genetic testing (Khouzam et al, 2015).

Finally, allowing a child to take part in the decision making process was given an average rating of 2.5 out of 5. This is consistent with a study by Aldefer et al (2017) which interviewed a group of adolescents and young adults who underwent predictive genetic testing during childhood for FAP. Only 1 of the 12 participants interviewed felt that testing should be deferred until an age at which a child can take part in the decision making process.

Overall, variation was reported for all 8 factors ranging from not important to very important (1-5) (Figure 3.4). Similarly, a qualitative study by Geelen et al (2011) reported that families differ with regard to the importance they place on the potential risks and benefits of predictive genetic testing which may result in opposing decisions around uptake of testing or the timing of testing. Respondents in our study who placed higher importance on the benefits were more likely to support offering testing at an earlier age compared to individuals who place higher importance on the potential risks. These findings support a personalized shared decision making approach to testing in which the decision around testing is discussed in the context of a family's personal values and perspectives.

Study Limitations

This study reports the opinions of individuals with a genetic diagnosis or who have a partner with a genetic diagnosis of LQTS, HCM and ARVC. The response rate is unknown and the sample is biased with regard to gender, education and income. Therefore it may be difficult to generalize these results to all families with a diagnosis of LQTS, HCM or ARVC.

3.2.5 Conclusions

Determination of the optimal age to perform predictive genetic testing for children *at risk* of LQTS, HCM or ARVC is complex and may differ from family to family. This study revealed that the majority of families believe that testing should be offered prior to 5 years of age for LQTS and before 10 years of age for HCM and ARVC. Variation was reported with regard to the importance placed on various factors influencing the timing of testing suggesting that the decision should be made in the context of a discussion with a genetic specialist incorporating the family's specific values.

Chapter 4: IMPACT OF PHYSICAL ACTIVITY RESTRICTION ON SPORT PARTICIPATION AND WEIGHT STATUS

Research has shown that people are resistant to changing their behaviour even when it is supported by improved health outcomes (Hollands et al, 2016). Health Canada has done much work to encourage involvement in moderate- and vigorous-intensity physical activity in an effort to control the obesity epidemic in Canada. Contrary to these efforts, due to the link between vigorous-intensity physical activity and SCA, this level of physical activity is often discouraged for individuals with a diagnosis of LQTS, CPVT, HCM or ARVC. In this chapter, moderate and high dynamic sport participation are described in a group of children with or *at risk* of one of these conditions. We also explore the relationships between physical activity restriction, moderate and high dynamic sport participation, weight status and change in body mass index (BMI) scores over time.

4.1 Physical activity restriction for children and adolescents diagnosed with an inherited arrhythmia or cardiomyopathy and its impact on body mass index.

4.1.1 Introduction

Vigorous-intensity physical activity can induce arrhythmogenic events in individuals with LQTS, CPVT, HCM and ARVC (Vaseghi et al, 2012). Based on this finding, international practice guidelines have historically recommended that individuals diagnosed with these conditions avoid competitive sport- defined as sport with organized practice and competition (Maron and Zipes 2005; Pelliccia et al, 2005; Priori et al, 2013a). Professional practice guidelines have been less consistent with regards to acceptable sport participation for individuals who are genotype positive phenotype negative.

Consequently, individuals with physical activity restriction may be more susceptible to weight gain unless caloric intake is also carefully monitored. In addition, beta blocker therapy is the mainstay of treatment for these conditions and has also been associated with weight gain (Martinez-Mir et al, 1993; Maggioni et al, 2005). This constellation of clinical management could have long term implications including the development of obesity. Obesity and decreased physical activity are associated with numerous health problems including type 2 diabetes, hypertension, depression, coronary heart disease and all-cause mortality (Barker et al, 2002; Engeland et al, 2003; Eriksson et al, 2003; Field et al, 2005; Nocon et al, 2008; Al Mamun et al, 2009; Andersen et al, 2010; Mammen and Faulkner, 2013).

BMI is a standardized method to assess weight status (BMI=weight/height^2). Reineck et al (2013) reported significantly higher BMI scores in a group of adults diagnosed with HCM compared to adult participants in the National Health and Nutrition Examination Survey (NHANES). It is unclear, however, if higher BMI scores resulted from exercise intolerance related to the disease or physical activity restriction.

The goal of this study is to describe the physical activity recommendations of pediatric cardiologists in the geographically confined province of Alberta for children and adolescents diagnosed with LQTS, CPVT, HCM and ARVC. We also describe post diagnosis sport participation in this population and evaluate the impact of physical activity restriction on BMI scores over time. We have not identified other studies that have evaluated the impact of physical activity restriction on BMI in this patient population. These outcomes are important as healthcare professionals strive to help families adjust to a new diagnosis.

4.1.2 Methods

Study population

The study population included pediatric patients (<21 years of age) with a clinical or genetic diagnosis of LQTS, CPVT, HCM or ARVC. Patients were identified though the Genetics & Genomics databases and the Western Canadian Children's Heart Network (WCCHN) database. All patients were managed at the Stollery Children's Hospital in Edmonton, or the Alberta Children's Hospital or the Providence Pediatric Clinic in Calgary. Exclusion criteria included being less than 5 years of age at last visit and the presence of an additional health condition that could affect the child's capacity to perform physical activity (ie. syndrome, developmental delay or involvement of other organ systems).

Data collection

Patients identified through the Genetics & Genomics and WCCHN databases were cross referenced with the clinical databases within the 3 pediatric cardiology departments in Alberta. The demographic and clinical data collected are described in Table 4.1. Age at diagnosis was described based on either clinical or genetic diagnosis, whichever was first. Phenotype positive was defined as the presence of cardiomyopathic or electrophysiological findings with or without clinical symptoms. Clinical symptoms included chest pain, shortness of breath, syncope, heart palpitations, seizures and cardiac arrest.

Physical activity recommendations were described as restriction from competitive sport, endurance activities, unsupervised swimming, swimming, weight training or recreational sport (i.e. gym class). General comments regarding physical activity restriction were also noted. Sporting activities were classified based on the Task Force 8: Classification of Sport (Mitchell et al, 2005). Participation in sport following cardiac diagnosis was described according to involvement in a Class B (moderate dynamic component) or C (high dynamic component) sport.

Impact of physical activity on weight was evaluated by looking at the change in BMI percentile over time and the child's final weight status. BMI percentiles were calculated using the Centers for Disease Control and Prevention BMI growth curves based on height and weight measurements from the child's first evaluation (>2 year of age) and most recent evaluation (CDC Accessed March 2018). Children were categorized as underweight (BMI <5th%), normal weight (BMI= 5-84th%tile), overweight (BMI= 85-94%tile), or obese (BMI ≥ 95th%tile) (Centre for Disease Prevention, 2016). Documentation of discussion relating to concerns with weight status were also noted.

The study included patients followed between September 2000 and November 2017. Ethics approval was obtained through the University of Alberta and the University of Calgary.

Data analysis

Continuous variables are presented as means with standard deviation and range when applicable. Categorical variables are presented as counts with percentages. For continuous outcomes, linear regression was used to assess the significance of associations. Wald's chi square test, Fisher's exact test, and logistic regression were used for categorical outcomes. The proportion of overweight and obese children between 5 and 17 years at the last evaluation was compared to the Canadian population rates using the one sample test of proportions (Roberts et al, 2012). *Stata Statistical Software: Release 13* (College Station, TX: StataCorp LP) was used for statistical analysis.

4.1.3 Results

Study population

In total, the study population was composed of 109 children who were followed in pediatric cardiology between the age of 5 and 21 years and had a clinical or genetic diagnosis of LQTS, CPVT, HCM or ARVC. An additional 22 children were excluded from the study because they were under 5 years of age at their last visit (n=12) or due to the presence of other health conditions including a syndrome (n=5), developmental delay (n=2), renal disease, stroke and pulmonary hypertension, and pregnancy at follow-up.

Characteristics of the sample are described in Table 4.1. Eighty three percent (n=90/109) of children carried a pathogenic variant. Two thirds of the children were diagnosed with an arrhythmia (LQTS=61 and CPVT=8) and one third were diagnosed with a cardiomyopathy (HCM=32 and ARVC=8). Overall, 70 (64%) children were on beta blocker therapy including 48 (79%) LQTS patients and 8 (100%) CPVT patients. Clinical symptoms were reported for 59 (55%) of the children with 51 (47%) having experienced an arrhythmogenic event (syncope, palpitations, seizure or cardiac arrest). There was no reported cardiac arrest event, post diagnosis, for any patient during this study period.

Table 4.1: Study demographic and clinical characteristics; n (%) and mean +/- standard deviation

Characteristic	Cohort n=109
Male	53 (49%)
Age at diagnosis (years)	9.9 +/- 4.8
Age at last follow-up (years)	14.1 +/- 3.9
Diagnosis:	
LQTS	61 (56%)
CPVT	8 (7%)
HCM	32 (30%)
ARVC	8 (7%)
Genetic status:	
Pathogenic variant carrier	90 (83%)
Proband- gene panel negative	15 (14%)
No result available	4 (4%)
Phenotype:	
Positive	90 (83%)
Negative	19 (17%)
Clinical symptoms	59 (55%)
Change in BMI over time (percentile)	3.9 +/- 18.0
Follow-up time (years)	3.9 +/- 2.3
Final weight status:	
Underweight	3 (3%)
Normal weight	65 (61%)
Overweight	22 (21%)
Obese	12 (9%)
Family history of SCA/D	47 (44%)
Physical Activity recommendation:	
Restricted	79 (73%)
Not restricted	19 (17%)
Not documented	11 (10%)
ICD	18 (17%)

LQTS- long QT syndrome, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy, BMI- body mass index, SCA/D- Sudden cardiac arrest/death, ICD- implantable cardioverter defibrillator

Physical Activity Recommendations

Physical activity restriction was documented following initial diagnosis in 79 (73%) of the pediatric cardiology charts, no restriction was specifically indicated in 19 (17%) of the charts, and no recommendation was documented in 11 (10%) of the charts. The most common restriction was to avoid competitive sport (n=77) followed by swimming or unsupervised swimming (n=25). Five individuals were told to avoid endurance activities, 4 to avoid free weight training and 2 to avoid even recreational sport. Table 4.2 describes restrictions based on diagnosis.

Table 4.2: Physical activity recommendations based on diagnosis (n)

Recommendation	LQTS	CPVT	HCM	ARVC
Restriction	49/61	7/8	19/32	4/8
No competitive sport	48	6	19	4
No unsupervised swimming/ swimming	24	0	0	1
No endurance sports	2	1	0	2
No weight training	2	0	2	0
No recreational sport	2	0	0	0
No restrictions	6/61	1/8	9/32	3/8
Not documented	6/61	0/8	4/32	1/8

Physical activity restriction was significantly associated with a positive phenotype (Table 4.3). Children who were phenotype positive had 11.4 times the odds (95% CI: 3.0, 44.3, $p<0.001$) of being prescribed physical activity restriction compared to children who were phenotype negative. Figure 4.1 describes the breakdown of physical activity recommendation based on phenotype. Physical activity was not associated with any other factors after adjusting for phenotype (Table 4.3).

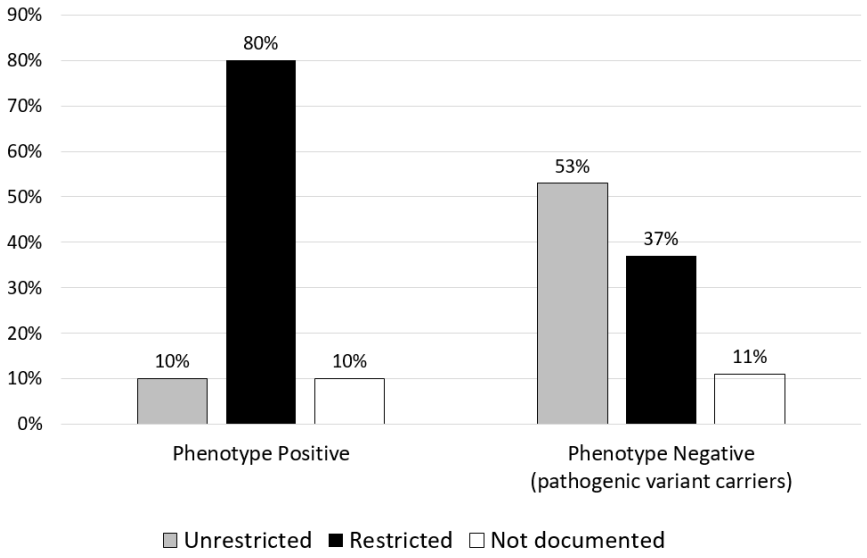


Figure 4.1: Physical activity recommendation based on phenotype

Table 4.3: Assessment of factors associated with physical activity restriction; n (%) and mean +/-standard deviation

Characteristic	Cohort*	Restricted n=77	Unrestricted n=19	Not documented n=11	*p* value (Restricted vs Unrestricted)
Male	53 (49%)	37 (47%)	10 (53%)	6 (55%)	0.65
Diagnosis: LQTS CPVT HCM ARVC	 61 (56%) 8 (7%) 32 (30%) 8 (7%)	 49 (80%) 7 (88%) 19 (59%) 4 (50%)	 6 (10%) 1 (13%) 9 (28%) 3 (38%)	 6 (10%) 0 (0%) 4 (13%) 1 (13%)	0.14** (LQTS/CPVT vs HCM/ARVC)
Phenotype positive[ł]	**90 (83%)**	**72 (91%)**	**9 (47%)**	**9 (82%)**	**<0.001**
Change in BMI percentile	+3.9 +/-18.0	+5.10 +/-18.0	+2.00 +/-13.5	-2.6 +/- 23.12	0.54
Follow-up time (months)	47 +/- 27.7	45 +/-24.8	53 +/- 32.6	52 +/- 39.3	0.32
Weight status at last follow up: Under or normal weight^ Overweight or Obese	 68 (67%) 34 (33%)	 49 (64%) 27 (36%)	 12 (75%) 4 (25%)	 7 (70%) 3 (30%)	 0.56
Family history of SCA/D	49 (45%)	34 (43%)	9 (47%)	6 (55%)	0.82
Beta blocker therapy	70 (64%)	58 (73%)	6 (32%)	6 (55%)	0.13**
ICD	18 (17%)	13 (16%)	0 (0%)	5 (45%)	0.07

*n varies between 102-109, **Adjusted for phenotype, [ł]Significance at <0.05
^Reference group. LQTS- long QT syndrome, CPVT- catecholaminergic polymorphic ventricular tachycardia, HCM- hypertrophic cardiomyopathy, ARVC- arrhythmogenic right ventricular cardiomyopathy, BMI- body mass index, SCA/D- Sudden cardiac arrest/death, ICD- implantable cardioverter defibrillator

Participation in Sport

Thirty children reported participating in a Class C (high dynamic component) sport following their diagnosis. An additional 11 individuals were involved in at least one Class B (moderate dynamic component) sport. Of the children participating in a Class B and/or C sport, 33 (81%) had been prescribed some level of physical activity restriction.

This did not significantly differ from those not participating in this level of sport (p=0.66). Post diagnosis sport participation is described in Table 4.4.

Table 4.4: Post diagnosis sport participation

Sporting Activities	**n***
Low dynamic	
Gymnastics/ Dance	*12*
Weight lifting	*2*
Martial arts	*2*
Curling	*4*
Cadets	*2*
Golf	*2*
Horseback riding	*2*
Moderate dynamic	
Skiing/Snowboarding	*8*
Football/Ruby	*7*
Volleyball	*6*
Baseball	*4*
High dynamic	
Soccer	*16*
Swimming	*12*
Basketball	*9*
Hockey	*8*
Badminton	*3*
Tennis	*2*
Running	*3*
Nordic skiing	*1*
Kick boxing	*1*

* Many children were involved in multiple sports.

Change in BMI and weight status

BMI was measured as a percentile using age and gender based comparisons (CDC accessed March 2018). Of the 109 charts reviewed, 100 children had at least 2 BMI measurements documented. The children were on average 14.1 +/- 3.9 years of age at the time of the second BMI measurement with an average follow-up time between measurements of 3.9 +/- 2.3 years (*range*= 0.5-11.7 years). The average BMI percentile score at initial visit was 58.3 percentile with an average change over time of +3.9 +/- 18.0 percentile (*range*= -45% to +50 percentile, *median*=2). Children who had a healthy weight or who were underweight at initial visit had an average change of +7.2 percentile compared to -4.3 percentile for children who were overweight or obese at initial visit (p=0.003). There was no association between change in BMI percentile and gender, diagnosis, phenotype, presence of symptoms, physical activity restriction, beta blocker therapy, or implantable cardioverter defibrillator (ICD) placement (Table 4.5). Focusing on the children prescribed physical activity restriction, we also compared the mean change in BMI percentile based on whether or not they participated in a Class B and/or Class C sport. No significant difference was observed between these 2 groups (p=0.56). Finally, follow-up time and age at diagnosis were also not significantly associated with change in BMI percentile scores.

In total, 34 of the 100 children with 2 BMI measurements were either overweight (n=22) or obese (n=12) at follow-up. Final weight status was significantly associated with initial weight status (p<0.001). It was not, however, associated with physical activity restriction, beta blocker therapy, age at diagnosis, diagnosis, phenotype, presence of symptoms or ICD placement. Eighty nine of these children were between 5 and 17 years of age for comparison with Canadian statistics. The proportion of overweight and obese children did not differ from the Canadian pediatric population (p=0.83) (Roberts et al, 2012).

Although height and weight were documented in the majority of charts, concerns relating to weight status were only specifically addressed in the charts of 7 of the 34 children who were overweight or obese.

Table 4.5: Assessment of factors associated with change in BMI percentile

Characteristics and change in BMI percentile scores	Confidence Interval	P value
Female =+3.2 Male=+4.5	-8.4, +5.9	0.73
Arrhythmia=+3.8 Cardiomyopathy=+3.9	-7.4, +7.6	0.98
Phenotype positive= +3.4 Phenotype negative=+6.3	-12.9, +7.2	0.58
Symptoms=+5.8 No symptoms=+1.4	-2.8, +11.6	0.23
Physical activity restriction=+5.1 No physical activity restriction=+2.0	-6.7, +12.9	0.53
Participation in class B or C sport (if restricted)= +6.5 No participation in class B or C sport (if restricted)= +4.0	-10.9, +5.9	0.56
Beta blocker therapy= +3.4 No beta blocker therapy= +4.9	-9.1, +6.0,	0.69
ICD= +4.2 No ICD=+2.1	-11.7, +7.4	0.66

BMI- body mass index, ICD- implantable cardioverter defibrillator

4.1.4 Discussion

This study evaluated 109 children with a clinical or genetic diagnosis of LQTS, CPVT, HCM, or ARVC. We recorded the physical activity recommendation, post diagnosis sport participation and BMI measurements over time. With an average follow-up time of 3.9 years, there was no significant change in BMI despite physical activity recommendation or actual sport participation. We are not aware of other published studies evaluating the impact of physical activity restriction on BMI in children with an inherited arrhythmia or cardiomyopathy.

Some level of physical activity restriction was prescribed for the majority of phenotype positive children (80%) but was less common for phenotype negative individuals (37%). The association between physical activity restriction and phenotype is consistent with some of the published guidelines as well as a recent international survey of pediatric electrophysiologists administered by our group (Pelliccia et al, 2008; Christian et al, 2016). We did not find a difference in physical activity restriction based on diagnosis after adjusting for phenotype.

Thirty eight percent (n=41) of our study population reported participating in a moderate or high dynamic sport following their diagnosis. This is consistent with 37% of individuals with LQTS, followed through the Mayo Clinic, who continued to participate in competitive sport (Johnson and Ackerman, 2013). Post diagnosis participation did not appear to be associated with the prescription of physical activity restriction. This may, however, be the result of under reporting of sport participation in the unrestricted group due to lack of perceived importance. We did not evaluate the overall relationship between post diagnosis sport participation and other variables based on the likelihood of under reporting in the unrestricted groups. It is unclear if continued sport participation is the result of a lack of understanding of the recommendation or if some children are intending to participate at lower intensity than would be expected for these sports, potentially reducing their cardiac risks.

No difference was seen between BMI scores over time based on physical activity restriction. Likewise, there was no difference observed based on participation in a Class B and/or Class C sport in the restricted group. In addition, the proportion of overweight and obese children and adolescents at follow-up in our study population is consistent with that seen in the Canadian pediatric population (Roberts et al, 2012). Our results are consistent with a study by Elias et al (2017) who found no association between physical activity restriction and BMI scores over time when looking at a sample of children with anomalous aortic origin of a coronary artery. In addition, although a study involving Canadian children with a congenital heart defect found that physical activity restrictions were associated with significant increased BMI scores over time, the proportion of overweight and obese children at follow-up was not significantly different from the general population (Stefan et al, 2005). Finally, although weight gain has previously been reported as a possible side effect of beta blocker therapy, our data does not support this association (Martinez-Mir et al, 1993; Maggioni et al, 2005).

The lack of impact of physical activity restriction on BMI and weight status may be related to lifestyle modifications, such as diet and decreased caloric intake, due to non-compliance with physical activity restriction, or due to insufficient follow-up time. This highlights the importance of counselling on complementary means to protect children during sport participation such as compliance with medications, CPR training, automated external defibrillators (AEDs) in sporting facilities and/or funding for portable AEDs for families.

Our findings suggest that children with LQTS, CPVT, HCM and ARVC face similar challenges to the Canadian pediatric population with regard to obesity. Physicians may, however, face greater struggles in developing weight management strategies in light of the potential risks relating to physical activity.

Study limitations

The high proportion of genotype positive children in our study is likely biased based on the approach we used to identify eligible patients. This study is limited by its reliance on documentation in the medical charts. No physical activity recommendation was documented in 10% of the charts. It is unclear if this is due to the cardiologist not recommending physical activity restriction, because the child was not involved in sports, because no discussion of restriction was felt to be relevant, or because the discussion and counselling were not documented. Documentation of sport participation is likely under reported for unrestricted individuals as it may have also been deemed irrelevant. Follow-up time was also limited for some of the children.

An additional limitation is that BMI percentile for the obese classification (>95 percentile) has an upper limit of 99% which restricted the change in BMI percentile scores possible for this group. BMI is also a crude outcome measure to assess the impact of decreased physical activity. Recording a more direct measure of fitness such as VO_2 max, may provide greater insight. As well, measurement of average heart rate and daily activity may be a better marker for physical activity than documented reports.

4.1.5 Conclusions

In this study, physical activity restriction was prescribed for the majority of phenotype positive patients with an inherited arrhythmia or cardiomyopathy although many continue to participate in restricted activities. BMI status did not differ between children prescribed physical activity restriction and those that were unrestricted. It is unclear if this finding

was impacted by the high rate of non-compliance with physical activity restriction or to other lifestyle modifications. These findings highlight the need to further assess how children modify their physical activity based on recommendations by their cardiologist and to investigate other parameters for the potential impact of physical activity restriction on cardiovascular health.

Chapter 5: THE IMPACT OF DIAGNOSIS AND MANAGEMENT ON WELL-BEING

In Chapter 5 we further explore the impact of diagnosis and management on well-being by assessing physical activity and health related quality of life (HRQL) for children diagnosed with an inherited arrhythmia or cardiomyopathy. Previous qualitative research in the area has suggested that the need to change one's behaviour may negatively impact their well-being (Bonner et. al. 2018). In addition, some parents in our online survey indicated that children diagnosed at an earlier age may be encouraged to participate in low-intensity activities instead of vigorous-intensity activities. We, therefore, recruited a cohort of children diagnosed with LQTS, CPVT, HCM or ARVC and evaluated the impact of modification to physical activity and age at diagnosis with regard to physical activity and HRQL.

5.1 The impact of age at diagnosis on physical activity modification and health related quality of life in a cohort of children with an inherited arrhythmia or cardiomyopathy

5.1.1 Introduction

Physical activity improves long term cardiovascular health, psychological well-being, and academic performance (Penedo and Dahn, 2005; Nocon et al, 2008; de Greeff et al, 2018). It is also associated with a lower risk of diabetes mellitus and certain types of cancer (Rezende et al, 2018; Sigal et al, 2018). In an effort to maximize the well-being of Canadian children, The Canadian Society for Exercise Physiology (CESP) currently recommends that children and youth aged 5-17 years accumulate at least 60 minutes of moderate-to vigorous-intensity physical activity (MVPA) per day (CESP 2019). They also urge children to participate in vigorous-intensity activity at least three days per week.

In contrast to these recommendations, vigorous-intensity physical activity has been linked to an increased risk of arrhythmogenic events for children diagnosed with long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC). Further, research supports an association between the amount and intensity of physical activity, and disease progression and severity for individuals diagnosed with ARVC (James et al, 2013; Saberniak et al, 2014). Consequently, children diagnosed with these conditions are frequently advised to limit their involvement in vigorous-intensity physical activity and to avoid competitive sport (Maron et al, 2015; Pelliccia et al, 2005). This often translates to restriction from organized sports with a moderate or

high dynamic component and encouragement to participate in low-intensity physical activity.

Disqualification from sport during adolescence due to a cardiac diagnosis has been shown to have adverse psychological consequences as many athletes develop their self-identity and social networks around sport (Asif et al, 2015). Predictive genetic testing has been developed as a tool to improve health outcomes in families diagnosed with an inherited arrhythmia or cardiomyopathy and may allow parents an opportunity to choose alternatives to competitive sports for their at risk child(ren) (Christian et al, 2018). This could potentially prevent the observed concerns related to disqualification from sport during adolescence. However, limited data exists on how age at diagnosis impacts the physical and psychosocial well-being of children. In this prospective cohort study, we evaluated children diagnosed with LQTS, CPVT, HCM or ARVC with regard to time involved in MVPA and measures of health related quality of life (HRQL). We hypothesized that earlier age at diagnosis would be associated with less time involved in MVPA and higher HRQL scores.

5.1.2 Methods

Study Population

Pediatric patients (8-17 years of age) with a clinical or genetic diagnosis of LQTS, CPVT, HCM or ARVC were recruited to participate through the Stollery Children's Hospital (Edmonton, AB), and the Alberta Children's Hospital and the Providence Pediatric Cardiology Clinic (Calgary, AB) from May 2017 to April 2019. Families were informed of the study by a mailed letter or by a healthcare specialist during their medical appointment. Patients were excluded from the study if they were less than three months post diagnosis, did not speak English or if they had additional health concerns that may have impacted their HRQL or physical activity level. Research Ethics Board approval was obtained through the University of Alberta and the University of Calgary and participants provided written informed consent (Appendix 4).

Measures:

Physical Activity

Participants wore an Actigraph GT3X accelerometer (Actigraph LLC) above their right hip at all times during a 7-day period except when sleeping or when immersed in water (i.e. bathing/showering or swimming). Cut-point thresholds published by Evenson et al,

(2008) were used to calculate the intensity of participants' physical activity and data was reported using 60-second epochs to allow for comparison with published data. A valid day (minimum number of wearing hours) was defined as 10 hours (Trost et al, 2005). Data was required for a minimum of 4 days including 1 weekend day for each participant. Data was not collected over summer vacation (July and August) in an effort to capture a representative week and total precipitation (mm) was recorded for each day of physical activity data collection to evaluate variation related to weather.

A parent or guardian for each participant completed a questionnaire that included information on the child's involvement in organized activities and their understanding of the physical activity recommendations (Appendix 5). Sport participation was defined as participation in a Class A (low dynamic component), Class B (moderate dynamic component) or Class C (high dynamic component) organized sport throughout a 1-year period (Mitchell et al, 2005). Physical activity restriction was described as restriction from competitive sport, endurance activities, swimming, and/or weight training.

In addition, parents were asked to rate on a scale of 1 to 5, how much their child had modified their physical activity because of their diagnosis (1= not at all and 5= completely), and how difficult and how upsetting it was for their child to adjust to the physical activity recommendations (1= not at all and 5= very difficult/upsetting). These questions were adapted from a study by Luiten et al, (2016) which assessed the psychological impact of physical activity restriction in an adult population. Parents were also asked to describe "how often they participated in active sport or vigorous physical activity long enough to get sweaty, during leisure time" within the past four months and during their teen years (Godin et al, 1986).

Health-related quality of life (HRQL)

Participants completed the Pediatric Quality of Life Inventory 4.0 (PedsQL) and the Pediatric Cardiac Quality of Life Inventory (PCQLI) to evaluate HRQL (Marino et al, 2011; Varni, 2016). The PedsQL is a 23 item generic measure and the PCQLI is a 23 to 29 item disease specific measure. Three summary PedsQL scores were calculated for each participant according to the PedsQL user guide: physical, psychosocial and total health. Each scale has a maximum score of 100. In addition, three PCQLI scores were calculated for each participant: disease, psychosocial and total impact. The disease and psychosocial impact scales have a maximum score of 50 and the total impact scale has a maximum score of 100. Higher scores for all scales indicate better HRQL.

Pediatric cardiology charts were also reviewed to collect data on diagnosis, symptoms, phenotype, physical activity restriction, beta blocker therapy, and family history of sudden cardiac arrest. Physical activity restriction was again described based on documentation of restriction from competitive sport, endurance activities, swimming, and/or weight training as outlined in the patients' clinic letter.

Data Analysis

Continuous variables are presented as mean with standard deviation (SD). Categorical variables are presented as percentages (counts). The primary relationships examined were the impact of age at diagnosis and change to physical activity on time involved in MVPA and measures of HRQL. Other potential predictors were also evaluated including participation in a Class B or C sport, and difficulty and upset adapting to physical activity recommendations. The relationships between predictors and time involved in MVPA and HRQL scores were analysed using simple linear regression. Age at diagnosis was also assessed as a predictor of participation in a Class B or C sport, change to physical activity, and difficulty and upset adapting to physical activity recommendations. These associations were assessed, univariate logistic regression. Responses were categorized as no change, not difficult, not upsetting (rating = 1) and some change, somewhat difficult and somewhat upsetting (rating >1). Age at diagnosis was assessed as a categorical variable (<7 years versus ≥7 years). Seven years of age was selected as a cut-off point as this is a common age at which children enter either a recreational or competitive path for the most popular sports in Alberta. Time involved in MVPA and sedentary behavior, and PedsQL scores were compared to normative data using the one-sample t-test.

5.1.3 Results

The study cohort included 35 children affected with an inherited arrhythmia or cardiomyopathy from 30 unrelated families. The participation rate was 49% (n=35/72). Two participants did not meet the minimum requirement of 10 hours of activity data on 4 days (including 1 weekend day). Although they were included in the study, their activity data was excluded from analysis. In addition, one of them did not complete the PCQLI. Characteristics of the cohort are described in Table 5.1. Nonparticipants were older compared to participants with a mean (SD) age of 14.4 (2.7) years.

Table 5.1: Characteristics of the cohort (n=35)

Characteristics	N (%) or Mean (SD)
Male	20 (57%)
Age	12.3 (3.2)
Age at diagnosis	6.9 (5.5)
Diagnosed < 7 years	17 (49%)
Diagnosed ≥ 7 years	18 (51%)
Diagnosis	
LQTS	14 (40%)
CPVT	5 (14%)
HCM	14 (40%)
ARVC	2 (6%)
Phenotype positive	27 (77%)
Symptoms	17 (49%)
Physical activity restriction	25 (71%)
Beta blocker therapy	25 (71%)
Side effects	14 (56%)
ICD	0 (0%)
Family history of SCA*	20 (59%)
Weight status	
Healthy	25 (71%)
Overweight	5 (14%)
Obese	5 (14%)
Sport participation ł	
Class A	8 (22%)
Class B	13 (37%)
Class C	13 (37%)
Class B or C	19 (54%)
Any class of sport	22 (63%)

N= Number, SD= Standard Deviation, LQTS=long QT syndrome, CPVT= catecholaminergic polymorphic ventricular tachycardia, HCM= hypertrophic cardiomyopathy, ARVC= arrhythmogenic right ventricular cardiomyopathy, ICD= implantable cardioverter defibrillator, SCA= sudden cardiac arrest

* Note one participant was adopted and family history was unknown.

ł Many children were involved in more than one class of sport.

The mean (SD) age of participants was 12.3 (3.2) years and mean (SD) time since diagnosis was 5.3 (4.2) years. Approximately half (54%) of the cohort were diagnosed with an inherited arrhythmia (LQTS or CPVT) and half were diagnosed with a

cardiomyopathy (HCM or ARVC). The majority were phenotype positive (77%) and treated with beta blockers (71%). Seventy one percent (n=25/35) were advised to avoid some type of physical activity (competitive sport (n=21), endurance activities (n=4), or swimming (n=4)). Approximately half (49%) received a diagnosis at <7 years compared to ≥7 years.

Accelerometers were worn for an average of 13.0 hours/day (range 10.6-14.7 hours/day) for 6.5 days (range 4-8 days). Participants were involved in a mean (SD) of 35 (23) min of MVPA per day with a mean (SD) of 7 (6) min/day of vigorous-intensity physical activity. When the cohort was divided based on the prescription of physical activity restriction we found that the restricted group participated in an average of 34 (22) min/day of MVPA with 6 (6) min/day of vigorous-intensity physical activity, while the unrestricted group participated in an average of 37 (28) min/day of MVPA with 8 (8) min/day of vigorous-intensity physical activity. Of children prescribed physical activity restriction, 52% (n=13/25) were involved in at least one Class B or Class C sport.

Fourteen percent (n=5/35) of participants in accumulated an average of ≥60 minutes of MVPA per day. Overall, they were involved in less MVPA per day compared to the Canadian pediatric population (6-17 year olds) (55 min/day) (p<0.001) (Colley et al, 2017). The average time being sedentary was 439 (90) min/day (median= 421, interquartile range= 113) which was similar to normative data (461 min/day) (p=0.17).

Univariate analyses of factors associated with time involved in MVPA are described in Table 5.2. Male gender and participation in a Class B or Class C sport were associated with more time involved in MVPA, and older age and obesity were associated with less time involved in MVPA.

Table 5.2: Factors associated with time involved in MVPA

Characteristic	Coefficient	Confidence Interval	p value
Female gender*	**-25.7**	**-39.7, -11.7**	**0.001**
Age*	**-2.6**	**-5.1, -0.2**	**0.04**
Cardiomyopathy versus arrhythmia	7.1	-9.5, 23.8	0.39
Symptoms	-2.6	-19.4, 14.2	0.75
Phenotype positive	-17.9	-36.7, 2.4	0.08
Diagnosed ≥7 years versus <7 years	-9.3	-25.8, 7.1	0.26
Body weight status			
Overweight	-6.1	-28.5, 16.3	0.58
Obesity*	**-26.2**	**-50.6, -1.6**	**0.04**
Beta blocker therapy	-3.3	-22.1, 15.5	0.72
Participation in Class B or C sport *	**21.1**	**6.2 36.1**	**0.007**
Physical activity restriction	-2.9	-21.7, 15.9	0.76
Change to physical activity	-0.1	-16.9, 16.7	0.99
Mother's physical activity	-0.4	-5.0, 4.3	0.87
Father's physical activity	2.5	-2.1, 7.0	0.28

* Significant at p<0.05

The mean (SD) PedsQL physical, psychosocial, and total health scores were 82 (19), 78 (15), and 79 (15), respectively. These scores were lower when compared to normative data, reaching significance for total health (physical health: 88 (13), psychosocial health: 82 (14) and total health: 84 (12)) (p=0.07, p=0.09 and p=0.05, respectively) (Varni et al, 2003). The mean (SD) PCQLI disease, psychosocial and total impact scores were 38 (9), 38 (11) and 77 (16), respectively. On univariate analysis, obesity was associated with lower PedsQL physical (p=0.03), psychosocial (p=0.02) and total health (p=0.01) scores as well as lower PCQLI disease (p=0.004) and total impact (p=0.006) scores (Table 5.3). Participation in a Class B or Class C organized sport was associated with higher PCQLI psychosocial (p=0.02) and total impact (p=0.05) scores (Table 5.3).

Fifty one percent (n=18/35) of participants had to modify their physical activity because of their diagnosis. Change to physical activity was associated with lower PedsQL physical (p=0.05), psychosocial (p=0.05) and total health (p=0.03) scores, and lower PCQLI disease (p=0.001) and total impact (p=0.02) scores (Table 5.3). Parents

reported that it was difficult and upsetting for the majority (84% and 84%, respectively) of children who had to modify their physical activity because of their diagnosis. Children who were reported to have difficultly or upset adapting to the physical activity recommendations also had lower PedsQL physical health (p=0.04 and p=0.02) and PCQLI disease impact (p=0.04 and p=0.02) scores. Modifications to physical activity were described as: (1) stopping participation in sport, (2) modifying the intensity of physical activity, and (3) reducing additional risk factors such as not exercising when hot outside.

Age of diagnosis was not significantly associated with time involved in MVPA or HRQL scores (Table 5.2 and Table 5.3). However, only 30% (3/10) of children diagnosed at <7 years and prescribed physical activity restrictions were participating in a Class B or C sport. This compares to 67% (10/15) of children diagnosed ≥7 years and given restrictions (OR (95% CI): 4.7 (0.6, 38.6) p=0.11). Children diagnosed ≥7 years were significantly more likely to have had to modify their physical activity because of their diagnosis (OR (95% CI): 6.2 (1.4, 27.1), p=0.01) and were more likely to find it difficult (OR (95% CI): 5.7 (1.3, 25.1), p=0.02) or upsetting (OR (95% CI): 7.8 (1.67, 36.06), p=0.009) to adapt to physical activity recommendations compared to children diagnosed <7 years.

Table 5.3: Factors associated with PedsQL and PCQLI scores (Coefficient (95% Confidence Interval) p value)

	PedsQL			PCQLI		
Characteristics	**Physical Health**	**Psychosocial Health**	**Total Health**	**Disease Impact**	**Psychosocial Impact**	**Total Impact**
Male	-11.3 (-24.4, 1.8) p=0.09	-5.13 (-15.6, 5.4) p=0.33	-7.3 (-17.3, 2.8) p=0.15	-2.4 (-8.4, 3.7) p=0.43	0.9 (-7.7, 8.8) p=0.82	-4.2 (-15.5, 7.2) p=0.46
Age	-0.9 (-3.0, 1.3) p=0.40	0.3 (-1.3, 2.0) p=0.69	-0.1 (-1.7, 1.5) p=0.91	-0.5 (-1.5, 0.4) p=0.27	0.1 (-1.1, 1.3) p=0.88	-0.1 (-1.9, 1.7) p=0.90
Cardiomyopathy versus Arrhythmia	-5.8 (-19.3, 7.6) p=0.39	1.3 (-9.3, 11.8) p=0.81	-1.2 (-11.5, 9.1) p=0.81	-2.1 (-8.1, 4.0) p=0.49	-4.0 (-11.8, 3.7) p=0.30	-3.0 (-14.4, 8.4) p=0.59
Symptoms	-1.4 (-12.0, 9.1) p=0.79	-6.9 (-20.2, 6.5) p=0.30	-3.3 (-13.6, 6.9) p=0.51	-4.9 (-10.7, 1.0) p=0.10	-1.2 (-9.0, 6.6) p=0.75	-4.4 (-15.6, 6.8) p=0.43
Phenotype positive	-4.2 (-20.3, 11.9) p=0.60	-3.2 (-15.7, 9.3) p=0.61	-3.6 (-15.7, 8.6) p=0.56	-3.0 (-10.5, 4.4) p=0.41	-1.2 (-10.8, 8.5) p=0.81	-3.15 (-17.1, 10.8) p=0.65
Diagnosed ≥ 7 years versus < 7 years	-10.2 (-23.3, 2.8) p=0.12	2.6 (-8.0 13.1) p=0.62	-1.9 (-12.1, 8.4) p=0.71	-3.0 (-9.7, 2.2) p=0.21	2.9 (-4.9, 10.7) p=0.45	-2.6 (14.0, 8.7) p=0.64
Body weight status (reference: healthy weight)						
Overweight	1.6 (-16.9, 20.1) p=0.86	3.5 (-10.6, 17.6) p=0.62	2.8 (-10.6, 16.3) p=0.67	4.4 (-3.1, 11.8) p=0.54	6.5 (-4.2, 17.2) p=0.22	9.7 (4.3, 23.7) p=0.17
Obesity*	**-20.2; (-38.7 -1.7) p=0.03**	**-17.2 (-31.2 -3.1) p=0.02**	**18.2 (-31.7, -4.7) p=0.01**	**-12.6 (-20.7, -4.5) p=0.004**	-8.5 (-20.2, 3.2) p=0.15	**-22.2 (-37.5, -6.9) p=0.006**
Beta blocker therapy	-7.4 (-22.2, 7.4) p=0.32	-3.7 (-15.3, 7.9) p=0.53	-5.0 (-16.2, 6.3) p=0.37	-3.7 (-10.4, 3.0) p=0.27	1.4 (-7.5, 10.3) p=0.75	-1.2 (-14.0, 11.4) p=0.86
Participation in Class B or C sport	1.2 (-12.4, 14.8) p=0.86	6.4 (-3.9, 16.8) p=0.22	4.6 (-5.6, 14.8) p=0.37	5.2 (-0.6, 11.0) p=0.08	**8.7 (1.4, 15.9) p=0.02**	**10.8 (0.1, 21.5) p=0.05**
Physical activity restriction	-6.5 (-21.4, 8.3) p=0.38	0.9 (-12.5, 10.8) p=0.88	-2.9 (-14.2, 8.5) p=0.61	-5.1 (-11.7, 1.5) p=0.13	-6.1 (-14.7, 2.5) p=0.16	-10.0 (-22.4, 2.3) p=0.11
Some change to physical activity*	**-13.0 (-25.7, -0.2) p=0.05**	-9.91 (-19.9, 0.0) p=0.05	**-11.0 (-20.5, -1.5) p=0.03**	**-9.1 (-14.2, -4.0) p=0.001**	-4.9 (-12.5, 2.8;) p=0.20	**-12.3 (-22.7, -1.8) p=0.02**
***Some difficulty adapting to physical activity recommendations**	**-13.6 (-26.6, -0.5) p=0.04**	-6.2 (-16.8, 4.5) p=0.25	-8.7 (-18.9, 1.4) p=0.09	**-6.0 (-11.8, -0.2) p=0.04**	-1.2 (-9.3, 6.9) p=0.76	-5.7 (-17.2, 5.9) p=0.32
***Some upset adapting to physical activity recommendations**	**-15.2 (-28.0, -2.4) p=0.02**	-5.4 (-16.1, 5.3) p=0.31	-8.9 (-19.0, 1.2) p=0.08	**-7.0 (-12.7, -1.4) p=0.02**	-3.9 (-11.2, 4.8) p=0.42	-8.5 (-19.8, 2.7) p=0.13

* Significant at p<0.05

5.1.4 Discussion

This study evaluated 35 children with a clinical or genetic diagnosis of LQTS, CPVT, HCM, or ARVC. We recorded time involved in MVPA, evaluated measures of HRQL, and assessed the impact of age at diagnosis on these outcomes. Our cohort was involved in significantly less MVPA per day (35 min/day) compared to the Canadian pediatric population (6-17 year olds) (55 min/day) (Colley et al, 2017). This data supports that the majority of children in our cohort were making some effort to comply with physical activity recommendations. The average time being sedentary was similar between our cohort (439 min/day) and normative data (461 min/day) suggesting that our cohort is involved in more low-intensity physical activity which is also consistent with recommendations (Garriguet et al, 2017).

Overall, 14% (n=5/35) of participants in the cohort accumulated an average of ≥60 minutes of MVPA per day compared to 33% of children in the Canadian pediatric population (Colley et al, 2017). Sweeting et al (2016) similarly reported that only 13% of adults diagnosed with HCM were meeting the minimum recommendation of 150 min/week of MVPA. Research has shown that decreased cardiorespiratory fitness is a strong independent predictor of cardiovascular disease and all-cause mortality later in life (Gaesser et al, 2015). This raises the concern that decreased MVPA may help protect this patient population from arrhythmogenic events but may increase the risk for other adverse health outcomes later in life. Therefore, the development of cardiac rehabilitation programs that help patients remain safe and fit will be important (Thrush, 2018). Factors such as gender, age, body weight status and sport participation are important elements to consider when developing a personalized fitness plan.

Our cohort had significantly lower PedsQL total health scores compared to the general population and similar PedsQL and PCQLI scores to data published for children with LQTS (Czosek et al, 2016). We found lower HRQL scores for children who were obese and for those who reportedly changed their physical activity because of their diagnosis. Although obesity has previously been identified as a risk factor for impaired HRQL in the general population, the impact of changing one's physical activity on HRQL has not previously been examined in children with an inherited arrhythmia or cardiomyopathy (Varni et al, 2007) Half of our cohort modified their physical activity because of their diagnosis and this was described as difficult and upsetting for the majority. Changes to

physical activity included discontinuation of sport participation, participating at a lower intensity and avoiding additional risk factors during sport participation.

A larger proportion of children diagnosed ≥7 years of age were participating in an organized Class B or C sport which explains why they were more commonly faced with the decision of modifying their physical activity because of their diagnosis. The negative impact of changing one's behaviour was previously articulated by a group of adults diagnosed with HCM in a qualitative study (Bonner et al, 2018). They reported that a genetic diagnosis had a higher impact when the individual had to decrease their physical activity and had a lower impact when the individual was not very physically active (Bonner et al, 2018). Discontinuation of sport removes involvement in an activity that was likely felt to be enjoyable, important in developing and maintaining friendships, managing weight and dealing with stress (Luiten et al, 2016). Luiten et al (2016) further examined the issue of psychological adjustment to physical activity restriction in a group of adult athletes diagnosed with HCM. Approximately half of their group described it as being upsetting and/or difficult to adjust to the physical activity recommendations. Together, these results highlight the need for psychological support for individuals who discontinue sport participation as they search for a new normal (new social groups and new activities). Additional support may also be beneficial as individuals adapt their level of participation in sport to a lower intensity. Learning how to listen to their body in the presence of peer and self-imposed pressures may have additional challenges.

Although these results highlight some challenges related to a diagnosis made later in childhood, parents have also previously raised concerns regarding a diagnosis made earlier in childhood. For instance, they have expressed concerns about higher levels of fear, worry, stigmatization and overprotection for the child (Geelen et al, 2011). The PedsQL and the PCQLI measures contain a number of items that specifically address these concerns, such as, "I am afraid of dying," "I worry what will happen to me" and "Grown-ups around me are too protective." Responses to these items are reflected by the psychosocial health/impact scores. Our study did not find an association between earlier age at diagnosis and lower psychosocial scores suggesting that these outcomes are not negatively impacted by an earlier diagnosis. Additional research is required to address these concerns in more detail.

Study Limitations

Our cohort was small and heterogeneous with regard to diagnosis and physical activity restriction thus limiting our ability to identify more subtle differences between our cohort and normative data. A contemporary comparative normal cohort was not used for data comparison. Although family history of SCA was not associated with our outcomes, we noted a relatively high incidence of SCA in the families that participated in the study suggesting a potential bias. Physical activity was reported in 60 second intervals to allow for comparison with published data, however, research has shown that children tend to participate in vigorous-intensity activity in shorter intervals (Nettlefold et al, 2016). Therefore the time involved in MVPA may be under represented in both our cohort and normative data. Finally, we assessed changes to physical activity and adaptation to physical activity recommendations from the perspective of the parent. It would be useful to record the child's point of view and assess how it correlates with parental views.

5.1.5 Conclusions

We found that, on average, our cohort was involved in less MVPA and had lower PedsQL total health scores compared to normative pediatric data. Children diagnosed with LQTS, CPVT, HCM or ARVC ≥7 year of age were significantly more likely to have had to change their physical activity because of their diagnosis and experienced more difficulty and upset when trying to adapt to the physical activity recommendations. Change to physical activity was also associated with lower HRQL. Results of this study are useful for families and healthcare professionals caring for children who are adjusting to a new cardiac diagnosis of an inherited arrhythmia or cardiomyopathy.

Chapter 6: DISCUSSION AND CONCLUSIONS

This final chapter reviews the overall conclusions drawn from studies presented in this dissertation, and discusses their impact on clinical practice and future research. Firstly, variability in practice was observed with regard to the diagnosis and management of LQTS, CPVT, HCM and ARVC. Variability in practice is likely largely impacted by gaps in knowledge which have resulted in inconsistent professional guidelines based mainly on expert opinion. In addition, the personal perceptions and values of patients and healthcare providers influence decision making. I propose the development of a decision aid to promote a consistent, family centred care approach to predictive genetic testing. I also advocate for the use of one of two different counselling methods to discuss physical activity participation, depending on one's perspective. The observed variability in practice supports the need for further research in the areas of diagnosis and management and as evidence accumulates, it should prompt review and revision of published guidelines.

Secondly, although we found that many children adjusted well to their diagnosis of an inherited arrhythmia or cardiomyopathy, two vulnerable groups of children were identified. Children with lower HRQL scores were significantly more likely to be obese or have changed their physical activity because of their diagnosis. Reflection on these findings suggests a need to modify the clinical approach taken with some families and the potential value of referral for dietary and/or psychological counselling for specific patients. Screening tools are useful to help identify who would benefit from additional services. Further work is also needed to support the development of safe physical activity programs for these children.

6.1 Variability in uptake of predictive genetic testing and the optimal age to offer predictive genetic testing

A review of medical genetics charts in Alberta revealed that 66% of families performed predictive genetic testing for their a*t risk* children. Predictors of uptake of testing included recommendation of the healthcare professional and gender of the affected parent in the absence of symptoms. The two primary medical genetic clinics in Alberta were inconsistent in their practice with regard to the age at which predictive genetic testing was offered to children *at risk* of an inherited cardiomyopathy. One group offered genetic testing to children *at risk* of HCM or ARVC after 10 years of age in accordance with the European Society of Cardiology guidelines (Charron et al, 2010). The other group offered genetic testing at all ages.

The inconsistent practice identified within Alberta led to an assessment of international practice among genetic counsellors. Variability was observed among genetic counsellors practicing across Canada, the United States, the United Kingdom, Australia and New Zealand. Greater variability was seen regarding when to offer predictive genetic testing for HCM and ARVC compared to LQTS and CPVT. Factors found to influence practice were both counsellor specific and family specific. For example, years of experience, country of practice and clinical setting were associated with when genetic counsellors felt that testing should be offered. More experienced genetic counsellors were more likely to offer testing before 5 years of age for LQTS, and genetic counsellors practicing within North America and working primarily with a cardiologist were more likely to offer testing at an earlier age for HCM and ARVC. Onset of the condition in a family also influenced when testing would be offered.

Families also expressed varied opinions with regard to when predictive genetic testing should be offered and why. Level of education was associated with offering testing at an earlier age for LQTS while female gender and younger age of the respondent were associated with earlier testing for HCM and ARVC. In addition, younger presentation of the condition in the family was associated with offering testing at an earlier age for HCM and ARVC. Finally, the importance families placed on potential risks and benefits of initiating predictive genetics testing as different points in childhood varied. Regardless of diagnosis, however, respondents ranked factors relating to beneficence higher than factors relating to non-maleficence and autonomy/informed consent.

It should be acknowledged that much of our data on the topic of the timing of predictive genetic testing was obtained from online surveys with unclear response rates. Survey data has inherent biases including question bias, answer bias, sample bias and reporting bias. Care was taken to reach out to a broad sample, define concepts, and compose clearly worded questions at an appropriate grade level for all potential respondents. However, avoiding bias is challenging as was demonstrated by the family survey which exhibited bias based on gender, education, and income. Therefore the conclusions drawn from this data should be considered with this in mind.

Some variability in practice can be attributed to the fact that historically predictive genetic testing in minors was limited to situations where testing had a clear and immediate impact on medical management (Botkin et al, 2015). Because LQTS and CPVT can present in infancy and beta blocker therapy can provide some protection from

arrhythmogenic events, predictive genetic testing is generally offered at a young age and uptake by families is high. In comparison, the onset of HCM and ARVC is more variable with the average age of onset occurring in adulthood. In addition, there is currently no available treatment to prevent or delay disease onset. Benefits of predictive genetic testing for these conditions are (1) personal- reducing stress and anxiety for children found not to inherit the familial cardiac variant; (2) practical- determining who requires regular cardiovascular screening; and (3) circumstantial- providing an opportunity to steer children away from competitive sport and avoid the harms that come with disqualification of sport at an older age.

Published guidelines are also inconsistent leading to further variability. These guidelines are based mainly on expert opinion due to limited evidence on the topic. The European Society of Human Genetics and Human Genetics Society of Australasia state that predictive genetic testing should be offered at the age a condition is predicted to present and when medical intervention is available (Borry et al, 2006; HGSA, 2017). This perspective is reflected in the European Society of Cardiology's position statement and the Australian/New Zealand guideline for cardiomyopathies which suggest that predictive genetic testing be deferred until 10 to 12 years of age (Charron et al, 2010; Ingles et al, 2011). In comparison, the North American approach is more relaxed and the American Society of Human Genetics suggests deferring to parents in the presence of clinical uncertainty (Botkin et al, 2015). The European and Australian groups place greater emphasis on the principle of autonomy whereas the North American group acknowledges that there may be non-medical benefits of predictive genetics testing.

Implications for Clinical Practice

Genetic counsellors work with families to help them better understand the risks and benefits of predictive genetic testing. They strive to aid families in making a decision around testing that is consistent with their personal and family values. As differing views were observed among families we surveyed, I believe that a comprehensive genetic counselling session should include an in-depth discussion of the family's perceived risk of their child developing the condition, the potential for increased anxiety for both the child and parents, and the family's rationale or motivation for testing.

To further promote the provision of consistent, family centred care, I also propose the development of a cardiac predictive genetic testing decision aid. Decision aids have proven to be a valuable tool for healthcare professionals in supporting both family

centered care and shared decision making in situations where there is not an obvious choice (Legare et al, 2016). Decision aids nicely complement genetic counselling by incorporating personal values into the decision making process.

Future Research

Based on the variability observed among published guidelines, genetic counsellors' practice and families' views, more research is required to better understand the impact of predictive genetic testing at different points in childhood. This requires a longitudinal examination of children who undergo predictive genetic testing at different ages. The approach should focus on potential benefits and concerns raised by families including the impact of predictive genetic testing on health outcomes, quality of life, adjustment, stigmatization, anxiety/worry, and discrimination (career and insurance). Published research on the potential benefits and harms of cardiac predictive genetics testing is currently limited to one small prospective study (n=21) involving adults at risk for a variety of different cardiac conditions and qualitative studies which have mainly focused on the parent's perspective of how a child's diagnosis impacts their well-being (Ingles et al, 2012; Geelen et al, 2011; Lim et al, 2017). Additional research from the child's/adolescent's perspective would provide further insight into the effects of predictive genetic testing.

Families and genetic counsellors both report using family history as a tool to guide when testing is deemed appropriate. Risk stratification based on a specific genetic diagnosis is currently available for only a limited number of families (i.e. TMEM43 c.1073C>T carriers and carriers of multiple variants) (Ingles et al, 2005; Hodgkinson et al, 2016; Calkins et al, 2017). A targeted management approach is needed that is related to the specific natural history of each variant. More research is required to better define the age related penetrance based on the gene, variant, and personal characteristics of the individual (i.e. sex). Large national registries collecting data in a prospective manner will help to clarify some of these questions. However, meta-analysis of international registries is likely required due to the rarity of many of the specific genetic variants and the multitude of potential confounders.

Review and Revision of Guidelines

Many families in our survey expressed a strong desire to initiate predictive genetic testing at a young age (<5 years of age) for children *at risk* of an inherited cardiomyopathy (HCM and ARVC). This perspective is in opposition to the European

and Australian/New Zealand position statement/guideline (Charron et al, 2010; Ingles et al, 2011). Greater variability in age of onset has also, more recently, been reported for both HCM and ARVC (Ackerman et al, 2002; Deshpande et al, 2016; Maurizi et al, 2018). As such the Heart Failure Society and the American College of Medical Genetics now recommend at least one cardiac evaluation prior to 5 years of age for first degree relatives of an individual with one of these diagnoses (Hershberger et al, 2018). This further supports offering predictive genetic testing at an earlier age for HCM and ARVC. Consideration should be given to review and revision of guidelines pertaining to predictive genetic testing for cardiomyopathies in order to reflect the family's perspective and current evidence.

6.2 Variability in physical activity recommendations

We found that the physical activity recommendations provided for individuals diagnosed with LQTS, CPVT, HCM or ARVC varied among a group pediatric electrophysiologists. Although the majority of respondents in our study restrict phenotype positive individuals from competitive sport, recommendations varied more with regard to restriction from other behaviors such as endurance activities. In addition, approximately 50% of respondents in our study restrict phenotype negative individuals from competitive sport, across all conditions. Review of pediatric cardiology charts in Alberta revealed similar findings with 80% of phenotype positive children being prescribed some level of physical activity restriction whereas only 37% of phenotype negative individuals being given similar restriction. We found a trend towards more active physicians being less likely to restrict patients diagnosed with an inherited arrhythmia or cardiomyopathy. This likely points towards the active physicians perceiving greater physical and psychological benefits from physical activity and sport participation. There are likely other personal factors that influence recommendations including physician experience with having a patient suffer a SCA while participating in physical activity.

Variability in physical activity recommendations reflect inconsistent professional guidelines which have been developed based on limited research. The European Society of Cardiology (ESC) consensus document is more conservative and is largely influenced by data originating from the introduction of an Italian law, in 1982, requiring annual medical assessments (including an ECG) for all athletes participating in official competitive sporting events (Charron et al, 2010; Corrado et al, 2006). Through disqualification of athletes diagnosed with a cardiovascular abnormality, this program

reportedly led to a significant decrease in athlete deaths. It is questionable whether the data from this study can be generalized to other parts of the world. The incidence of SCA during the pre-screening time period, in the described region of Italy, was significantly higher (2.1/year) compared to the incidence reported in a similar sized region in the United States (0.96/year) over the same time period (Maron et al, 2009). In addition, the incidence of ARVC is significantly higher in Italy compared to other parts of the world with approximately a quarter of the athlete deaths in the Italian study being attributed to this diagnosis (Corrado et al, 2006).

The scientific statement by the American Heart Association and American College of Cardiology (AHA/ACC) is more liberal with no restrictions for phenotype negative individuals or for individuals with LQTS who have been stable on beta blocker therapy for a minimum of 3 months (Maron et al, 2015). These guidelines are based on data that suggest that the overall risk of SCA is low, particularly for these specific patient populations. They reference data by Johnson et al, who described the experience of a cohort of 353 individuals (6-40 years of age) over an average follow-up period of 5 years (2013). In this cohort, of 130 individuals who remained involved in competitive sport (60 phenotype positive and 70 phenotype negative), only one experienced sport related cardiac events. They highlight that this individual had poor compliance with beta blocker therapy. A low risk (0.03-0.1%/ year) is also described for the HCM population based on the low frequency of athlete deaths attributed to HCM and the overall high prevalence of HCM (Maron et al, 2009; Harmon et al, 2014). Our data further supports a low risk as no cardiac events were observed during an average follow-up period of 3.9 ± 2.3 years in our cohort of 109 children diagnosed with LQTS, CPVT, HCM or ARVC, regardless of participation in sport. The most convincing argument against this more relaxed approach it that SCD is so tragic and finite.

More evidence has become available over the last few years regarding the link between physical activity, and penetrance, severity and risk of arrhythmogenic events for patients with ARVC (James et al, 2013; Saberniak et al, 2014). Although physical activity recommendations are not directly addressed in the ESC and AHA/ACC consensus/scientific statements, the International Task Force has indicated that restriction from competitive sports and endurance sports is recommended for phenotype positive ARVC patients and should be considered for phenotype negative ARVC patients (Corrado et al, 2015). Only 55% of pediatric electrophysiologists in our survey reported

restricting phenotype negative ARVC patients from competitive sport. In addition, review of pediatric cardiology charts in Alberta revealed that only 4 of 8 ARVC patients were told to avoid competitive sports or endurance activities. This may reflect a natural delay in translation of research into clinical practices.

Finally, many physicians restrict patients from competitive sport, indicating that recreational sport is acceptable (Maron and Zipes, 2005). We found that between 38% (physician report) and 54% (parent report) of children diagnosed with LQTS, CPVT, HCM or ARVC continue to participate in sports with a moderate or high dynamic component. Many of these sports likely straddle the definitions of competitive and recreational sports, consisting of systematic training and competition against others but in a more relaxed setting with less pressure to perform. Using wearable accelerometers for a period of one week, we found that the average time that our cohort was involved in MVPA was significantly less than the general pediatric population suggesting that as a whole, the cohort is likely reducing the intensity at which they are participating in sport.

Implications for Clinical Practice

In light of the differing views, two counselling approaches may be considered depending on one's perspective about physical activity restriction: shared decision making or motivational interviewing.

1. Shared decision making: One may believe that in the face of limited evidence, a shared decision making model is most appropriate. This approach involves review of the risks attributed to participation in physical activity as well as the benefits of physical activity. The process involves the integration of current evidence, and both the physician's potential biases and the family's values around the importance of physical activity for the overall well-being of the child. Appropriate time should be allotted to permit an in depth discussion including the voice of the child (age dependent). For families who choose to enrol their child(ren) in sport, emphasis should be placed on additional measures that can be taken to further protect the child during sport involvement such as compliance with medication, adequate hydration, temperate environmental conditions, CPR training and availability of a portable AED.

2. Motivational interviewing: In contrast, one may believe that in the presence of limited information regarding what is considered a safe level of physical activity, restriction from sport is the most appropriate advice. In this situation, motivational interviewing may be considered to assist the family in successfully achieving what is viewed as the safest

outcome. Motivational interviewing involves 4 key steps (1) engaging- establishing a relationship with the patient; (2) focusing- identifying goals; (3) provoking- exploring the patient's motivations for change; and (4) planning- working with the patient to develop a plan of action to achieve their goal (Zomahoun et al, 2017). This process has been shown to significantly improve the rate of behavior change and is highly dependent on working with the patient's motivations and ambivalence for changing their behavior (Lundahl et al, 2013). Motivational interviewing can be used to improve compliance with medication and encourage regular participation in low- to moderate- intensity physical activity. Accelerometers and heart rate monitors may also be useful tools to help families appreciate the various intensities of physical activities and how the body responds.

Future Research

The variability in physical activity recommendations relates to a limited understanding of the risk of an arrhythmogenic event during physical activity. Due to the rarity of these conditions, large multisite studies are required to clarify the risks associated with various forms and intensities of physical activity. Further, risk stratification needs to be refined based on the role of specific genes/genetic variants, demographics factors and cardiac findings. Currently, there is evidence to suggest that individuals who carry a KCNQ1 variant have a higher risk of an arrhythmogenic event during physical activity compared to variants in other LQTS genes (Schwartz et al, 2001). There are likely additional genes and genetic variants associated with a higher risk of SCA induced by vigorous-intensity physical activity.

Ideally, a randomized clinical trial would be performed to address these questions. However, due to the ethical challenges of this study design in the face of current knowledge, a large prospective observational study called LIVE- LQTS/HCM is currently underway to help shed some light on this topic. This study is funded by the National Institute of Health in the United States. The primary goal is to identify the risk of death, cardiac arrest, ventricular arrhythmias, or syncope in individuals with LQTS or HCM who are participating in various intensities of physical activity over a 3 year period (https://clinicaltrials.gov/ct2/show/NCT02549664). Similar studies are needed to address the same questions for patients with CPVT and ARVC.

Review and Revision of Guidelines

In the presence of inconsistent guidelines, healthcare professional's personal biases have the potential to influence management recommendations. Once more research becomes available, an effort should be made to review published guidelines with the goal of creating consistent evidence based international guidelines. This is likely required before consistent practice will be seen.

6.3 Vulnerable subpopulations

Our chart review and cohort study examining children diagnosed with LQTS, CPVT, HCM or ARVC found that diagnosis and management had minimal impact on the daily lives of many of the children. They felt well, continued to be active and had a high quality of life. In contrast, we identified 2 subpopulations of children with lower physical and psychosocial HRQL scores: (1) children who were obese, and (2) children who had to modify their physical activity because of their cardiac diagnosis. Specific strategies should be developed to identify these vulnerable children and address their risk factors.

6.3.1 Subpopulation #1: Children who are obese

Similar to 12% of the Canadian pediatric population, we found that 12% (n=12/100) of children (5-21 years) diagnosed with LQTS, CPVT, HCM or ARVC in our chart review and 14% (n=5/35) of children (8-17 years) in our cohort study had BMI scores consistent with obesity (≥95th percentile) (Roberts et al, 2012). We also found that children in the cohort study were involved in significantly less MVPA per day compared to the general population. Decreased MVPA during childhood and adolescence has the potential to lead to exaggerated obesity rates in adults diagnosed with an inherited arrhythmia or cardiomyopathy. This is supported by Reineck et al (2013) who reported obesity rates between 40% and 55% for adult HCM patients compared to 36% for the general population. In addition, Olivotto et al (2013) found that obesity was correlated with a 120% increase in left ventricular index mass when compared to HCM patients with a normal BMI score. Due to the cross sectional nature of the Olivotto study, it is unclear if progressive HCM led to individuals being obese or if being obese resulted in the progression of HCM. Regardless, these studies highlight the concern that obesity may impact these populations to an even greater extent with age.

We found that obesity was a strong predictor of decreased physical and psychosocial HRQL scores for children diagnosed with an inherited arrhythmia or cardiomyopathy which is similar to what has been reported in the general population (Varni et al, 2007). Research in the general population has also found a strong link between obesity and

higher rates of type 2 diabetes, hypertension, coronary heart disease, clinical depression and all-cause mortality (Nocon et al, 2008; Penedo and Dahn, 2005; Sigal et al, 2018; Andersen et al, 2010; Engeland et al, 2003). Obesity is, therefore, a considerable risk factor for poor health outcomes later in life for children with an inherited arrhythmia or cardiomyopathy.

Implications for Clinical Practice

Management of obesity involves being mindful of caloric intake, making healthy food choices, and being more active. Early identification is key and BMI is an inexpensive and easy screening tool to recognize *at risk* children and to monitor weight status overtime. It is concerning that in our survey of pediatric electrophysiologists, 22% of respondents rarely or never assess BMI and 42% rarely or never discuss the option of dietary counselling. Similarly, in our chart review, concerns relating to weight status were only specifically addressed in the charts of 21% (n=7/34) of children who were overweight or obese. BMI scores should be calculated and reviewed at each visit and concerns related to weights status or significantly weight gain should be promptly addressed.

Management of obesity for children with an inherited arrhythmia or cardiomyopathy has added challenges in the presence of physical activity restriction. A more aggressive dietary approach may be required with encouragement of increased involvement in low- to moderate- intensity physical activity. This requires timely access to qualified specialists familiar with the challenges faced by this patient population. Management of obesity during childhood is key to protect this patient population from co-morbidities later in life as most obese children go on to become obese adults (Field, Cook, and Gillman 2005).

Future Research

Future research should include a prospective, longitudinal assessment of BMI and physical activity as children transition to adulthood. This would help clarify the causal relationship between decreased physical activity and obesity and the relationship between obesity and disease progression. It will also be important to evaluate the incidence of comorbidities such as diabetes and coronary heart disease in this adult population. National registries may be useful in addressing these questions.

The effectiveness of management interventions should also be assessed in this patient population using a systematic approach. Multi-site randomized control trials would be useful comparing the impact of no intervention, traditional dietary counselling, and the introduction of a personalized physical activity program in managing weight and physical activity levels for children diagnosed with an inherited arrhythmia or cardiomyopathy.

6.3.2 Subpopulation #2: Children who change their physical activity because of their diagnosis

Half of the children diagnosed with LQTS, CPVT, HCM or ARVC in our cohort study reportedly changed their physical activity in some way because of their diagnosis. Changes were described as discontinuing participation in sports, modifying the intensity level at which they participated, and reducing additional risk factors. Change to physical activity was further reflected by the finding that the cohort, as a whole, was involved in less MVPA compared to normative data. These results provide insight into how families are translating physical activity recommendations into real life in an attempt to limit the risk of an arrhythmogenic event for their child. As additional precautions, 83% of the families had CPR training and 33% purchased a portable AED.

Competitive sport participation was previously evaluated in a group of adolescents and young adults diagnosed with LQTS by Johnson et al (2013) They found that of individuals involved in competitive sport, 17% (n=27/157) chose to discontinue participation following their diagnosis. For the 87% of athletes who chose to continue to take part in competitive sport, the medical team recommended a number of precautions including ensuring proper hydration, replenishing electrolytes and minimising elevation in core body temperature. They also recommended that athletes carry a portable AED as part of their sports gear. They did not report the proportion of families that followed through with these recommendations.

We found that children who changed their physical activity had lower HRQL scores and found it more difficult and upsetting to adapt to physical activity recommendations. These findings are consistent with results of a qualitative study by Asif et al (2015)who interviewed 25 athletes who were disqualified from sport due to a cardiac diagnosis. A number of the athletes in this study stopped participating at a competitive level but continued to take part at a recreational level. The authors describe 4 stages of adjustment that the athletes transitioned through: (1) immediate reactions and challenge to athlete identify (2) grief/coping (3) adaptation, and (4) acceptance. Adjustment time

was negatively influenced by playing at a higher level of competition and by complete arrest of playing the sport. They describe psychological distress related to losing a natural coping mechanism and having their social networks disrupted. Similar themes were described by Luiten et al (2016)based on a survey of adult athletes regarding the impact of exercise restriction. Respondents reported a decrease in the time they spent involved in exercising and identified less as an athlete following their diagnosis. They also reported long term weight gain and anxiety about exercising safely. Avoidance of exercise completely was deemed detrimental to their coping efforts.

Clinical Implications

These findings have several implications on clinical practice for the medical team.

1) Counselling about physical activity recommendations should include a conversation about the child's interest in sport, the families understanding of the recommendations, how the recommendations would translate into real life for the child and how they would impact the child's quality of life. An athlete in the study by Asif et al (2015) reported that "physicians were unclear about activity restrictions…. Simply telling athletes that they could not compete or that they had to monitor their own symptoms for over-exertion was not successful". My proposed approach is consistent with a model described by Sweeting et al (2016) which is based on clinical factors (disease severity, family history, ICD placement, genetic variant, phenotype positive vs negative); exercise factors (intensity, frequency and duration, sport; health and social benefits); adverse clinical outcomes (SCD, ICD shocks, psychological trauma); and personal factors (patient preference, quality of life, and psychosocial impact..

2) Children and adolescents that require significant modifications to their behavior (i.e. disqualification from sport and those attempting to participation at a lower intensity) may benefit from psychological counselling. A psychologist could normalize the reaction these children are experiencing, assist them with developing strategies to deal with anxiety and support them through the grieving process. Connecting children directly or through support groups such as patient/family forums, would allow them to learn from one another and could provide them with a new support system at a time when they may feel isolated and alone.

3) Older age (≥7 years) at diagnosis was associated with a larger impact on changing physical activity because of one's diagnosis and worse adaptation to physical activity recommendations. The negative impact of changing one's behaviour was previously

described by a group of adults diagnosed with HCM in a qualitative study by Bonner et al (2018). They reported that a genetic diagnosis had a higher impact when an individual had to decrease their physical activity and a lower impact when an individual was not very physically active. Further, a respondent in a study by Ormondroyd et al (2014) stated that if a genetic diagnosis was made at an earlier age, they may have altered their choice of activities while growing up. This would ultimately avoid the impact of dramatic changes later in life. These findings support offering predictive genetic testing at an early age to allow children more time to adapt to their diagnosis before their health is impacted. Parents should be counselled about the value of encouraging a range of both physical and non-physical interest for *at risk* children from a young age. This would allow children to develop a secondary support system in case their condition progressed and they had to modify their physical activity. Early diagnosis of ARVC may also lead parent to steer their carrier children away from vigorous-intensity physical activity. Limiting the time involved in MVPA during childhood and adolescence could potentially decrease penetrance or severity of the condition (James et al, 2013; Saberniak et al, 2014).

In summary, a multidisciplinary team approach is key to help this population of children better adjust to their diagnosis. Screening tools should be in place to identify children *at risk* for poor physical and psychosocial outcomes and care should be personalized based on the needs of each child.

Future Research

There are several avenues for further research in this area. Our assessment of how children changed their physical activity based on their cardiac diagnosis was limited to single open ended questions. A larger qualitative study is needed to further explore how children and families are translating physical activity recommendations into real life. Our cohort was also heterogeneous with regard to children who were phenotype positive and phenotype negative. Evaluation of a larger group of genotype positive/phenotype negative individuals would help shed light on the impact of a genetic diagnosis on well-being. Finally, it is important to ask families how the medical team can better support them and to evaluate the effectiveness of interventions such as psychological counselling and connecting patients either directing or through patient organizations.

6.4 Overall Conclusion

A number of key findings were identified from studies described in this dissertation. Variability in practice and perspectives emphasize that predictive genetic testing and physical activity recommendations are likely patient specific and dependent on many interrelated factors. More research is required in the field. Although many children adapt well to their diagnosis, there are subpopulations of vulnerable children. The medical team must continually strive to stay abreast of the latest evidence, listen to the family's perspective, work with families to develop the best care plan for each child and closely monitor the well-being of children over time.

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Appendix 1: Questionnaire assessing physical activity and beta blocker therapy recommendations in inherited arrhythmogenic conditions

We invite you to participate in a research study entitled **"Diagnosis and Management of Familial Arrhythmias and Cardiomyopathies"** which involves a survey to assess current practices regarding the diagnosis and management of certain familial arrhythmias and cardiomyopathies. The survey takes 10 minutes or less to complete.

Significant advances have been made over the last few years regarding the identification of genetic causes for familial arrhythmias and cardiomyopathies. This has led to 2 populations of patients: patients who are **genotype positive/phenotype positive and patients who are genotype positive/phenotype negative** . We aim to assess the utilization of genetic testing among cardiologists and determine how these 2 populations are currently being managed with regard to exercise restrictions and medication. We also hope to identify factors that influence cardiologist's management decisions.

This study has been reviewed by the Research Ethics Board at the University of Alberta. If you have any questions regarding one's rights as a research participant, please feel free to contact the University of Alberta Research office at 780-492-2615. Questions about the study itself can be directed to Susan Christian at smc12@ualberta.ca or 780-407-1015.

By clicking **next** you are agreeing to participate in the research.

Genetic Testing

1. Which statement best describes your view on genetic testing for patients who, clinically, are thought to have the following phenotype: (Check all that apply)

	Long QT syndrome (LQT)	Catecholaminergic polymorphic ventricular tachycardia (CPVT)	Hypertrophic Cardiomyopathy (HCM)	Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)
I do not think that there is any value in genetic testing	☐	☐	☐	☐
I think that genetic testing should be offered in specific situations	☐	☐	☐	☐
I think that genetic testing should be offered to all patients	☐	☐	☐	☐
I have not seen patients with this condition	☐	☐	☐	☐

2. What factors influence your decision regarding genetic testing? (Check all that apply)

	LQT	CPVT	HCM	ARVC
Presence of at risk family members	☐	☐	☐	☐
Genotype specific prognostic information	☐	☐	☐	☐
Certainty of diagnosis	☐	☐	☐	☐
Funding	☐	☐	☐	☐

Other (please specify)

3. If/when you want genetic testing performed on a patient, you:

- ◯ Organize testing through cardiology
- ◯ Refer to a genetic specialist
- ◯ Organize testing as part of a multidisciplinary clinic (includes genetics)

Other (please specify)

4. What guideline do you base your decisions on regarding genetic testing?

- ☐ Canadian Cardiovascular Society/Canadian Heart Rhythm Society joint position paper
- ☐ Heart Rhythm Society/European Heart Rhythm Association Consensus Statement
- ☐ None

Other (please specify)

Recommendations for Physical Activity

5. In Phenotype Positive/ Genotype Positive patients without an implantable cardioverter defibrillator (ICD), which statement(s) best describes your exercise recommendation(s): (Check all that apply)

	LQT1	LQT2	LQT3	CPVT	HCM	ARVC
Unrestricted Physical Activity	☐	☐	☐	☐	☐	☐
No Competitive Sports (team or individual)	☐	☐	☐	☐	☐	☐
No Endurance Activities (i.e. distance running or cycling)	☐	☐	☐	☐	☐	☐
No Swimming	☐	☐	☐	☐	☐	☐
No Weight Training (low repetition, high weight)	☐	☐	☐	☐	☐	☐
No Recreational Sports (i.e. school gym class)	☐	☐	☐	☐	☐	☐
I have not seen patients with this condition	☐	☐	☐	☐	☐	☐

6. In Phenotype Negative/ Genotype Positive patients without an ICD, which statement(s) best describes your exercise recommendation(s): (Check all that apply)

	LQT1	LQT2	LQT3	CPVT	HCM	ARVC
Unrestricted Physical Activity	☐	☐	☐	☐	☐	☐
No Competitive Sports (team or individual)	☐	☐	☐	☐	☐	☐
No Endurance Activities (i.e. distance running or cycling)	☐	☐	☐	☐	☐	☐
No Swimming	☐	☐	☐	☐	☐	☐
No Weight Training (low repetition, high weight)	☐	☐	☐	☐	☐	☐
No Recreational Sports (i.e. school gym class)	☐	☐	☐	☐	☐	☐
I have not seen patients with this condition	☐	☐	☐	☐	☐	☐

7. What factor(s) do you consider when making exercise recommendations? (Check all that apply)

- [ ] Age of patient
- [ ] Sex of patient
- [ ] Current level of physical activity
- [ ] History of syncope
- [ ] History of palpitations
- [ ] Family history of sudden cardiac death
- [ ] Beta blocker treatment
- [ ] Presence of an ICD
- [ ] ECG/Echo findings
- [ ] Genetic result

Other (please specify)

8. Which guidelines do you base your recommendations for physical activity on? (Check all that apply)

- [ ] Bethesda Conference #36 Guidelines
- [ ] European Society of Cardiology Guidelines
- [ ] None

Other (please specify)

9. How often do you discuss the option of dietary counseling with your patients and/or their parents?

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

10. How often do you assess body mass index for your patients?

- ◯ Never
- ◯ Rarely
- ◯ Sometimes
- ◯ Often
- ◯ Always

11. Who do you feel should be responsible for the disqualification of an athlete from competitive sport?

- ◯ The athlete's cardiologist
- ◯ The sporting organization
- ◯ The athlete (or parent if athlete is a minor)

Other (please specify)

Beta-Blocker Treatment

12. In Phenotype Positive/Genotype Positive patients, which statement best describes your approach regarding prescription of beta-blockers?

	LQT 1	LQT 2	LQT 3	CPVT	HCM	ARVC
I do not discuss	☐	☐	☐	☐	☐	☐
I discuss as an option for some patients	☐	☐	☐	☐	☐	☐
I discuss as an option for all patients	☐	☐	☐	☐	☐	☐
I have not seen patients with this condition	☐	☐	☐	☐	☐	☐

13. In Phenotype Negative/ Genotype Positive patients, which statement best describes your approach regarding prescription of beta-blockers?

	LQT 1	LQT 2	LQT 3	CPVT	HCM	ARVC
I do not discuss	☐	☐	☐	☐	☐	☐
I discuss as an option for some patients	☐	☐	☐	☐	☐	☐
I discuss as an option for all patients	☐	☐	☐	☐	☐	☐
I have not seen patients with this condition	☐	☐	☐	☐	☐	☐

Demographics

14. How many total patients do you see per month with LQT, HCM, ARVC, or CPVT

- ◯ <1
- ◯ 1-5
- ◯ 5-10
- ◯ >10

15. What is your main sub-specialty?

- ◯ Adult General Cardiology
- ◯ Adult Electrophysiology
- ◯ Pediatric General Cardiology
- ◯ Pediatric Electrophysiology

Other (please specify)

16. How many years have you been practicing in Cardiology?

- ◯ <1 yr
- ◯ 1-5 yrs
- ◯ 5-10 yrs
- ◯ >10 years

17. Are you:

- ◯ Male
- ◯ Female

18. How often did you participate in active sports or vigorous physical activity long enough to get sweaty, during leisure time within the past four months?

- ◯ Not at all
- ◯ Less than once a month
- ◯ About once a month
- ◯ About 2 or 3 times a month
- ◯ About 1 to 2 times a week
- ◯ 3 or more times a week

19. When you were an adolescent (i.e. 12-17 years), how often did you participate in active sports or vigorous physical activity long enough to get sweaty, during leisure time?

- ◯ Not at all
- ◯ Less than once a month
- ◯ About once a month
- ◯ About 2 or 3 times a month
- ◯ About 1 to 2 times a week
- ◯ 3 or more times a week

20. What Country do you currently practice in?

- ◯ Canada
- ◯ United States
- ◯ Other

Other (please specify)

Demographics

21. What province do you currently practice in?

- ◯ British Columbia
- ◯ Alberta
- ◯ Saskatchewan
- ◯ Manitoba
- ◯ Ontario
- ◯ Quebec
- ◯ Nova Scotia
- ◯ New Brunswick
- ◯ Prince Edwards Island
- ◯ Newfoundland
- ◯ Yukon
- ◯ Northwest Territories
- ◯ Nunavat

Appendix 2: Questionnaire assessing practice of an international group of genetic counsellors on when to offer predictive genetic testing to children at risk of an inherited arrhythmia or cardiomyopathy

Presymptomatic genetic testing for children at risk for inherited arrhythmias and cardiomyopathies

We invite you to participate in a short survey titled "Presymptomatic genetic testing for children at risk for an inherited arrhythmia or cardiomyopathy" . The survey takes approximately 5 minutes to complete.

Significant advances have been made over the last few years regarding the identification of genetic causes for familial arrhythmias and cardiomyopathies. We would like to assess the current practices of genetic counselors with regard to offering presymptomatic genetic testing and referral to cardiology for at risk children. There are no direct benefit to participants.

The survey is anonymous and no personal identifiers or IP addresses are being collected. This survey is being hosted by Survey Monkey and involves a secure, encrypted connection. You should know that while we will keep the information you provide confidential, under the US privacy laws, the government has the right to access all information held in electronic databases.

This study has been reviewed by the Research Ethics Board at the University of Alberta. If you have any questions regarding one's rights as a research participant, please feel free to contact the University of Alberta Research office at 780-492-2615. Questions about the study itself can be directed to Susan Christian at smc12@ualberta.ca or 780-407-1015.

Consent is implied by completing and submitting the survey.

Presymptomatic genetic testing for children at risk for inherited arrhythmias and cardiomyopathies

1. At what age do you think asymptomatic children at 50% risk for the following inherited arrhythmia or cardiomyopathy should be **offered presymptomatic genetic testing**?

	0- 5 years	6-9 years	10-15 years	16-18 years	> 18 years
Long QT syndrome (LQTS)	☐	☐	☐	☐	☐
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	☐	☐	☐	☐	☐
Hypertrophic cardiomyopathy (HCM)	☐	☐	☐	☐	☐
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	☐	☐	☐	☐	☐

2. Why?

Presymptomatic genetic testing for children at risk for inherited arrhythmias and cardiomyopathies

3. At what age do you think asymptomatic children at 50% risk for the following inherited arrhythmia or cardiomyopathy should be **offered their first cardiac evaluation**?

	0- 5 years	6-9 years	10-15 years	16-18 years	> 18 years
Long QT syndrome (LQTS)	☐	☐	☐	☐	☐
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	☐	☐	☐	☐	☐
Hypertrophic cardiomyopathy (HCM)	☐	☐	☐	☐	☐
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	☐	☐	☐	☐	☐

4. Why?

Presymptomatic genetic testing for children at risk for inherited arrhythmias and cardiomyopathies

5. In what country do you currently reside?

- ◯ United States
- ◯ Canada

Other (please specify)

6. Are you male or female?

- ◯ Male
- ◯ Female

7. How long have you been practicing in cardiac genetics?

- ◯ 0-2 years
- ◯ 3-5 years
- ◯ 6-10 years
- ◯ >10 years

Presymptomatic genetic testing for children at risk for inherited arrhythmias and cardiomyopathies

8. Where do you practice?

- ☐ In a Medical Genetics Clinic
- ☐ In a Cardiology Clinic
- ☐ As part of a multidisciplinary clinic

Other (please specify)

9. Please mark all patient populations you see?

	Pediatric	Adult
Long QT syndrome (LQTS)	☐	☐
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	☐	☐
Hypertrophic Cardiomyopathy (HCM)	☐	☐
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	☐	☐

10. Additional comments?

Appendix 3: Questionnaire assessing families' perspectives on when to offer predictive genetic testing to children at risk of an inherited arrhythmia or cardiomyopathy

Predictive genetic testing for children at risk of an inherited heart condition- What do families think?

We are looking for individuals over 18 years of age who have or have a partner with long QT syndrome, hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC) where a genetic cause has been found.

We want to know at what age you think that genetic testing should be offered to a healthy child. We also want to better understand what factors you would consider when deciding when to test a healthy child.

You will not directly benefit by completing the survey, however we hope that information gathered will help inform healthcare providers on when testing should be offered to children. There are no known risks or discomforts associated with this survey. No personal identifiers or IP addresses are being collected. This survey is being hosted by REDCap. This database has a secure, encrypted connection. Data is stored on a secure server at the University of Alberta.

Taking part in this survey is your choice. You can close the survey at any time. However after you click submit, you will not be able to withdraw your survey from the study.

This study has been reviewed by the Research Ethics Board at the University of Alberta. If you have any questions about your rights to take part in the study, please contact the University of Alberta Research office at 780-492-2615. If you have questions about the study please contact Susan Christian at smc12@ualberta.ca or 780-407-1015.

By clicking, "Next Page" you are agreeing to take part in the survey.

Sincerely,

Susan Christian, MSc CGC
Genetic Counsellor/ PhD Candidate
Department of Medical Genetics, University of Alberta

Joseph Atallah, MD CM, SM(Epi), FRCPC
Assistant Professor, University of Alberta Division of Pediatric Cardiology
Section of Electrophysiology, Stollery Children's Hospital

Martin Somerville, PhD, FCCMG, FACMG ,
Professor, Department of Medical Genetics, University of Alberta
Medical/Scientific Director, Genetic Laboratory Services, Alberta Health Services

Clinical Information

What heart condition have you or your spouse been diagnosed with?

◯ Long QT syndrome
◯ Hypertrophic cardiomyopathy
◯ Arrhythmogenic right ventricular cardiomyopathy

Who is affected with this heart condition?

◯ You
◯ Your partner

How old were you when you were diagnosed with this heart condition?

◯ 0-10 years
◯ 11-20 years
◯ 21-30 years
◯ 31-40 years
◯ 41-50 years
◯ 51-60 years
◯ >60 years

How old was your partner when they were diagnosed with this heart condition?

◯ 0-10 years
◯ 11-20 years
◯ 21-30 years
◯ 31-40 years
◯ 41-50 years
◯ 51-60 years
◯ >60 years

Has a genetic cause been found for your heart condition?

◯ Yes a genetic cause was found
◯ No a genetic cause was not found
◯ Unclear (a genetic change was found but is unclear)
◯ I have not had genetic testing
◯ I am unsure if I have had genetic testing
◯ Other

Please specify

_____

Has a genetic cause been found for your partner's heart condition?

◯ Yes a genetic cause was found
◯ No a genetic cause was not found
◯ Unclear (a genetic change was found but is unclear)
◯ They have not had genetic testing
◯ I am unsure if they have had genetic testing
◯ Other

Please specify

_____

Have you experienced any of the following symptoms due to your heart condition? (check all that apply)

☐ Dizziness
☐ Fainting
☐ Racing heart
☐ Chest pain
☐ Cardiac arrest
☐ None of the above
☐ Other

Please specify

_____

Has your partner experienced any of the following symptoms due to your heart condition? (check all that apply)

☐ Dizziness
☐ Fainting
☐ Racing heart
☐ Chest pain
☐ Cardiac arrest
☐ None of the above
☐ Other

Please specify

_____

Has anyone in your family had a cardiac arrest due to the same heart condition?

◯ No
◯ Yes
◯ Other

Please specify

_____

Please specify their relationship to you and how old they were?

_____

Has anyone in your partner's family had a cardiac arrest due to the same heart condition?

◯ No
◯ Yes
◯ Other

Please specify

_____

Please specify their relationship to your partner and how old they were??

_____

Facts about long QT syndrome:
• Long QT syndrome can present as early as birth but more commonly presents after 8 years of age.
• Children at risk for familial LQTS should be followed by a heart doctor. Genetic testing can identify which children need to be followed and which do not.
• Healthy children found to carry a genetic change in the long QT syndrome gene may be given medication to prevent heart problems. They may also be told not to participate in competitive sports because it can trigger cardiac arrest.
• Testing children when they are young can cause worry and could lead to discrimination later in life with regard to insurance and jobs.
• Testing children when they are young limits their ability to take part in the decision making process.

Facts about hypertrophic cardiomyopathy (HCM):
• HCM can present as early as birth but more commonly presents in teens and adults.
• Children at risk for familial HCM should be followed by a heart doctor starting around 10 years of age. Genetic testing can identify which children need to be followed and which do not.
• Children affected with HCM may be told not to participate in competitive sports because it can trigger cardiac arrest.
• Testing children when they are young can cause worry and could lead to discrimination later in life with regard to insurance and jobs.
• Testing children when they are young limits their ability to take part in the decision making process.

Facts about arrhythmogenic right ventricular cardiomyopathy (ARVC):
• ARVC has been reported in children as young as 4 years of age, however, it more commonly presents in teens and adults.
• Children at risk for familial ARVC should be followed by a heart doctor starting around 10 years of age.
• Genetic testing can identify which children need to be followed and which do not.
• Healthy children found to carry a genetic change may be told not to participate in competitive sports because it can trigger cardiac arrest. Physical activity is also linked to disease progression later in life.
• Testing children when they are young can cause worry and could lead to discrimination later in life with regard to insurance and jobs.
• Testing children when they are young limits their ability to take part in the decision making process.

Do you have biological children?

◯ No
◯ Yes
◯ Other

Please specify

_____

Did any of your children have genetic testing before the age of 18 years?

◯ No
◯ Yes
◯ Genetic testing was not available when my children were under 18 years of age
◯ Other

Please specify

_____

How old were your child(ren) when they were tested? (check all that apply)

☐ 0-5 years
☐ 6-9 years
☐ 10-14 years
☐ 15-17 years
☐ >18 years

Assume that genetic testing is available to identify who in a family is at risk of developing your heart condition. What is the YOUNGEST age that you think a person should be tested?

◯ 0-5 years
◯ 6-9 years
◯ 10-14 years
◯ 15-18 years
◯ >18 years
◯ I do not see value in genetic testing

Predictive genetic testing has pros and cons for children. On a scale of 1 to 5, how important do you feel the following factors are in deciding WHEN to test a healthy child.

1=Not Important and 5=Very Important

	1	2	3	4	5
Determining if a child needs to be followed by a heart doctor.	○	○	○	○	○
Identifying if a child should start taking medication.	○	○	○	○	○
Deciding if a child should play sports.	○	○	○	○	○
Decreasing worry for a child who tests negative.	○	○	○	○	○
Allowing a child to take part in the decision about genetic testing.	○	○	○	○	○
Allowing a child to adjust to their diagnosis before their health is affected.	○	○	○	○	○
Creating worry for a child who tests positive.	○	○	○	○	○
Impacting a child's ability to get insurance when they are older if they test positive.	○	○	○	○	○

Please describe any other factors that you feel are important in deciding when predictive genetic testing should be offered to children.

Demographic Information

Where do you live?

◯ Canada
◯ United States
◯ Other

Please specify

_____

What is your gender?

◯ Male
◯ Female

How old are you?

◯ < 21 years
◯ 21-30 years
◯ 31- 40 years
◯ 41-50 years
◯ 51- 60 years
◯ >60 years

What is the highest level of education you completed?

◯ No formal education
◯ High school
◯ College
◯ Vocational training
◯ Undergraduate studies
◯ Graduate studies (doctor, lawyer, masters degree/PhD)
◯ Other

Please specify

_____

What is the net income in your household before tax?

◯ < $30 000
◯ $30 000-$50 000
◯ $50 000-$75 000
◯ $75 000-$100 000
◯ $100 000- $150 000
◯ >$150 000
◯ I prefer not to answer

Additional comments?

Thank you for taking our survey!

Appendix 4a: University of Alberta consent form for children participating in study assessing the impact of age at diagnosis on physical activity modification and health related quality of lie in children diagnosed with an inherited arrhythmia or cardiomyopathy

UNIVERSITY OF ALBERTA

PARTICIPANT CONSENT FORM

Title of Study: Effect of age of diagnosis of an inherited heart condition on physical activity level and quality of life.

Principal Investigator:	Dr. J. Atallah	t) 780-407-3963
	Dr. M. Somerville	t) 780-407-3635
Study Coordinator:	Susan Christian	t) 780-407-1015

Why is your child being asked to take part in this study?

Your child is being asked to take part in this study because he/she has or is at risk for an inherited heart condition. Before you make a decision a member of the study team will go over this form with you. Please ask questions if you feel anything needs to be made clearer. You will be given a copy of this form.

What is the reason for doing the study?

The purpose of this study is to understand how specific heart conditions affect the physical activity and quality of life of children and teens. An accelerometer will be used to measure physical activity over 7 days. This is a small device that records the amount and level of physical activity someone does. It is worn on a belt during all activities except swimming, bathing, and sleeping. The information from the accelerometer will be compared with an activity journal. Two surveys will look at quality of life. The study team hopes that 50 individuals with an inherited heart condition will take part in the study.

What will you and your child be asked to do?

Your child will be asked to do the following things:

1. Wear an accelerometer for 7 days during all activities except bathing, swimming and sleeping.
2. Fill in an activity journal for 7 days. The journal will include when your child puts on and took off the accelerometer and what activities they did. The journal will take about 5 minutes to fill in at the end of each day.
3. Answer 2 surveys about their quality of life. This will take about 5 minutes to fill in.

Your child's health record will be reviewed to obtain information about their family history, clinical findings, test results, diagnosis, and treatment.

You as the parent/guardian will be asked to do the following things:

1. Help your child fill in an activity journal for 7 days. The journal will include when your child puts on and took off the accelerometer and what activities they did. The journal will take about 5 minutes to fill in at the end of each day.
2. Complete an additional survey about your child, yourself and your family. This will take about 10- 15 minutes to complete.
3. Return the accelerometer, the activity journal and surveys in a postage paid envelope provided.

UNIVERSITY OF ALBERTA

You will receive either an email or phone call immediately before and during the 7 day study period to see if you have any additional questions.

What are the risk and discomforts?
It is not possible to know all of the risks that may happen in a study. The study team have taken all reasonable safeguards to minimize any known risks to study participants.

What are the benefits to me?
After return of the accelerometer, your child will be sent a $10 gift card. Your child is otherwise not expected to benefit from being in this study. This study may help children and teens with these heart conditions in the future by better understanding the pros and cons of testing at different points in childhood.

Do I have to take part in the study?
Being in the study is your and your child's choice. You and your child can change your mind at any time and withdraw from the study by contacting Susan Christian. This will in no way affect the care or treatment that your child is entitled to.

Will you or your child be paid to be in the study?
After return of the accelerometer, your child will be sent a $10 gift card.

Will my information be kept private?
During the study we will be collecting health information about your child. We will do everything we can to make sure that this data is kept private. No data that includes your child's name will be release outside the study team or published by the study team. Sometimes, by law, we may have to release your child's data with his/her name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your child's health data is kept private. By signing this consent you are saying that it is okay for the study team to collect, use and disclose information about your child from their personal health records as described above.

If you provide an email address, you will be contacted by the study team by email during your participation in the study.

After the study is done, we will securely store your child's health information that was collected as part of the study. At the University of Alberta, we keep information stored for a minimum of 5 years after the end of the study.

What if I have question?
If you have any questions about the study now or later, please contact Susan Christian at 780-407-1015.

If you have any questions regarding your child's rights as a study participant, you may contact the Health Research Ethics Board at 780-492-2615. This office has not affiliation with the study investigators.

UNIVERSITY OF ALBERTA

PARTICIPANT CONSENT FORM

Title of Study: Effect of age of diagnosis of an inherited heart condition on physical activity level and quality of life.

Principal Investigator: Dr. J. Atallah t) 780-407-3963
Dr. M. Somerville t) 780-407-3635
Study Coordinator: Susan Christian t) 780-407-1015

	Yes	No
Do you understand that your child has been asked to be in a study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in your child taking part in this study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that your child is free to leave the study at any time, without having to give a reason and without affecting his/her future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your child's records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your child's family doctor that he/she is participating in this study? If so, give his/her name _____	☐	☐

Who explained this study to you?

_____

I agree to take part in this study:

Signature of Parent/Guardian:_____

Printed Name: _____

Date:_____

Signature of Witness _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee_____ Date _____

Appendix 4b: University of Calgary consent form for children participating in study assessing the impact of age at diagnosis on physical activity modification and health related quality of lie in children diagnosed with an inherited arrhythmia or cardiomyopathy

UNIVERSITY OF CALGARY

PARTICIPANT CONSENT FORM

Title of Study: Effect of age of diagnosis of an inherited heart condition on physical activity level and quality of life.

Principal Investigator: Dr. R. Clegg t) 403-955-7858
Study Coordinator: Susan Christian t) 780-407-1015

Why is your child being asked to take part in this study?

Your child is being asked to take part in this study because he/she has or is at risk for an inherited heart condition. Before you make a decision a member of the study team will go over this form with you. Please ask questions if you feel anything needs to be made clearer. You will be given a copy of this form.

What is the reason for doing the study?

The purpose of this study is to understand how specific heart conditions affect the physical activity and quality of life of children and teens. An accelerometer will be used to measure physical activity over 7 days. This is a small device that records the amount and level of physical activity someone does. It is worn on a belt during all activities except swimming, bathing, and sleeping. The information from the accelerometer will be compared with an activity journal. Two surveys will look at quality of life. The study team hopes that 50 individuals with an inherited heart condition will take part in the study.

What will you and your child be asked to do?

Your child will be asked to do the following things:

1. Wear an accelerometer for 7 days during all activities except bathing, swimming and sleeping.
2. Fill in an activity journal for 7 days. The journal will include when your child puts on and took off the accelerometer and what activities they did. The journal will take about 5 minutes to fill in at the end of each day.
3. Answer 2 surveys about their quality of life. This will take about 5 minutes to fill in.

Your child's health record will be reviewed to obtain information about their family history, clinical findings, test results, diagnosis, and treatment.

You as the parent/guardian will be asked to do the following things:

1. Help your child fill in an activity journal for 7 days. The journal will include when your child puts on and took off the accelerometer and what activities they did. The journal will take about 5 minutes to fill in at the end of each day.
2. Complete an additional survey about your child, yourself and your family. This will take about 10- 15 minutes to complete.
3. Return the accelerometer, the activity journal and surveys in a postage paid envelope provided.

You will receive either an email or phone call immediately before and during the 7 day study period to see if you have any additional questions.

UNIVERSITY OF CALGARY

What are the risk and discomforts?

It is not possible to know all of the risks that may happen in a study. The study team have taken all reasonable safeguards to minimize any known risks to study participants.

What are the benefits to me?

After return of the accelerometer, your child will be sent a $10 gift card. Your child is otherwise not expected to benefit from being in this study. This study may help children and teens with these heart conditions in the future by better understanding the pros and cons of testing at different points in childhood.

Do I have to take part in the study?

Being in the study is your and your child's choice. You and your child can change your mind at any time and withdraw from the study by contacting Susan Christian. This will in no way affect the care or treatment that your child is entitled to.

Will you or your child be paid to be in the study?

After return of the accelerometer, your child will be sent a $10 gift card.

Will my information be kept private?

During the study we will be collecting health information about your child. We will do everything we can to make sure that this data is kept private. No data that includes your child's name will be release outside the study team or published by the study team. Sometimes, by law, we may have to release your child's data with his/her name so we cannot guarantee absolute privacy. However, we will make every legal effort to make sure that your child's health data is kept private. By signing this consent you are saying that it is okay for the study team to collect, use and disclose information about your child from their personal health records as described above.

If you provide an email address, you will be contacted by the study team by email during your participation in the study.

After the study is done, we will securely store your child's health information that was collected as part of the study. At the University of Alberta, we keep information stored for a minimum of 5 years after the end of the study.

What if I have question?

If you have any questions about the study now or later, please contact Susan Christian at 780-407-1015.

If you have any questions regarding your child's rights as a study participant, you may contact the Conjoint Health Research Ethics Board, University of Calgary at 403-220-7990. This office has not affiliation with the study investigators.

UNIVERSITY OF CALGARY

PARTICIPANT CONSENT FORM

Title of Study: Effect of age of diagnosis of an inherited heart condition on physical activity level and quality of life.

Principal Investigator: Dr. R. Clegg t) 403-955-7858
Study Coordinator: Susan Christian t) 780-407-1015

	Yes	No
Do you understand that your child has been asked to be in a study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in your child taking part in this study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that your child is free to leave the study at any time, without having to give a reason and without affecting his/her future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your child's records, including personally identifiable health information?	☐	☐
Do you want the investigator(s) to inform your child's family doctor that he/she is participating in this study? If so, give his/her name _____	☐	☐

Who explained this study to you?
_____

Your signature on this form indicates that you have understood to your satisfaction the information regarding your participation in the research project and agree to participate as a participant. In no way does this waive your legal rights nor release the investigators or involved institutions from their legal and professional responsibilities.

Signature of Parent/Guardian:_____

Printed Name: _____

Date:_____

Signature of Witness _____

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of Investigator or Designee_____ Date _____

The University of Calgary Conjoint Health Research Ethics Board has approved this research study.

Appendix 5: Parent questionnaire for study assessing the impact of age at diagnosis on physical activity modification and health related quality of lie in children diagnosed with an inherited arrhythmia or cardiomyopathy

PARTICIPANT GENERAL QUESTIONNAIRE **CODE:**
(to be completed by parent/guardian) **Today's date:**

Thank you for participating in this study looking at the effect of age of diagnosis on physical activity and quality of life. Please answer the following questions the best you can.

1. Does your child participate in gym class? o NO o YES

2. What organized activities (outside of gym class) is your child involved in throughout the year? (eg. soccer, bowling, piano, girl guides)

Activity	**Frequency (times per week)**	**Duration (minutes each time)**	**Length of time (weeks or months per year)**
Example- Swimming	*3 X/ week*	*60 minutes*	*6 months*

3. On a scale of 1 to 5 how much has your child changed his/her physical activity because of his/her heart condition?

1 2 3 4 5

Not at all Partially Completely

If your child has changed their physical activity, please describe how?

_____
_____
_____

4. How old was your child when they were diagnosed with a heart condition

_____

5. Does your child currently take a beta blocker?
   - o No (skip to question 8) o Yes

6. If your child takes a beta blocker, has he/she had any side effects?
   (eg. tiredness, dizziness, recurrent nightmares)
   - o No
   - o Yes- please describe _____

7. If your child takes a beta blocker, during an average week, how many times does he/she forget to take their beta blocker medication?
    - Less than once per month
    - About once per month
    - 1-2 times per week
    - 3 or more times per week

8. What has the heart doctor told you and your child about acceptable physical activity? (Check all that apply)
    - All activities are acceptable
    - Avoid competitive sports (ie. organized sports such as soccer, hockey)
    - Avoid endurance activities (ie. long distance running or cycling)
    - Avoid unsupervised swimming
    - Avoid free weights
    - Avoid all recreational physical activity (including gym class)
    - The heart doctor has not discussed acceptable physical
    - My child is not interested in sports

9. On a scale of 1 to 5 how difficult was it for your children to adjust to the physical activity recommendations?

1	2	3	4	5
Not at all				Very Difficult

10. On a scale of 1 to 5 how upsetting was it for your children to adjust to the physical activity recommendations?

1	2	3	4	5
Not at all				Very Upsetting

11. Does your child own a medical alert bracelet?
    - No
    - Yes

    If yes, how often does your child wear their medical alert bracelet?

    o Never o Sometimes o Usually o Always

12. Does anyone in your family have CPR training?
    - No o Yes – If yes, who? _____

13. Does your family own a portable defibrillator?
    - No o Yes

14. As parents, have either of you been restricted from physical activity due to a heart condition?

Mother:	o No	o Yes
Father:	o No	o Yes

15. How often have you, as parents, participated in active sports or vigorous physical activity long enough to get sweaty, during leisure time within the past four months? (if available)

Mother:

- o Not at all
- o Less than once a month
- o About once a month
- o About 2 or 3 times a month
- o About 1 or 2 times a week
- o 3 or more time a week

Father:

- o Not at all
- o Less than once a month
- o About once a month
- o About 2 or 3 times a month
- o About 1 or 2 times a week
- o 3 or more time a week

16. When you, as parents, were a TEEN (ie. 12- 17 years), how often did you participate in active sports or vigorous physical activity long enough to get sweaty, during leisure time? (if available)

Mother:

- o Not at all
- o Less than once a month
- o About once a month
- o About 2 or 3 times a month
- o About 1 or 2 times a week
- o 3 or more time a week

Father:

- o Not at all
- o Less than once a month
- o About once a month
- o About 2 or 3 times a month
- o About 1 or 2 times a week
- o 3 or more time a week

17. Estimate of height and weight of you as parents (if available):

Mother: Height_____ Weight_____ Father: Height _____Weight _____

18. Occupations of you as parents (if available):

Mother _____ Father_____