Psychometric Testing of Scales Designed to Monitor the Psychosocial Impact of Arrhythmogenic Right Ventricular Cardiomyopathy: A Pilot Study

By

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Abstract

This pilot study validated two psychometric scales, the Psychosocial Adjustment to Hereditary Disease (PAHD) and the Hereditary Diseases and Genetic Testing (HD-GT) scales, for use in the Newfoundland and Labrador Arrhythmogenic Right Ventricular Cardiomyopathy population. Both scales were previously validated in the Newfoundland hereditary non-polyposis colorectal cancer (HNPCC) population.

The target population for this study was individuals born at an *a priori* 50% risk for the *TMEM43* mutation that causes ARVC who had undergone genetic testing. In total, 73 participants returned completed surveys.

Psychometric testing of both scales followed the procedures outlined by Ware and Gandek (1998) and demonstrated satisfactory data quality, reliability and validity. Results indicated potential usefulness in the ARVC population warranting analysis with a larger sample size.

No large-scale differences were found between carriers and non-carriers; however, small differences in particular aspects of psychosocial adjustment based on gender, gender of transmitting parent, and age were found.

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List of Abbreviations

ARVC	
BK	Arrhythmogenic right ventricular cardiomyopathy
CGL	Burden of Knowing
DI	Communication Around Genetic Link
FCGT	Disclosure Issues
GTP	Family Challenges in Genetic Testing
HBOC	Genetic Testing Preparation
HD-GT	Hereditary Breast and Ovarian Cancer
HNPCC	Hereditary Disease and Genetic Testing
IARVC	Hereditary non-polyposis colorectal cancer
ICD	Impact of ARVC
LS	Implantable cardioverter defibrillator
PAHD	Lynch syndrome
SCD	Psychosocial Adjustment to Hereditary Disease
SGTR	Sudden cardiac death
TB	Support with Genetic Testing Results
TMEM43	Transmission Beliefs
UR	Transmembrane protein 43
WTC	Understanding Risk
	Wait Time Concerns

CHAPTER 1

Introduction

In the early 1990s, the human genome project created opportunities for genetic testing for a wide range of hereditary conditions (Rew, 2010). Prior to the advent of genetic testing, an individual could not be diagnosed definitively with a hereditary condition until he or she began to manifest symptoms. Once symptoms appeared, one could undergo clinical testing, but for some hereditary conditions this process was ineffective as the opportunity for treatment had passed. For example, a person with a hereditary cancer syndrome might only become aware of the condition once a late stage tumor was found.

As the field of genomic science evolved, so too did the availability of predictive genetic testing for hereditary conditions (Erskine et al., 2014; Manuel & Brunger, 2014; Smart et al., 1996) . These tests, which can be conducted from a small blood or tissue sample, can provide valuable health information for individuals and families, identify pre-symptomatic individuals, and sometimes improve medical management of the condition (Erskine et al., 2014; Lodder & Bezzina, 2013; Murray, 2012) . Pre-symptomatic or predictive genetic testing does not change the disease course but it allows for a definitive diagnosis prior to the onset of symptoms, when treatment may be more effective.

While there are many potential benefits associated with genetic testing, it is a technology with the potential to cause psychological harm (Rew, 2010). Hereditary conditions are unique in that the individual may be burdened not only by the

condition itself but also by transmission implications (Aatre & Day, 2011) . Families can endure years of speculation, assumptions, and uncertainties associated with the family illness. Within the context of family relationships, the process of predictive genetic testing can be very complex (Ormondroyd, Oates, Parker, Blair, & Watkins, 2014) .

Reasons for seeking or refusing genetic testing are highly variable but certain themes are consistent across the literature. The most common motivator is the need to define one's own risk to protect one's own health and/or the health of children (Aatre & Day, 2011; Erskine et al., 2014; Ormondroyd et al., 2014) . Other common motivators include needing an explanation for a family member's death, needing a definitive diagnosis, guiding medical management, taking control of the future, or pressure from family members or clinicians (Claes, Denayer, Evers-Kiebooms, Boogaerts, & Legius, 2004; Clark et al., 2000; Erskine et al., 2014; Esplen et al., 2007; Satia, McRitchie, Kupper, & Halbert, 2006) . Common reasons for refusing genetic testing include concerns about the effect of the results on other family members, fear of results, misconceptions or lack of knowledge surrounding risk, and not fully understanding the advantages of testing (Erskine et al., 2014).

Many reasons people have to seek or refuse genetic testing are common across a wide range of hereditary conditions. This is likely due to the fact that decisions surrounding genetic testing are made within the context of the family and are not necessarily autonomous. While the literature is lacking in the psychosocial impact of inherited heart conditions, and specifically arrhythmogenic right ventricular cardiomyopathy (ARVC), many of the themes that emerge from

inherited cardiac conditions and inherited cancer studies are related to the effects of genetic testing on the family as a whole. Some of the best-studied hereditary conditions follow an autosomal dominant pattern, meaning that an individual need inherit the defective gene from just one parent to be affected, versus autosomal recessive in which an affected individual inherits the defective gene from both parents. As ARVC follows an autosomal dominant pattern, it is plausible that many of these concepts will be relevant for families affected by ARVC as well.

The idea that decisions about hereditary conditions are made within a social context rather than in isolation may help explain conflicting results in psychosocial studies. While positive genetic test results provide individuals with a sense of closure and control leading to better psychosocial well being, they may also disrupt family relationships and lead to feelings of guilt and anger (Djurdjinovic, 1998; Duncan et al., 2008; Erskine et al., 2014). Similarly, individuals who test negative may be relieved while other individuals may experience a form of survivor's guilt (d'Agincourt-Canning, 2006; Schwartz et al., 2002). In order to properly anticipate and manage the various psychosocial impacts associated with genetic conditions, clinicians and counsellors must understand the social context in which an individual's attitudes are embedded.

There is a conspicuous lack of research specifically focused on the psychosocial impacts of inherited cardiac conditions. With the exception of studies focused on the psychosocial impact of implantable cardioverter defibrillators (ICDs), no research has quantitatively explored the psychosocial burden of living with ARVC.

The purpose of this study is to validate two psychosocial survey tools, originally created for use with families affected by hereditary non-polyposis colorectal cancer (also known as HNPCC or Lynch syndrome (LS)), which is also an autosomal dominant condition. The tools are: 1. the Psychosocial Adjustment to Hereditary Disease (PAHD) Scale, and 2. the Hereditary Diseases and Genetic Testing (HD-GT) Scale (Watkins et al., 2013; Way et al., 2011) . The purpose is to explore whether these tools are valid for use in the Newfoundland ARVC population, as well as to provide support for the results of preliminary qualitative research with ARVC families in the province (Etchegary, Pullman, Simmonds, Young, & Hodgkinson, 2014; Manuel & Brunger, 2014) . If the tools prove to be valid it will allow the use of quantitative scores to determine which, if any, social or clinical factors are related to the psychosocial impact on individuals at risk for ARVC.

Background and Rationale

ARVC is an autosomal dominant condition characterized by fibrofatty infiltration of the myocardium, resulting in life-threatening arrhythmias that may lead to sudden cardiac death (SCD) or biventricular heart failure (K. A. Hodgkinson et al., 2013) . There are currently 11 genes known to be associated with ARVC, each with its own penetrance, expressivity, and disease progression. The subgroup of ARVC being studied here is a particularly lethal genetic subtype of ARVC caused by a missense mutation (which changes the amino acid serine to the amino acid leucine: p.S358L) in transmembrane protein 43 (*TMEM43*) (Christensen, Andersen, Tybjaerg-Hansen, Haunso, & Svendsen, 2011; Merner et al., 2008; Te Riele, Tandri, & Bluemke, 2014) . While other subtypes of ARVC demonstrate reduced penetrance

and variable expressivity, this subtype is distinct in that it is fully penetrant and often lethal in young adults (Merner et al., 2008). The median age of death is 41 years in men and 71 years in women, while the median age at which the condition reaches 100% penetrance is 63 years in men and 76 years in women (Merner et al., 2008). The prevalence of ARVC is estimated to be between 1 in 1000 to 1 in 5000 in the general population; however, due to the founder effect of the island population in the province, the prevalence of ARVC in Newfoundland and Labrador is estimated to be between 1 in 1000 and 1 in 500 (Etchegary et al., 2014; Sen-Chowdhry, Syrris, & McKenna, 2005) . With 24 families known (at the time of writing, and where 'family' can reflect between 500 to 1000 persons in the family tree) to have a history of this particularly lethal subtype, the unusually high prevalence makes ARVC a priority for genetics research in the province.

ARVC and Genetic Testing

Prior to 1998, genetic testing was not available for ARVC (Hodgkinson et al., 2009; Manuel & Brunger, 2014) . Diagnosis was based on family history and clinical manifestations including, but not limited to, ventricular tachycardia, heart failure, or SCD; this method of diagnosis had a sensitivity of less than 20% (K. A. Hodgkinson et al., 2013; Manuel & Brunger, 2014; McKenna et al., 1994) .

As the field of genomics moved forward, this particular subtype of ARVC was linked to the locus 3p25, which allowed clinicians to determine whether a person was high-risk or low-risk via haplotype analysis (Ahmad et al., 1998). Though there remained a theoretical error with this process and it was not possible to completely rule out the possibility of ARVC, a nearly definitive positive diagnosis could be made

(Hodgkinson et al., 2009) . It was later found that the causative gene was present in 100% of those who tested positive for the associated haplotype, therefore confirming the accuracy of haplotype analysis (Hodgkinson et al., 2009)

Direct mutation testing became possible in 2007 with the discovery of the causative gene for this subtype of ARVC (Merner et al., 2008). Merner et al. (2008) found a missense mutation (*p.S358L*) in *TMEM43*, which was present in all symptomatic individuals as well as 28.8% of non-symptomatic individuals. This discovery opened the door for direct mutation analysis using DNA extracted from peripheral lymphocytes (K. A. Hodgkinson et al., 2013) .

Probands, the first individuals in a family diagnosed with an inherited condition, were identified when they presented with symptoms that fit the ARVC diagnostic criteria. Pedigrees were then built from a proband's family history to identify other at-risk relatives. Prior to the advent of genetic testing, this was the only way to determine if an asymptomatic individual was at risk for the condition. Today, individuals identified through the pedigree as being at risk have genetic testing available to them for confirmation. When an affected person is identified, implantation of an ICD may significantly improve life expectancy by increasing the chance of survival during potentially fatal arrhythmias (K. A. Hodgkinson et al., 2005) . Since this subtype of ARVC is fully penetrant, a positive gene test indicates that an individual will eventually show symptoms; however, expressivity is varied, particularly in women. Family history may also influence an individual's decision about when to have children tested for the gene, based on the estimated age of onset

of symptoms. Though the genetic test itself is conclusive, variable expressivity adds an element of uncertainty as the exact symptoms and age of onset can vary.

Psychosocial Implications of Genetic Testing

Research on the psychosocial impact of hereditary disease has been conflicting, especially in terms of the outcomes of genetic testing. However, virtually all authors attribute these differences at least partially to social dynamics. Regardless of how an individual reacts to test results initially, it has been shown that the availability of social support is associated with better psychosocial adjustment over time, an effect that is more pronounced in carriers than non-carriers (Lapointe et al., 2013).

As with any inherited condition, ARVC is embedded in family context. Differing attitudes toward genetic testing have the potential to strain relationships, but conversely, making use of a family support network can bring those dealing with ARVC closer together. Active sharing is a key factor in maintaining close relationships and building social support; therefore, open discussions about genetic information can serve to strengthen family relationships (Lapointe et al., 2013).

For those with weak family relationships, it may be difficult to have open discussions about hereditary disease. The duty to be tested is a consistent theme in genetics research, especially in conditions such as ARVC, where ameliorative treatment is available or children are involved (Aatre & Day, 2011; Erskine et al., 2014; Etchegary et al., 2014; Hodgkinson & Pullman, 2010; Manuel & Brunger, 2014; Pullman & Hodgkinson, 2006) . Due to the nature of hereditary conditions, a

positive test result has implications for the family as a whole. One family member's result has the potential to inadvertently reveal the genetic status of other family members who may have not agreed to testing or could raise issues of adoption or paternity that had not yet been previously discussed (Aatre & Day, 2011) . For close families, the decision to go through with testing and coping with the outcomes is a collaborative process, but for those families with already strained relationships, one family member challenging the autonomy of another serves only to strain those relationships further (Aatre & Day, 2011; Manuel & Brunger, 2014) .

This study represents the first attempt to quantify the level of psychosocial adjustment for individuals at risk for ARVC and to identify potential areas for concern. It is critical for clinicians and genetic counsellors to understand how decisions are made and how family dynamics benefit or harm an individual in order to improve the process of testing and ongoing care. This study may also provide some insight into similarities and differences among various inherited conditions.

Problem Statement

Qualitative studies conducted by the research team as part of a larger project found a number of similarities between ARVC and other inherited conditions in terms of attitudes toward genetic testing and psychosocial adjustment to risk (Etchegary et al., 2014; Manuel & Brunger, 2014) . Consistent with the literature, those at risk for ARVC are driven to genetic testing mainly due to a strong family history of the illness, the availability of a reliable predictive test, and a sense of relational responsibility (Manuel & Brunger, 2014) . Also consistent with the

literature, psychosocial adjustment to ARVC risk is highly dependent on the strength of an individual's social support network.

Due to the similarities between ARVC and other inherited conditions, it is plausible that two psychometric survey tools developed for use in LS families may also be valid in the ARVC population. Two survey tools, the PAHD scale and the HD-GT scale, were modified for use in this study. Using the final validated version of the survey for LS, several items were reworded such that all survey items were applicable to ARVC families. The information generated by this pilot study will provide insight into the similarities and differences between the psychosocial impacts of two different hereditary conditions by examining the reliability and validity of the two survey tools. It will also identify potential clinical factors, if any, that significantly influence an individual's score and consequently provide direction for future research and clinical practice in the field of genetic counselling.

Purpose and Research Questions

The primary objective of this study is to validate two psychometric survey tools, the PAHD scale and the HD-GT scale, for use in the Newfoundland ARVC population. The secondary objective is to identify which, if any, clinical factors have an influence on the overall score for individuals at risk for ARVC.

This pilot study aims to address the following questions:

1. Are the subscales reliable for both tools?
2. Are the subscales valid for both tools?
3. Are overall scores correlated with any particular clinical variables?

The following chapters outline the literature surrounding the psychosocial issues surrounding the genetic process, the psychometric testing of both scales in the Newfoundland ARVC population, and significant differences in subscale scores in terms of age, sex, sex of the transmitting parent, and mutation status.

CHAPTER 2

Literature Review

The purpose of this literature review is to examine the current evidence on the factors that influence an individual's decision to undergo genetic testing and the resulting impact of testing on the individual and his or her family. This chapter examines the psychosocial issues surrounding the genetic testing process beginning with the first knowledge of a familial link, through to the long-term impact of testing results. The first section explores how individuals and families make decisions about genetic testing which includes perception of risk, as well as factors that motivate individuals to seek or forego genetic testing. The second section examines the reaction to test results, short-term and long-term psychosocial adjustment, and communication of results to others.

Family Context

Any illness has an associated psychosocial burden, but inherited diseases bring unique anxieties related to risk to other family members and transmission to children and grandchildren (Aatre & Day, 2011) . Being at risk for a hereditary condition implies risk for first-degree relatives which can elicit feelings of guilt, fear, anger, denial, grief, or despair (Djurdjinovic, 1998). The decision to undergo genetic testing for a hereditary condition does not occur in a vacuum; the decision cannot be truly autonomous due to the implications for other family members (Etchegary et al., 2014; Manuel & Brunger, 2014) . The complexity of family dynamics may make the conversation about disease risk more difficult for certain individuals, especially when family members have differing perceptions of risk or viewpoints of genetic

testing (Ormondroyd et al., 2014). For example, genetic testing for a hereditary condition has the potential to reveal a previously undisclosed adoption, the paternity of a child, or implicate first-degree relatives (Aatre & Day, 2011) .

Risk Perception

Perception of risk weighs heavily on motivation to seek or forego genetic testing for a hereditary disease. One study showed that low personal risk perception is a key factor in choosing not to test (Erskine et al., 2014; Ormondroyd et al., 2014) and similarly, qualitative data show that an increase in risk perception, for oneself or for a child, often results in seeking testing (Manuel & Brunger, 2014) . In some families, misconceptions and uncertainties allow individuals to justify to themselves that their risk is lower than it really is. In these families, direct contact with clinicians drastically increases uptake of testing as clinicians are able to clarify and correct misunderstandings and misconceptions and have a sense of authority that other family members do not (Ormondroyd et al., 2014).

A qualitative study by Manuel and Brunger (2014) examined the relationships between genetic testing uptake and risk perception in the Newfoundland ARVC population. One important result of that study was that genetic testing uptake was directly related to the progress made by genetic science, implying that risk perception is highly dependent on the availability of scientific knowledge (accuracy of testing, availability of treatment options, understanding of the disease itself). Those who participated in clinical testing prior to the availability of any genetic testing knew they were at risk for something but awareness of the condition did not translate into an increase in risk perception. When these

individuals were provided with the option of haplotype testing in 1998, there was no prolonged decision making process. However these individuals had already spent significant time contemplating the origins of the condition so that when testing became available, it was viewed as the next step in deciphering the condition and they were ready to know and prepared to take on this additional knowledge. The same increase in testing uptake was seen in 2007 with the introduction of direct mutation testing. In both instances, patients were offered immediate, definitive testing with increased accuracy.

Another significant result of this study was that the presence of symptoms significantly increased the chance that an individual underwent testing. The decision was especially difficult for those who did not exhibit any of the typical risk factors for heart disease; i.e., those who felt healthy, were physically active, and had a healthy diet. Similarly, women put much more thought into their decision due to the fact that women tend not to be as severely affected. Noted was a sudden increase in the number of women being tested in the 1990s when many of the women who initially underwent clinical testing in the 1980s began showing early symptoms of ARVC. Parents also showed this change in perspective when their children began to exhibit symptoms. This may partially be a reflection of some of the misconceptions within certain families, as SCD is often the first symptom of this particular subtype of ARVC.

Also noteworthy, was the lack of urgency from young family members. With advances in pre-symptomatic testing and treatment for ARVC, most young people had not witnessed as many deaths in the family as did the older generations. Similar

to how the onset of symptoms encouraged previously asymptomatic individuals to seek testing, having first-hand experience with deaths in the family caused by ARVC resulted in a heightened perception of risk.

This study demonstrated that scientific evidence and experiential knowledge greatly influenced risk perception, which in turn encourages pre-symptomatic genetic testing.

Genetic Testing Decision Making

The desire to define risk for children and other family members is often cited as the primary motivator for genetic testing. Studies of two types of inherited cancers, Hereditary Breast and Ovarian Cancer (HBOC) and Lynch syndrome (LS), found the desire to provide a risk estimate for children to be the primary motivator for seeking out genetic testing (Claes et al., 2004; Clark et al., 2000; Esplen et al., 2007). Studies of inherited heart conditions report the same result (Aatre & Day, 2011; Ormondroyd et al., 2014) . Qualitative studies in the Newfoundland ARVC population found that at-risk individuals felt a relational responsibility or moral duty to children and other first-degree relatives to be tested (Etchegary et al., 2014; Manuel & Brunger, 2014) . The desire for closure following the death of one or more family members has also been cited as a family-driven motivator to seek genetic testing. Those who have lost a child or other family member feel empowered by taking preventative measures (Erskine et al., 2014). The family connection can also be a factor in deterring people from genetic testing either due to fear that one has already passed the gene onto a child or due to the reaction from other family members if the gene test is positive (Erskine et al., 2014).

Almost as prevalent as the desire to protect the health of family members is the desire to protect one's own health (Claes et al., 2004; Clark et al., 2000; Erskine et al., 2014; Esplen et al., 2007; Manuel & Brunger, 2014; Ormondroyd et al., 2014; Satia et al., 2006) . ARVC, like many inherited conditions, can be well managed with medication and prophylactic surgery so there is a significant benefit to be gained through genetic testing (Manuel & Brunger, 2014) . Through early detection and early intervention, the life expectancy of individuals with ARVC can be extended significantly. As ARVC symptoms including SCD can appear in individuals under the age of 18, it may be beneficial for children to be tested. In most ARVC families, loss is part of a child's life from a very early age and genetic testing can be a natural part of the experience (Manuel & Brunger, 2014) . The American College of Medical Genetics recommends that minors be tested only if there are clinical implications before the age of 18 and if the medical benefits outweigh potential psychological harm (Botkin et al., 2015). Male youth with ARVC may be susceptible to SCD starting in the late teen years, so it is not uncommon for youth or for parents of at-risk youth to choose genetic testing.

Those who have been diagnosed clinically or those who suspect they may be a carrier often seek genetic testing to eliminate uncertainty (Claes et al., 2004; Clark et al., 2000; Decruyenaere et al., 1997; Decruyenaere et al., 2003; Erskine et al., 2014; Esplen et al., 2007; Etchegary et al., 2014). Unlike hereditary cancers and most inherited heart conditions, the subtype of ARVC being studied here is 100% penetrant so genetic testing is able to eliminate uncertainty (Merner et al., 2008). For this reason, pre-symptomatic testing may be highly valuable to ARVC patients in

terms of preventative measures, since the outcome has a level of certainty that many other hereditary conditions do not have.

Those who have experienced a critical event such as the death of a family member or the onset of the symptoms are much more likely to opt for genetic testing (Armstrong et al., 2000; Cox, 2003; d'Agincourt-Canning, 2005; Etchegary, 2006; Etchegary, Lemyre, & Wilson, 2010; Kasparian, Meiser, Butow, Simpson, & Mann, 2009; Klitzman, Thorne, Williamson, Chung, & Marder, 2007; Manuel & Brunger, 2014; McAllister, 2002; Norris, Spelic, Snyder, & Tinley, 2009; Smith, Michie, Stephenson, & Quarrell, 2002) . As previously referenced, the onset of symptoms increases perception of personal risk and greater perceived risk tends to increase likelihood of opting for genetic testing. Those who are affected by ARVC have typically witnessed the death of relatives and are aware of the severity (Etchegary et al., 2014).

Most individuals at risk for the subtype of ARVC under examination here describe their decision to be tested as something that "had to be done" rather than a "decision" (Etchegary et al., 2014).

Reaction to Status and Psychosocial Adjustment

Owing to small populations and lengthy study follow-up, the long-term harms and benefits of genetic testing remain underexplored (Rew, 2010). Results from a small number of studies have shown conflicting results; however, the majority show that individuals diagnosed with hereditary conditions do not experience negative psychosocial effects, at least in the short term.

As with any hereditary condition, genetic testing for ARVC is often a family decision and coping with the results is a collaborative process (Manuel & Brunger, 2014) . It has been shown that availability of social support is associated with better psychosocial adjustment to a positive gene test (Lapointe et al., 2013). Depending on the level of psychosocial support available, receiving genetic test results can range from being very stressful to being a non-event (Cox, 2003). Low levels of social support have previously been shown to increase psychological distress in those undergoing genetic counselling (Bjorvatn, Eide, Hanestad, & Havik, 2008; Esplen et al., 2007; Lammens et al., 2010; Schlich-Bakker et al., 2006) .

Some studies have shown that gene carriers experience psychosocial distress immediately following diagnosis but show no evidence that these effects are long lasting (Aatre & Day, 2011; Baumann, 2006; Broadstock, Michie, & Marteau, 2000; Collins et al., 2007; Lapointe et al., 2013; Lerman, Croyle, Tercyak, & Hamann, 2002) . These studies provide evidence for some distress immediately following diagnosis but subsiding with time. These negative emotions however, may return at transition points in one's life such as marriage or deciding to have children when the result of the gene test is again relevant (Aatre & Day, 2011) . Other studies have failed to find evidence that a positive gene test causes any significant psychosocial distress (Bonis et al., 2007; Broadstock et al., 2000; Eijzenga, Hahn, Aaronson, Kluijt, & Bleiker, 2014; Foster et al., 2007; Heshka, Palleschi, Howley, Wilson, & Wells, 2008) . Some causes of distress throughout the testing process and after testing include anxiety while waiting for test results, the burden of regular medical exams, and the burden of knowing (Broadstock et al., 2000; Collins et al., 2007; Croyle, Smith, Botkin, Baty,

& Nash, 1997; J. G. Hamilton, Lobel, & Moyer, 2009) . Some individuals who are phenotype negative and genotype positive, especially those who are otherwise healthy, find the concept difficult to comprehend which can lead to some level of distress following testing (Ormondroyd et al., 2014).

Several factors have been determined to increase the risk of negative psychosocial effects in hereditary cancers including young age (Bjorvatn et al., 2008; Schlich-Bakker et al., 2006), previous cancer diagnosis (Douma et al., 2010; Kasparian, Meiser, Butow, Simpson, & Mann, 2008; Keller et al., 2008) , and experience of cancer in close relatives (Turner-Cobb, Bloor, Whittemore, West, & Spiegel, 2006) , and avoidant coping style (Esplen et al., 2007; Mellon et al., 2008; Schlich-Bakker et al., 2006). Similarly, for hereditary cardiac conditions, previous experience with a life-threatening arrhythmia, high level of anxiety about the condition, and uncertainty about prognosis have been found to be predictors of poor psychosocial adjustment(Carroll, Hamilton, & McGovern, 1999) .

Despite the potential negative effects, the purpose of genetic counselling and testing is to reduce uncertainty and increase perceived control over future health. Several studies have shown a decrease in depression and anxiety as a test result, regardless of the outcome, eliminates uncertainty(Aatre & Day, 2011; Bonis et al., 2007) . Aatre (2010) found that non-carriers experienced relief, while positive carrier status did not compound existing distress and anxiety. One study of HBOC found that a positive test result validated an individual's concerns, allowed individuals to mentally prepare for the onset of disease, and increased access to surgical options (Lim et al., 2004). Similarly, a study of LS found that 89% of

individuals who tested positive experienced instrumental advantages (e.g. access to treatment) and 33% experienced a reduction in uncertainty (Claes et al., 2004).

Outcomes of those who test negative for a disease-causing gene are conflicting. In a study of individuals at risk for LS, 50% of those who tested negative felt reassured by the result and 39% felt reassured that they would not put their children at risk (Claes et al., 2004). However, in the same study, it was found that a large number of people expressed difficulties arising from having different results than family members such as survivor guilt, feelings of exclusion and negative reactions from relatives. These results are consistent with studies of inherited cardiac conditions (Aatre & Day, 2011; Claes et al., 2004; d'Agincourt-Canning, 2006; Schwartz et al., 2002) .

Most of the relevant literature is focused on hereditary cancers, but cardiac conditions are different for several reasons: treatments exist for the prevention of SCD, a positive test result could be of immediate concern, these conditions more commonly affect individuals under the age of 18, and lifestyle may be significantly affected (Ormondroyd et al., 2014). Consequently, genetic testing may be of particular importance to minors. There have been conflicting results in studies of psychosocial distress in minors undergoing genetic testing but overall, it has been found that children cope well with genetic testing(Aatre & Day, 2011) . Initial reactions immediately following testing are similar to adults: guilt, worry, anger, and fear, but also a sense of decreased uncertainty (Rew, Mackert, & Bonevac, 2009) . Overall, at risk children do not experience high levels of psychological distress (Codori, Petersen, Boyd, Brandt, & Giardiello, 1996; Codori et al., 2003;

Michie, Bobrow, & Marteau, 2001; Smets et al., 2008) . Particularly with inherited heart conditions, children tend to be articulate about their condition, and being able to explain their condition to peers reduces social isolation and increases social support (Aatre & Day, 2011) . However, like adults, when children reach transition points later in life, negative reactions to testing are often revisited and individuals who were tested as young children may experience resentment over not being included in the decision making process (Manuel & Brunger, 2014) .

Negative psychosocial effects may also appear in carriers after testing in response to treatment or life changes resulting from the testing outcome. The need for medications, implantation of an ICD, the psychosocial implications of which are also conflicting, and the possibility of early death may affect educational and professional goals, as well as intimate relationships (Aatre & Day, 2011; Friedmann et al., 2006; Hamang et al., 2010) .

Communication About ARVC Risk

Communication is a key element in maintaining relationships and social support networks. Sharing genetic information has been shown to strengthen family relationships (Lapointe et al., 2012; van Oostrom et al., 2007). More open family discussions surrounding genetic status have been associated with greater levels of social support and greater social support has, in turn, been shown to improve psychosocial adjustment (Bowen, Bourcier, Press, Lewis, & Burke, 2004; den Heijer et al., 2011; van Oostrom et al., 2007) . However, understanding communication between family members can be complicated as family members receive different results (Hamann et al., 2008; Peterson et al., 2003). The disclosure of one's test

results can be burdensome, particularly for the proband as they may feel a responsibility to inform the rest of the family (Bakos et al., 2008; Carlsson & Nilbert, 2007; Di Prospero et al., 2001; Hallowell, 2006) . One study has shown that carriers tend to have more difficulty sharing their results, and that carriers tend to share their results with fewer people than do non-carriers (Lapointe et al., 2013). A positive gene result often has implications for non-relatives including partners and spouses, as the need for treatment and the possibility of early death may influence personal, educational, and financial goals, as well as the development of intimate relationships (Aatre & Day, 2011) .

For parents who test positive for hereditary conditions, there is the added complication of transmission guilt (Aatre & Day, 2011) . When dealing with hereditary heart conditions where there is a real risk of SCD, disclosure of risk to a child with aspirations of a physically demanding career could be devastating (Aatre & Day, 2011) .

A negative gene test may also lead to survivor's guilt in individuals who have other relatives who are carriers (Carlsson & Nilbert, 2007; d'Agincourt-Canning, 2006; Hallowell, 2006) .

Regardless of result, some individuals do not feel supported by family members with differing results, making psychosocial adjustment more difficult (Appleton, Fry, Rees, Rush, & Cull, 2000; Frost, Venne, Cunningham, & Gerritsen-McKane, 2004; R. Hamilton & Hurley, 2010; Lim et al., 2004) .

While family dynamics influence how results are communicated, the duty to warn is a consistent theme among many studies of hereditary conditions (Aatre &

Day, 2011; Pullman & Hodgkinson, 2006) . In qualitative studies of individuals in Newfoundland and Labrador at risk for ARVC, the majority hold the opinion that genetic testing is a positive thing and should be pursued where intervention is available (Etchegary et al., 2014).

Discussion of Literature

While there is a significant body of literature surrounding the psychosocial impact of hereditary cancers, little research has been conducted on those at risk for cardiomyopathies, particularly ARVC. Individuals with cardiomyopathies may have unique anxieties due to the risk of SCD, an imminent danger for some individuals who test positive for *TMEM43*. Unlike many hereditary conditions, ARVC caused by *TMEM43* is 100% penetrant, and SCD is a common symptom (Merner et al., 2008). When compared to other inherited heart conditions, including Long QT Syndrome and Hypertrophic Cardiomyopathy, this subtype of ARVC has a much higher risk of death, which may result in a significantly different psychosocial impact(Jackson, Huisman, Sanatani, & Arbour, 2011; Maron & Maron, 2013; Merner et al., 2008; Murray, 2012; Ventura, Napolitano, Buquicchio, Cecere, & Arsieni, 2012) .

However, as shown in Table 1, ARVC shares a number of key characteristics with the conditions discussed above. All the conditions discussed above commonly follow an autosomal dominant inheritance pattern with the exception of some less common subtypes, as well as variable expressivity, and treatment options. Uncertainty is a common theme throughout studies of the psychosocial impact of hereditary disease; conditions with the same inheritance pattern and variable expressivity should be similar in level of uncertainty.

Table 1: Comparable inherited conditions

Condition	**Inheritance Pattern**	**Life Expectancy or risk of death**	**Penetrance**	**Expressivity**	**Treatment Available**
ARVC caused by p.S358L TMEM43	Autosomal dominant (Hodgkinson, 2013)	41 years in males, 71 years in females (untreated) (Merner et al., 2008)	100% (Merner et al., 2008)	Variable in both males and females, but more malignant in males	Implantable cardioverter defibrillator (ICD)
ARVC in general	Autosomal dominant or recessive depending on causative gene (Murray, 2012; Towbin, 2008)	Variable (Murray, 2012)	30% - 50% (Towbin, 2008)	Variable (Murray, 2012)	ICD/Antiarrhythmic medication, beta blockers
Long QT Syndrome	Autosomal dominant or autosomal recessive depending on gene. (Vincent, 1998)	Risk of death 15% to 70% depending on a number of factors	Incomplete (Vincent, 1998)	Variable (Vincent, 1998)	Oral medications, ICD in some cases
Hypertrophic Cardiomyopathy	Autosomal dominant (Maron & Maron, 2013)	Risk of death 1% when treated (Maron & Maron, 2013)	Incomplete (Maron & Maron, 2013)	Highly variable (Maron & Maron, 2013)	Oral medications, ICD in some cases
Lynch Syndrome (HNPCC)	Autosomal Dominant (Kopciuk et al., 2009)	Variable (Kopciuk et al., 2009)	98% for men, 93% for females by age 70 (Kopciuk et al., 2009)	Variable (Kopciuk et al., 2009)	Treatment for identified cancer
Hereditary Breast and Ovarian Cancer (HBOC)	Autosomal Dominant or Autosomal recessive depending on causative gene (Rainville & Rana, 2014)	Variable (Rainville & Rana, 2014)	20%-90% depending on causative gene (Rainville & Rana, 2014)	Variable (Rainville & Rana, 2014)	Treatment for identified cancer

Among the conditions discussed above, hereditary cancers are the most similar in terms of penetrance, one of the factors that distinguish this subtype of ARVC from the other conditions (Kopciuk et al., 2009; Rainville & Rana, 2014) . LS has a penetrance higher than 90% and has also been studied in the Newfoundland population; therefore, it might also be similar in psychosocial impact. It is believed that psychosocial surveys developed for use in LS populations will be relevant for ARVC populations.

CHAPTER 3

Methodology

This pilot study was a part of a larger study investigating a number of key molecular and GE^{3}LS (Genomics-related Ethical, Environmental, Economic, Legal and Social) issues associated with SCD in Newfoundland and Labrador. Appendix A outlines the GE^{3}LS research program and where this project fits in the broader research context. This particular study is a quantitative follow-up to qualitative research recently completed by Etchegary et al (2014). The primary goal of the current study was to examine the reliability and validity of two psychometric testing tools previously developed for LS for use in the ARVC population. The secondary goal was to identify clinical factors that may potentially be associated with the psychosocial impact on individuals at risk for ARVC.

Development of HD-GT and PAHD Scales

Development of Scales for Lynch Syndrome

To create the original scales developed for LS, survey items were generated using a qualitative database created during interviews with members of eight different LS families. The list of items was refined by removing items that were unclear, contained jargon, or contained negative wording. A common likert scale was applied to each item, with responses ranging from 0-4 (not at all to extremely). Once the list was refined and wording was clarified, items were reviewed for content and usefulness of the rating scales by two genetic counsellors familiar with

LS families, a carrier of the gene, and a non-carrier of the gene. Items were subsequently reworded to remove ambiguity (LeDrew, 2009; Way et al., 2011).

Readability was then assessed using the Flesch-Kincaid Grade Level and Flesch Reading Ease, SMOG (Simple measure of gobbledygook), and the Fog Index. Scales were determined to be at a grade 9 level and therefore met readability criteria.

These scales were chosen for this study because they were developed locally and within a local context. The populations LS and ARVC populations are homogenous, island populations with an evident founder effect and contain large families. Because of the strength of development of both scales for local families, we wanted to know if their use could be extended to other families with an autosomal-dominant condition. While other psychosocial instruments are available in the literature (e.g. Genetic Psychosocial Risk Instrument, Genetic Risk Assessment Coping Evaluation, etc) the two scales under study were chosen due to the similarities in local context and the relation of themes explored within the scales to qualitative work with ARVC families.

Modification of Scales for ARVC

Members of the supervisory committee first met with the original scale developers to begin discussion about whether and how tools might be modified for use in the ARVC population. This meeting included Drs. Hodgkinson, Etchegary, and Pullman from the ARVC study team, as well as Drs. Chris Way and Kathy Watkins from the School of Nursing, Memorial University who had created the scales for use in LS populations. There was agreement in principle to avoid duplication of effort

and that demonstrating generalizability of the tools to another inherited condition would be useful. In order to be as transparent as possible, the team held a series of meetings to discuss issues of wording and to change any items not applicable to ARVC. Where possible, exact wording was maintained. The team also discussed the population to which surveys would be sent (e.g., those who had undergone genetic testing), as well as practical and logistical issues with survey mail outs. After three meetings, two items were removed and several items were modified, but the meaning of items was consistent. For example, questions about screening were changed to reflect the differences in screening between cancer and heart conditions, but the purpose of the questions remained the same. Prior to analysis, any items not included in the final, validated versions of the scales for LS were also removed from the ARVC versions for future comparability. Original versions of surveys, modified for ARVC, were sent to study participants are included in appendix B (HD-GT) and appendix C (PAHD).

Scale Readability

Measures were taken to assure an appropriate reading level for all participants. In their original forms for use in LS, both scales were determined to be at a 9th grade reading level to assure maximum comprehension. Modification of the scales for use in the ARVC population did not affect readability. Since all participants have previously undergone genetic testing for ARVC, they have been exposed to the terms carrier/non-carrier, inherited, generation, geneticist/genetic counsellor, ECG, Holter monitor, etc. Terms such as these increase the overall readability scores but would be familiar to all participants.

Psychometric Evaluation of Scales

Population and Sample

The target population for this study was individuals born at an *a priori* 50% risk for the *TMEM43* mutation known to cause ARVC who had undergone genetic testing. Survey respondents were recruited from an ARVC dataset maintained by members of the ARVC research program, Drs. Kathy Hodgkinson and Susan Stuckless. The dataset contains a large number of clinical variables for each member of the 24 Newfoundland and Labrador families identified as having a history of ARVC. Individuals who were excluded from the study include those who were not born at 50% a priori, were under the age of 14, did not have a well-ascertained sibship (see figure 1), had died since the last dataset update, had no contact information available, or had previously refused to be contacted for research purposes. Whole families were also excluded if the ARVC gene had recently been identified. Individuals in these families would have been going through the genetic testing process and dealing with the diagnosis at the time of the study, so it was decided that it would be in the best interest of the families to be excluded from this phase of the project.

The version of the dataset used for analysis contains information for 885 individuals. In total, 238 individuals were contacted, representing approximately half of all living individuals in the dataset, 176 agreed to participate in the study and 73 returned completed surveys and consent forms (41% overall response rate).

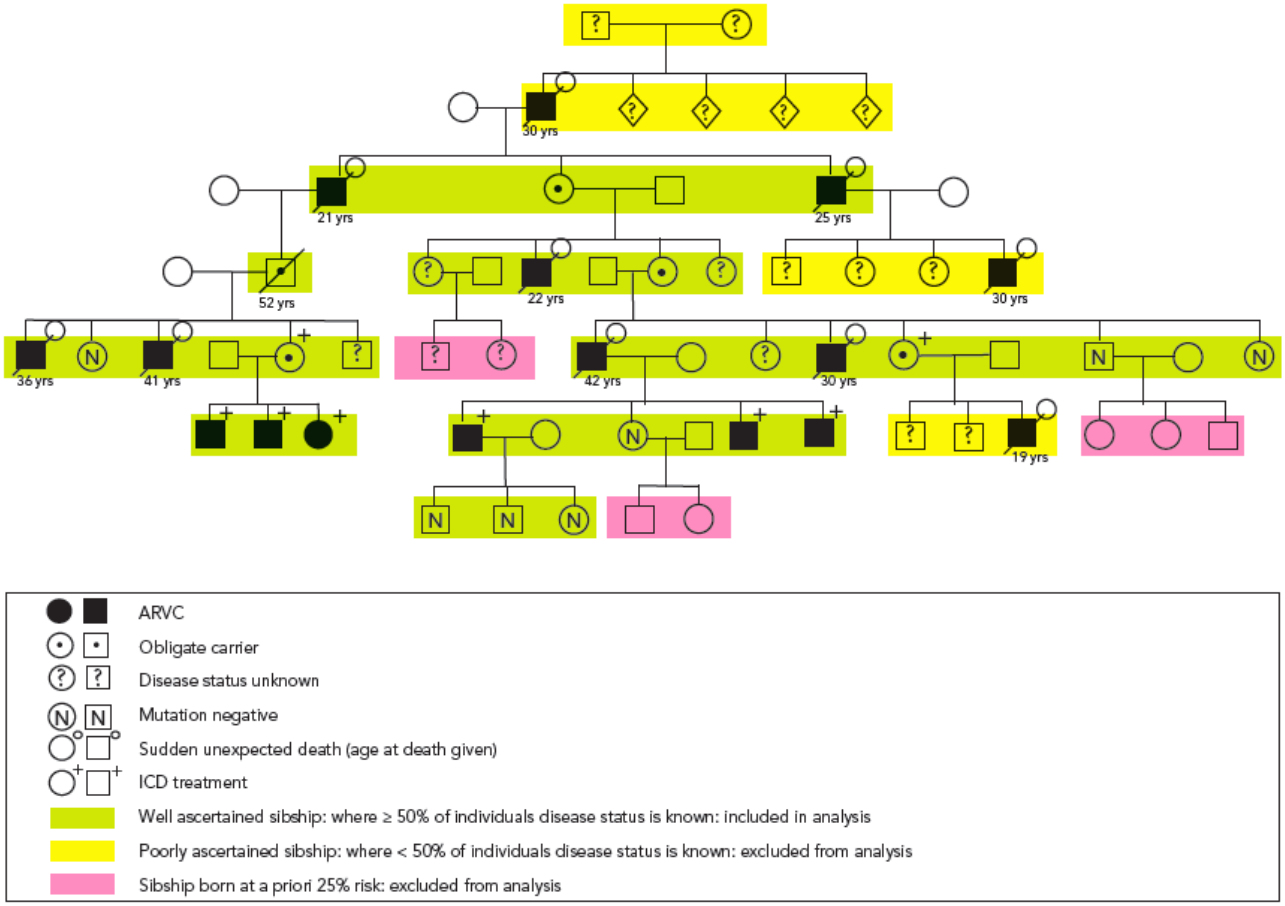

Figure 1: Representative pedigree of an ARVC family, illustrating the method used to remove ascertainment bias

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Due to the fact that the dataset is not linked to vital statistics, deaths are not always captured in a timely fashion. Attempts were made to contact four individuals who had died since the dataset was last updated.

Four individuals with unknown or unconfirmed gene status were also contacted; however, none returned the survey package and were not included in the analysis. The majority of individuals with unknown gene status are unknown because they have not gone through testing at the cardiac clinic in St. John's and thus, their contact information was not available to the research team. Figure 2 summarizes the recruitment process.

Procedure

Recruitment and data collection began following receipt of ethical approval from the Health Research Ethics Authority (approval of final amendment approval included in appendix E). Initial contact with potential study participants was made via telephone by a genetic counsellor or a representative of the genetics team. Those who agreed to receive a survey package verbally gave consent to be contacted for follow up by other members of the research team. Participating parents with children aged 14 to 18 years were also given the opportunity to volunteer their children provided the child(ren) met all other inclusion criteria. It was thought that youth would have a unique perspective that would be valuable to the study, but that the child's willingness and ability to complete the survey would be at the discretion of the parent. Participants were given the choice between a paper copy of the survey package and an emailed fillable PDF version of the survey package.

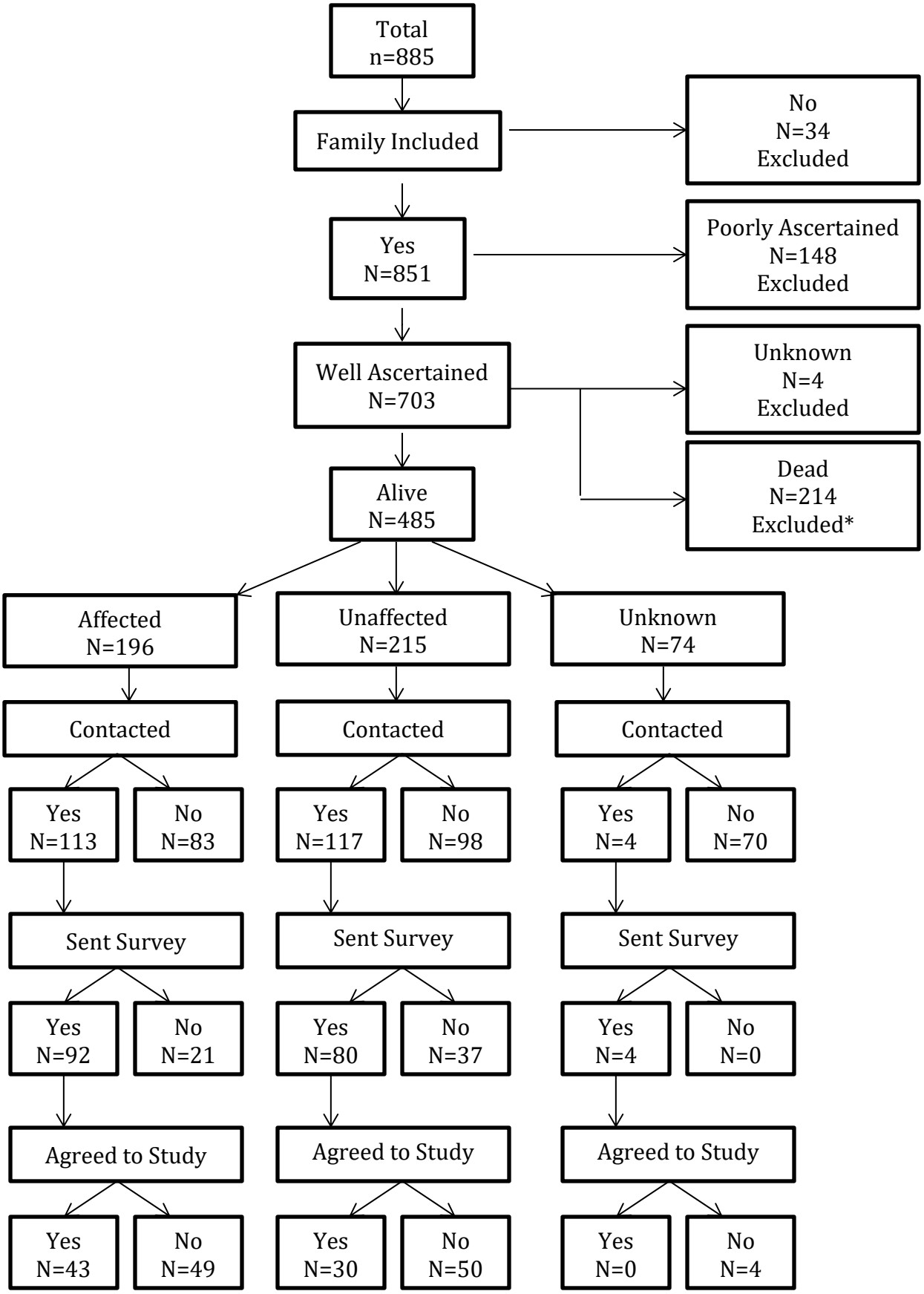


Figure 2: Recruitment flow chart

If surveys were not received within four weeks of dispatch, participants were called by a member of the research team to check the surveys had been received. Those who did not receive the study package were sent a second copy by mail. Those who had received the surveys and had not filled them out or had not yet sent them back were thanked for their participation. In the case of those who could not be reached (no answer or call was answered by someone else and participant was not available), repeat calls were made one week apart to a maximum of four calls. To maintain participant privacy, no messages were left.

HD-GT Scale

The original version of the HD-GT scale modified for ARVC contained 10 sections and 63 items. This content of this scale guides participants through the journey from learning about risk, to becoming aware of genetic testing and making a decision, and finally to the process of testing.

The first section focuses on learning about risk and how ARVC risk affects familial relationships (e.g. “It was scary to see the same pattern of early sudden cardiac death showing up in every generation of my family”.)

The second section focuses on becoming aware of available genetic testing. This section was removed following final validation in LS populations and was therefore not included in analysis for this study.

Sections 3 through 10 capture attitudes toward genetic testing at various stages of the process. Sections 3 and 4 examine emotional preparedness (e.g. It is important to know if one has the ARVC gene to help children/grandchildren) and struggling with relatives who refuse testing (e.g. “I feel obligated to encourage

family members who refuse genetic testing to rethink their decision"). Section 5 looks at wait time considerations, but was excluded from the final LS scale and was therefore excluded from analysis for this study. Sections 6, 7, 9 and 10 are designed to measure perceived adequacy of clinical and social support (e.g. "It is important to have face-to-face contact with a geneticist/genetic counsellor when receiving your results"), preparedness for results (e.g. "Knowing whether or not I had the ARVC gene for early sudden cardiac death brought a sense of closure to everything"), awareness of risk and inheritance patterns (e.g. Men and women seem to be affected differently), and issues of disclosure to other family members (e.g. "In our family, we struggle with knowing when to tell young family members about early sudden cardiac death"). Section 8 was also removed as it was not included in the final LS version.

PAHD Scale

The PAHD scale modified for ARVC contains two sections: burden of knowing (BK) and family support in ARVC (FSARVC). This scale aligns closely with the content of the first section of the HD-GT, but examines the concepts of living with risk and managing family relationships in more detail. Examples of some items in this scale include "I think about being a carrier/non-carrier more than I should" and "I worry that all the suffering and death from ARVC is placing too much burden on family members".

Ethical Considerations

Measures were taken to maintain participant privacy and confidentiality at each step of the process. Individuals were initially contacted by a genetic counsellor

or a representative with whom they had previously had contact. Those who agreed to participate agreed to have contact information released to the research team for the purpose of follow up. As part of the study package, each participant was also sent a detailed description of the study as well as a consent form. Only those who returned completed consent forms were included in analysis. The consent form confirmed that participants understood the purpose of the study, the potential risks involved, and that a genetic counsellor would be available to respond to any concerns that may arise from the survey questions. Contact information for a genetic counsellor was included so that it would be accessible to participants while completing the surveys.

Surveys were tracked using only a patient ID. A separate list linking patient ID to patient contact information was kept in a locked cabinet within an office accessible only to the research team and did not leave the room at any time. During follow up calls, members of the research team did not leave messages and did not discuss the reason for the call with anyone other than the survey respondent. In a small number of cases, family members who answered the phone were worried that the reason for the call was a problem with test results. In cases such as these where the study participant was not available, the family member was told only that the call was for research purposes, to relieve anxiety.

Data Analysis

Data were entered into the IBM SPSS Statistics for Mac, version 22 for analysis. Analysis was broken into two segments: 1) survey validation and 2) exploration of psychosocial impact.

The first validation step involved using descriptive statistics to confirm approximate equivalence of means and variances for each item as well as each scale. Scales were constructed by summing appropriate items and removing missing data. The second validation included multi-item/multi-trait correlation matrices to test assumptions of linearity, item-convergent validity, and item-discriminant validity. Each step is explored in detail in the following chapter.

CHAPTER 4

Results

Study findings are presented in three sections. 1) The first section summarizes descriptive statistics for the study as a whole and for each survey tool. 2) The second section provides reliability and validity data for each survey tool used in the Newfoundland ARVC population. 3) The third provides a brief overview of preliminary psychosocial findings.

Descriptive Profile of Participants

A total of 73 individuals participated in this pilot; 43 individuals (59%) were *TMEM43* carriers and 30 (41%) were not. The majority of respondents were female. Table 2 summarizes the descriptive statistics for study participants.

Table 2: Descriptive profile of survey participants

	N	%
Sex		
Male	19	26.0
Female	54	74.0
Sex of transmitting parent		
Male	34	46.6
Female	37	50.7
Unknown	2	2.7
Positive for *TMEM43* gene		
Yes	43	58.9
No	30	41.1

Subscale Structure

Following removal of any items not included in the final LS version of the HD-GT scale, items were organized into nine subscales: Impact of ARVC (IARVC), Family Challenges in Genetic Testing (FCGT), Genetic Testing Preparation (GTP), Wait Time Concerns (WTC), Support with Genetic Testing Results (SGTR), Understanding Risk

(UR), Transmission Beliefs (TB), Communication Around Genetic Link (CGL), and Disclosure Issues (DI).

Similarly, items from the PAHD scale were organized into two subscales: BK and FSARVC.

Data Quality

Tables 3 and 4 summarize item-level descriptive statistics for the HD-GT and PAHD scales, respectively. Missing data for both scales were minimal, ranging from 0% to 4.1%, and random, indicating there were no significant issues of question interpretation. All responses were used in all items with the exception of items related to the importance of healthy living and one item related to understanding of the gene, where the "not at all" option was not used. These items refer to uncommon states (believing that healthy living is not important to overall well-being, and family members not having an understanding of the ARVC gene) and therefore one would not expect a full range of responses (Ware & Gandek, 1998) . The frequency distribution was also skewed in GTP, FCGT, and UR sections. These results were expected as participants have all participated in genetic testing and are more likely to attach a high importance to understanding risk, undergoing testing, and encouraging family members to be tested.

Table 3: Item Level Descriptive Statistics HD-GT Scale

Item	Mean	SD	Missing (%)	Response Values Frequency				
				0	1	2	3	4
Scale: Impact of ARVC (IARVC)								
A1.1_R: SCD more frequent and younger	1.35	1.39	2.7	25	21	9	7	9
A1.2_R: Memories of close family members dying young	1.58	1.50	2.7	26	11	12	11	11
A1.3_R: Presence of SCD hard to accept	1.41	1.47	2.7	29	12	12	8	10
A1.4_R: Scary to see pattern of SCD every generation	1.29	1.36	4.1	27	19	8	9	7
A1.5_R: Draining to lose relatives	2.06	1.64	2.7	20	11	6	13	21
A1.6_R: Worry about own health and death	1.80	1.52	2.7	20	13	15	7	16
A1.7_R: Worry about other types of heart disease showing up	2.50	1.46	4.1	8	14	10	11	27
Scale: Genetic Testing Preparation (GTP)								
A3.1: Getting enough information in a timely manner	3.13	1.00	2.7	2	2	13	22	32
A3.2: Receiving enough information about the process	3.15	0.90	2.7	0	3	15	21	32
A3.4: Knowing if one has the ARVC gene	3.57	0.73	4.1	0	2	4	16	48
A3.5: Understanding one's risk and accepting need for testing	3.55	0.77	2.7	1	0	6	16	48
A3.6: Knowing if one has the gene for children/grandchildren	3.61	0.96	2.7	3	1	3	7	57
Scale: Family Challenges Genetic Testing (FCGT)								
A4.1: Important for all family members to take part in testing	3.77	0.70	0	1	0	5	3	64
A4.2: Concern about family members who refuse testing	3.30	1.18	4.1	5	2	5	13	45
A4.3: Family members who refuse do not understand risk	3.01	1.32	1.4	7	3	10	14	38
A4.4: Family members who refuse are fearful of result	3.47	0.80	0	1	0	8	19	45
Scale: Wait-time Concerns (WC)								
A5.1_R: Trying thinking about the gene	1.46	1.49	2.7	28	13	9	11	10
A5.2_R: Not prepared for such a long wait time	2.63	1.30	2.7	4	12	17	11	27
A5.3_R: Unsure about how results would be received	3.12	1.17	1.4	3	6	9	15	39
A5.4_R: Spent a lot of time thinking about own reaction	2.23	1.60	2.7	15	13	9	9	25
A5.5_R: Wondering if one would understand meaning of result	2.39	1.44	1.4	8	15	16	7	26

Scale: Support for Genetic Testing Results (SGTR)								
A6.1: Having a family member present	2.31	1.55	1.4	16	6	14	12	24
A6.2: Receiving phone call from geneticist/genetic counsellor prior to receiving results	2.18	1.38	1.4	13	7	22	14	16
A6.3: Face to face contact when receiving results	1.42	1.42	1.4	9	3	12	10	38
A6.4: Receive letter explaining meaning of carrier/non-carrier	2.92	1.40	0	9	5	5	18	36
Scale: Understanding Risk (UR)								
A8.1: Regular monitoring will detect disease at early stage	3.41	1.04	0	4	0	6	15	48
A8.2: Appropriate monitoring important for timely detection	3.71	0.54	0	0	0	3	15	55
A8.3: Early detection will help treatment and management	3.77	0.51	0	0	0	3	11	59
A8.4: Healthy living & positive attitude will increase well-being	3.62	0.68	0	0	1	5	15	52
A8.5: Taking responsibility for healthy living & monitoring	3.64	0.59	0	0	0	4	18	51
Scale: Transmission Beliefs (TB)								
A9.1: Family members affected at younger age	2.73	1.34	2.7	7	7	12	17	28
A9.2: Men and women affected differently	2.83	1.19	1.4	5	6	9	28	24
A9.3: Different types of heart disease showing up more	2.58	1.35	2.7	7	11	10	20	23
A9.4: Number of affected family members greater	2.50	1.36	4.1	9	8	12	21	20
Scale: Communication around Genetic Link (CGL)								
A10.3: Young family members open to information about gene	2.28	1.08	2.7	2	16	25	16	12
A10.4: Young family members understand what the gene means	2.18	1.05	2.7	4	14	25	21	7
A10.7: Family members open to information about gene	3.01	0.93	2.7	1	4	12	30	24
A10.8: Family members understand what the gene means	2.89	0.93	4.1	0	6	16	28	20
Scale: Disclosure Issues (DI)								
A10.2: Difficult to tell younger family members	2.24	1.52	2.7	13	14	8	15	21
A10.6: Hard telling family members about possible risk	2.85	1.19	2.7	3	8	14	18	28
A10.9: Helpful for family messenger to have guidance/support from geneticist/genetic counsellor	2.97	1.10	2.7	1	6	19	13	32
A10.10: Important to protect the rights of others	3.20	1.14	2.7	4	2	10	15	40

Table 4: Item Level Descriptive Statistics PAHD Scale

Item	Mean	SD	Missing (%)	Response Values Frequency				
				0	1	2	3	4
Scale: Burden of Knowing (BK)								
B1.1_R: Think about being carrier/non-carrier	2.14	1.47	1.4	13	15	11	15	18
B1.4_R: Hard changing frequency of monitoring	2.99	1.25	1.4	4	6	14	11	37
B1.5_R: Bothered by others not accepting status	3.18	1.35	1.4	8	1	8	8	47
B1.7_R: Hard to deal with young family members with gene	1.96	1.55	1.4	18	14	12	9	19
B1.8_R: Worry about future of young family members	1.29	1.40	1.4	30	16	8	11	7
B2.4_R: Presence of SDC has hurt family relations	2.90	1.41	1.4	6	10	8	9	39
B2.5_R: Worry that ARVC placing too much burden on family	1.81	1.32	1.4	13	20	18	10	11
Scale: Family Support in ARVC (FSARVC)								
B2.1: Feeling supported by family & friends has helped accept status	2.72	1.20	2.7	5	6	15	23	22
B2.2: Easy to seek help from family	2.69	1.27	2.7	6	6	17	17	25
B2.3: Important to talk openly about SCD risk	2.99	1.13	1.4	2	4	22	9	35
B2.6: Providing care for family has helped accept the future	1.74	1.36	1.4	19	12	19	13	9
B1.6: Young people need to be encouraged to talk about SCD	2.80	1.21	0	4	7	17	17	28

Item Level Scale Assumptions

Within each subscale, mean and standard deviation were approximately equal with few exceptions. This indicates that overall, data were not skewed and responses were normally distributed.

Two items, A1.7 and B2.6, with outlying means highlight the differences between ARVC and cancer. The first asks about worry of other types of heart disease appearing in those who test negative for the ARVC gene. The genes associated with LS put an individual at increased risk for several types of cancer, but those without the gene can also develop cancer. Conditions similar to ARVC are much more uncommon than cancer, so individuals who test negative for an ARVC gene do not typically develop a related condition. The second item has to do with family members coming to accept their own future by acting as a caregiver for another family member with the condition. Individuals with ARVC do not typically require ongoing care from friends or family members so this type of relationship, which can be common with cancer, is relatively uncommon with ARVC.

Some items have inherently skewed means. One example is item B1.8 that deals with concern for young family members. Within families, individuals tend to place more importance on the health of younger family members, particularly children and grandchildren, than on their own health. Compared to other family relationships, individuals tend to place more importance on younger family members. Similarly, item 5.1, dealing with the impact of uncertainty while waiting for test results has a different mean than other items in the scale. The other items in the scale deal with uncertainties about how the results will be received and are

much less emotionally charged. Another item with an inherently skewed mean is A6.4, which deals with the importance of receiving a letter detailing test results and the meaning of the result. Individuals going through a stressful event such as genetic testing may forget details or may not fully understand all the details when results are revealed face to face. Regardless of the specific situation, when receiving a large amount of information, a paper copy of the information is often preferred and/or expected.

Overall, there were no major unexplained discrepancies in means or variances so the subscale structure was appropriate and data were valid.

Scale Level Assumptions

Following verification of the subscale structure and data quality, multi-item scale scores were computed for each participant by summing scores of the items contained within each subscale. Where one or more questions were omitted, the individual was excluded from analysis of that particular subscale. Between zero and six individuals (0% - 8%) were excluded from a given scale for this reason.

Summated scores can be used successfully under the Likert scaling assumptions (Ware & Gandek, 1998) . The three assumptions are as follows: 1) items in each grouping should contribute approximately the same amount of information to the subscale, 2) items should have approximately equal variances within each subscale, and 3) items should be linearly related to the subscale score (Likert, 1932). The second assumption has already been made based on the descriptive statistics provided above. Assumptions one and three can be verified

using a multi-trait/multi-item correlation matrix. Tables 5 and 6 contain these findings for the HD-GT survey and PAHD survey, respectively.

Item Internal Consistency

Item internal consistency is the measure of how well an item linearly correlates to its subscale score. This value is computed by removing the item in question from its subscale, calculating a summated scale score from the remaining items, and then computing the Pearson correlation coefficient of the item with the new summated score. A correlation is considered statistically significant if the value of this correlation is greater than 0.40 (Ware et al., 1980). Most (47) items satisfied this condition, four items fell within the 0.30-0.40, and three items fell within the 0.20-0.30 range. All seven items that fell below 0.40 were related to an extreme so they may still be valuable, but may fail the item internal consistency test due to the skew to one side. For example, item A9.2 had a correlation value of 0.226, well below the 0.40 cut-off. This question was contained in the UR section where participants were asked to rate the degree to which the statement reflected their families' situation. This item states "Men and women seem to be affected differently" and since ARVC does in fact, affect men and women very differently, the majority of participants agreed with the statement. It is a significant aspect of understanding risk, but the score for this particular item is not necessarily indicative of a person's overall understanding of his or her risk (the total scale score). Overall, the items satisfy the third Likert assumption since they are linearly related to their respective subscales.

Equality of item-scale correlations

The correlation values computed in tables 5 and 6 represent the amount that each item contributes to its respective subscale. Ideally, items in a given scale will be approximately equal and will have a value between 0.40 and 0.70 (Ware & Gandek, 1998) . Items in the IARVC subscale are approximately equal but have greater values than all other scales, with a range of 0.542 to 0.821. With the exception of the items with a correlation value lower than 0.40, all other scales are approximately equal and are contained within the ideal range.

Item Discriminant Validity

While it is important for an item to correlate well with its hypothesized scale, it is also important that the same item does not correlate well with any other scale. For this study, an item is said to have satisfactory discriminatory power if it correlates with its own scale better than another scale by two standard errors. Depending on the degree to which an item correlates with its hypothesized scale compared to another given scale, a value of 2, 1, -1, or -2 is assigned. A value of 2 signifies that an item correlates better to its own scale than other scales, and the result is statistically significant, a value of 1 signifies that an item correlates better to its own scale but the result is not statistically significant. Similarly, a value of -2 or -1 is assigned if the item correlates better to another scale than to its own scale. Tables 7 and 8 provide summaries of item discriminant validity tests for the HD-GT survey and PAHD scale respectively. Item discriminant validities were calculated

Table 5: Correlation matrix for HD-GT survey corrected for overlap

Item Name			Pearson Item-Scale Correlations								
	Mean	SD	IARVC	GTP	FCGT	WC	SGTR	UR	TB	CGL	DI
Scale: IARVC											
A1.1_R	1.35	1.39	**0.704**	-0.167	-0.144	0.109	0.073	-0.072	-0.143	-0.263	-0.115
A1.2_R	1.58	1.50	**0.777**	-0.210	-0.252	0.120	0.100	-0.054	-0.295	-0.304	-0.162
A1.3_R	1.41	1.47	**0.821**	-0.250	-0.276	0.144	0.017	0.011	-0.281	-0.277	-0.233
A1.4_R	1.29	1.36	**0.744**	-0.377	-0.349	0.060	-0.056	-0.147	-0.259	-0.318	-0.119
A1.5_R	2.06	1.64	**0.678**	-0.226	-0.370	0.234	0.014	0.018	-0.364	-0.157	-0.209
A1.6_R	1.80	1.52	**0.717**	-0.132	-0.187	0.223	0.025	-0.126	-0.385	-0.222	-0.165
A1.7_R	2.50	1.46	**0.542**	-0.103	-0.248	0.283	-0.078	-0.291	-0.511	-0.328	-0.228
Scale: GTP											
A3.1	3.13	1.00	-0.168	**0.640**	0.280	0.045	0.219	0.164	0.129	0.178	0.283
A3.2	3.15	0.90	-0.275	**0.687**	0.370	-0.025	0.284	0.347	0.231	0.383	0.327
A3.4	3.57	0.73	-0.285	**0.605**	0.318	-0.141	0.346	0.395	0.194	0.243	0.195
A3.5	3.55	0.77	-0.242	**0.708**	0.395	-0.047	0.202	0.281	0.210	0.156	0.279
A3.6	3.61	0.96	-0.092	**0.423**	0.355	-0.164	0.298	0.307	0.341	0.255	0.197
Scale: FCGT											
A4.1	3.77	0.70	-0.292	0.461	**0.411**	-0.142	0.201	0.421	0.263	0.213	0.355
A4.2	3.30	1.18	-0.401	0.191	**0.491**	-0.291	0.188	0.096	0.188	0.229	0.278
A4.3	3.01	1.32	-0.163	0.418	**0.492**	-0.061	0.169	0.118	0.287	0.133	0.254
A4.4	3.47	0.80	-0.220	0.334	**0.506**	-0.246	0.293	0.149	0.124	0.222	0.236
Scale: WC											
A5.1_R	1.46	1.49	0.178	-0.257	-0.184	**0.629**	-0.457	-0.307	-0.151	-0.319	-0.411
A5.2_R	2.63	1.30	0.115	-0.145	-0.098	**0.459**	-0.215	-0.347	-0.128	-0.109	-0.195
A5.3_R	3.12	1.17	0.071	-0.040	-0.205	**0.504**	-0.209	-0.241	-0.148	-0.175	-0.104
A5.4_R	2.23	1.60	0.191	0.008	-0.129	**0.684**	-0.291	-0.255	-0.347	-0.175	-0.170
A5.5_R	2.39	1.44	0.307	0.023	-0.170	**0.573**	-0.332	-0.236	-0.392	-0.307	-0.068
Scale: SGTR											

A6.1	2.31	1.55	-0.052	0.210	0.406	-0.458	**0.414**	0.336	0.253	0.323	0.323
A6.2	2.18	1.38	-0.024	0.229	0.279	-0.347	**0.411**	0.301	0.015	0.472	0.202
A6.3	1.42	1.42	0.023	0.356	0.284	-0.266	**0.620**	0.373	0.037	0.340	0.300
A6.4	2.92	1.40	0.076	0.265	0.079	-0.114	**0.290**	0.174	0.009	0.202	0.123
Scale: UR											
A8.1	3.41	1.04	0.017	0.135	0.017	-0.459	0.346	**0.332**	0.281	0.266	0.160
A8.2	3.71	0.54	-0.174	0.439	0.291	-0.248	0.352	**0.656**	0.293	0.214	0.237
A8.3	3.77	0.51	-0.249	0.503	0.357	-0.249	0.344	**0.630**	0.311	0.344	0.120
A8.4	3.62	0.68	-0.165	0.215	0.112	-0.178	0.267	**0.517**	0.207	0.373	0.070
A8.5	3.64	0.59	-0.051	0.229	0.115	-0.086	0.253	**0.621**	0.155	0.318	0.043
Scale: TB											
A9.1	2.73	1.34	-0.379	0.438	0.369	-0.282	0.216	0.298	**0.539**	0.304	0.166
A9.2	2.83	1.19	-0.107	0.064	0.118	-0.217	-0.044	0.139	**0.226**	0.049	0.034
A9.3	2.58	1.35	-0.190	0.051	0.157	-0.132	0.026	0.273	**0.456**	0.225	0.190
A9.4	2.50	1.36	-0.389	0.178	0.208	-0.309	0.141	0.225	**0.560**	0.235	0.191
Scale: CGL											
A10.3	2.28	1.08	-0.183	0.226	0.162	-0.267	0.421	0.478	0.212	**0.683**	0.366
A10.4	2.18	1.05	-0.318	-0.010	0.181	-0.300	0.345	0.260	0.237	**0.596**	0.216
A10.7	3.01	0.93	-0.268	0.483	0.406	-0.043	0.413	0.334	0.253	**0.620**	0.154
A10.8	2.89	0.93	-0.348	0.458	0.279	-0.281	0.304	0.242	0.244	**0.465**	0.279
Scale: DI											
A10.2	2.24	1.52	-0.032	0.206	0.257	-0.152	0.203	0.114	0.172	0.235	**0.514**
A10.6	2.85	1.19	-0.188	0.303	0.234	-0.151	0.115	0.052	0.169	0.012	**0.522**
A10.9	2.97	1.10	-0.220	0.305	0.347	-0.287	0.426	0.222	0.178	0.294	**0.394**
A10.10	3.20	1.14	-0.349	0.224	0.189	-0.135	0.237	0.119	0.104	0.391	**0.267**

Table 6: Correlation matrix for PAHD survey corrected for overlap

Item Name			**Pearson Item-Scale Correlations**	
	Mean	**SD**	**BK**	**FSARVC**
Scale: BK				
B1.1_R	2.14	1.47	**0.588**	-0.453
B1.4_R	2.99	1.25	**0.395**	-0.390
B1.5_R	3.18	1.35	**0.424**	-0.356
B1.7_R	1.96	1.55	**0.390**	-0.149
B1.8_R	1.29	1.40	**0.520**	-0.446
B2.4_R	2.90	1.41	**0.465**	-0.099
B2.5_R	1.81	1.32	**0.594**	-0.343
Scale: FSARVC				
B2.1	2.72	1.20	-0.433	**0.685**
B2.2	2.69	1.27	-0.211	**0.536**
B2.3	2.99	1.13	-0.458	**0.677**
B2.6	1.74	1.36	-0.381	**0.441**
B1.6	2.80	1.21	-0.372	**0.464**

Table 7: Item discriminant validity tests for HD-GT survey

Item Name			Item-discriminant validity test								
	Mean	SD	IARVC	GTP	FCGT	WC	SGTR	UR	TB	CGL	DI
Scale: IARVC											
A1.1_R	1.35	1.39	n/a	2	2	2	2	2	2	2	2
A1.2_R	1.58	1.50	n/a	2	2	2	2	2	2	2	2
A1.3_R	1.41	1.47	n/a	2	2	2	2	2	2	2	2
A1.4_R	1.29	1.36	n/a	2	2	2	2	2	2	2	2
A1.5_R	2.06	1.64	n/a	2	2	2	2	2	2	2	2
A1.6_R	1.80	1.52	n/a	2	2	2	2	2	2	2	2
A1.7_R	2.50	1.46	n/a	2	2	2	2	2	2	2	2
Scale: GTP											
A3.1	3.13	1.00	2	n/a	2	2	2	2	2	2	2
A3.2	3.15	0.90	2	n/a	2	2	2	2	2	2	2
A3.4	3.57	0.73	2	n/a	2	2	2	2	2	2	2
A3.5	3.55	0.77	2	n/a	2	2	2	2	2	2	2
A3.6	3.61	0.96	2	n/a	1	2	1	1	1	1	2
Scale: FCGT											
A4.1	3.77	0.70	2	-1	n/a	2	1	-1	1	1	1
A4.2	3.30	1.18	2	2	n/a	2	2	2	2	2	2
A4.3	3.01	1.32	2	1	n/a	2	2	2	2	2	2
A4.4	3.47	0.80	2	2	n/a	2	2	2	2	2	2
Scale: WC											
A5.1_R	1.46	1.49	2	2	2	n/a	2	2	2	2	2
A5.2_R	2.63	1.30	2	2	2	n/a	2	2	2	2	2
A5.3_R	3.12	1.17	2	2	2	n/a	2	2	2	2	2
A5.4_R	2.23	1.60	2	2	2	n/a	2	2	2	2	2

A5.5_R	2.39	1.44	2	2	2	n/a	2	2	2	2	2
Scale: SGTR											
A6.1	2.31	1.55	2	2	1	2	n/a	1	2	1	1
A6.2	2.18	1.38	2	2	1	2	n/a	1	2	1	2
A6.3	1.42	1.42	2	2	2	2	n/a	2	2	2	2
A6.4	2.92	1.40	2	1	2	2	n/a	1	2	1	2
Scale: UR											
A8.1	3.41	1.04	2	2	2	2	1	n/a	1	1	1
A8.2	3.71	0.54	2	2	2	2	2	n/a	2	2	2
A8.3	3.77	0.51	2	2	2	2	2	n/a	2	2	2
A8.4	3.62	0.68	2	2	2	2	2	n/a	2	2	2
A8.5	3.64	0.59	2	2	2	2	2	n/a	2	2	2
Scale: TB											
A9.1	2.73	1.34	2	1	2	2	2	2	n/a	2	2
A9.2	2.83	1.19	2	1	1	2	2	1	n/a	1	1
A9.3	2.58	1.35	2	2	2	2	2	2	n/a	2	2
A9.4	2.50	1.36	2	2	2	2	2	2	n/a	2	2
Scale: CGL											
A10.3	2.28	1.08	2	2	2	2	2	2	2	n/a	-1
A10.4	2.18	1.05	2	2	2	2	2	1	2	n/a	2
A10.7	3.01	0.93	2	1	1	2	1	2	2	n/a	2
A10.8	2.89	0.93	1	1	1	1	1	2	2	n/a	1
Scale: DI											
A10.2	2.24	1.52	2	1	1	2	1	2	1	2	n/a
A10.6	2.85	1.19	2	1	2	2	2	2	2	2	n/a
A10.9	2.97	1.10	2	1	1	2	-1	1	1	1	n/a
A10.10	3.20	1.14	2	1	1	2	1	2	2	1	n/a

Table 8: Item discriminant validity tests for PAHD survey

Item Name			Item discriminant validity test	
	Mean	SD	BK	FSARVC
Scale: BK				
B1.1_R	2.14	1.47	n/a	2
B1.4_R	2.99	1.25	n/a	2
B1.5_R	3.18	1.35	n/a	2
B1.7_R	1.96	1.55	n/a	2
B1.8_R	1.29	1.40	n/a	2
B2.4_R	2.90	1.41	n/a	2
B2.5_R	1.81	1.32	n/a	2
Scale: FSARVC				
B2.1	2.72	1.20	2	n/a
B2.2	2.69	1.27	2	n/a
B2.3	2.99	1.13	2	n/a
B2.6	1.74	1.36	2	n/a
B1.6	2.80	1.21	2	n/a

using the statistical program 'R' (R Core Team, 2013). Most items demonstrate an acceptable discriminatory power. An item may fail the discriminant validity test if it correlates well with two or more scales, or if it has a low item-internal consistency. Within the IARVC and WC subscales of the HD-GT survey, all items demonstrated acceptable discriminatory power. Most of the items that did not receive a value of 2 were correlated with several scales. Items A6.4, A8.1, A9.2 had a low internal consistency which may have resulted in low discriminatory power. Item 3.6 had neither low internal consistency nor correlation with other scales, but its mean was significantly different than other items in the scale, which may have influenced correlation values. Both sub-scales, BK and FSARVC in the PAHD survey demonstrated acceptable discriminatory power.

Reliability and Validity

The Chronbach's alpha coefficient was used to determine internal consistency of the subscales of each survey tool. These results are summarized in tables 9 and 10. A minimum Chronbach's alpha coefficient of 0.70 is required to confirm reliability of a scale (Nunally & Bernstein, 1994) . Four of the nine scales in the HD-GT survey fell below this cut-off; however, the range of values for these scales was 0.637 to 0.661. Given the relatively small margin, some scales may reach the 0.70 cut-off if used in a larger population. Both scales within the PAHD showed extremely high levels of internal consistency with coefficients of 0.993 and 0.986. All scales had weak, positive correlations with each other except for those that were reverse coded; these had weak, negative correlations. One exception was the correlation between IARVC and SGTR. As IARVC is reverse coded and SGTR was not,

Table 9: Reliability coefficients and inter-scale correlations for HD-GT survey

Scale	IARVC	GTP	FCGT	WC	SGTR	UR	TB	CGL	DI
IARVC	**0.901**								
GTP	-0.349	**0.812**							
FCGT	-0.268	0.462	**0.651**						
WC	0.224	-0.102	-0.219	**0.790**					
SGTR	0.007	0.410	0.385	-0.436	**0.648**				
UR	-0.140	0.379	0.201	-0.371	0.439	**0.736**			
TB	-0.423	0.278	0.312	-0.325	0.124	0.337	**0.661**		
CGL	-0.340	0.367	0.325	-0.294	0.476	0.424	0.300	**0.783**	
DI	-0.264	0.364	0.361	-0.261	0.342	0.178	0.222	0.329	**0.637**

Chronbach's alpha coefficient is bolded on the diagonal

Table 10: Reliability coefficients and inter-scale correlations for PAHD survey

Scale	BK	FSARVC
BK	**0.993**	
FSARVC	-0.5	**0.986**

Chronbach's alpha coefficient is bolded on the diagonal

there should have been a negative correlation, instead, there is a very small (near-zero) positive correlation.

All scales also have an alpha coefficient larger than any item's Pearson coefficient. This finding along with those above demonstrates that each scale contributes something unique to the overall survey.

Psychosocial Analysis

Findings discussed above support the reliability and validity of the HD-GT and PAHD surveys for use in the ARVC population so the analysis was taken one step further to identify potential factors that may influence the psychosocial impact of ARVC. Four key factors were examined: sex, parent from whom the gene was inherited, carrier status, and age. Sex, carrier status, and age have been discussed in the literature as influential factors in terms of attitudes toward genetic testing and psychosocial impact of risk. The transmitting parent was also included in this analysis due to the drastic difference in how men and women with the *TMEM43* gene are affected. Data for each of the four factors was available for the majority of study participants so sample size for the psychosocial analysis was not significantly different from sample size for reliability and validity testing. Tables 11 and 12 summarize the descriptive statistics for each. Means and variances were approximately equal within each subscale, which supports the validity of the scales for this analysis.

An analysis of variance (ANOVA) was conducted using these four factors to build a model. Adjusted r squared values for each subscale model ranged from 0 to

Table 11: Descriptive statistics for psychosocial analysis of HD-GT survey

		IARVC	GTP	FCGT	WC	SGTR	UR	TB	CGL	DI
Female	**mean**	11.31	17.52	13.75	11.35	11.06	18.24	10.65	10.72	11.65
	n	52	52	51	52	53	54	52	51	52
	s.d	8.24	3.17	2.65	4.96	3.41	2.52	3.77	3.13	3.51
Male	**mean**	14.00	15.39	13.78	13.22	8.16	17.90	10.59	9.32	10.16
	n	17	18	18	18	19	19	17	19	19
	s.d	8.35	3.40	2.78	5.82	4.84	2.23	3.41	2.93	3.10
Inherited from Mother	**mean**	14.00	17.14	13.80	11.17	11.32	18.43	10.69	10.05	11.24
	n	35	36	35	35	37	37	35	37	37
	s.d	8.24	3.38	2.82	4.79	3.38	2.32	3.15	2.68	3.27
Inherited from Father	**mean**	10.22	16.82	13.66	12.24	9.70	17.88	10.41	11.10	11.41
	n	32	33	32	33	33	34	32	31	32
	s.d	7.91	3.38	2.61	5.61	3.99	2.56	4.19	3.23	3.75
Carrier	**mean**	13.41	16.49	14.00	11.49	11.00	18.21	10.56	10.48	11.58
	n	39	41	39	39	41	42	39	40	40
	s.d	8.03	3.79	2.65	5.32	3.42	2.35	3.63	2.98	3.61
Non-carrier	**mean**	9.76	17.64	13.59	12.03	9.37	18.00	10.76	10.14	10.90
	n	29	28	29	30	30	30	29	29	30
	s.d	8.18	2.51	2.61	5.07	4.66	2.60	3.83	3.40	3.28

Table 12: Descriptive statistics for psychosocial analysis of PAHD survey

		BK	FSARVC
Female	**mean**	15.73	13.29
	n	51	52
	s.d	6.14	4.75
Male	**mean**	17.11	11.84
	n	18	19
	s.d	6.46	3.50
Inherited from Mother	**mean**	15.69	13.70
	n	35	37
	s.d	6.77	3.93
Inherited from Father	**mean**	16.41	12.25
	n	32	32
	s.d	5.78	4.94
Carrier	**mean**	15.33	13.51
	n	39	41
	s.d	5.95	4.11
Non-carrier	**mean**	16.83	12.14
	n	29	29
	s.d	6.48	4.94

0.190. The IARVC and FSGT had the highest r squared values at 0.156 and 0.190 meaning that the variables included in the models for these subscales account for approximately 16% and 19% of the variance, respectively. The seven remaining subscales in the HD-GT survey and the two subscales in the PAHD survey had r-squared values ranging from 0 to 0.073. Tables 13 and 14 summarize the r squared, adjusted beta, and t values for each subscale. Four correlations were found to be substantial and statistically significant. First, there was a negative correlation between age in years and the IARVC scale. The IARVC scale deals with the psychosocial impact of living in a family with ARVC, particularly the negative emotions associated with deaths in the family. The negative correlation signifies that as age increases, psychosocial adjustment decreases. As medical science moves forward, so does the ability to delay or prevent SCD from ARVC. Older individuals may have memories of family members experiencing SCD before ARVC could be diagnosed or treated. Younger individuals may not experience as many deaths as older relatives due to advances made in the treatment of ARVC and may therefore score better on a scale designed to measure the negative experiences within the family. Second, there was a positive correlation between sex and the GTP scale. The GTP scale was designed to measure the importance an individual places on various aspects of preparing for genetic testing. At the data level, men were assigned a value of 1 and women were assigned a value of 2.

Table 13: ANOVA for each subscale of HD-GT

		Sex		Carrier/Non-Carrier		Sex of transmitting parent		Age in years	
	Adjusted r square	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**
IARVC	0.156	-0.180	-1.600	-0.082	-0.722	-0.197	-1.666	**-0.313[b]**	**-2.696**
GTP	0.048	**0.259[c]**	**2.178**	0.148	0.218	-0.062	-0.513	0.028	0.232
FCGT	-0.017	0.002	0.019	-0.174	-1.381	-0.010	-0.079	0.147	1.139
WC	0.033	-0.155	-1.292	0.085	0.704	0.080	0.643	0.194	1.588
SGTR	0.190	**0.299[b]**	**2.752**	-0.179	-1.632	**-0.292[b]**	**-2.589**	0.009	0.080
UR	-0.038	0.052	0.425	0.010	0.083	-0.101	0.083	-0.055	-0.440
TB	-0.044	0.001	0.006	0.004	0.032	-0.008	-0.062	0.133	1.027
CGL	-0.001	0.205	1.668	-0.071	-0.578	-0.005	-0.037	0.113	0.902
DI	0.057	0.210	1.722	-0.143	-1.162	0.023	0.182	0.003	0.021

[a]$p \leq 0.001$; [b]$0.001 < p \leq 0.01$; [c]$0.01 < p \leq 0.05$

*beta values are standardized

Table 14: ANOVA for each subscale of PAHD

		Sex		Carrier/Non-Carrier		Sex of transmitting parent		Age in years	
	Adjusted r square	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**	**Beta**	**t**
BK	-0.019	-0.105	-0.841	0.169	1.356	0.036	0.282	-0.002	-0.016
FSARVC	0.073	0.124	1.060	-0.173	-1.467	-0.227	-1.872	0.212	1.773

[a]$p \leq 0.001$; [b]$0.001 < p \leq 0.01$; [c]$0.01 < p \leq 0.05$

*beta values are standardized

The positive correlation signifies that women place more value on preparation than men. Third, there was a positive correlation between sex and the SGTR scale. The SGTR scale was intended to measure the importance an individual places on having social support when receiving test results. The positive correlation signifies that women place more importance on social support at this stage than do men. Fourth, and not previously studied in the literature, is a negative correlation between transmitting parent and the SGTR scale. At the data level, mothers were assigned a value of 1 and fathers a value of 2. The negative correlation signifies that those who inherited the ARVC gene from their mother score better on this scale. As ARVC affects men more severely, survey participants who inherited the gene from the paternal side likely experienced the death of his or her father at a young age and may not have a parent who has experienced the process as a source of guidance. Those who inherited the gene from the maternal side may have a living parent who has lived through the process and is able to act as a source of support when undergoing the testing process.

Summary

This pilot study was designed to assess the validity and reliability of two surveys designed for LS for use in the ARVC population. Study findings support item level and scale level assumptions set forth in the literature. Most item-scale correlations fell within the ideal 0.40 to 0.70 range with few exceptions, and internal consistency of the scales was supported by alpha values at or near the recommended value of 0.70. Given the small sample size of this study, items below

recommended thresholds cannot be discounted and should be reassessed in a larger study.

Preliminary psychosocial analysis identified influences of age, sex, and transmitting parent, but did not demonstrate any differences in scores between carriers and non-carriers.

CHAPTER 5

Discussion

This chapter begins with a discussion of the testing of two psychometric testing tools: the HD-GT scale and the PAHD scale for use in the Newfoundland ARVC population. This is followed by a discussion of the resulting scores for each survey.

Psychometric Properties

Testing of both surveys was based on the work of Ware and Gandek (1998), whose validation process has been used in numerous psychometric testing studies including the validation of the HD-GT and PAHD scales for LS in the Newfoundland and Labrador population (LeDrew, 2009; Way et al., 2011).

Target Population and Sample

The target population of this study was individuals born at an *a priori* 50% risk for the *TMEM43* mutation known to cause ARVC who had undergone direct mutation testing. The numbers of individuals whose mothers had the mutation and those whose fathers had the mutation responded in approximately equal numbers. Slightly more carriers than non-carriers responded. This may be because carriers perceived they had more to contribute to a research study about psychosocial impacts than non-carriers. The first symptom of ARVC is often SCD; as a result, the Newfoundland ARVC population has been very receptive to research designed to improve treatment of the condition. Those who are carriers of the mutation may have felt more inclined to participate in this study because the results may directly benefit themselves or their children/grandchildren. Significantly more women than

men participated in this study, which may be due to the nature of the condition itself. Since ARVC affects men earlier and more severely than it does women, women who are carriers tend to live much longer than men who are carriers and therefore the living ARVC population is more than 50% women.

Subscale Structure

The finalized LS versions of both surveys were used to create the subscale structure for this study. Items that were ultimately removed in LS studies were also excluded here for future comparability of results.

Data Quality and Item-Level Scaling Assumptions

Data quality is evaluated in terms of the amount of missing data, and the frequency distribution of response choices (Ware & Gandek, 1998) . A large amount of missing data, or missing data that seem systematic may be indicative of difficulty understanding particular items. Missing data in this study were minimal and random so we can conclude that there were no major comprehension issues with any particular item. As stated in a previous chapter, newly diagnosed families were excluded during recruitment, so individuals participating in the current study have had experience with ARVC and would therefore be familiar with any terminology specific to ARVC or genetics (e.g. carrier/non-carrier, inherited, generation, geneticist/genetic counsellor, ECG, Holter monitor).

Quality data should also include the full range of response choices and the frequency of response choices for each item should be approximately equal with the exception of questions that are emotionally charged or identify uncommon states. Items with severely skewed frequency distributions all met the criteria for

exception. All items in the scales GTP, FCGT, and UR were severely skewed, but all represent uncommon states for the sample population. The GTP scale measured the importance individuals place on various aspects of preparing for genetic testing such as understanding the testing process, understanding one's risk, and knowing if one has the mutation for children or grandchildren. Since all study participants have undergone genetic testing, they have already made the decision to be tested and therefore must consider testing to be an important part of living with the risk of ARVC. The FCGT scale measured the concern for family members who refuse genetic testing. Similarly, since all participants have undergone genetic testing, they would be the individuals within the family to encourage others to be tested. It would be highly unusual for people to undergo genetic testing and to then claim that is it not important to them or to discourage other family members from being tested. Since low scores on both scales represent an uncommon state in the context of the target population, items within these scales are not required to have symmetrical frequency distributions. A low UR scale score also represents an uncommon state. The scale measures the extent of an individual's belief that early detection of the condition and healthy living habits contribute to the management ARVC. It would be highly unusual for someone to opt for genetic testing and have the attitude that early detection is not beneficial. For this reason, the UR scale can be included in the survey despite skewed scores on all items.

At the item level, the standard deviation and mean for each item within a scale are assumed to be similar. This holds true for the majority of items with few exceptions. Items that did not meet the criteria were emotionally charged or items

that had expected answers but still represent an important element of its scale. According to Ware and Gandek, these are acceptable reasons for inclusion.

Scale Level Assumptions

Three Likert scale assumptions were tested by determining item internal consistency and equality of item-scale correlations. The majority of items correlated to their respective scales with Pearson item-scale correlations at or above 0.40, the cut-off proposed by Ware and Gandek. A small number of items did not quite reach 0.40; however, because these items did provide a unique piece of information and the small sample size in this study, these items were not discounted.

Item discriminant validity was also calculated to determine the strength of each item's correlation with its own scale when compared to other scales. The majority of items received the recommended value of 2, meaning that the strength of the item's correlation with its own scale was at least 2 standard errors greater than the item's correlation with another scale. Most items that did not reach a value of 2 were the items with low internal consistency. Items with low internal consistency or those that correlate with two or more scale may fail the item discriminant validity test in a small sample but should not be discounted until the items are retested in a larger sample(Ware & Gandek, 1998) .

Reliability and Validity

The Chronbach's Alpha coefficient was used to determine scale internal consistency. Five of the nine scales for the HD-GT survey met the recommended cut-off of 0.70 and the four scales that did not meet the cut-off were all above 0.60. Again, due to the small margin and the small sample size, retesting in a larger

population may result in an improvement of these values. Overall, internal consistency of each scale was higher than any one item-scale correlation, and correlations between scales were all relatively weak. Both scales in the PAHD survey exceeded the recommended cut-off. This supports the reliability and validity of both surveys in the ARVC population.

Interpretation of Scores

Results from the HD-GT and PAHD align well with psychosocial literature surrounding ARVC and other genetic conditions, and offer some insight into internal conflicts individuals may face.

Low scores after reverse coding on the IARVC scale indicate that the experience of living in a family with ARVC has a substantial impact on the decision to undergo genetic testing. The IARVC scale measures the negative implications of living in a family with ARVC such as the loss of family members, the fear of losing family members in the future, and fear for one's own future health. Low scores on this scale indicate these factors carried more weight in the decision to seek testing. Studies of various inherited conditions consistently conclude that individuals who have experienced the death of a family member or the onset of disease symptoms are more likely to opt for genetic testing(Armstrong et al., 2000; Cox, 2003; d'Agincourt-Canning, 2005; Etchegary, 2006; Etchegary et al., 2010; Kasparian et al., 2009; Klitzman et al., 2007; Manuel & Brunger, 2014; McAllister, 2002; Norris et al., 2009; Smith et al., 2002) . SCD can often be the first symptom of ARVC, so the onset of symptoms is less likely than the loss of family members to be a contributing factor. The lasting effects of losing a family member may also explain the negative

correlation between score on the IARVC scale and age. The negative correlation implies that older respondents scored lower on this scale, and a low score indicates that the experience of living in a family with ARVC weighs heavily on the decision to undergo testing.

This subtype of ARVC was first found in Newfoundland families in the 1980s so some survey respondents would have memories of family members dying suddenly before ever hearing of ARVC. Many others would have experienced living at risk for ARVC prior to the availability of haplotype testing in 1998, when ARVC could only be diagnosed when an individual began showing symptoms. During this time period, SCD was unpredictable and relatively unpreventable so there would have been a great deal of uncertainty and worry surrounding ARVC risk. Once haplotype testing became available in 1998, it was possible to identify pre-symptomatic individuals and take measures to prevent SCD through the use of implantable cardioverter defibrillators (ICDs) and medications. Younger survey respondents likely have fewer first-hand experiences with losing family members suddenly to ARVC as treatment options were more widely available. For this reason, younger individuals may be less influenced by the death of family members when making genetic testing decisions than their older family members.

The second subscale (GTP) measures the importance given to preparation when making a genetic testing decision. High scores on this subscale indicate that survey respondents believe it is important to know whether or not one has the gene and to be informed about the process. Three items dealing with the importance of knowing whether one has the gene had the highest scores within this scale. This is

consistent with the literature as the desire to define one's own risk and risk for children is often cited as the primary motivation to undergo genetic testing (Aatre & Day, 2011; Claes et al., 2004; Clark et al., 2000; Esplen et al., 2007; Ormondroyd et al., 2014) . This also corroborates the findings from qualitative research in the ARVC population that individuals feel a relational responsibility to other family members, particularly children and grandchildren to be tested (Etchegary et al., 2014; Manuel & Brunger, 2014) . In conditions where treatment is available, as is the case with ARVC, this motivation is amplified (Manuel & Brunger, 2014) . Also noteworthy is that females scored significantly higher on this scale. This may be due to the emotionally charged content dealing with the health of children and grandchildren. Since men tend to be affected at a younger age than women, male respondents may be less likely to have children or grandchildren of their own. The difference seen here between male and female scores may be confounded by the inherent age bias in this sample.

The third scale, FCGT, identifies challenges that families face when family members have differing opinions surrounding genetic testing. This scale also had particularly high scores, indicating that survey respondents felt it important for all family members to undergo testing and felt concern for family members who refuse testing. This theme was also present in the qualitative research as participants felt that it is a person's duty to be tested and that testing should be sought whenever available (Manuel & Brunger, 2014) .

Moderate scores were seen in the fourth and fifth subscales, WC and SGTR. These scales deal with waiting for and receiving genetic testing results. A moderate

mean and relatively symmetrical frequency distributions for items within these scales indicate that individuals were not particularly concerned with the time between testing and receiving results and have different preferences for the way in which results are disclosed.

One noteworthy result here was the impact of the sex of the transmitting parent on the importance an individual places on having social support when receiving test results. Those who inherited the mutation from their father scored worse on the SGTR scale. As ARVC affects men more severely, survey participants who inherited the gene from their father likely experienced their father's death at a young age. Those who inherited the gene from their mother may not have lost their mother to the disease and she could have acted as their source of social support. Those who have a parent who has lived with ARVC who can guide them through the testing process would be more likely to assign a greater value to the social support received from their parent while receiving test results. Additionally, women scored significantly higher than men on this scale. This was expected as women tend to value social support during emotional events more so than men.

High scores on the UR scale indicate that the majority of the at-risk population has a good understanding of their ARVC risk and what that risk means. This may be due partly to selection bias as new families were excluded and all participants have undergone genetic testing. The majority of survey respondents have been living with the knowledge of their test results for some time and have had time to learn about the condition and what it means to be a carrier or non-carrier. This scale deals with the knowledge of screening and treatment options as well as

the influence of healthy living behaviors so anyone who has undergone testing would be well-informed on the topic.

Scores on the TB scale were moderate and variable. With high scores in the UR scale, implying a good understanding of the condition, the variable scores in this scale may be due to the perception of different patterns in different families. However, the majority of respondents agreed that men and women are affected differently, something that is a fact with this subtype of ARVC.

The final two subscales of the HD-GT survey, CGL and DI deal with communication issues within families. Both scales showed moderate and varying scores, indicating that families communicate differently about the genetic link and each family has unique issues. One item that is particularly variable is item A10.2 that deals with difficulty informing young family members of ARVC risk. This particular item was split, with large numbers of respondents choosing one extreme or the other. This could indicate that families may need guidance or assistance from clinicians to inform younger family members of the ARVC risk.

One item that had a particularly high mean score when compared to the other items in the scale was A10.10, which asks respondents about the importance of protecting the rights of others when disclosing risk. While most respondents place great importance on testing and encourage others to be tested, the majority of respondents answered strongly in favor of protecting the rights of others. Genetic testing can be a highly valuable tool, but the decision to be tested does not occur in isolation. Revealing one's own result has the potential to implicate the result of another family member. This can be particularly troublesome when a family

member does not want to know their own result, where there may be a previously undisclosed adoption or question of paternity, or where disclosure of risk or test results to a child may have negative psychosocial effects. One female survey respondent expressed gratitude for not being informed of risk until adulthood as there was no immediate risk to her health if she were not told, and she was particularly athletic and her social circle in childhood and adolescence was rooted in sport. The decision may be more difficult for a parent in the case of male children, as withholding information about risk or test results may put the child's life at risk.

Both BK and FSARVC scales within the PAHD survey had moderate and variable scores. One item, B1.8_R, in the BK scale had a mean significantly different than the other items in the scale. This item has to do with the worry for the future of young family members and had a particularly low score, meaning that respondents do indeed worry about young family members. This is expected as concern for other family members, particularly children, is a consistent theme across all hereditary conditions. Since ARVC can affect teens and young adults, the risk is more immediate than with many other hereditary conditions that may not appear until later in adulthood.

Item B2.6 also had a particularly low mean. This item has to do with the acceptance of one's own future through caring for an affected family member. Since people affected by ARVC do not typically show symptoms and rarely show symptoms that require ongoing care from another person, individuals are not typically in caregiver roles for a family member unless it is for a condition other than ARVC. These surveys were developed for hereditary cancers where family

members may regularly act as caregivers for the condition under study. As this dynamic is relatively uncommon in ARVC, this item's low mean is expected.

Summary

Based on the preliminary findings from this pilot, the HD-GT and PAHD Surveys were considered to be reliable and valid in an ARVC population, with the exception of a small number of items that require re-examination in a larger study. Items and subscales satisfied the assumptions set forth in an accepted method of survey validation. Items that did not satisfy the assumptions met the criteria for inclusion, and scales that did not meet cut-offs were very close to an acceptable value, warranting re-examination in a larger study. Overall, both surveys being studied show promise for clinical use in ARVC populations.

CHAPTER 6

Limitations and Implications

This chapter discusses the limitations, strengths, and implications of study findings. The first section examines the limitations and strengths of the study. The second section examines implications for healthcare providers at all levels as well as for new and current ARVC patients.

Limitations and Strengths

As the current study is a pilot, the small sample size limits the generalizability of the data. Most items that failed various stages of psychometric testing could were borderline and could not be discounted due to the small sample size. Rather, results of this study indicate that both scales have some merit in the ARVC population and warrant further testing in a larger sample to verify the conclusions. The small sample size also limited the ability to analyze subgroups.

Ability to analyze subgroups or other key variables was also limited by the dataset being used. While updated information is kept on file in clinic charts, the dataset used for this study is regularly updated. The dataset contains a great deal of missing or out of date information so some potentially clinically or socially significant variables were excluded as they were not readily available. Within the time constraints of this study, it was not possible to update the dataset from clinical charts.

This pilot may also be somewhat limited by selection bias. Newly ascertained families were excluded from recruitment as it was thought that individuals who had been newly diagnosed had not had time to process their test results and that

participating in psychosocial research might cause additional distress. This may have resulted in skewed results in subscales related to knowledge of ARVC and the causative gene. Excluding newly ascertained families may also result in an overrepresentation of the long-term impact. While some individuals in the included families may be newly diagnosed, they would still be relatively familiar with ARVC through other family members.

One of the strengths of this study is the ascertainment of the population. Individuals in the Newfoundland ARVC database are identified through pedigrees and then sought out by the genetics team. Unlike ARVC studies in populations outside Newfoundland, we have knowledge of all family members regardless of whether or not they have been to a genetics clinic.

Another strength of this study is the alignment of quantitative results found here and qualitative results from previous studies within the same population. This indicates that both scales have the potential to accurately quantify emotions and attitudes toward genetic testing for ARVC. Another notable strength is the readability of both scales. Surveys were self-administered and the percentage of missing data was low, indicating that there were no major comprehension problems for any particular item.

Implications

Study findings have implications for both healthcare professionals and patients in terms of clinical management and education.

Clinical Management

Results of both scales have implications for any healthcare professional who works with ARVC patients on a regular basis including but not limited to family physicians, cardiologists, geneticists, genetic counsellors and other Cardiac Genetics clinic staff. In 2004, a Cardiac Genetics clinic was opened in St. John's, NL for families at risk for ARVC. For individuals in ARVC families, visits to this clinic are often associated with very emotional stages of the genetic testing and treatment process: receiving information about the testing process, receiving genetic test results, receiving information about treatment options, check-ups or investigation following the onset of symptoms, etc. These tools may therefore provide healthcare providers within specialized clinics such as these with insight into areas of concern that are likely contributing to the emotional state of specific patients. Results of these surveys may provide clinicians with information about a patient's level of understanding, attitudes toward various aspects of the testing process, and his or her specific concerns, which may influence the steps taken to guide the patient through the testing process and beyond. There may be a psychosocial effect highlighted by an individual's survey results that had not been previously identified or was not expected. By receiving additional information, an individual's circle of care may be able to provide anticipatory guidance throughout the testing process and subsequent treatment plan to reduce any negative psychosocial effects.

However, due to the sparse geography of the province of Newfoundland and Labrador and the location of specialized physicians, a large number of ARVC patients receive care primarily from family physicians. A large number of ARVC

patients live in rural areas where access to geneticists and cardiologists is extremely limited. Family physicians are often tasked with managing complex conditions such as ARVC, particularly when patients do not have easy access to specialized care. Having reliable psychometric tools may help family physicians better understand the specific needs of their ARVC patients so that appropriate care can be provided. Further studies may be able to relate scores obtained on these scales to standardized measures of coping or distress to guide clinicians.

Similarly, patients may directly benefit from the surveys as completing the surveys requires a great deal of self-reflection. Completing the surveys may bring up topics or emotions that an individual had not previously considered which may guide that person to seek out appropriate resources. For example, an individual may become more aware of tension between family members when asked about conflicts arising from disclosure issues, and seek out family counselling. These tools offer the option of patient-centered care, which in turn may improve the psychosocial well being of those affected. Scores on particular scales may identify specific problem areas for an individual and allow the health care provider administering the survey to suggest appropriate resources.

If common themes arise from larger scale use of these surveys, this may also help guide the formation of new psychosocial resources. For example, if a large number of family conflicts arise from disclosure issues, it may warrant the training of family counsellors with specialized knowledge of ARVC or the development of tools to assist families with communication about inherited risk.

Education

Both surveys also have the potential to highlight educational needs for clinicians and patients. For clinicians who do not have a great deal of experience with ARVC, these survey tools may highlight the range of possible psychosocial effects. Since a large number of ARVC patients reside in rural areas, local healthcare providers may not fully understand the condition, much less the range of emotional issues patients may experience as a result. Utilization of these tools may raise awareness of possible psychosocial issues and result in better overall care.

These tools may also be useful for clinicians by identifying gaps in patient knowledge, particularly for newly diagnosed individuals. This study excluded individuals in newly ascertained families however there several mid to low scores on items related to understanding ARVC and the genetic basis of the condition. When clinicians can identify misconceptions held by older families, it may help them avoid those same misconceptions in newer families. For example, if survey results show that individuals in older families do not understand their own risk for ARVC, clinicians may spend more time explaining the inheritance pattern to new patients so to maximize understanding of personal risk. These surveys may also be used to identify gaps in understanding for individual patients. Newly diagnosed individuals receive a great deal of information in a short period of time, so completion of the survey may highlight information that was not initially understood or was not received. Individuals who were tested at a young age or many years ago may also have missed or forgotten key information. By identifying these gaps in

understanding, healthcare providers may be able to offer more education on specific topics.

Conclusion

This pilot study examined two psychometric testing tools for use in the Newfoundland ARVC population. This was the first quantitative study of psychosocial adjustment in an ARVC population.

Preliminary findings indicate potential for both survey tools to be used in the ARVC population as the majority of items and subscales were found to be valid and reliable. Further testing in a larger study is required to confirm these results and polish the surveys for clinical use. Further psychometric testing may be able to identify items that are unnecessary resulting in shorter surveys and reduced patient burden.

Findings from this study also highlighted a small number of clinical variables that may have an affect on overall psychosocial impact. Statistically significant correlations aligned with current qualitative psychosocial research, further supporting the future usefulness of the two survey tools.

References

Aatre, R. D., & Day, S. M. (2011). Psychological issues in genetic testing for inherited cardiovascular diseases. *Circulation: Cardiovascular Genetics, 4*(1), 81-90. doi:10.1161/CIRCGENETICS.110.957365

Ahmad, F., Li, D., Karibe, A., Gonzalez, O., Tapscott, T., Hill, R., . . . Roberts, R. (1998). Localization of a gene responsible for arrhythmogenic right ventricular dysplasia to chromosome 3p23. *Circulation, 98*(25), 2791-2795. doi:10.1161/01.CIR.98.25.2791

Appleton, S., Fry, A., Rees, G., Rush, R., & Cull, A. (2000). Psychosocial effects of living with an increased risk of breast cancer: An exploratory study using telephone focus groups. *Psycho-Oncology, 9*(6), 511-521. doi:10.1002/1099-1611(200011/12)9:6<511::AID-PON469>3.0.CO;2-E [pii]

Armstrong, K., Calzone, K., Stopfer, J., Fitzgerald, G., Coyne, J., & Weber, B. (2000). Factors associated with decisions about clinical BRCA1/2 testing. *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 9*(11), 1251-1254.

Bakos, A. D., Hutson, S. P., Loud, J. T., Peters, J. A., Giusti, R. M., & Greene, M. H. (2008). BRCA mutation-negative women from hereditary breast and ovarian cancer families: A qualitative study of the BRCA-negative experience. *Health*

Expectations : An International Journal of Public Participation in Health Care and Health Policy, 11(3), 220-231. doi:10.1111/j.1369-7625.2008.00494.x [doi]

Baumann, S. L. (2006). Family systems genetic illness model-- breast cancer. *Clinical Journal of Oncology Nursing, 10*(3), 377.

Bjorvatn, C., Eide, G. E., Hanestad, B. R., & Havik, O. E. (2008). Anxiety and depression among subjects attending genetic counseling for hereditary cancer. *Patient Education and Counseling, 71*(2), 234-243. doi:10.1016/j.pec.2008.01.008 [doi]

Bonis, P. A., Trikalinos, T. A., Chung, M., Chew, P., Ip, S., DeVine, D. A., & Lau, J. (2007). Hereditary nonpolyposis colorectal cancer: Diagnostic strategies and their implications. *Evidence Report/Technology Assessment,* (150), 1-180.

Botkin, J. R., Belmont, J. W., Berg, J. S., Berkman, B. E., Bombard, Y., Holm, I. A., . . . Mcinerney, J. D. (2015). Points to consider: Ethical, legal, and psychosocial implications of genetic testing in children and adolescents. *The American Journal of Human Genetics,* doi:10.1016/j.ajhg.2015.05.022

Bowen, D. J., Bourcier, E., Press, N., Lewis, F. M., & Burke, W. (2004). Effects of individual and family functioning on interest in genetic testing. *Public Health Genomics, 7*(1), 25-32. Retrieved from http://www.karger.com/DOI/10.1159/000080301

Broadstock, M., Michie, S., & Marteau, T. (2000). Psychological consequences of predictive genetic testing: A systematic review. *European Journal of Human Genetics, 8*(10), 731. doi:10.1038/sj.ejhg.5200532

Carlsson, C., & Nilbert, M. (2007). Living with hereditary non-polyposis colorectal cancer; experiences from and impact of genetic testing. *Journal of Genetic Counseling, 16*(6), 811-820. doi:10.1007/s10897-007-9117-0 [doi]

Carroll, D. L., Hamilton, G. A., & McGovern, B. A. (1999). Changes in health status and quality of life and the impact of uncertainty in patients who survive life-threatening arrhythmias. *Heart & Lung - the Journal of Acute and Critical Care, 28*(4), 251-260. doi:10.1016/S0147-9563(99)70071-3

Christensen, A. H., Andersen, C. B., Tybjaerg-Hansen, A., Haunso, S., & Svendsen, J. H. (2011). Mutation analysis and evaluation of the cardiac localization of TMEM43 in arrhythmogenic right ventricular cardiomyopathy. *Clinical Genetics, 80*(3), 256-264. doi:10.1111/j.1399-0004.2011.01623.x

Claes, E., Denayer, L., Evers-Kiebooms, G., Boogaerts, A., & Legius, E. (2004). Predictive testing for hereditary non-polyposis colorectal cancer: Motivation, illness representations and short-term psychological impact. *Patient Education and Counseling, 55*(2), 265-274. doi:S0738399103003045 [pii]

Clark, S., Bluman, L., Borstelmann, N., Regan, K., Winer, E., Rimer, B., & Skinner, C. (2000). Patient motivation, satisfaction, and coping in genetic counseling and

testing for BRCA1 and BRCA2. *Journal of Genetic Counseling, 9*(3), 219-235. doi:10.1023/A:1009463905057

Codori, A. M., Petersen, G. M., Boyd, P. A., Brandt, J., & Giardiello, F. M. (1996). Genetic testing for cancer in children. short-term psychological effect. *Archives of Pediatrics & Adolescent Medicine, 150*(11), 1131-1138.

Codori, A. M., Zawacki, K. L., Petersen, G. M., Miglioretti, D. L., Bacon, J. A., Trimbath, J. D., . . . Giardiello, F. M. (2003). Genetic testing for hereditary colorectal cancer in children: Long-term psychological effects. *American Journal of Medical Genetics.Part A, 116A*(2), 117-128. doi:10.1002/ajmg.a.10926 [doi]

Collins, V. R., Meiser, B., Ukoumunne, O. C., Gaff, C., St John, D. J., & Halliday, J. L. (2007). The impact of predictive genetic testing for hereditary nonpolyposis colorectal cancer: Three years after testing. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 9*(5), 290.

Cox, S. (2003). Stories in decisions: How at-risk individuals decide to request predictive testing for huntington disease. *Qualitative Sociology, 26*(2), 257-280. doi:10.1023/A:1022971113683

Croyle, R. T., Smith, K. R., Botkin, J. R., Baty, B., & Nash, J. (1997). Psychological responses to BRCA1 mutation testing: Preliminary findings. *Health Psychology, 16*(1), 63-72. doi:10.1037/0278-6133.16.1.63

d'Agincourt-Canning, L. (2005). The effect of experiential knowledge on construction of risk perception in hereditary breast/ovarian cancer. *Journal of Genetic Counseling, 14*(1), 55-69. doi:10.1007/s10897-005-1500-0 [doi]

d'Agincourt-Canning, L. (2006). A gift or a yoke? women's and men's responses to genetic risk information from BRCA1 and BRCA2 testing. *Clinical Genetics, 70*(6), 462-472. doi:CGE720 [pii]

Decruyenaere, M., Evers-Kiebooms, G., Boogaerts, A., Cloostermans, T., Cassiman, J. J., Demyttenaere, K., . . . Van den Berghe, H. (1997). Non-participation in predictive testing for huntington's disease: Individual decision-making, personality and avoidant behaviour in the family. *European Journal of Human Genetics : EJHG, 5*(6), 351-363.

Decruyenaere, M., Evers-Kiebooms, G., Cloostermans, T., Boogaerts, A., Demyttenaere, K., Dom, R., & Fryns, J. P. (2003). Psychological distress in the 5-year period after predictive testing for huntington's disease. *European Journal of Human Genetics : EJHG, 11*(1), 30-38. doi:10.1038/sj.ejhg.5200913 [doi]

den Heijer, M., Seynaeve, C., Vanheusden, K., Duivenvoorden, H. J., Bartels, C. C. M., Menke-Pluymers, M. B. E., & Tibben, A. (2011). Psychological distress in women at risk for hereditary breast cancer: The role of family communication and perceived social support. *Psycho-Oncology, 20*(12), 1317-1323. doi:10.1002/pon.1850

Di Prospero, L. S., Seminsky, M., Honeyford, J., Doan, B., Franssen, E., Meschino, W., . . . Warner, E. (2001). Psychosocial issues following a positive result of genetic testing for BRCA1 and BRCA2 mutations: Findings from a focus group and a needs-assessment survey. *CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne, 164*(7), 1005-1009.

Djurdjinovic, L. (1998). Psychosocial counseling. In D. L. Baker, J. L. Schuette & W. R. Uhlmann (Eds.), *A guide to genetic counselling* (pp. 127-170). New York, NY: Wiley-Liss.

Douma, K. F., Aaronson, N. K., Vasen, H. F., Gerritsma, M. A., Gundy, C. M., Janssen, E. P., . . . Bleiker, E. M. (2010). Psychological distress and use of psychosocial support in familial adenomatous polyposis. *Psycho-Oncology, 19*(3), 289-298. doi:10.1002/pon.1570 [doi]

Duncan, R. E., Gillam, L., Savulescu, J., Williamson, R., Rogers, J. G., & Delatycki, M. B. (2008). "You're one of us now": Young people describe their experiences of predictive genetic testing for huntington disease (HD) and familial adenomatous polyposis (FAP). *American Journal of Medical Genetics.Part C, Seminars in Medical Genetics, 148C*(1), 47-55. doi:10.1002/ajmg.c.30158 [doi]

Eijzenga, W., Hahn, D., Aaronson, N., Kluijt, I., & Bleiker, E. (2014). Specific psychosocial issues of individuals undergoing genetic counseling for cancer – A literature review. *Journal of Genetic Counseling, 23*(2), 133-146. doi:10.1007/s10897-013-9649-4

Erskine, K. E., Hidayatallah, N. Z., Walsh, C. A., McDonald, T. V., Cohen, L., Marion, R. W., & Dolan, S. M. (2014). Motivation to pursue genetic testing in individuals with a personal or family history of cardiac events or sudden cardiac death. *Journal of Genetic Counseling, 23*(5), 849-859. doi:10.1007/s10897-014-9707-6

Esplen, M. J., Madlensky, L., Aronson, M., Rothenmund, H., Gallinger, S., Butler, K., . . . McLaughlin, J. (2007). Colorectal cancer survivors undergoing genetic testing for hereditary non-polyposis colorectal cancer: Motivational factors and psychosocial functioning. *Clinical Genetics, 72*(5), 394-401. doi:CGE893 [pii]

Etchegary, H. (2006). Genetic testing for huntington's disease: How is the decision taken? *Genetic Testing, 10*(1), 60-67. doi:10.1089/gte.2006.10.60 [doi]

Etchegary, H., Pullman, D., Simmonds, C., Young, T. L., & Hodgkinson, K. (2014). 'It had to be done': Genetic testing decisions for arrhythmogenic right ventricular cardiomyopathy. *Clinical Genetics,* doi:10.1111/cge.12513; 10.1111/cge.12513

Etchegary, H., Lemyre, L., & Wilson, B. (2010). Bringing the social into genetics: The psychosocial genetics risk assessment and management framework (PG-RAM). *Current Psychology, 29*(3), 171-187. doi:10.1007/s12144-010-9085-7

Foster, C., Watson, M., Eeles, R., Eccles, D., Ashley, S., Davidson, R., . . . Psychosocial Study Collaborators. (2007). Predictive genetic testing for BRCA1/2 in a UK clinical cohort: Three-year follow-up. *British Journal of Cancer, 96*(5), 718-724. doi:6603610 [pii]

Friedmann, E., Thomas, S. A., Inguito, P., Kao, C. W., Metcalf, M., Kelley, F. J., & Gottlieb, S. S. (2006). Quality of life and psychological status of patients with implantable cardioverter defibrillators. *Journal of Interventional Cardiac Electrophysiology, 17*(1), 65-72. doi:10.1007/s10840-006-9053-1

Frost, C. J., Venne, V., Cunningham, D., & Gerritsen-McKane, R. (2004). Decision making with uncertain information: Learning from women in a high risk breast cancer clinic. *Journal of Genetic Counseling, 13*(3), 221-236. doi:486127 [pii]

Hallowell, N. (2006). Risky relations. family, kinship and the new genetics by featherstone, K., atkinson, P., bharadwaj, A. and clarke, A. *Sociology of Health & Illness, 28*(7), 990-992. doi:10.1111/j.1467-9566.2006.522_2.x

Hamang, A., Eide, G. E., Nordin, K., Rokne, B., Bjorvatn, C., & Oyen, N. (2010). Health status in patients at risk of inherited arrhythmias and sudden unexpected death compared to the general population. *BMC Medical Genetics, 11*, 27-2350-11-27. doi:10.1186/1471-2350-11-27 [doi]

Hamann, H. A., Smith, T. W., Smith, K. R., Croyle, R. T., Ruiz, J. M., Kircher, J. C., & Botkin, J. R. (2008). Interpersonal responses among sibling dyads tested for BRCA1/BRCA2 gene mutations. *Health Psychology, 27*(1), 100-109. doi:10.1037/0278-6133.27.1.100

Hamilton, J. G., Lobel, M., & Moyer, A. (2009). Emotional distress following genetic testing for hereditary breast and ovarian cancer: A meta- analytic review. *Health Psychology, 28*(4), 510-518. doi:10.1037/a0014778

Hamilton, R., & Hurley, K. E. (2010). Conditions and consequences of a BRCA mutation in young, single women of childbearing age. *Oncology Nursing Forum, 37*(5), 627-634. doi:10.1188/10.ONF.627-634 [doi]

Heshka, J. T., Palleschi, C., Howley, H., Wilson, B., & Wells, P. S. (2008). A systematic review of perceived risks, psychological and behavioral impacts of genetic testing. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 10*(1), 19-32. doi:10.1097/GIM.0b013e31815f524f [doi]

Hodgkinson, K. A., Connors, S. P., Merner, N., Haywood, A., Young, T., McKenna, W. J., . . . Parfrey, P. S. (2013). The natural history of a genetic subtype of arrhythmogenic right ventricular cardiomyopathy caused by a p.S358L mutation in TMEM43. *Clinical Genetics, 83*(4), 321-331. doi:10.1111/j.1399-0004.2012.01919.x

Hodgkinson, K. A., Parfrey, P. S., Bassett, A. S., Kupprion, C., Drenckhahn, J., Norman, M. W., . . . Connors, S. P. (2005). The impact of implantable cardioverter-defibrillator therapy on survival in autosomal-dominant arrhythmogenic right ventricular cardiomyopathy (ARVD5). *Journal of the American College of Cardiology, 45*(3), 400-408. doi:10.1016/j.jacc.2004.08.068

Hodgkinson, K., Dicks, E., Connors, S., Young, T., Parfrey, P., & Pullman, D. (2009). Translation of research discoveries to clinical care in arrhythmogenic right ventricular cardiomyopathy in newfoundland and labrador: Lessons for health

policy in genetic disease. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 11*(12), 859.

Hodgkinson, K., & Pullman, D. (2010). Duty to warn and genetic disease. *Canadian Journal of Cardiovascular Nursing = Journal Canadien En Soins Infirmiers Cardio-Vasculaires, 20*(1), 12.

Jackson, H., Huisman, L., Sanatani, S., & Arbour, L. T. (2011). Long QT syndrome. *CMAJ : Canadian Medical Association Journal = Journal De L'Association Medicale Canadienne, 183*(11), 1272. doi:10.1503/cmaj.100138

Kasparian, N. A., Meiser, B., Butow, P. N., Simpson, J. M., & Mann, G. J. (2008). Predictors of psychological distress among individuals with a strong family history of malignant melanoma. *Clinical Genetics, 73*(2), 121-131. doi:10.1111/j.1399-0004.2007.00949.x [doi]

Kasparian, N. A., Meiser, B., Butow, P. N., Simpson, J. M., & Mann, G. J. (2009). Genetic testing for melanoma risk: A prospective cohort study of uptake and outcomes among australian families. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 11*(4), 265. doi:10.1097/GIM.0b013e3181993175

Keller, M., Jost, R., Haunstetter, C. M., Sattel, H., Schroeter, C., Bertsch, U., . . . Brechtel, A. (2008). Psychosocial outcome following genetic risk counselling for familial colorectal cancer. A comparison of affected patients and family members. *Clinical Genetics, 74*(5), 414-424. doi:10.1111/j.1399-0004.2008.01089.x [doi]

Klitzman, R., Thorne, D., Williamson, J., Chung, W., & Marder, K. (2007). Disclosures of huntington disease risk within families: Patterns of decision-making and implications. *American Journal of Medical Genetics.Part A, 143A*(16), 1835-1849. doi:10.1002/ajmg.a.31864 [doi]

Kopciuk, K. A., Choi, Y., Parkhomenko, E., Parfrey, P., Mclaughlin, J., Green, J., & Briollais, L. (2009). Penetrance of HNPCC-related cancers in a retrolective cohort of 12 large newfoundland families carrying a MSH2 founder mutation: An evaluation using modified segregation models. *Hereditary Cancer in Clinical Practice, 7*(1), 16. doi:10.1186/1897-4287-7-16

Lammens, C. R., Aaronson, N. K., Wagner, A., Sijmons, R. H., Ausems, M. G., Vriends, A. H., . . . Bleiker, E. M. (2010). Genetic testing in li-fraumeni syndrome: Uptake and psychosocial consequences. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 28*(18), 3008-3014. doi:10.1200/JCO.2009.27.2112 [doi]

Lapointe, J., Bouchard, K., Patenaude, A. F., Maunsell, E., Simard, J., & Dorval, M. (2012). Incidence and predictors of positive and negative effects of BRCA1/2 genetic testing on familial relationships: A 3-year follow-up study. *Genetics in Medicine : Official Journal of the American College of Medical Genetics, 14*(1), 60-68. doi:10.1038/gim.0b013e3182310a7f [doi]

Lapointe, J., Dorval, M., Noguès, C., Fabre, R., Julian-Reynier, C., & GENEPSO Cohort. (2013). Is the psychological impact of genetic testing moderated by support and

sharing of test results to family and friends? *Familial Cancer, 12*(4), 601. doi:10.1007/s10689-013-9621-3

LeDrew, H. (2009). *Psychometric testing of a scale designed to monitor the psychosocial and behavioral impact of genetic testing for hereditary nonpolyposis colorectal cancer (HNPCC): A pilot study.* (Unpublished Masters). Memorial University of Newfoundland, Newfoundland.

Lerman, C., Croyle, R. T., Tercyak, K. P., & Hamann, H. (2002). Genetic testing: Psychological aspects and implications. *Journal of Consulting and Clinical Psychology, 70*(3), 784-797. doi:10.1037/0022-006X.70.3.784

Likert, R. (1932). A technique for the measurement of attitudes. *Archives of Psychology, 22 140*, 55.

Lim, J., Macluran, M., Price, M., Bennett, B., Butow, P., & kConFab, P. G. (2004). Short- and long- term impact of receiving genetic mutation results in women at increased risk for hereditary breast cancer. *Journal of Genetic Counseling, 13*(2), 115-133. doi:10.1023/B:JOGC.0000018822.56297.a6

Lodder, E. M., & Bezzina, C. R. (2013). Arrhythmogenic right ventricular cardiomyopathy: Growing evidence for complex inheritance. *Circulation.Cardiovascular Genetics, 6*(6), 525-527. doi:10.1161/CIRCGENETICS.113.000367 [doi]

Manuel, A., & Brunger, F. (2014). Making the decision to participate in predictive genetic testing for arrhythmogenic right ventricular cardiomyopathy. *Journal of Genetic Counseling, 23*(6), 1045-1055. doi:10.1007/s10897-014-9733-4

Maron, B. J., & Maron, M. S. (2013). Hypertrophic cardiomyopathy. *The Lancet, 381*(9862), 242-255. doi:http://dx.doi.org.qe2a-proxy.mun.ca/10.1016/S0140-6736(12)60397-3

McAllister, M. (2002). Predictive genetic testing and beyond: A theory of engagement. *Journal of Health Psychology, 7*(5), 491-508. doi:10.1177/1359105302007005628 [doi]

McKenna, W. J., Thiene, G., Nava, A., Fontaliran, F., Blomstrom-Lundqvist, C., Fontaine, G., & Camerini, F. (1994). Diagnosis of arrhythmogenic right ventricular dysplasia/cardiomyopathy. task force of the working group myocardial and pericardial disease of the european society of cardiology and of the scientific council on cardiomyopathies of the international society and federation of cardiology. *Heart, 71*(3), 215-218. doi:10.1136/hrt.71.3.215

Mellon, S., Gold, R., Janisse, J., Cichon, M., Tainsky, M. A., Simon, M. S., & Korczak, J. (2008). Risk perception and cancer worries in families at increased risk of familial breast/ovarian cancer. *Psycho-Oncology, 17*(8), 756-766. doi:10.1002/pon.1370 [doi]

Merner, N. D., Hodgkinson, K. A., Haywood, A. F. M., Connors, S., French, V. M., Drenckhahn, J., . . . Young, T. (2008). Arrhythmogenic right ventricular

cardiomyopathy type 5 is a fully penetrant, lethal arrhythmic disorder caused by a missense mutation in the TMEM43 gene. *The American Journal of Human Genetics, 82*(4), 809-821. doi:10.1016/j.ajhg.2008.01.010

Michie, S., Bobrow, M., & Marteau, T. M. (2001). Predictive genetic testing in children and adults: A study of emotional impact. *Journal of Medical Genetics, 38*(8), 519-526.

Murray, B. (2012). Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C): A review of molecular and clinical literature. *Journal of Genetic Counseling, 21*(4), 494-504. doi:10.1007/s10897-012-9497-7

Norris, J., Spelic, S. S., Snyder, C., & Tinley, S. (2009). Five families living with hereditary breast and ovarian cancer risk. *Clinical Journal of Oncology Nursing, 13*(1), 73-80. doi:10.1188/09.CJON.73-80 [doi]

Nunally, J., & Bernstein, I. (1994). Psychometric theory, 3rd edition. *New York: Mcgraw-Hill,*

Ormondroyd, E., Oates, S., Parker, M., Blair, E., & Watkins, H. (2014). Pre-symptomatic genetic testing for inherited cardiac conditions: A qualitative exploration of psychosocial and ethical implications. *European Journal of Human Genetics : EJHG, 22*(1), 88. doi:10.1038/ejhg.2013.81

Peterson, S. K., Watts, B. G., Koehly, L. M., Vernon, S. W., Baile, W. F., Kohlmann, W. K., & Gritz, E. R. (2003). How families communicate about HNPCC genetic testing:

Findings from a qualitative study. *American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 119*(1), 78-86. doi:10.1002/ajmg.c.10010

Pullman, D., & Hodgkinson, K. (2006). Genetic knowledge and moral responsibility: Ambiguity at the interface of genetic research and clinical practice. *Clinical Genetics, 69*(3), 199-203. doi:10.1111/j.1399-0004.2006.00581.x

Rainville, I., & Rana, H. (2014). Next-generation sequencing for inherited breast cancer risk: Counseling through the complexity. *Current Oncology Reports, 16*(3), 1-11. doi:10.1007/s11912-013-0371-z

Rew, L. (2010). Systematic review of psychosocial benefits and harms of genetic testing. *Issues in Mental Health Nursing, 31*(10), 631-645. doi:10.3109/01612840.2010.510618

Rew, L., Mackert, M., & Bonevac, D. (2009). A systematic review of literature about the genetic testing of adolescents. *Journal for Specialists in Pediatric Nursing, 14*(4), 284-294. doi:10.1111/j.1744-6155.2009.00210.x

Satia, J. A., McRitchie, S., Kupper, L. L., & Halbert, C. H. (2006). Genetic testing for colon cancer among african-americans in north carolina. *Preventive Medicine, 42*(1), 51-59. doi:http://dx.doi.org/10.1016/j.ypmed.2005.10.004

Schlich-Bakker, K. J., Warlam-Rodenhuis, C. C., van Echtelt, J., van den Bout, J., Ausems, M. G., & ten Kroode, H. F. (2006). Short term psychological distress in patients actively approached for genetic counselling after diagnosis of breast

cancer. *European Journal of Cancer (Oxford, England : 1990), 42*(16), 2722-2728. doi:S0959-8049(06)00561-2 [pii]

Schwartz, M. D., Peshkin, B. N., Hughes, C., Main, D., Isaacs, C., & Lerman, C. (2002). Impact of BRCA1/BRCA2 mutation testing on psychologic distress in a clinic-based sample. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 20*(2), 514-520.

Sen-Chowdhry, S., Syrris, P., & McKenna, W. J. (2005). Genetics of right ventricular cardiomyopathy. *Journal of Cardiovascular Electrophysiology, 16*(8), 927-935. doi:10.1111/j.1540-8167.2005.40842.x

Smart, R. V., Yu, B., Le, H., French, J. A., Richmond, D. R., Jeremy, R. W., . . . Trent, R. J. (1996). DNA testing in familial hypertrophic cardiomyopathy: Clinical and laboratory implications. *Clinical Genetics, 50*(4), 169.

Smets, E. M., Stam, M. M., Meulenkamp, T. M., van Langen, I. M., Wilde, A. A., Wiegman, A., . . . Tibben, A. (2008). Health-related quality of life of children with a positive carrier status for inherited cardiovascular diseases. *American Journal of Medical Genetics.Part A, 146A*(6), 700-707. doi:10.1002/ajmg.a.32218 [doi]

Smith, J. A., Michie, S., Stephenson, M., & Quarrell, O. (2002). Risk perception and decision-making processes in candidates for genetic testing for huntington's disease: An interpretative phenomenological analysis. *Journal of Health Psychology, 7*(2), 131-144. doi:10.1177/1359105302007002398 [doi]

Te Riele, A. S., Tandri, H., & Bluemke, D. A. (2014). Arrhythmogenic right ventricular cardiomyopathy (ARVC): Cardiovascular magnetic resonance update. *Journal of Cardiovascular Magnetic Resonance : Official Journal of the Society for Cardiovascular Magnetic Resonance, 16*(1), 50-50. doi:10.1186/s12968-014-0050-8

Towbin, J. A. (2008). Arrhythmogenic right ventricular cardiomyopathy: A paradigm of overlapping disorders. *Annals of Noninvasive Electrocardiology, 13*(4), 325-326. doi:10.1111/j.1542-474X.2008.00241.x

Turner-Cobb, J. M., Bloor, L. E., Whittemore, A. S., West, D., & Spiegel, D. (2006). Disengagement and social support moderate distress among women with a family history of breast cancer. *The Breast Journal, 12*(1), 7-15. doi:TBJ178 [pii]

van Oostrom, I., Meijers-Heijboer, H., Duivenvoorden, H. J., Brocker-Vriends, A. H., van Asperen, C. J., Sijmons, R. H., . . . Tibben, A. (2007). Family system characteristics and psychological adjustment to cancer susceptibility genetic testing: A prospective study. *Clinical Genetics, 71*(1), 35-42. doi:CGE731 [pii]

Ventura, M. T., Napolitano, S., Buquicchio, R., Cecere, R., & Arsieni, A. (2012). An approach to urticaria in the elderly patients. *Immunopharmacology and Immunotoxicology, 34*(3), 530-533. doi:10.3109/08923973.2011.631549

Vincent, M.,G.M. (1998). *THE MOLECULAR GENETICS OF THE LONG QT SYNDROME: GENES CAUSING FAINTING AND SUDDEN DEATH* doi:10.1146/annurev.med.49.1.263

Ware, J. E., Brook, R., Davies-Avery, A., Williams, K., Stewart, A., & Rogers, W. (1980). *Model of health and methodology*. Santa Monica, CA: RAND Corporation.

Ware, J. E., & Gandek, B. (1998). Methods for testing data quality, scaling assumptions, and reliability. *Journal of Clinical Epidemiology, 51*(11), 945-952. doi:10.1016/S0895-4356(98)00085-7

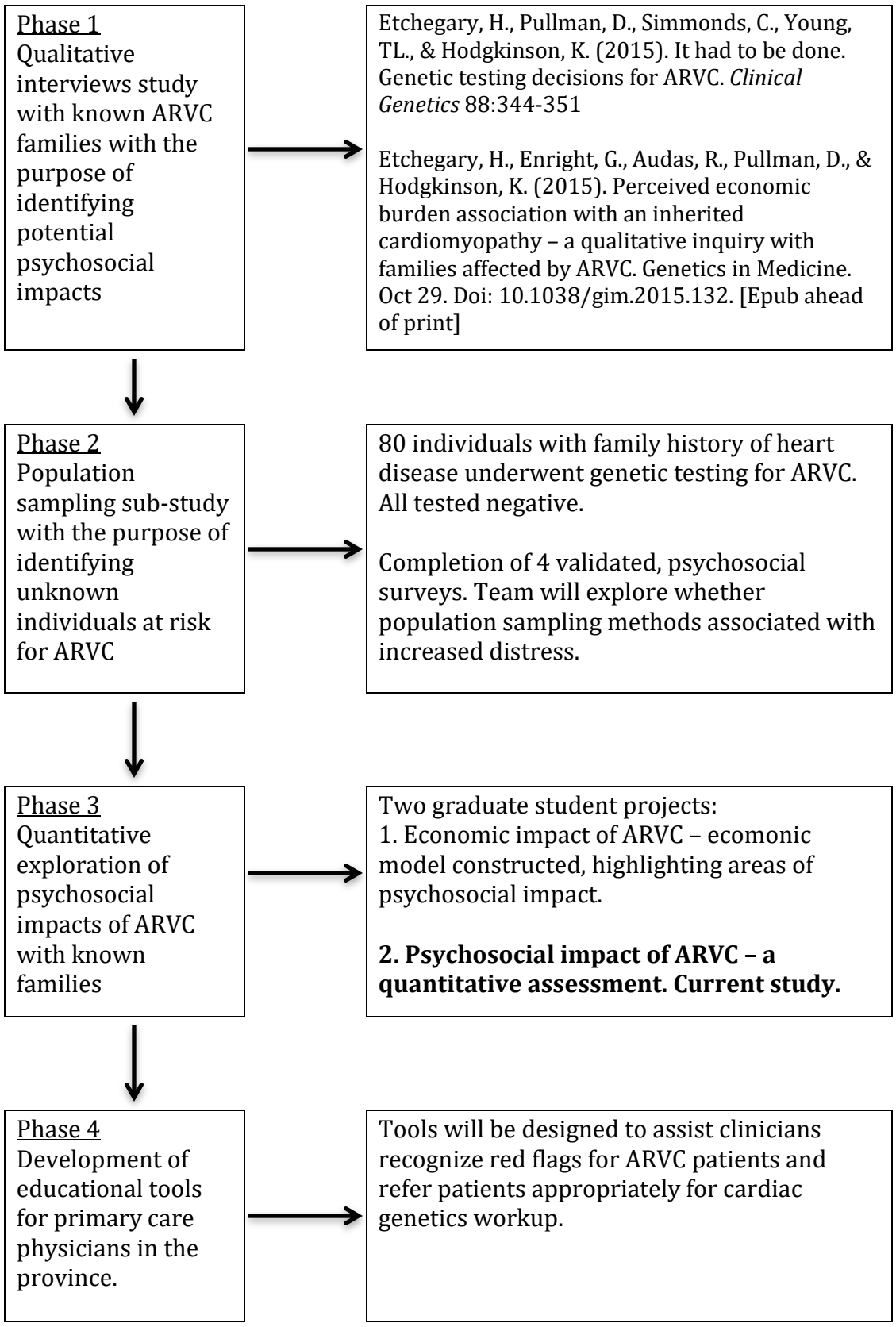
Watkins, K. E., Way, C. Y., Gregory, D. M., LeDrew, H. M., Ludlow, V. C., Esplen, M. J., Parfrey, P. S. (2013). Development and preliminary testing of the psychosocial adjustment to hereditary diseases scale. *BMC Psychology, 1*(1), 7-7. doi:10.1186/2050-7283-1-7

Way, C., Watkins, K., LeDrew, H., Ludlow, V., Esplen, M., Gregory, D., & Parfrey, P. (2011). Development and testing of the hereditary diseases and genetic testing (HD-GT) scale. *Hereditary Cancer in Clinical Practice, 9*(1)

APPENDIX A

GE^{3}LS Research Program Structure

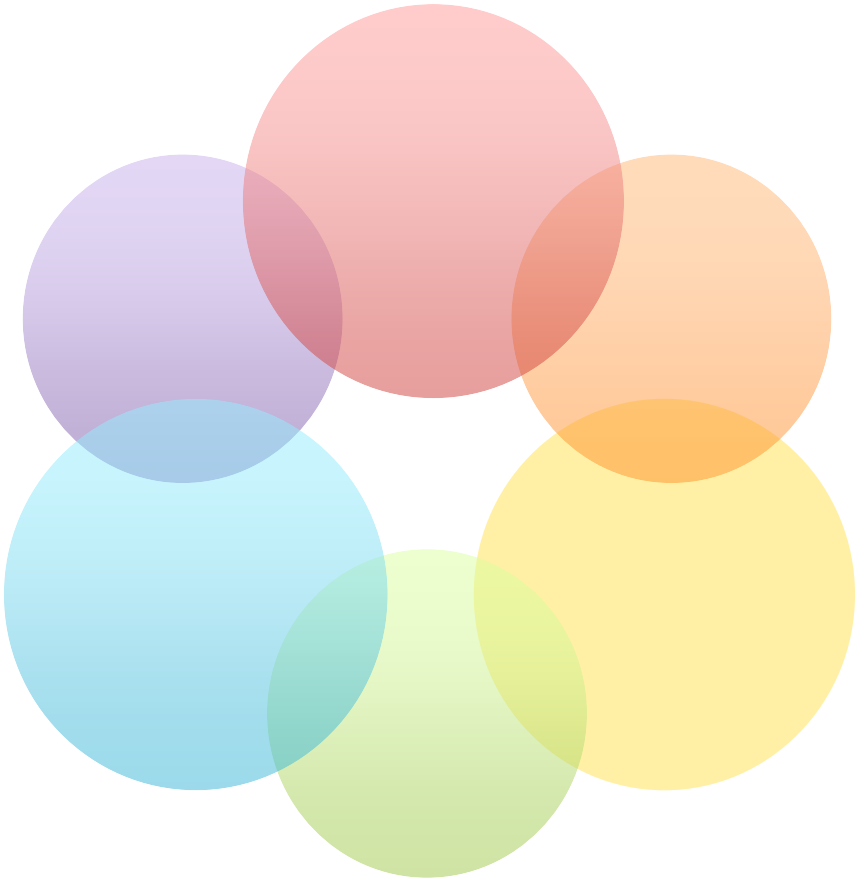
GE³LS Program - Sudden Cardiac Death in Newfoundland and Labrador



APPENDIX B

Sudden Cardiac Death Team

Sudden Cardiac Death Team



Clinical Epidemiological Research	Dr. K Hodgkinson
GEELS	Dr. D. Pullman and Dr. H Etchegary
Molecular Genetics	Dr. T-L Young
Medical Genetics	Dr. B. Fernandez
Clinical Cardiac Care	Dr. S. Connors
Knowledge Transfer	Dr. T-L Young, Dr. B. Fernandez, Dr. K. Hodgkinson, Dr. S Connors, and Dr. H Etchegary

APPENDIX C

Hereditary Disease and Genetic Testing Survey

Hereditary Diseases and Genetic Testing (HD-GT) Scale
(ARVC Version)

The HD-GT Scale has 10 sections ***with a total of 63 questions***.

Each section has several statements that we would like for you to rate from **0 (Not at all)** to **4 (Extremely).**

Please circle the answer which best applies to you for all of the statements in each section.

Thank you

A1: We are interested in the degree to which a family history of early sudden cardiac death caused by the ARVC gene influences a person's decision to have genetic testing.

Using the scale given, you are asked to rate how important each statement was in helping you to decide to have genetic testing.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. It seemed like a lot of family members were dying suddenly of cardiac problems more often and at a younger age than in other families.	0 1 2 3 4
2. I have many memories of close family members dying suddenly at a young age.	0 1 2 3 4
3. The presence of so much early sudden cardiac death in the family was hard to accept, and I wanted to know why.	0 1 2 3 4
4. It was scary to see the same pattern of early sudden cardiac death showing up in every generation of my family.	0 1 2 3 4
5. It was so draining to lose close relatives to early sudden cardiac death that every time the phone rang I wondered who was sick this time.	0 1 2 3 4
6. With so much suffering and early sudden cardiac deaths, I was worried about my own health and death.	0 1 2 3 4
7. What worried me was that even when a family member seemed to beat the odds and not have the ARVC gene, another type of heart disease showed up.	0 1 2 3 4
8. I grew tired of how certain family members tried to hide the family history of ARVC from the children.	0 1 2 3 4

A2. We want to know how much you were thinking about a genetic link (ARVC gene) to early sudden cardiac deaths in your family prior to and following contact by a geneticist/genetic counsellor.

Using the scale given, you are asked to rate how well each statement reflects your situation.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. Over the years concerns were expressed by some relatives that there was an ARVC gene in our family.	0 1 2 3 4
2. It was only after a geneticist contacted the family that I really began to think that the early sudden cardiac deaths might be a family thing and I could be at risk.	0 1 2 3 4
3. When I was told there was a test that could find the ARVC gene in the family, it was not a matter of "would I go for genetic testing", but "when I could have it".	0 1 2 3 4
4. I really questioned whether knowing if I had the ARVC gene would do me more harm than good (i.e., restricted insurance coverage and job prospects).	0 1 2 3 4
5. Getting heart related testing (e.g., ECG, Holter monitor) was such a pain that I did not want to do it unless I needed it.	0 1 2 3 4

A3. Going through genetic testing may not be the same for everyone. We want to know how informed and emotionally prepared you were for this experience.

Using the scale given, you are asked to rate each statement in terms of its importance in helping you and others decide to take part in genetic testing.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

It is important to:	
1. Get enough information in a timely manner from geneticists/genetic counselors.	0 1 2 3 4
2. Receive enough information from geneticists/genetic counselors about the genetic testing process.	0 1 2 3 4
3. Feel no pressure to have genetic testing done.	0 1 2 3 4
4. Know if one has the ARVC gene.	0 1 2 3 4
5. Understand one's risk for hereditary early sudden cardiac death and accept the need for genetic testing.	0 1 2 3 4
6. Know if one has the ARVC gene to help children/grandchildren.	0 1 2 3 4
7. Receive support from geneticists/genetic counselors during the genetic testing process.	0 1 2 3 4
8. Feel support and encouragement from family and/or friends to take part in genetic testing.	0 1 2 3 4

A4. There are individuals within every family who struggle with the idea of being tested for an early sudden cardiac death gene. When close relatives refuse genetic testing, concerns are expressed not only for their future well-being but also for their children.

Using the scale given, you are asked to rate how well each statement describes your thoughts about family members who refuse genetic testing.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. It is important for all family members at risk for early sudden cardiac death to take part in genetic testing.	0 1 2 3 4
2. I am really concerned about family members who refuse to go for genetic testing.	0 1 2 3 4
3. I feel that family members who refuse to go for genetic testing do not understand their risks.	0 1 2 3 4
4. I believe that family members who refuse genetic testing are fearful of knowing their results.	0 1 2 3 4
5. I feel obligated to encourage family members who refuse genetic testing to rethink their decision.	0 1 2 3 4

A5. Different thoughts and emotions are experienced by individuals within and across families as they wait for the results of genetic testing.

Using the scale given, please rate how well each statement describes your feelings about the wait time between the giving of blood for genetic testing and the actual receipt of your results.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. It was a very trying time thinking about if I could carry a gene for early sudden cardiac death .	0 1 2 3 4
2. I was not really prepared for such a long time between having the test done and getting the results.	0 1 2 3 4
3. I was unsure about how I would receive my results (e.g., phone, letter, in person).	0 1 2 3 4
4. I spent a lot of time thinking about how I would react to finding out my genetic testing results.	0 1 2 3 4
5. I wondered if I would understand what my genetic testing results really meant for me.	0 1 2 3 4

A6. People report different support needs during and following receipt of their genetic testing results. We are interested in knowing what you felt was helpful at the time.

Using the scale given, you are asked to rate the following statements in terms of their importance for you.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

It is important to:	
1. Have a family member and/or friend present.	0 1 2 3 4
2. Get a phone call from geneticist/genetic counsellor prior to receiving your results.	0 1 2 3 4
3. Have face-to-face contact with a geneticist/genetic counsellor when receiving your results.	0 1 2 3 4
4. Receive a letter explaining what it means to be a carrier/non-carrier for yourself and others.	0 1 2 3 4

A7. People react differently to receiving their genetic testing results no matter how prepared they think they are. We are interested in knowing about your reactions and expectations.

Using the scale given, you are asked to rate these statements in terms of how well they reflect your situation after getting your results.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. I felt fully prepared to receive my genetic testing results.	0 1 2 3 4
2. I was surprised by my genetic testing results.	0 1 2 3 4
3. Knowing whether or not I had the ARVC gene for early sudden cardiac death brought a sense of closure to everything.	0 1 2 3 4
4. The information received from the geneticist/genetic counsellor about my risk for early sudden cardiac death risk was very clear and useful.	0 1 2 3 4
5. Follow-up contact with the geneticist/ genetic counsellor to discuss healthy lifestyles and recommendations about ongoing cardiac monitoring would have been helpful.	0 1 2 3 4
6. Overall, it was better to know whether or not I had the ARVC gene.	0 1 2 3 4

A8. We want to know if being a carrier/non-carrier of an ARVC gene changes how a person values healthy living and monitoring for reducing the risk of sudden cardiac death.

Using the scale given, you are asked to rate the following statements in terms of how closely they reflect your beliefs.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. Regular clinical monitoring (e.g., ECG, Holter monitor, echocardiography) will help detect cardiac problems that show I have this disease at an early stage.	0 1 2 3 4
2. Appropriate monitoring is important for timely detection of cardiac problems.	0 1 2 3 4
3. Early detection of cardiac problems will help improve treatment and disease management.	0 1 2 3 4
4. Healthy living (exercise, diet) and a positive attitude will help increase well-being and decrease stress.	0 1 2 3 4
5. Taking responsibility for healthy living and regular monitoring is important.	0 1 2 3 4

A9. The presence of early sudden cardiac deaths in the family is often important in helping understand personal risk. We are interested in how awareness of early sudden cardiac death trends within the family influence beliefs and who might be at greater risk for cardiac events.

Using the scale given, you are asked to rate how well these statements reflect what you perceive to be happening in your family.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. Family members seem to be affected at a younger age.	0 1 2 3 4
2. Men and women seem to be affected differently.	0 1 2 3 4
3. Different types of heart disease seem to be showing up today more than in past generations	0 1 2 3 4
4. The number of family members affected seems to be greater with each generation.	0 1 2 3 4
5. Some family members who get the ARVC gene seem to be better able to fight the disease than others.	0 1 2 3 4

A10. Not everyone is open to receive information about early sudden cardiac death or understand what this could mean for them. We are interested in knowing whether family members openly communicate about and have a good understanding of their risk. We are also interested in difficulties, if any, in telling others about the ARVC gene in the family.

Using the scale given, you are asked to rate how well these statements apply to your situation.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. In our family, we struggle with knowing when to tell young family members about early sudden cardiac death.	0 1 2 3 4
2. It is difficult having to tell younger family members about their possible risk for early sudden cardiac death.	0 1 2 3 4
3. Younger family members seem to be open to information about the ARVC gene for early sudden cardiac death in the family.	0 1 2 3 4
4. Younger family members seem to understand what an ARVC gene in the family could mean for them.	0 1 2 3 4
5. It is important for all family members to be told about the ARVC gene.	0 1 2 3 4
6. It is hard telling family members about their possible risk for early sudden cardiac death.	0 1 2 3 4
7. Family members seem to be open to information about the ARVC gene.	0 1 2 3 4
8. Family members seem to understand what the ARVC gene could mean for them.	0 1 2 3 4
9. It would be helpful if the family messenger had guidance and support from geneticists/ genetic counselors on how to tell others about the ARVC gene.	0 1 2 3 4
10. It is important to protect the rights of others when talking about the risk of early sudden cardiac death in the family.	0 1 2 3 4

11. I feel comfortable telling family members about the ARVC gene in the family and the availability of genetic testing.	0 1 2 3 4
12. I find it difficult telling family members who I have limited contact with about the ARVC gene and the availability of genetic testing.	0 1 2 3 4

APPENDIX D

Psychosocial Adjustment to Hereditary Disease Survey

Psychosocial Adjustment to Hereditary Diseases (PAHD) Scale (ARVC Version)

The PAHD Scale has 2 sections with a total of 19 questions.

Each question has several statements that we would like you to rate from **0 (Not at all)** to **4 (Extremely)**.

Please circle the best answer for each.

Thank you

B1: We are interested in the long-term effects of a confirmed ARVC gene for early sudden cardiac death in families. Everyone goes through periods of trying to make sense of inner feelings about what the future might hold for the self and other family members.

Using the scale given, you are asked to rate how well each statement reflects your situation.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. I think about being a carrier/non-carrier more than I should.	0 1 2 3 4
2. I try to be positive about my future health and overall well-being.	0 1 2 3 4
3. It is important for my future health not to dwell on the hereditary link to early sudden cardiac death in the family.	0 1 2 3 4
4. It was hard changing how often I had to be monitored for cardiac disease.	0 1 2 3 4
5. It bothers me when others do not accept my carrier/non-carrier status.	0 1 2 3 4
6. Younger people need to be encouraged to talk about all the early sudden cardiac deaths in the family.	0 1 2 3 4
7. I find it hard dealing with younger family members who get the ARVC gene.	0 1 2 3 4
8. I worry about what the future might hold for younger family members.	0 1 2 3 4
9. The stress of so much early sudden cardiac death in the family, more so in younger members, pulled some of us closer together but pushed others apart.	0 1 2 3 4
10. Regular monitoring for cardiac problems became a constant reminder of my risk by being in this family.	0 1 2 3 4

B2: Some families handle the challenges of an early sudden cardiac death (ARVC) gene presence better than others do. We want to know how well individuals in your family support one another.

Using the scale given, you are asked to rate how well each statement reflects your situation.

0 – Not at all
1 – A little bit
2 – Moderately
3 – Quite a bit
4 – Extremely

1. Feeling supported by family and friends has helped me accept being a carrier/non-carrier.	0 1 2 3 4
2. I find it easy to seek help from family members when I need it.	0 1 2 3 4
3. It is important for everyone to talk openly about the high early sudden cardiac death risk in the family.	0 1 2 3 4
4. I am concerned that the presence of early sudden cardiac death has hurt family relations.	0 1 2 3 4
5. I worry that all the suffering and death from ARVC is placing too much burden on family members.	0 1 2 3 4
6. Providing care to other family members with ARVC has helped me become more accepting of my future.	0 1 2 3 4
7. With so much early sudden cardiac death in the family I worried that something would show up on my next screening test.	0 1 2 3 4
8. When I knew there was a test to see if my family had the ARVC gene for early sudden cardiac death, I was relieved.	0 1 2 3 4
9. Encouragement and support from family and friends helps one accept the need for healthy living.	0 1 2 3 4

Please tell us anything else you think is important for you or your family in living with ARVC.

APPENDIX E

Final Amendment to Ethics Approval

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

RECEIVED NOV 13 2013

Version June 2013

Request for Amendment to an Approved Application

HREB #: 13.096	**Current Date:** November 12th 2013

Title of study: Include protocol number, if any.

Understanding the economic and psychosocial impact of Arrythmogenic Right Ventricular Cardiomyopathy (ARVC) on families in Newfoundland and Labrador.	
Amendment Date: November 12th 2013	**Version #** (if applicable):

Are these changes editorial and/or administrative?	Yes	**No**
Will there be any increase in risk, discomfort or inconvenience to the participants?	Yes (Specify below)	**No**
Are there changes to inclusion or exclusion criteria?	Yes (Specify below)	**No**
Is a modification to the consent form required?	**Yes** (Append form)	No

Summarize the significant changes being requested. It is not necessary to itemize editorial, administrative and similar changes.

1.The economic survey has been updated from six sections with 43 questions to eight sections with 76 questions (Youth 67 questions) and now uses a different scale. There has been no change to the general topics covered in the survey questions.
2. Participants will be given the option to receive the study documents by email. The invitation process will not change as a member of the research team with a long standing relationship (Kathy Hodgkinson or Fiona Curtis) with potential participants will make the initial contact. After the initial invitation, the research team will confirm contact information and the study documents will be distributed using mail, email or in person chosen by the participants. The consent form has been amended to include email as a distribution option for survey documents.

What is the rationale for the amendment(s)?

1.Additional professionals with clinical experience involving ARVC patients and the research team reviewed the economic survey and new questions were identified. These additional questions aim to better meet the study objectives particularly the impact of ARVC on families in addition to individuals at risk.
2. It has come to the attention of the research team that some potential participants would prefer email communication as their means to participate. Allowing participants to choose how they receive the study documents should increase convenience for participants and improve the response rate.

Other pertinent information – List ALL documents, including version dates, to be reviewed:

Final_Economic Survey ARVC_Nov 11 2013
Final_ Youth Economic Survey ARVC_Nov 11 2013
Final _Quantitative phase consent form November 12, 2013

Glenn Enright
Printed Name of Principal Investigator

Signature of Principal Investigator

2013/11/12
Date

HREB #: 13.096	Amendment Date: Nov 12, 2013	Version:

Health Research Ethics Board
777-6974 (Phone)
777-8776 (Fax)

Version June 2013

This Health Research Ethics Board (the HREB) has reviewed the amendment as noted above for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Health Research Ethics Board currently operates according to Tri-Council Policy Statement (TCPS2) and applicable laws and regulations. The membership of this research ethics board complies with the membership requirements for research ethics boards defined in TCPS2.

Full Board* Review and Approval granted at** N/A ***Meeting

Signature Chair (Dr. Fern Brunger) ***Date***

Signature Vice-Chair (Patricia Grainger) ***Date***

OR

Reported to Full Committee at Nov 28, 2013 ***Meeting***

Approved by:

Signature Chair (Dr. Fern Brunger) APPROVED NOV 15 2013 ***Date***

Signature Vice-Chair (Patricia Grainger) ***Date***

*Attach additional documentation if necessary

HREB #: 13.096	Amendment Date: Nov 12, 2013	Version:

APPENDIX F

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