Identifying individuals at risk for Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) caused by *TMEM43* p. S358L: A genetics educational tool for Primary Care Physicians

by © Lauren Rickert A Thesis submitted to the School of Graduate Studies in partial fulfillment of the requirements for the degree of Master of Science in Medicine (Applied Health Services Research)

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ABSTRACT:

Introduction: Newfoundland and Labrador (NL) has an increased incidence of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is caused by a p.S358L mutation in *TMEM43*, the first symptom of which may be sudden cardiac death (SCD). When diagnosed and treated, mortality is significantly reduced. Primary care physicians (PCPs) are often the first point of health system contact for families affected by ARVC. PCPs acknowledge the importance of integrating genetics into their practice, but report uncertainty regarding appropriate counseling and referral strategies. Web-based tools can be effective education methods. This project aimed to create a tool designed to increase the likelihood of appropriate management and referral of persons at risk of ARVC caused by p.S358L in *TMEM4*3.

Methods: We used a multiple methods, iterative approach to develop an educational tool. This included initial creation, a working lunch with five PCPs, subsequent revision of the tool, use of pre-existing *TMEM43* data providing additional family information and then further revision. It was distributed to a cohort of PCPs and Family Medicine Residents (n= 780) for feedback via an online survey containing nine Likert-scale questions, two qualitative questions and five demographic questions.

Results: Initial feedback requested greater clarity on whom to refer to appropriate genetic and cardiac services. Pedigree information showed that 56%, 39%, and 31% of affected persons had at least one first-, second-, or third degree relative with a known history of severe cardiac problems at time of their initial presentation. This information was then integrated into the updated version of the tool, to ensure PCPs are prompted to ask about patients family history, including first-, second-, and third-degree relatives. Opinion on

the final tool was provided by 43 online surveys completed by PCPs in NL. Overwhelmingly positive responses were noted.

Discussion: Feedback from PCPs and multi-generational, historic pedigree information was used to create an educational tool for PCPs which may more easily identify those at risk for ARVC caused by the p. S358L mutation in *TMEM43*. Future research will evaluate the tool in practice.

KEYWORDS: Arrhythmogenic Right Ventricular Cardiomyopathy, ARVC, primary care physicians, PCPs, educational tools

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Arrhythmogenic Right Ventricular Dysplasia – ARVD

Congestive Heart Failure - CHF

Echocardiogram – ECHO

Electrocardiography – ECG

Evidence-based Practice - EBPs

Familial Dilated Cardiomyopathy – FDM

Family History – FH

Genetics Education Canada Knowledge Organization Centre – GECKO

Health Sciences Information and Media Services - HSIMS

Hypertrophic Cardiomyopathy – HCM

Implantable Cardioverter Defibrillator - ICD

Magnetic Resonance Imaging - MRI

Newfoundland and Labrador – NL

Newfoundland and Labrador Medical Association - NLMA

Poor R-Wave Progression - PRWP

Premature Ventricular Contractions - PVCs

Primary Care Physicians – PCPs

Randomized Controlled Trials - RCTs

Signal-Average ECG – SAECG

Sudden Cardiac Arrest - SCA

Sudden Cardiac Death – SCD

Venous Thromboembolism - VTE

Ventricular Fibrillation - VF

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Quality of Life - QOL

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Introduction

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic heart condition. Several genes are implicated in its etiology. A specific type of ARVC is caused by the p. S358L mutation in *TMEM43* and is prevalent in the population of Newfoundland and Labrador (NL), Canada. This type of ARVC is highly lethal in affected individuals. It often causes sudden cardiac death (SCD) in undiagnosed individuals as young as 19 years old in males and 37 years old in females; the median age of death for males is 40 years and females is 67 years (Hodgkinson et al., 2016). To prevent SCD from occurring, primary care physicians (PCPs) need to correctly identify these individuals. This identification is essential as PCPs are the gate keepers to specialized care, such as cardiac and genetic services, and highly effective care is available to prevent SCD (Hodgkinson et al., 2016).

The impetus for this thesis is the desire to assist PCPs to accurately ascertain those at risk of ARVC caused by the p.S358L mutation in *TMEM43* before a catastrophic event, such as SCD.

Currently, individuals and families who are known to carry the mutation are seen by cardiac and genetic specialists and undergo cascade screening. Cascade screening identifies all individuals at risk within a family tree. At risk individuals are identified by their level of relation to the original case of ARVC, otherwise known as the proband, and are thus assessed and offered further screening (Definition of cascade screening-NCI Dictionary of Genetics Terms). The problem remains, however, that new families are usually discovered as the result of the death of an apparently healthy individual in a

previously unknown family.

This thesis will explore one method to increase the likelihood of determining at risk families, prior to an SCD occurring. The way we have chosen to do this is to develop an educational tool to inform PCPs about this type of ARVC. The methodology we will use to accomplish this is as follows: (a) the creation of a draft tool utilizing past expertise and data from a long standing ARVC project and dataset (HREB 00-76), (b) input from a small group of PCPs in a focus group and (c) modification of the tool via input from PCPs and /or PCP residents to obtain a final product.

This thesis discusses ARVC as a general disease, as well as ARVC caused by p.S358L in *TMEM43* prevalent in NL. It provides a review of the use of multi-generational family histories, educational tools in primary care, and genetics and genomics. It is my hope that the tool created through this thesis will help PCPs identify patients who may be at risk for ARVC as well as those at risk for other forms of SCD.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

While all cardiovascular disorders have a genetic component, some can be further identified as Mendelian disorders. These types of cardiovascular diseases occur when one mutation in a single gene is inherited through an affected family member, causing the disease. Mendelian disorders are often identified because of the pattern of disease seen in family trees. Included in these disorders are inherited cardiomyopathies such as: hypertrophic cardiomyopathy (HCM), familial dilated cardiomyopathy (FDCM), and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Ingles et al., 2013). These cardiomyopathies are all heart muscle disorders, which are characterized by structural and functional defects of the heart (Richard et al., 2010). Mendelian autosomal dominant

forms of ARVC are caused by a mutation that occurs in a non-sex chromosome, where a single copy of the mutation is required to cause the disease in affected individuals. The pattern seen in families for this disease is vertical, or from parents to offspring. Therefore, it occurs across generations from affected parents to affected offspring (Rogers, 2019). Comparatively, in autosomal recessive diseases, the same mutation from each parent must be inherited for the disease to be expressed, which is seen in a cardiac disease such as Naxos disease, a recessive form of ARVC. It is important to note that Naxos disease presents as a horizontal pattern of inheritance, so the disease is seen in sibships (brothers and sisters) only (French, 2008; Rogers, 2019).

ARVC is defined pathologically by the replacement of cardiac muscle tissues in the right or left ventricle of the heart with fibrous and fatty tissue. As the ventricles are the main pumping chambers of the heart responsible for (a) pumping oxygenated blood to the body (left side), and (b) pumping oxygen depleted blood to the lungs (right side) (Redington et al., 2009), the replacement of the normally strong cardiac muscles with fibro-fatty tissue can cause numerous complications. One of these complications arises from the development of life-threatening ventricular tachyarrhythmia (VT). This arises (as the name implies) in the ventricles, which can cause a resting heart rate of greater than 300 beats per minute. VT is caused when an electrical conduction path of the heart, which controls the beating, is blocked, or slowed down. This can cause the electrical impulses of the heart to fire incorrectly, or erratically (Tung et al., 2010). Symptoms of VT include heart palpitations, presyncope (light headedness), syncope (fainting), and dizziness (René & Jackson, 2002). When VT becomes too fast, the heart is unable to maintain the speed at which it is beating, the heart muscle begins to fibrillate, or quiver, which subsequently

results in ventricular fibrillation (VF). VF will then cause SCD, as the heart is failing to beat in a purposeful manner; oxygen is not perfusing to the body, and inevitably the heart stops (René & Jackson, 2002). SCD accounts for about 50% of all deaths with a cardiovascular cause (Myerburg et al., 1997), with about 20% of these deaths caused by an inherited genetic cardiomyopathy (Zipes & Wellens, 1998).

The first systematic description of ARVC was from Marcus et al., in 1982, where a possible familial effect was identified. ARVC was initially called pre-excitation syndrome (Fontaine et al., 1977). It was later referred to as a dysplastic disorder (abnormal growth and development of cells) (Frank et al., 1978). This later expanded to include an arrhythmic factor, subsequently identified as arrhythmogenic right ventricular dysplasia (ARVD) (Fontaine et al., 1982). In 1996, the disease was recognized as a cardiomyopathy, effectively changing the name to that with which it is currently known, ARVC (WHO/ISFC, 1996). Since the recognition of ARVC in 1996, 12 Mendelian autosomal dominant forms of ARVC have been identified and numbered in the order of their discovery: ARVD1-ARVD12 (Hodgkinson, 2009).

Natural History of ARVC

The natural history of a disease is defined as the symptom presentation seen in an affected individual from birth until death (Raina, 2016). The natural history of ARVC has traditionally been separated into four stages. In the first (concealed) phase, affected individuals are normally asymptomatic but subtle changes to the structure of the right ventricle may be present that may or may not cause an arrhythmia. SCD can occur in this stage, as the first manifestation of the disease. The second stage results in obvious arrhythmias, which again may cause SCD. This stage also displays obvious right

ventricular structural and functional abnormalities. Ventricular arrhythmias are prominent during this stage. In the third phase, there is a progression and extension of muscle disease, known as the global right ventricle dysfunction phase. Contractions of the heart may be impaired in this stage and isolated right heart failure may be present. The final stage results in bi-ventricular pump failure as well as obvious left ventricular failure, which can lead to congestive heart failure (CHF) and other complications (Corrado et al., 2000). These stages are seen in all forms of ARVC, regardless of underlying mutation or locus and are often fluid and variable in their manifestations (as discussed below).

Variable Expression and Reduced Penetrance.

As ARVC is an autosomal dominant disorder, variable expression and reduced penetrance occurs. Variable expressivity occurs when the same disease, caused by the same mutation, affects related individuals in different ways (Genetics Home Reference-NIH, 2019). Some individuals may show many clinical symptoms, while others show few. Therefore, diagnosed ARVC in one family member can look very different than in another. Likewise, reduced penetrance is an extreme form of variable expression, in that the presence of the gene mutation in one family member may not result in any clinical presentation of the disease in another affected family member (Genetics Home Reference-NIH, 2019). All autosomal dominant disorders seem to demonstrate variable expressivity and reduced penetrance (Azaouagh et al., 2011; & Hodgkinson, 2009). Notably, though, for many newly described autosomal dominant disorders, there are not enough data to robustly define the extent of variability or level of penetrance (Dr. K. Hodgkinson, personal communication, November 20, 2018).

Diagnosis of ARVC.

1994 Criteria

In 1994, leading cardiologists collaborated and provided expert opinions of ARVC. Subsequently, diagnostic criteria for ARVC were defined. Cardiologists identified major and minor criteria, some of which had to be met for an ARVC diagnosis (McKenna et al., 1994). The main classes of heart irregularities assessed as part of the criteria were: dysfunction and structural abnormalities, histological changes, repolarisation and depolarisation abnormalities, arrhythmias, and family history (FH). Features of each class were defined and separated into major and minor criteria. To meet a diagnosis of ARVC, an individual would have to present with two major, or one major plus two minor, or four minor criteria (see Appendix A).

Critiques of the criteria identified that individuals were only diagnosed when presenting with symptoms severe enough to necessitate medical attention, resulting in an ascertainment bias. Therefore, there was a gap in diagnosing individuals who: (a) had the disease and had not sought medical attention, and (b) those who died from the disease prior to any medical attention.

2002 Criteria

Because of the advancements made in clinical test modalities and the identification and assessment of at risk relatives who manifested clinical features and who did not meet the diagnostic criteria of 1994, the diagnostic criteria were modified in 2002. In the updated criteria (see Appendix A), fewer clinical features were required for diagnosis of a relative when there was a known family member affected by ARVC (Hamid et al., 2002). Families were identified by clinical presentation of the disease, rather than an underlying genetic mutation. Relatives had cardiac testing that looked for

cardiac clinical symptoms, which may not have been a part of the existing diagnostic criteria in place at that time (Hodgkinson, 2009).

Limitations still existed with the 2002 criteria, however, including failure to recognize deceased individuals who had ARVC. While autopsy results might have proposed a cause of death as ARVC, there was a lack of confirmation of the diagnosis.

Failure to recognize those at risk for ARVC had and continues to have potentially severe consequences, given the linkage of SCD and ARVC. Due to limitations of the 2002 diagnostic criteria, individuals and families could have been living unknowingly with ARVC. The disease and associated threats could be passed on to a population that has no knowledge it is at risk (Merner, 2011).

2010 Criteria

In 2010, Marcus et al. provided a further update to the diagnostic criteria. They incorporated advances made in diagnostic imaging, including 2D Echocardiogram (ECHOs) and magnetic resonance imaging (MRIs), as well as genetic information (see Appendix A). The updated criteria improved diagnostic sensitivity (the number of people who have ARVC and who are identified positively), while maintaining diagnostic specificity (those who do not have ARVC and are correctly identified as such) (Saah & Hoover, 1997). New quantitative parameters were set; however, a similar approach of classifying structural, histological, electrocardiography (ECG), arrhythmic, and genetic features of the disease as major and minor criteria remained (Marcus et al., 2010).

While these changes to the diagnostic criteria are pivotal to the diagnosis and treatment of those with ARVC, there is still the potential for bias to exist when considering the modern testing required for diagnosis. Not all geographic areas have the

technology to test as required by the new diagnostic criteria. There should be an acknowledgement that individuals and their family members in these areas may not be properly diagnosed, nor in a timely manner, potentially resulting in a selection bias. The 2010 criteria also included genetic mutation analysis. Inclusion of genetic mutation analysis helped with sensitivity, but the clinical repercussions of mutations are not fully understood, due to ascertainment bias, as often those with genetic mutations are the only group studied.

Clinical tests for ARVC.

There are several cardiac clinical tests that can be used to test for ARVC.

12-Lead Electrocardiography (ECG).

ECGs test for abnormalities in the electrical activity of the heart. Electrodes are placed strategically on the chest and heart activity is translated to waves that are traced to paper. This test can measure if electrical impulses are sent through the heart too fast, slow, or irregularly. This test is easy, inexpensive, and available in many health centers (DiMino et al., 2013).

The signal-average ECG (SAECG).

SAECG are similar to ECGs but are more detailed. The SAECG collects "average" heartbeat data. The test captures about 500 beats of the heart, then sums the components of the heartbeat to come up with an "average" heartbeat. This test identifies subtle abnormalities present in the normal heart rhythm, known as "late potentials", which are indicative of arrhythmias, including VT (Cain et al., 1996).

The Holter Monitor.

The Holter Monitor is worn for 24 to 48 hours. Heartbeat and rhythm data are

recorded for the duration the monitor is worn and stored in a device worn by the individual being tested. During the time that patients are wearing the monitor, they are asked to complete a diary where they are to note any symptoms they feel. Information such as the time the patient experiences a symptom, as well as what they were doing when the symptom presented itself, are used in collaboration with the data obtained from the monitor (Maron et al., 2003). The Holter Monitor can measure Premature Ventricular Contractions (PVCs), which are extra heart beats that begin in one of the two lower chambers of the heart. These extra beats can disrupt the heart's normal rhythm. This can lead to arrhythmias and weakening of the heart muscle (Mayo Clinic, 2019). The number of PVCs seen during a 24-hour Holter Monitor has been shown to be the best clinical test in predicting if an individual has ARVC caused by the p. S358L mutation in *TMEM43*.

Echocardiography (ECHO).

An ECHO is an ultrasound of the heart, which produces sound waves that create pictures of the heart's chambers, valves, walls and blood vessels. The ECHO provides an accurate picture of the heart's structure and function through measurements of the heart's chambers, function of the valves, and effectiveness of the ability of the heart to pump (that is, the ejection fraction or how much blood is leaving the heart when it contracts). It can also detect abnormal movements of the heart muscle and valves, which is pertinent when examining for potential heart conditions (Mankad, 2016; & Nicoll et al., 2012). Ultimately, they can provide an accurate measure of the movement and efficiency of the heart (Blanchard & DeMaria, 2013). ECHOs are also widely available; however, they require an operator to complete the test.

Cardiac biopsy.

During a cardiac biopsy, tissue is removed from the heart while the individual is alive. The tissue is examined for the presence of fat and fiber. This test is limited in diagnosing ARVC, however, in that the sample may be taken from an area of the heart not yet impacted by ARVC, therefore yielding an incorrect diagnosis. There are also complications associated with this procedure, including cardiac perforation and electrical complications, such as arrhythmias, that may lead to death (Liang et al., 2014).

Magnetic Resonance Imaging (MRI).

MRIs offer a less invasive method for examining the heart for presence of fat and fiber. Signals are sent through the heart, and tissue density is determined through comparison of signals sent through normal heart muscle. Fat and fibrous tissue increases signal density, while normal heart tissue decreases signal density. Access to an MRI can be a challenge for patients, particularly those in rural areas, as MRI machines are not always available in these hospitals and health centers (Bogaert et al., 2011). Other considerations include that MRIs can be problematic for those over a certain weight and for those with claustrophobia.

Treatment of ARVC.

Three treatment options exist for ARVC, none of which cure the disease but try to make living with it more manageable. Antiarrhythmic drug therapies are prescription drug interventions that aim to prevent fatal arrhythmias, though often they have significant side effects. Catheter ablation involves burning, or destroying, a small section of the heart muscle. This creates a scar that disrupts the area in which the electrical signals in the heart have been blocked or slowed down, which results in the individual experiencing VT. This small scar, about 3 to 5 mm in size, helps re-route the electrical impulses so that the

heart can beat correctly again (Tung et al., 2010).

The most successful intervention has been the implantable cardioverter defibrillator (ICD). The ICD is typically placed in the upper left-hand side of the chest. From the ICD, wires are run which are fed through the venous system into the heart. Usually the placement and location of an ICD are the same as a pacemaker. The ICD is a battery-operated device which monitors the heart rhythm and shocks the heart when abnormal rhythms are detected. This prevents SCD by bringing the heart back into a normal rhythm. Prior to a shock discharge, an ICD can pace the heart back to a normal rhythm. If this pacing fails to correct the heartbeat, a shock then occurs. The success of ICDs was determined early through randomized controlled trials (RCTs). Through these trials, the effectiveness of ICDs was compared to antiarrhythmic drugs in patients who survived life-threatening VT, often following a myocardial infarction, and were at risk for further lethal events that could cause SCD (Antiarrhythmics versus Implantable Defibrillators (AVID) Investigators, 1997). ICDs were found to be superior in treating these individuals as compared to antiarrhythmic drugs.

Acknowledging the success of ICDs evident in the literature, Corrado et al. (2015) reported that any further RCTs that examined the ability of antiarrhythmic drugs versus ICDs in treating those with a history of, or potential for, VT would be unethical. Corrado et al. (2015) also reported that ICD treatment for ARVC patients who experienced VT should be the treatment option of choice. Similarly, Boriani et al. (2007) demonstrated that "ICD implantation is highly effective for prevention of sudden death in ARVC," (p. 184). Evidence justifying the implantation of an ICD in high risk ARVC patients was also echoed earlier by Corrado et al. (2010). They identified that the high number of correct

firings of the ICD (instances where a patients VT would have turned into a fatal VF) confirms the life-saving efficacy of prophylactic ICD therapy - one fourth of patients received correct, lifesaving ICD firing.

Though very effective, ICD placement is not risk free and has potential side effects such as risk of infection, inappropriate firing, and an increase in morbidity and mortality (Ingles et al., 2013). Inappropriate firings occur when the ICD shocks the heart in the absence of an abnormal rhythm. According to Shenoy et al. (2016), incorrect ICD firings have occurred from "external electromagnetic interference from electrocautery, welding, acupunctures, low-output transcutaneous electric nerve stimulators, and electronic muscle stimulators" (p. 139) as well as device dysfunction. This can have serious physiological and psychological impacts on the individual who experiences these inappropriate firings.

Prevalence.

While ARVC has been reported worldwide (Cho et al., 2007; Fung & Sanderson, 2001; Kaartinen et al., 2007; & Perzanowski et al., 2000), the prevalence and incidence rates are in effect unknown. Prevalence, referring to the number of cases at a single point in time, and incidence, referring to the number of cases over a specified period, require a definitive diagnosis, which is problematic with ARVC due to the difficulty in making a positive clinical diagnosis (Corrado et al., 2000). In Italy, where many ARVC studies have been conducted, the prevalence is reported as 1/5000, and it is assumed to account for 20% of all deaths in young adults (Thiene et al., 1988). Another Italian study reported an incidence of 6/10,000 (Rampazzo et al., 1994). In the USA, one study suggests that 17% of SCD deaths seen in young individuals aged 20 to 40 were the result of ARVC (Shen et

al., 1995). In France, 36% (18 out of 50) of cases of sudden perioperative death were considered to be caused by ARVC in seemingly healthy individuals (Tabib et al., 2000).

ARVC caused by the p. S853L mutation in *TMEM43*.

Specific to this thesis is the genetic sub-type of ARVC caused by the p. S358L mutation in *TMEM43*. The disease was first recognized in NL in the 1970s as a familial disorder that caused SCD in young males (Guiraudon et al., 1983). In 1998, using Newfoundland families, linkage studies determined the likely locus for this gene was on the short arm of chromosome 3 (Ahmad et al., 1998). This helped narrow down the location of the mutation. In 2008, a research team at Memorial University in NL located the p. S358L mutation in *TMEM43* (Merner et al., 2008).

ARVC caused by the p. S358L mutation in *TMEM43* is prevalent in NL. Currently, 27 families have been found to have disease caused by p.S358L in TMEM43 (K. Hodgkinson, personal communication, February 3, 2020). The prevalence of ARVC caused by *TMEM43* p.S358L in NL is estimated to be about 1/500 to 1/1000 individuals (Etchegary et al., 2015).

As a result of this research, a working database has been established which contains pertinent and valuable information on individuals affected by ARVC caused by the p. S358L mutation in *TMEM43*. The SCD research team maintains this database containing in-depth information on over 1000 people (across generations) from 27 families in the province. The database contains demographic and clinical variables relevant to research and ongoing clinical care.

In affected individuals, the age of cardiac complications occurs earlier than those in a control population. Males are hospitalized four times more often than affected

females and with younger ages of death than affected females. Heart failure is seen in 16% of affected males by 40, and 46% in males by age 60. Holter Monitor testing is the only test able to clinically diagnose disease prior to death. PVCs greater than 200 in 24 hours are seen in affected males by a median age of 25, while in females, the median age is 48 years. Median survival in affected males is 40 years (Merner, 2008).

While females are affected by this specific type of ARVC, clinical manifestations and death are delayed and do not occur at such an early age. Females have a later onset of symptoms, fewer hospitalizations, and longer survival (median age of death 67 years). When looking at clinical data, with the exceptions of syncope and palpitations, there is no difference in symptoms between affected and unaffected females (Hodgkinson et al., 2013).

Treatment of ARVC caused by the p. S358L mutation in TMEM43.

As determined early in the literature (Hodgkinson et al., 2005), the effectiveness of ICDs in families in NL who were linked to having ARVC, was proven successful. They identified that ICDs had a positive impact on survival for males with ARVC. At this point, the mutation had not been discovered, so clinical descriptions regarding the ICD were made based on research haplotype results. In 2016, using mutation analysis, long-term evidence for ARVC caused by the p. S358L mutation in *TMEM43* was provided based on the success of ICDs. Hodgkinson et al. (2016) identified that males with ARVC caused by the p. S358L mutation in *TMEM43* who received an ICD obtained "a significant and substantial survival benefit" (p. 5), with females obtaining a significant effect as well. Males who had a history of VT/VF and were treated with ICD placement had a 95% 5-year survival rate, while those who were given an ICD prior to any event of VT/VF had a

100% 5- year survival rate. This is comparable to 65% and 50% survival rate, respectively, of controls who did not receive an ICD. In females, there was a 97% 5-year survival rate found in those with an ICD, compared to 85% in controls. This data equates to an increase in life expectancy by 30 years for affected males who had been provided with an ICD based on the genetic mutation alone (Hodgkinson et al., 2016).

Psychosocial impact of living with an ICD.

While the success of ICD therapy cannot be ignored in increasing survivability for those with ARVC, it is important to highlight research which gives insight to the psychosocial impacts of living with an ICD. Recent evidence from Etchegary et al., (2017) reveals some of the psychosocial burdens of living with an ICD. This study interviewed individuals who were mutation positive, mutation negative and their spouses/partners and found four major themes in their qualitative analysis:

(1) Acceptance and gratitude. Across participants, it was clearly shown that the survival benefits of having an ICD were understood. This was especially true in families in which a young family member died due to SCD or in cases where an ICD appropriately fired, thus saving an individual's life.

(2) Grudging acceptance. While the benefits of having an ICD were recognized, acceptance of needing an ICD took time, and often came with a sense of resignation.

(3) Psychological effects. Emotional and psychological well-being were identified as being negatively affected by mutation carriers, mainly due to the constant awareness of the ICD and subsequent negative recurring thoughts causing anxiety, depression and fear. Fear and doubt were reflected by all participants, particularly their spouses. Survivor guilt was also identified by siblings found not to have the mutation. Romantic and social

relationship difficulties were expressed by participants as well. Anxiety around the fear of the ICD firing caused feelings of isolation and negatively impacted social relationships.

(4) Practical concerns. Clothing and travel choices, ability to drive, and continuation of recreational activities were all concerns identified by participants.

These findings were in line with quantitative research that reported individuals who had inherited cardiomyopathies and were fitted with an ICD reported higher rates of depression and lower Quality of Life scores (QOL) as compared to those who received an ICD for ischemic or valvular heart disease (Jacq et al., 2009).

These issues may be minimized by clinicians, who understandably focus on the clinical aspects of ICD management rather than focusing on the psychological, social, and economic impact of living with an ICD. Psychosocial outcomes might be improved or at least better managed if psychological screening and counselling were provided pre-implantation, and psychological services were broadened to include unaffected family members and spouses of affected individuals (Etchegary et al., 2017; Manuel & Brunger, 2016).

The multitude of psychosocial issues that can be experienced by families affected with ARVC highlights additional issues of importance for clinicians in primary care who are often the first point of contact with affected individuals. Incorrect referrals or not referring high risk individuals to cardiology and genetics divisions have implications not only for clinical outcomes, but also a host of psychosocial and familial impacts.

Importance of Establishing Multi-Generation Family Histories in Primary Care

Obtaining family histories is one of the core competencies and roles of a PCP (Korf et al., 2014 & Mikat-Stevens et al., 2015). The importance of obtaining accurate

family histories has been identified by PCPs (Carroll et al, 2016b; & Wilson et al., 2016). However, it has been demonstrated that PCPs have concerns obtaining and interpreting FH including: issues with what information to include in the FH, how to integrate obtaining FH information within the patient's primary care visit, and integrating FH information into electronic health records. Other reported issues with obtaining accurate FH include the dependence on patients to self-report their own FH (Mikat-Stevens et al., 2015).

Regardless of the concerns raised by PCPs on how to obtain and interpret accurate FH, the literature demonstrates the importance of obtaining multi-generation family histories and its importance in providing holistic care to patients. Waddell-Smith et al. (2016) identified that with multi-generational FH taking, inherited diseases clearly become highlighted through cascade screening. Waddell-Smith et al. (2016) found that it was possible to detect eight to nine affected family members of a genetic heart condition when employing family cascade screening for family members identified though FH, though typically two to four affected family members are detected. These individuals are often otherwise asymptomatic. This translates to 25-40% of asymptomatic individuals who are at risk of having the genetic heart condition being detectable though use of FHs. Furthermore, the importance of multi-generational FH was echoed by Dunn et al. (2013), who commented that multi-generational FHs are critical when considering diseases which may vary in symptom presentation or may seemingly "skip generations" due to their non-penetrance. Dunn et al. (2013) demonstrate the importance of multi-generational FH in identifying affected family members who are undiagnosed and may be affected but are not yet presenting with symptoms. The importance of cascade screening is not just that it

identifies those at risk for a specific condition. It also removes those who may be at risk but do not have the disease in question. This individual's descendants are removed from testing, limiting the need for unnecessary clinical investigations. Cascade screening also limits the unnecessary use of expensive medical equipment, unnecessary hospital visits and appointments, and helps ensures that those in need have timely access to services and equipment for testing (Dunn et al., 2013).

ARVC can present with variable expression in affected family members (Azaouagh et al., 2011; & Hodgkinson, 2009). Therefore, the disease may not present and progress the same in all affected family members. A multi-generational FH will enable an accurate snapshot, which reflects not only disease and death, but also other symptom presentation.

Family Pedigrees.

Family pedigrees (see Appendix B) are a graphic depiction of a family's medical history. Integrating symbols into the diagram, which represents specific information such as sex, birth relation, and degree of relatives, they help inform health care providers on an individual's risk of certain illnesses and other conditions. In addition, certain medical conditions and the individuals they affect are documented within the pedigree (Bennett, 2019). Family members represented in the pedigrees ideally will go back at least three generations, and include parents, aunts, uncles, cousins and grandparents. Within the pedigree, males are typically depicted with a square, females with circles, and people of unknown sex as diamonds. Death of an individual is shown with a diagonal line across the symbol, with age or year of death follow the notation "d." Marriage or mating couples are connected with horizontal lines, with offspring suspended from these lines and

connected with vertical lines (Craft-Rosenberg & Pehler, 2011). From these depictions, first-, second-, and third-degree relatives can be determined. First-degree relatives consist of parents, children, and siblings; second-degree relatives are aunts, uncles, nieces, nephews, and grandchildren; and third-degree relatives are first cousins, as well as great-grandparents, great-grandchildren, and great aunts and uncles (Sadovnick & Macleod, 1981). As ARVC is an autosomal dominant disease, it is pivotal that this information be obtained in order to determine risk of inheriting the disease.

Use of Genetics and Genomics in Primary Care

As ARVC is a genetic disease, it is integral to discuss the role of genetics and genomics medicine in further advancing the understanding, recognition, and treatment of this disease. The integration of genetic and genomics medicine into primary care has grown in recent years (Melo et al., 2015). Advances in genetics and genomics offer an enhanced understanding of diseases and allow for more individualized, patient centered care. With this enhanced understanding, prevention and treatment of diseases takes individual differences into account, blending genetic and genomic information together with clinical care. For the full benefits to be reaped from this collaboration, patient-centered care, or precision medicine, needs to be fully integrated into primary care (Carroll et al., 2016b).

While evidence indicates that PCPs do acknowledge their role in providing initial genetic risk assessment and counselling to their patients (Wilson et al., 2016), PCPs have identified several challenges and concerns regarding this integration. This includes a lack of confidence in referring and counselling patients at risk for, or diagnosed with, a genetic condition. Also reported by PCPs is a general lack of knowledge, skills, and experience in

genetics and genomics medicine. As such, PCPs have identified that they feel inadequate in fulfilling their growing role with the integration of genetics and genomics medicine into primary care (Mikat-Stevens et al., 2015). The complex nature of knowing who to test for a genetic condition, the appropriate time to test them, recognizing triggers that indicate a need for genetic counselling and testing, the appropriate test to use, and how to interpret the results all present compounding concerns that must be considered by PCPs. Additionally, once a genetic condition is confirmed, treatment provided by PCPs must integrate this diagnosis into primary and acute care provided to the patient (Carroll et al., 2016b; & Scott & Trotter, 2013). PCPs have identified barriers in accessing recent, relevant knowledge about specific genetic conditions in general (Carroll et al., 2016b), as well as professional standards and guidelines on testing patients at risk for genetic conditions (Mikat-Stevens et al., 2015). Additionally, lack of personal connections within genetics medicine and PCPs have left PCPs feeling like they are referring patients into an "abyss", with little interaction, and guidance (Carroll et al., 2016b). Furthermore, Carroll et al. (2016b) identified that PCPs may not be aware of their incorrect assumptions and beliefs, or lack of knowledge, of genetics and genomics and the restriction this places on further integration.

In addition to the expression of overall lack of knowledge, skills, experience, and access to information, PCPs have also identified ethical concerns in the integration of genetics and genomics into primary care. Carroll et al. (2016b) reported that PCPs expressed concern over the impact of the doctor-patient relationship with increasing integration of genetic and genomic medicine. PCPs explained that patients trust them as their patients have shared their medical and personal histories. With this trust, patients

value the input of PCPs in the decision-making process of testing for a specific disease. If PCPs cannot be relied upon to provide accurate information in that decision-making process, the question remains as to who will.

The potential for increased patient anxiety and psychological distress over testing and confirmation of the presence of a genetic condition has been identified in the literature (Mikat-Stevens et al., 2015). Coinciding with this is the potential impact genetic testing could have on both social and insurance discrimination. PCPs reported concerns over the impact of positive tests on patients' ability to access medical insurance, as well as patients' inhibition to get genetic testing done over their own fears of the negative impact it would have on accessing insurance (Mikat-Stevens et al., 2015). However, current legislation in the United States, set forth in the Genetic Information Non-discrimination Act in 2008, limits discrimination in health insurance and employment that may be caused by genetic testing and subsequent results (U.S. Congress, 2008). In Canada, Bill S-201 (Genetic Non-Discrimination Act) was passed into law on May 4, 2017 (Parliament of Canada, 2017). This law prohibits any person from requiring an individual to undergo genetic testing, or disclosing of any genetic testing result "as a condition of providing goods or services to, entering into or continuing a contract or agreement with, or offering specific conditions in a contract or agreement with, the individual." Notable exceptions exist, such as for health care providers and researchers. The law also relates to the Canada Labour Code, which protects employees from being required to have a genetic test done or disclose the result of a genetic test, as well as the Canadian Human Rights Act which prohibits discrimination based on genetic characteristics (Parliament of Canada, 2017).

Suggestions on how to improve the integration of genetics and genomics medicine into primary care offer a pathway for bridging the gaps expressed by PCPs. Carroll et al. (2016b) reported that increasing PCPs' knowledge about genetics and genomics medicine, increasing their accessibility to genetic specialists, and having reliable and relevant resources available at the point of care were potential solutions to increasing PCPs' confidence with, and knowledge of, the integration of genetics and genomics medicine into primary care. Furthermore, continuing medical education programs and interactive educational interventions have been proposed as cost-effective ways to facilitate the integration of genetics and genomics medicine into primary care (Wilson et al., 2016).

Use of Educational Tools in Primary Care

Giving consideration to the concerns and issues acknowledged previously, there is an identified need to provide PCPs with information on how to best integrate genetics and genomics medicine into family medicine, improve overall knowledge, increase the identification of those affected by a genetic condition and refer them to appropriate services, and provide evidence based findings so that those who are referred to genetics services are done so properly (Carroll et al., 2011). Printed educational materials have been identified as a common way to communicate important health information to PCPs that is relatively low cost (Genova et al., 2014; & Grimshaw et al., 2014), and improves overall knowledge (Williams et al., 2015).

Printed educational materials can vary, and may include monographs, articles in peer-reviewed journals, and clinical guidelines (Farmer et al., 2008). However, for the material to be effective, the information within them must be interesting and easy to understand and motivate PCPs to change their behaviours and attitudes (Genova et al.,

2014). Readability, content, organization, tone/language, illustrations, appearance/topography, and appeal have all been identified as important areas of focus to increase uptake of printed educational materials, ensuring that those areas are reflective to the intended audience (Williams et al., 2015).

As reported by Watson et al. (2001), some studies have shown that written guidelines can be helpful to PCPs; however, printed materials alone may have little impact on disseminating new knowledge, and subsequently, changing practice. Improvements in care offered by PCPs after an intervention of printed materials are on-par with more expensive interventions such as academic outreach (Zwarenstein et al., 2014). Evidence does indicate that an integration of educational tools and other knowledge translation efforts such as interactive workshops, produce the greatest impact on PCPs' knowledge, confidence, and skills, as well as integration into practice (Carroll, et al., 2011; Williams et al., 2015).

Project Overview

This project sought to create a simple, easy to use, paper-based educational tool to be used by PCPs to identify those at risk for carrying the *TMEM43* p.S358L mutation for ARVC as well as their family members. To achieve this, we sought initial feedback from a small group of PCPs using a rough draft of the tool, then integrated their feedback to create a revised tool. The revised tool was sent to a larger group of practicing PCPs and Family Medicine Residents in the Faculty of Medicine, Memorial University, in NL.

Genetics and genomics medicine have been increasingly integrated within primary care for some time. Gaps in knowledge and practice, however, have been identified by PCPs as an area of concern with the increasing integration. Educational tools have been

identified as cost-effective methods to increase medical health care knowledge on specific topics in PCPs. Acknowledging this, as well as the previously discussed importance of identifying those with the p.S358L *TMEM43* mutation early, a simple two-page educational tool was created specifically for PCPs to utilize in their practice.

The goal of this project was tool creation. The motivation for this work was to integrate patient-orientated experiences with supporting academic literature. The author of this thesis has been living with ARVC since being diagnosed in 2007 after a sibling suffered from sudden cardiac arrest (SCA). While it was suspected for decades that the family suffered from a genetic heart condition, it was not until the sibling's SCA, and identification of the mutation by the team at Memorial University of Newfoundland, that a diagnosis was provided to the family. It is hoped that through the tool creation, individuals and families within the province who unknowingly have this condition can be more easily identified before a tragic event, such as SCA, or worse, SCD, occurs.

Future work will address the translation and uptake of the tool in practice.

Methods

This project was completed over several stages and utilized a multiple methods approach to develop the final version of the tool for PCPs. The stages included:

- Initial tool development using working knowledge from practitioners, and the existing 'ARVC caused by p.S358L in *TMEM43'* database
- A working lunch with PCPs to obtain feedback on the first draft of the tool
- Incorporating feedback from the working lunch to revise the tool; and,
- Providing an opportunity to review the revised tool and offer feedback via an online survey distributed through an e-mail invitation to all PCPs and Family Medicine Residents in NL.

Stage 1 - Initial Tool Development

Based on the team's clinical experience, as well as current guidelines for screening and referring individuals at risk for ARVC (Gollob et al., 2011), a draft educational tool on ARVC caused by the *TMEM43* p. S358L mutation was developed as a three-page Word document (see Appendix C).

Information in the initial draft of the tool included an introduction to SCD, ARVC as a genetic cardiac disorder in general and ARVC caused by the *TMEM43* p. S358L mutation specifically, treatment options for those confirmed to have this specific type of ARVC, as well as important points to consider in determining an individual's risk for this specific type of ARVC. Visual aids (e.g., graphs) were also provided.

The first draft of this tool was loosely modelled on national 'GEC-KO On the Run' tools for healthcare providers practising in Canada, created by the Genetics Education Canada Knowledge Organization Centre (GECKO). These are freely available online (http://geneticseducation.ca/), and are written by healthcare teams comprising PCPs, geneticists, genetic counsellors, and genetic researchers. Genetic topics covered by GECKO knowledge translation tools are broad, but all are meant to aid in the translation of genetics into primary care, with a goal of increasing appropriate referrals to genetic services and decreasing wait times. Tools are short, but provide a concise summary of genetic disorders, technologies, and red flags for referral from primary care. Tools are reviewed by family physicians and include scholarly, referenced research. Topics covered by these tools include *BRCA1* and *BRCA2*, Huntington Disease, Hypertrophic Cardiomyopathy and newborn screening, amongst several others. Information found within these two-page PDF files include an introduction to the disease in question, considerations to make in determining if a patient is at high risk for the disease, including genetic testing, and treatment methods, including clinical test results. The initial draft of the ARVC educational tool for the current study was modeled loosely on the Hypertrophic Cardiomyopathy tool (Honeywell et al., 2014). Similar concepts found within this ARVC tool and comparable models, such as that from Honeywell et al. (2014) include an overview of ARVC, specifically the type of ARVC of focus in this thesis, common red flags seen in this condition, information on genetic testing, and interpretation of genetic test results. Unique information found only within the ARVC tool include clinical testing information and the demonstrated importance of obtaining accurate family histories. Additionally, local genetic testing referral information had also been included.

Stage 2 - Working Lunch with Physicians

When the draft tool had been reviewed by the SCD research team: Drs. Kathy Hodgkinson, Holly Etchegary, Sean Connors and Ms. Fiona Curtis (genetic counsellor), a working lunch with PCPs was scheduled in May 2016 at Memorial University's St. Johns campus with the goal being to present the initial tool and obtain immediate feedback.

Recruitment of PCPs for the working lunch.

SCD team members used their personal and professional networks and contacts to invite PCPs to the working lunch. With this convenience sampling, no demographic or practice factors were considered in the selection process. Rather, the goal was to assemble a small group of PCPs – whatever their practice environment, years in practice, sex, age, etc., in order to begin the process of obtaining initial feedback. Those who expressed an interest in the lunch but could not make the date were given the option of receiving the tool via email and invited to provide their feedback through that medium. PCPs affiliated with Memorial University's Faculty of Medicine in NL, as well as Family Medicine Residents, were also sent an e-invite (see Appendix D) to attend the working lunch through a Family Medicine list-serve at the Faculty of Medicine, Memorial University. Family Medicine Residents were thought to be key stakeholders for this project, as they would be the PCPs that would be working with families and individuals at risk for ARVC as practising PCPs in the near future.

Based on the literature, the team aimed for a response rate of six to eight PCPs (Bloor et al., 2001) for the working lunch.

Format of the working lunch.

The working lunch was designed to provide an informal opportunity for PCPs to come together with the research team and talk about the tool. To start, a brief presentation on ARVC caused by the *TMEM43* mutation was given by the author. Topics covered in this brief presentation included disease symptomology and presentation, rates of SCD seen in this type of ARVC and treatment options. Participants were also informed about the referral process for suspected high-risk individuals. After the presentation, PCPs were asked for their initial thoughts about ARVC and their familiarity with it in their practice. They were asked to review the tool with the team and have an open-ended discussion about the information found in the tool, and the predicted ease and applicability of the tool in family practice. It was hoped that through this open-ended discussion, information obtained would help modify the tool to better reflect the needs expressed by PCPs regarding what they would need to know in order to determine if an individual was at high risk for having ARVC.

Team members present included Dr. Kathy Hodgkinson, Dr. Holly Etchegary, and Lauren Rickert. All team members helped facilitate the discussion with PCPs and all took detailed field notes for further interpretation and thematic analysis. Feedback was also sought through a short, eight question Likert survey with three open-ended questions for physicians to provide feedback on the tool, specifically ways to improve the tool and any important information that PCPs felt was missing. These surveys were answered anonymously and returned to the team by PCPs on completion (see Appendix E). Likert scale questions included asking PCPs if "the tool seemed easy to use"; "the layout was easy to follow"; and "overall, this tool will help me correctly refer high-risk cardiac families to the genetics cardiology service". The scales for responses on these items

ranged from 1-Strongly Disagree to 5-Strongly Agree. In addition, the open-ended questions asked more general questions, such as "Was there important information missing? Please explain"; and "Please identify one way this tool could be improved."

Qualitative data collected through open-ended items were analyzed using descriptive thematic analysis to help highlight and prioritize areas on the first draft of the tool that needed modification. Two team members (Dr. Holly Etchegary and Lauren Rickert) read PCPs' comments and team members' field notes to identify common themes using the method of constant comparison (Pope et al., 2000; & Sandelowski, 2000). Here, notes and open comments on the survey were read and re-read to identify emerging similarities or differences in PCP comments about the tool. Descriptive statistics (means, counts, percentages) were determined to help describe PCPs opinions on the draft tool.

Stage 3 – Revising the Initial Draft of the Tool

The team met after the working lunch following the return of all physical and electronic copies of the survey, to discuss the results and to incorporate them into an updated tool. The verbal feedback and results from the surveys were analyzed to determine what PCPs identified as gaps in the tool and information that was needed to make the tool more applicable and/or easy to use in practice. At this time, the team also reflected on the existing clinical and research database containing information on all the families in the province affected by ARVC due to *TMEM43* p.S358L. Previous research using the database (Hodgkinson et al., 2013) had shown that symptoms and clinical tests, with the exception of the Holter Monitor, were poor discriminators of those with ARVC caused by *TMEM43* p. S358L mutation. It was also recognized that persons presenting to

PCPs would likely have (a) had no clinical testing done themselves, likely being non-discriminatory anyway, and (b) would not know what clinical testing others in their family would have had. However, family pedigrees might hold more information than was currently captured in the database. Therefore, it was decided that to better inform the tool, more information from family pedigrees would be extracted, and added to the database.

Acknowledging the areas identified by PCPs as needing clarity and modifications, an updated tool was drafted (see Appendix F). It provided background information on ARVC caused by the *TMEM43* p.S358L mutation, as well as clinical data that might indicate a problem. These risk-factors were characterized as:

1. Symptomology (syncope/pre-syncope)
2. Heart rhythm data (PVC's) and presence of non-sustained VT. Information for items 1 and 2 came from the natural history paper (Hodgkinson et al., 2013) and the existing dataset
3. Number of relatives who have documented evidence of SCD or an obvious cardiac problem (an ICD or cardiac transplant)
4. Recommendations for referral to the Cardiac Genetics Clinic in St. John's, NL.

Using the pedigrees to inform the tool.

As persons attending a PCP office would not necessarily have had any cardiac clinical tests done ahead of time, (and even if they had, it has already been noted in the

papers describing ARVC due to *TMEM43* p.S358Lthat the first symptom may be death) it was felt that the most compelling data may come from the FH.

The *TMEM43* p.S358L dataset is not linked directly to a pedigree, so there was no ability to determine from the dataset itself the level of FH each affected person had at the time they presented to the medical care system. In other words, how many relatives had a significant cardiac event, and how close were those relatives to the patient. These would be questions which a PCP could ask a patient, and which they would likely know. Family pedigrees would need to be closely examined to determine this.

Family Pedigrees.

Geneticists can analyze a large family tree and, with experience, know what this is suggesting in terms of the FH of a condition. PCPs are expected to be able to complete a family tree, as it is a core competency. However, family trees in general practice tend to focus on the nuclear family, such as parents and siblings, and are considered extensive if they capture three generations. The pedigrees used to inform the database include over 1000 persons, comprising of greater than 10 generations. Therefore, the research team could access far more information than a PCP would ever typically have or be able to collect during a routine appointment. Thus, we wanted to assess the pedigrees to quantify how many obviously affected relatives a person who is *now* known to be affected had in their family tree at the time they presented to the medical professional (e.g., those in their family who had died suddenly, those post-transplant, or those with an ICD).

We hoped to quantify the level of information that would be useful based upon the degree of relatedness. For example, many PCPs might presume that the only person in whom one is interested is the first-degree relative. However, knowing that each individual

with ARVC can have extreme variability in expression of the mutation, as well as acknowledging that each child of an affected individual has a 50% risk of inheriting the mutation, examination of first degree relatives who died before age 50 due to SCD is not enough. For example, it is known that this form of ARVC is less severe in females. While the female may carry the mutation and pass it to her offspring, she may never know she is a carrier for the disease due to the less obvious physical expression of the disease (if we do clinical cardiac tests, the disease is seen in females, but often not to an extent that brings them to a doctor). Therefore, her male offspring may present to the physician, and if only SCD in first degree relatives is noted, the male offspring's risk could be missed since his first-degree relatives may be clinically well. However, if we look back to the patient's second or third-degree relatives, we may find that the patient's maternal grandfather died at 45 from SCD and his maternal great-grandfather at 39.

Two team members (Dr. Kathy Hodgkinson and student Lauren Rickert) met weekly for a period of three months to discuss and extract the family pedigree data. The pedigrees were well established and documented. As mentioned, a variable which would denote the number of obviously affected relatives within the data set was necessary. In order to create this variable, all affected individuals were determined from the dataset (n= 409). At the point of ascertainment of the affected person (which was the date they became known to the medical team), the pedigree was assessed for relatives to this person with obvious disease (SCD, ICD placement, or cardiac transplant), who would have had this diagnosis prior to the date the ascertained person was first seen. Typically, people tend to know of relatives with severe disease, while they may not necessarily know of relatives who have been to the hospital and had abnormal clinical tests. Therefore, this

search was to document the number of relatives the affected person could potentially have known about just prior to the date of their ascertainment by the health care system.

Using this methodology, all first-, second-, and third-degree relatives with obvious disease were counted, and added to the dataset as a variable associated with that specific affected individual. The purpose of this was to explore if an easy question, such as "do you have any relatives who have had an early death, a heart transplant, or the implantation of a device designed to pace and shock the heart back to a normal rhythm?" would be useful as a clear red flag. To do this, it was necessary to know how many at risk individuals had, and what degree of relation, a first-, second-, or third-degree relative. This was a question we had not previously asked of the dataset in this context, and thus, was not currently captured in the existing dataset.

Clinical test results.

The on-going research has determined which clinical features are common in persons with ARVC caused by *TMEM43* p.S358L. However, none are useful diagnostically themselves, with the exception of ectopy (number of PVCs, or VTs) on the Holter Monitor. Poor R-Wave Progression (PRWP) or a 12-lead ECG is a clinical test that is not used for diagnosis, but if paired in conjunction with a FH, would be important. Acknowledging this, we felt we could use the clinical features, in conjunction with FH to help PCPs. Therefore, these were taken into account in the final version of the tool.

Stage 4 – Surveying a Larger Sample of PCPs and Family Medicine Residents: Revised Tool

Relevant PCPs, Family Medicine Residents, and professional organizations were contacted between March to July 2018. Groups were provided with an e-mail describing

the project as well as an updated draft of the tool, with a request to review the contents and provide feedback via an on-line survey. Careful consideration was given to include practicing PCPs in NL, Family Medicine Residents from Memorial University of NL who would soon be practicing PCPs, as well as their governing professional body, the Newfoundland and Labrador Medical Association (NLMA).

Through a working collaboration with the Health Sciences Information and Media Services (HSIMS), Faculty of Medicine, Memorial University of Newfoundland, the tool finalized in Stage 3 was adapted to an electronic PDF, with the same information found in Appendix F. Additionally, an online version of the survey was created utilizing the Survey Planet platform (https://surveyplanet.com) and a link to the survey was integrated into the PDF copy of the tool.

The updated version of the tool was sent to all Family Medicine Residents within Memorial University of Newfoundland through the list serve for the Faculty of Medicine in March 2018. Specifically, Family Medicine Residents were sent an e-mail (see Appendix H) with a description of the project, as well as a PDF attachment of the tool, and a link to the online survey (https://s.surveyplanet.com/Bym_glXtG) containing nine Likert-scale questions, two qualitative questions and five demographic questions (see Appendix G). An e-mail reminder was sent to Family Medicine Residents approximately one month after the initial e-mail was distributed. Data were collected and analyzed up to July 1, 2018.

Additionally, the NLMA provided an advertisement in their newsletter, inviting PCPs to review and provide feedback through an online survey (see Appendix I). This advertisement was posted in June 2018.

Furthermore, all PCPs practising within NL were sent an e-mail with the PDF attachment and online survey link through the list serve of the NL College of Family Physicians (see Appendix J). This e-mail was distributed in May 2018. The physicians who attended the original working lunch were also personally contacted and advised of the revised tool. They were provided the PDF copy of the tool, as well as a link to the survey (see Appendix K). All data on the feedback of the tool was only used if it was received prior to July 1, 2018. No financial incentives were used to help in recruitment.

The literature suggests a mean response rate of 56% for paper-based surveys, and 33% for online surveys (Nulty, 2008). Acknowledging there are about 710 PCPs in the province of NL (Ms. Debbie Rideout, personal communication, June 2018), and 70 Family Medicine Residents (Dr. Susan Avery, personal communication, September 2016), this gives an anticipated response rate of the survey to be about 117 PCPs and Family Medicine Residents. However, it is important to acknowledge here that recruitment of PCPs in research studies is a known obstacle faced by researchers. They are a documented difficult group to recruit, and with limited empirical data on the effectiveness of various recruitment strategies to help guide the research design, actual response rates will not be reflective of the rate anticipated in the literature (Boulet et al., 2013).

Qualitative description was used to analyze responses to two open-ended qualitative survey items. Comments were independently read by the author, then re-read by another team member (Dr. Holly Etchegary) to identify emerging categories and themes within the narrative feedback. A correlational analysis was conducted on

quantitative data to explore any relationships among survey demographic items and items assessing the tool.

Summary

Based on a working lunch held with PCPs, a number of areas of concern were identified with the original draft of the educational tool. Utilizing their feedback, and pre-existing FH data on families with this type of ARVC, a modified tool was created and distributed via an on-line resource, as well as through e-mail for PCPs and Family Medicine Residents to view and provide further feedback on. The results of the feedback obtained will be explored in the subsequent section.

Results

Working Lunch

Recruitment

In total, 10 physicians were contacted via e-mail or in person and asked to attend the working lunch.

Participants

The draft tool (see Appendix C) was presented to PCPs during a working lunch in May 2016 at the Faculty of Medicine, Memorial University, Health Sciences Centre. Feedback on the tool was provided by a total of five PCPs (four male). Three PCPs attended the working lunch (two males, one female), and two PCPs provided their feedback electronically (two male). All participants were practicing in an academic setting; none were community physicians.

Analysis.

Quantitative and qualitative data recorded through the working lunch and an eight item, five-point Likert scale survey with open-ended questions provided the team with the feedback necessary to revise the first draft of the tool.

Quantitative data.

Descriptive statistics (means, counts, percentages) are provided to describe PCPs' opinion on the draft tool. Overall, the results from the survey from the working lunch revealed that the tool needed substantial revision to increase the ease of readability, as well as its potential for integration into practice. The response distribution is displayed in Table 1.

Table 1: Response distribution from Focus Group Survey, May 2016 [n (%)]

Question/Mean Response	Strongly Disagree	Disagree	Undecided	Agree	Strongly Agree
The tool seems easy to use	0	3 (60%)	1 (20%)	1 (20%)	0
The purpose of the tool was clearly stated	0	0	1 (20%)	1 (20%)	3 (60%)
The instructions were clear*	0	3 (60%)	0	1 (20%)	0
The layout was easy to follow	0	4 (80%)	1 (20%)	0	0
The information was easy to understand	0	0	1 (20%)	4 (80%)	0
I feel this tool has increased my knowledge about ARVC in NL	0	0	1 (20%)	2 (40%)	2 (40%)
Overall, this tool would be helpful to me in my practice	0	1 (20%)	1 (20%)	2 (40%)	1 (20%)
Overall, this tool will help me correctly refer high-risk cardiac families to the genetics cardiology service	0	2 (40%)	1 (20%)	1 (20%)	1 (20%)

*indicates that a response was missing from this question

60% of PCPs indicated the tool did not seem easy to use; 60% did not find the instructions clear nor the layout easy to follow. Forty percent did not agree the tool would help refer high-risk cardiac patients to the cardiac genetics clinic. Alternatively, however, 60% of PCPs felt that they were either undecided, agreed, or strongly agreed that the tool would help refer high risk cardiac patients appropriately. Most participants agreed the purpose of the tool was clearly stated, with 80% agreeing that the information itself was easy to understand, and 80% of PCPs agreed or strongly agreed that the tool helped increase their knowledge on ARVC. Overall, 60% agreed or strongly agreed (40% and 20%, respectively) that the tool would be helpful in their practice.

Qualitative data.

Two qualitative questions were asked in the survey for additional feedback: “Was there important information missing? Please explain.” and “Please identify one way this

tool can be improved." Qualitative data collected through open-ended items were analyzed using descriptive thematic analysis to help highlight and prioritize areas on the first draft of the tool that needed modification. Two team members (Dr. Holly Etchegary and Lauren Rickert) read PCPs' comments and team members' field notes to identify common themes using the method of constant comparison (Pope et al., 2000; & Sandelowski, 2000). Here, notes and open comments on the survey were read and re-read to identify emerging similarities or differences in PCP comments about the tool. Overall, two key themes were identified. These were (a) the ease of using the tool in practice, and (b) the need for clear descriptions of symptom presentation.

1) Ease of utilizing the tool in practice.

PCPs noted the need to shorten the tool, pointing to the importance of short, concise messages that would facilitate its use in practice. One noted the tool needed to present practical information first.

PCPs also asked for clarity regarding what they should do when faced with an individual or family who are at risk for carrying the *TMEM43* p.S358L mutation. Notably, they wanted clear instructions on how to refer families properly to appropriate health care services including genetic screening or the cardiac clinic. They noted a need for clear decision trees for who is appropriate to refer and advice on how to triage patients to prevent unnecessary referral.

> *More clear decision trees for who is appropriate for referral, probably including Holter results.*
>
> *How to triage patients to prevent unnecessary genetics referrals (ECK, CXR, Echo…)*

The message might be that anyone with pre-syncope or palpitations would be referred. The (genetics) clinic would not be happy.

This sort of practical information was thought to make the tool easier to use in practice.

2) More precise descriptions of symptom presentation.

PCPs noted that clear descriptions of symptom presentation would enable them to screen at risk individuals appropriately. As suggested by one PCP, the tool could provide advice on whether findings on ECG, CXR, or echo are useful in triaging patients.

Advice on whether findings on ECG, CXR, or echo are useful in triaging the positive likelihood of ARVC would also be useful in triaging Pts.

Notably, PCPs indicated that recognizing the symptoms and clinical presentation of individuals at risk would be easier if quantitative data reflecting early warning signs of the disease could be incorporated into the tool.

Family Pedigree Data

Past work by the team had clearly shown that no signs and symptoms of the disease were useful in discerning those with and without the disease, within known families. Therefore, it was clear that these would be even less useful in a general population sample (Hodgkinson, 2013). Even symptoms which would be suspected, for example palpitations and syncope, had no diagnostic utility when assessed within the larger ARVC families (using those found to not have the *TMEM 43* p. S358L mutation as controls). In terms of clinical tests, only the Holter Monitor was diagnostically useful when assessing ectopy.

The 27 known families were assessed for the number of first-, second-, or third-degree relatives (with SCD) greater than or equal to 50 years of age) of affected individuals (n=409). The number of relatives in the family who would have clearly shown evidence of the disease prior to their death were then pulled from the data; this included (a) SCD, (b) surgery for ICD placement, and (c) heart transplant. Of these 409, 160 were diagnosed following SCD (i.e., unrecognized as being at risk prior to their final symptom). Of these 160, 56%, 39% and 31% had *at least* one first-, one second- and one third- degree relative presenting with an SCD (less than or equal to 50 years of age) respectively, with 19% having no known affected relatives (Figure 1).

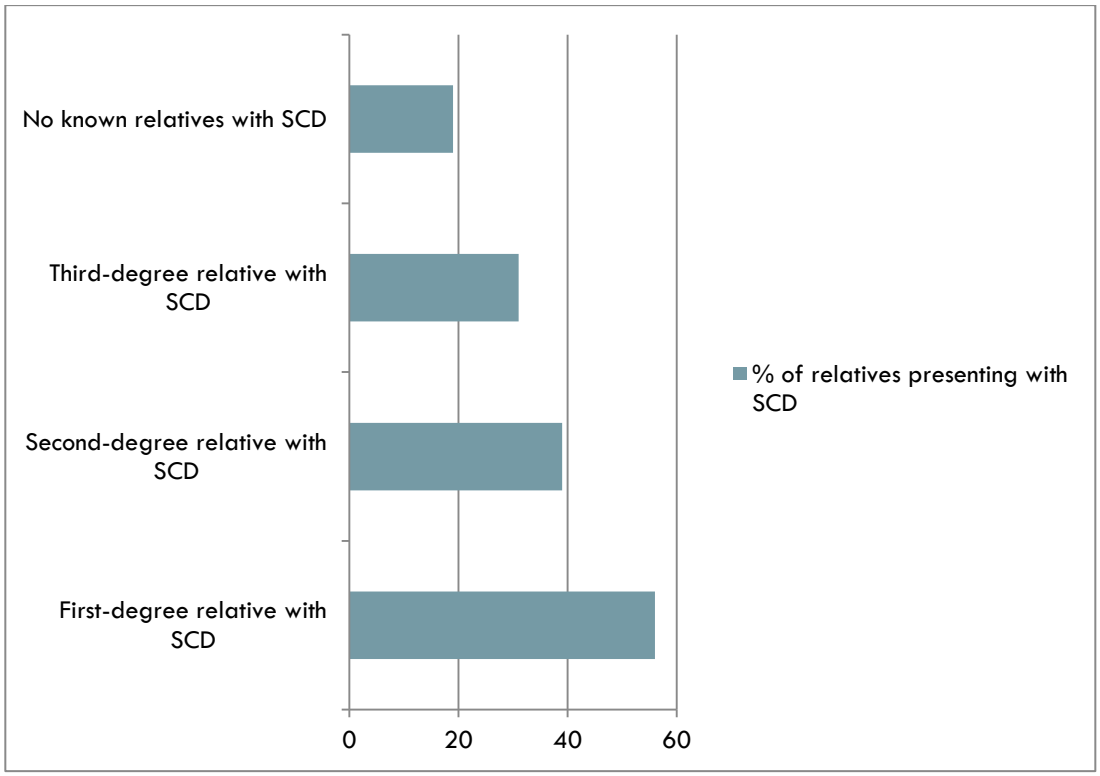

Figure 1: Percentage of Relatives with SCD/ICD/Heart Transplant among Individuals with SCD

This was the first time the data set and family histories had been assessed in this manner. It permitted for a clear demonstration of the usefulness of accurate, multi-generational FH in this disease.

As seen in Figure 1, 56% of people who had a SCD event had at least one first-degree relative with a history of SCD, 39% of people who had a SCD event, ICD placement, or a heart transplant, had at least one second-degree relative with a history of SCD, 31% of people who had a SCD event, ICD placement, or a heart transplant, had at least one third-degree relative with a history of SCD, and finally, 19% of people who had a SCD event, ICD placement, or a heart transplant, had no known relatives with any SCD events. It was evident from these findings that some individuals had a first-, second-, *and* third-degree relatives who had a SCD event, ICD placement, or a heart transplant.

The qualitative feedback, as well as the information obtained from the Family Pedigree data were used to inform the next iteration of the tool. For example, additional information was added to the tool to prompt providers to discuss an extended family history with patients (see Appendix F for revised tool).

Online Survey

Participants

43/780 online surveys were completed by this group. This represents roughly 5.5% of Family Medicine Residents and PCPs completing the online survey. While upwards of 780 Family Medicine Residents and PCPs would have received some notification either through e-mail or through the NLMA website and advertisement, there is no way to determine exactly how many received the e-mail, opened it, or saw the ad. Thus, it is difficult to determine exactly the response rate to the online survey.

Participants were almost equally male (n=22, 52.4%) and female (n=20, 47.6 %), with 59.5% being between the ages of 45 to 64 (n=25). 32.2% of respondents were between the ages of 24-44 (n=14), with 9.1% were 65 or older (n= four). Participants were most likely to indicate having their practice in the community (n=26, 61.9%). Other settings for practice included hospital (n=ten, 23.8%), academic, and other (n=three each, 6.8%) (Figure 2). 27 participants, or 61.4%, were most likely to be practicing within the Eastern Regional Health Authority, with eight participants, or 19.5% practicing within the Central Regional Health Authority, and a smaller number of representatives from the Western Regional Health Authority (n=four) and two participants from the Labrador-Grenfell Regional Health Authority (9.8% and 4.9%, respectively, Figure 3).

Participants reported to have been practicing an average of 13.4 years, with a range of 1 to 20 years. Responses were combined for both Family Medicine Residents and practicing PCPs as response rates were low and answers did not vary greatly between these two groups. Table 2 contains responses to each item from the online survey.

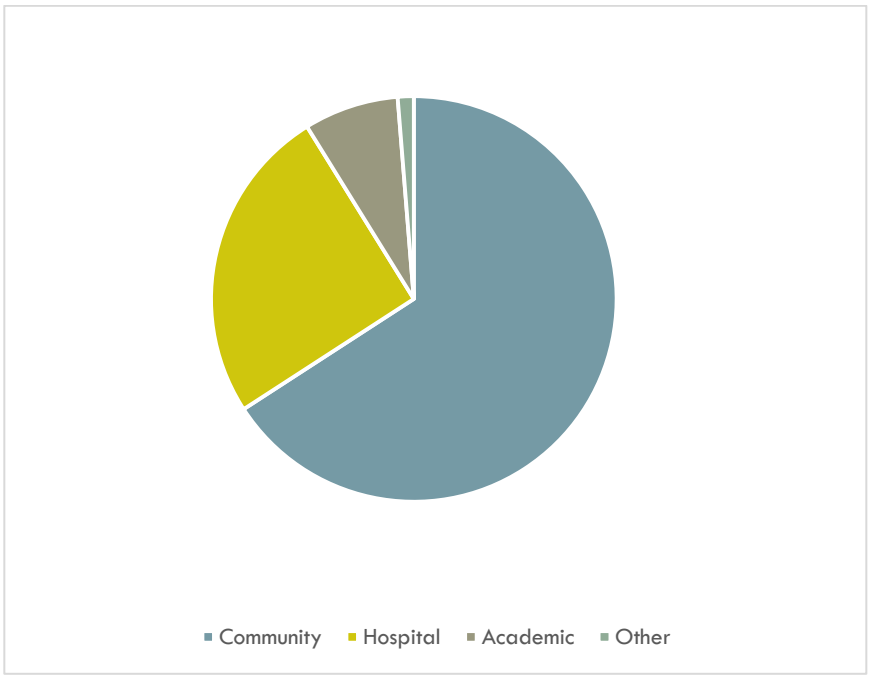

Figure 2: Setting of Physician Practice

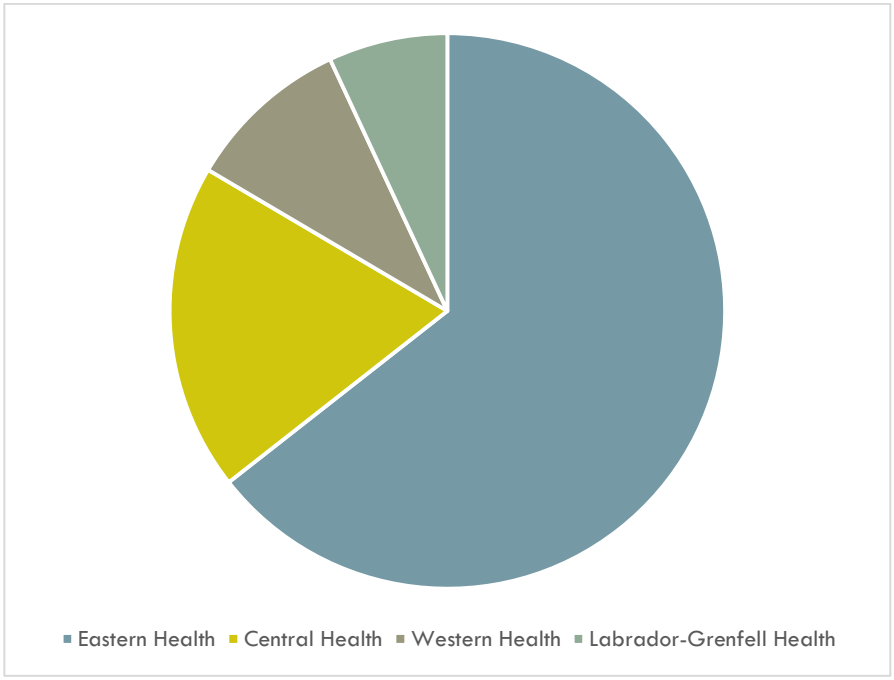

Figure 3: Location of Physician Practice

Missing Data.

It is important to note, however, that some questions were not answered by all participants. Questions two through eight have responses from 42 participants, and question one had responses from 43 participants. The total percentage of missing data was 2.3% for question one, and 4.5% for questions two through eight. No imputation was performed for this small amount of missing data as they are assumed to be missing at random. The percentages are reflective of the total number of responses, with missing data excluded from the calculations.

Quantitative Data.

Table 2 and Figure 4 display descriptive statistics for items on the online survey

Table 2: Mean Response from Online Survey

Question	Mean Response (SD)
The tool seems easy to use	4.21 (.742)
The purpose of the tool was clearly stated	4.36 (.791)
The instructions were clear	4.29 (.742)
The layout was easy to follow	4.07 (.921)
The information was easy to understand	4.36 (.727)
I feel this tool has increased my knowledge about ARVC in NL	4.38 (.731)
Overall, this tool would be helpful to me in my practice	4.24 (.576)
Overall, this tool will help me correctly refer high-risk cardiac families to the genetics cardiology service	4.29 (.636)

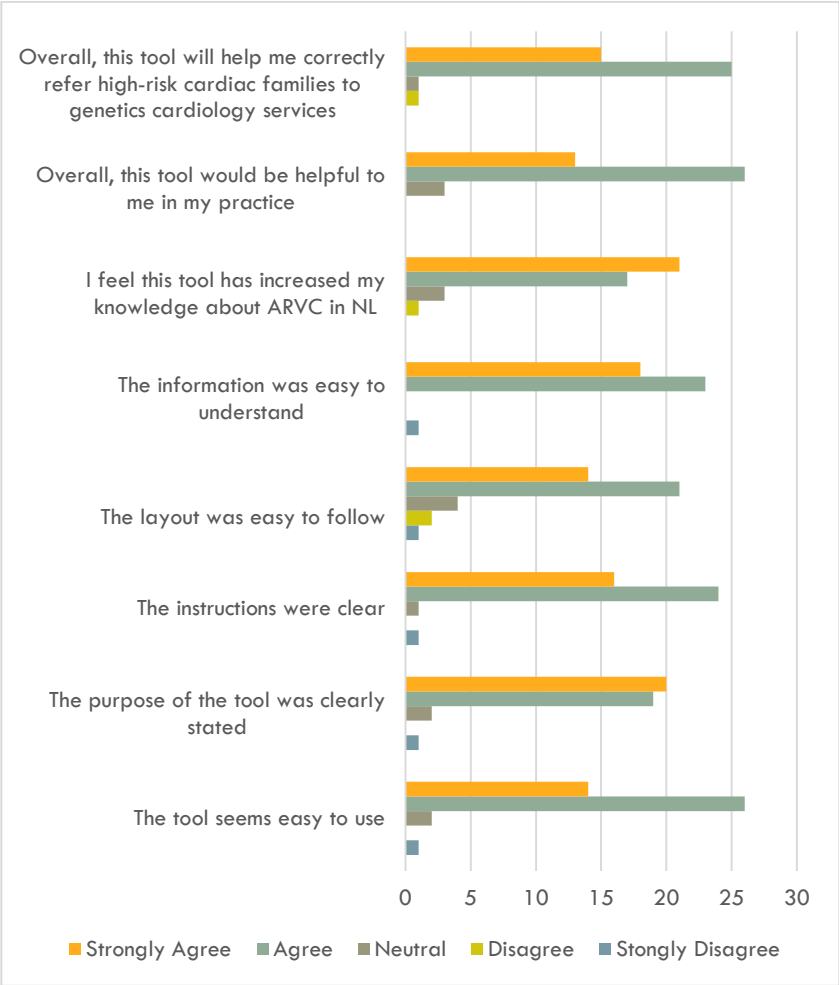

Figure 4: Response Rates from Online Survey

Overall, the survey results indicated a great improvement of the tool from the initial draft. Almost all participants (93.1%) agreed or strongly agreed that the tool seemed easy to use, and that the purpose of the tool was clearly stated (92.8%). Similarly, 95.2% of participants felt the instructions on the revised tool were clear, and 83.3% agreed or strongly agreed that the layout was easy to follow. Almost all participants agreed or strongly agreed (97.7%) that the information was easy to understand, with 90.5% identifying that the tool had increased their knowledge about ARVC in NL. Furthermore, and perhaps one of the most important features of the tool, almost all participants (92.9%) reported that the tool would be helpful in their practice. Finally, 95.2% of participants reported that they felt the tool would help them correctly refer potentially high-risk cardiac families to the genetics cardiology services.

Statistical Analysis.

A correlational analysis was undertaken to explore any relationships among survey demographic items and items assessing the tool. Table 3 presents the results of the correlational analysis.

Table 3: Correlational Analysis of Survey Items and Demographic Items

	Gender	Age	Years in Practice	Location of Practice	Setting of Practice
Question 1: The tool seems easy to use	r= -.211 N= 42 p= .170	r= -.082 N= 43 p= .599	r= -.016 N= 43 p= .920	r= .219 N= 41 p= .168	r= .094 N= 42 p= .553
Question 2: The purpose of the tool was clearly stated	r= -.070 N= 42 p= .661	r= -.109 N= 42 p= .491	r= -.013 N= 42 p= .937	r= -.091 N= 41 p= .571	r= .171 N= 42 p= .278
Question 3: The instructions were clear	r= -.177 N= 42 p= .263	r= -.120 N= 42 p= .447	r= .022 N= 42 p= .889	r= .043 N= 41 p= .792	r= .211 N= 42 p= .180
Question 4: The layout was easy to follow	r= -.232 N= 42 p= .139	r= -.041 N= 42 p= .798	r= -.032 N= 42 p= .839	r= .185 N= 41 p= .246	r= .093 N= 42 p= .557
Question 5: The information was easy to understand	r= -.209 N= 42 p= .185	r= .075 N= 42 p= .635	r= .052 N= 42 p= .745	r= .019 N= 41 p= .905	r= .187 N= 42 p= .237
Question 6: I feel this tool has increased my knowledge about ARVC in NL	r= .091 N= 42 p= .566	r= -.145 N= 42 p= .361	r= .021 N= 42 p= .896	r= .155 N= 41 p= .333	r= .054 N= 42 p= .734
Question 7: Overall, this tool would be helpful to me in my practice	r= -.148 N= 42 p= .351	r= -.263 N= 42 p= 0.92	r= -.229 N= 42 p= .145	r= -.210 N= 41 p= .187	r= .049 N= 42 p= .760
Question 8: Overall, this tool will help me correctly refer high-risk cardiac families to the genetics cardiology service	r= -.054 N= 42 p= .733	r= -.077 N= 42 p= .628	r= .010 N= 42 p= .950	r= .141 N= 41 p= .380	r= -.090 N= 42 p= .570

As shown in Table 3, there was no significant correlation between participants' demographic information and their responses to any of the survey items. As a result, further analyses were not undertaken.

While scale validation was not the intent of this study, nor possible with the study's small sample, an exploratory reliability analysis revealed the survey items did appear reliable (Cronbach's $\alpha = .887$). Thus, the items used to measure attitude towards the educational tool developed in this study do appear a useful place to start in research with larger samples.

Qualitative Data.

Qualitative description was used to analyze responses to two open-ended survey items. Comments were independently read by the author, then re-read by another team member to identify emerging categories and themes within the narrative feedback. Very minor differences in themes were resolved through discussion and review of the data. Thematic analysis was shared with the full research team to derive the final, following themes. Appendix L contains the full set of all qualitative responses from participants.

The main themes that arose during analysis related to areas for tool improvement and ease of utilizing the tool in practice.

1. Suggested improvements to the tool:

Participants made several suggestions on areas for improvements in the tool, or similar tools, in the future. Several participants expressed a need for the Genetics Referral Form to be connected, or accessible, from the tool itself:

> *A referral form is referred to CH1632-where to find it?* Participant (P) 35, Male, 45-54, Hospital setting, Eastern Health (Note to readers: Form CH1632 is the

Provincial Medical Genetics Referral form, used for referrals to the Genetics program throughout the province of NL)

Put the form required for a genetics referral at the end of the tool in a format which can be printed. P. 25, Female, 55-64, Community setting, Eastern Health

Other suggestions pointed to the accessibility of the information and the ease with which it is located:

Flow chart visual for office would help. P.36, Female, 45-54, Community setting, Central Health

A schematic or something more visual/ flow sheet etc. would be helpful... P.16, Female, 45-54, Academic setting, Eastern Health

Add it to the Med Access list of templates-perhaps ensure that the referral form is also available in the Med Access platform. P.14, Male, 45-54, Community setting, Eastern Health

A simple highlight box somewhere on the document could helpful as a quick reference to those 6 clinical pearls (red flags/clinical tests. P.12, Male, 24-34, Community setting, Eastern Health

2. Ease of utilizing the tool in practice:

Participants identified some features of the tool which could be improved upon in order to increase the ease of utilizing the tool in practice:

How urgent should the referral be? How long will my patients be expected to wait to see cardiology or genetics? P.41, Male, 35-44, Hospital setting, Eastern Health

Very busy form-probably not every detail is necessary. P.35, Male, 45-54, Hospital setting, Eastern Health

One-page screening form with checkboxes. P.26, Male, 55-64, Community setting, Eastern Health

Single page format would have been best... P.24, Male, 55-64, Hospital setting, Eastern Health

> *...would be doing a "patient version" that could be given to patients at the same time we are using ours as clinicians to get the process started.* P.4, Male, 24-34, Community setting, Central Health

One participant highlighted that narrowing down those patients who are most in need of a referral was critical:

> *In Newfoundland, there are many cases of early ischemic heart disease likely linked to diabetes, obesity, hypertension and genetics. So, every relative of one of these patients should be referred to genetics? I feel that would overwhelm the system.* P.23, Female, 45-54, Community setting, Eastern Health

While the quantitative results indicated largely positive impressions of the tool, the qualitative data highlight nuanced areas of improvement for an easily accessible, easy to understand tool which will help identify individuals and families potentially affected with ARVC caused by the *TMEM43* mutation. One very positive response should be identified as to the success of the tool, and potential for similar tools in the future for diseases prevalent within the province:

> *There is nothing missing! I have had several patients with ARVC in my practice over the years and this teaching tool is an absolute gem. It is concise, very well organized, and flows extremely well. All of the information is there. It's short and very sweet. Well done and please keep up the good work, as it is very well appreciated.* P. 15, Male, 55-64, Community setting, Central Health

Discussion

ARVC is a Mendelian, autosomal dominant disorder with at least 12 genes identified as clinically associated with the condition ("ARVC-Genetics Home Reference-NIH", 2019). A specific type of ARVC caused by the p. S358L mutation in *TMEM43* is of focus in this thesis and is of particular importance to the population of NL, Canada. One manifestation of this disease, which is often the first symptom presentation, is SCD, particularly in males, at a very young age. However, with appropriate medical intervention, most successfully with implantation of ICDs, mortality is significantly reduced (Hodgkinson et al., 2006; Hodgkinson et al., 2016). Mortality can only be reduced through proper diagnosis of the disease. Healthcare professionals must be able to identify individuals and families at risk, and offer appropriate medical intervention, prior to an unexpected death. For the population of focus in this thesis, those within the *TMEM43* population, once an individual has been shown to have the disease and/or the mutation, the individual's at risk family members can be tested and treated, if necessary, before a SCD event. However, this assumes that the initial individual with the mutation is identified before a serious and potentially fatal cardiac event. Thus, the purpose of this thesis is to facilitate the identification of the initial individual, and subsequently, at risk family members, prior to a serious event.

A short, paper-based draft tool was given to a small group of PCPs. Considering the feedback obtained, work needed to be included in the revised version of the tool including ease of tool use and clarity of instructions. Feedback obtained also indicated a need for clinical test results, if available, and concerns on how to prevent unnecessary referrals to the genetics clinic. However, the tool was deemed appropriate in referring

high risk patients appropriately. A second version of the tool was created which utilized information from a large, pre-existing data set on all 27 known ARVC families within the province of NL. This revised tool was distributed to a larger group of PCPs and Family Medicine Residents. A survey was also distributed with the tool seeking feedback on the revised version. 43 surveys were completed. Overall, responses from the survey were positive, with suggestions provided on how to further improve the tool.

Genetic and genomic medicine has increasingly become integrated into primary care (Melo et al., 2015). This integration can allow for more precise, patient-centered care; however, it has not come without its resistance (Carroll et al., 2016b). Evidence indicates that PCPs recognize the importance of integrating genetics and genomics into their family practice, but a number of concerns have been identified, such as lack of confidence in referring and counselling patients regarding genetic conditions, and a general lack of knowledge, skills and experience in genetics and genomics medicine. (Harding et al., 2019; & Mikat-Stevens et al., 2015).

One important core competency of PCPs is establishing a FH (Korf et al., 2014; & Mikat-Stevens et al., 2015). More importantly, multi-generational family histories clearly highlight inherited diseases when accurately obtained (Waddell-Smith et al., 2016). The importance of obtaining accurate family histories is indicated in other literature, further highlighting the significance. Forsti et al. (2016) reported that informative family pedigrees were essential in determining the genes and variants associated with Mendelian-type cancers. In Sweden, Hemminki et al. (2018) utilized hospital records of the Multigenerational Register to assess if there was a genetic link to urinary tract stone disease; by analyzing familial data over generations, they found strong evidence of a

genetic link for this condition. Sundquist et al. (2015) reported that a FH presence of venous thromboembolism (VTE) is a predictor of VTE reoccurrence; however, they only examined VTE history in first-degree relatives.

Accurate family histories allow for the recognition of persons who were not recently thought to have a specific disease or condition, but in fact do. This can be caused by variable expression of the condition, as well as reduced penetrance. Also, accurate family histories help clarify those who thought they had a certain disease or condition, but actually do not. Clarification in these situations further demonstrates the importance of obtaining accurate family histories, an invaluable resource to PCPs as well as other specialized practitioners (Dunn et al., 2013).

While the clinical importance of obtaining multi-generation family histories has long been noted (e.g., Carroll et al, 2016b; Dunn et al., 2013; Waddell-Smith et al., 2016; & Wilson et al., 2016), it is particularly important for a condition where the first symptom is often death. Obtaining multi-generational family histories to identify those most at risk for inheriting this lethal type of ARVC could potentially prevent SCD. Importantly, Kauferstein et al. (2017) did note that together with clinical testing data, FH can be an important diagnostic tool, especially in diseases which have variable expression and reduced penetrance. Ranthe et al. (2012) also reported findings from their study, which advised that FH of premature cardiovascular death is an accurate predictor of risk for cardiovascular disease (p. 821). Additionally, Hookana et al. (2012) reported that FH is a strong predictor of SCD caused by ischemic SCD, though investigators only examined first degree relatives. However, in a review of the relevant literature which examined cardiac diseases and family histories, it was evident that researchers often only

investigated participants' first-degree relatives when examining cardiac diseases (Chinushi et al., 2012; Dekker et al., 2006; Emery et al., 2018; & Hookana, et al., 2012). Other research provides no clear distinction on what degree of FH was investigated (Petri et al., 2014). However, there is some evidence of the inclusion of second-degree relatives, and to a lesser extent, third-degree relatives, in the literature (Kauferstein et al., 2017; Ranthe et al., 2012; & Waddel-Smith et al., 2016). While noting the concerns raised by PCPs about obtaining family histories, and genetics and genomics medicine, this study has further reinforced the need to obtain accurate multi-generational family histories. As discussed above, other authors (Waddell-Smith et al., 2016; Wilson et al. 2016; & Wood et al., 2013), have all identified issues with PCPs accurately taking FH data from patients, whether it is from inconsistencies in obtaining the data, or due to PCPs perceptions of their roles in obtaining family histories.

As identified by Waddell-Smith et al. (2016), detailed family histories are not often obtained by inpatient general medicine and cardiology staff, and when they are recorded, it is often done incorrectly with misleading information. Wood et al. (2013) also reported inconsistencies with PCPs in their FH taking in practice. Finally, as demonstrated by Wilson et. al. (2016), PCPs did report high, positive intentions for completing patients' family histories; however, it was identified that a proportion of their PCP respondents noted that FH taking was not something they felt was expected of them or something in which they felt confident in doing. Given the concerns raised by PCPs regarding the integration of genetics and genomics into primary care, as well as acknowledging the importance of accurately obtaining multi-generational family histories, point-of-care resources for PCPs are needed.

Educational tools are an effective, cost efficient method of highlighting important information for PCPs (Carroll et al., 2011; Genova et al., 2014; & Grimshaw et al., 2014). The implications of this are suggested in the literature, including more accessible guides to management and referral options for higher risk patients (Wood et al., 2013), point-of-care tools which highlight competencies and content knowledge (Wilson et al., 2016), and knowledge translation efforts like those seen by Carroll et al. (2016a). In that study, a GenetiKit was created, which consisted of a knowledge translation package of a case-based interactive educational workshop, portfolio of primary care-appropriate genetics tools, and responsive timely knowledge support service called Gene Messenger. This study found that 90% of PCPs who participated wanted to continue to receive Gene Messengers, two-page evidence based structured summaries of various gene-disease associations or other genetic conditions heard commonly in the media. Continuing education efforts for currently practicing PCPs are an effective way to communicate genetic information. Increased training in medical school, as well as during residencies, is another suggestion on how to bridge the gap between knowledge and practice (Carroll et al., 2016b). The unique findings in this thesis clearly highlight the importance of obtaining accurate family histories to include at least third-degree relatives.

The motivation for this work was the desire to enable PCPs to more accurately ascertain those potentially at risk of ARVC caused by the p.S358L mutation in *TMEM43* before a catastrophic event, such as SCD. One way to do this, and the method we chose to use in this project, would be to develop an educational tool which informs PCPs about this type of ARVC. This was accomplished by (a) the creation of a draft tool utilizing past expertise and data from a long standing ARVC project and dataset (HREB 00-76), (b) the

input from a small group of PCPs in a focus group, and (c) modification of the tool via input from PCPs and PCP residents to obtain a final product. Implementation and evaluation of the tool are beyond the scope of this project, and therefore, the purpose was to develop an educational tool which could potentially be used to inform PCPs about this specific type of ARVC.

Our findings illustrated several issues and suggest some tentative conclusions. Firstly, through consultation with PCPs, we developed a tool for ARVC caused by the p. S358L mutation in *TMEM43* that was rated as easy to use, having a clear purpose and instructions, and containing comprehensible information. PCPs agreed the tool helped increase their knowledge about ARVC, would be helpful in practice, and has the potential to help physicians correctly identify those at high-risk and needing a referral to the genetics program. This study revealed that a short, inexpensive tool could be created that PCPs rate highly. Tools similar to the one created for this thesis may help bridge the gap between bench-side genomics research and help with the implementation of genetics findings into primary care practice (Carroll et al., 2016a; Mikat-Stevens et al., 2015; & Scott and Trotter, 2013). Furthermore, this study provides evidence that printed educational tools in primary care practice can be created in a cost-effective manner, are rated highly by PCPs, and can be effective ways to communicate important health information (Genova et al., 2014; Grimshaw et al., 2014; & Williams et al., 2015). As the results from the online survey demonstrate, PCPs identified an increase in knowledge and a desire to integrate the tool into practice, similar to other studies of genetics educational tools (Carroll et al., 2011; & Williams et al., 2015).

Printed educational materials have had positive impacts on patient care, in both genetic and non-genetic patient samples. For example, Shah et al. (2010) reported in their trial that the use of printed educational materials had a small to moderate impact on PCPs and patient care. This study explored the impact of guidelines established by the Canadian Diabetes Association to improve cardiovascular disease screening, prevention, and treatment for those with diabetes. Given the relatively low cost and feasibility of printed educational materials, it was suggested that these should be considered to improve patient care. Watson et al. (2001) also reported similar positive findings in their study on the use of printed educational materials for referral decisions for individuals with a FH of breast and ovarian cancer. Utilizing laminated summary cards with simple referral guidelines, and booklets with more detailed background information and patient leaflets, they found a major improvement on general practitioners' referral decisions. Alternatively, they also presented general practitioners with an in-person education session, in combination with the printed educational materials, and found it had no additive benefit for referral decisions compared to the group who only received the printed educational materials. Another study which examined the use of paper-based educational tools on evidence-based practices (EBPs) found that these tools can be effective in disseminating EBPs to health care professionals, particularly if there was pre-existing interest in EBPs with supportive attitudes. Using a coloured, two-page reference sheet and a 12-page booklet, the authors found that their information package was a well-received tool to disseminate information on EBPs. Similar to tool development in this thesis, the authors first conducted a pilot study of the information package to garner feedback that informed a second version, which was distributed to a larger audience (Williams et al., 2015).

Finally, a study from Carroll et al. (2011) looked at family physicians and genetic testing referrals. The authors implemented an interactive educational workshop, a collection of practical primary care clinical genetics tools and a knowledge service called Gene Messenger. This multi-faceted intervention significantly improved genetics referral decision making specifically pertaining to provincial guidelines regarding hereditary breast and ovarian cancer, while also increasing confidence regarding core genetic competencies seen in primary care.

However, here it is important to highlight criticisms or critiques of paper-based educational tools. As cited in Zwarenstein et al. (2014), screening of retinopathy, a serious eye complication in patients with diabetes, was done through family physician referrals. Family physicians typically initiate these referrals. Their interventions of either an evidence-based, post-card sized document, or a two-page document highlighting the same information, had no impact on physician referral rates for retinal screening rates for diabetes patients. A Cochrane systematic review on the use of printed educational materials concluded that, when compared to no intervention, printed educational materials may have a slight positive impact on process outcomes (the behavior of the healthcare professional) but no impact on improving patient outcomes or patient health (Farmer et al., 2008). Finally, as reported by Presseau et al. (2016), printed educational materials had no impact on family physician prescribing behavior for a medication to treat hypertension.

There are, however, suggestions made in the literature to increase knowledge uptake of the important information often found within these printed educational materials. The GenetiKit trial included not only printed materials, but also an interactive

workshop with a family physician and a genetic counsellor, and as reported above, improved family physician referrals for patients at risk for hereditary breast and ovarian cancer (Carroll et al., 2011). Pimenta et al., (2014) also similarly reported on the success of a multi-faceted approach to knowledge translation. Here, one small group discussion of routine practices for hypertensive patients, one outreach visit by cardiologists to family physician offices, and three e-mail reminders on risk stratification and measures of high-risk patients were compared to quality of hypertensive patient treatment obtained through patient interviews and chart reviews. The comparison group of physicians received only the paper-based educational tools. The group of physicians who were in the multi-faceted intervention improved the treatment of the hypertensive patients. Though there was some improvement seen in the paper-based only educational tools, improvement in patient treatment did not reach the same level as that seen in the multi-faceted group. Other evidence indicates that PCPs' perceived ease of use of the educational material, perceived usefulness of the material, and attitude towards the material need to be increased in order to increase uptake of the information. Working with PCPs in establishing ease of use and usefulness will positively improve attitude towards the material, and thus increase uptake (Grudniewicz et al., 2015).

In this study, it is encouraging that PCPs qualitatively rated the tool as easy to use and agreed it would be useful in practice. It is important here, as well, to reference the data from the online survey. For this tool, or similar tools, to be successful in their implementation, information needs to be easily accessible to PCPs, including referrals to appropriate specialized departments, which may include the proper referral forms or referral instructions. Visual information was requested from several participants who

noted flow charts or other visuals would be beneficial. Further information on how to grade the urgency of the referral and anticipated wait times based on that urgency would also help facilitate the uptake of this or similar tools. If possible, summation of information to one page may also increase uptake and use. Also, it is important to consider how to streamline referrals such that the system is not more overwhelmed than it already is, so that only the most appropriate persons are be provided the most appropriate referral. For the disease of focus in this thesis, accurate multi-generational FH data would perhaps help facilitate this process and narrow down the number of individuals who are referred to the Cardiac Genetics Clinic. Obtaining accurate FH data would also help PCPs narrow down questions asked to patients regarding possible familial genetic conditions, facilitating more efficient medical care (Dunn et al, 2013).

Acknowledging this, further efforts could include interactive workshops, or educational sessions, at the PCP level, as well as with Family Medicine Residents. Furthermore, using the tool as a template, other diseases could be highlighted to determine their applicability in practice. Ultimately, to measure the success of this specific tool, implementation of the tool into practice and the success of preventing SCD in undiagnosed individuals with ARVC caused by the p. S358L mutation in *TMEM43* would need to be measured over a period of time. This is outside the scope of this thesis but represents an important area for future research.

Secondly, we have demonstrated that family pedigrees are vitally important. Family pedigrees were analyzed utilizing a pre-existing data set that contains all individuals born with an a priori 50% risk of inheriting ARVC caused by the p. S358L mutation in *TMEM43*. Previously, the data set utilized in this study was applied to

determine the natural history and clinical course of the disease (Hodgkinson et al., 2013). The dataset, and analysis presented in the Hodgkinson et al. (2013) study, demonstrated that there were no clinical tests, symptoms, or signs of the disease that could be used in diagnosis. This limits the ability for the data set to be used in predicting the disease in an undiagnosed individual or determining risk of other family member. There was a gap, therefore, in the useful information found within a patient's FH and the dataset and applying that data in determining risk in an undiagnosed individual and their family members. This limits the confirmed diagnosis of the disease to a genetic test, which are expensive and should be limited to those most likely to have the disease.

While genetic counsellors and geneticists can read and understand an individual's FH, PCPs often do not have access to this information, certainly not to the depth that detailed, multi-generational family histories provide. As previously discussed, PCPs also may have limitations on their abilities to read and interpret multi-generational family histories. The gap between the information found within family histories, and applying that information to help screen at risk individuals and family members could be narrowed by providing PCPs with easy to understand and use FH data, assessed through the FH data set, which explained the risk a specific individual would have for inheriting the mutation. Knowing that people often are aware of early SCD or major surgeries, such as heart transplants within their family, we created a variable, which was integrated into the tool and given to PCPs, which would help PCPs more easily determine an individual's risk for inheriting the disease. This variable, which clearly establishes the number of first-, second- and third-degree relatives who were carriers for the mutation, is clear, simple, and easy to understand information that can be presented in a tool, and the tool given to

PCPs, to help determine an individual's risk of inheriting this mutation. Doing this work, and creating the variable, allowed us to see the importance of family history of these events in determining risk. Giving PCPs this data can help them determine those most in need of a referral to appropriate genetics and cardiology services, limiting unnecessary referrals. As this tool is provided as a guideline only, it is important to consider that unnecessary referrals to cardiology genetic services may still occur. Used appropriately, and with the referring physician using their own clinical judgment on patients' presenting symptoms, and FH, it is hoped that unnecessary referrals will be limited. More prompt referrals by PCPs to genetics and cardiology services, therefore, would allow the individual quicker access to diagnostic utilities, with the potential to prevent SCD seen with this disease, in both the individual and within potential at risk family members.

Analysis of the data set revealed that family pedigree data is an important red flag in determining an individual's risk for having ARVC caused by a mutation in *TMEM43*. Clinically, this finding is notable as FH data can be used to help determine an *undiagnosed* individual's risk of SCD caused by the disease of focus. The findings of this thesis are unique, in that the literature, as noted, indicates obtaining only first-degree family histories. It has been shown that obtaining family histories to the third-degree is necessary, and essential, when trying to determine an individual's risk for this specific type of ARVC (Chinushi et al., 2012; Dekker et al., 2006; Emery et al., 2018; & Hookana et. al., 2012).

The novel approach seen in this thesis, utilizing a pre-existing data set and FH bank, clearly demonstrates the importance of obtaining family histories greater than just the first-degree relative. We have demonstrated that when assessing relatives of those

who have had SCD (i.e., unrecognized as being at risk prior to their final symptom), 56%, 39% and 31% had *at least* one first-, one second- and one third- degree relative presenting with an SCD (less than or equal to 50 years of age) respectively. Therefore, should an individual have presented themselves to their PCP prior to their own SCD, and an accurate FH was obtained, it would have been evident that this person had a substantial FH of SCD, measurable to the at least the third-degree relative. A PCP, upon seeing this very strong evidence in the FH of SCD, would be prompted to refer the individual to more appropriate medical services, such as genetics and cardiology, potentially preventing the SCD eventually seen in that individual. The tool, in this case, would make the decision making more streamlined, ensuring that the highest risk individuals receive the adequate and appropriate care.

Study results represent important clinical findings. Firstly, participants expressed positive attitudes and reviews towards the tool and agreed it would be helpful in practice. Utilizing it as a template, other diseases common to the province can be highlighted quickly, easily, and accessibly by PCPs. This would be advantageous for less common diseases, diseases with variable expression, or for PCPs who are from outside the province and may not be familiar with common illnesses and syndromes found in NL.Packages of tools for common diseases within the province could be provided through the NLMA, at the university level, or through each regional health authority.

Furthermore, acknowledging the unique geography and size of the province, similar tools would easily disseminate information to PCPs practicing anywhere in NL. Providing similar tools via e-mail or through regular mail permits for easier knowledge translation efforts within a province where geography can be a restriction towards

knowledge transfer. Though again, it is important to highlight that implementation of this specific tool is outside the scope of this thesis. Finally, as demonstrated by the work done with the family pedigrees and highlighting the risks seen with first-, second-, and third-degree relatives with a history of SCD, ICD implantation, and heart transplants, clearly there is strong evidence to indicate the worth of obtaining multi-generational family histories, as has been noted in the literature. Effort should be maintained during medical school such that students understand and acknowledge the importance of obtaining family histories beyond the first degree relative. Additionally, this could include providing medical students with a package of tool which highlight common diseases within the province.

Some limitations of this study should be discussed. Firstly, the initial working lunch included a limited number of physicians strictly from an academic setting. The data collected during the working lunch do not reflect the perceptions and concerns of practitioners outside an academic setting. However, this was likely off-set by the large number of respondents for the online survey who were from community and hospital settings. Additionally, physicians are a difficult group to recruit for surveys, and response rates for surveys are known to be lower when physicians are asked to complete surveys compared to the general population (Brtnikova et. al., 2018). It has been documented that physician response rates can be 10% lower than that of the general population (James et al., 2011). Similarly, it was noted by Field et. al. (2002), physician response rates ranged from 11-39% (p. 597). The literature therefore provides some precedent for the low survey response rate seen in this study. Findings, therefore, may not generalize to the population of family practitioners in the province. Alternatives to an online based survey

that may provide a higher response rate is suggested by Brtnikova et al. (2018), who reported that a mixed methodology including an online survey, followed by a postal survey, may yield a higher response rate. Other incentives, such as monetary incentives as well as non-financial incentives have been found to increase physician response rates for surveys (Pit et al., 2013; & Young et al, 2015).

ARVC is a genetic heart condition caused by the p. S358L mutation in *TMEM43*. This specific mutation is prevalent in the province of NL, Canada. This type of ARVC is highly lethal in affected individuals, causing SCD in undiagnosed individuals as early as 19 years old for males and 37 years old for females. Highly effective treatment is available to prevent SCD (Hodgkinson et al., 2016); however, for those individuals who may not have been captured through cascade screening, there is a need for an educational tool for PCPs to help accurately identify those most at risk. This tool has been identified by PCPs to be an important educational piece that would help facilitate the decision-making process of those most at risk for carrying this mutation, and thus preventing SCD. Additionally, the highlighted importance of obtaining multi-generational family histories demonstrates the need for PCPs to obtain accurate family histories in order to determine an individual's risk of having this disease, and ultimately prevent deaths caused by SCD.

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Appendicies

Appendix A: Diagnostic Criteria for ARVC

1994 Task Force of the Working Group Myocardial and Pericardial disease of the European Society of Cardiology and the Scientific Council on Cardiomyopathies of the International Society and Federation of Cardiology diagnostic criteria

	Major criteria	**Minor criteria**
Global and/or regional dysfunction and structural Alterations	Severe dilatation and reduction of right ventricular ejection fraction with no (or only mild) LV Localized right ventricular aneurysms (akinetic or dyskinetic areas with diastolic bulging) Severe segmental dilatation of the right ventricle	Mild global right ventricular dilatation and/or ejection fraction reduction with normal left ventricle Mild segmental dilatation of the right ventricle Regional right ventricular hypokinesia
Tissue characterization of walls	Fibro-fatty replacement of myocardium on endomyocardial biopsy	
Repolarisation abnormalities		Inverted T waves in right precordial leads (V2 and V3) (people aged older than 12 years in the absence of right bundle branch block)
Depolarisation/conduction abnormalities	Epsilon waves or localized prolongation (> 11 Oms) of the QRS complex in right precordial leads (V1-	Late potentials (signal averaged ECG)

	V3)	
Arrhythmias		Left bundle branch block type ventricular tachycardia (sustained and non-sustained) (ECG, Holter, exercise testing) Frequent ventricular extrasystoles (more than 1000/24 hours on Holter)
Family History	Familial disease confirmed at necropsy or surgery	Family history of premature sudden death (< 35 years) due to suspected ARVC Family history (clinical diagnosis based on present criteria)

2002 Modification of original task force diagnostic criteria

ARVC in first degree relative plus one of the following
ECG
Signal averaged ECG (SAECG)
Arrhythmia
Structural or functional abnormality of the RV

2010 Updated diagnostic criteria

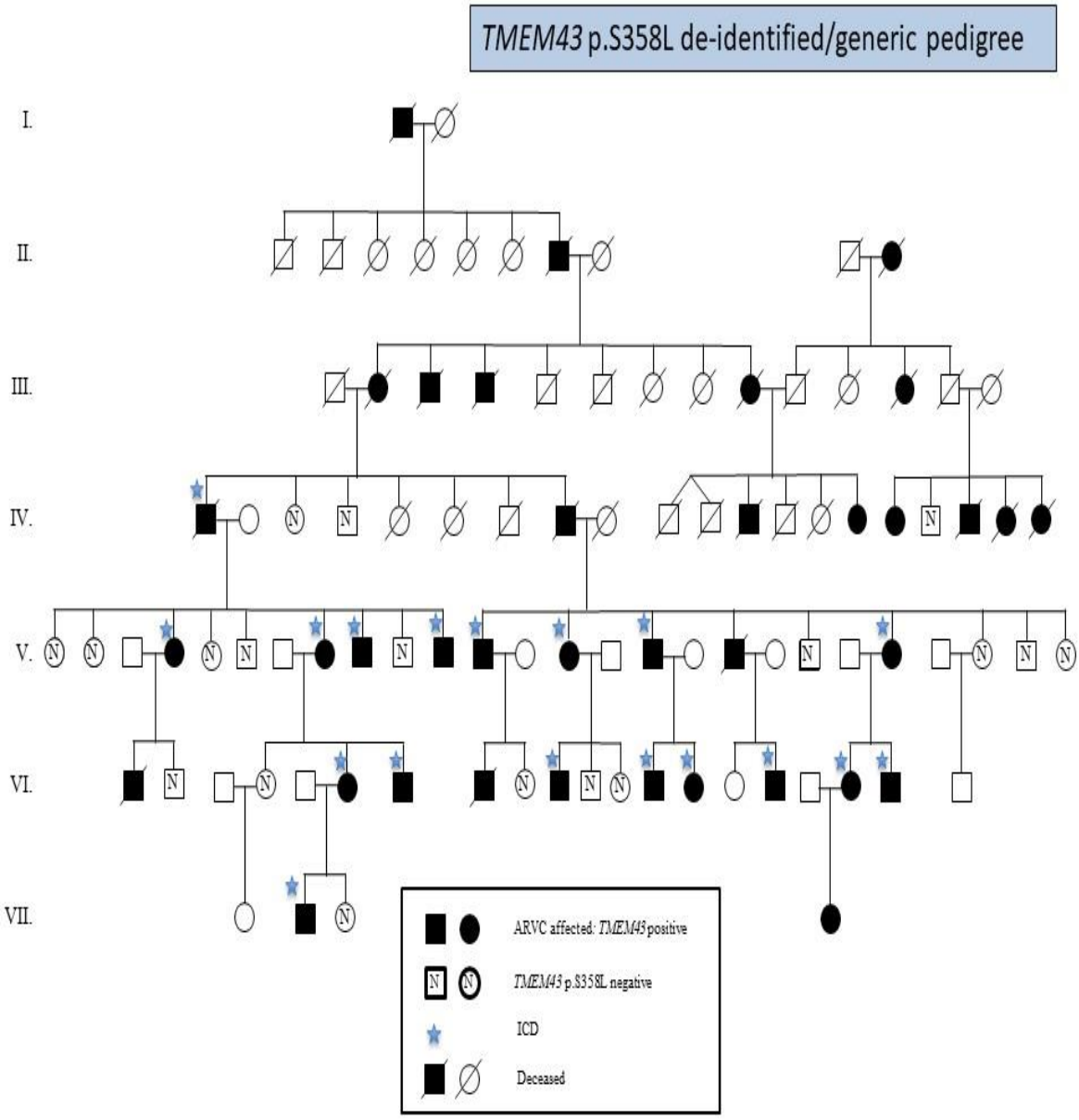
	Major criteria	**Minor criteria**
Global and/or regional dysfunction and structural alterations	By 2D echo: -Regional RV akinesia, dyskinesia, or aneurysm -and 1 of the following (end diastole): • PLA X RVOT ≥	By 2D echo: -Regional RV akinesia or dyskinesia -and 1 of the following (end diastole): • PLA X RVOT ≥

	32 mm (corrected for body size [PLAX/BSA] ≥19 mm/m2) • PSA X RVOT ≥ 36 mm (corrected for body size [PSAX/BSA] ≥ 21 mm/m2) • or fractional area change ≤ 33% By MRI: -Regional RV akinesia or dyskinesia or dyssynchronous RV contraction -and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥ 110 mL/m2 (male) or ≥ 100 mL/ m2 (female) • or RV ejection fraction ≤ 40% By RV angiography: -Regional RV akinesia, dyskinesia, or aneurysm	29 to < 32 mm (corrected for body size [PLAX/BSA] ≥ 16 to < 19 mm/m2) • PSA X RVOT ≥ 32 to < 36 mm (corrected for body size [PSAX/BSA] ≥ 18 to < 21 mm/m2) • or fractional area change > 33% to < 40% By MRI: -Regional RV akinesia or dyskinesia or dyssynchronous RV contraction -and 1 of the following: • Ratio of RV end-diastolic volume to BSA ≥ 100 to < 110 mL/m2 (male) or ≥ 90 to < 100 mL/m2 (female) • or

		RV ejection fraction > 40% to ≤ 45%
Tissue characterization of walls	-Residual myocytes < 60% by morphometric analysis (or < 50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	-Residual myocytes 60% to 75% by morphometric analysis (or 50% to 65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarisation abnormalities	-Inverted T waves in right-precordial leads (V1, V2, and V3) or beyond in individuals > 14 years of age (in the absence of complete right bundle-branch block QRS ≥ 120 ms)	-Inverted T waves in leads V1 and V2 in individuals > 14 years of age (in the absence of complete right bundle-branch block) or in V4, V5, or V6 -Inverted T waves in leads V1, V2, V3, and V4 in individuals > 14 years of age in the presence of complete right bundle-branch block
Depolarisation/conduction abnormalities	-Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of the T wave) in the right precordial leads (V1 to V3)	-Late potentials by SAECG in ≥ 1 of 3 parameters in the absence of a QRS duration of ≥ 110 ms on the standard ECG -Filtered QRS duration (fQRS) ≤ 114 ms -Duration of terminal QRS < 40 μV (low-amplitude signal duration) ≥ 38 ms -Root-mean-square

		voltage of terminal 40 ms ≤ 20 μV -Terminal activation duration of QRS ≥ 55 ms measured from the nadir of the S wave to the end of the QRS, including R', in V1, V2, or V3, in the absence of complete right bundle-branch block
Arrhythmias	-Nonsustained or sustained ventricular tachycardia of left bundle-branch morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in lead aVL)	-Nonsustained or sustained ventricular tachycardia of RV outflow configuration, left bundle-branch block morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in lead aVL) or of unknown axis - >500 ventricular extrasystoles per 24 hours (Holter)
Family History	-ARVC/D confirmed in a first-degree relative who meets current Task Force criteria -ARVC/D confirmed pathologically at autopsy or surgery in a first-degree relative -Identification of a pathogenic mutation† categorized as associated or probably associated with ARVC/D in the patient under evaluation	-History of ARVC/D in a first-degree relative in whom it is not possible or practical to determine whether the family member meets current Task Force criteria -Premature sudden death (< 35 years of age) due to suspected ARVC/D in a first-degree relative -ARVC/D confirmed pathologically or by current Task Force Criteria in second-degree relative

Appendix B: Diagram of a Family Pedigree



Appendix C: Initial Tool

Sudden Cardiac Death caused by ARVC: Information tool for primary physicians

Purpose

This brief information tool is designed to provide pertinent and easily accessible information about arrhythmogenic right ventricular cardiomyopathy (ARVC) in Newfoundland, particularly about the genetic subtype of ARVC (*TMEM43*, p.S358L) which is common in the Province.

Introduction

Sudden cardiac death (SCD) in young people (under 40 years) is a devastating event. The majority of these early deaths have a genetic component, and may be caused by known cardiac genetic disorders such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), catecholaminergic polymorphic ventricular tachycardia (CPVT), Long QT syndrome (LQTS) and arrhythmogenic right ventricular cardiomyopathy (ARVC) amongst others. All these conditions are known to have multiple potential causative genes. Getting the correct diagnosis is therefore extremely important.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC)

One of the most difficult to clinically diagnose is ARVC. It is usually an autosomal dominant disorder where the variability of expression of the disease is extremely wide. As a dominant disease, the risk to children from affected parents of inheriting the gene and thus the disorder at some point in their lives is 50%. The clinical diagnosis of ARVC in individuals suspected of having the condition requires a set of high level tertiary clinical tests which produce major and minor criteria, upon which the diagnosis is graded from

unlikely through probable to definite. Tragically one of the first symptoms of ARVC can be SCD in otherwise healthy individuals and the clinical cardiac testing required is inefficient at detecting the disorder. There are multiple genetic subtypes (8 known genes to date) thought to cause ARVC. One of these genetic subtypes is present in Newfoundland and responsible for several early deaths in young men. This is the focus of this information tool.

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) caused by p.S358L in *TMEM43*

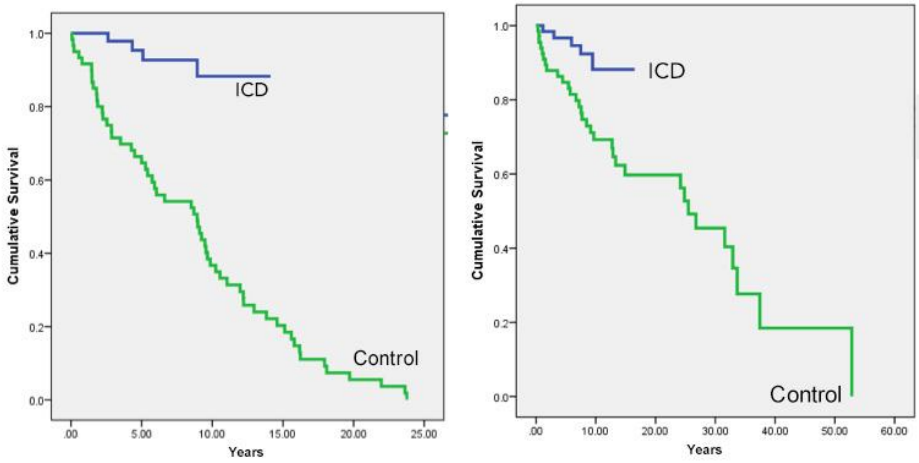
ARVC caused by the mutation p.S358L in the gene *TMEM43* is a common cause of this disease and early deaths in Newfoundland and Labrador. The gene and the causative mutation was discovered by Memorial University researchers. It is known to be responsible for the deaths of 50% of males who have this mutation before the age of 40 years (and 80% before the age of 50 years). The equivalent figures in women are 5% and 20%. Males are thus affected to a far greater degree than females. It is also a cause of heart failure in those who do not die suddenly.

The change in the gene is a single spelling error. A cytosine nucleotide is changed to a thymine, which changes the amino acid serine to a leucine at position 358 in the protein

TREATMENT

Recent research from the team has shown that the implantable cardioverter defibrillator (ICD) is effective at increasing survival by potentially 30 years in recipients who get the ICD based on a **mutation test alone**. Thus recognising families where this mutation may be segregating is important.

Survival Curves for Males and Females following ICD treatment compared to a control group of ancestral family members of the same sex who did not receive an ICD.



MALES FEMALES

INSTRUCTIONS:

What to look for and questions to ask.

1. Pre syncope and syncope, palpitations, particularly during exercise, and particularly in males.

2. Family history of early SCD. It is very important that family history is NOT restricted to first degree relatives. This condition can be present in females who do not present with symptoms (although may show some clinical signs on testing) and so the death of a great uncle at 25 years where the linkage to the current generation is through females may be very significant.

3.A family history also does not have to be present at all.

4. Referrals to the Cardiac Genetics clinic (senior cardiologist: Dr. Sean Connors) are encouraged in cases of potential high risk.

Appendix D: Recruitment E-mail for Stage 1

Dear Dr. XXXX/Family Medicine Resident,
Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease with a high incidence in Newfoundland and Labrador and is a common cause of young sudden cardiac death in otherwise healthy individuals. Early diagnosis significantly increases survival. Recognizing high-risk cardiac families for appropriate referral to the cardiogenetics service is challenging, but results in massive benefits.
We have developed a short educational tool to help physicians identify individuals and families who might be at risk for ARVC. We need your opinion on whether you find the format and accessibility of this tool helpful. We would therefore like to invite you to attend a one-hour working lunch at *Fill in location* on *Fill in date* at *fill in time* to discuss this new tool and provide feedback to the research team. If you would like to attend this working lunch please RSVP to this email so a place can be held for you.
We hope this tool will be of help to you and your colleagues in general practice.

Thank you for your time.

Appendix E: Initial survey (May 2016)

Question followed by the total number of responses in that category. The response with the majority of responses are highlighted.

1. The tool seems easy to use:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

2. The purpose of the tool was clearly stated:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

3. The instructions were clear:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

4. The layout was easy to follow:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

5. The information was easy to understand:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

6. I feel this tool has increased my knowledge about ARVC in NL:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

7. Overall, this tool would be helpful to me in my practice:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

8. Overall, this tool will help me correctly refer high-risk cardiac families to the genetics cardiology service:
1-Strongly Disagree; **2**-Disagree; **3**-Undecided; **4**-Agree; **5**-Strongly Agree

Was there important information missing? Please explain
Please identify one way this tool can be improved:

Appendix F: Revised Version of Tool

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY IN NEWFOUNDLAND AND LABRADOR

AN INFORMATION TOOL FOR PRIMARY CARE PHYSICIANS

2) Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease that causes ventricular tachycardia (VT), heart failure and sudden cardiac death (SCD).
3) Clinical cardiac testing (12 lead ECG, Holter Monitor, Echocardiography) is insensitive in the young.
4) **One of the first symptoms of ARVC may be SCD**
5) Every child born to an ARVC parent has a 50% risk of inheriting ARVC.
6) There is wide variability of expression of ARVC, so all affected individuals do not present in the same way; even those from the same family.
7) There are many different gene mutations which can cause ARVC.
8) Several occur in Newfoundland and Labrador(NL).

ONE IMPORTANT TYPE OF ARVC IN NEWFOUNDLAND AND LABRADOR

9) One mutation (p. S358L) in the *TMEM43* gene is common in NL and is the focus of this information tool
10) **50% of untreated males with this mutation will die before the age of 40 years**, with 80% dead before 50 years. In females the equivalent figures are 5% and 20%, respectively. It can also cause heart failure.
11) **Effective treatment is an implantable cardioverter defibrillator (ICD).** ICDs in the NL population have been found to increase survival by 30 years in male mutation carrier ICD recipients. Transplantation is an option following heart failure.

Sadly, most families are recognised following the untimely and unexpected death of a young adult, which then leads to cascade screening of relatives.

WHAT SHOULD I LOOK FOR IN DETERMINING INDIVIDUALS AT RISK FOR ARVC?

The most important tool is the **FAMILY HISTORY**

Here are some 'RED FLAGS' which should prompt the referral of a family

1. EARLY DEATHS (under 50 years) due to any cardiac event.

2. ICDs or heart transplants under 50 years.

3. Unusual accidental deaths with no contributing factors (e.g. single vehicle automobile accidents excluding alcohol, moose, bad weather etc.)

IMPORTANT

Of the 160 people in NL who were discovered with this mutation AFTER death, 56% had **at least** one first degree relative 81% had **at least** one third degree relative with one or more of the above Red Flags.

So family history to AT LEAST third degree relatives and across as many generations as are available is invaluable.

CLINICAL TESTS

Often have not been done. On their own, the clinical signs listed below are relatively common and may be benign. If however any of the following occur **in conjunction with a family history as previously described** then a referral should be made.

1. **12 lead ECG**: poor R-wave progression (PRWP) in the precordial leads and premature ventricular contractions (PVCs) in any lead.
2. **ECHOCARDIOGRAPHY:** ANY ventricular enlargement
3. **HOLTER MONITOR**: PVC's >200 in 24 hours

WHAT GENETIC TESTS CAN BE DONE?

This type of ARVC has genetic testing available at the Health Sciences Centre in St. John's which is very quick and at least **99.9%** accurate

Testing involves a simple buccal swab or blood sample provided by the patient.

RESULTS

Positive: will accelerate cardiac screening tests, treatment and cascade screening for family members.

Negative: the *TMEM43* p.S358L mutation has not been detected.

If there was a family history of any of the RED FLAGS alluded to earlier the necessity of further testing for the family (to assess other genetic cardiac causes) will be determined by the cardiac genetics clinic.

HOW DO I REFER AN AT-RISK PATIENT FOR GENETIC TESTING?

Complete: form Ch-1632: Provincial Medical Genetics Referral

fax to: (709)777-4190

Provincial Medical Genetics Program, Cardiac Genetic Clinic

Attention: Ms. Fiona Curtis, M.Sc., Genetic Counsellor, Eastern Health

Dr. Sean Connors, MD, D.Phil, FRCPC

Dr. Kathy Hodgkinson, Ph.D.

Dr. Anne Williams, MD, FRCPC

& Dr. Bridget Fernandez, MD, FRCPMG

Appendix G: Second Online Survey

1. The tool seems easy to use
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

2. The purpose of the tool was clearly stated
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

3. The instructions were clear
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

4. The layout was easy to follow
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

5. The information was easy to understand
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

6. I feel this tool has increased my knowledge about ARVC in NL
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

7. Overall, this tool would be helpful to me in my practice
Strongly Disagree; Disagree; Neutral; Agree; Strongly Agree

8. Please identify anything you feel is missing, or could be added to the tool, to improve it (qualitative question)

9. Please identify anything you feel is missing, or could be added to the tool, to improve it (qualitative question)

10. Please use this space to provide any other comments or suggestions (qualitative question)

11. Setting of your practice (demographic question)

12. Location of practice (demographic question)

13. Years in practice (demographic question)

14. Age (demographic question)

15. Gender (demographic question)

Appendix H: Recruitment E-mail to Family Medicine Residents

Dear Family Medicine Resident,

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease with a high incidence in Newfoundland and Labrador and is a common cause of young sudden cardiac death in otherwise healthy individuals. Early diagnosis significantly increases survival. Recognizing high-risk cardiac families for appropriate referral to the cardiogenetics service is challenging, but results in massive benefits.

We have developed a short educational tool to help physicians identify individuals and families who might be at risk for ARVC. We would like your opinion on whether you find the format and accessibility of this tool helpful.

It would be greatly appreciated if you would take a few minutes to view this genetics educational tool which is attached to this e-mail and complete the *Short Survey*. An active link for the survey can also be found at the end of the tool. This should take about 10 minutes of your time.

Please contact Lauren Rickert (llm.rickert@gmail.com), Dr. Kathy Hodgkinson (khodgkin@mun.ca), or Dr. Holly Etchegary (holly.etchegary@med.mun.ca) if you have any questions.

We thank you for your time and input.

Appendix I: Online Advertisement placed by NLMA

Dear Family Physician,

Newfoundland and Labrador has a higher incidence of Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) than anywhere in Canada. ARVC is a genetic disease whose first outcome is often sudden cardiac death. However, when properly diagnosed, patients can benefit greatly from medical management. It is important that physicians can recognize high-risk cardiac families and individuals so that they are appropriately referred to genetic services.

We (Dr's Kathy Hodgkinson and Holly Etchegary, Masters student Lauren Rickert) have developed a two-page educational tool to help physicians identify families who are at risk for ARVC and need referral to genetics. We would like your opinion on whether you find the format and accessibility of the tool helpful. It would be greatly appreciated if you would take a few minutes to view the tool (*link to tool*) and complete the one-page survey (*link to online survey*). This should take about 10 minutes of your time.

We thank you for your time and input. Please contact Lauren Rickert (llm.rickert@gmail.com), Drs. Kathy Hodgkinson (khodgkin@mun.ca), or Holly Etchegary (holly.etchegary@med.mun.ca) if you have any questions.

Appendix J: Recruitment E-mail Distributed by Newfoundland and Labrador College of Family Physicians

Dear Family Physician,

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a genetic disease with a high incidence in Newfoundland and Labrador and is a common cause of young sudden cardiac death in otherwise healthy individuals. Early diagnosis significantly increases survival. Recognizing high-risk cardiac families for appropriate referral to the cardiogenetics service is challenging, but results in massive benefits.

We have developed a short educational tool to help physicians identify individuals and families who might be at risk for ARVC. We would like your opinion on whether you find the format and accessibility of this tool helpful.

It would be greatly appreciated if you would take a few minutes to view this genetics educational tool which is attached to this e-mail and complete the *Short Survey*. An active link for the survey can also be found at the end of the tool. This should take about 10 minutes of your time.

Please contact Ms. Lauren Rickert (llm.rickert@gmail.com), Dr. Kathy Hodgkinson (khodgkin@mun.ca), or Dr. Holly Etchegary (holly.etchegary@med.mun.ca) if you have any questions.

We thank you for your time and input.

Appendix K: Personal E-mail Sent to Original Working Lunch Participants

Hi Dr. XX
In May 2016 you attended a working lunch with myself, Lauren Rickert, and my supervisors Drs Kathy Hodgkinson and Holly Etchegary.
Since that time, we have vastly updated the tool you reviewed in that working lunch, with the valuable feed back that was provided.
I'm writing you today to let you know we have a final draft of the tool completed, and since you attended the lunch, wanted to pass that along to you. If you are able, it would be greatly appreciated if you could review this version of the tool (attached to this e-mail) and complete a short survey, very similar to the one you completed during the working lunch (https://s.surveyplanet.com/Bym_glXtG). A link for the survey can also be found at the very end of the tool.
Thank you in advance for your contribution. If you have any further questions or comments, please let me know.
Sincerely,
Lauren Rickert

Appendix L: Qualitative Results from Online Survey

Please identify anything you feel is missing, or could be added to the tool, to improve it

- How urgent should the referral be? How long will my patient be expected to wait to see cardiology or genetics? -***P41***
- nothing -***P37***
- Flow chart visual for office would help There is a lot of valuable information which is helpful but not a quick reference -***P36***
- Very busy form - probably not every detail is necessary. A referral form is referred to Ch1632 - where to find it? -***P35***
- one-page screening form with checkboxes. -***P26***
- Put the form required for a genetics referral at the end of the tool in a format which can be printed.-***P25***
- Most of the information I already knew. But, I might be the odd ball here. It was well written, a little long. Single page format would have been best but it is hard to do or road map. -***P24***
- In Newfoundland there are many cases of early ischemic heart disease likely linked to diabetes, obesity, hypertension and genetics. So every relative of one of these patients should be referred to genetics? I feel that would overwhelm the system. -***P23***
- a schematic or something more visual / flow sheet etc would be helpful doing a fhx to 3rd degree relative is not common in FP -***P16***
- There is nothing missing! I have had several patients with ARVC in my practice over the years and this teaching tool is an absolute gem. It is concise, very well organized, and flows extremely well. All of the information is there. It's short and very sweet. Well done and please keep up the good work, as it is very well appreciated. -***P15***
- Add it to the Med Access list of templates- perhaps ensure that the referral form is also available in the Medaccess platform. -***P14***
- A simple highlight box somewhere on the document could helpful as a quick reference to those 6 clinical pearls (red flags/ clinical tests). -***P12***

- None. -***P11***
- Nil -***P6***
- Nil -***P4***

Please use this space to provide any other comments or suggestions

- helpful -***P37***
- Very useful tool-***P30***
- Good tool and info. -***P26***
- Nil-***P24***
- As already stated in the previous page. -***P15***
- See previous. -***P12***
- No patient so far in my practice with his medical issue. -***P11***
- Nil. Looks good. Would help in practice. Only suggestion, I wonder, would be doing a "patient version" that could be given to patients at the same time we are using ours as clinicians to get the process started. -***P4***