Cascade Health Service Use in Families of Children with Cardiomyopathy: Implications for Health Technology Assessment

by

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Abstract

Background: Cardiomyopathy (CMP) is a genetically heterogeneous disease of the myocardium. Clinical practice guidelines recommend cascade genetic testing and clinical screening to relatives of affected individuals, however health technology assessment (HTA) does not account for these cascade effects.

Purpose: To report the pattern and costs of cascade health service use in relatives of children with CMP.

Methods: A retrospective cohort study was conducted among children with CMP who underwent genetic testing. A cost analysis of services offered to probands' relatives was undertaken from the health care payer perspective.

Results: Data were available for relatives of 53 probands. The mean cost of offered cascade health services was $1,173 per family. Multiple one-way sensitivity and scenario analyses were undertaken to address uncertainty.

Conclusions: Quantifying cascade health services is essential to economic evaluation of emerging genetic technologies. Optimizing HTA methods for incorporating cascade effects will enhance economic evaluation of genomics for funding decisions.

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List of Abbreviations

ACE:	angiotensin converting enzyme
ACMG:	American College of Medical Genetics and Genomics
ARVC:	arrhythmogenic right ventricular cardiomyopathy
BrS:	Brugada syndrome
BUN:	blood urea nitrogen
CADTH:	Canadian Agency for Drugs and Technologies in Health
CAF:	clinical activity form
CBC:	complete blood count
CEA:	cost-effectiveness analysis
CF:	cystic fibrosis
CHD:	congenital heart defect
CHEO:	Children's Hospital of Eastern Ontario
CMA:	chromosomal microarray
CMP:	cardiomyopathy
CNV:	copy number variant
CT:	computed tomography
CUA:	cost-utility analysis
DCM:	dilated cardiomyopathy
ECG:	electrocardiogram
EHR:	electronic health record

EMR:	electronic medical record
FH:	familial hypercholesterolaemia
FMA:	familial mutation analysis
GI:	gastrointestinal
HCM:	hypertrophic cardiomyopathy
HCP:	health care provider
HF:	heart failure
HH:	hereditary haemochromatosis
HTA:	health technology assessment
ICD:	implantable cardioverter defibrillator
ICER:	incremental cost-effectiveness ratio
LFTs:	liver function tests
LQTS:	long QT syndrome
LVAD:	left ventricular assist device
LVNC:	left ventricular non-compaction cardiomyopathy
MCS:	mechanical circulatory support
MIBI:	myocardial perfusion imaging test
MRI:	magnetic resonance imaging
NA:	not applicable
NGS:	next generation sequencing

NIH:	National Institutes of Health
ODB:	Ontario Drug Benefit
OHIP:	Ontario Health Insurance Plan
PCMR:	Paediatric Cardiomyopathy Registry
PGCRL:	Peter Gilgan Centre for Research and Learning
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSA:	probabilistic sensitivity analysis
QALY:	quality-adjusted life-year
RCM:	restrictive cardiomyopathy
SCA:	sudden cardiac arrest
SCD:	sudden cardiac death
SD:	standard deviation
SIGN:	Scottish Intercollegiate Guidelines Network
SMA:	spinal muscular atrophy
SoB:	Schedule of Benefits: Physician Services Under the Health Insurance Act
SoBLS:	Schedule of Benefits for Laboratory Services
Tb:	terabase
TTE:	transthoracic echocardiogram
VUS:	variant of uncertain significance
WES:	whole exome sequencing

WGS: whole genome sequencing

XP-A: xeroderma pigmentosum complementation group A

Chapter 1:
Background

This chapter provides the background information and rationale for an analysis of cascade health resource use resulting from conventional genetic testing for paediatric cardiomyopathy (CMP) in Canada.

This chapter begins with a description of relevant conventional genetic testing technologies, their strengths and limitations, and the clinical aspects of paediatric CMP. Genetic testing in the context of this disease state is subsequently discussed, and the concept of cascade testing is then introduced. This chapter concludes with a summary of the knowledge gap that this thesis is designed to fill, as well as the specific aims to be investigated.

1.1 Genetic Testing

A genetic test is "the analysis of human DNA, RNA, chromosomes, proteins, and certain metabolites in order to detect heritable disease-related genotypes, mutations, phenotypes, or karyotypes for clinical purposes" (Task Force on Genetic Testing, 1997). This is a broad definition; for the purpose of this thesis, the terms genetic test and genetic testing will refer solely to the analysis of DNA. Such an analysis, in the context of testing related to disease may be performed to: confirm the diagnosis of a present disease state; predict the risk of disease in an asymptomatic individual; or to determine carrier status (Task Force on Genetic Testing, 1997). Included in the genetic testing arsenal are karyotyping and chromosomal microarray (CMA), single gene and multi-gene panel testing, and DNA sequencing.

Conventional genetic testing is used in this thesis as a generic term for a multitude of genetic tests, including: karyotyping; CMA; single gene tests; and multi-gene panels. It does not include whole exome sequencing (WES) or whole genome sequencing (WGS), emerging genomic technologies being used as research applications. The Cardiac Genome Clinic at the Hospital for Sick Children (SickKids) in Toronto, Canada was established in 2014 (Centre for Genetic Medicine, 2013) to begin to provide WGS for a variety of paediatric cardiac populations. Paediatric CMP patients have undergone this type of testing, but they have not received results to date as the sequencing data are being used for gene discovery rather than clinical care. Consequently, this thesis only explores the costs and consequences of cascade genetic testing

resulting from conventional genetic testing. As the use of WGS in paediatric CMP patients increases, independent evidence for this technology in this population will need to be developed. In addition, this thesis only addresses genetically based and/or idiopathic paediatric CMPs, rather than those caused by well-understood metabolic or infectious diseases.

1.1.1 Karyotyping and Chromosome Microarray

Karyotyping is the process by which an organism's chromosomes are stained to reveal their characteristic structural features, then paired and ordered by size from largest to smallest (O'Connor, 2008). Karyotype analysis can be used to detect whether large portions of genetic material have been deleted or duplicated, and are useful in diagnosing aneuploidies such as trisomy 21 (Down syndrome) (O'Connor, 2008). Similarly, CMA (sometimes referred to as *molecular karyotyping* (Miller et al., 2010)), also detects DNA aneuploidies, duplications, amplifications, and deletions (Committee on Genetics, 2016). However, CMA has comparatively greater genomic resolution – 250,000 base pairs *versus* five to 10 million base pairs (Helm & Freeze, 2016) – so it can detect subtler, submicroscopic chromosomal anomalies that karyotyping cannot (Committee on Genetics, 2016). A duplicated or deleted section of DNA differing from the reference genome by 1,000 base pairs or more is called a *copy number variant* (CNV) (Committee on Genetics, 2016; Helm & Freeze, 2016).

CMA is able to detect aneuploidies, duplications, amplifications, and deletions, and has been shown to be a powerful diagnostic tool (Miller et al., 2010). It has been found that 18%-21% of patients with congenital heart defects (CHDs) as well as other, non-cardiac features have pathogenic CNVs (Breckpot et al., 2010; Goldmuntz et al., 2011). Several well-characterized syndromes with CHDs are known to be caused by CNVs, for example DiGeorge syndrome (*22q11.2* deletion) (Helm & Freeze, 2016). Among patients with isolated CHDs, 3%-14% have pathogenic or suspected pathogenic CNVs (Erdogan et al., 2008; Lander & Ware, 2014; Soemedi et al., 2012). The diagnostic yield of CMA for patients with CHDs ranges from 12.8% to 18.5%, with 74% of identified CNVs being too small to be detected with traditional karyotyping (Geng et al., 2014). CMA has been recommended as a first-tier test for this patient population (Helm & Freeze, 2016).

CMA has several limitations. For example, not all CNVs are clinically significant; while a CNV may be classified as either pathogenic or benign, it may also be considered a variant of uncertain

significance (VUS) if there is little data describing the impact of that chromosomal anomaly on phenotype (Committee on Genetics, 2016; Miller et al., 2010). The concept of incomplete penetrance adds further complexity, as it is not possible to make accurate predictions regarding the risk of certain health outcomes (Helm & Freeze, 2016). In addition, CMA is unable to identify balanced chromosomal rearrangements (i.e., translocations and inversions) (Shen et al., 2010), nor is it able to identify small changes that have occurred at the level of the genetic code (i.e., point mutations). In one study exploring the diagnostic yield of CMA compared with karyotyping in a large clinical cohort of patients with autism spectrum disorders, 19 patients had an abnormal karyotype, but CMA was only able to detect the abnormality in 42.1% of these because the rest had balanced rearrangements that appeared normal (Shen et al., 2010). This limitation is remedied by genetic sequencing, which is able to detect mutations at the sequence level.

1.1.2 Genetic Sequencing

The first milestone in the history of sequencing occurred in 1950, when Fred Sanger sequenced insulin and showed that proteins have specific amino acid residue patterns (Shendure et al., 2017). Over the course of the next decade and a half, researchers developed different techniques to sequence other peptides, then RNA, and finally DNA (Shendure et al., 2017). These methods were, at first, inefficient: in 1973, it took Gilbert and Maxam (Gilbert & Maxam, 1973) two years to identify 24 nucleotides that coded for the lactose-repressor binding site (i.e., they were able to sequence at a rate of one base per month). The field was transformed in 1977, when Sanger, Nicklen, and Coulson published their seminal paper detailing a method of sequencing – now known as Sanger sequencing – through which hundreds of nucleotide bases could be sequenced in a single afternoon (Sanger et al., 1977).

1.1.2.1 Sanger Sequencing

Despite being over 40 years old, Sanger sequencing is still considered the gold-standard sequencing technology (Beck et al., 2016; ThermoFisher Scientific). It is able to accurately detect point mutations, small deletions and duplications (Heather & Chain, 2016), and has an accuracy of over 99.99% (Liu et al., 2012). One challenge of Sanger sequencing though, is that it cannot detect variants present at low frequencies – for example, if mosaicism occurs in less than 20% of cells, Sanger sequencing cannot identify it (Gomes & Korf, 2018; Morey et al., 2013).

An additional difficulty is that Sanger sequencing has low throughput: a maximum of 384 sequences between 600 – 1,000 base pairs in length can be sequenced in parallel, yielding 80,000 – 100,000 sequenced base pairs per hour (Morey et al., 2013). The human genome contains approximately three billion base pairs (National Human Genome Research Institute, 2010), so using only one machine, sequencing the entire genome would take 30,000 hours, or approximately three and a half years.

1.1.2.2 Next Generation Sequencing

The newest genetic sequencing technology being applied in the clinical setting is next-generation sequencing (NGS), also referred to as *massively parallel sequencing* or *high-throughput sequencing*. Rather than running one reaction at a time as in Sanger sequencing, thousands to millions of sequencing reactions are run in parallel (Shendure et al., 2017; van Dijk et al., 2014).

NGS is able to detect a large spectrum of genetic mutations, including: base substitutions; small DNA insertions and deletions; CNVs; deletions of exons or whole genes; and inversions and translocations (Behjati & Tarpey, 2013). Therefore, NGS can provide the same data as karyotyping, CMA, and Sanger sequencing, and more. These new technologies also have greater sensitivity, allowing for improved detection of mosaicism (Behjati & Tarpey, 2013). NGS has a much higher throughout and faster run times than Sanger sequencing (van Dijk et al., 2014); for instance, Illumina's HiSeq X Ten has a run time of less than three days, in which time it can generate 1.8 terabases (Tb) of sequence data (Illumina Inc., 2019). NGS can be used to interrogate a single gene, multiple genes at a time, an individual's whole exome (22,000 coding genes), or their whole genome (Behjati & Tarpey, 2013). The cost of NGS, although reduced from previous years, is high and its cost-effectiveness in particular patient populations and clinical applications remains to be demonstrated (Jegathisawaran et al., 2019; Tsiplova et al., 2017).

One weakness of NGS technologies is that they have short read lengths (typically 100 – 400 base pairs, though the Pacific Biosciences RS II system can reportedly read sequences of a maximum length of 20,000 nucleotides) (Mardis, 2017; van Dijk et al., 2014). This is problematic because short reads are difficult to align with the reference genome (Morey et al., 2013), resulting in a high false-positive rate for certain types of anomalies (Mardis, 2017). Despite this, the accuracy of these systems ranges from 98% to above 99.9% (Liu et al., 2012). Positive results from NGS

are typically verified with Sanger sequencing, with a validation rate of approximately 99.97% (Beck et al., 2016; ThermoFisher Scientific). Finally, like with CMA, not all identified anomalies are pathogenic, and can instead have uncertain or unknown significance. While VUS can be found during the interrogation of specific genes (as in a single gene or multi-gene panel test), they become a much larger concern as the proportion of genome sequenced increases (as in WES or WGS). Plainly put, the more places one searches, the greater the likelihood of finding a VUS. As scientific understanding and research progress, laboratories routinely reclassify VUS, either upgrading them to pathogenic status or downgrading them to benign (Hoffman-Andrews, 2017). Both health care providers (HCPs) and patients need to be alerted when such changes are made (Hoffman-Andrews, 2017).

There is growing interest in applying genetic testing to CMP, but understanding the genetic origin of this condition first requires an explication of the clinical disease.

1.2 Disease State: Paediatric Cardiomyopathy

CMP is a rare disease of the myocardium characterized by changes in cardiac chamber size, thickness of the ventricular walls, and abnormal heart contraction in the absence of coronary artery disease, valvular or congenital heart disease, or increased blood pressure (National Heart Lung and Blood Institute, 2018; Sabater-Molina et al., 2018). There are multiple phenotypic subtypes: dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), left ventricular non-compaction cardiomyopathy (LVNC), and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Ellepola et al., 2018; Ouellette et al., 2018). Paediatric CMP is complicated by the fact that, in addition to these five subtypes, children may belong to a mixed category (Lee et al., 2017). In these cases, phenotypic overlap hinders the identification of a specific diagnosis (Lee et al., 2017). For example, HCM caused by sarcomeric genetic mutations can transition into DCM, and HCM or DCM phenotypes are sometimes observed in LVNC (Lee et al., 2017).

1.2.1 Epidemiology

The Paediatric Cardiomyopathy Registry (PCMR) contains information about over 3,500 children with primary and idiopathic CMPs from approximately 100 paediatric cardiology centres in both the United States and Canada (Wilkinson et al., 2015). Based on the registry data,

it is estimated that the incidence of paediatric CMP in the United States is 1.13 cases per 100,000 children (Lipshultz et al., 2003). This is similar to results from other countries: a 10-year Australian study (Nugent et al., 2003) estimated that the annual incidence of paediatric CMP is 1.24 cases per 100,000 children and a 12-year Finnish study found an annual incidence of 0.65 new cases per 100,000 children per year (Arola et al., 1997).

Of the CMP phenotypic subtypes, DCM is the most common, accounting for 51% of cases with an incidence of 0.34 – 0.73 cases per 100,000 children (Arola et al., 1997; Nugent et al., 2003; Towbin et al., 2006; Wilkinson et al., 2015). HCM is responsible for 42% of cases and has an estimated incidence of 0.24 – 0.36 per 100,000 (Arola et al., 1997; Colan et al., 2007; Nugent et al., 2003; Wilkinson et al., 2015). RCM is the least common paediatric CMP, comprising 4.5% of cases with an incidence of 0.03 – 0.04 per 100,000 children (Lee et al., 2017; Nugent et al., 2003; Webber et al., 2012; Wilkinson et al., 2015). CMP incidence is higher among males under the age of one (Alvarez et al., 2011; Lipshultz et al., 2003; Towbin et al., 2006). An Australian study found that there is a higher incidence of DCM among Indigenous children than among non-Indigenous children (Nugent et al., 2003).

1.2.2 Medical Evaluation and Clinical Concepts

Medical evaluation of children with CMP includes a thorough medical history, a comprehensive physical examination with assessment for heart failure (HF), and a three- or four-generation pedigree in an attempt to identify an underlying metabolic, congenital, or acquired aetiology (Elliott et al., 2014). Cardiac phenotype is generally established through echocardiography, which is also a useful tool in predicting disease severity and prognosis (Lee et al., 2017). For example, the degree of ventricular dysfunction and dilation in paediatric DCM is a predictor of the need for a heart transplant or of sudden cardiac death (SCD) (Alvarez et al., 2011; Bharucha et al., 2015; Towbin et al., 2006). In the case of paediatric HCM, the thickness of the left ventricular posterior wall is a measure of interest (Bharucha et al., 2015). Cardiac catheterization is used to distinguish RCM from constrictive pericarditis and can be used to assess filling pressures and pulmonary hypertension (Lee et al., 2017).

In general, children present with gastrointestinal (GI) symptoms (abdominal pain, nausea, vomiting, and decreased appetite); respiratory symptoms (such as shortness of breath or coughing); fluid overload; and chest pain (Hollander et al., 2013). Approximately 71% – 90% of

children with DCM (Alvarez et al., 2011; Nugent et al., 2003; Towbin et al., 2006), 7.5% – 9.9% of those with HCM (Colan et al., 2007; Nugent et al., 2003), and 50% of those with RCM (Nugent et al., 2003) present with signs and symptoms of HF. Some HCM, RCM, and LVNC patients experience HF with a preserved ejection fraction, and have laboured breathing (dyspnea), shortness of breath (orthopnea), and growth failure due to diastolic dysfunction and reduced cardiac output (Elliott et al., 2014; Lee et al., 2017). Morbidity and mortality greatly depend on comorbid conditions; in particular, anemia and hyponatremia are associated with death, transplant, and mechanical circulatory support (MCS) (i.e., ventricular assist devices) (Goldberg et al., 2016; Price et al., 2016).

1.2.2.1 Dilated Cardiomyopathy

A diagnosis of DCM is made when patients have both left ventricular enlargement and systolic dysfunction (Hershberger & Morales, 2018). Patients with DCM may be completely asymptomatic, while others may present with HF, arrhythmias, or thromboembolic disease (Daubeney et al., 2006; Hershberger & Morales, 2018; Wilkinson et al., 2015). Many display a failure to grow (Alvarez et al., 2011). A large proportion of children, especially those between the ages of 11 and 18 years may present with GI complaints as their only symptoms (Hollander et al., 2013).

Although there are large differences in age, disease aetiology, comorbidities, and outcomes between adult and paediatric patient populations, adult HF therapies, such as beta blockers and angiotensin converting enzyme (ACE) inhibitors are often employed in the management of children (Daubeney et al., 2006; Hsu & Shaddy, 2016; Towbin et al., 2006). More invasive strategies – MCS and heart transplantation – are also treatment options, but the possibility of full recovery is a consideration in their use (Lee et al., 2017).

The outcomes of paediatric DCM are highly variable. Some patients regain normal function, while others require a heart transplant (Everitt et al., 2014). American, European, and Australian registries report that, within five years of diagnosis, the rate of transplant-free survival is 58% to 72%, and that 22% of patients regain normal cardiac function two years after diagnosis (Daubeney et al., 2006; den Boer et al., 2015; Everitt et al., 2014; Towbin et al., 2006; Tsirka et al., 2004). Freedom from death is 84% at one year following diagnosis, and 76% after five years

(Towbin et al., 2006). Children younger than six years old have been found to have better survival rates than those who are older (Daubeney et al., 2006; Wilkinson et al., 2015).

1.2.2.2 Hypertrophic Cardiomyopathy

HCM is defined by increased left ventricular wall thickness not solely explained by abnormal loading conditions (such as hypertension or valvular disease) (Elliott et al., 2014; Sabater-Molina et al., 2018). The age of clinical presentation of HCM depends on the genetic cause of disease (Elliott et al., 2014). In HCM caused by inborn errors of metabolism or malformation syndromes, symptoms are usually noticed in infancy or early childhood; when HCM is the result of a neuromuscular disorder, it more commonly manifests in adolescence or early adulthood and is sometimes identified in asymptomatic individuals (Elliott et al., 2014; Sabater-Molina et al., 2018). HCM patients are at risk for atrial fibrillation due to progressive left atrial enlargement resulting from diastolic dysfunction (Patten et al., 2018). In some cases, cardiac arrest or SCD are the first indication of HCM in a previously healthy child (Sabater-Molina et al., 2018).

As with DCM, treatment strategies for paediatric HCM are adapted from those used in adults (Lee et al., 2017). Beta blockers are commonly used in symptomatic children, and it is possible they may decrease the risk of SCD (Ostman-Smith et al., 1999; Sabater-Molina et al., 2018). In cases where beta blockers are ineffective or are not tolerated, verapamil, a calcium channel blocker, is introduced (Elliott et al., 2014; Sabater-Molina et al., 2018). In addition to medication, it is also recommended that HCM patients do not play intense competitive sports, because the risk of SCD is greater during exercise (Elliott et al., 2014). However, survival has not been demonstrated to increase when restrictions around exercise are implemented, and such restrictions are associated with a variety of other problems, including social isolation, mental health issues, and obesity (Lee et al., 2017). When medications fail to reduce symptoms, surgical intervention, specifically myectomy (removal of a portion of the cardiac septum) or septal alcohol ablation is considered (Elliott et al., 2014; Sabater-Molina et al., 2018). Implantation of an implantable cardioverter defibrillator (ICD) is considered when children have multiple major risk factors for SCD as defined by practice guidelines (Elliott et al., 2014).

Survival for paediatric idiopathic HCM at five and 10 years following presentation is 90% and 85% respectively (Colan et al., 2007). The most common cause of death in this patient population is HF (Lipshultz et al., 2013). The risk of SCD is greatest before children turn one

year old, and from eight years old to age 16 (Ostman-Smith et al., 2013). Children with mixed HCM/DCM or HCM/RCM phenotypes have high rates of death or transplantation at two years following diagnosis (45% and 38% respectively) (Wilkinson et al., 2015).

1.2.2.3 Restrictive Cardiomyopathy

RCM is "characterized by normal or decreased volume of both ventricles associated with bi-atrial enlargement, normal [left ventricular] wall thickness and [atrioventricular valves], impaired ventricular filling with restrictive physiology, and normal ... systolic function" (Maron et al., 2006). The clinical presentation ranges from asymptomatic, to overt HF, syncope, or SCD (Brown & Diaz, 2019; Nugent et al., 2003). One third of patients present with an RCM/HCM mixed phenotype (Webber et al., 2012). Children may experience ischemia, arrhythmia, thromboembolism, pulmonary hypertension, and, as the disease progresses, failure of systolic function (Zangwill et al., 2009). They may also be at risk of SCD despite a lack of evidence of HF (Zangwill et al., 2009).

Therapies for paediatric RCM are limited. Volume overload (i.e., pulmonary and systemic venous congestion) can be managed with diuretics, however this carries the risk of tissue hypoperfusion because cardiac output in RCM patients is maintained predominantly by high filling pressures (Brown & Diaz, 2019; Muchtar et al., 2017). RCM patients are at increased risk for thrombi; these can be prevented with anticoagulants (Muchtar et al., 2017). For some, advanced HF therapies such as left ventricular assist devices (LVADs) or a heart transplant may be the best course of action (Muchtar et al., 2017).

Paediatric RCM has comparatively poorer outcomes than DCM and HCM: survival five years following diagnosis is only 68% (Webber et al., 2012; Wilkinson et al., 2015). Patients with pure RCM are more likely to undergo heart transplants than those with an RCM/HCM combination phenotype, and as a result fare worse in terms of one-year and five-year transplant-free survival (48% and 22% for those with RCM/HCM, compared with 65% and 43% for those with pure RCM) (Webber et al., 2012).

1.2.2.4 Left Ventricular Non-Compaction Cardiomyopathy

LVNC (also referred to as non-compaction CMP, left ventricular hypertrabeculation, spongy/fetal/honeycomb myocardium, or hypertrabeculation syndrome), is characterized by the

presence of abnormal trabeculations within the left ventricle, giving the left ventricular myocardium a spongy appearance (Finsterer et al., 2017; Maron et al., 2006). It is usually diagnosed with echocardiography (Finsterer et al., 2017), with the median age of diagnosis in children being five to seven years old (Finsterer et al., 2017). Patients with LVNC are usually asymptomatic, though they may experience HF, ventricular arrhythmias, thromboemboli, or SCD (Finsterer et al., 2017). Clinically, these complications may appear as chest pain, dyspnoea, palpitations, syncope, lower extremity edema, embolism, or cardiac arrest (Finsterer et al., 2017). Paediatric LVNC patients often have an undulating phenotype, in which their CMP features change over the course of several months (Finsterer et al., 2017).

Symptomatic patients (i.e., those with arrhythmias, or who have systolic or diastolic dysfunction) should avoid heavy physical exercise and should not engage in high intensity sports (Finsterer et al., 2017). HF in LVNC patients should be treated in the same manner as HF resulting from other causes; systolic and diastolic dysfunction can be managed with beta blockers, ACE inhibitors, angiotensin II-receptor blockers, mineralocorticoid-receptor antagonists, and diuretics (Finsterer et al., 2017). Beta blockers can also be used to decrease left ventricular mass (Finsterer et al., 2017). It has been recommended that patients with atrial fibrillation, as well as those with severe systolic dysfunction, take oral anticoagulants (Finsterer et al., 2017). Daily baby aspirin in all infants and children with LVNC is becoming standard practice (Finsterer et al., 2017). In more severe cases, an ICD may be necessary to prevent cardiac arrest (Finsterer et al., 2017). As with other CMP phenotypic subtypes, heart transplantation may eventually be required as the condition evolves (Finsterer et al., 2017).

Time to death or transplant differs significantly depending on whether children have isolated (pure) LVNC, or whether they have a mixed phenotype (Jefferies et al., 2015). Paediatric patients with pure LVNC have the best outcomes, followed by those with LVNC/HCM, while children with LVNC/DCM fare the poorest (Jefferies et al., 2015). Among 155 children from the PCMR with LVNC, the following percentages of patients were free from death or heart transplant at five years follow-up: 67% of the entire study sample; 94% of pure LVNC patients; 75% of children with LVNC/HCM; and 57% of those with LVNC/DCM (Jefferies et al., 2015). Of children with isolated LVNC, 12% progressed to an associated CMP phenotype within two years of diagnosis (Jefferies et al., 2015).

1.2.2.5 Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is a progressive CMP characterized by fibrofatty replacement of the myocardium of the right ventricle, ventricular arrhythmias, and ventricular dysfunction (Krahn et al., 2016; Maron et al., 2006; Steinmetz et al., 2018; te Riele et al., 2015). Clinical presentation consists of ventricular tachycardia, cardiac arrest, or SCD, though patients may remain completely asymptomatic until late adulthood (Krahn et al., 2016; te Riele et al., 2015). Children have a statistically significant greater likelihood than adults to present with SCD or resuscitated sudden cardiac arrest (SCA) (te Riele et al., 2015). Paediatric patients with a genetic predisposition for ARVC generally begin to experience signs and symptoms of disease around four or five years of age (te Riele et al., 2015). A diagnosis is made on the basis of family history; imaging; and results from a 12-lead electrocardiogram (ECG), Holter monitoring, a biopsy of the myocardium, and/or genetic testing (Steinmetz et al., 2018).

Similar to other forms of CMP, rigorous exercise increases the risk of SCD in ARVC patients and also promotes disease progression (Corrado et al., 2015). As a result, it is recommended that young people with ARVC refrain from engaging in competitive, high-intensity athletic activities (Corrado et al., 2015). While this type of lifestyle change may be sufficient for asymptomatic patients, patients with ventricular arrhythmias or HF may be prescribed anti-arrhythmic drugs, ACE inhibitors, angiotensin II-receptor blockers, beta blockers, and/or diuretics (Corrado et al., 2015). In more severe cases, patients may undergo catheter ablation of the abnormal right ventricular fibrofatty tissue; have an ICD placed; or have a heart transplant (Corrado et al., 2015).

Outcomes in paediatric ARVC are difficult to comment on because very few studies have explored ARVC as a paediatric condition. However, one study comparing ARVC progression in children *versus* adults found that at five- and ten-years follow-up after diagnosis, 25% and 37% of paediatric patients respectively, developed sustained ventricular tachyarrhythmia (te Riele et al., 2015). This same study also showed that transplant- and death-free survival at these time points is very high among paediatric ARVC patients – nearly 100% at both five- and ten-years following diagnosis for both events.

1.2.3 Genetics of Cardiomyopathy

While CMP can be caused by coronary artery abnormalities, tachyarrhythmias, infection, and environmental factors, in the paediatric context it is typically a genetic disease (Ellepola et al., 2018; Lee et al., 2017; Ware, 2017). Paediatric CMPs are genetically heterogeneous: approximately 100 genes have been implicated to-date (Ouellette et al., 2018), including genes related to the sarcomere, Z-disk, nuclear membrane, desmosome, mitochondria, and calcium-handling proteins (Bates et al., 2012; Kindel et al., 2012; Sabater-Molina et al., 2018; Taylor et al., 2007; Towbin, 2014). Moreover, variants in the same gene can have different phenotypic manifestations, and variants in different genes can lead to the same phenotypic subtype (Towbin, 2014; Watkins et al., 2011). CMP-associated variants can be inherited as autosomal dominant, autosomal recessive, X-linked, or mitochondrial, or they can arise *de novo* (Elliott et al., 2014; Sabater-Molina et al., 2018). Autosomal dominant CMPs have variable ages of onset and penetrance (National Institutes of Health, 2019; Teekakirikul et al., 2013). An autosomal recessive pattern of inheritance for a gene previously associated with autosomal dominant adult-onset HCM has been described in infants with a lethal form of HCM (Zahka et al., 2008). Determining the underlying genetic cause of disease is important because it impacts clinical management (i.e., treatments and surveillance may be started or ceased based on test results) (Stark et al., 2019; Ware, 2017). In addition, although a patient may present with a mild phenotype, prognosis may be quite poor depending on the genetic mutation(s) they possess (Sabater-Molina et al., 2018). In fact, it has been found that children with a genetic diagnosis have a worse prognosis than those without, and they require cardiac transplantation and experience death in larger proportions (48% *versus* 34% for transplantation; 17% *versus* 2% for death) (Ellepola et al., 2018; Sabater-Molina et al., 2018).

Although the mechanism of the phenotypic variability inherent to CMP is not well understood, it appears that the genes associated with disease are all involved in a particular “final common pathway” specific to a phenotypic subtype (Towbin, 2014). For example, HCM is understood as a disease caused by poor contractile protein function (i.e., it is a disease of the sarcomere) (Sabater-Molina et al., 2018; Teekakirikul et al., 2013; Towbin, 2014; Watkins et al., 2011). In addition to disrupting the normal function of the structure in which they are embedded or integrated, the mutated protein(s) can also interfere with a binding partner protein (Towbin, 2014).

Common genes associated with paediatric CMPs are shown in **Table 1**.

1.2.3.1 Dilated Cardiomyopathy

Inherited DCM typically follows an autosomal dominant pattern of inheritance, although autosomal recessive and X-linked patterns of inheritance have also been described (Teekakirikul et al., 2013; Towbin, 2014). Over 40 genes have been implicated in autosomal dominant DCM, the majority of which code for cytoskeletal, sarcomeric, or Z-disk proteins (Towbin, 2014). Several genes involved in DCM have been found to encode proteins related to ion channels or desmosomes (Towbin, 2014). Mutations in cytoskeletal proteins cause abnormal force transmission while mutations in sarcomeric proteins lead to poor force generation (Towbin, 2014). Mutations in desmosomal proteins cause a disruption in the links between the sarcomere, Z-disk, and intercalated disk (Towbin, 2014).

The LINC complex is responsible for linking a cell's nucleus to its cytoplasm; mutations in components of this complex, including the Lamin A and C proteins, emerin, and nesprins-1 and 2 have been found in patients with DCM (Fatkin et al., 1999; Puckelwartz et al., 2010). Titin (*TTN*) is a commonly-mutated gene in patients with DCM (Begay et al., 2015; Norton et al., 2013; Yoskovitz et al., 2012). As noted previously, variants of the same gene can lead to different phenotypic subtypes of CMP. For example, mutations in the genes for troponin T (*TNNT2*) and β-myosin heavy chain 7 (*MYH7*) can cause either DCM or HCM, depending on where in the gene the mutation occurs (Towbin, 2014).

Patients who have a positive family history for at least two closely related relatives with DCM are considered to have familial DCM (which is clinically and diagnostically identical to idiopathic DCM or DCM caused by non-genetic factors) (Colombo et al., 2008). Ten to 16% of cases of familial DCM are caused by mutations in sarcomeric protein-encoding genes (Colombo et al., 2008). It is estimated that mutations in *TTN* may contribute up to a quarter of familial DCM cases (Herman et al., 2012).

1.2.3.2 Hypertrophic Cardiomyopathy

Like DCM, HCM is predominantly an autosomal dominant disease, though there have been some cases of *de novo* mutations and autosomal recessive inheritance (Sabater-Molina et al., 2018; Zahka et al., 2008). The majority of HCM-associated genes are sarcomeric, but genes

encoding Z-disk proteins or intracellular calcium modulators have also been implicated (Towbin, 2014). 70%-80% of mutations occur in *MYH7* and the gene that encodes myosin binding protein C (*MYBPC3*) (Sabater-Molina et al., 2018; Towbin, 2014). The majority of sarcomeric mutations involved in HCM are single nucleotide substitutions; the resulting aberrant protein is incorporated into the sarcomere and exerts a poison peptide effect (Towbin, 2014). Less than 1% of HCM cases are due to CNVs (Sabater-Molina et al., 2018). Molecular effects caused by these mutations include increased actin-activated ATPase activity, disruption of the interaction between actin and myosin leading to altered ability to generate contractile force, and altered intracellular calcium signalling within cardiomyocytes (Teekakirikul et al., 2013).

Mutations in sarcomeric protein-encoding genes are found in 60% – 70% of patients with HCM who also have a positive family history for this form of CMP (Teekakirikul et al., 2013; Towbin, 2014). Mutations are often shared by only one or a small number of families (Sabater-Molina et al., 2018), but even among close relatives with identical mutations, clinical presentation and outcomes are heterogeneous and vary with age and sex (Colombo et al., 2008; Sabater-Molina et al., 2018; Towbin, 2014). A genotype-phenotype correlation has only been established for handful of genes. For example, mutated *TNNT2* is thought to be associated with an increased risk of SCD (Ho, 2010). Children with HCM are more likely to have a family history of CMP than are those with DCM (Nugent et al., 2003).

1.2.3.3 Restrictive Cardiomyopathy

RCM has been found to have autosomal dominant, autosomal recessive, X-linked, and mitochondrial-transmitted inheritance (Towbin, 2014). The genetic aetiology of RCM is very poorly defined, but like in HCM, the majority of associated genes that have been identified are sarcomeric (Towbin, 2014) and include the gene that encodes troponin I (*TNNI3*) (Mogensen et al., 2003), *MYH7*, the gene that codes for α-cardiac actin (*ACTC1*), *TTN* (Peled et al., 2014), and genes that code for the myosin light chain (Olson et al., 2002).

1.2.3.4 Left Ventricular Non-Compaction Cardiomyopathy

LVNC has a poorly understood genetic aetiology; autosomal dominant, autosomal recessive, and X-linked patterns of inheritance have been described (Sasse-Klaassen et al., 2003; Xing et al., 2006). Genes encoding proteins related to the sarcomere, Z-disk, cytoskeleton, and mitochondria have been associated with LVNC (Bagnall et al., 2014; Bainbridge et al., 2015; Sasse-Klaassen

et al., 2003). In one study analyzing unrelated paediatric and adult LVNC patients, mutations in *MYH7* and *MYBPC3* accounted for 27% of mutations among children (van Waning et al., 2018). In another (Miszalski-Jamka et al., 2017), one study participant had two different mutations in the gene for the cardiac sodium channel (*SCN5A*) and a third mutation in the gene that codes for α-tropomyosin (*TPM1*).

LVNC does not often segregate such that one family carries a particular mutation, however, even when this does occur, phenotypes are highly variable (Finsterer et al., 2017). There is additional confusion around the heritability of LVNC because sometimes in families with a history of autosomal dominant disease, LVNC may skip a generation (Finsterer et al., 2017).

1.2.3.5 Arrhythmogenic Right Ventricular Cardiomyopathy

ARVC is typically inherited in an autosomal dominant manner (Teekakirikul et al., 2013; Towbin, 2014). Cytoskeletal, nuclear envelope, desmosomal, and calcium/sodium-handling genes have been implicated, including the gene that codes for desmin (DES) and TTN; the gene encoding Lamin A/C (LMNA); the genes for desmocollin 2 (DSC2), desmoglein 2 (DSG2), desmoplakin (DSP), junction plakoglobin (JUP), and plakophilin 2 (PKP2); and the genes for phospholamban (PLN) and the ryanodine receptor 2 (RYR2) (Te Rijdt et al., 2014). Mutations in genes encoding proteins that interact with desmosomal proteins have also been associated with ARVC, including the genes for the transforming growth factor β3 (TGF β3) and transmembrane protein 43 (TMEM43) (Te Rijdt et al., 2014). Overall these mutations disrupt two “final common pathways” (the desmosome and ion channels) to produce the ARVC disease state: decreased integrity of the desmosome affects gap junctions and the function of sodium channels, promoting ventricular arrhythmia despite the lack of structural damage (Towbin, 2014). It is estimated that 30% to 50% of ARVC cases are familial (Corrado et al., 2009). However, because ARVC-associated genes demonstrate incomplete penetrance, genetically affected relatives often display mild-to-no phenotype, so familial disease prevalence is frequently underestimated (Towbin, 2014).

Table 1: Common genes associated with paediatric CMPs.

LOCATION/ROLE	GENE	ASSOCIATED CMP SUBTYPES					INHERITANCE
		DCM	HCM	RCM	LVNC	ARVC	
Desmosome	*DSC2*	X				X	AD
	DSG2	X				X	AD
	DSP	X				X	AD, AR
	JUP					X	AD, AR
	PKP2	X				X	AD
Dystrophin-associated protein complex	*SGCD*	X					AD, AR
Intermediate filament	*DES*	X		X		X	AD
Growth factor	*TGF β3*					X	AD
Nuclear membrane	*LMNA*	X			X	X	AD
Sarcomere	*ACTC1*	X	X	X	X		AD
	MYBPC3	X	X		X		AD
	MYH6	X	X				AD
	MYH7	X	X	X	X		AD
	MYL2		X				AD
	MYL3		X				AD
	TNNI3	X	X	X			AD
	TNNT2	X	X	X	X		AD
	TPM1	X	X				AD
	TTN	X	X		X	X	AD
Sarcoplasmic reticulum	*PLN*	X	X			X	AD
Sodium channel	*SCN5A*	X			X		AD
Transmembrane protein	*TMEM43*					X	AD
Z-disk	*ACTN2*	X	X				AD
	ANKRD1	X	X				IU
	BAG3	X	X	X			AD
	CSRP3	X	X				AD
	MYOZ2	X					AD
	NEBL	X					IU
	NEXN	X	X				AD
	TCAP	X	X				AD, AR
	VCL	X	X		X		AD

AD: autosomal dominant
AR: autosomal recessive
IU: inheritance unknown

1.3 Genetic Testing in Paediatric Cardiomyopathy

Genetic testing for CMP emerged more than twenty years ago, when HCM was mapped to a causative locus on chromosome 14 in 1989 (Jarcho et al., 1989). Since then, thousands of gene variants associated with CMP have been discovered, and multiple publications have described the outcome of genetic testing for this disease in the clinical setting (Alfares et al., 2015; Ellepola et al., 2018; Maron et al., 2012; Ouellette et al., 2018; van Spaendonck-Zwarts et al., 2013).

Genetic testing is typically indicated for children with CMP when well-understood metabolic and infectious diseases have been eliminated as potential causes. It has been recommended that genetic screening be considered beginning at 10 years of age (Elliott et al., 2014). In early-onset familial cases of CMP, or when children have cardiac symptoms, genetic testing at a younger age may be appropriate (Elliott et al., 2014; Hershberger et al., 2018).

Standard genetic tests for this population are karyotypes and CMA, single gene tests, multi-gene panel tests (Children's Hospital of Eastern Ontario, 2015b), and increasingly, WES (Alfares et al., 2015). Different institutions/organizations offer different multi-gene panels (**Table 2**). LifeLabs Genetics offers a 50-gene DCM panel (LifeLabs Genetics, 2019b); a 36-gene HCM panel (LifeLabs Genetics, 2019c); a 14-gene ARVC panel (LifeLabs Genetics, 2019a); and a 76-gene combined CMP panel (LifeLabs Genetics, 2019d). At the Children's Hospital of Eastern Ontario (CHEO) in Ottawa, Canada, the available multi-gene panels include a 25-gene DCM panel; a 19-gene HCM panel; a 7-gene ARVC panel; and a 45-gene pan-CMP panel that comprises of all the genes tested for by the DCM, HCM, and ARVC panels (Children's Hospital of Eastern Ontario, 2015a). Partners Healthcare, which is affiliated with Harvard University, offers a 62-gene pan-CMP panel (Partners Healthcare, 2019). A 5-gene ARVC panel is available at SickKids (Hospital for Sick Children, 2019). Results may be pathogenic or likely pathogenic (positive), benign or likely benign (negative), VUS (inconclusive), or a secondary variant (an incidental finding). The classification of a variant into one of these categories is performed by a laboratory scientist according to criteria set out by the American College of Medical Genetics and Genomics (ACMG) (Richards et al., 2015). A medical geneticist or genetic counsellor assesses the identified genetic anomalies in the context of the patient's phenotype and family history and may help determine whether a variant is diagnostic in that particular case. However, the majority of pathogenic variants would be considered diagnostic, with this assessment being made in the laboratory and indicated on the laboratory report. Patients and their families typically undergo pre- and post-test counselling from a genetic counsellor.

Single gene tests, multi-gene panels, WES, and WGS are performed with additional Sanger sequencing being done for relevant regions with insufficient coverage, as well as for the confirmation of positive results (Children's Hospital of Eastern Ontario, 2015b). Results can be returned within three to four weeks for variant-specific analyses and within 10 weeks for full

panel tests (Children's Hospital of Eastern Ontario, 2015b), however there is notable variation in the time for return of results between institutions.

Table 2: Genes included in multi-gene CMP panels offered by LifeLabs Genetics, CHEO, Partners Healthcare, and SickKids.

	LIFELABS GENETICS				CHILDREN'S HOSPITAL OF EASTERN ONTARIO				PARTNERS HEALTHCARE	HOSPITAL FOR SICK CHILDREN
GENE	**DCM Panel (50 Genes)**	**HCM Panel (36 Genes)**	**ARVC Panel (14 Genes)**	**Combined CMP Panel (76 Genes)**	**DCM Panel (25 Genes)**	**HCM Panel (19 Genes)**	**ARVC Panel (7 Genes)**	**Pan-CMP Panel (45 Genes)**	**Pan-CMP Panel (62 Genes)**	**ARVC Panel (5 Genes)**
ABCC9	X			X	X			X	X	
ACTC1	X	X		X	X	X		X	X	
ACTN2	X	X		X	X	X		X	X	
ANKRD1	X	X		X				X	X	
BAG3	X			X					X	
BRAF	X			X						
CALR3	X	X		X						
CASQ2								X	X	
CAV3	X	X		X		X		X	X	
CBL	X			X						
CHRM2									X	
CRYAB	X	X		X				X	X	
CSRP3	X	X		X	X	X		X	X	
CTF1					X			X		
CTNNA3			X							
DES	X	X	X	X	X			X	X	
DMD	X			X					X	
DNAJC19	X			X						
DOLK	X			X					X	
DSC2	X		X	X			X	X	X	X
DSG2	X		X	X			X	X	X	X
DSP	X		X	X			X	X	X	X
DTNA									X	
EMD	X			X	X			X	X	
EYA4	X			X						
FHL2	X	X		X				X	X	
FKTN	X			X						

FLNC	X	X		X						
GATA4	X			X						
GATAD1	X			X					X	
GLA	X	X		X		X		X	X	
HRAS	X			X						
ILK									X	
JPH2	X	X		X					X	
JUP			X				X	X	X	
KAT6B	X			X						
KRAS	X			X						
LAMA4	X			X				X	X	
LAMP2	X	X		X	X	X		X	X	
LDB3	X	X		X	X			X	X	
LMNA	X		X	X	X			X	X	
LZTR1	X			X						
MAP2K1	X			X						
MAP2K2	X			X						
MURC									X	
MYBPC3	X	X		X	X	X		X	X	
MYH6	X	X		X	X			X	X	
MYH7	X	X		X	X	X		X	X	
MYL2	X	X		X		X		X	X	
MYL3	X	X		X		X		X	X	
MYLK2		X		X				X	X	
MYOM1									X	
MYOZ2						X		X	X	
MYPN	X	X		X					X	
NEBL	X			X					X	
NEXN	X	X		X	X	X		X	X	
NF1	X			X						
NRAS	X			X						
PDLIM3	X	X		X					X	
PKP2	X		X	X			X	X	X	X
PLN	X	X	X	X	X	X		X	X	
PRDM16	X			X					X	

PRKAG2	X	X		X		X		X	X	
PTPN11	X			X					X	
RAF1	X			X					X	
RASA2	X			X						
RBM20	X			X	X			X	X	
RIT1	X			X						
RYR2			X				X	X	X	
SCN5A	X		X	X					X	
SGCD	X			X	X			X	X	
SHOC2	X			X						
SLC5A4	X	X		X						
SOS1	X	X		X						
SOS2	X			X						
SPRED1	X			X						
TAZ	X			X	X			X	X	
TBX20	X			X						
TCAP	X	X		X	X			X	X	
TGFB3			X							
TMEM43			X				X	X	X	X
TNNC1	X	X		X	X	X		X	X	
TNNI3	X	X		X	X	X		X	X	
TNNT2	X	X		X	X	X		X	X	
TPM1	X	X		X	X	X		X	X	
TRDN									X	
TRIM63	X	X		X						
TTN	X	X	X	X	X			X	X	
TTR	X	X		X		X		X	X	
VCL	X	X		X	X			X	X	

Information presented in the table found in (Children's Hospital of Eastern Ontario, 2015a; Hospital for Sick Children, 2019; LifeLabs Genetics, 2019a, 2019b, 2019c, 2019d; Partners Healthcare, 2019).

The above tests are limited in their detection as the discovery of CMP-associated genes is ongoing (Ouellette et al., 2018; Ware, 2017). The diagnostic yield for isolated CHDs with CMA is only 4.3% – 9.3% (Geng et al., 2014). With current conventional genetic sequencing methods, pathogenic gene variants are found in 30% – 60% of HCM or ARVC patients, and in less than 20% of those presenting with DCM, RCM, or LVNC (Ouellette et al., 2018). Studies in paediatric patients with HCM have shown overall genetic testing diagnostic yields between 21% and 53% (Kaski et al., 2009; Kindel et al., 2012; Morita et al., 2008; Nugent et al., 2005). Diagnostic yield is higher among individuals with a positive family history for CMP (Ingles et al., 2013).

Multiple authors (Alfares et al., 2015; Ouellette et al., 2018) have suggested that the pan-CMP panel may not have substantially greater rates of detection of pathogenic variants than CMP subtype-specific panels. Alfares et al. (Alfares et al., 2015) tested over 600 individuals using both a targeted 18-gene HCM panel and the pan-CMP panel, and found that expanded testing identified only one additional pathogenic or likely pathogenic variant in a gene not interrogated by the HCM panel (Alfares et al., 2015). In Ouellette and colleagues' study of 151 paediatric CMP patients, the pan-CMP panel only identified pathogenic variants in genes that overlapped with targeted panels (Ouellette et al., 2018). It is suggested that targeted panels may be more useful than the pan-CMP panel for most patients, and that it may be appropriate to reserve the expanded panel for patients with atypical phenotypes (Alfares et al., 2015; Ouellette et al., 2018).

Despite these limitations, genetic testing can provide clinicians and patients with valuable information and is therefore an important component of the diagnostic process for paediatric CMP. In addition to the information that is directly relevant to the care of the child, genetic findings about the paediatric proband may also have important implications for the management of cardiac risk in family members.

1.4 Cascade Genetic Testing and Clinical Screening

The National Institutes of Health (NIH) National Cancer Institute defines cascade screening (or cascade testing; family-based screening; family-based testing; or predictive DNA testing) as:

> *"A systematic process for the identification of individuals at risk for a hereditary condition. The process begins with the identification of an individual with the condition and/or a pathogenic variant associated with the condition and then*

> *extending genetic testing to his/her at-risk biological relatives. This process is repeated as more affected individuals or pathogenic variant carriers are identified" (National Cancer Institute).*

The first affected person in a family who makes clinicians aware of the presence of a genetic condition, is termed the proband (National Human Genome Research Institute) – also referred to as the index case or index patient. Relatives are tested in order based on their genetic closeness to the proband, with first-degree relatives tested first, followed by second- and third-degree relatives. A first-degree relative is someone who shares approximately 50% of their genes with the proband, and includes parents, siblings, and offspring (National Human Genome Research Institute). Second-degree relatives share 25% of their DNA with the proband and include the "aunts, uncles, grandparents, grandchildren, nieces, nephews, or half-siblings" of the proband (National Cancer Institute). Cousins, who share only 12.5% of their genetic material with the proband are considered third-degree relatives.

1.4.1 Cascade Testing and Screening in Cardiomyopathy

Canadian, European, and American clinical practice guidelines all recommend cascade testing or screening (referred to collectively as *cascade investigations*) in the relatives of patients with CMP (Ackerman et al., 2011; Elliott, 2015; Elliott et al., 2014; Ezekowitz et al., 2017; Hershberger et al., 2018; Hospital for Sick Children, 2013, 2016). Specifically, these guidelines indicate that a probands' first-degree relatives should undergo screening with ECG and echocardiography, as well as genetic testing to determine whether they carry the same pathogenic or likely pathogenic mutation(s). Multiple authors echo these recommendations, indicating that one of the reasons it is important to identify the genetic cause of disease in someone with CMP is because it allows for genetic testing of that individual's family members (Ingles et al., 2012; Monserrat, 2018; Te Rijdt et al., 2014; Ware, 2017). This practice enables the early identification of those who are potentially affected (which may have important implications – for example, athletes may need to stop competitive sports despite the absence of overt disease (Sabater-Molina et al., 2018)) as well as the cessation of unnecessary cardiac follow-up evaluations and surveillance in family members who do not possess pathogenic variants (Monserrat, 2018; Te Rijdt et al., 2014). These evaluations include ECG; transthoracic echocardiogram (TTE); and potentially other non-DNA biomarker testing, such as bloodwork to assess serum levels of troponin, inflammatory markers, and electrolytes. Surveillance consists of

clinical assessment once every 12-18 months in children and adolescents, and once every five years in adults (Gersh et al., 2011).

It has been previously reported that a majority of caregivers (including parents, grandparents, step-parents, and adoptive parents) of children with HCM would consider undergoing genetic testing (Fitzgerald-Butt et al., 2010), and there have been studies in which cascade genetic testing in family members of affected individuals has been used to help identify CMP-related mutations (Bagnall et al., 2014; Herman et al., 2012; Kaski et al., 2008; Norton et al., 2013; van Spaendonck-Zwarts et al., 2013; Yoskovitz et al., 2012).

There have also been several studies exploring the uptake, costs, or downstream consequences of cascade testing in the context of CMP or other similar cardiac conditions based on the genetic test results of adult patients, or of patients of unspecified age. One study (Christiaans et al., 2008) explored the uptake of genetic counselling and predictive DNA testing in first- and second-degree relatives of HCM patients in the Netherlands. The ages of the probands was not specified, but relatives aged 10 years or older were eligible for cascade testing. Uptake of genetic counselling among first- and second-degree relatives was 40.4% and 27.5% respectively, with a global uptake of 39.0%. Uptake of genetic counselling was much higher in paediatric (age 10-18 years, 56.1%) than adult (37.2%) relatives. Of family members who attended genetic counselling sessions, 99% proceeded with predictive DNA testing, resulting in an overall uptake of cascade genetic testing of 38.6%.

Hofman *et al*. (Hofman et al., 2010) asked whether active cascade screening of relatives of patients with primary inherited arrhythmia syndromes would result in prophylactic treatment of carriers. They identified 130 probands with a genetically diagnosed arrhythmia syndrome for whom cascade testing of family members followed. In all, 509 consecutive relatives of 100 probands tested positive for the disease-causing familial mutation. The probands' ages were not provided, but the tested relatives included both children and adults. Relatives' relation to the proband (i.e., first- or second-degree) was not specified. Mutation-positive relatives proceeded with cardiac evaluations including ECG, Holter monitoring, and exercise testing. After an average follow-up time of 62 months, treatment (medication and/or implantation of a pacemaker or ICD) was begun and ongoing in the majority of mutation carriers. One of the benefits of cascade testing highlighted by the authors was that it enabled the initiation of preventative

therapy in asymptomatic mutation carriers: 78% of long QT syndrome (LQTS) carriers who were identified during the study and who received treatment were not yet showing symptoms of disease. There was no discussion of the costs associated with cascade testing or the subsequent changes in medical management.

More recently, the uptake of cascade testing in children from families that carry a pathogenic variant associated with HCM, ARVC, or LQTS was investigated in Alberta, Canada (Christian et al., 2018). A sample of 59 adults found to carry an HCM-, ARVC-, or LQTS-related mutation were included. Fifty-seven came from different families and in one family, both parents were carriers. Families had one to four children, with a median of two. Based on parental testing, 97 children at risk of a CMP were identified. Children from 38 of the 58 families (66%) underwent cascade genetic testing. Families with an asymptomatic carrier father were significantly less likely to accept the offer of cascade testing in their children than those with an asymptomatic carrier mother (30% compared with 92%). There was no association between the sex of the carrier parent and uptake of cascade genetic testing when the parent was symptomatic – uptake was 83% and 81% when the father or mother was affected, respectively. Uptake of cascade genetic testing in children was not statistically significantly associated with a family history of SCA or SCD, disease state, age of the oldest child in the family, the number of children in the family, and year in which testing was completed. The need for cardiac evaluation was discussed with all families in which at least one child was mutation-positive and in a number of additional families based on the children's age and parental genotype. Families were nearly nine times more likely to pursue cardiac evaluation if they had agreed to cascade genetic testing.

Ko *et al*. (Ko et al., 2018) asked adult HCM probands about the outcome of cardiac screening among their first-degree relatives with a median follow-up time of four years. Probands with a genetic diagnosis of HCM or family history of HCM reported that 34 of 203 (17%) first-degree family members received a positive genetic test for an HCM-associated mutation, and probands with a VUS reported that 3 out of 29 (10%) family members received a positive result. Importantly, among mutation-*negative* probands with no family history of HCM, 2 of 64 (3%) screened relatives were found to possess a pathogenic HCM-related mutation. Ko *et al*. also analyzed probands' clinical characteristics and found that a positive genetic test in the proband, proband age, and prior family history of HCM in the proband were statistically significant factors predictive of a positive result in a relative. A family history of HCM in the proband was

also a statistically significant predictor of an adverse event in a genetically diagnosed family member.

1.4.1.1 Cost-Effectiveness of Cascade Testing and Screening

Identification of HCM in the asymptomatic children of patients with HCM through cascade genetic testing has been found to be cost-effective compared with identification through cascade clinical screening alone, from the perspective of a United Kingdom hospital (Wordsworth et al., 2010). The model developed by Wordsworth and colleagues used a hypothetical cohort of patients in which the proband was between 44 and 48 years old and families had one to three children all aged 18 years or older. The cost of genetic testing in the proband, the probability of identifying a pathogenic HCM-associated variant in the proband, and the acceptance rate of cascade testing by the proband's children (assigned a mean of 48.7%) were all incorporated. Clinical screening included physical examination, ECG, and echocardiogram. Genetic testing involved interrogation of four genes (MYH7, MYBPC3, TNNT2, and TNNI3). The model compared four strategies: cascade genetic testing with repeated clinical investigations every five years for those whose tests were initially normal; cascade clinical screening with repeated clinical investigations every five years for those whose investigations were initially normal; cascade genetic testing with no follow-up surveillance following a negative initial test; and cascade clinical screening with no follow-up surveillance following normal initial investigations. Pre-test genetic counselling was provided in all cases. No follow-up was provided to individuals who declined genetic or clinical investigations. The discounted lifetime cost per patient for cascade genetic testing without surveillance every five years was €19,459 (2007 currency, equivalent to 2007 CDN $28,587.22). The discounted lifetime cost per patient of cascade genetic testing with surveillance every five years was €21,803 (2007 CDN $32,030.79). Overall, the incremental cost per life-year saved for cascade genetic testing with long-term surveillance in comparison with cascade clinical screening with long-term surveillance was €21,561 (2007 CDN $31,675.26), while the incremental cost per life-year saved for cascade genetic testing without any follow-up compared with cascade clinical screening without follow-up was €14,397 (2007 CDN $21,150.63). Both cascade genetic testing strategies were considered cost-effective compared to the cascade clinical screening strategies, a result that was robust to variation in the values of most parameters during one-way sensitivity analyses. In probabilistic sensitivity

analysis (PSA) with a cost-effectiveness threshold of €18,000 per life-year saved, a genetic testing strategy was cost-effective 70% of the time.

Another study used a probabilistic Markov model to determine whether clinical surveillance that includes genetic testing is cost-effective compared with cardiac surveillance consisting of traditional screening and assessment alone among family members of HCM patients using a lifetime time horizon from the perspective of a third-party payer (Ingles et al., 2012). Clinical surveillance was defined as consultation with a cardiologist, ECG, and echocardiogram. Screening took place once every two years for individuals between the ages of 18-30 years and every three years for those older than 30. The addition of genetic testing to cardiac surveillance had an incremental cost of AU $305 (2011 currency, equivalent to 2011 CDN $303.51), an incremental effect of 0.39 quality-adjusted life-years (QALYs), and an incremental cost-effectiveness ratio (ICER) of AU $785 (2011 CDN $781.15) per QALY gained. The model included a probability of identifying a mutation in the proband of 63%. Relatives eligible for genetic testing entered the model at age 18 years and the uptake of genetic testing among the family members of genotype-positive probands was assumed to be 100% (Ingles et al., 2012). This uptake rate is much higher than has been observed in population-based cohort studies (Christiaans et al., 2008; Christian et al., 2018; Miller et al., 2013) and likely contributed to the small ICER.

A 2013 analysis of the cost of genetic testing of probands and their relatives for common genes involved in HCM, ARVC, LQTS, and Brugada syndrome (BrS), found that genotyping was less expensive than the clinical follow-ups avoided in non-carrier relatives (Sabater-Molina et al., 2013). A sample of 234 unrelated probands, of whom 115 (49%) had HCM and 18 (7.7%) had ARVC, were included. All probands underwent diagnostic WES and once a disease-associated mutation was identified, a targeted genetic test was offered to the individual's relatives. A total of 738 relatives from these 234 probands underwent genotyping (on average, 3.1 relatives per index patient). Of 517 relatives of HCM patients, 224 received negative results and could cease cardiac surveillance. Genetic testing of HCM probands and non-carrier relatives was €220,710 (2012 currency, equivalent to 2012 CDN $327,886.78) less costly than the periodic screening that those non-carrier relatives would have had to undergo. This periodic screening consisted of ECG and echocardiogram annually from the ages of 10 to 20 years and then once every three years from the ages of 20 to 60 years. Of 76 relatives of ARVC patients, 40 received negative

testing results. Genetic testing of these probands and their relatives was €9,405 (2012 CDN $13,972.07) less costly than periodic screening consisting of ECG, signal-averaged ECG, echocardiogram, cardiac magnetic resonance imaging (MRI) at the first examination, and ECG and echocardiogram in follow-up examinations at the same frequency as for relatives of HCM patients. This study suffered from several limitations: the cost of clinical examination in probands or carriers was not included in the analysis, nor was the cost of genetic testing and follow-up clinical examinations in mutation-positive relatives. Moreover, for HCM patients, only two genes were analyzed (*MYBPC3* and *MHY7*). Interrogation of a greater number of genes would have likely resulted in the identification of more carrier relatives and consequently the calculated cost savings would have been smaller.

Finally, Catchpool and colleagues (Catchpool et al., 2019) conducted a model-based cost-utility analysis (CUA) to determine whether cascade genetic testing in the asymptomatic first-degree relatives of DCM patients is cost-effective compared with periodic clinical surveillance alone. The proband population consisted of adult DCM patients who underwent WES. All index patients had a family history of DCM or SCD. The CUA itself was conducted with a hypothetical cohort of these patients' relatives, all of whom were assumed to be above the age of 18 years and were clinically unaffected by DCM. A lifetime time horizon was adopted, and the analysis was conducted from the perspective of the Australian health care system. Cascade genetic testing was offered to the family members of genotype-positive probands, and the modelled uptake of cascade testing was 40%. The identification of a pathogenic variant in relatives led to a lifetime of clinical surveillance in those individuals, with the authors assuming a 100% uptake rate of cascade screening. Genotype-negative family members were not offered ongoing surveillance. For those relatives who were not offered genetic testing, there was the option to accept or decline periodic clinical surveillance. An uptake rate of 48% was assumed. Clinical surveillance consisted of consultation with a cardiologist, ECG, and echocardiography, with screening occurring once every two years. Ultimately, the addition of cascade genetic testing to periodic clinical surveillance resulted in an incremental cost of AU $300 (2018 currency, equivalent to 2018 CDN $290.61) per relative compared with clinical surveillance alone, an incremental gain in QALYs of 0.04 per relative, and an ICER of $6,100 (2018 CDN $5,909.07) per additional QALY. Using PSA, the authors found that at a cost-effectiveness

threshold of AU $50,000 per QALY, the probability that genetic testing in addition to clinical surveillance is cost-effective compared with clinical surveillance alone, is 90%.

1.4.2 Cascade Health Service Use and Health Technology Assessment

A health technology is any drug, medical device, procedure, or system designed to address a health problem and improve quality of life (World Health Organization, 2011). New technologies can dramatically change the face of medicine – an excellent example of this is the advent of the anaesthetic – and future innovations will only continue to alter the way in which health care is delivered. However, the promises of new technologies must be balanced against a health system's limited resources, and it is important to understand the comparative value of a new technology versus an established one.

Health technology assessment (HTA) emerged in the 1970s, when the rapid diffusion of computed tomography (CT) scanning became a public policy issue due to the high cost of the machines (Jonsson & Banta, 1999). The purpose of HTA is to inform technology-related health policy decisions through the "systematic evaluation of the properties and effects of a health technology, addressing the direct and intended effects of this technology, as well as its indirect and unintended consequences" (International Network of Agencies for Health Technology Assessment & Health Technology Assessment international). The clinical effectiveness, cost-effectiveness, and ethical, legal, and social implications of a health technology are all assessed (CADTH, 2015).

In addition to its cost and health service consequences, cascade testing and screening of family members has implications for HTA methodology. Specifically, the inclusion of health service use by individuals other than the index patient challenges how economic evaluations are designed, as well as how both costs and health outcomes are measured and incorporated. Moreover, the practice of cascade testing and screening raises ethical concerns that should be addressed in HTAs focused on the ethical and societal implications of technologies.

1.4.2.1 Economic Evaluations

A main component of HTA is the economic evaluation, which facilitates the comparison of costs and health outcomes associated with the implementation of two or more technologies (CADTH, 2017).

1.4.2.1.1 Study Design

One of the challenges associated with designing an economic evaluation incorporating cascade health service use is that a decision must be made as to how many family members will be included in analysis. An economic evaluation could consider only first-degree relatives, or its scope could be expanded to include second- or even third-degree family members as well. Another difficulty is that a researcher must determine the most appropriate time horizon for the analysis. Usually a lifetime time horizon is preferred (Drummond et al., 2015), but the question then becomes whose lifetime should be considered. Probands and their family members may have differing life expectancies, and relatives could outlive the index patient (or vice versa).

Including cascade testing and screening in economic evaluation raises an additional methodological challenge of whether the proband should remain the unit of analysis, or whether it is more appropriate to calculate costs and health benefits on a per relative basis. On one hand, assigning all costs and health benefits to the proband as the unit of analysis can be defended because testing in the proband is the point of origin for all cascade health service use offered to and consumed by family members. On the other hand, the size of probands' families – and therefore the number of relatives who undergo cascade testing per proband – may vary greatly from patient to patient, as may the type and amount of cascade testing that family members accept and pursue. If costs and health benefits are calculated in aggregate, there may be a large amount of variation from one proband to the next as a function of family size. Additionally, if the study sample includes predominantly probands with family members who are enthusiastic about testing and follow-up services, this may result in a high estimate of costs and health benefits and reduce the generalizability of results to smaller families and to families more reluctant to undergo investigations. Quantifying costs and health outcomes associated with cascade genetic testing as a function of the number of people involved may provide a clearer understanding of the impact that cascade testing of family members has on the health care system and the resources that are required to support it.

1.4.2.1.2 Costing

Economic evaluations in HTA subscribe to the principle in welfare economics that individuals are themselves the best judge of what contributes most to their utility. Thus, the results of economic evaluations are expressed in terms of the additional cost of implementing one technology over another per unit of benefit on a per patient basis. However, when cascade health service use is incorporated into an economic evaluation, the costs associated with the testing or screening of patients' relatives must also be accounted for. A primary challenge with doing so is that it may be difficult to identify and measure all of the health resources that should be accounted for. This may be especially true in the case of a long time horizon, when all ongoing surveillance and management protocols initiated in family members must be considered.

Moreover, assumptions may be required when attempting to understand the logistics of family members accessing services. For example, it is possible that a set of parents undergoing cascade testing may have a joint appointment with their HCP, but it is also possible that they will have two separate appointments on two different days. The number of appointments that relatives have may then affect the calculated cost of cascade services. This is especially true for HTAs conducted from the societal perspective rather than the public payer perspective, as there are costs associated with time losses as well as out of pocket travel or private insurance plans that may be distributed among multiple family members.

1.4.2.1.3 Measuring and Incorporating Health Outcomes

In addition to challenges for around study design and cost estimation, cascade genetic testing and clinical screening also poses a problem for measuring health outcomes in economic evaluations. Cost-effectiveness analyses (CEAs) by definition use disease-specific health outcomes. The challenge with this is that the outcome of interest in the proband may be different than and therefore not comparable to the relevant outcome in a family member. Alternatively, in the case where the same health outcome is appropriate in both the proband and the family member, the outcome of interest may occur many years – perhaps even decades – into the future in some family members. This separation in time may make it difficult to identify when or if the outcome occurs in the relative and also may raise a question as to the appropriateness of associating the family members' health outcomes with the initial use of technology in the proband. CUAs assess participants' preference-based quality of life (utility) to determine the QALYs gained due to a

technology. Cascade testing poses a problem because its results may not have any discernable effect on quality of life or, as before, the change in quality of life may be identifiable only after a number of years when an asymptomatic relative becomes symptomatic.

It is important to note that the relatives who undergo cascade testing may be a mixture of adults and children. Different tools are used to measure health outcomes or quality of life in adult *versus* paediatric populations. The results of these tools often cannot be combined into one overall outcome measure, which is a significant difficulty if both adults and children are referred for investigations. Even if a single tool can be used, aggregating health benefits such as life-years and QALYs across multiple individuals is problematic as these outcomes are defined and interpreted in terms of an individual's life expectancy.

1.4.2.2 Ethical Analyses

In addition to economic evaluations, HTAs are also concerned with the ethical implications of technologies. Cascade testing and screening raises a number of ethical concerns that should be discussed in the ethical analysis of a technology that has the potential to trigger a cascade.

To begin, cascade genetic testing could pose a challenge to family members' privacy. When the relative of a child with a genetic disease learns genetic information about themselves, it is possible that they may be able to infer whether other family members are affected or potential carriers of the condition in question. This may be a difficult situation if those family members have undergone testing and wish to keep their results confidential, but it is especially challenging in the case where some family members have not undergone genetic testing, have no desire to do so, but the information may have some clinical utility. In such a circumstance, relatives in possession of this information do not seem to have any good potential course of action: on one hand they can respect their loved ones' wishes and not discuss any of their genetic testing results despite the fact that that information could have important medical ramifications. On the other hand, they can infringe on their family members' *right not to know* in the hopes that this knowledge can be used to maximize their health and wellbeing.

Ethical analyses should also address ethical concerns regarding cascade testing of family members who are children. In general, young children are unable to make informed decisions and provide informed consent, so their parents or guardians decide whether they should undergo

a particular medical test or procedure, and give permission on their behalf. One of the difficulties is that when these children grow up, they may come to disagree with the decision made for them by their parents. A potential solution would be to wait to test children until they are considered competent to make their own medical decisions (i.e., until they attain mature minor status), but if a child does carry a serious pathogenic mutation, delaying the test could be detrimental. The return of positive, VUS, or inconclusive results for a child may also be distressing to parents and may result in unnecessary disruptions to that child's routine if parents begin to monitor them very closely or take them to see a physician at an unreasonably high frequency.

1.4.2.3 Implementation of Emerging Technologies and Health Technology Assessment

As technologies such as WES and WGS are introduced and become used with more frequency in paediatric cardiology, the cascade implications and the challenges associated with conducting HTAs are multiplied significantly. Because these technologies are able to detect mutations associated with a variety of conditions, not just CMP, it is possible that screening and surveillance related to such incidental or secondary findings will be initiated in family members. The costs associated with such investigations would likely also need to be considered in an economic evaluation accounting for cascade genetic testing. Moreover, the potential for family members to learn about conditions other than the one of primary interest also has implications for measuring health outcomes. The pathophysiology of and complications associated with diseases are different, and therefore the significant outcomes that could reveal the effect of a technology would vary not just between the proband and family members, but from relative to relative as well. Finally, with regards to ethical concerns, there is some debate as to whether clinicians should inform patients about incidental or secondary findings, especially when the findings are not medically actionable or are inconclusive (Delanne et al., 2019). There is also concern around the psychological implications of returning secondary findings (Wynn et al., 2018). Return of a child's results is even less clear, and is complicated by the fact that some results, such as those regarding an adult-onset condition, may not be medically actionable in the present, but may become so in the future (Richer & Laberge, 2019). While it may be argued that informing that child about their disease risk is important, there is debate as to whether informing that child or their parents *now* is essential (Richer & Laberge, 2019).

Cascade genetic testing and health service use stemming from the genetic testing of a child therefore has important practical and methodological implications for HTA. However, it is a relatively new practice and further research is required to understand the phenomenon in-and-of-itself and to explore how the challenges it presents may be surmounted.

1.5 Rationale and Aims

The previous sections provide a partial picture of the implications of cascade testing and screening in the CMP patient population, as well as some of the implications of cascade genetic testing and screening on how HTAs are conducted (**Figures 1** – **3**). The care and cost consequences associated with cascade investigations spurred by a genetic diagnosis of CMP in a child remain poorly understood. No publications have been found that quantify the cardiology and other health service referrals, phenotypic screening, treatment, and surveillance in parents and other family members of children with CMP. This is a significant gap, especially given the consensus that family members at risk for CMP should engage in cascade investigations (Ackerman et al., 2011; Elliott, 2015; Elliott et al., 2014; Ezekowitz et al., 2017; Hershberger et al., 2018; Ingles et al., 2012; Monserrat, 2018; Te Rijdt et al., 2014; Ware, 2017). At SickKids, cascade testing and screening are routinely offered to the families of children diagnosed with CMP, with little consideration of the downstream impact on the health care system. This impact will only grow with the increasing implementation of technologies such as WES and WGS in paediatric cardiology.

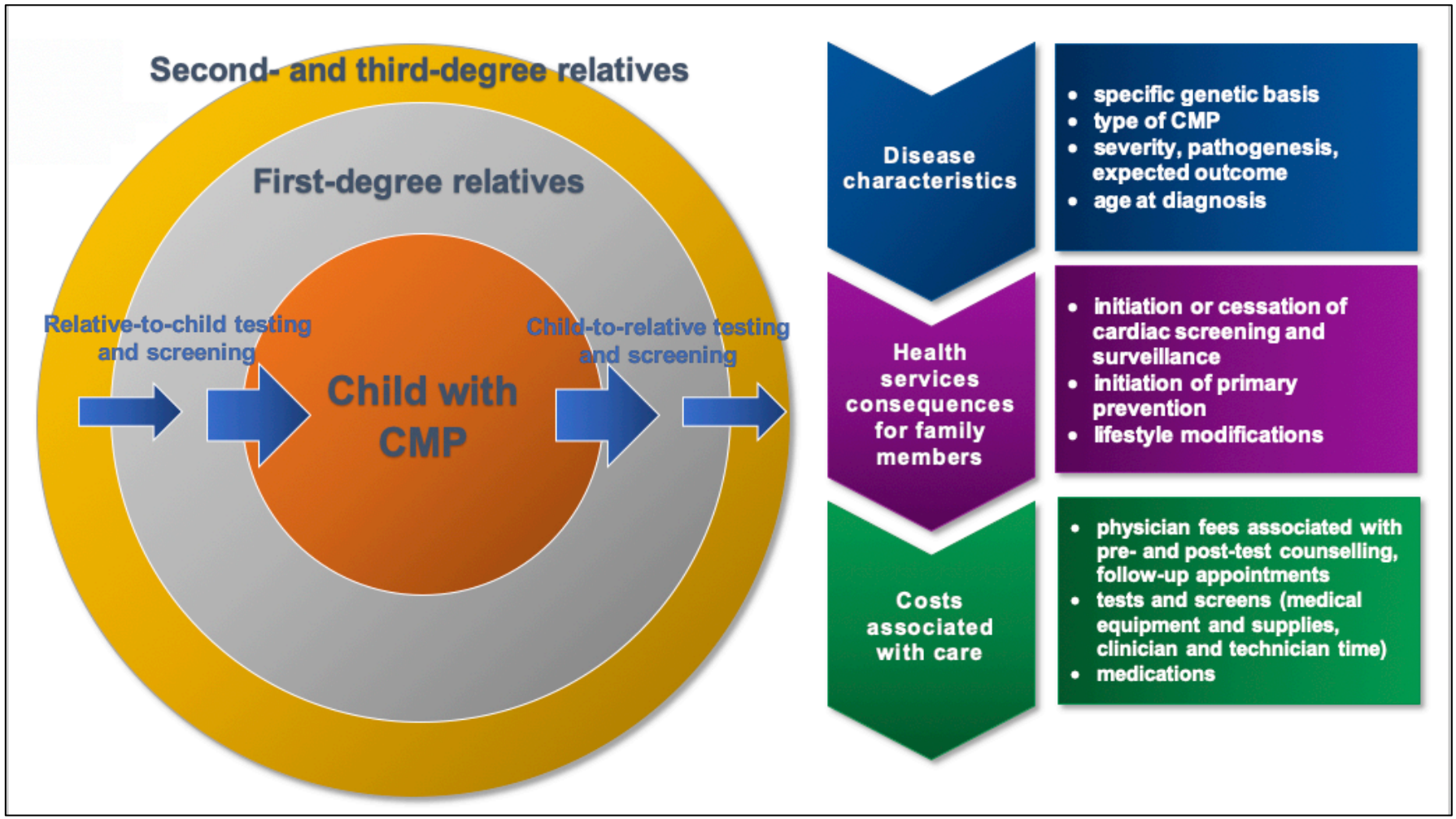

Figure 1: The cascade genetic testing and clinical screening process, implications for health service use among family members, and costs associated with care.

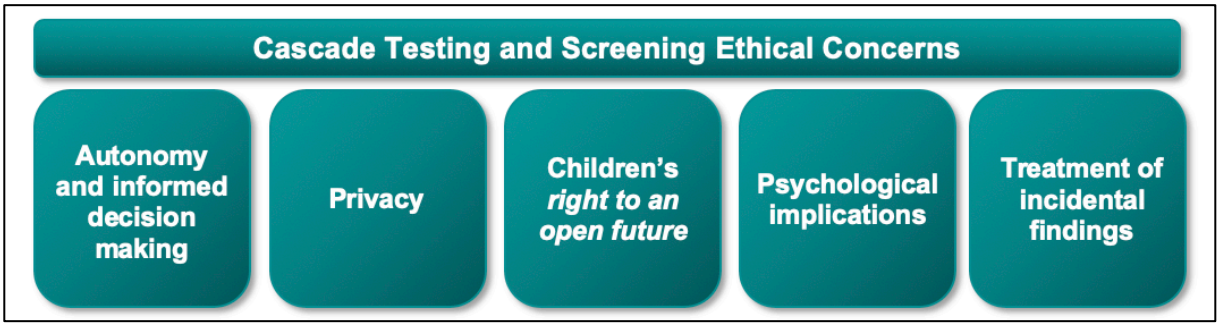

Figure 2: Ethical concerns associated with cascade testing and clinical screening important for consideration in ethical analysis of technologies that trigger health service cascades.

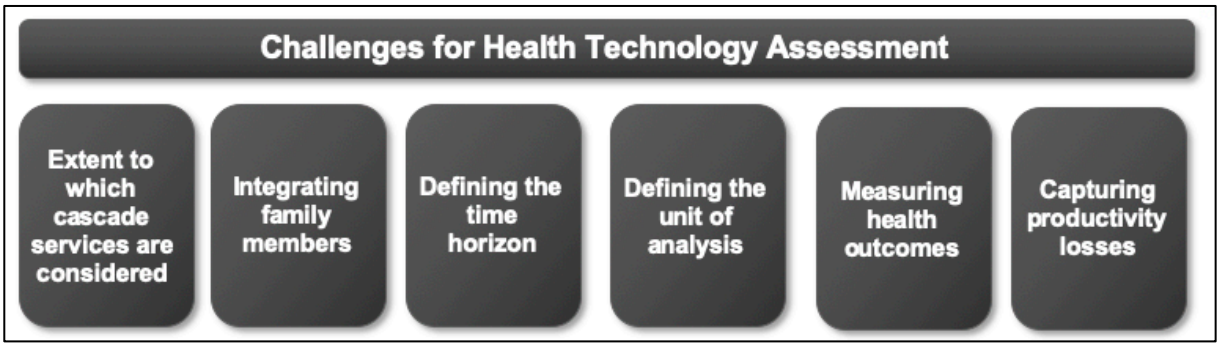

Figure 3: Challenges to HTA methodology associated with incorporation of cascade health service use in analyses.

Understanding the pattern of care resulting from cascade genetic testing for paediatric CMP as well as the economic implications of offering and/or consuming cascade health resources is important in the context of health policy development. Decision makers need to be aware of the manner in which clinicians offer cascade genetic testing, how these offers are accepted or refused, and the costs of the required cascade health services in order to: effectively modify or eliminate outdated policies; make new policies that account for rapidly evolving technology to protect and enhance the quality of patient care; and to make funding decisions in such a way that policies regarding cascade genetic testing are sustainable. In addition to this, having an understanding of how clinicians offer cascade testing is also important for individuals who assess and update clinical practice guidelines, as it provides them with a stronger foundation of evidence on which to base their recommendations for standard practice. This research is also required as a first step to indicate how cascade testing and health service use in multiple family members might be incorporated in future HTAs of genetic testing.

The overall purpose of this thesis is therefore to examine the patterns and costs of cascade health services offered to the family members of paediatric CMP patients resulting from conventional genetic testing in the child with CMP. The specific research objectives are to:

1. Describe and compare patterns of offered cascade health services in family members as a function of the result of genetic testing in the child with CMP.

2. Describe and compare the patterns of offered cascade health services in family members as a function of the amount of genetic testing in the child with CMP.

3. Describe and compare patterns of offered cascade health services in family members as a function of the type of genetic testing in the child with CMP.

4. Calculate the costs of offered cascade health services in family members of children with CMP.

Chapter 2:
Methods

This chapter begins with an outline of the methodology for a scoping literature review exploring the work-to-date around cascade testing and clinical screening prompted by the genetic testing of a child for any disease. After this, the methods for an analysis of the care and cost consequences associated with cascade testing and screening in the families of children with CMP are presented. A description of the study design is provided first, followed by a discussion of the study setting, study sample, and data collection process. The methods for both a primary and secondary analysis are subsequently described, in which two different approaches for determining the pattern of offered cascade genetic testing and screening are outlined. The methods used to approximate the cost of offered cascade health services are then presented. The assumptions made about the data for the purpose of the analyses follow. The chapter ends with a description of the uncertainty analyses that were performed and a brief section on the research ethics associated with this study.

2.1 Scoping Literature Review

Prior to analysis of data related to cascade testing among children with CMP, empiric research related to the pattern and costs of cascade health service use by family members of children with any condition diagnosed through genetic testing was characterized through a scoping literature review. Scoping reviews "aim to map *rapidly* the key concepts underpinning a research area and the main sources and types of evidence available, and can be undertaken as stand-alone projects in their own right, especially where an area ... has not been reviewed comprehensively before," (Mays et al., 2001). Given that the downstream care and cost consequences of cascade testing and screening stemming from a paediatric proband are new areas of study that have not yet been widely explored, this type of review was most appropriate. The review was guided by the following research questions: *What is the rate and pattern of uptake of cascade testing or screening of family members of paediatric patients who have a genetically diagnosed condition? What are the costs and downstream health services associated with this type of cascade testing and screening?*

2.1.1 Search Strategy and Eligibility

Ovid Medline and Embase were searched for studies published from January 1, 2000 to January 8, 2020 using keywords, MeSH terms, and Emtree subject headings including: genetic testing, high-throughput nucleotide sequencing, gene sequencing, chromosome disorders, genetic predisposition to disease, chromosomal anomaly, paediatric proband, paediatric index patient, carrier screening, cascade testing, and familial mutation analysis (FMA). The powerful microarray hybridization methods used in genetic testing were developed during the 1990's (Durmaz et al., 2015) and the first NGS technologies became available in 2005 (van Dijk et al., 2014), so there was confidence that limiting the search to articles published on or after January 1, 2000 would capture all relevant literature. The search strategy is provided in **Appendix I**. The electronic search was supplemented with hand-searching, including checking the reference lists of eligible publications for additional studies relevant to the review.

Included publications were English-language papers reporting primary quantitative empirical research findings regarding the uptake, costs, downstream consequences/health service use, and cost-effectiveness of cascade testing or screening of family members of genetically diagnosed paediatric patients, even if assessing cascade testing was not the primary aim of the study. Studies were included if the index cases were diagnosed using genetic testing. A genetic diagnosis could have been achieved through any conventional genetic testing method, or through WES or WGS. Studies in which the reported index case or proband population consisted of both paediatric *and* adult patients were also included, as were studies with a hypothetical rather than real cohort of patients. The search was not limited based on the location of the studies. Only published studies (i.e., no theses) were included. The quantitative portion of mixed methods studies was included. Case reports and case series were included. Studies not in English, animal and *in vitro* studies, qualitative studies, editorials or commentaries, and studies not presenting any primary data were excluded. Studies addressing the knowledge or attitudes of relatives towards cascade testing or screening, as well as those addressing topics other than cascade testing or screening were excluded. Publications that did not include paediatric patients as the probands or those that did not specify their index case or proband population were excluded. Studies in which all paediatric index cases were clinically rather than genetically diagnosed, or in which the method of diagnosis was unspecified, were also excluded. The inclusion and exclusion criteria are summarized in **Table 3**.

Table 3: Inclusion and exclusion criteria for scoping literature review around cascade testing and screening.

INCLUSION CRITERIA	EXCLUSION CRITERIA
• English language full-text publications • Studies published between January 1, 2000 and January 8, 2020 • Primary quantitative research (including the quantitative portion of mixed methods studies) • Published work (i.e., no theses), including case reports and case series • Studies addressing the uptake, costs, and implications of cascade testing and screening of relatives of paediatric patients • Studies with paediatric or mixed paediatric and adult index case/proband populations • Studies with genetically diagnosed index case/proband populations	• Publications not in English • Studies not presenting primary data • Qualitative studies • Editorials or commentaries • Animal or *in vitro* studies • Studies addressing family members' knowledge of or attitudes towards cascade testing or screening • Studies addressing topics other than cascade testing or screening • Studies with adult or unspecified index case/proband populations • Studies with index case/proband populations diagnosed by methods other than genetic testing, or in which the method of diagnosis was unspecified

Each title and abstract were reviewed by a single reviewer and for those studies meeting the eligibility criteria, full-text articles were obtained. Full-text articles were also obtained to establish eligibility in cases where the title and abstract alone were insufficient to do so. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram was constructed to depict the flow information through the review in accordance with the PRISMA Statement (Moher et al., 2009). The diagram shows the number of records identified in the search, the number of excluded articles along with the rationale for exclusion, and the final number of studies included.

2.1.2 Data Extraction and Analysis

For all included studies, a data extraction form consisting of bibliographic information, purpose, study design, methodology, participant characteristics, and main findings, was used. This was an iterative process, with the extraction form continually updated as familiarity with the data grew and uncertainty about the nature and extent of data that should be extracted decreased. For quantitative studies, the data source included the results sections of the relevant studies.

The literature was categorized according to the age of the proband population (i.e., paediatric probands only or a combination of paediatric and adult index patients), and the findings of the included papers were summarized. Although a scoping review usually necessitates a formal thematic analysis (Arksey & O'Malley, 2005), this area of research is sufficiently new that a

summary of existing literature is a sufficient and important first step to better understanding the field.

2.1.3 Critical Appraisal of Included Literature

Although scoping literature reviews do not typically include an assessment of the quality of included studies (Arksey & O'Malley, 2005; Grant & Booth, 2009), literature meeting the inclusion criteria was critically appraised using the Scottish Intercollegiate Guidelines Network (SIGN) critical appraisal checklist appropriate to the study design (see **Appendix II**) (Scottish Intercollegiate Guidelines Network (SIGN)). This is the best quality appraisal instrument as identified by CADTH through their Quality Assessment Tools Project (Bai et al., 2012). The quality of included case reports and case series was not appraised, in accordance with the SIGN Algorithm for Classifying Study Design for Questions of Effectiveness (Scottish Intercollegiate Guidelines Network (SIGN)), with the understanding that these types of studies are by definition of much lower quality than empiric observational studies. The quality of studies was reported, with the overall assessment of each publication being reported as *high quality*, *acceptable*, or *low quality*. Because the goal of this review was to provide coverage of all the available literature, no work was excluded on the basis of this critical appraisal.

2.2 Retrospective Cohort Study

A retrospective cohort study was conducted in the families of children with a positive phenotype for any CMP for whom genetic testing was conducted. The study included as index cases paediatric CMP patients who received the standard of care, including conventional genetic tests (i.e., karyotyping, CMA, single gene tests, or multi-gene panels) or WES, and were followed for one year after undergoing genetic testing, as has been described elsewhere (Ungar et al., 2017). Family members of these patients included first-, second, and third-degree relatives. An analysis of the pattern and costs of health services offered to family members within one year of disclosure of the proband's genetic test results was undertaken from the health care payer perspective.

2.2.1 Study Setting and Usual Care

Paediatric cardiac patients receive consultation and care from one of several cardiology clinics within the Division of Cardiology at SickKids. The CMP clinic follows an estimated 500

children annually and provides patients with clinical examinations, cardiac investigations and laboratory tests, genetic counselling, and genetic testing as indicated. All genetic testing is ordered by cardiologists or geneticists, and pre-test genetic counselling is provided as part of the clinic service. Results are reported to the ordering clinician within 10 weeks, at which time the clinician and genetic counsellor advise the patient's family of the results, and discuss the recommended clinical management for the child and the potential need for cascade testing. Results can be positive (a pathogenic or likely pathogenic variant was identified); negative (a benign or likely benign variant was identified); or inconclusive (a VUS was identified).

All post-test genetic counselling around the proband's results occurs in-person with a genetic counsellor, and usually only the patient, their parents, and their siblings (i.e., only first-degree relatives) are present (L. Zahavich, personal communication, 2020). The length of the session depends on whether the proband's test results are positive, inconclusive, or negative, but generally these post-test counselling appointments are 45 minutes, 30 minutes, and 15 minutes long, respectively (L. Zahavich, personal communication, 2020). Typically, if it is decided that cascade genetic testing of family members is required, the proband's post-test counselling session serves simultaneously as the pre-test counselling session for first-degree relatives (L. Zahavich, personal communication, 2020). Second- and third-degree relatives are usually seen by a genetic counsellor separately (L. Zahavich, personal communication, 2020). Cascade genetic test results are generally returned to relatives over the phone, regardless of whether these results are positive, inconclusive, or negative (L. Zahavich, personal communication, 2020). Since relatives receive comprehensive pre-test counselling prior to undergoing cascade genetic testing, the phone appointment for return of their results is usually short (approximately 15 minutes in length). All genetic counselling is provided by a genetic counsellor only (L. Zahavich, personal communication, 2020). A medical geneticist is only involved in cases where the proband's CMP is syndromic (i.e., a component of a metabolic disease) (L. Zahavich, personal communication, 2020), but as will be discussed below, all of the probands included in this study had non-syndromic CMP.

2.2.2 Study Sample

The study sample included the family members of children with a positive phenotype for DCM, HCM, RCM, LVNC, or ARVC for whom a multi-gene panel test or WES was indicated as the

first line test, and for whom well-understood metabolic or infectious diseases were ruled out as the cause of the CMP. All paediatric probands were identified through the Heart Centre Biobank Registry, a research database (REB # 1000011232), and were diagnosed between January 1, 2009 and December 31, 2016. They were included in the study if they met the following inclusion criteria: (i) children with CMP for whom genetic testing was completed; (ii) children aged 18 years or younger; (iii) children who were English-speaking; (iv) children whose post-genetic test clinical consults took place at SickKids; and (v) children for whom informed consent was obtained. Children who were deceased before their genetic test results were disclosed were excluded. Relatives included in this study may have been first-, second-, or third-degree and included, but were not limited to: parents, siblings, grandparents, aunts, uncles, and cousins.

2.2.3 Data Collection

Information about probands' use of health services at SickKids was extracted by the study research coordinator from existing SickKids clinical databases, including electronic patient charts, KidCare, CVIS-Lumedx, and the SickKids data warehouse. Data collection occurred retrospectively through chart extraction and, where necessary, was verified by the proband's HCP. Chart extraction consisted of populating a study-specific Clinical Activity Form (CAF). Data collected about probands relevant to this study included: CMP subtype; the type and amount of genetic testing undergone; the type and amount of clinical testing or screening, specialist referrals, and other interventions undertaken in the proband following the most recent genetic test; whether any relatives were offered cascade genetic testing or screening; and the number and type of family members involved in cascade investigations.

Information about cascade testing and screening in family members was noted in and obtained from the paediatric probands' electronic medical records (EMRs). The medical records of the family members themselves were not available. The portion of the CAF pertaining to cascade health service use is provided in **Appendix III**. Data collected about each relative included: their relationship to the proband; whether recommendations for risk mitigation through cascade testing or screening were made by the consulting clinician for the paediatric proband; and the type of clinical activities offered. Where possible, information as to whether the offer of cascade testing or screening was accepted or declined was also collected. It was assumed that any health services accepted or declined by family members were first offered by a clinician. The extracted

data were compiled in an excel database by the research coordinator for use in the present study. Given the relatively small amount of information about family members that is recorded in the probands' electronic patient charts, these data were limited and subject to a number of assumptions that are discussed below. The results of any cascade testing or screening undergone by family members was out of the scope of this study.

2.2.4 Description of Measures: Offered Health Services

Following disclosure of the proband's genetic test results, clinicians make recommendations related to the mitigation of family member risk as part of the standard of care. These recommendations, or offers, of health services may be accepted or declined. The offers captured by this study were related to either (a) determining family members' level of genetic risk for CMP through genetic testing, or (b) family members risk stratification for SCA, SCD, or other cardiac complications through ECG, echocardiogram, Holter monitoring, or other screening modalities. Recommendations to family members related to mitigating disease progression through prescriptions for preventative medications or through specialist referrals for the purpose of surveillance were not captured.

This study focused on offered, rather than consumed, health services to ensure that the analysis accurately reflects the practice of care, which includes all cascade clinical activities prompted by genetic testing in the proband. An understanding of this practice of care is vital at the level of the decision maker as it is the type, amount, and cost of offered clinical activities that the health care system must be prepared to support. Moreover, data collected for this study captured only the first year following the receipt of proband genetic testing results.

Some probands underwent multiple genetic tests, but it is the most recent test that was considered the index genetic test in this study. It is possible that some of the family members of these probands underwent genetic testing or clinical screening following a genetic test in the index patient, but that this occurred prior to the index test as it has been defined here. Such clinical activities were not considered to be cascade health service use in the context of this study and were not included in the offered health services with which this thesis is concerned.

2.2.5 Analysis

A descriptive analysis of the data collected about probands and their family members was performed in R Studio (R Core Team, 2018). The study sample was described in terms of the proband's age at the time of their index genetic test; their sex; ethnicity; CMP subtype; family size; and the type, degree, and number of relatives who were offered cascade health services. Categorical data was summarized using frequency distributions and continuous data with means and standard deviations. The amount of missing data was quantified and reported.

It was recognized that probands' medical records may only contain partial information about health services offered to their family members. To address this challenge, two analyses were undertaken. In the primary analysis, ideal practice was assumed and clinical practice guidelines were used to determine the type and volume of cascade services offered to relatives. In the secondary analysis, offered cascade health services were quantified based on the empiric data about family members available in probands' records, with the understanding that this was not necessarily an accurate reflection of real-world practice. The results of the two analyses were compared, enabling an assessment of the completeness of proband medical records with respect to health services offered to their families.

2.2.5.1 Primary Analysis: Clinical Practice Guideline-Based

In the primary analysis, it was assumed that for all probands, offers of cascade genetic testing or clinical screening were made to family members in accordance with the clinical practice guidelines associated with the CMP subtype identified or suspected in the child (Hospital for Sick Children, 2013, 2016). For all CMP subtypes, cascade genetic testing is only offered to the family members of genotype-positive probands. Clinical practice guidelines for paediatric DCM state that if a proband is found to have a VUS, parents may be offered cascade genetic testing to determine whether the variant segregates with disease (Hospital for Sick Children, 2016). However, this is done on a case-by-case basis, and an expert cardiologist clarified that recommending cascade genetic testing to the families of genotype-inconclusive probands would still be considered a departure from guideline recommendations (S. Mital, personal communication, 2019). Therefore, for the purposes of this analysis, none of the relatives of children found to possess a VUS were offered genetic testing. Relatives are offered FMA only (rather than, for instance, a multi-gene panel) to determine whether they have the same mutation

as was identified in their associated proband. Cascade clinical screening is offered to all first-degree relatives, including those of index patients who are genotype-negative or genotype-inconclusive, or who have not yet undergone genetic testing. However, the specific screening recommendations change depending on the CMP subtype, as well as on the genotype and phenotype of the family member in question (Hospital for Sick Children, 2013, 2016). The guidelines for cascade clinical screening are summarized in **Table 4**. Three categories of family members are included: relatives who are phenotype-negative and who have an unknown genotype; family members who are phenotype-negative but who have been found to carry a pathogenic mutation associated with CMP; and relatives who are phenotype-positive but are asymptomatic. For the last group, the same set of guidelines are applied regardless of an individual's genotype. The term *phenotype-negative* is used here to describe relatives who have not undergone any clinical assessment but who do not have history of cardiac dysfunction and are therefore assumed to not be presenting with signs or symptoms of CMP.

Ongoing clinical surveillance is *not* required in family members who are found to be genotype-negative. However, the test results of any cascade genetic test offered to relatives were out of the scope of the present study. Moreover, information about relatives' physical health was not available. Therefore, in the reference case, it was assumed that all family members were phenotype-negative and had an unknown genotype.

Table 4: Clinical practice guidelines for cascade clinical screening in family members of children with CMP.

CMP SUBTYPE	CASCADE CLINICAL SCREENING RECOMMENDATIONS BASED ON RELATIVE PHENOTYPE AND GENOTYPE			GUIDELINE/ SOURCE
	PHENOTYPE-NEGATIVE, GENOTYPE-UNKNOWN	**PHENOTYPE-NEGATIVE, GENOTYPE-POSITIVE**	**PHENOTYPE-POSITIVE, ASYMPTOMATIC (ANY GENOTYPE)**	

DCM	Not described in guidelines.
	Assumption, based on guidelines for the relatives of paediatric HCM and ARVC patients, as well as on expert opinion (S. Mital, personal communication, 2019):
	• **ECG and echocardiogram**
	  • Once every 3-5 years.
		• **ECG and echocardiogram**
		  • Once per year for relatives aged 0-18 years.
		  • Once every 1-2 years in cases of malignant family history or if relative is participating in competitive sports.
			• **ECG and echocardiogram**
			  • Once per year and as needed if change in clinical status.
			• **24-hour Holter monitor**
			  • Once per year and as needed.
			• **Exercise test**
			  • At diagnosis and once every 2-3 years in clinical stable patients.
			• **Cardiac MRI**
			  • At diagnosis (optional) and once every 3-5 years.
			• Bloodwork including **CBC**, **creatinine**, **lactate**, **BUN**, and **LFTs** as needed.
				SickKids 2016 Paediatric DCM Guidelines (Hospital for Sick Children, 2016).

HCM	• **ECG and echocardiogram**
	  • Once every 3-5 years for relatives aged 18-30 years.
	  • Once every 3 years in cases of malignant family history.
	• Ongoing clinical screening is **not** indicated in genotype-negative relatives.
		• **ECG and echocardiogram**
		  • Once per year for relatives aged 0-18 years.
		  • Once every 3 years for relatives aged 18-30 years.
		  • Once every 5 years for relatives aged 30+.
		• **24-hour Holter monitor**
		  • Once every 2 years.
		• **Exercise test**
		  • If ECG or echocardiogram abnormalities develop.
			• **ECG and echocardiogram**
			  • Once per year and as needed.
			• **24-hour Holter monitor**
			  • Once per year and as needed.
			• **Exercise test**
			  • Once every 2 years.
			• **Exercise (stress) echocardiogram**
			  • At diagnosis (optional).
			• **Cardiac MRI**
			  • At diagnosis (optional).
				SickKids 2013 Paediatric HCM Guidelines (Hospital for Sick Children, 2013).

RCM	Not described in guidelines.
	Assumption, based on guidelines for the relatives of paediatric HCM and
		• **ECG and echocardiogram**
		  • Once per year for relatives aged 0-18 years.
			• **ECG and echocardiogram**
			  • Once per year and as needed if change in clinical status.
				Same guidelines as for DCM (Hospital for Sick

	ARVC patients, as well as on expert opinion (S. Mital, personal communication, 2019):
	• **ECG and echocardiogram**
	  • Once every 3-5 years.
		• Once every 1-2 years in cases of malignant family history or if relative is participating in competitive sports.	• **24-hour Holter monitor**
			  • Once per year and as needed.
			• **Exercise test**
			  • At diagnosis and once every 2-3 years in clinical stable patients.
			• **Cardiac MRI**
			  • At diagnosis (optional) and once every 3-5 years.
			• Bloodwork including **CBC**, **creatinine**, **lactate**, **BUN**, and **LFTs** as needed.
				Children, 2016), based on (S. Mital, personal communication, 2019).

LVNC	Not described in guidelines.
	Assumption, based on guidelines for the relatives of paediatric HCM and ARVC patients, as well as on expert opinion (S. Mital, personal communication, 2019):
	• **ECG and echocardiogram**
	  • Once every 3-5 years.
		• **ECG and echocardiogram**
		  • Once per year for relatives aged 0-18 years.
		  • Once every 1-2 years in cases of malignant family history or if relative is participating in competitive sports.
			• **ECG and echocardiogram**
			  • Once per year and as needed if change in clinical status.
			• **24-hour Holter monitor**
			  • Once per year and as needed.
			• **Exercise test**
			  • At diagnosis and once every 2-3 years in clinical stable patients.
			• **Cardiac MRI**
			  • At diagnosis (optional) and once every 3-5 years.
			• Bloodwork including **CBC**, **creatinine**, **lactate**, **BUN**, and **LFTs** as needed.
				Same guidelines as for DCM (Hospital for Sick Children, 2016), based on (S. Mital, personal communication, 2019).

ARVC	• **ECG and echocardiogram**[a]
	  • Once every 3-5 years.
	• **24-hour Holter monitor**
	  • Once every 3-5 years.
		• **ECG and echocardiogram**
		  • Once per year and as needed.
		• **24-hour Holter monitor**
		  • Once per year and as needed.
			Not described.
			Assumption, based on guidelines for the other CMP subtypes:
			• **ECG and echocardiogram**
			  • Once per year and as needed if change in clinical status.
			• **24-hour Holter monitor**
			  • Once per year and as needed.
			• **Exercise test**
				(S. Mital, personal communication, 2019).

			• At diagnosis and once every 2-3 years in clinical stable patients. • **Cardiac MRI** • At diagnosis (optional) and once every 3-5 years. • Bloodwork including **CBC**, **creatinine**, **lactate**, **BUN**, and **LFTs** as needed.	

ARVC: arrhythmogenic right ventricular cardiomyopathy
BUN: blood urea nitrogen
CBC: complete blood count
DCM: dilated cardiomyopathy
ECG: electrocardiogram
HCM: hypertrophic cardiomyopathy
LFTs: liver function tests
LVNC: left ventricular non-compaction cardiomyopathy
MRI: magnetic resonance imaging
RCM: restrictive cardiomyopathy

[a]These are the guidelines for phenotype-negative, genotype-negative relatives. It was assumed that the standard practice is the same for genotype-unknown family members.

Based on these guidelines (Hospital for Sick Children, 2013, 2016), for the purpose of this primary analysis, only relatives of genotype-positive probands were offered cascade genetic testing within the study period. All relatives of probands with DCM, HCM, RCM, and LVNC were offered one ECG and one echocardiogram within the study period (Hospital for Sick Children, 2013). All relatives of probands with ARVC were offered one ECG, one echocardiogram, and one 24-hour Holter monitor within the study period (Hospital for Sick Children, 2016).

2.2.5.1.1 Pattern of Cascade Health Services Offered

The first aim of this thesis was to describe and compare the pattern of cascade health services offered to family members as a function of the result of genetic testing in the child with CMP. The index case patients were stratified according to their genetic testing results (i.e., positive, inconclusive, or negative). As recommendations for cascade clinical screening differed according to the type of CMP identified in the child, the index case patients were further stratified according to CMP subtype.

An overall and relation-specific pattern of offered health services among relatives was determined, with the proband as the unit of analysis, for each proband subgroup. For the overall pattern of offered services, the average number of relatives per proband who should have been offered cascade testing or screening based on the guidelines was determined. The average number of each type of resource that should have been offered per family over the course of the one-year study period was then established. These numbers were compared between subgroups. For the relation-specific pattern of offered cascade health services, the average number of *each type* of family member (i.e., mother, father, sibling, etc.) per proband who guidelines indicate should have been offered cascade testing or screening was determined. The average number of each type of resource that should have been offered to each type of family member throughout the one-year study period was then established. As before, the results for each group of probands were compared with one another. Parametric or non-parametric statistical comparisons were made between groups if statistical power was sufficient. Otherwise, comparisons were reported qualitatively.

The second and third aims of this thesis were to describe and compare the pattern of cascade health services offered to relatives as a function of the amount and type, respectively, of genetic testing in the child with CMP. These aims were not addressed in the primary guideline-based analysis because the offers of cascade testing and screening outlined in the guidelines are independent of these variables.

2.2.5.1.2 Costs of Cascade Health Services Offered

The fourth aim of this thesis was to calculate the costs of offered cascade health services in the family members of children with CMP. All health resources offered to relatives were assigned to the proband as the unit of analysis. The cost per proband of offered cascade health services was calculated by multiplying the volume of each resource over the one-year study period by its unit price. **Table 5** shows the unit price and offered resource use for cost items included in the primary, guideline-based analysis. Cost categories taken into consideration included genetic diagnostic tests and clinical screening procedures or services. The cost associated with the proband's post-test genetic counselling session was not included in analysis because this appointment occurs regardless of whether cascade genetic testing is offered to family members and is therefore not strictly part of the cascade of health services with which this thesis is concerned. The cost associated with return of relatives' cascade genetic testing results and post-test counselling session (i.e., one 15-minute telephone session per family) was included. When determining the cost of offered health services for each relative individually, it was assumed that these 15 minutes were divided equally among family members. For example, if a proband had one mother, one father, and one sibling who underwent cascade genetic testing, then five minutes of the genetic counsellor's time would be allocated to each family member.

Current prices of resources were used. For example, if a gene panel was performed in 2016, the price of that panel in 2019 was applied. All costs were reported in 2019 Canadian dollars. After the cost for each proband was determined, an average cost per patient for the entire subset of index cases was calculated. It was not possible to adjust the mean cost per patient for sociodemographic factors because that information was not available.

Table 5: Unit price and resource use of cost items included in primary analysis.

COST ITEM	UNIT PRICE ($)	SOURCE	RESOURCE USE	SOURCE
CASCADE GENETIC TESTING				
GENETIC TESTS				
Familial mutation analysis (FMA)	337.18[a]	(O. Jarinova, personal communication, 2019; J. Jegathisawaran, personal communication, 2019)	Per test; 1 test per relative	
RETURN OF RESULTS AND POST-TEST COUNSELLING OF RELATIVES				
Genetic counsellor	14.27[b]	(J. Jegathisawaran, personal communication, 2019)	1 session of 15 minutes per family	(L. Zahavich, personal communication, 2020)
CASCADE CLINICAL SCREENING				
Electrocardiogram (ECG) (12-lead)	11.05	(Ministry of Health, 2019)	Per screen; 1 screen per relative	
Technical component	6.60	(Ministry of Health, 2019) SoB fee code: G310		
Professional component	4.45	(Ministry of Health, 2019) SoB fee code: G313		
Echocardiogram	208.80	(Ministry of Health, 2019)	Peer screen; 1 screen per relative	
Technical component	112.60	(Ministry of Health, 2019) SoB fee code: G570		
Professional component	96.20	(Ministry of Health, 2019) SoB fee code: G571		
Holter monitor (level 1, 24 hours)	104.50	(Ministry of Health, 2019)	Per screen; 1 screen per relative	
Technical component (recording)	23.90	(Ministry of Health, 2019) SoB fee code: G651		
Technical component (scanning)	32.70	(Ministry of Health, 2019) SoB fee code: G652		
Professional component	47.90	(Ministry of Health, 2019) SoB fee code: G650		

SoB: Schedule of Benefits: Physician Services Under the Health Insurance Act

[a]Based on the equation used by CHEO to estimate the unit price of FMA using hourly wages at SickKids.
[b]Unit price per 15-minute interval, based on hourly wages at SickKids.

The unit price of FMA was obtained from the CHEO Genetics Diagnostic Laboratory because the majority of patient samples taken at SickKids for the purpose of genetic testing for CMP are analyzed at CHEO. A minority are sent to Invitae Corporation in the United States, a private sector genetic testing facility. The costs associated with other procedures and laboratory tests were taken from the Ontario Health Insurance Plan (OHIP) physician Schedule of Benefits (SoB), as well as the fee schedules of other allied health professionals. Genetic counsellor, laboratory technologist, and laboratory scientist fees were based on average hourly rates at SickKids.

This analysis was conducted from the provincial health care payer perspective in accordance with Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines (CADTH, 2017). Cascade health resources that should be offered to family members of children with CMP based on clinical practice guidelines within one year of disclosure of the proband's genetic test results were captured. This analysis was concerned with cascade testing and screening that directly resulted from the genetic testing of index case patients; any recommendations for intervention for relatives based on such testing would be made sooner, rather than later, following the return of results. A one-year time horizon was therefore sufficient to ensure that the relevant offered clinical activities were captured. Given the one-year time horizon, no discounting of costs was performed, which is in keeping with CADTH guidelines (CADTH, 2017).

2.2.5.1.3 Assumptions

It was assumed that for all probands, cascade genetic testing or clinical screening offers were made to family members in complete accordance with the clinical practice guidelines associated with the CMP subtype identified or suspected in the child (Hospital for Sick Children, 2013, 2016; Mital, 2019). When guidelines recommended that family members undergo clinical screening once every few years, it was assumed that the first time a relative was screened was within one year of disclosure of the proband's genetic test results. It was further assumed that all cascade genetic testing occurred with the appropriate pre- and post-test genetic counselling. Specifically, pre-test counselling for first-degree relatives occurred during a 45-minute, in-person session with a genetic counsellor, while post-test counselling consisted of a 15-minute discussion over the phone with a genetic counsellor. It was assumed that all post-test sessions were the same

length, regardless of whether relatives received positive, inconclusive, or negative results. These assumptions were made based on expert opinion (L. Zahavich, personal communication, 2020). Finally, it was assumed that all cascade genetic testing took place at CHEO.

Clinical practice guidelines were not explicit about the type of ECG and 24-hour Holter monitoring that should be offered to family members (Hospital for Sick Children, 2013, 2016). For the reference case analysis, it was therefore assumed that a 12-lead ECG was offered, and where Holter monitoring was indicated, a Level 1 24-hour Holter monitor was offered.

In some cases, clinical practice guidelines made reference to a "malignant family history" (Hospital for Sick Children, 2016). It was assumed that for the population of patients included in this study, no such family history existed. Detailed demographic information about probands' relatives was not available, but because all included index patients were children, it was assumed that any siblings captured in analysis were also aged younger than 18 years.

2.2.5.2 Secondary Analysis: Empiric Data-Based

A secondary, data-driven empiric analysis was also conducted, in which the pattern of cascade health services offered to family members was determined based on the data available in proband medical records. Because only a limited amount of information about relatives is noted in the index patient's records, the pattern of cascade testing and screening described in this secondary analysis may not be an accurate reflection of the standard of care and of all recommendations that were made. This secondary analysis was conducted from the health care payer perspective as well.

2.2.5.2.1 Pattern of Cascade Health Services Offered

To address the first aim of this thesis (i.e., to describe and compare the pattern of cascade health services offered to family members as a function of the result of genetic testing in the child with CMP), the same methodology as for the primary analysis was applied. An additional step consisted of first determining the proportion of index patients for whom recommendations of cascade testing or screening of relatives was noted. The pattern of cascade health service use was determined based on available patient data rather than clinical practice guidelines. Any health services declined by family members were considered offered and were captured in analysis. The number of family members who declined the offer of cascade investigations was reported.

The second and third aims of this thesis were to describe and compare the pattern of cascade health services offered to relatives as a function of the amount and type of genetic testing in the child with CMP, respectively. However, the majority of probands underwent only one genetic test, and all probands received a multi-gene panel rather than a single gene test. Therefore, there were insufficient data to conduct these two analyses.

2.2.5.2.2 Costs of Cascade Health Services Offered

The fourth aim of this thesis was to calculate the costs of cascade health services offered to the family members of children with CMP, however this aim was not addressed in the secondary analysis. As has been previously acknowledged, the data available in proband medical records about family members were limited, and therefore the costs of offered cascade health services calculated based on those data would be associated with a high degree of uncertainty. Moreover, any future work, such as CEAs, would incorporate the costs of cascade health services based on high quality empiric data or recommendations outlined in clinical practice guidelines (i.e., the results of the primary analysis).

2.2.5.2.3 Assumptions

The data available about cascade health service use in the family members of children with CMP were limited and, as a result, were subject to a number of assumptions. It was assumed than any cascade health resources accepted or declined by family members were first offered by a clinician. As in the primary analysis, it was assumed that all cascade genetic testing offered by physicians at SickKids took place at CHEO, and occurred with the appropriate pre- and post-test genetic counselling as previously described. It was also assumed that any genetic testing undergone by family members was an FMA (rather than a multi-gene panel, for example), unless it was explicitly stated otherwise in the index patient's records. There were no details noted in probands' medical records as to the type of ECG and Holter monitoring that were offered; it was assumed that family members were offered a 12-lead ECG and Level 1 24-hour Holter monitoring. The number of each type of screen that was offered was not provided either, so it was assumed that screen was offered or undergone only once within the study period.

2.2.6 Uncertainty Analyses

Assumptions made about the data introduced uncertainty into analysis. A number of one-way sensitivity and scenario analyses were conducted to assess the effect of this uncertainty on the costs of cascade health services offered to the families of paediatric CMP patients calculated in the primary analysis.

2.2.6.1 One-Way Sensitivity Analyses

In one-way sensitivity analysis, the value of a single variable was altered and the impact that each change had on the results was examined (Drummond et al., 2015). One variable that was altered was the cost of genetic tests offered to family members. The unit price of FMA was estimated using an equation from CHEO that incorporated hourly wages for laboratory technologists, genetic counsellors, and laboratory scientists at SickKids (J. Jegathisawaran, personal communication, 2019). However, different institutions may have different hourly wages associated with these positions or they may have a different method of pricing FMA altogether. One-way sensitivity analyses were performed on this variable in recognition that the unit price of the test may change depending on clinical setting. Several assumptions in the primary analysis were also tested in one-way sensitivity analyses: the number and length of genetic counselling appointments attended by family members, and the type of Holter monitoring relatives underwent (e.g. a one-way sensitivity analysis where family members were offered a Level 2 24-hour Holter monitor rather than a Level 1 24-hour Holter monitor). In the reference case, it was assumed that all relatives were offered a 12-lead ECG. The alternative to this would have been a 15-lead ECG, however these are not listed in the physician SoB (Ministry of Health, 2019). It was therefore assumed that the price of a 15-lead ECG is the same as that of a 12-lead ECG, and no one-way sensitivity analysis was performed on this variable. More detailed information is provided in **Table 6**.

No sensitivity analyses were performed for the secondary analysis.

Table 6: One-way sensitivity analyses performed to assess uncertainty in the primary analysis.

PARAMETER	REFERENCE CASE	ONE-WAY SENSITIVITY ANALYSIS	SOURCE FOR VALUE(S) USED IN SENSITIVITY ANALYSIS
Cost of FMA	$337.18[a]	$252.89 – $421.48	Assumption: ± 25% of reference case
Number of genetic counselling appointments attended by family members	One post-test counselling session for all first-degree relatives, 15 minutes in length. $14.27[b] per family	One pre-test counselling session for all first-degree relatives (separate from proband post-test counselling session), 30 minutes in length, *and* one post-test counselling session for all first-degree relatives, 15 minutes in length. $14.27[b] x 3 = $42.81 per family	(L. Zahavich, personal communication, 2020)
Type of Holter monitor	Level 1, 24 hours $104.50 per screen	Level 2, 24 hours $72.50 per screen	(Ministry of Health, 2019) SoB fee codes: G654 (technical component, recording, $22.80), G655 (technical component, scanning, $15.60); and G653 (professional component, $34.10)

FMA: familial mutation analysis
SoB: Schedule of Benefits: Physician Services Under the Health Insurance Act

[a]Based on the equation used by CHEO to estimate the unit price of FMA and on hourly wages at SickKids.
[b]Unit price per 15-minute interval, based on hourly wages at SickKids.

2.2.6.2 Scenario Analyses

Several scenario analyses were also performed in the context of the primary analysis. In the reference case, it was assumed that relatives were phenotype-negative and of an unknown genotype, and the appropriate cascade clinical screening guidelines were used to determine the pattern and cost of health services that should have been offered to these individuals. Multiple scenario analyses were undertaken such that first it was assumed that all relatives were phenotype-negative, however those who would have been offered genetic testing (i.e., the family members of probands with a positive test result) were genotype-positive. In this scenario analysis, the family members of probands with an inconclusive or negative test result were still considered phenotype-negative and genotype-unknown, the same as in the reference case. The guidelines for HCM for relatives who are phenotype-negative and genotype-positive indicate that an exercise test should be performed if ECG and echocardiogram abnormalities develop. It was assumed that when family members first receive screening no such abnormalities exist.

For the second scenario analysis, it was assumed that all relatives were phenotype-positive, and could be genotype-positive, inconclusive, or negative (the same clinical practice guidelines apply in all three cases). Where clinical practice guidelines indicated that an exercise test should be performed in relatives, it was assumed that a basic exercise test (i.e., no flow volume loop, spirometry, or ECG monitoring during the test) was conducted. Where guidelines stated that family members should undergo bloodwork, it was assumed that all suggested tests (i.e., complete blood count (CBC), creatinine, lactate, blood urea nitrogen (BUN), and liver function tests (LFTs)) were ordered. All other assumptions and variables were the same as in the reference case. The costs associated with all health services incorporated in the scenario analyses are shown in **Table 7**.

No scenario analyses were performed for the secondary analysis.

Table 7: Unit price and resource use of cost items included in scenario analyses.

COST ITEM	UNIT PRICE ($)	SOURCE	RESOURCE USE	SOURCE
CASCADE GENETIC TESTING				
GENETIC TESTS				
Familial mutation analysis (FMA)	337.18[a]	(O. Jarinova, personal communication, 2019; J. Jegathisawaran, personal communication, 2019)	Per test; 1 test per relative	
RETURN OF RESULTS AND POST-TEST COUNSELLING OF RELATIVES				
Genetic counsellor	14.27[b]	(J. Jegathisawaran, personal communication, 2019)	1 session of 15 minutes per family	(L. Zahavich, personal communication 2020)
CASCADE CLINICAL SCREENING				
Electrocardiogram (ECG) (12-lead)	11.05	(Ministry of Health, 2019)	Per screen; 1 screen per relative	
Technical component	6.60	(Ministry of Health, 2019) SoB fee code: G310		
Professional component	4.45	(Ministry of Health, 2019) SoB fee code: G313		
Echocardiogram	208.80	(Ministry of Health, 2019)	Peer screen; 1 screen per relative	
Technical component	112.60	(Ministry of Health, 2019) SoB fee code: G570		
Professional component	96.20	(Ministry of Health, 2019) SoB fee code: G571		
Stress echocardiogram	238.00	(Ministry of Health, 2019)	Per screen; 1 screen per relative	
Technical component	127.85	(Ministry of Health, 2019) SoB fee code: G582		
Professional component	110.15	(Ministry of Health, 2019) SoB fee code: G583		
Holter monitor (level 1, 24 hours)	104.50	(Ministry of Health, 2019)	Per screen; 1 screen per relative	
Technical component (recording)	23.90	(Ministry of Health, 2019) SoB fee code: G651		
Technical component (scanning)	32.70	(Ministry of Health, 2019) SoB fee code: G652		
Professional component	47.90	(Ministry of Health, 2019) SoB fee code: G650		

Exercise test (graded exercise to maximum tolerance)	113.20	(Ministry of Health, 2019) SoB fee code: J315	Per screen; 1 screen per relative
Technical component	62.45	(Ministry of Health, 2019)	
Professional component	50.75	(Ministry of Health, 2019)	
Cardiac MRI	73.35	(Ministry of Health, 2019) SoB fee code: X441	Per screen; 1 screen per relative
Bloodwork	42.68	(Ministry of Health, 1999)	Per requisition; 1 requisition per relative
Complete blood count (CBC)	8.27	(Ministry of Health, 1999) SoBLS fee code: L393	
Creatinine	2.59	(Ministry of Health, 1999) SoBLS fee code: L065	
Lactate	13.69	(Ministry of Health, 1999) SoBLS fee code: L415	
Blood urea nitrogen (BUN)	2.59	(Ministry of Health, 1999) SoBLS fee code: L251	
Liver function tests (LFTs)	15.54	(Ministry of Health, 1999)	
Bilirubin, total	2.59	(Ministry of Health, 1999) SoBLS fee code: L030	
Alanine transaminase	2.59	(Ministry of Health, 1999) SoBLS fee code: L223	
Aspartate transaminase	2.59	(Ministry of Health, 1999) SoBLS fee code: L222	
Alkaline phosphatase	2.59	(Ministry of Health, 1999) SoBLS fee code: L191	
Albumin	2.59	(Ministry of Health, 1999) SoBLS fee code: L005	
Gamma glutamyl transpeptidase	2.59	(Ministry of Health, 1999) SoBLS fee code: L107	

MRI: magnetic resonance imaging
SoB: Schedule of Benefits: Physician Services Under the Health Insurance Act
SoBLS: Schedule of Benefits for Laboratory Services

[a]Based on the equation used by CHEO to estimate the unit price of FMA and on hourly wages at SickKids.
[b]Unit price per 15-minute interval, based on hourly wages at SickKids.

2.2.7 Research Ethics

This study received ethics approval from the SickKids Research Ethics Board (REB # 1000052596). The study protocol and other associated documentation were also submitted to the University of Toronto for Administrative Ethics Review and received administrative approval.

For all included paediatric probands, a written informed consent was obtained from one of their parents during a new or follow-up visit to a SickKids cardiology clinic.

All study data were de-identified by assigning each participant a six-digit study ID. Prior to analysis, the data were anonymized by replacing this ID with a random code that cannot be linked back to any personal information. Participant anonymity will be maintained by presenting aggregate data in any presentations and publications resulting from this work.

All study files were maintained on a secure, password protected server. These files can be accessed from within SickKids and the Peter Gilgan Centre for Research and Learning (PGCRL), as well as remotely. Study files containing patient data were accessed and/or modified in the online environment only. No files containing patient data were stored on personal computers.

Chapter 3:
Results

This chapter begins with the results of a scoping literature review exploring the work-to-date regarding cascade genetic testing and cascade clinical screening in the families of children with any genetically-diagnosed condition. The publications with a paediatric proband population are summarized first, after which the studies with a combined paediatric and adult index patient population are presented. After the summaries of all included publications, the results of the critical appraisal of included studies are presented. The literature review results are followed by the results of an analysis of the care and cost consequences associated with cascade genetic testing and cascade clinical screening in the families of children with CMP. The primary analysis reference case results are presented first, describing the pattern of offered cascade health services as per clinical practice guidelines and the costs of those services. After this, the results of the secondary analysis are shown, consisting of the pattern of offered cascade health services as noted in the included probands' medical records. Finally, the results of several uncertainty analyses are presented. All uncertainty analyses were conducted on the costs of health services determined in the primary analysis. First, one-way sensitivity analysis results are shown. The chapter ends with the results of two scenario analyses.

3.1 Scoping Literature Review

The literature search yielded 19 publications. There were no duplicate records. Eleven studies proceeded to full-text review. An additional 18 articles not captured in the search were retrieved through hand-searching. In total, 21 studies were eligible for inclusion. **Figure 4** illustrates the PRISMA search process. The included studies are summarized in **Table 8**, including geographic location, disease state, the number and type of participants, and main findings.

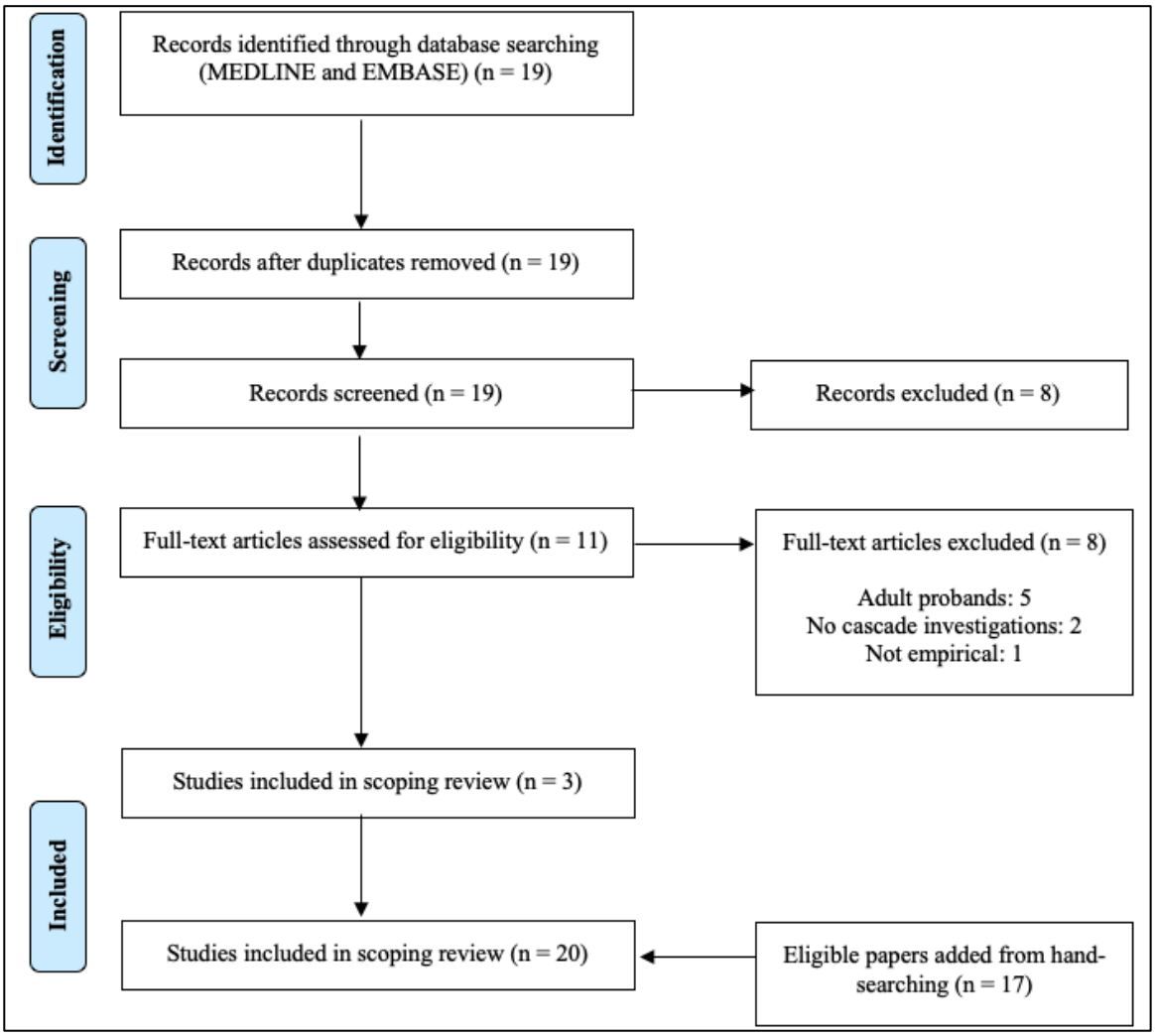

Figure 4: PRISMA flow diagram.

Table 8: Summary of studies included in scoping literature review.

AUTHOR, YEAR	STUDY LOCATION	DISEASE STATE	FOCUS OF STUDY	PROBAND POPULATION	INCLUDED RELATIVES	MAIN FINDINGS/CONCLUSIONS
(Knight et al., 2020)	United States	LQTS and HCM	• Uptake and yield of genetic testing in children with LQTS or HCM • Uptake and yield of cascade genetic testing	• 168 children with LQTS • 147 children with HCM	• 553 relatives	*Probands*: • 92% with LQTS underwent genetic testing; 81% positive • 65% with HCM underwent genetic testing; 60% positive *Relatives*: • 46% clinical screening only; 38% clinical screening and genetic testing; 17% genetic testing only → 1.6 cascade interventions per relative • 40% of all relatives positive • Larger proportion positive among LQTS families than HCM families (42% vs 37%) • Higher yield with combined cascade screening and genetic testing than cascade screening or genetic testing alone
(Stark et al., 2019)	Australia	Rare monogenic disorders	• Clinical and cost impacts of genomic sequencing in infants with suspected monogenic disorders	• Paediatric (number not specified)	• 88 first-degree relatives	*Relatives*: • 90% underwent genetic testing (total cost: AU $28,000) • 2 first-degree relatives changed medical management based on genetic test results (yearly costs: AU $146 and AU $329) • 16 couples accessed reproductive genetic services (total cost: AU $56,904.37)
(Truong et al., 2018)	Vietnam	FH	• Outcomes of cascade genetic testing	• 2 children • 3 adults	• 107 first- and second-degree relatives from 4 families	*Relatives*: • 83% underwent cascade genetic testing; 52% positive

(Wu et al., 2017)	China	FH	• Yield of cascade genetic testing and screening	• 47 consecutive paediatric patients	• 70 parents • 10 siblings • 46 second-degree relatives	*Relatives*: • 100% first-degree positive and 89% second-degree positive → mean yield of cascade genetic testing: 2.8 new FH cases per proband
(Wald et al., 2016)	United Kingdom	FH	• Feasibility of child-to-parent FH screening in primary care settings	• 10,095 children tested; 37 positive for FH mutation; 32 participated	• 64 parents	*Parents*: • 63% positive • For every 1,000 children screened, 8 individuals (4 children and 4 parents) had positive cascade test or screen
(Alfares et al., 2015)	United States	HCM	• Results of genetic testing for non-syndromic HCM in probands and family members	• 2912 paediatric and adult probands referred for HCM genetic testing	• 1209 asymptomatic relatives	*Probands*: • 32% positive (28% paediatric) • 15% inconclusive *Asymptomatic family members of mutation-positive probands*: • 57% negative → no longer needed cardiac evaluations → health systems savings of ~ US $1,000 per relative
(Famula et al., 2015)	United States	Fragile X syndrome	• Identification of affected child through newborn screening • Outcome of cascade genetic testing	• 1 child	• 3 family members (mother and 2 siblings)	*Relatives*: • all 3 relatives found to have full *FMR1* (fragile X-associated) mutation
(Tairaku et al., 2015)	Japan	Severe congenital protein C deficiency	• Outcome of prenatal diagnosis in sibling of affected child	• 1 child	• 1 fetus *in utero*	*Fetus*: • Heterozygous carrier; would not experience symptoms
(McClaren et al., 2013)	Australia	CF	• Uptake of relative carrier testing and factors	• Paediatric (number not specified)	• 225 relatives	*Relatives*: • 37% underwent carrier testing

			influencing uptake			
(Miller et al., 2013)	United States	HCM and DCM	• Uptake of cardiac screening and genetic testing among at-risk relatives • Factors influencing uptake of cascade genetic testing	• 57 paediatric and adult probands (46 HCM and 11 DCM)	• 302 first- and second-degree relatives	*Probands*: • 40/57 positive *Relatives of mutation-positive probands*: • 39% underwent cascade genetic testing • 59% underwent cascade screening • Uptake of cascade services greater in first-degree than second-degree relatives • No statistically significant association between proband's age at diagnosis, family history of SCD, and number of living affected relatives, with uptake of cascade genetic testing • No statistically significant association between proband's genetic testing results and uptake of cascade clinical screening
(Sorensen et al., 2013)	United States	Fragile X syndrome	• Description of pilot project: newborn screening followed by cascade testing	• 3024 newborns screened; 14 positive	• 44 relatives of mutation-positive probands	*Relatives*: • 27/44 (61%) positive
(Moriwaki et al., 2012)	Japan	XP-A	• Experience of 1 centre with prenatal diagnosis of XP-A	• Children from 9 families (number not specified)	• 10 fetuses *in utero*	*Fetuses*: • 2/10 XP confirmed • 6/10 XP carriers • 2/10 unaffected
(Sorensen et al., 2012)	United States	Fragile X syndrome	• Description of fragile X syndrome sibship	• Brother and sister pair; brother was true proband	• First- and second-degree relatives (number not specified)	*Relatives*: • Parents both carriers • Third sibling unaffected • Maternal grandmothers obligate carriers

			• Outcome of cascade genetic testing			
(McClaren et al., 2010)	Australia	CF	• Uptake of cascade genetic testing by non-parent adult relatives	• 30 children	• 59 parents • 716 non-parent first- and second-degree relatives	*Parents*: • 64.4% underwent genetic testing *Non-parent relatives*: • 11.5% underwent genetic testing • 2.7 relatives tested per child • Female relatives 1.61 times more likely than males to undergo cascade testing
(Gorakshakar & Colah, 2009)	India	β-thalassemia	• Uptake and results of cascade screening	• Paediatric, number of affected children not specified • 490 children from "high risk" communities	• 691 relatives from 44 families, including 25 siblings of index cases	*Children from "high risk" communities*: • 96/490 (20%) heterozygotes *Relatives*: • Among siblings of index cases, 10/25 (40%) heterozygotes
(Baig et al., 2008)	Pakistan	β-thalassemia	• Cascade genetic testing results	• 1 child	• 27 relatives	*Relatives*: • 44.4% carriers
(Smith et al., 2007)	Australia	SMA	• Carrier frequency of SMA in Australia	• Paediatric (number not specified)	• 117 parents of affected children • 158 individuals with family history • 146 individuals without family history	• SMA carrier frequency ~1/49
(Cadet et al., 2005)	France	HH	• Yield of cascade testing and screening of at-risk adults identified through	• Neonatal (number not specified)	• 11 families of *C282Y*[a] homozygous infants • 10 families of heterozygous infants	*Families of homozygous infants*: • 5 relatives from 4 families homozygous *Families of heterozygous infants*: • 5 relatives from 2 families homozygous

			neonatal screening of infants		• Number/type of relatives not described	- 6/10 homozygous relatives began treatment; 4/10 homozygous relatives under surveillance
(Leren et al., 2004)	Norway	FH	• Outcome of cascade genetic testing	• 188 paediatric and adult index patients	• 851 relatives, "primarily" first-degree	*Relatives*: • 47.9% positive • 78/146 affected relatives used test results to change medications
(Rudolph et al., 2001)	Germany	X-linked ocular albinism	• Outcomes of genetic testing and clinical screening	• 1 male	• 22 relatives	*Family members*: • 6 male relatives affected • 6 other relatives identified as obligate carriers

CF: *cystic fibrosis*
DCM: *dilated cardiomyopathy*
FH: *familial hypercholesterolaemia*
HCM: *hypertrophic cardiomyopathy*
HH: *hereditary haemochromatosis*
LQTS: *long QT syndrome*
SCD: *sudden cardiac death*
SMA: *spinal muscular atrophy*
XP-A: *xeroderma pigmentosum complementation group A*

[a]HH-conferring mutation

3.1.1 Studies with a Paediatric Proband Population

The uptake, cost, and implications of cascade testing due to genetic testing of a paediatric proband (sometimes referred to as *reverse cascade testing* (Cadet et al., 2005; Truong et al., 2018; Wu et al., 2017)) in the context of any disease state have received very little attention. The majority of studies have focused only on the uptake of testing among probands' family members (Gorakshakar & Colah, 2009; Knight et al., 2020; McClaren et al., 2013; McClaren et al., 2010; Wu et al., 2017) and have not attended to costs. The included studies have been conducted in a number of countries, including Australia (McClaren et al., 2013; McClaren et al., 2010; Stark et al., 2019), China (Wu et al., 2017), India (Gorakshakar & Colah, 2009), the United Kingdom (Wald et al., 2016), and the United States (Famula et al., 2015; Knight et al., 2020; Sorensen et al., 2012; Sorensen et al., 2013), but none are from the Canadian setting.

In 2005, Cadet and colleagues (Cadet et al., 2005) explored the effectiveness of a "reverse cascade screening" strategy to identify adults at risk for hereditary haemochromatosis (HH) in Picardie, France. The authors organized a neonatal HH screening programme, through which 7038 of 8280 babies (85%) born during the study period were screened for *C282Y* and *H63D* (HH-conferring) mutations. Through this programme, 19 infants from 18 families were identified as *C282Y* homozygotes, and 11 of these families (61%) underwent cascade genetic testing. Five individuals from four families were found to also be homozygous for the *C282Y* mutation. The neonatal screening programme also identified 657 infants heterozygous for the *C282Y* mutation. However, uptake of cascade genetic testing was much lower, with only ten families (1.6%) requesting cascade investigations. Five relatives from two of these families were found to be *C282Y* homozygotes. There was no family history of HH in any of the 21 families involved in cascade genetic testing. Ultimately, Cadet *et al*. concluded that cascade testing beginning with a neonate is a much more effective strategy than random screening for the detection of unknown affected individuals in the context of HH.

Smith and colleagues (Smith et al., 2007) conducted cascade testing in 117 parents of children with spinal muscular atrophy (SMA) to estimate the SMA carrier frequency in Australia. In addition to these parents, 158 unaffected individuals with a significant family history of SMA and 146 unaffected individuals with no family history of SMA were also included. Of the tested parents, 94% were found to be carriers. Of the 158 individuals with a family history of SMA,

47% were identified as carriers, and of the 147 individuals without a family history of SMA, 2% were found to be carriers. Overall, Smith *et al*. estimated the SMA carrier frequency in Australia to be approximately 1/49.

Gorakshakar and Colah (Gorakshakar & Colah, 2009) contacted the family members of children with β-thalassemia across Mumbai, India to give them the opportunity to undergo genetic screening for the disease. Six hundred and ninety-one family members of affected children, over at least two generations, underwent genetic testing and 151 (22%) were identified as carriers. The authors determined that targeted cascade screening was five to six times more effective than untargeted community screening approaches at identifying β-thalassemia carriers.

In Australia, uptake of cascade genetic testing among relatives of a newborn diagnosed with cystic fibrosis (CF) has been found to be very low (16.3%) and even lower among non-parent relatives (11.8%) (McClaren et al., 2010). Larger families (i.e., 20 or more members) had lower uptake (15.4%) than smaller families (19.6%), and on average three non-parent relatives had carrier testing for each child. Female relatives were 1.6 times more likely than males to undergo carrier testing, and relatives with a carrier risk of 1 in 2 were five times more likely than those with a carrier risk of 1 in 4 to undergo carrier testing. Uptake of cascade genetic testing differed among relatives: parents, 64.4%; grandparents, 23.4%; aunts or uncles, 38.9%; great-aunts or great-uncles, 5.7%; first cousins, 15.4%; half-siblings, 50%; and half-aunts or half-uncles, 7.7%. Only two half-siblings and 13 half-aunts or uncles were eligible for testing. The majority (88.5%) of non-parent relatives eligible for carrier testing did *not* accept the offer to test. The median time taken for a relative to undergo testing following the affected child's birth was 4.8 months for non-parent relatives, but some relatives were still undergoing testing eight years after the child was diagnosed. A follow-up study with 225 parents and relatives of these children revealed that the most common reasons non-parent relatives did not pursue cascade testing was because they had already had their children; they had simply never thought about cascade testing; there was no immediate need to undergo testing; or they had never been offered testing (McClaren et al., 2013).

There has also been a publication describing the experience of one Japanese centre performing prenatal diagnosis for xeroderma pigmentosum complementation group A (XP-A) in families with an affected child (Moriwaki et al., 2012). While this article focused more on the laboratory

techniques of testing, the authors did report the prenatal diagnosis results: of ten fetuses, two were found to be affected, six were identified as carriers, and two were unaffected.

Wald et al. (Wald et al., 2016) tested over ten thousand British children between one and two years of age for familial hypercholesterolaemia (FH). Children had positive screening results if they either tested positive for a genetic mutation or if they still had elevated cholesterol three months after initial testing (Wald et al., 2016). The parents of children with positive screens were also tested for mutations associated with FH, and a parent had a positive result if he or she had the same genetic mutation as their child, or if they had a higher cholesterol level than the other parent. Of the 10,095 included children, 37 (0.37%) were genetically diagnosed with FH. Both parents of 32 of these children underwent clinical screening and genetic testing. The majority of parents who tested positive for FH but were not yet receiving statins began treatment based on their results. The early identification and treatment of affected relatives was highlighted as one of the benefits of identifying children with FH at an early age. The authors briefly commented on the costs of DNA sequencing, noting that costs have decreased and that they would be even lower if sequencing was performed on a large scale.

Another study was performed in the context of FH, this time in Beijing, China (Wu et al., 2017). The parents, siblings, and second-degree relatives (aunts, uncles, and cousins) of 47 children with genetically diagnosed FH underwent cascade genetic testing. FH was genetically diagnosed in 12 of the tested relatives (a mean of 2.8 new cases of FH per proband), but the proportion of cases identified in parents compared with second-degree relatives was not reported.

More recently in 2019, Stark *et al*. (Stark et al., 2019) investigated the longer-term clinical and health economic impacts of WES for rare diseases in a cohort of 80 Australian infants with suspected monogenic disorders. Among other things, they were interested in family outcomes, specifically the uptake and cost of cascade testing among the first-degree relatives (parents and siblings) of the included infants; the cost and impact of any changes in the medical management of the children's first-degree relatives based on the results from their cascade genetic testing; and the use of reproductive genetic services and the reproductive outcomes of the first-degree relatives of the infants followed in this study. They found that, of 88 eligible first-degree relatives, 79 (90%) accepted the offer to undergo testing, for a total cost of AU $28,000 (2018 currency, equivalent to 2018 CDN $27,123.60). Additionally, two asymptomatic first-degree

relatives experienced a change in their medical management due to the results from their cascade genetic testing. For one of the relatives, this change translated into a yearly cost of AU $146 (2018 CDN $141.43) and for the other, a yearly cost of AU $329 (2018 CDN $318.70). Perhaps the most novel aspect of this study, however, was the fact that Stark *et al*. also assessed the use of reproductive genetic services by 16 couples (14 with diagnosed children and two with undiagnosed children). Of the couples with diagnosed children, three sought pre-implantation genetic diagnosis, two of those proceeded with pre-implantation genetic diagnosis, and one of them established a pregnancy. The 11 other couples with diagnosed children sought prenatal diagnostic services; four of these underwent prenatal diagnosis. Four couples proceeded with pregnancy without undergoing prenatal diagnosis, and one of these couples had two successful pregnancies. Two couples with undiagnosed children had pregnancies, but one was terminated at ten weeks gestation. The cost of the pre-implantation genetic services used was AU $29,804 (2018 CDN $28,871.13), and the cost of the prenatal diagnostic services used was AU $27,100 (2018 CDN $26,251.77).

Finally, Knight and colleagues (Knight et al., 2020) examined the uptake and yield of cascade genetic testing in the family members of children with long QT syndrome (LQTS) and HCM across six paediatric centres in the United States. A total of 315 index patients from 315 families were identified, and genetic testing was performed in 250 (79%). The authors specify that the index patient was not necessarily the proband for the family, but rather was the first family member to be seen at the participating centre. Uptake was higher among LQTS patients (92%) than HCM patients (65%). Of tested index patients, 81% with LQTS and 60% with HCM received a positive result. Of the 315 families captured in this study, 234 (74%) agreed to cascade genetic testing and/or screening, with a total of 553 relatives (i.e., 2.4 family members per family) undergoing cascade investigations. Participation in cascade testing or screening was highest among families with a mutation-positive index patient (90%), however 67% of families in which the index patient received a negative or inconclusive genetic test result agreed to screening. Interestingly, uptake of cascade investigations among families in which the index case did not undergo genetic testing, or in which the genetic testing status of the index patient was unknown, was 43%. Overall, a mean of 1.6 cascade investigations were performed per family member screened, with 17% or relatives undergoing cascade genetic testing only, 46% undergoing cascade clinical screening only, and 38% undergoing both cascade genetic testing

and cascade clinical screening. Although all relatives of mutation-positive index patients were eligible for cascade genetic testing, 26% chose to undergo clinical screening only. In total, 221/553 relatives (40%) were found to be affected (i.e., 0.94 relatives detected per included family). The proportion of positive relatives was higher for LQTS (42%) than for HCM (37%). Knight *et al*. also compared the yield of positive results between the three screening strategies (genetic testing only, screening only, and combined genetic testing and screening), and found that the combined strategy had the highest yield (58%) compared with the genetic testing only (34%) and screening only (19%) strategies.

Aside from these studies, there have been case reports or case series of individual families in which a child was genetically diagnosed with severe congenital protein C deficiency (Tairaku et al., 2015), Fragile X syndrome (Famula et al., 2015; Sorensen et al., 2012), β-thalassemia (Baig et al., 2008), or the Nettleship-Falls type of X-linked ocular albinism (Rudolph et al., 2001), and the child's family members subsequently underwent genetic testing to identify any disease-related mutations. Sorensen *et al.* (Sorensen et al., 2013) reported on a pilot project for newborn screening and cascade testing for *FMR1* (Fragile X syndrome-associated) mutations in the United States. As of 2013, 3,042 newborns were screened, and 44 extended family members of newborns who received positive results underwent genetic testing. In all, 14 newborns and 27 extended family members from ten families possessing mutations associated with Fragile X syndrome were identified. Sorensen *et al.* also presented a case series from the project of three newborns identified as having premutations in *FMR1* where carrier testing revealed family members who were mutation or premutation carriers. A full mutation in the context of Fragile X syndrome consists of a CGC-repeat expansion of more than 200 repeats in the *FMR1* gene, while premtations are smaller expansions of only 55 to 200 repeats (Tassone et al., 2014). Family members tested as part of the pilot project included parents, aunts and uncles, grandparents, and even great-grandparents (Sorensen et al., 2013). There have been no papers about this pilot project published more recently.

3.1.2 Studies with a Combined Paediatric and Adult Proband Population

A small number of studies have explored cascade testing for CMP or other disease states with a genetically diagnosed combined adult and paediatric proband population. A systematic family

screening program for FH was established in Norway in the early 2000's (Leren et al., 2004). Three years after the initiation of this program, 851 relatives of 188 probands had undergone genetic testing, and of them, 407 (47.9%) were affected (Leren et al., 2004). The relatives of both paediatric and adult probands were included, but the number of index patients in each age group was not specified (Leren et al., 2004). A follow-up survey to which 146 of the affected family members responded found that approximately half had made changes to their pharmaceutical regimen as a result of their genetic results (Leren et al., 2004).

In 2013, Miller *et al*. (Miller et al., 2013) investigated the uptake of cardiac screening and clinical genetic testing among the families of patients with HCM or DCM in the United States. The cohort consisted of 57 probands and 302 relatives who were recommended to undergo cardiac screening and/or clinical genetic testing. Inclusion was not restricted by age. Eighty-one percent and 19% of probands had HCM and DCM respectively. The average age at HCM diagnosis was 16 years and the average age at DCM diagnosis was 11 years. The majority (70%) of probands who underwent clinical genetic testing were found to have a pathogenic variant and 10% of those were also found to have a VUS. Genetic testing for a known familial mutation was indicated for 213 relatives (140 first-degree and 73 second-degree) of mutation-positive probands. Seventy-two first-degree (51%) and 12 second-degree (16%) relatives accepted the offer of testing for a total uptake of 39%. Of these 84 relatives, 63% were asymptomatic at the time of testing and 37% had already been diagnosed with CMP. A statistically significantly greater proportion of first-degree relatives than second-degree relatives underwent both cardiac screening and genetic testing (83% *versus* 30% for cardiac screening and 51% *versus* 16% for genetic testing). There was no statistically significant association between the proband's age at diagnosis, family history of SCD, and number of living affected relatives, with uptake of genetic testing among relatives.

Alfares *et al.* (Alfares et al., 2015) performed genetic testing in 2,912 unrelated probands and familial variant testing in 1,209 of their asymptomatic family members to identify HCM-associated pathogenic variants and to assess the costs associated with cascade genetic testing. Genetic testing was performed with targeted HCM panels and the expanded pan-CMP panel. The cost of genetic testing in family members was US $400 (2015 currency, equivalent to 2015 CDN $511) per sample, and clinical assessments including the cardiologist, ECG, and echocardiogram were priced at US $150 (2015 CDN $192). Individuals of all ages were included. Resource use

was not measured empirically. The number of clinic visits for at-risk family members was varied based on age: those 12 years old or younger were assumed to have 20 clinic visits (one per year from age 12 to 20, and then one every five years from ages 21 to 75); those aged 50 to 75 were assigned three visits; and it was assumed that individuals older than 75 did not undergo clinical screening at all. A pathogenic or likely pathogenic variant was identified in 917 of 2,192 probands (32%) and was inconclusive in 444 individuals (15%). Nearly one-third (28%) of positive genetic tests were found in probands 16 years old or younger. Twenty percent of children with a positive test result were younger than two years old. Among the included asymptomatic family members of mutation-positive probands, 691 received a negative result and no longer required the cardiac evaluations that were recommended for high-risk relatives. It was estimated that this cessation of surveillance translated into savings of approximately US $1,000 (2015 CDN $1,279) per family member, or US $700,000 (2015 CDN $895,090) in total. It was not reported, however, how many of the tested family members were related to a paediatric proband *versus* an adult proband, and the estimated cost savings were only presented as a total number rather than by proband age group. Furthermore, the number of clinic visits and the type and amount of other health resources used by family members were based on screening guidelines and were uniform within the defined the age groups, rather than reflecting real consumption.

Lastly, a case series describing outcomes of cascade genetic testing and clinical screening for FH in five families in Vietnam was published in 2018 (Truong et al., 2018). Five index patients (two children and three adults) were included, and 107 relatives underwent cascade investigations. Of these family members, 89 agreed to genetic testing. An FH-associated mutation was found in 47 individuals, with 3 homozygotes and 44 heterozygotes.

3.1.3 Critical Appraisal of Included Literature

Critical appraisal of included studies was conducted using the SIGN checklists (Scottish Intercollegiate Guidelines Network (SIGN)) for economic evaluations and cohort studies as appropriate (**Tables 9** and **10**). Case reports and case studies were not appraised, in accordance with the SIGN Algorithm for Classifying Study Design for Questions of Effectiveness (Scottish Intercollegiate Guidelines Network (SIGN)).

Following assessment, studies were categorized as *high quality*, *acceptable*, or *low quality*. The majority of appraised studies were determined to be acceptable, with only one (Gorakshakar & Colah, 2009) being considered low quality. The cohort studies included in review were all either retrospective and/or single cohort studies (i.e., no comparison groups). The implications of this were twofold. First, many of the criteria on the checklist for cohort studies were not applicable to the included papers as can be seen in **Table 10**, since those criteria were meant for prospective and/or multi-cohort studies. Second, none of the appraised publications were classified as *high quality* because, according to the guidance from SIGN around using their tools, "retrospective studies or single cohort studies are generally regarded as weaker design and should not receive a rating higher than [acceptable]" (Scottish Intercollegiate Guidelines Network (SIGN)).

In general, the included studies stated their main purpose or objective well, described their methodology in sufficient detail, and reported both primary and secondary findings. However, several of these studies lacked sufficient information about their participant selection process and did not provide adequate demographic information about included participants (Cadet et al., 2005; Gorakshakar & Colah, 2009; McClaren et al., 2010; Smith et al., 2007; Stark et al., 2019; Wu et al., 2017). The publication determined to be of low quality (Gorakshakar & Colah, 2009) was considered as such because the methodology was unclear and was lacking in detail.

Although the case reports (Baig et al., 2008; Famula et al., 2015; Rudolph et al., 2001; Sorensen et al., 2012; Tairaku et al., 2015) and case series (Moriwaki et al., 2012; Sorensen et al., 2013; Truong et al., 2018) were not subjected to a critical appraisal process, it was recognized that they were of inherently poorer quality than cohort studies. In general case reports and case series suffer from a number of flaws related to study design, including lack of a control group and inherent selection bias (Sayre et al., 2017). Among the case reports included in this literature review, a common weakness was a failure to provide takeaway lessons (Baig et al., 2008; Sorensen et al., 2012; Tairaku et al., 2015). None of the included case series described their methodology for patient identification or criteria for inclusion in the series well (Moriwaki et al., 2012; Sorensen et al., 2013; Truong et al., 2018).

Table 9: Critical appraisal of economic evaluations.

		REFERENCE
CRITERION		(Stark et al., 2019)
1.	The study addresses an appropriate and clearly focused question.	Y
2.	The economic importance of the question is clear.	Y
3.	The choice of study design is justified.	N
4.	All costs that are relevant from the viewpoint of the study are included and measured and valued appropriately.	N
5.	The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately.	Y
6.	If discounting future costs and outcomes is necessary, it has been performed correctly.	NA
7.	Assumptions are made explicit and a sensitivity analysis was performed.	C
8.	The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.	Y
9.	The results provide information of relevance to policy makers.	Y
OVERALL ASSESSMENT		**A**

Y (pale green cells): *yes* *A (dark yellow cell):* *acceptable*
N (pale orange cells): *no*
C (pale yellow cell): *cannot say*
NA (pale blue cell): *not applicable*

Table 10: Critical appraisal of cohort studies.

	CRITERION	REFERENCE										
		(Knight et al., 2020)	(Wu et al., 2017)	(Wald et al., 2016)	(Alfares et al., 2015)	(McClaren et al., 2013)	(Miller et al., 2013)	(McClaren et al., 2010)	(Gorakshakar & Colah, 2009)	(Smith et al., 2007)	(Cadet et al., 2005)	(Leren et al., 2004)
1.	The study addresses an appropriate and clearly focused question.	Y	Y	Y	Y	Y	Y	Y	C	C	Y	C
2.	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	NA	NA	NA	NA	NA	NA	NA	NA	C	NA	NA
3.	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	NA	NA	NA	NA	NA	NA	NA	NA	N	NA	NA
4.	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
5.	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
6.	Comparison is made between full participants and those lost to follow-up, by exposure status.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
7.	The outcomes are clearly defined.	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
8.	The assessment of outcome is made blind to exposure status. If the study is retrospective, this may not be applicable.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
9.	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA

10.	The method of assessment of exposure is reliable.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
11.	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	C	Y	C	Y	NA	N	N	N	Y	N	Y
12.	Exposure level or prognostic factor is assessed more than once.	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
13.	The main potential confounders are identified and taken into account in the design and analysis.	NA	NA	N	NA	Y	Y	Y	NA	NA	NA	Y
14.	Have confidence intervals been provided?	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
OVERALL ASSESSMENT		**A**	**A**	**A**	**A**	**A**	**A**	**A**	**LQ**	**A**	**A**	**A**

Y (pale green cells): *yes*
N (pale orange cells): *no*
C (pale yellow cells): *cannot say*
NA (pale blue cells): *not applicable*

HQ: *high quality*
A (dark yellow cells): *acceptable*
LQ (dark orange cells): *low quality*

3.2 Retrospective Cohort Study

Fifty-three paediatric probands with CMP were included in the retrospective cohort study. The mean ± standard deviation (SD) age at the time of genetic testing was 8.80 ± 6.00 years. The majority of probands had HCM (29/53 or 55%) or DCM (14/53 or 26%). All index patients underwent a multigene panel test. Nineteen (36%) were mutation-positive, 16 (30%) received an inconclusive result, and 18 (34%) were mutation-negative. Identified family members included 53 mothers, 53 fathers, 74 siblings, two grandparents, two uncles, two aunts, and two cousins. Due to the low number of second-degree relatives, only first-degree family members (i.e., parents and siblings) were included in analysis. Detailed demographic information is displayed in **Table 11**.

Table 11: Baseline demographics of included paediatric probands (n=53).

CHARACTERISTIC	n	%
AGE AT TIME OF INDEX GENETIC TEST (IN YEARS)		
Mean	8.80	NA
Median	10.10	NA
Standard Deviation	6.00	NA
SEX		
Female	15	28.30
Male	38	71.70
ETHNICITY		
African American	4	7.55
Asian	7	13.21
Caucasian	18	33.96
European	9	16.98
South Asian	8	15.09
Mixed descent (African American and Caucasian)	1	1.89
Mixed descent (Caucasian and Hispanic)	1	1.89
Mixed descent (not specified)	1	1.89
Missing	4	7.55
DIAGNOSIS		
ARVC	1	1.89
DCM	14	26.42
HCM	29	54.72
LVNC	7	13.21
RCM	2	3.77
NUMBER OF GENETIC TESTS		
1	45	84.91
2	6	11.32
3	1	1.89
4	1	1.89
INDEX GENETIC TEST REPORT YEAR[a]		
2008	5	9.43
2009	14	26.42
2010	15	28.30

2011	3	5.66
2012	7	13.21
2013	3	5.66
2014	2	3.77
2015	3	5.66
2018	1	1.89
INDEX GENETIC TEST TYPE		
Panel	52	98.11
Reanalysis of past panel	1	1.89
INDEX GENETIC TEST PANEL TYPE		
DCM	7	13.21
HCM	25	47.17
DCM and HCM	14	26.42
PanCardiomyopathy (Pan-CMP)	7	13.21
INDEX GENETIC TEST INTERPRETATION		
Positive	19	35.85
Inconclusive	16	30.19
Negative	18	33.96
FAMILY MEMBER INFORMATION		
MOTHERS	**53**	**NA**
FATHERS	**53**	**NA**
SIBLINGS	**74**	**NA**
Number of probands with 1 known sibling	24	45.28
Number of probands with 2 known siblings	8	15.09
Number of probands with 3 known siblings	4	7.55
Number of probands with 4 known siblings	3	5.66
Number of probands with 5 known siblings	2	3.77
Number of probands with unknown number of siblings	12	22.64
GRANDPARENTS	**4**	**NA**
Number of probands with 1 known grandparent	2	3.77
Number of probands with 2 known grandparents	1	1.89
Number of probands with unknown number of grandparents	50	94.34
UNCLES	**2**	**NA**
Number of probands with 1 known uncle	2	3.77
Number of probands with unknown number of uncles	51	96.23
AUNTS	**2**	**NA**
Number of probands with 1 known aunt	2	3.77
Number of probands with unknown number of aunts	51	96.23
COUSINS	**2**	**NA**
Number of probands with 1 known cousin	2	3.77
Number of probands with unknown number of cousins	51	96.23

ARVC: arrhythmogenic cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
NA: not applicable
RCM: restrictive cardiomyopathy

[a]The report date of the index genetic test may be after the test results were disclosed to the proband's family and a decision about cascade testing or screening was made. Some of the included probands underwent genetic testing prior to the implementation of Epic © software in care centres (V. Venkataramanan, personal communication, 2020). Before use of this software, test reports were scanned and manually uploaded to a hospital's system (V. Venkataramanan, personal communication, 2020). These reports were sometimes sent to physicians before they were incorporated into the system, so in some cases the "report date" recorded is actually the date of upload rather than the date results were received and/or disclosed (V. Venkataramanan, personal communication, 2020).

3.2.1 Primary Analysis

The results of the primary analysis in which it was assumed that for all probands, offers of cascade genetic testing or clinical screening were made in accordance with clinical practice guidelines, are presented below. The pattern of offered cascade health services is described first, followed by the costs associated with those health services. The volume of offered cascade health services corresponds to a one-year time period following the return of the proband's genetic test results. Only first-degree relatives were included.

3.2.1.1 Pattern of Cascade Health Services Offered

The pattern of offered cascade health services was first quantified for the entire family, and subsequently for each type of first-degree relative. According to clinical practice guidelines (Hospital for Sick Children, 2013, 2016), only the relatives of mutation-positive probands should be offered cascade genetic testing while all first-degree relatives of all probands should be offered cascade clinical screening. Relatives of probands with DCM, HCM, RCM, or LVNC should be offered one ECG and one echocardiogram each. Relatives of probands with ARVC should be offered one ECG, one echocardiogram, and one 24-hour Holter monitor each.

All results are stratified by proband test result as well as by the proband's CMP subtype. There was only one proband with the following combinations of genetic test result/CMP subtype: positive/RCM; negative/RCM; and negative/ARVC. For these subgroups, it was therefore not possible to calculate any standard deviations. No probands were positive/ARVC, inconclusive/RCM, or inconclusive/ARVC.

3.2.1.1.1 General Pattern

The general, or per family, pattern of offered health services is shown in **Table 12**. Across the entire study sample, probands had a mean ± SD of 3.40 ± 1.29 relatives each. Probands who received a positive genetic test result had a mean of 3.42 ± 1.30 relatives each, so a mean total of 3.42 ± 1.30 cascade genetic tests should have been offered per index patient (or per family). Across the entire study sample, a mean total of 3.40 ± 1.29 ECGs, 3.40 ± 1.29 echocardiograms, and 0.08 ± 0.55 24-hour Holter monitors should have been offered per proband (or per family).

Table 12: Pattern of health services offered to all first-degree relatives in the primary analysis.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL FIRST-DEGREE RELATIVES													
				CASCADE GENETIC TESTING				CASCADE CLINICAL SCREENING							
		TOTAL NUMBER OF RELATIVES PER PROBAND		NUMBER OF RELATIVES PER PROBAND THAT SHOULD BE OFFERED CASCADE GENETIC TESTING		TOTAL NUMBER OF CASCADE GENETIC TESTS PER FAMILY		NUMBER OF RELATIVES PER PROBAND THAT SHOULD BE OFFERED CASCADE SCREENING		TOTAL NUMBER OF CASCADE ECGs PER FAMILY		TOTAL NUMBER OF CASCADE ECHOs PER FAMILY		TOTAL NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER FAMILY	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	2.83	0.75	2.83	0.75	2.83	0.75	2.83	0.75	2.83	0.75	2.83	0.75	0.00	0.00
	HCM (n=9)	4.00	1.66	4.00	1.66	4.00	1.66	4.00	1.66	4.00	1.66	4.00	1.66	0.00	0.00
	RCM (n=1)	3.00	NA	3.00	NA	3.00	NA	3.00	NA	3.00	NA	3.00	NA	0.00	NA
	LVNC (n=3)	3.00	0.00	3.00	0.00	3.00	0.00	3.00	0.00	3.00	0.00	3.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**3.42**	**1.30**	**3.42**	**1.30**	**3.42**	**1.30**	**3.42**	**1.30**	**3.42**	**1.30**	**3.42**	**1.30**	**0.00**	0.00
INCONCLUSIVE	DCM (n=4)	4.75	1.71	0.00	0.00	0.00	0.00	4.75	1.71	4.75	1.71	4.75	1.71	0.00	0.00
	HCM (n=10)	2.70	0.67	0.00	0.00	0.00	0.00	2.70	0.67	2.70	0.67	2.70	0.67	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	3.00	1.41	0.00	0.00	0.00	0.00	3.00	1.41	3.00	1.41	3.00	1.41	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**3.25**	**1.34**	**0.00**	**0.00**	**0.00**	**0.00**	**3.25**	**1.34**	**3.25**	**1.34**	**3.25**	**1.34**	**0.00**	0.00
NEGATIVE	DCM (n=4)	5.00	1.63	0.00	0.00	0.00	0.00	5.00	1.63	5.00	1.63	5.00	1.63	0.00	0.00
	HCM (n=10)	3.20	0.79	0.00	0.00	0.00	0.00	3.20	0.79	3.20	0.79	3.20	0.79	0.00	0.00
	RCM (n=1)	2.00	NA	0.00	NA	0.00	NA	2.00	NA	2.00	NA	2.00	NA	0.00	NA
	LVNC (n=2)	2.50	0.71	0.00	0.00	0.00	0.00	2.50	0.71	2.50	0.71	2.50	0.71	0.00	0.00
	ARVC (n=1)	4.00	NA	0.00	NA	0.00	NA	4.00	NA	4.00	NA	4.00	NA	4.00	NA
	ALL (n=18)	**3.50**	**1.29**	**0.00**	**0.00**	**0.00**	**0.00**	**3.50**	**1.29**	**3.50**	**1.29**	**3.50**	**1.29**	**0.22**	0.94
TOTAL (n=53)		3.40	1.29	1.23	1.83	1.23	1.83	3.40	1.29	3.40	1.29	3.40	1.29	0.08	0.55

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy

ECG: *electrocardiogram*
Echo: *echocardiogram*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
NA: *not applicable*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

3.2.1.1.2 Relation-Specific Pattern

The pattern of cascade health services offered per parent per proband is shown in **Table 13**. Each proband had one mother and one father, and the number and types of cascade health services that should have been offered to each type of parent based on clinical practice guidelines (Hospital for Sick Children, 2013, 2016) were identical in all cases. Therefore, one cascade genetic test should have been offered per mother of a mutation-positive proband, and one cascade genetic test should have been offered per father of a mutation-positive proband. Across all included probands, a mean of 1.00 ± 0.00 ECGs and 1.00 ± 0.00 echocardiograms should have been offered per parent per proband. There was only one proband with ARVC across the entire study sample, and both of this individual's parents should have been offered one 24-hour Holter monitor each in addition to an ECG and echocardiogram. As a result, across the entire study sample, 0.02 ± 0.14 24-hour Holter monitors should have been offered per parent per proband.

The pattern of cascade health services offered to each proband's siblings is shown in **Table 14**. Siblings were treated as a unit (i.e., results are presented per all of a proband's siblings, *not* per individual sibling). Across the entire study sample, probands had a mean ± SD of 1.40 ± 1.29 siblings each. However, not all probands had siblings. For index patients with a positive genetic test result, and including only those index patients with known siblings, the mean number of siblings was 1.80 ± 1.21. Therefore, 1.80 ± 1.21 cascade genetic tests should have been offered to the siblings of these probands. Similarly, a mean of 1.80 ± 1.19 ECGs and 1.80 ± 1.19 echocardiograms should have been offered per proband. The proband with ARVC had two siblings, and each of these siblings should have been offered a 24-hour Holter monitor as well as an ECG and echo. Consequently, across the entire study sample, a mean of 0.05 ± 0.31 24-hour Holter monitors should have been offered per proband.

Table 13: Pattern of cascade health services offered per parent per proband in the primary analysis.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	INDIVIDUAL PARENTS[a]													
				CASCADE GENETIC TESTING				CASCADE CLINICAL SCREENING							
		NUMBER OF EACH PARENT PER PROBAND		NUMBER OF EACH PARENT PER PROBAND THAT SHOULD BE OFFERED CASCADE GENETIC TESTING		NUMBER OF CASCADE GENETIC TESTS PER PARENT PER PROBAND		NUMBER OF EACH PARENT PER PROBAND THAT SHOULD BE OFFERED CASCADE SCREENING		NUMBER OF CASCADE ECGs PER PARENT PER PROBAND		NUMBER OF CASCADE ECHOs PER PARENT PER PROBAND		NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER PARENT PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	HCM (n=9)	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	1.00	NA	1.00	NA	1.00	NA	1.00	NA	0.00	NA
	LVNC (n=3)	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**0.00**	**0.00**
INCONCLUSIVE	DCM (n=4)	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**0.00**	**0.00**
NEGATIVE	DCM (n=4)	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	0.00	NA	0.00	NA	1.00	NA	1.00	NA	1.00	NA	0.00	NA
	LVNC (n=2)	1.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	ARVC (n=1)	1.00	NA	0.00	NA	0.00	NA	1.00	NA	1.00	NA	1.00	NA	1.00	NA
	ALL (n=18)	**1.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**1.00**	**0.00**	**0.06**	**0.24**
TOTAL (n=53)		1.00	0.00	0.36	0.48	0.36	0.48	1.00	0.00	1.00	0.00	1.00	0.00	0.02	0.14

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM dilated cardiomyopathy

ECG: *electrocardiogram*
Echo: *echocardiogram*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
NA: *not applicable*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

[a]Each proband had two biological parents, one mother and one father. The pattern of services that should be offered to mothers is identical to the pattern of services that should be offered to fathers.

Table 14: Pattern of cascade health services offered to each proband's siblings in the primary analysis.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL SIBLINGS													
				CASCADE GENETIC TESTING				CASCADE CLINICAL SCREENING							
		NUMBER OF SIBLINGS PER PROBAND		NUMBER OF SIBLINGS PER PROBAND THAT SHOULD BE OFFERED CASCADE GENETIC TESTING[a]		NUMBER OF CASCADE GENETIC TESTS PER PROBAND[a]		NUMBER OF SIBLINGS PER PROBAND THAT SHOULD BE OFFERED CASCADE SCREENING[a]		NUMBER OF CASCADE ECGs PER PROBAND[a]		NUMBER OF CASCADE ECHOs PER PROBAND[a]		NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER PROBAND[a]	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	0.83	0.75	1.25	0.50	1.25	0.50	1.25	0.50	1.25	0.50	1.25	0.50	0.00	0.00
	HCM (n=9)	2.00	1.66	2.57	1.40	2.57	1.40	2.57	1.40	2.57	1.40	2.57	1.40	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	1.00	NA	1.00	NA	1.00	NA	1.00	NA	0.00	NA
	LVNC (n=3)	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.42**	**1.30**	**1.80**	**1.21**	**1.80**	**1.21**	**1.80**	**1.21**	**1.80**	**1.21**	**1.80**	**1.21**	**0.00**	**0.00**
INCONCLUSIVE	DCM (n=4)	2.75	1.71	0.00	0.00	0.00	0.00	2.75	1.71	2.75	1.71	2.75	1.71	0.00	0.00
	HCM (n=10)	0.70	0.67	0.00	0.00	0.00	0.00	1.17	0.41	1.17	0.41	1.17	0.41	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	1.41	0.00	NA[b]	0.00	NA[b]	2.00	NA[b]	2.00	NA[b]	2.00	NA[b]	0.00	NA[b]
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.25**	**1.34**	**0.00**	**0.00**	**0.00**	**0.00**	**1.82**	**1.25**	**1.82**	**1.25**	**1.82**	**1.25**	**0.00**	**0.00**
NEGATIVE	DCM (n=4)	3.00	1.63	0.00	0.00	0.00	0.00	3.00	1.63	3.00	1.63	3.00	1.63	0.00	0.00
	HCM (n=10)	1.20	0.79	0.00	0.00	0.00	0.00	1.33	0.71	1.33	0.71	1.33	0.71	0.00	0.00
	RCM (n=1)	0.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.50	0.71	0.00	NA[b]	0.00	NA[b]	1.00	NA[b]	1.00	NA[b]	1.00	NA[b]	0.00	NA[b]
	ARVC (n=1)	2.00	NA	0.00	NA	0.00	NA	2.00	NA	2.00	NA	2.00	NA	2.00	NA
	ALL (n=18)	**1.50**	**1.29**	**0.00**	**0.00**	**0.00**	**0.00**	**1.80**	**1.21**	**1.80**	**1.21**	**1.80**	**1.21**	**0.13**	**0.52**
TOTAL (n=53)		1.40	1.29	0.66	1.13	0.66	1.13	1.80	1.19	1.80	1.19	1.80	1.19	0.05	0.31

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
ECG: electrocardiogram

Echo: *echocardiogram*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
NA: *not applicable*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

[a]Includes only those probands with known siblings.
[b]There was only one proband with this combination of genetic test result and CMP subtype who had siblings. Therefore, it was not possible to calculate the subsample standard deviation.

3.2.1.2 Costs of Cascade Health Services Offered

Similar to the pattern of offered cascade health services, the costs of all health services offered to a proband's family were first calculated, after which the costs associated with cascade health services offered to each type of relative were determined.

3.2.1.2.1 General Costs

The mean total cost of all health care services that should have been offered per proband was $1,173.19 ± 746.92 (**Table 15**). The mean cost of cascade genetic testing across the entire study sample was $418.64 ± 621.79, while the mean cost of cascade clinical screening was $754.55 ± 293.26. The mean cost of cascade genetic testing in only those families where testing should have been offered (i.e., in the families of mutation-positive probands) was $1,167.78 ± 439.86 per family.

Table 15: Total costs associated with cascade health services offered to all of a proband's first-degree relatives in the reference case.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL FIRST-DEGREE RELATIVES					
		COST OF CASCADE GENETIC TESTING		COST OF CASCADE SCREENING		TOTAL COST OF ALL CASCADE HEALTH SERVICES	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	969.61	253.82	622.91	165.50	1,592.52	419.32
	HCM (n=9)	1,362.99	559.15	879.40	364.58	2,242.39	923.73
	RCM (n=1)	1,025.81	NA	659.55	NA	1,685.36	NA
	LVNC (n=3)	1,025.81	0.00	659.55	0.00	1,685.36	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1,167.78**	**439.86**	**752.12**	**286.80**	**1,919.90**	**726.65**
INCONCLUSIVE	DCM (n=4)	0.00	NA	1,044.29	375.47	1,044.29	375.47
	HCM (n=10)	0.00	NA	593.60	148.39	593.60	148.39
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	NA	659.55	310.91	659.55	310.91
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**NA**	**714.51**	**294.96**	**714.51**	**294.96**
NEGATIVE	DCM (n=4)	0.00	NA	1,099.25	359.01	1,099.25	359.01
	HCM (n=10)	0.00	NA	703.52	173.42	703.52	173.42
	RCM (n=1)	0.00	NA	439.70	NA	439.70	NA
	LVNC (n=2)	0.00	NA	549.63	155.46	549.63	155.46
	ARVC (n=1)	0.00	NA	1,297.40	NA	1,297.40	NA
	ALL (n=18)	**0.00**	**NA**	**792.70**	**310.07**	**792.70**	**310.07**
TOTAL (n=53)		**418.64**	621.79	**754.55**	293.26	**1,173.19**	746.92

ARVC: *arrhythmogenic right ventricular cardiomyopathy*
DCM: *dilated cardiomyopathy*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
NA: *not applicable*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

All costs are in 2019 Canadian dollars.

3.2.1.2.2 Relation-Specific Costs

The mean total cost of all cascade health services that should have been offered per parent per proband was $344.38 ± 164.65, with cascade genetic testing accounting for $122.56 and cascade clinical screening accounting for $221.82 (**Table 16**). Across mutation-positive probands only, the mean cost of cascade genetic testing per parent per proband was $341.87 ± 1.56. The mean cost of cascade screening was higher for parents of mutation-negative probands. This was due to the fact that the only proband with ARVC (and therefore the only proband whose relatives required 24-hour Holter monitors) had received a negative genetic test result.

Table 16: Costs associated with cascade health services offered per parent per proband in the reference case.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	INDIVIDUAL PARENTS[a]					
		COST OF CASCADE GENETIC TESTING PER PARENT PER PROBAND		COST OF CASCADE SCREENING PER PARENT PER PROBAND		TOTAL COST OF ALL CASCADE HEALTH SERVICES PER PARENT PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	342.53	1.46	219.85	0.00	562.38	1.46
	HCM (n=9)	341.41	1.89	219.85	0.00	561.26	1.89
	RCM (n=1)	341.94	NA	219.85	NA	561.79	NA
	LVNC (n=3)	341.94	0.00	219.85	0.00	561.79	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**341.87**	**1.56**	**219.85**	**0.00**	**561.72**	**1.56**
INCONCLUSIVE	DCM (n=4)	0.00	0.00	219.85	0.00	219.85	0.00
	HCM (n=10)	0.00	0.00	219.85	0.00	219.85	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	0.00	219.85	0.00	219.85	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**0.00**	**219.85**	**0.00**	**219.85**	**0.00**
NEGATIVE	DCM (n=4)	0.00	0.00	219.85	0.00	219.85	0.00
	HCM (n=10)	0.00	0.00	219.85	0.00	219.85	0.00
	RCM (n=1)	0.00	NA	219.85	NA	219.85	NA
	LVNC (n=2)	0.00	0.00	219.85	0.00	219.85	0.00
	ARVC (n=1)	0.00	NA	324.35	NA	324.35	NA
	ALL (n=18)	**0.00**	**0.00**	**225.66**	**24.63**	**225.66**	**24.63**
TOTAL (n=53)		**122.56**	165.52	**221.82**	14.35	**344.38**	164.65

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
NA: not applicable
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars.

[a]Each proband had two biological parents, one mother and one father. The costs associated with cascade health services offered to each mother and the costs associated with cascade health services offered to each father were equal.

The mean total cost of all cascade health services that should have been offered to the siblings of each proband was $626.21 ± 539.24, with cascade genetic testing contributing $224.31 of that cost and cascade clinical screening contributing $401.90 (**Table 17**). Across mutation-positive probands only, the mean cost of cascade genetic testing was $613.11 ± 408.96 per index patient.

Table 17: Costs associated with cascade health services offered to probands' siblings in the reference case.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL SIBLINGS					
		COST OF CASCADE GENETIC TESTING PER PROBAND[a]		COST OF CASCADE SCREENING PER PROBAND[a]		TOTAL COST OF ALL CASCADE HEALTH SERVICES PER PROBAND[a]	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	426.83	169.78	274.81	109.93	701.64	279.70
	HCM (n=9)	874.51	473.24	565.33	307.19	1,439.84	780.43
	RCM (n=1)	341.94	NA	219.85	NA	561.79	NA
	LVNC (n=3)	341.94	0.00	219.85	0.00	561.79	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**613.11**	**408.96**	**395.73**	**265.39**	**1,008.84**	**674.35**
INCONCLUSIVE	DCM (n=4)	0.00	0.00	604.59	375.47	604.59	375.47
	HCM (n=10)	0.00	0.00	256.49	89.75	256.49	89.75
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	NA[b]	439.70	NA[b]	439.70	NA[b]
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**0.00**	**399.73**	**274.91**	**399.73**	**274.91**
NEGATIVE	DCM (n=4)	0.00	0.00	659.55	359.01	659.55	359.01
	HCM (n=10)	0.00	0.00	293.13	155.46	293.13	155.46
	RCM (n=1)	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	LVNC (n=2)	0.00	NA[d]	219.85	NA[d]	219.85	NA[d]
	ARVC (n=1)	0.00	NA	648.70	NA	648.70	NA
	ALL (n=18)	**0.00**	**0.00**	**409.66**	**273.23**	**409.66**	**273.23**
TOTAL (n=53)		**224.31**	384.61	**401.90**	264.03	**626.21**	539.24

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular noncompaction cardiomyopathy
NA: not applicable
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars.

[a]Includes only those probands with known siblings.
[b]There was only one proband with LVNC and an inconclusive genetic test result that had known siblings. Therefore, it was not possible to calculate the subsample standard deviation.
[c]There was only one proband with RCM and a negative genetic test result, and this individual did not have any siblings.
[d]There was only one proband with LVNC and a negative genetic test result that had known siblings. Therefore, it was not possible to calculate the subsample standard deviation.

3.2.2 Secondary Analysis

The results of the secondary, data-driven empiric analysis are presented below. The data for first-degree relatives recorded in proband EMRs are first described, after which the pattern of cascade

health services offered to family members based on these data is presented and compared with the pattern in the primary analysis.

3.2.2.1 Availability of Relative Data from Proband Medical Records

The cascade genetic testing status of one or more family members was known for 33/53 (63%) probands (**Table 18**). The test status was known for 26/53 (49%) mothers, 27/53 (51%) fathers, and 31/74 (42%) siblings. *Test status known* means that information about cascade genetic testing was noted in the paediatric proband's chart. Possible test statuses included: testing not offered; testing recommended; to be decided; testing refused; testing in progress; or tested. Tests that were recommended, refused, or undergone, and those cases where testing was "to be decided" were all considered "offered" for the purposes of this thesis. Among these relatives for whom the cascade genetic testing status was known, 22/26 (85%) mothers, 22/27 (81%) fathers, and 17/31 (55%) siblings were offered genetic testing. The remaining 4 mothers, 5 fathers, and 14 siblings were not offered testing. Of the 19 families of mutation-positive probands, at least one relative in 10 (53%) of the families agreed to cascade genetic testing; all relatives declined testing in 2 (10%) families; and for 7 (37%) families, testing was offered, but it was unknown whether the offer was accepted by at least one relative or if it was declined by all family members.

A divergence from clinical practice guidelines was observed, such that the relatives of some probands who received either an inconclusive or negative genetic test result were still offered cascade genetic testing. Specifically, 11 mothers, 9 fathers, and 5 siblings of probands with inconclusive genetic test results; and 2 mothers, 2 fathers, and 4 siblings of mutation-negative probands were offered genetic testing.

Table 18: Cascade genetic testing data retrieved from proband medical records.

CHARACTERISTIC	TEST RESULT			
PROBAND INDEX GENETIC TEST RESULT	**POSITIVE (n=19)**	**INCONCLUSIVE (n=16)**	**NEGATIVE (n=18)**	**TOTAL (n=53)**
CASCADE GENETIC TESTING				
TEST STATUS KNOWN FOR ONE OR MORE FAMILY MEMBERS (NUMBER OF FAMILIES)	**14**	**13**	**6**	**33**
TEST STATUS UNKNOWN FOR ALL FAMILY MEMBERS (NUMBER OF FAMILIES)	5	3	12	20
TYPE OF TESTING UNDERGONE BY EACH FAMILY (n=33)				
Familial mutation analysis (FMA)	2	2	0	4
Missing	12	11	6	29
MOTHERS (n=53)				
Test status known	**9**	**13**	**4**	**26**
Test status unknown	10	3	14	27
Mother test status, where known (n=26)				
Offered	9	11	2	22
Not offered	0	2	2	4
FATHERS (n=53)				
Test status known	**11**	**11**	**5**	**27**
Test status unknown	8	5	13	26
Father test status, where known (n=27)				
Offered	11	9	2	22
Not offered	0	2	3	5
SIBLINGS (n=74)				
Test status known for one or more siblings (number of families, n=53)	6	5	4	15
Test status unknown for all siblings (number of families, n=53)	13	11	14	38
Total number of siblings	27	20	27	74
Test status known (number of siblings)	**10**	**12**	**9**	**31**
Test status unknown (number of siblings)	17	8	18	43
Sibling test status, where known (n=31)				
Offered	8	5	4	17
Not offered	2	7	5	14

"Test status known for one or more family members" means that information about cascade genetic testing in one or more family members was noted in the paediatric proband's chart. Possible test statuses included: testing not offered; testing recommended; to be decided; testing refused; testing in progress; or tested. Tests that were recommended, refused, or undergone, and those cases where testing was "to be decided" were all considered "offered" for the purposes of this thesis and are categorized as such in the table.

The cascade clinical screening status of one or more family members was known for 50/53 (94%) probands (**Table 19**). The clinical screening status was known for 42/53 (79%) mothers, 43/53 (81%) fathers, and 73/74 (99%) siblings. *Clinical screening status known* means that information about cascade clinical screening was noted in the paediatric proband's chart. Possible screen statuses included: screening recommended, to be screened, screened, or screening refused. Screens that were recommended, refused, or undergone, or screen statuses of "to be screened" were all considered "offered" for the purposes of this thesis. Among those relatives for whom the cascade clinical screening status was known, 40/42 (95%) mothers, 41/43 (95%) fathers, and 70/73 (96%) siblings were offered screening. The majority of relatives offered screening were offered either an echocardiogram only (80/158 or 51%), or an ECG and echocardiogram (47/158 or 30%). In one family, both mother and father were offered an ECG, echocardiogram, cardiac MRI, and stress myocardial perfusion imaging test (MIBI). Among the 50 families in which the screening status of at least one member was known, at least one family member in 45 (90%) families agreed to screening; 1 (2%) family was explicitly not offered screening; and in 4 (8%) families, screening was offered but it is unknown whether at least one relative accepted the offer, or whether it was declined by all family members.

Table 19: Cascade clinical screening data retrieved from proband medical records.

CHARACTERISTIC	TEST RESULT			
PROBAND INDEX GENETIC TEST RESULT	**POSITIVE (n=19)**	**INCONCLUSIVE (n=16)**	**NEGATIVE (n=18)**	**TOTAL (n=53)**
CASCADE CARDIAC SCREENING				
SCREEN STATUS KNOWN FOR ONE OR MORE FAMILY MEMBERS (NUMBER OF FAMILIES)	**19**	**14**	**17**	**50**
SCREEN STATUS UNKNOWN FOR ALL FAMILY MEMBERS (NUMBER OF FAMILIES)	0	2	1	3
MOTHERS (n=53)				
Screen status known	**15**	**14**	**13**	**42**
Screen status unknown	4	2	5	11
Mother screen status, where known (n=42)				
Offered	**15**	**14**	**11**	**40**
Not offered	0	0	2	2
Mother offered screen type (n=40)				
ECG and echo	2	3	2	7
ECG, echo, MRI, and stress MIBI	1	0	0	1
Echo	10	9	7	26
Missing	2	2	2	6
FATHERS (N=53)				
Screen status known	**16**	**14**	**13**	**43**
Screen status unknown	3	2	5	10
Father screen status, where known (n=43)				
Offered	**16**	**13**	**12**	**41**
Not offered	0	1	1	2
Father offered screen type (n=41)				
ECG and echo	2	3	3	8
ECG, echo, MRI, and stress MIBI	1	0	0	1
Echo	9	8	7	24
Missing	4	2	2	8
SIBLINGS (n=74)				
Screen status known for one or more siblings (number of families, n=53)	14	11	15	40
Screen status unknown for all siblings (number of families, n=53)	5	5	3	13
Total number of siblings	27	20	27	74
Screen status known (number of siblings)	**26**	**20**	**27**	**73**
Screen status unknown (number of siblings)	1	0	0	1

Sibling screen status, where known (n=73)				
Offered	**26**	**20**	**24**	**70**
Not offered	0	0	3	3
Sibling offered screen type (n=70)				
ECG and echo	7	9	16	32
ECG, echo, and Holter monitor	1	0	0	1
Echo	16	8	6	30
Echo and fetal ultrasound	1	0	0	1
Echo and other	1	0	1	2
Missing	0	3	1	4

ECG: electrocardiogram
Echo: echocardiogram
MIBI: stress myocardial perfusion imaging test
MRI: magnetic resonance imaging

"Screen status known for one or more family members" means that information about cascade clinical screening in one or more family members was noted in the paediatric proband's chart. Possible screen statuses included: screening recommended, to be screened, screened, or screening refused. Screens that were recommended, refused, or undergone, or screen statuses of "to be screened" were all considered "offered" for the purposes of this thesis and are categorized as such in the table.

3.2.2.2 Pattern of Cascade Health Services Offered

The pattern of cascade health services offered was first determined for the entire family, and subsequently for each type of first-degree relative, based on the data available in proband medical records.

3.2.2.2.1 General Pattern

Across the entire study sample, the mean number of relatives per proband who were offered cascade genetic testing was 1.19 ± 1.35. Each of these relatives was offered one genetic test, so the mean total number of cascade genetic tests offered per proband was 1.19 ± 1.35. Among paediatric probands who received a positive genetic test result, a mean of 1.58 ± 1.17 cascade genetic tests were offered per proband. This is 1.84 tests fewer per mutation-positive proband than the primary analysis value of 3.42, indicating that not all relatives of mutation-positive probands were offered cascade genetic testing, or not all offers of cascade testing were recorded in proband medical records. Offers of cascade testing were also made to some of the family members of 11 probands with an inconclusive genetic testing result and 2 probands with a negative genetic testing result, with 1.56 ± 1.55 cascade tests being offered per proband with an inconclusive result, and 0.44 ± 1.04 cascade tests being offered per mutation-negative proband. None of the family members of these probands were assumed to receive cascade testing in the primary analysis as per clinical practice guidelines (Hospital for Sick Children, 2013, 2016).

Across the entire study sample, 2.85 ± 1.49 relatives per proband were offered cascade clinical screening. Since the mean total number of relatives per proband was 3.40 ± 1.29, not all relatives were offered cascade screening, or not all offers were recorded in proband medical records. A mean total of 0.94 ± 1.67 ECGs, 2.51 ± 1.69 echocardiograms, and 0.08 ± 0.43 24-hour Holter monitors were offered per proband (or per family). Based on this, not all relatives were offered both an ECG and echocardiogram as indicated in clinical practice guidelines, or these offers were not captured in proband records. However, nearly all relatives who were offered screening were offered an echocardiogram. There were also a number of cascade clinical screens noted in proband records that were not present in the primary analysis. Specifically, 0.04 ± 0.27 cardiac MRIs, 0.04 ± 0.27 stress MIBIs, and 0.02 ± 0.14 fetal ultrasounds were offered per proband (or

per family). The pattern of cascade health services offered to all first-degree relatives in this secondary analysis is tabulated in Appendix IV.

3.2.2.2.2 Relation-Specific Pattern

In the observational data, the pattern of cascade health services offered to mothers differed from the pattern of services offered to fathers (the corresponding tables can be found in Appendix V). Each proband had a mother available for cascade services. Across the whole study sample, a mean of 0.42 ± 0.50 mothers per proband were offered cascade genetic testing, with one test offered per mother. The mean number cascade genetic tests offered per mother of a mutation-positive proband was 0.47 ± 0.51; per mother of a proband with an inconclusive genetic test result was 0.69 ± 0.48; and per mother of a mutation-negative proband was 0.11 ± 0.32. Among mutation-negative probands, only the mother of the proband with ARVC was offered genetic testing. Regarding cascade clinical screening, across the whole study sample, a mean of 0.75 ± 0.43 mothers per proband were offered screening. A mean of 0.15 ± 0.36 ECGs, 0.64 ± 0.48 echocardiograms, 0.02 ± 0.14 cardiac MRIs, and 0.02 ± 0.14 stress MIBIs were offered per proband. No 24-hour Holter monitors were offered. The screening status of only two of four mothers of negative/DCM probands was known, and according to patient charts neither were offered cascade screening. The mother of the negative/ARVC proband was not offered screening either.

Each proband also had one father available for cascade services. Across the whole study sample, a mean of 0.42 ± 0.50 fathers per proband were offered cascade genetic testing, with one test offered per father. The mean number of cascade genetic tests offered per father of a mutation-positive proband was 0.58 ± 0.51; per father of a proband with an inconclusive genetic test result was 0.56 ± 0.51; and per father of a mutation-negative proband was 0.11 ± 0.32. Among mutation-negative probands, one of four fathers of probands with DCM and one of two fathers of probands with LVNC were offered cascade testing. With respect to cascade clinical screening, across the whole study sample, a mean of 0.77 ± 0.42 fathers per proband were offered screening. A mean of 0.17 ± 0.38 ECGs, 0.62 ± 0.49 echocardiograms, 0.02 ± 0.14 24-hour Holter monitors, 0.02 ± 0.14 cardiac MRIs, and 0.02 ± 0.14 stress MIBIs were offered per proband. The father of the negative/ARVC proband was not offered cascade screening.

The mean number of siblings per proband was 1.40 ± 1.29, though not all probands had siblings. Across the whole study sample, and including only those probands with known siblings, 0.46 ± 1.05 siblings per proband were offered cascade genetic testing, with one test offered per sibling. The mean number of genetic tests per mutation-positive proband was 0.67 ± 1.18; per proband with an inconclusive genetic test was 0.45 ± 1.21; and per mutation-negative proband was 0.27 ± 0.80. Among mutation-negative probands, cascade genetic testing was offered to some of the siblings of probands with DCM and ARVC. Regarding cascade clinical screening, across the whole study sample but including only those probands with known siblings, a mean of 1.71 ± 1.23 siblings per proband were offered screening. A mean of 0.80 ± 1.42 ECGs, 1.61 ± 1.30 echocardiograms, and 0.07 ± 0.35 24-hour Holter monitors were offered per proband. One sibling was assessed using a fetal ultrasound. Although neither parent of the negative/ARVC proband underwent clinical screening, both of the index patient's siblings did. The pattern of cascade health services offered to each proband's siblings in this secondary analysis can also be found in Appendix V.

3.2.3 Uncertainty Analyses

The results of one-way sensitivity and scenario analyses performed to address uncertainty within the primary analysis are presented below. No uncertainty analyses were performed for the secondary analysis.

3.2.3.1 One-Way Sensitivity Analyses

Three one-way sensitivity analyses were performed, in which the cost of FMA, the number of genetic counselling appointments attended by family members, and the type (and therefore cost) of the offered 24-hour Holter monitor was varied. The tornado diagram in Figure 5 shows how the mean total cost of all cascade health services offered per family is affected when each of these three variables is altered. The greatest divergence from the reference case value was observed when the cost of FMA was varied. At its minimum unit price of $252.89 per test, the mean cost of cascade genetic testing per proband, across the entire study sample, was $315.26 ± 467.92, and the mean cost of cascade genetic testing per proband including mutation-positive probands only was $879.42 ± 329.90. The mean total cost of all cascade health services offered per family was $1,069.81 ± 607.36. At its maximum unit price of $421.48 per test, the mean cost

of cascade genetic testing per proband, across the entire study sample, was $522.03 ± 775.68, and the mean cost of cascade genetic testing per proband including mutation-positive probands only was $1,456.18 ± 549.83. The mean total cost of all cascade health services offered per family was $1,276.57 ± 891.21.

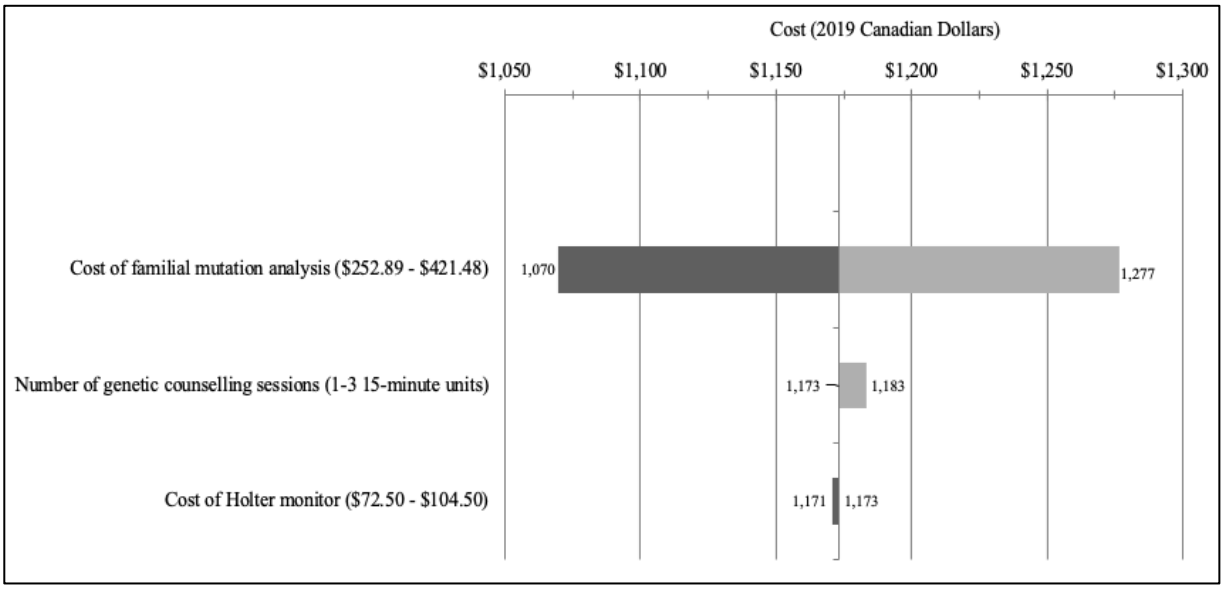

Figure 5: Tornado diagram of mean total cost of all cascade health services offered per family in one-way sensitivity analyses.

3.2.3.2 Scenario Analyses

In the reference case, it was assumed that all relatives were phenotype-negative and genotype-unknown, and cascade clinical screening was offered accordingly. However, recommendations for cascade screening change depending on the family member's genetic testing results, as well as if they develop a CMP phenotype (Hospital for Sick Children, 2013, 2016). Two scenario analyses were therefore conducted to explore how cascade health service costs change when a pathogenic variant is identified in relatives, or when they begin displaying a disease phenotype. In the first scenario, all first-degree relatives were assumed to be phenotype-negative and genotype-positive. In the second, all first-degree relatives were assumed to be phenotype-positive and could have had any genotype.

3.2.3.2.1 All Relatives Assumed to be Phenotype-Negative and Genotype-Positive

Offers of cascade genetic testing remained the same as in the reference case, with only the relatives of mutation-positive probands being eligible for testing. However, offers of cascade

screening were varied, such that relatives of probands with DCM, RCM, or LVNC would each be offered one ECG and one echocardiogram and relatives of probands with HCM or ARVC would each be offered one ECG, one echocardiogram, and one 24-hour Holter monitor.

3.2.3.2.1.1 General Costs

The mean total cost of all health care services that should have been offered per proband in this scenario was $1,360.50 ± 827.69 (**Table 20**). The mean cost of cascade genetic testing across the entire study sample was $418.64 ± 621.79, while the mean cost of cascade clinical screening was $941.86 ± 382.10. The mean cost of cascade clinical screening increased by $187.31 per family compared with the reference case.

Table 20: Total costs associated with cascade health services offered to all first-degree relatives, where family members were assumed to be phenotype-negative and genotype-positive.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL FIRST-DEGREE RELATIVES					
		COST OF CASCADE GENETIC TESTING		COST OF CASCADE SCREENING		TOTAL COST OF ALL CASCADE HEALTH SERVICES	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	969.61	253.82	622.91	165.50	1,592.52	419.32
	HCM (n=9)	1,362.99	559.15	1,297.40	537.87	2,660.39	1,097.02
	RCM (n=1)	1,025.81	NA	659.55	NA	1,685.36	NA
	LVNC (n=3)	1,025.81	0.00	659.55	0.00	1,685.36	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1,167.78**	**439.86**	**950.12**	**500.94**	**2,117.90**	**929.75**
INCONCLUSIVE	DCM (n=4)	0.00	NA	1,044.29	375.47	1,044.29	375.47
	HCM (n=10)	0.00	NA	875.75	218.92	875.75	218.92
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	NA	659.55	310.91	659.55	310.91
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**NA**	**890.86**	**277.41**	**890.86**	**277.41**
NEGATIVE	DCM (n=4)	0.00	NA	1,099.25	359.01	1,099.25	359.01
	HCM (n=10)	0.00	NA	1,037.92	255.85	1,037.92	255.85
	RCM (n=1)	0.00	NA	439.70	NA	439.70	NA
	LVNC (n=2)	0.00	NA	549.63	155.46	549.63	155.46
	ARVC (n=1)	0.00	NA	1,297.40	NA	1,297.40	NA
	ALL (n=18)	**0.00**	**NA**	**978.48**	**330.14**	**978.48**	**330.19**
TOTAL (n=53)		**418.64**	621.79	**941.86**	382.10	**1,360.50**	827.69

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy

LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars. The cells shaded in blue represent a departure from the reference case.

3.2.3.2.1.2 Relation-Specific Costs

The mean cost of all cascade health services that should have been offered per parent per proband was $401.56 ± 166.44 (**Table 21**). The mean cost of cascade genetic testing across the entire study sample was $122.56 ± 165.52, while the mean cost of cascade clinical screening was $279.00 ± 52.29, per parent per proband. The mean cost of cascade clinical screening increased by $57.18 per parent per proband compared with the reference case.

Table 21: Costs associated with cascade health services offered per parent per proband, where all relatives were assumed to be phenotype-negative and genotype-positive.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	INDIVIDUAL PARENTS					
		COST OF CASCADE GENETIC TESTING PER PARENT PER PROBAND		COST OF CASCADE SCREENING PER PARENT PER PROBAND		TOTAL COST OF ALL CASCADE HEALTH SERVICES PER PARENT PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	342.53	1.46	219.85	0.00	562.38	1.46
	HCM (n=9)	341.41	1.89	324.35	0.00	665.76	1.89
	RCM (n=1)	341.94	NA	219.85	NA	561.79	NA
	LVNC (n=3)	341.94	0.00	219.85	0.00	567.79	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**341.87**	**1.56**	**269.35**	**53.61**	**611.22**	**53.17**
INCONCLUSIVE	DCM (n=4)	0.00	0.00	219.85	0.00	219.85	0.00
	HCM (n=10)	0.00	0.00	324.35	0.00	324.35	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	0.00	219.85	0.00	219.85	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**0.00**	**285.16**	**52.25**	**285.16**	**52.25**
NEGATIVE	DCM (n=4)	0.00	0.00	219.85	0.00	219.85	0.00
	HCM (n=10)	0.00	0.00	324.35	0.00	324.35	0.00
	RCM (n=1)	0.00	NA	219.85	NA	219.85	NA
	LVNC (n=2)	0.00	0.00	219.85	0.00	219.85	0.00
	ARVC (n=1)	0.00	NA	324.35	NA	324.35	NA
	ALL (n=18)	**0.00**	**0.00**	**283.71**	**52.42**	**283.71**	**52.42**
TOTAL (n=53)		**122.56**	165.52	**279.00**	52.29	**401.56**	166.44

ARVC: *arrhythmogenic right ventricular cardiomyopathy*
DCM: *dilated cardiomyopathy*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

All costs are in 2019 Canadian dollars. The cells shaded in blue represent a departure from the reference case.

Each proband had two biological parents, one mother and one father. The cost associated with cascade health services offered to each mother and the costs associated with cascade health services offered to each father were equal.

The mean cost of all cascade health services that should have been offered to the siblings of each proband was $720.51 ± 622.31 (**Table 22**). The mean cost of cascade genetic testing across the entire study sample was $224.31 ± 384.61, while the mean cost of cascade screening was $496.20 ± 326.48 per proband. The mean cost of cascade clinical screening increased by $94.30 per proband compared with the reference case.

Table 22: Costs associated with cascade health services offered to probands' siblings, where all relatives were assumed to be phenotype-negative and genotype-positive.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL SIBLINGS					
		COST OF CASCADE GENETIC TESTING PER PROBAND[a]		COST OF CASCADE SCREENING PER PROBAND[a]		TOTAL COST OF ALL CASCADE HEALTH SERVICES PER PROBAND[a]	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	426.83	169.78	274.81	109.93	701.64	279.70
	HCM (n=9)	874.51	473.24	834.04	453.21	1,708.55	926.45
	RCM (n=1)	341.94	NA	219.85	NA	561.79	NA
	LVNC (n=3)	341.94	0.00	219.85	0.00	561.79	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**613.11**	**408.96**	**521.13**	**427.60**	**1,134.24**	**834.64**
INCONCLUSIVE	DCM (n=4)	0.00	0.00	604.59	375.47	604.59	375.47
	HCM (n=10)	0.00	0.00	378.41	132.42	378.41	132.42
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	NA[b]	439.70	NA[b]	439.70	NA[b]
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**0.00**	**466.23**	**251.82**	**466.23**	**251.82**
NEGATIVE	DCM (n=4)	0.00	0.00	659.55	359.01	659.55	359.35
	HCM (n=10)	0.00	0.00	432.47	29.35	432.47	229.35
	RCM (n=1)	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	LVNC (n=2)	0.00	NA[d]	219.85	NA[d]	219.85	NA[d]
	ARVC (n=1)	0.00	NA	648.70	NA	648.70	NA
	ALL (n=18)	**0.00**	**0.00**	**493.26**	**273.90**	**493.26**	**273.90**
TOTAL (n=53)		**224.31**	384.61	**496.20**	326.48	**720.51**	622.31

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular noncompaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars. The cells shaded in blue represent a departure from the reference case.

[a]Includes only those probands with known siblings.
[b]There was only one proband with LVNC and an inconclusive genetic test result that had known siblings. Therefore, it was not possible to calculate the subsample standard deviation.
[c]There was only one proband with RCM and a negative genetic test result, and this individual did not have any siblings.
[d]There was only one proband with LVNC and a negative genetic test result that had known siblings. Therefore, it was not possible to calculate the subsample standard deviation.

3.2.3.2.2 All Relatives Assumed to be Phenotype-Positive, with Any Genotype

Offers of cascade genetic testing remained the same as in the reference case, with only the relatives of mutation-positive probands being eligible for testing. However, offers of cascade screening were varied, such that relatives of probands with DCM, RCM, LVNC, or ARVC, regardless of genotype status, would each be offered one ECG, one echocardiogram, one 24-hour Holter monitor, one exercise test, one cardiac MRI, and bloodwork, and relatives of probands with HCM would each be offered one ECG, one echocardiogram, one 24-hour Holter monitor, one exercise test, one stress echocardiogram, and one cardiac MRI.

3.2.3.2.2.1 General Costs

The mean total cost of all health care services that should have been offered per proband was $2,648.82 ± 1,226.85 (**Table 23**). The mean cost of cascade genetic testing across the entire study sample was $418.64 ± 621.79, while the mean cost of cascade clinical screening was $2,230.19 ± 872.55. The mean cost of cascade clinical screening increased by $1,475.64 per family compared with the reference case.

Table 23: Total costs associated with cascade health services offered to all first-degree relatives, where all family members were assumed to be phenotype-positive and of any genotype.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL FIRST-DEGREE RELATIVES					
		COST OF CASCADE GENETIC TESTING		COST OF CASCADE SCREENING		TOTAL COST OF ALL CASCADE HEALTH SERVICES	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	969.61	253.82	1,568.48	416.72	2,538.09	670.54
	HCM (n=9)	1,362.99	559.15	2,995.60	1,241.91	4,358.59	1,801.06
	RCM (n=1)	1,025.81	NA	1,660.74	NA	2,686.55	NA
	LVNC (n=3)	1,025.81	0.00	1,660.74	0.00	2,686.55	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1,167.78**	**439.86**	**2,263.91**	**1,115.11**	**3,431.69**	**1,544.58**
INCONCLUSIVE	DCM (n=4)	0.00	NA	2,629.51	945.42	2,629.51	945.42
	HCM (n=10)	0.00	NA	2,022.03	505.47	2,022.03	505.47
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	NA	1,660.74	782.88	1,660.74	782.88
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**NA**	**2,128.74**	**690.35**	**2,128.74**	**690.35**
NEGATIVE	DCM (n=4)	0.00	NA	2,767.90	903.99	2,767.90	903.99
	HCM (n=10)	0.00	NA	2,396.48	590.74	2,396.48	590.74
	RCM (n=1)	0.00	NA	1,107.16	NA	1,107.16	NA
	LVNC (n=2)	0.00	NA	1,383.95	391.44	1,383.95	391.44
	ARVC (n=1)	0.00	NA	2,214.32	NA	2,214.32	NA
	ALL (n=18)	**0.00**	**NA**	**2,284.77**	**759.98**	**2,284.77**	**759.98**
TOTAL (n=53)		**418.64**	621.79	**2,230.19**	872.55	**2,648.82**	1,226.85

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars. The cells shaded in blue represent a departure from the reference case.

3.2.3.2.2.2 Relation-Specific Costs

The mean cost of all cascade health services that should have been offered per parent per proband was $783.01 ± 182.79 (**Table 24**). The mean cost of cascade genetic testing across the entire study sample was $122.56 ± 165.52, while the mean cost of cascade clinical screening was

$660.45 ± 98.15, per parent per proband. The mean cost of cascade clinical screening increased by $438.63 per parent per proband compared with the reference case.

Table 24: Costs associated with cascade health service offers per parent per proband, where all relatives were assumed to be phenotype-positive and of any genotype.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	INDIVIDUAL PARENTS					
		COST OF CASCADE GENETIC TESTING PER PARENT PER PROBAND		COST OF CASCADE SCREENING PER PARENT PER PROBAND		TOTAL COST OF ALL CASCADE HEALTH SERVICES PER PARENT PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	342.53	1.46	553.58	0.00	896.11	1.46
	HCM (n=9)	341.41	1.89	748.90	0.00	1,090.31	1.89
	RCM (n=1)	341.94	NA	553.58	NA	895.52	NA
	LVNC (n=3)	341.94	0.00	553.58	0.00	895.52	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**341.87**	**1.56**	**646.10**	**100.20**	**987.97**	**99.75**
INCONCLUSIVE	DCM (n=4)	0.00	0.00	553.58	0.00	553.58	0.00
	HCM (n=10)	0.00	0.00	748.90	0.00	748.90	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	0.00	553.58	0.00	553.58	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**0.00**	**675.66**	**97.66**	**675.66**	**97.66**
NEGATIVE	DCM (n=4)	0.00	0.00	553.58	0.00	553.58	0.00
	HCM (n=10)	0.00	0.00	748.90	0.00	748.90	0.00
	RCM (n=1)	0.00	NA	553.58	NA	553.58	NA
	LVNC (n=2)	0.00	0.00	553.58	0.00	553.58	0.00
	ARVC (n=1)	0.00	NA	553.58	NA	553.58	NA
	ALL (n=18)	**0.00**	**0.00**	**662.09**	**99.87**	**662.09**	**99.87**
TOTAL (n=53)		**122.56**	165.52	**660.45**	98.15	**783.01**	182.79

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars. The cells shaded in blue represent a departure from the reference case.

Each proband had two biological parents, one mother and one father. The cost associated with cascade health services offered to each mother and the costs associated with cascade health services offered to each father were equal.

The mean cost of all cascade health services that should have been offered to the siblings of each proband was $1,399.72 ± 1,020.90 (**Table 25**). The mean cost of cascade genetic testing across

the entire study sample was $224.31 ± 384.61, while the mean cost of cascade screening was $1,175.41 ± 769.96 per proband. The mean cost of cascade clinical screening increased by $773.51 per proband compared with the reference case.

Table 25: Costs associated with cascade health services offered to probands' siblings, where all relatives were assumed to be phenotype-positive and of any genotype.

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL SIBLINGS					
		COST OF CASCADE GENETIC TESTING PER PROBAND[a]		COST OF CASCADE SCREENING PER PROBAND[a]		TOTAL COST OF ALL CASCADE HEALTH SERVICES PER PROBAND[a]	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	426.83	169.78	691.98	276.79	1,118.80	446.57
	HCM (n=9)	874.51	473.24	1,925.74	1,046.42	2,800.25	1,519.66
	RCM (n=1)	341.94	NA	553.58	NA	895.52	NA
	LVNC (n=3)	341.94	0.00	553.58	0.00	895.52	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**613.11**	**408.96**	**1,230.83**	**970.14**	**1,843.94**	**1,377.31**
INCONCLUSIVE	DCM (n=4)	0.00	0.00	1,522.35	945.42	1,522.35	945.42
	HCM (n=10)	0.00	0.00	873.72	305.74	873.72	305.74
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.00	NA[b]	1,107.16	NA[b]	1,107.16	NA[b]
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**0.00**	**0.00**	**1,130.80**	**644.92**	**1,130.80**	**644.92**
NEGATIVE	DCM (n=4)	0.00	0.00	1,660.74	903.99	1,660.74	903.99
	HCM (n=10)	0.00	0.00	998.53	529.55	998.53	529.55
	RCM (n=1)	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]	NA[c]
	LVNC (n=2)	0.00	NA[d]	553.58	NA[d]	553.58	NA[d]
	ARVC (n=1)	0.00	NA	1,107.16	NA	1,107.16	NA
	ALL (n=18)	**0.00**	**0.00**	**1,152.70**	**670.95**	**1,152.70**	**670.95**
TOTAL (N=53)		**224.31**	384.61	**1,175.41**	769.96	**1,399.72**	1,020.90

ARVC arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

All costs are in 2019 Canadian dollars. The cells shaded in blue represent a departure from the reference case.

[a]Includes only those probands with known siblings.
[b]There was only one proband with LVNC and an inconclusive genetic test result that had known siblings. Therefore, it was not possible to calculate the subsample standard deviation.
[c]There was only one proband with RCM and a negative genetic test result, and this individual did not have any siblings.
[d]There was only one proband with LVNC and a negative genetic test result that had known siblings. Therefore, it was not possible to calculate the subsample standard deviation.

Chapter 4:
Discussion

This chapter discusses the results of a scoping literature review and retrospective cohort study conducted to examine cascade genetic testing and clinical screening initiated in families after genetic testing in a child. First, key findings of the studies included in the scoping literature review are discussed, and strengths and limitations of the review are described. A discussion regarding the retrospective cohort analysis follows, beginning with the results of the primary analysis, secondary analysis, and then uncertainty analyses. The strengths and limitations of the retrospective cohort study are then discussed, followed by a presentation of this study's implications for health technology assessment (HTA) and Canadian stakeholders. The chapter concludes with recommendations for future research in this field.

4.1 Scoping Literature Review

This scoping review characterized the prior empiric research related to the pattern and costs of cascade health service use by the families of children with any condition diagnosed using genetic testing. In total, 20 studies were included. No thematic analysis was conducted, but the findings of each publication were summarized.

4.1.1 Key Findings

The included studies were conducted in a variety of disease states, including CMP (Alfares et al., 2015; Knight et al., 2020; Miller et al., 2013), FH (Truong et al., 2018; Wald et al., 2016; Wu et al., 2017), and HH (Cadet et al., 2005). One study (Stark et al., 2019) had a broader focus and was concerned with infants potentially affected by any rare monogenic disorder. In general, studies were conducted in diseases known to display incomplete penetrance and/or variable expressivity, like CMP (Alfares et al., 2015; Knight et al., 2020; Miller et al., 2013), FH (Truong et al., 2018; Wald et al., 2016; Wu et al., 2017), or β-thalassemia (Baig et al., 2008; Gorakshakar & Colah, 2009). Cascade testing and screening in the context of these types of conditions is unsurprising, as genotype and phenotype do not always correlate with one another. Asymptomatic individuals may still be at-risk and could require monitoring by a clinician. Two studies were conducted in CF (McClaren et al., 2013; McClaren et al., 2010). This condition displays high penetrance, but it is inherited in an autosomal recessive fashion so it can be

difficult to identify heterozygous carriers in a family through pedigree construction alone. This information may have implications for family planning, especially for relatives who may be at a reproductive age. One study was conducted in HH (Cadet et al., 2005). Since HH is typically an adult-onset condition (National Institutes of Health, 2020), the rationale for examining the effects that cascade from paediatric probands was unclear.

Studies mainly reported on the uptake and/or yield of cascade genetic testing in probands' family members. Uptake of testing varied in the studied conditions. For example, uptake of cascade genetic testing in the families of paediatric HCM patients ranged from 39% (Miller et al., 2013) to 65% (Knight et al., 2020). In contrast, uptake of cascade testing by family members of children with CF was low at 37% (McClaren et al., 2013), while uptake among families of infants suspected to have a rare monogenic condition was as high as 90% (Stark et al., 2019). Rate of uptake may be influenced in part by a condition's penetrance, expressivity, and inheritance pattern: the more direct relationship that exists between genotype and phenotype, the easier it may be for an individual to infer their carrier status based on the genotype of a relative, and the less the need for that person to undergo genetic testing themselves. For instance, some relatives of CF patients decline the offer of cascade screening because they "know [they] must be a carrier" (McClaren et al., 2013). The ability to infer one's carrier status though, is, of course, often complicated by the absence of certainty about the directness of the genotype-phenotype relationship. Treatability of disease is another factor that may play a role in uptake of cascade genetic testing, since it is conceivable that few or no treatment options may impede testing in risk-averse individuals. However, it appears that potential for receiving non-medically actionable results does *not* deter individuals from undergoing genetic testing. A study in individuals receiving WGS results found that, even though some participants were concerned about the psychological impact of receiving results around untreatable diseases, the majority would still want to receive those results because "the benefits of knowing outweigh the risks of being fearful" (Sanderson et al., 2016). Among adult research participants from families at high genetic risk of cancer who underwent WES or WGS, 97% preferred to receive both clinically-validated research genetic test results and incidental findings (Loud et al., 2016). The incidental findings were defined as "genetic changes with potential health implications unrelated to … cancer risk," so although not explicitly stated it is likely that some of these incidental findings would have been non-medically actionable (Loud et al., 2016).

Only two of the included publications addressed costs (Alfares et al., 2015; Stark et al., 2019), and of them only one (Stark et al., 2019) was a full economic evaluation. The findings of these studies will be discussed in more length to help interpret the results of the primary analysis conducted in the retrospective cohort study portion of this thesis.

4.1.2 Strengths and Limitations

One of the primary strengths of this scoping literature review was that inclusion was not limited by disease state. Additionally, a variety of different types of studies were included, from cohort studies to case reports. This enabled a more complete understanding of the state of research of cascade genetic testing stemming from a genetically diagnosed paediatric proband. Qualitative works were, however, excluded because they likely would not have provided meaningful data regarding the uptake, yield, or costs of cascade health service use. This is a limitation of the review, as understanding families' perspectives on cascade testing or screening could have provided important context and individual reasoning around the uptake of these services.

The main limitation, though, was the search strategy itself, despite having been developed in consultation with a librarian at SickKids. Of the included studies, only 3 (15%) were identified through an electronic search of Medline or Embase, and the remaining 17 (85%) were found manually. When designing the search, a great deal of emphasis was placed on capturing the idea of a paediatric proband. This was challenging in-and-of-itself, largely because authors described their index patient populations using a variety of terms. However, it is possible that the focus on a child as the index patient may have compromised the identification of papers with a combined paediatric and adult proband population. In addition, there is no MeSH term or Emtree subject heading for cascade genetic testing, so there is no index for articles specifically about this topic. There is wide variation in the keywords that authors use to describe cascade testing, for instance, some call it *cascade testing* or *cascade screening* (Cadet et al., 2005; Gorakshakar & Colah, 2009; Knight et al., 2020; Smith et al., 2007; Sorensen et al., 2013; Wu et al., 2017); others refer to it as *carrier screening* (McClaren et al., 2013; McClaren et al., 2010); others still describe it as *family screening* (Lafreniere-Roula et al., 2019). These terms were included as terms in the search strategy, however, they do not appear in the title, abstract, or list of keywords of all articles, for example, (Alfares et al., 2015). Moreover, some of the included papers were case reports or case series that did not have abstracts and or keywords at all, such as (Gorakshakar &

Colah, 2009), making it difficult to identify them through the search strategy despite their presence in the citation databases.

A future review on this topic, whether systematic or scoping in design, will be beneficial, with the search strategy being fully developed and validated by an expert, as well as submitted to peer review using the PRESS guidelines from CADTH (McGowan et al., 2016).

4.2 Retrospective Cohort Study

The purpose of this retrospective cohort study was to determine the pattern and costs of cascade genetic testing and clinical screening offered to the families of children with CMP. Cascade health service recommendations were first quantified according to clinical practice guidelines (Hospital for Sick Children, 2013, 2016), and subsequently with empiric data collected from the medical records of included paediatric probands.

4.2.1 Primary Analysis

In the primary analysis, the pattern of offered cascade health services was determined based on clinical practice guidelines (Hospital for Sick Children, 2013, 2016) and the cost of offered services was calculated.

4.2.1.1 Key Findings

In the reference case, only the relatives of genotype-positive probands were offered cascade genetic testing. These family members were offered familial mutation analysis (FMA) rather than a single gene test or a multi-gene panel, and they were assumed to be offered one test each. Across the study sample, 1.23 ± 1.83 cascade genetic tests were offered per proband, and the mean cost of cascade testing was $418.64 ± 621.79 per proband. The fact that the SD exceeds the mean indicates that the costs of cascade testing are not normally distributed. This occurred because all of the costs resided with genotype-positive probands (i.e., cascade genetic testing costs were associated with only 19/53 probands, or 36%).

The relatives of all probands were offered cascade clinical screening, with all relatives being offered one ECG and one echocardiogram. In addition to these two screens, family members of ARVC probands were offered a 24-hour Holter monitor. Overall, 3.40 ± 1.29 ECGs, 3.40 ± 1.29

echocardiograms, and 0.08 ± 0.55 24-hour Holter monitors were offered per proband. The mean cost of cascade screening was $754.55 ± 293.26 per proband. The mean total cost of cascade health services offered to probands' families within the one-year study period was $1,173.19 ± 746.92.

As stated in section 2.2.5.1 of this thesis, cascade testing following an inconclusive result in the proband may be done on a case-by-case basis, but consultation with an expert cardiologist clarified that such testing would still be considered as diverging from guideline recommendations (S. Mital, personal communication, 2019). Guideline stipulations to only offer cascade genetic testing to the families of genotype-positive probands are sensible; it is not possible to recommend FMA without knowing which mutation to look for, and it is highly unlikely that a multi-gene panel would yield a positive result in a family member when it did not yield a result in the proband (false negatives notwithstanding). However, relatives of genotype-inconclusive and genotype-negative probands may still be at risk of developing CMP, especially because the genetic aetiology of this disease is poorly understood. Therefore, while cascade genetic testing in these individuals may not be warranted, the current practice of offering them cascade *screening* should not be viewed as wasteful. It is possible, for instance that a proband may possess a pathogenic mutation in a gene not yet known to be associated with CMP, and thus not interrogated on standard CMP panels. If so, relatives could carry the same mutation and also have a genetic risk, and would require clinical surveillance. It is important to emphasize that this is a distinct situation from relatives who undergo genetic testing themselves and receive a negative genetic test result. Ongoing clinical surveillance in these genotype-negative relatives is generally considered unnecessary, as there is generally a high level of confidence that they will not develop the disease (Deo & MacRae, 2010). This is recognized in clinical practice guidelines, which state that clinical screening is not indicated in relatives who are found to be genotype-negative unless they develop a phenotype consistent with CMP (Hospital for Sick Children, 2013, 2016).

Keeping this in consideration, it becomes clear that the costs of cascade screening calculated in this thesis are likely an over-estimate. In the reference case, no assumptions about relatives' genetic testing results were made, so all family members were considered genotype-unknown. As a result, all relatives were assumed to receive cascade screening consistent with the subtype of CMP in their proband. In reality, a portion of family members who received screening in this

analysis would have had a negative genetic test result and would *not* have undergone screening. This avoidance of cascade ECGs, echocardiograms, and/or 24-hour Holter monitors would have decreased the mean cost per proband of offered cascade health services. Nonetheless, it was important to structure the analysis such that all relatives were assumed to undergo cascade clinical screening. It is a possible scenario that captures a greater volume of resource use and is thus a better reflection of the maximum consumption and costs that the health care system should be prepared to support. A scenario in which a portion of relatives received a negative genetic test result was *not* explored in uncertainty analysis. This will be discussed later in this chapter.

4.2.1.2 Comparison with Previously Published Literature

There have only been a handful of studies to explore the costs associated with cascade testing in CMP (Alfares et al., 2015; Catchpool et al., 2019; Ingles et al., 2012; Sabater-Molina et al., 2013; Wordsworth et al., 2010). Even so, it is difficult to compare the results of the primary analysis undertaken here with previously published literature. Wordsworth and colleagues (Wordsworth et al., 2010) conducted a model-based CEA to compare the effectiveness of cascade genetic testing with cascade clinical screening for identifying HCM in the asymptomatic children of HCM patients. Their analysis was undertaken from the perspective of a hospital in the United Kingdom, and they adopted a lifetime time horizon. They compared four different cascade genetic testing and/or screening strategies. The strategy most similar to the guidelines applied in this thesis consisted of cascade genetic testing with repeated clinical investigations once every five years. The discounted lifetime cost of this strategy was approximately €21,803 (2007 currency, equivalent to 2007 CDN $32,031) per HCM patient. Wordsworth and colleagues did not break this cost down to show what proportion was due to cascade genetic testing and what proportion was due to periodic clinical surveillance. They also incorporated a number of services in their analysis that were not included in this thesis, such as implantation of an ICD in high-risk relatives. The difference in time horizons as well as health services included between the study by Wordsworth *et al*. and this thesis precludes a direct comparison of findings. However, it is possible to compare the unit prices used by Wordsworth and colleagues to those in this thesis. In the work by Wordsworth *et al*., the unit prices of a 12-lead ECG, echocardiogram, and a 24-hour Holter monitor were €32 (2007 CDN $47), €68 (2007 CDN $100), and €66 (2007 CDN $97), respectively. In this thesis, the unit prices of those resources were $11.05, $208.80, and $104.50, respectively. The unit price of one genetic counselling session in Wordsworth and

colleagues' study was €148 (2007 CDN $217), while the unit price of one (15-minute) session in this thesis was $14.27. Therefore, with the exception of the unit price for an ECG and for one genetic counselling session, the unit prices found by Wordsworth *et al*. are lower than the ones in the present analysis.

Another model-based study sought to determine the cost-effectiveness of cascade screening combined with cascade genetic testing, compared with cascade screening alone, in the family members of individuals with HCM (Ingles et al., 2012). Ingles and colleagues found that the addition of genetic testing to clinical screening had an incremental cost of AU $305 (2011 currency, equivalent to 2011 CDN $304) per family and an incremental effect of 0.389 QALYs. In 2019 Canadian dollars, this incremental cost is approximately $358.14. This is similar to the cost of cascade genetic testing per proband of $418.64 that was calculated in this thesis. However, Ingles *et al*. explicitly assumed that a portion of family members who underwent cascade testing would have a negative genetic test result and would consequently no longer undergo clinical surveillance. Therefore, the incremental cost of adding cascade testing to cascade screening presented in (Ingles et al., 2012) represents the cost of genetic testing in family members, *minus* the cost of cascade screening avoided in genotype-negative relatives. It is not possible to compare the unit prices of health services used by Ingles and colleagues to the ones in this thesis, as Ingles *et al*. provide unit prices in an aggregate format. For instance, the cost of a cascade test includes the cost of pre- and post-test counselling with a clinical geneticist.

In a 2013 publication (Sabater-Molina et al., 2018), genetic testing of HCM probands and genotype-negative relatives was determined to cost €220,710 (2012 currency, equivalent to 2012 CDN $327,887) less than the periodic screening those family members avoided as a result of receiving negative test results. Genetic testing of ARVC probands and their genotype-negative relatives was €9,405 (2012 CDN $13,972) less costly than the periodic screening avoided by those family members. A lifetime time horizon was used, and the costs presented were for the entire study subsample in question, rather than on a per proband or per relative basis. The generalizability of these results is limited because Sabater-Molina and colleagues did not include the cost of clinical examination in probands or family members who received a positive genetic test result, or the cost of genetic testing and clinical investigations in genotype-positive relatives in their analysis. More than that, the pattern of cascade clinical screening offered to first-degree relatives was different than the one identified in this thesis: an ECG and echocardiogram was

offered to family members of HCM patients; and an ECG, signal-averaged ECG, echocardiogram, and cardiac MRI was offered to family members of ARVC patients. The unit prices identified by Sabater-Molina and colleagues for FMA and ECG were higher than those found in the present study: €250 (2012 CDN $371) *versus* $337.18 per FMA; and €51.40 (2012 CDN $76) *versus* $11.05 per ECG. However, the unit price per echocardiogram was higher in this thesis: $208.80 *versus* €95.80 (2012 CDN $142) in the study by Sabater-Molina *et al*.

Finally, Catchpool and colleagues (Catchpool et al., 2019) conducted a CUA to assess the cost-effectiveness of cascade genetic testing in addition to periodic clinical surveillance, compared with clinical surveillance alone, in the asymptomatic relatives of DCM patients. They found that the incremental cost per relative of adding genetic testing to clinical screening was AU $300 (2018 currency, equivalent to 2018 CDN $291); the incremental gain in QALYs was 0.04; and the calculated ICER was AU $6,100 (2018 CDN $5,909) per QALY. Similar to (Wordsworth et al., 2010), Catchpool and colleagues (Catchpool et al., 2019) included a number of services in their analysis that were not included in this thesis. For example, they incorporated pharmacological management of DCM as part of clinical surveillance. They also included events such as ICD implantation or SCD. Aside from the unit price associated with a cascade genetic test, the unit prices identified by Catchpool *et al*. are greater than those found in this thesis.

The four publications discussed above all had adult proband populations. To date, there has only been one study to investigate cascade testing of relatives of genetically diagnosed paediatric probands using economic evaluation (Stark et al., 2019). However, the probands included were suspected to have a variety of rare monogenic disorders, not only CMP, and there are some methodological concerns that may limit the applicability and comparability of Stark and colleagues' results to those of this thesis. For example, they did not indicate which tests or services each relative received. It is unclear whether family members underwent WES or targeted gene tests based on the infant's test results, nor is the number of genetic counselling sessions per relative disclosed. Therefore, it is difficult to understand exactly how the total cost of cascade testing (AU $28,000; 2018 currency, equivalent to 2018 CDN $27,124) was calculated. They also presented a cost-utility analysis that examined the changes in costs and hypothesized QALYs due to changed management, cascade testing, and reproductive planning in the patients and their first-degree relatives. However, their methods do not clearly describe the

counterfactuals used (i.e., the outcome in the absence of the interventions) were based upon conjecture rather than real patients (there was no control group).

There was one study with a combined adult and paediatric proband population to present cost information, though it was not a full economic evaluation (Alfares et al., 2015). Alfares and colleagues found that, among asymptomatic family members of probands positive for HCM-associated mutations, 57% received a negative genetic test result and therefore no longer needed the cardiac evaluations recommended for high-risk relatives. This translated to lifetime health system savings of approximately US $1,000 per (2015 currency, equivalent to 2015 CDN $1,279) family member, based on the Medicare fee schedule.

4.2.2 Secondary Analysis

In the secondary analysis, the pattern of offered cascade health services was determined based on empiric data extracted from the medical records of paediatric CMP probands.

4.2.2.1 Availability of Relative Data from Proband Medical Records

The data for first-degree relatives available from probands' medical records was fairly sparse. This was especially true of cascade genetic testing data: of 53 families, the genetic testing status of one or more relatives was known for only 33 (63%), and of the 180 individual family members captured in analysis, the testing status was only known for 84 (47%). Missing data was less pronounced for cascade clinical screening: the screening status of one or more relatives was known in 50/53 (94%) families, and the screening status was known for 158/180 (88%) individual family members.

There was little detail about the nature of the cascade health services that were offered, for both genetic testing and clinical screening. The type of genetic test offered was only specified for 4 of the 33 families (12%) for whom genetic testing data were available. All four of those families were offered FMA, and although it is likely that the other 29 families were also offered FMA, this remains an assumption in the absence of data to confirm. For the four families known to have been offered FMA, only one type of testing was indicated for the family as a whole, as opposed to listing the type of genetic testing offered to each individual relative. It is most probable that all family members were offered the same type of test, but without corroborating

data, this too is an assumption. Furthermore, no empiric data were available regarding pre- and post-test genetic counselling.

In terms of cascade screening, if an offer was made, the type of screen was typically listed, with this information being known for 133 of the 151 (88%) relatives who were offered screening. However, the number of each type of screen that each relative was offered or the frequency of screening within the one-year study period were not provided.

Importantly, the outcome of cascade genetic testing or screening was not available. This was a significant gap. Family members' genotypes influence the type and volume of clinical screening they are offered, so relatives' genetic testing results could have provided context for the observed pattern of cascade screening offers. Moreover, if any clinical screens revealed that a family member was beginning to display a CMP phenotype, this may have prompted additional screening and could potentially help explain why some relatives were offered services such as a cardiac MRI or stress MIBI that were atypical among the study sample.

There were instances where the cascade health services offered represented a perplexing divergence from clinical practice guidelines. For example, some relatives of genotype-inconclusive and genotype-negative probands were offered cascade testing. This recommendation, particularly with regard to the families of genotype-negative probands, is unusual, and at first glance appears to be an inappropriate use of health care resources. That is not necessarily the case, and it would have been useful if information regarding the reasoning behind these offers of testing were available to provide a more complete picture of the clinical context for these families. This information would also shed light on some of the clinical dilemmas that physicians may encounter for which further guidance could be beneficial. Recommendations that may reflect inattention to or inappropriate use of clinical practice are discussed in greater detail in subsection 4.2.2.2.

While data for first-degree relatives available from probands' medical records were incomplete, data for second-degree relatives were nearly non-existent. For the entire study sample, only six second-degree relatives and two third-degree relatives from four families were identified, consisting of two grandparents, two uncles, two aunts, and two cousins. For the other 49 families, it was unclear whether this lack of information about second-degree relatives was because none of those relatives were offered cascade genetic testing or screening, or because

those relatives did not exist (i.e., the proband did not have grandparents, aunts, or uncles). In fact, data regarding the size of probands' families were completely unavailable. The siblings included in analysis were only identified because some form of information about an offer of cascade health services was provided. In some cases, siblings were not mentioned at all in the context of cascade testing, but appeared in the cascade screening data. When this occurred, it was assumed that the sibling(s) in question did not receive genetic testing, but their test status was still considered unknown in analysis. Likewise, it is possible that probands have siblings that were not involved with any form of cascade health service use and as a result were completely omitted from proband medical records. While this information was likely available in the family history, a detailed family history was not included in this dataset.

Of the included probands, 8 (15%) had undergone multiple genetic tests. Of those eight, the cascade genetic testing status of all family members was unknown for four. The most recent genetic test in a proband was considered the index test, and only health services offered to relatives within one year of that test were considered part of the cascade. It is therefore possible that some family members underwent genetic testing following a proband's first test, but not after the index test. No data were available (or none were collected) about this type of prior testing in relatives. Importantly, all included probands were true probands, meaning that in all cases, they were the first person in the family to be diagnosed with CMP and to undergo genetic testing. As a result, for the 45 (85%) probands who only had one genetic test, it would not have been possible for any prior testing to have occurred in family members.

It must be stressed that lack of family data in a proband's medical record does not necessarily mean that cascade health services were not offered. Rather, it is entirely possible that cascade testing and screening were appropriately offered, but simply not documented in the paediatric proband's chart. This raises the question as to the appropriateness of documenting information about parents, siblings, and second-degree relatives in children's medical records. One reason is that offers of cascade health services – or at minimum of cascade genetic testing – are often made during the post-test genetic counselling session where probands' genetic tests are discussed with their parents. The offer, or lack thereof, of cascade testing would therefore conceivably be an important part of the counselling conversation that a clinician would document. Alternatively, offers of cascade health services could be perceived as a component of a patient's broader

management plan, and would, in this case, also be worth describing in the proband's medical records.

4.2.2.1.1 Obtaining Better Data

The incompleteness of data regarding cascade health service use available from proband medical records impedes the ability to accurately trace family members' interactions with the health care system. This issue was obvious despite the short time horizon of this study and the narrow focus on first-degree relatives only. Simply put, to address the question at hand, better data are required.

There are a number of ways that better data could be obtained. Perhaps there should be a concerted effort to make recording cascade health service offers and uptake in proband medical records a component of standard practice. Of course, this is not the most feasible solution. Some clinicians may be resistant to incorporating this additional information in their patient notes because it would require additional time – a resource that is already in high demand and low supply – and clinical documentation is already a leading cause of lost physician productivity (Lin et al., 2018). Others may view it as extraneous information since the child is their patient, not their parents or siblings. However, one of the most important constraints may be that recording information about family members in a child's medical records could jeopardize those relatives' privacy. Any individual accessing the child's records would also learn confidential information about that child's relatives, potentially without consent, which is a significant ethical concern.

Alternatively, better, more complete data could be collected by expanding the data source to include the medical records of family members in addition to those of the proband, and linking relatives' charts to their proband's. It is much more likely that any genetic testing or clinical screening offered to a relative would be noted in that individual's records, along with other valuable information such as: the results of those tests and/or screens, any physician assessments or referrals to specialists, or any medications that may have been prescribed to prevent the development of symptoms or of a CMP phenotype. Moreover, the use of genetics and genomics in clinical care is increasing rapidly. By definition, these technologies require and promote a holistic, family-centred approach to care, and therefore *necessitate* the linkage of records between individuals.

More than just accessing relatives' records, it could also be illuminating to speak with family members directly or ask them to fill out a form about the health services they were offered as a result of their paediatric proband's genetic testing. This is certainly not a perfect solution either. Some families may not wish to participate. In the case of a retrospective study such as this one, the proband's genetic test and the resulting cascade genetic testing may have occurred even a decade in the past, and if a patient has moved or is under the care of a new physician, it may be difficult to contact them or their family.

Enhanced uptake of technology as well as the implementation of new technologies may help mitigate or overcome challenges around data availability. One of the issues with accessing relatives' records is that family members may have different physicians who work in different care settings, and depending on the clinician, patient charts may well still be in paper form. As of 2017, over 13,000 physicians in Ontario used EMRs in their practices, but this still only represented an adoption rate of 71% among family physicians and 55% among community-based specialists (Jones et al., 2017). Increased uptake of EMRs and better integration of EMR systems used in different care settings may help researchers access family members' complete records more easily, should these records be explored as a data source for cascade testing and screening information in the future (patient consent and institutional ethics approval may still be required). Systemic supports may be necessary to promote increased uptake, as some of the barriers hindering physicians from adopting EMRs may be beyond their control, for instance financial barriers related to high up-front and maintenance costs of EMR systems and technical issues that exceed the troubleshooting capabilities of physicians and their staff (Boonstra & Broekhuis, 2010). Integration of different EMR systems is also necessary to ensure completeness of data: health care providers (HCPs) use a variety of separate EMR systems which may be unable to connect with one another, so clinicians at different practices may not be able to access all records pertaining to a particular patient. eHealth Ontario began working to remedy this through the implementation of a provincially-integrated electronic health record system (EHR) in 2008 (eHealth Ontario, 2015; Office of the Auditor General of Ontario, 2016). Where an EMR is a partial health record maintained by a provider about a patient that is not designed to be shared outside of an individual practice, an EHR is a complete health record of a patient generated at multiple practices by multiple clinicians and is meant to be shared among authorized providers (Garrett & Seidman, 2011). Unfortunately, the current status of eHealth Ontario's project is

unclear, and it is difficult to predict when a fully integrated provincial EHR will be available. In the meantime, there has been a call to 'start from scratch' and build a single, national EHR system to facilitate better patient care as well as the creation of data sets for research purposes (Persaud, 2019).

4.2.2.2 Key Findings

The observational data used in the secondary analysis suggested that clinical practice sometimes diverges from recommendations stipulated in guidelines. Proband medical records showed that a mean of 1.58 ± 1.17 cascade genetic tests were offered per genotype-positive proband, and across the study sample, 1.19 ± 1.35 genetic tests were offered per proband. In other words, not all relatives of mutation-positive probands were offered cascade genetic testing (or not all offers were recorded) and some relatives of genotype-inconclusive and genotype-negative probands were offered cascade genetic testing as well.

Regarding the families of genotype-positive probands, and putting aside those families where test status was unknown for all relatives, there were two probands whose sole sibling was explicitly not offered cascade genetic testing. At first glance, it appears that in these families clinical practice guidelines may not have been strictly adhered to. However, in both cases, one or more parents were offered testing. It is therefore possible that the parent(s) received a negative result, indicating that the pathogenic variant in question was not familial, eliminating the need to conduct genetic testing on other children in the family. Of course, data about relatives' genetic testing results would be necessary to confirm that this was indeed the case, but it is one explanation for the observed pattern of offered testing. There were also two families in which, of the parents, only the father was offered genetic testing and the test status of the mother was unknown. One possible explanation for this was that only the fathers in each case were biological parents of the proband (i.e., the mother may have been a step-mother). Ideally, only relatives who were genetically related to the proband would have been included in this study, however detailed information about probands' family structures was not available, and as a result, it is possible that step-parents or step-siblings may have been inadvertently captured in analysis.

Clinical practice guidelines for CMP state that "genetic testing is not indicated in relatives when the index patient does not have a definitive pathogenic mutation" (Hospital for Sick Children, 2013) and cascade testing "should only be offered to relatives if [the] index case tests gene-

positive" (Hospital for Sick Children, 2016). Given this, it was somewhat unexpected to find that cascade genetic testing was offered to 11/16 (68%) families of a child with an inconclusive test result. However, it was also anticipated to a certain extent, as there are important reasons from both a scientific and clinical perspective to provide testing to these relatives. For example, assessing whether parents possess the same variant of uncertain (or unknown) significance (VUS) as their child could indicate whether the mutation was inherited or arose *de novo* and could help elucidate CMP aetiology. This is mentioned in paediatric DCM clinical practice guidelines (Hospital for Sick Children, 2016), but, as was indicated in section 2.2.5.1 in the second chapter of this thesis, discussions with an expert cardiologist at SickKids (S. Mital, personal communication, 2019) made it clear that in general, cascade genetic testing of the families of a genotype-inconclusive proband would be a departure from standard practice. Even so, it may be important that clinicians know whether a relative carries the same VUS as the proband, as laboratories may reclassify VUS, either upgrading them to pathogenic status or downgrading them to benign (Hoffman-Andrews, 2017). This affects the clinical management of any family members possessing the same variant, since screening guidelines are different for genotype-negative and genotype-positive individuals (Hospital for Sick Children, 2013, 2016). Guidelines (Hospital for Sick Children, 2013, 2016) do not specify a screening protocol for those cases in which a VUS is identified in family member.

In contrast, the finding that 4/18 (22%) families of a genotype-negative proband were offered cascade genetic testing was unexpected, and diverges from guidelines (Hospital for Sick Children, 2013, 2016). It is clear that these relatives did not undergo FMA since no mutation was identified in the paediatric proband, but data as to what type of genetic testing was offered were not available. One possibility is that relatives began to display symptoms indicative of CMP, so there was a clinical reason to offer genetic testing. Alternatively, it is possible that the decision to proceed with cascade genetic testing was made prior to receipt of proband test results, though this would be unusual since cascade health service recommendations depend on the genotype of the index patient. Regardless, there is precedent in the literature to provide testing to relatives of genotype-negative probands: in 2018, Ko and colleagues (Ko et al., 2018) found that 64 relatives of mutation-negative HCM probands with no family history of HCM had undergone cascade genetic testing. Two of those relatives were found to possess a pathogenic HCM-related mutation

(Ko et al., 2018). The phenotypes of these family members were not specified, so it is possible that they did have some clinical indication of disease.

In five families across the present study sample, one or more siblings were explicitly not offered cascade genetic testing, despite the fact that at least one parent or at least one other sibling was offered testing. It is possible that the siblings who were not offered testing were too young. Although clinical practice guidelines employed at SickKids (Hospital for Sick Children, 2013, 2016) do not specify an age at which cascade health services should begin to be offered to children, American guidelines state that, unless a child meets early screening criteria, screening should commence after age 12 (Gersh et al., 2011). European guidelines are similar, though they indicate screening in children should begin at age 10 (Elliott et al., 2014). As such, prior to indicated clinical screening, cascade genetic testing would be considered premature.

In terms of cascade screening, screening was offered to 2.85 ± 1.49 relatives per proband, with 0.94 ± 1.67 ECGs, 2.51 ± 1.69 echocardiograms, and 0.08 ± 0.43 24-hour Holter monitors being offered per proband. Whether or not screening was offered to one or more relatives in a proband's family was known for 50/53 (94%) probands. Of the family members whose screen status was known, 151/158 (96%) were offered screening. This represents close adherence to clinical practice guidelines, though all relatives should have been offered screening. All seven individuals who were not offered screening were related to a genotype-inconclusive or genotype-negative proband. Five of these individuals belonged to the same family (a mother, father, and three siblings), and it is unclear why they did not receive screening. The other two individuals, a mother and father from two different families, both underwent cascade genetic testing. It is possible that they received a negative genetic test result and as a consequence, it was no longer necessary for them to proceed with clinical investigations. However, more data pertaining to these individuals would be necessary to confirm this.

Although clinical practice guidelines indicate that all relatives (except for those who are genotype-negative) should be offered an ECG and echocardiogram, the observational data showed that very few family members were offered an ECG, but that the majority were offered an echocardiogram. Although changes on an ECG may appear before structural changes are apparent, echocardiography has greater specificity and therefore it is possible that the clinicians caring for these probands and their families felt an echocardiogram would be a more effective

tool for determining whether relatives were displaying a CMP phenotype (Deo & MacRae, 2010). If that is the case, it indicates that physicians are using health care resources judiciously and avoiding wasteful screening, while still providing their patients with appropriate care.

There were four individuals who received a cascade clinical screen that was not indicated according to clinical guidelines. Specifically, the mother and father of one proband both received a cardiac MRI and a stress MIBI, one sibling of an LVNC proband received a 24-hour Holter monitor, and one sibling was assessed using a fetal ultrasound. Although this is a departure from guidelines, clinicians must be given room to order screens that they believe will have an impact on the way in which they manage the care of a particular patient or family member. It is possible that the fetal ultrasound was performed for a non-CMP related reason. These ultrasounds are typically used to confirm pregnancy, evaluate fetal growth, identify certain birth defects, etc. (Mayo Clinic, 2019), while fetal *echocardiograms* are well-established tools for the diagnosis of fetal CMPs (Pedra et al., 2002; Zielinsky, 1991). However, the rationale for the offer of this cascade screen was not available.

While offers of cascade genetic testing and screening were not uniform from family to family, they were generally similar between relatives of the same type within the same family. In other words, mothers and fathers within one family usually had the same pattern of offers as one another, and siblings within one family were also usually offered the same cascade health services as one another. The test or screen status of related siblings was also usually the same. For example, if screening was performed in one sibling, it was typically pursued by all siblings in that family.

4.2.2.3 Comparison with Previously Published Literature

Of the 61 relatives who were offered cascade genetic testing in the present study, 28 (46%) accepted, and of the 151 relatives who were offered cascade screening, 120 (79%) accepted. Previously published uptake rates of cascade genetic testing in the context of CMP or other cardiac conditions have been highly variable, though the rate observed in this study is within the range seen in previous studies. Christiaans and colleagues (Christiaans et al., 2008) found that uptake of cascade genetic testing among first- and second-degree relatives of HCM patients was approximately 39%. Miller *et al.* (Miller et al., 2013) found that uptake of genetic testing was 51% among first-degree relatives and 16% among second-degree relatives of HCM and DCM

probands. Knight and colleagues (Knight et al., 2020) reported a higher uptake rate of cascade genetic testing: 65% among the families of probands with HCM. The highest rate of uptake was found by (Christian et al., 2018), who reported that 66% of children of parents with HCM, ARVC, or LQTS underwent genetic testing. There have not been studies to quantify the uptake of cascade clinical screening alone following genetic testing of an index patient.

These uptake rates are higher than have been observed in other disease states. For example, only 16.3% of relatives of children with CF accepted the offer of cascade genetic testing (McClaren et al., 2013). As was discussed in section 4.1.1 of this chapter, rates of uptake of genetic testing may be influenced by a condition's penetrance, expressivity, and inheritance pattern, with there potentially being a lesser impetus to engage in testing for conditions with clear genotype-phenotype relationships.

4.2.2.4 Costing

The cost of cascade health services based on data extracted from proband medical records was not calculated. The rationale for this was threefold. To begin, the quality of the data specific to cascade health service use were poor, with a great deal of data missing. Any cost calculation would have relied heavily on assumptions, and therefore would not reflect the cost of *observed* health service recommendations based on *empiric* data. In addition, there is a concern about the generalizability of the empiric data; there may be variations in practice among HCPs, as well as between institutions. Calculating the cost of health services offered according to clinical practice guidelines mitigates this concern as these guidelines help standardize care and can easily be applied to multiple jurisdictions. Finally, HTA and health economics methodology dictate that recommended rather than observed practice be modelled since health policy and funding decisions are made for entire populations based on optimal care and should not be based on information specific to a single practice, institution, or region (CADTH, 2017).

4.2.3 Uncertainty Analyses

A number of one-way sensitivity and scenario analyses were conducted to assess the effect of uncertainty on the calculated costs of guideline-based cascade health service offers in the primary analysis.

4.2.3.1 One-Way Sensitivity Analyses

The cost of guideline-based cascade health service recommendations was most sensitive to variations in the cost of FMA, with health services costing a mean of $1,069.81 ± 607.36 per proband when the cost of FMA was at its minimum unit price of $252.89 per test, and $1,276.57 ± 891.21 per proband when the cost of FMA was at its maximum unit price of $421.48 per test. This finding highlights that FMA in relatives, though a relatively inexpensive service on its own, can lead to nontrivial consumption of health care resources within a family. Decisions about genetic testing must be made judiciously, and clinicians need to carefully consider whether cascade genetic testing is truly appropriate. This finding is especially important in the face of emerging genetic and genomic technologies such as WGS, which are associated with very high per sample costs (Tsiplova et al., 2017). These technologies will be discussed in more depth later in this chapter.

4.2.3.2 Scenario Analyses

In the two scenario analyses that were conducted, a greater volume of cascade clinical screening was offered to probands' family members than in the reference case, leading to an increase in the mean cost of cascade health services per proband. When all relatives were assumed to be genotype-positive, the mean cost of cascade health services per proband was 1.16 times that of the reference case, and when all relatives were assumed to have a CMP phenotype, regardless of their genotype, the mean cost of cascade health services per proband was 2.26 times that of the reference case. Given the effect that relatives' genotypes and phenotypes have on costs to the health care system, these scenario analyses draw attention to the importance of data availability regarding the results of relatives' genetic tests and clinical investigations. Without understanding the proportion of family members who receive positive and negative genetic testing results, or the proportion who, upon investigation, are revealed to have clinical CMP, it is not possible to construct a more accurate picture of the implications of cascade testing and screening on the health care system.

Despite this, no scenario analysis in which a proportion of relatives across the study sample, or even within the same family, were assumed to be genotype-negative and a proportion were assumed to be genotype-positive was conducted. Only a small number of studies have explored the yield of cascade genetic testing in the families of paediatric probands with CMP (Alfares et

al., 2015; Knight et al., 2020; Miller et al., 2013). These publications reported similar results: (Knight et al., 2020) found that 37% of relatives from HCM families who underwent cascade genetic testing received a positive result; (Alfares et al., 2015) found that 42% of family members of probands with HCM were genotype-positive; and (Miller et al., 2013) found that 40% of asymptomatic relatives of index patients with HCM or DCM had a positive genetic test. While these studies could have been used to estimate that cascade testing for HCM would yield approximately 40% genotype-positive relatives and 60% genotype-negative relatives, their results could not be applied to DCM, RCM, LVNC, or ARVC because the yield of genetic testing in the different subtypes of CMP are different (Ouellette et al., 2018). It would also not have been possible to estimate the yield of cascade genetic testing for these four CMP subtypes using the yield of genetic testing in index patients, as genetic testing yields are different among probands than among their family members (Alfares et al., 2015; Knight et al., 2020; Miller et al., 2013).

4.2.4 Strengths and Limitations

Until now, cascade investigations have generally been performed and studied in families where one or multiple parents were diagnosed with a disease and children in the family were assessed afterward to determine if they had inherited the condition. One of the main strengths of this analysis is the focus on cascade testing and screening that proceeded in the opposite direction, beginning with children and radiating outward to their families. Genetic and genomic technologies are being applied to the paediatric care setting with increasing frequency, and in some institutions such as SickKids, offering cascade testing to the families of children with a genetic diagnosis is already the standard of care. The implications of this child-to-relative testing and screening therefore represent a pressing policy question of interest to Canadian stakeholders.

Another strength was the use of empiric data to assess whether proband medical records are an adequate source of information about cascade testing and screening. This is an important consideration as HTA methodology evolves and best practices for these types of analyses are established.

Additionally, the pattern of care for a child with CMP and estimates of volume of resources offered to families were elucidated through consultation with clinical experts at SickKids, including both a cardiologist and a genetic counsellor involved in the care of patients with this

condition. As a result, it was possible to account for resources not explicitly described in clinical practice guidelines, such as the number and length of genetic counselling sessions provided to the relatives of paediatric probands.

Another strength of the secondary analysis in the context of the particular aims of this thesis was that all health services offered to relatives within the study period were included, rather than only those offers that were accepted. It is possible that cascade testing or screening may have been offered to an individual within the study period, but that that individual chose to engage in the offered clinical activities after the one year elapsed. Such clinical activities would have been omitted had the analysis focused solely on consumed services.

It is important that the findings of both the primary and secondary analyses be interpreted within the context of certain limitations, one of the most important of which was limited data availability from medical charts. The extent to which data were missing from proband charts and the challenges this posed to interpreting the results of analysis have already been described earlier in this chapter. Another limitation was the fact that chart review was restricted to the proband's medical records, as more information about family members would have been available from the records of those relatives themselves. However, it is a strength of this study that the uncertainty introduced due to the incomplete nature of the data was assessed in one-way and scenario analyses.

A further limitation of the retrospective cohort study was that it only accounted for the initial cascade genetic test and screens underwent by relatives, while health services accessed as a follow-up to those cascade investigations were not considered. For example, depending on the outcomes of their tests and screens, family members may have received additional physician appointments, referrals to other specialists, or prescriptions for medications. All of these events would have resulted in costs to the health care system that are important to capture but cannot be quantified without more granular patient level data from relatives' medical records, questionnaires administered to these family members, or administrative data.

Finally, while this study provides important information about the costs and patterns of cascade services, the direct implications of this analysis on health policy may be limited because the health outcomes of relatives were not incorporated. On the one hand, cascade health services lead to consumption of scarce health resources. On the other hand, individuals' health, survival,

and quality of life may be improved by detecting a potentially fatal disease early, or perhaps preventing it entirely. Health resources may also be conserved to a certain degree through the cessation of unnecessary clinical surveillance. It is important to understand where the balance lies of benefits and burdens to the system and to individuals lays in order to make data-driven and well-reasoned health policy or funding decision at the population level.

4.2.5 Implementation of Emerging Technologies

Emerging genetic and genomic technologies such as WGS are being used with increasing frequency in the clinical setting. At the Cardiac Genome Clinic at SickKids, health services research is being conducted to better understand how to implement clinical WGS in children with heart failure, including those with heart failure caused by CMP (Jegathisawaran et al., 2020). WGS has a greater diagnostic yield than conventional genetic tests and WES, and it has been suggested that early use of this technology in the diagnostic process could be appropriate (Lionel et al., 2018; Mattick et al., 2018; Stavropoulos et al., 2016). Additionally, previously published CEAs comparing WES or WGS to conventional genetic testing have estimated that WES and WGS are cost-effective for children on protracted diagnostic odysseys (Schofield et al., 2017; Soden et al., 2014; Stark et al., 2017). However, none of these studies considered cascade testing in patients' families, and the cascade health service use following WGS could be quite costly.

If a child receives WGS, family members may receive the same cascade genetic testing as they would following a single gene or multi-gene panel in a child (i.e., after receipt of the proband's test results, family members could be offered FMA for any pathogenic variants identified in the child). However, genomic analysis with WGS does not only yield results related to CMP. The ACMG has published a list of conditions, genes, and variants that they recommend should be returned to patients as secondary findings following clinical WES or WGS (Green et al., 2013). Though there are ethical concerns associated with seeking and reporting secondary findings in children, and policy on this issue has not been finalized in Canada, the ACMG has indicated that they are outweighed by the potential benefit of information relating to the mutations on their list to the future health of the child or the health of the child's family members (Green et al., 2013). Depending on the secondary findings found in the proband, relatives may be offered FMA for multiple mutations, which could increase the cost of cascade genetic testing per proband.

Alternatively, in a clinic offering, WGS testing of family members could occur simultaneously with WGS in the index patient. For example, at the Cardiac Genome Clinic, the paediatric proband and their parents are considered a trio, with their genomes sequenced with WGS at the same time (Jegathisawaran et al., 2020). A microcosting analysis of a five-year program at SickKids estimated that the cost of WGS per trio for cardiac conditions in the first year was $8,053.10 (Jegathisawaran et al., 2020). Assuming a trio WGS replaces cascade genetic testing, the upfront costs associated with genetic testing in a patient's relatives will clearly increase. However, it could lead to lower long-term costs to the system if morbidity is avoided or mitigated by early identification of disease risk in a larger number of people.

WGS may also result in lower costs to the health care system for the diagnosis of the index patient, especially if it is deployed early in the diagnostic pathway. Approximately 50% of patients with rare genetic diseases never receive a diagnosis (Shashi et al., 2014). These patients often embark on diagnostic odysseys, wherein numerous consultations with specialists, imaging studies, laboratory testing, etc. are undertaken (Sawyer et al., 2016). Diagnostic odysseys are, by definition, slow and costly, and WES and WGS are currently deployed in an effort to end them (Shashi et al., 2014). A large amount of time and money could be saved by employing these technologies earlier in the diagnostic pathway, although this may be context-sepcific as, in some populations, second-tier WGS is more cost-effective than first-tier (Ontario Health (Quality), 2020).

4.2.6 Implications for Health Technology Assessment

Traditionally in HTA, the impact of a new technology is only assessed for a patient , and cascade health service consumption and consequent health outcomes for family members are not considered (CADTH, 2017). One of the possible reasons for this may be because the types of technologies which most often trigger these cascades routinely are relatively new, so until recently there was not much reason to develop methodology for the incorporation of cascade health service use in HTA. In the literature, all mentions of cascade testing or screening involve genetic testing, and the first publications on the topic are two 1994 papers examining the efficiency of active carrier screening for CF (Holloway & Brock, 1994; Super et al., 1994). Other types of health technologies – pharmaceuticals, medical devices, surgical procedures – are generally limited to the index patient, and may only seldomly spur cascade health service

consumption in a family member. As genetic and genomic technologies are implemented more widely, it becomes increasingly important to consider whether cascade health service consumption ought to be included in HTA. In some cases, these technologies are introduced with the express intent that they will improve surveillance and clinical management in patients' families as well, and that the triggered cascade consumption will result in improved quality and length of life in individuals other than the original patient. There seems to be a discord between valuing a technology (in part) for its potential to catalyze cascade health service use, but not quantifying or otherwise evaluating that cascade when attempting to assess the technology in a systematic way with the ultimate goal of making a funding or policy decision.

This thesis attempted to provide an account of the health system costs of cascade genetic testing and screening in the families of paediatric CMP patients who received genetic testing. In doing so it helps illustrate that there are a variety of methodological challenges associated with incorporating cascade health services in HTA. In the subsequent sections, issues pertaining to the following components of HTA are discussed: economic evaluation, ethical analyses, and assessment of patient preferences and values.

4.2.6.1 Economic Evaluations

Economic evaluations are one of the main components of HTA, producing estimates of the cost and health effect trade-offs of two or more interventions (CADTH, 2017). The inclusion of cascade health service use affects all parts of an economic evaluation, including its design, costing, measurement and valuation of health outcomes, and modelling.

4.2.6.1.1 Design

One challenge with designing an economic evaluation in which cascade health services are incorporated is that a decision must be made as to the types of family members that will be considered. An analysis could include only first-degree relatives, or it could also account for cascade testing and screening of second- and/or third-degree relatives as well.

In addition, an important element of economic evaluation study design is the time horizon selected in the reference case. The time horizon must be sufficiently long such that all relevant differences in the future costs and outcomes associated with the technologies being compared are captured (CADTH, 2017). Often, the most appropriate choice of time horizon is the patient's

lifetime (Drummond et al., 2015). This approach may become problematic when cascade health services are included in analysis, because a decision must be made as to which patient's lifetime is being considered. It is likely that probands and family members will have differing life expectancies. This could be because some of the included individuals will be children and others adults. Alternatively, depending on the disease under study, affected individuals may not be expected to live beyond a certain age or a certain number of years following onset. In any case, family members may outlive the proband, or the proband may outlive at least some of their family members. The most prudent decision may be to adopt a time horizon based on the lifetime of the youngest individuals included in the study, as this would provide an opportunity to capture as many cascade costs and outcomes as possible.

It is also important to recognize that use of an intervention in an index patient may lead to multiple cascades. There is the initial cascade health service consumption (captured by this and other studies), where the index patient's family undergoes testing or screening to assess their risk of developing a particular disease. This will be termed the *primary cascade*. But, when considering family members who, at the time of their testing or screening, have not yet reached reproductive age or have not yet had children, it is possible to foresee a *secondary cascade*, whereby these relatives' *future* children will receive screening as well. One of the decisions that must be made in designing an economic evaluation with the intention of incorporating cascade health service use is whether this secondary cascade should be included in analysis. If so, the question becomes whether the time horizon of the study should be expanded to encompass the lifetimes of these future children, especially since it is possible they will require medical surveillance (and therefore access health resources) their whole lives. Of course, such cascades could continue for multiple generations, and at a certain point including them in economic evaluation no longer becomes helpful. However, the time horizon in an economic evaluation should "relate to the maximum expected lifetime of future patients" and in some cases this means it should extend beyond the lifetime of a single cohort (CADTH, 2017).

4.2.6.1.2 Costing

In addition to implications on study design, the incorporation of cascade health services in economic evaluation also affects the identification, measurement, and valuation of health resource costs.

4.2.6.1.2.1 Resource Identification

To conduct a thorough economic evaluation, all health resources that are consumed within the chosen time horizon must be identified. Understanding the clinical care pathway associated with a disease helps with the identification of relevant resources, but accounting for cascade services adds complexity to this pathway, especially in the context of conditions with variable penetrance, expressivity, and/or ages of onset. The surveillance or treatment protocols that need to be initiated in an individual may depend on that person's age (since interventions in children may be different than those in adults) and on the severity of the condition, and may involve a wide array of different health resources. Some services may be offered on a case-by-case basis. Using the secondary analysis in this thesis as an example, there were two individuals who were offered a stress MIBI. This resource does not appear in clinical practice guidelines, and would have been difficult to identify in the absence of empiric data. There may also be challenges associated with identifying specific types of resources. For instance, family members may be prescribed drugs as part of their cascade health resource use, but it may be difficult to identify all of the pharmaceuticals that need to be accounted for in the analysis. There may certainly be a standard group of drugs prescribed to patients to prevent or treat a particular condition, but there may be cases in which additional medications are given (e.g., if an unexpected or rare complication were to occur). Availability of patient-level data for index patients' families may help facilitate resource identification by providing a clearer picture of the clinical pathway that family members follow after they undergo cascade testing or screening.

4.2.6.1.2.2 Resource Measurement

After resources are identified, their use must be quantified, and accounting for cascade health resources complicates this task. Different relatives within the same family may require or consume different volumes of resources, or may use resources at different frequencies. More than that, the volume of resources consumed by an individual may change over time depending on the progression of disease, and it may not be possible to predict when modifications to a clinical management plan may become necessary. An additional challenge is that variability may exist in the way in which relatives access health services. For example, in the case of genetic testing, it is possible that some individuals within the same family will attend joint genetic counselling appointments, while others have individual sessions. It may therefore be difficult to

accurately quantify the number of genetic counselling sessions per relative or per family. In these types of situations, resource measurement relies on input from clinical experts and on assumptions, and uncertainty can be assessed through sensitivity analyses.

Resource measurement may be improved if administrative databases were included as supplemental sources of data about index patients' family members. These databases contain real-world information about resource use within particular jurisdictions, and they can help with estimating resource consumption for a patient cohort over a specified period of time, especially when information about individuals is linked across multiple databases (CADTH, 2017). In Ontario, five of the most common administrative databases (Registered Persons Database; Ontario Drug Benefit (ODB) Claims; Ontario Health Insurance Plan Claims; Discharge Abstract Database; and National Ambulatory Care Reporting System) are linked for research purposes (Cadarette & Wong, 2015). Taken together, they provide data about drugs prescribed in Ontario (including dosage, strength, and quantity prescribed), though the ODB only includes individuals aged 65 or older; reasons for office visits and diagnoses made; laboratory and diagnostic tests; hospital inpatient data (including length of stay, diagnoses made, and procedures and interventions performed); and hospital outpatient data (including data related to day surgeries and visits to the emergency department) (Cadarette & Wong, 2015). Moreover, the data contained within these databases can be further supplemented by linkage with other data sources, such as patients' EMRs (Cadarette & Wong, 2015). Administrative databases are therefore rich sources of information that may be leveraged to help with the accurate measurement of cascade resource use in economic evaluations.

4.2.6.1.2.3 Resource Valuation

After resources are identified and quantified, their cost must be determined. For some technologies, the consideration of cascade health service use may complicate this resource valuation because it may not always be possible to separate the cost of implementing a technology in the index patient from the cost of cascade testing or screening in that patient's family. An example of this is the trio WGS being performed at the Cardiac Genome Clinic at SickKids. In this case, the trio consists of a paediatric proband and their parents (Jegathisawaran et al., 2020), and all of the DNA is processed and sequenced together. As a result, the trio cost cannot be divided to obtain the cost of genetic testing in the proband alone or in the probands'

family members alone. Of course, depending on the decision problem and technology being explored in an economic evaluation, and the unit of analysis, this inability to separate costs may not be an issue. Regardless, when a particular resource is difficult to monetize, it may be necessary to consult experts or use fees or charges associated with similar technologies (CADTH, 2017). Administrative databases may again be useful sources of information for the purposes of estimating costs. As always, uncertainty analyses should be conducted to assess the effect of different prices if a resource on the results of the economic evaluation.

4.2.6.1.3 Health Outcomes

The reference case of an economic evaluation should be a CUA whereby all health outcomes are expressed as QALYs (CADTH, 2017). QALYs are calculated by multiplying the number of life years an individual spends within a particular health state by a utility that reflects the health-related quality of life in that state (CADTH, 2017). *Utilities* are the "preferences individuals or society may have for any particular set of health outcomes" (Drummond et al., 2015), and they can be measured in a variety of ways (CADTH, 2017). Importantly, different tools are used to measure utilities in different age groups since children have less developed cognitive and linguistic abilities than adults, and because the dimensions of health relevant to adults may not be congruent with the dimensions of health relevant to children and adolescents (Keren et al., 2004). While the methods for obtaining utilities from adults are well established, the methods for doing so in paediatric populations are still being developed. Moreover, results from different tools often cannot be combined into one overall outcome measure. This is a significant challenge for the inclusion of cascade health effects in economic evaluation, as both adults and children may be referred for cascade investigations and may therefore experience changes to their quality of life that must be captured in the analysis. Even if it were possible to use a single tool to measure health utilities of multiple people in different stages of their lives, aggregating health benefits across multiple individuals is problematic because outcomes such as QALYs are defined and interpreted in terms of an individual's life expectancy.

It may be less challenging to incorporate cascade health outcomes in CEAs than in CUAs. In CEAs, health outcomes are expressed in natural units such as life years gained, lives saved, or number of clinical events avoided or achieved (CADTH, 2017), and these outcomes may be more easily measured than quality of life. For CEAs assessing genetic technologies in which cascade health effects are included, potential outcomes of interest could be the number of cases

of a particular disease that are diagnosed as a result of genetic testing in the proband (short-term), or the number of potentially fatal complications avoided due to the commencement of surveillance or preventative treatment (long-term). The difficulty with including cascade health outcomes in analysis though, is that the outcome of interest in children may be different and therefore not comparable to the relevant outcome in adults. In cases where the same health outcome is appropriate in all of an index patient's family members, that outcome may occur immediately for some relatives, but years or decades in the future for others. This separation in time may make it difficult to identify when (or if) the outcome occurs. Obtaining more data about patients' families may help mitigate challenges around identifying health outcomes. As has been emphasized in this chapter, index patients' medical records may not be adequate sources of data about health outcomes in their family members. These records should likely be supplemented with information about health outcomes in relatives from administrative databases, in addition to the EMRs of those family members themselves.

4.2.6.1.4 Modelling

Decision analytic models constructed for conducting economic evaluations must reflect the clinical care pathway associated with the disease under study and the interventions being assessed (CADTH, 2017). Therefore, the health states and clinical activities that form the model structure, and the associated health costs and outcomes, necessarily reflect the interactions with the health care system experienced by patients. Developing a model that includes cascade testing and screening in patients' families is inherently difficult, as cascade health service use is tangential and not directly relevant to the clinical trajectory of the index patient.

If a model consisting of health states and clinical events relevant to index patients as well as their family members *were* to be constructed, one challenge that could arise when developing the model structure is identifying all of the states or events that are relevant to the economic evaluation. The clinical pathway followed by index patients may be different than the pathway followed by their family members, and relatives themselves may have different clinical experiences than one another depending on their ages and comorbidities. As a result, a large number of health states or clinical events may need to be considered, especially as the amount of heterogeneity assumed to exist among family members increases. This can add a great deal of complexity to a model, and can make parameter estimation an especially difficult process. Some health states, or transitions between health states, may be common to both index patients and

their family members. This raises yet another challenge: an index patient may have one probability of transitioning between health state A and health state B, while their relative may have a completely different probability of doing so.

Of course, the notion of both index patients and their family members "passing through" the same model simultaneously is problematic. Index patients and their family members are not independent of one another in terms of the health services they consume. More than that, index patients must enter the model at the beginning and receive an intervention (either the new technology or the established one). Relatives, however, necessarily enter the model after their associated index patient and following the delivery of the intervention. Consequently, a model that can include both index patients and their family members would be required. Cohort models may not be sufficient to capture all of the nuances involved in cascade health service use. Use of more advanced modelling techniques, such as discrete event microsimulations which track the progress of individual persons through health states, may help ameliorate some the difficulties identified above. In any case, further research must be conducted to develop the methodology for incorporating cascade health service use in decision analytic models for economic evaluations.

4.2.6.2 Ethical Analyses

HTAs may also include an analysis of the ethical implications of a technology. Regardless of whether cascade health service consumption is to be a key aspect of an HTA, ethical analysis should always recognize the potential for a technology to trigger cascade testing or screening within a patient's family. However, if emphasis is placed on cascade health service use, it may be appropriate for an ethical analysis to engage in a lengthier discussion regarding the ethical issues raised by triggering the cascade. There are several moral "rights" which may be violated when relatives are offered cascade services. These rights are often invoked in the context of sharing genetic or genomic information with family members, so ethical analyses of genetic technologies in particular should discuss why early detection of a given condition justifies infringement upon these rights.

The first is the *right not to know* (Chadwick et al., 2014), which can be understood as the right "against being informed of particular types of information" (Morrissey & Walker, 2018). It is possible that some members of a family do not wish to be informed of genetic risk information, and therefore should not be offered cascade testing or screening as the offer alone indicates that

they may be at genetic risk of disease. This may create conflict within families if there is disagreement between relatives regarding the value of genetic risk information. The right not to know does not only create tension between family members, as sometimes it is a clinician who must contact a patient's relatives and disclose familial risk information. In the case of HCPs, an individual's right not to know is balanced against their *duty to warn*. The ACMG has suggested that, with regards to certain diseases, a physician's duty to warn and their obligations of beneficence and nonmaleficence take precedence (Green et al., 2013). However, for conditions not explicitly listed by the ACMG, it may remain unclear as to which of these ethical principles outweighs the other. Ethical analyses should explore this tension in depth.

Another consideration is that cascade genetic testing in children could violate those children's *right to an open future*, especially when technologies that yield a variety of secondary findings (eg., WGS) are implemented. The right to an open future is meant to protect children from having important, irreversible life decisions made for them before they are able to make those choices themselves (Millum, 2014). For example, Joel Feinberg, who coined the phrase "right to an open future", considered that the Amish violated children's right to an open future when they cut formal education short, as this severely limited the career options of those children ("Wisconsin v. Yoder," 1972). In the context of genetic testing, this ethical principle is usually discussed as an argument against testing children for adult-onset conditions. The idea is, that if a child undergoes such testing, they will be robbed of the opportunity to exercise their autonomy later on about what genetic information they wish to have about themselves. This is not an issue when cascade testing is performed in children using FMA, as there is little-to-no concern about secondary findings with this technology. However, as trio WGS testing becomes more common, children, such as a proband's sibling, may often be included in the trio, and a wide-array of secondary findings pertaining to adult-onset conditions could be identified. In such a case, it would be important to carefully consider the child's right to an open future both before receiving the genetic testing results, and after, when a decision must be made around informing the child of any identified variant(s) or implementing significant lifestyle changes which may have unclear benefits in terms of disease prevention but may be a nontrivial disruption in that child's life. As has been indicated earlier in this chapter, the ACMG has stated that for their list of conditions, genes, and variants (Green et al., 2013), results about any adult-onset conditions should be sought and reported in children. In other words, in some cases it is ethically acceptable to

infringe upon the child's right to an open future. Once again though, if an HTA is being conducted for a technology aimed at treating a disease that does not appear on the ACMG list, there may be an ethical dilemma as to how cascade testing in children should be approached. This dilemma should be addressed in ethical analysis.

4.2.6.3 Studies Exploring Patient Preferences and Values

Finally, HTAs may also seek to understand patients' preferences and values around a health condition and treatment for it. These patients may be individuals affected by the disease in question, or who have experience with the technology under review. When cascade health service use is included in an HTA, both patients and their relatives – whether or not they engaged in cascade testing and screening – should be invited to participate in this type of research.

A variety of methodology can be used to conduct research around patient preferences (Manafo et al., 2018), however some difficulty may arise when conducting qualitative research in particular. If participant interviews are to be undertaken as part of a qualitative study, one challenge may be deciding whether to conduct one-on-one interviews with family members affected by cascade testing, or whether to interview multiple family members together (i.e., in a focus group). In one-on-one interviews, it may be possible to spend more time probing each participant, and conversations may yield much richer data. In contrast, focus groups with multiple members of the same family may lead to insights around how a family *as a unit* may be affected by the implementation of a technology, and by cascade testing and screening. With such focus groups though, it is important to consider how family dynamics may influence the responses elicited. For example, two family members may have opposing attitudes toward cascade testing, but when interviewed together, one may agree with the other in order to avoid inciting a conflict. Susceptibility to bias, since the opinions of individuals and of the group as a whole can be influenced by dominant participants or by the interviewer themselves, is a recognized limitation of focus groups (Kitzinger, 1995).

Conducting qualitative research with index patients or family members who are children or adolescents raises a number of additional concerns. One of the main considerations is the need to obtain informed assent from the minors to be involved in the study, such as siblings undergoing cascade testing (Huang et al., 2016). Where "informed consent" is legal term used to describe the process of obtaining participants' agreement to take part in research, "informed assent" is an

ethical term to describe the process of obtaining consent from children, recognizing that those children are as of yet unable to make a fully autonomous decision (Huang et al., 2016). In addition, the power dynamic between a child and a researcher is especially pronounced, with children and researchers usually unable to treat one another as equals (Huang et al., 2016). This may jeopardize the research process, so researchers conducting qualitative studies involving children must make a special effort to build rapport and establish a trusting relationship with these participants (Huang et al., 2016). Finally, it is important to remember that eliciting the preferences and values of children regarding cascade health service use in an interview may be difficult depending on the cognitive development of the child and their communication abilities. Some creativity may be required on the researcher's part in order to collect rich data. A variety of nonverbal data collection methods have been used to supplement interviews with children in past qualitative studies, including drawing and photography (Huang et al., 2016).

4.2.6.4 Ethical Considerations for Incorporating Cascade Health Service Use in Health Technology Assessment

In addition to methodological challenges, there are several ethical issues with the incorporation of cascade health services in HTA. The first is a somewhat Kantian concern (Gregor, 1996): by including cascade health service use in HTA, the index patient may be unintentionally treated as a means to an end. The cost and care consequences of a technology associated with the family of a patient will likely be greater than those corresponding to the patient themselves, simply because cascade effects involve more than just one individual. This creates the possibility that any decision to implement or fund a technology for a particular patient population may be made more for the sake of patients' relatives than for the sake of the patient initially receiving the intervention. This does not mean that such a decision would represent a non-judicious allocation of health resources, or that it would result in detriment to the health of the patient or their loved ones. However, care must be taken to ensure that patients are not inadvertently viewed as instruments to improve the lives of those around them.

An additional consideration is that the incorporation of cascade health services in economic evaluations may lead to some illnesses receiving greater attention from decision makers than others. Uptake of cascade testing or screening may be greater in the context of severe conditions or in cases where genetic risk information may have implications on an individual's reproductive decisions. As the number of relatives who access cascade health services increases, so too does

the amount of aggregate health benefit captured in analysis. As a result, innovation in the context of diseases where cascade testing or screening occur more commonly may be prioritized.

4.2.7 Implications for Canadian Stakeholders

The retrospective cohort study conducted in this thesis is the first to explore the health service and cost consequences associated with cascade genetic testing and screening stemming from the genetic diagnosis of CMP in paediatric probands. As has been discussed, this is an important question in the context of conducting HTAs, as the methodology for incorporating cascade health services is still underdeveloped. However, the results of this analysis also have implications for multiple Canadian stakeholders, including health policy decision makers, clinicians, and probands' families.

4.2.7.1 Funding and Policy Decision Makers

Funding and policy decision makers rely on economic evidence to make equitable funding decisions about health technologies and services. This evidence typically only accounts for an intervention provided to the patient. This analysis shows that the costs associated with cascade genetic testing and screening are roughly $1,000 per paediatric proband in the first year alone after the child undergoes genetic testing – this is a large amount considering that relatives often have to undergo cascade investigations for the rest of their lives. These results may therefore highlight to decision makers the need to incorporate cascade health service use and costs in the economic evaluations upon which they base important, population-level decisions. It is important to consider though that the omission of cascade effects from HTA leads not only to an underestimation of the costs associated with a health technology, but also of the benefits. Cascade genetic testing and screening may lead to early detection and treatment of a condition in family members, resulting in improved health outcomes, whether in the form of increased life years, improved quality of life, or both. If cascade costs are incorporated in HTA and considered by decision makers, so too must be cascade health benefits.

4.2.7.2 Clinicians

A question for clinicians is whether clinical practice guidelines should be updated. An analysis such as this one, where the observed pattern of offered services is assessed against the guideline-prescribed pattern, may help identify areas in which guidelines are outdated or too easily

overlooked. For instance, one of the most common discrepancies from clinical practice guidelines observed in the secondary analysis was that most families were not offered ECGs. This observed pattern of cascade health service offers could raise the question of whether decision makers ought to rethink clinical practice guidelines for cascade testing and screening for CMP to better reflect the tools clinicians find useful in the clinical setting. However, some authors have stressed the importance of ECGs in the assessment of CMP patients (Merlo et al., 2019; Peters et al., 2008). Given this, perhaps clinical practice guidelines need to be revised to reduce the likelihood that this particular screen will be overlooked in the clinical setting. Additionally, physicians have already begun to question whether clinical practice guidelines should be modified such that children from families with a history of HCM should be offered cascade genetic testing or screening at younger ages (Lafreniere-Roula et al., 2019). European and American guidelines suggest that genetic testing and/or clinical screening should be initiated in children after age 10 or 12 years, respectively, unless they meet criteria for early screening (Elliott et al., 2014; Gersh et al., 2011). However, 31% of children who do not meet those criteria display an HCM phenotype, suggesting that there is a sufficiently important clinical reason to consider cascade genetic testing and screening at younger ages (Lafreniere-Roula et al., 2019).

Another implication for clinicians relates to the charting of cascade information. Including cascade information in proband medical records was discussed in the context of obtaining more complete data about cascade health service use in a proband's family. However, there are a range of issues with charting relatives' data in proband records. Making note of additional information not directly about their patient could be time consuming for clinicians and considered extraneous, as not all data about family members may be informative for management of CMP in the index patient. Moreover, there are privacy concerns associated with including relatives' medical information in proband records, and clinicians may rightfully be hesitant to put family members' privacy in jeopardy. In addition, increased uptake of EMRs was discussed as a way in which recording of cascade health service information, or accessing family member records, could be simplified. Privacy concerns aside, this would have a number of ramifications on clinicians, including financial since EMRs have high up-front and maintenance costs. There could also be time and technical constraints associated with learning how to use a new technology and troubleshooting when technological issues occur.

4.2.7.3 Patients and Their Families

It is also important to consider how cascade genetic testing and screening affect the patients and their families, and the relationships between family members. From the perspective of index patients, one of the main benefits of undergoing genetic testing is being able to share that information with other family members, alerting them to the possibility that they may require testing and screening themselves (Hallowell et al., 2017). Of course, in the case of paediatric probands, the need for cascade testing or screening of first-degree relatives is communicated to families by a HCP, and family member-to-family member communication of this information typically occurs from first-degree to second-degree relatives. Uptake of cascade health services in families may be impeded by psychological, educational, or geographical barriers related to discussing cascade investigations with one other, or ethical concerns related to privacy or family dynamics (Sturm, 2016). In some cases, patients believe it is the clinician's responsibility to inform relatives (Bruwer et al., 2013), but even in the absence of this belief patients would generally appreciate help from within the health care system for outreach to family members about cascade testing and screening (Henrikson et al., 2019).

Family members themselves have varying preferences about the way in which they are approached. In one Norwegian study conducted in FH, the majority (74%) of relatives interested in cascade genetic testing wished to be contacted directly by the proband's physician rather than by the index patient themselves (Tonstad et al., 1995). In contrast, an Australian study found that 32% of relatives who wanted to be informed of a familial risk of FH preferred to have this information conveyed to them by their family member; 26% preferred to be told by the clinic involved in screening; 4% preferred to be approached by someone else, for instance, a general practitioner; and the remaining 36% had no preference as to who informed them (Maxwell et al., 2009). Findings have been similar in other disease states. For example, in a study performed in the United Kingdom with relatives from families with muscular dystrophy, 53% of family members believed it was the proband's responsibility to pass on genetic risk information, 22% felt a clinical genetic service should be responsible, and 18% believed a general practitioner should contact them with this information (Kerzin-Storrar et al., 2002). Even so, 90% of family members thought it was acceptable for a clinical genetic service to inform them they may be at risk for muscular dystrophy, and 92% thought it was acceptable to first be approached by a general practitioner (Kerzin-Storrar et al., 2002).

European guidelines endorse the involvement of HCPs in sharing genetic risk information with probands' relatives, and have suggested that genetic counsellors should offer patients "written material to help the counselee spread the information in the family" (Kaariainen et al., 2009). Regardless, HCPs are generally hesitant to contact patients' family members directly, even though they do feel a responsibility to ensure patients' relatives are aware they may be at risk (Dheensa et al., 2017) and this type of direct contact is generally considered ethically justifiable (Newson & Humphries, 2005). One of the ethical concerns that has been raised by HCPs is that direct contact with probands' family members could be a breach of the index patient's privacy (van El et al., 2018). However, in the context of cascade genetic testing and screening, clinicians may not actually have to worry a great deal about infringing on proband privacy. To begin, a distinction has been drawn between disclosing personal medical information about a proband and providing relatives with information about familial risk, since HCPs can alert a patient's family members that they may be at risk of developing a condition without specifying clinical details about the index patient (Royal College of Physicians et al., 2019). For example, they can cite their source of concern about a relative as "family history" rather than the genetic testing results of a particular individual. Additionally, guidelines from both the United Kingdom (General Medical Council, 2017; Royal College of Physicians et al., 2019) and the United States (American Society of Human Genetics, 1998) suggest that "disclosure without consent" should be viewed as the rule in terms of sharing genetic information with a patient's family, rather than the exception. Specifically, the Joint Committee on Genomics in Medicine state that a "decision to breach confidentiality in the public interest will often involve complex decisions and finely balanced judgements, but one type of justification in genomics may be when a failure to disclose information leaves relatives ignorant of a significant risk of a condition that may be preventable or treatable" (Royal College of Physicians et al., 2019). The provisions set out by the General Medical Council speak to a broader "public interest," but they also indicate that disclosure of personal information may be justified if failure to do so could result in the serious harm or death of another individual (General Medical Council, 2017). Finally, the American Society of Human Genetics (ASHG) explicitly states that disclosure of genetic risk information to a patients' family by an HCP is permissible when the following conditions are met: the patient has declined to disclose the information themselves; harm is highly likely, serious, and foreseeable; at risk family members are identifiable; and the disease in question is preventable or treatable (American Society of Human Genetics, 1998). Guidance from professional governing bodies

notwithstanding, patients themselves consider genetic information as familial as opposed to something belonging to them alone (Dheensa et al., 2016), and outright refusal to share genetic risk information with relatives is highly uncommon (Royal College of Physicians et al., 2019).

Multi-family discussion groups may be a useful intervention in facilitating communication about inherited genetic conditions among family members, and genetic counsellors can be trained to facilitate these discussion groups successfully (Socio-Psychological Research in Genomics et al., 2016). This intervention was piloted in the United Kingdom in 2014, with six families attending 12 hours of multi-family discussion group activities, led by three genetic counsellors over the course of two days. The families who participated found it to be beneficial, and the genetic counsellors who were involved expressed enthusiasm at the prospect of facilitating such multi-family discussion groups in the future. As genetic testing and cascade testing become more common, this may be adopted as a preferred strategy for post-test genetic counselling, especially because there are so few genetic counsellors in Canada – only 350 across the country (Abacan et al., 2019). However, it should be noted that genetic counsellors required more extensive training than was originally anticipated, likely due to unfamiliarity with family systems therapy and limited-to-no experience counselling multiple families at once. If, in the future, genetic counsellors' scope of practice is expanded to include the facilitation of multi-family discussion groups, it may be beneficial to incorporate instruction around this specific type of counselling as part of their formal training.

4.2.8 Future Research

This retrospective cohort study has contributed to the evidence base for cascade health service use in families of children with CMP, however knowledge gaps remain. Therefore, there is value in conducting further research to better understand the clinical and economic implications of cascade genetic testing and screening stemming from paediatric probands who receive genetic testing in the context of CMP.

One of the knowledge gaps identified by scrutinizing previously published literature is that little work has been done to understand the uptake and results of cascade genetic testing triggered by probands with DCM, RCM, LVNC, or ARVC. Most studies exploring cascade health service use in the CMP context have focused on HCM (Alfares et al., 2015; Christiaans et al., 2008; Knight et al., 2020; Ko et al., 2018), with few including DCM (Miller et al., 2013) or ARVC probands

(Christian et al., 2018). This type of work has already begun for DCM; a DCM Precision Medicine Study was launched in 2016 with multiple study sites across the United States, however only a paper describing the study design and implementation has been published to date (Kinnamon et al., 2017). Briefly, the goal is to enroll 1,300 individuals who meet the diagnostic criteria for idiopathic DCM, as well as 2,600 of their relatives (Kinnamon et al., 2017). There will be an observational component to the study to determine the prevalence of familial DCM among probands of different ethnicities, as well as a randomized controlled trial to test the effectiveness of a communication aid in increasing uptake of cascade screening in first-degree relatives of DCM probands (Kinnamon et al., 2017).

Throughout this chapter, probands' medical records have been described as an inadequate source of data about their relatives. It has been suggested that probands' charts could be supplemented with the medical records of the family members themselves and with administrative data. It was also suggested that more complete data about offers of cascade health services could be obtained by administering surveys to, or conducting interviews with, index patients and their relatives. Future studies relying on these data sources need to be conducted in order to assess whether they provide more complete information. These will contribute to HTA methodology by helping to identify the ideal data sources for quantifying cascade genetic testing and clinical screening recommendations as accurately as possible.

As discussed, one of the limitations of this study was that it only accounted for the initial cascade genetic test and screens offered to relatives. This limitation can be addressed in future work that adopts a longer time horizon to enable the incorporation of the ongoing surveillance family members undergo. Another limitation was the fact that health outcomes were not addressed. This could be remedied in future work, by using the present analysis as a starting point for a cost-consequence analysis.

Future research must also consider the impact that emerging technologies will have on clinicians, patients, and the health care system. As WGS becomes used with increasing frequency in the clinical context, a CEA needs to be conducted, comparing cascade health service use spurred by a child's WGS results with cascade health service use resulting from conventional genetic testing in a child with CMP. This type of economic evaluation will help provide clinicians a better understanding of the impact of these technologies relative to one another on their patients, and it

will act as evidence for decision makers if they must choose which type of genetic or genomic technologies should be publicly funded in the context of this disease state. However, before such a CEA can be undertaken, there is a need for methodology research to develop techniques to incorporate cascade costs and health outcomes in economic evaluation.

Finally, this thesis has only addressed cascade genetic testing and clinical screening following the genetic diagnosis of a child who was already known to have CMP. In some of the studies identified in the scoping literature review, the paediatric probands were asymptomatic but underwent genetic testing as part of a newborn screening program (Cadet et al., 2005; Sorensen et al., 2013). It was found that cascade genetic testing following those programs was more effective than untargeted screening in identifying individuals at-risk for the condition in question (Cadet et al., 2005). It may be worth conducting a study in the future in which a newborn screening program is implemented for CMP, and at-risk relatives are identified based on the results of screening in their infant, although newborn screening for conditions which develop later in childhood and are not imminently treatable is complex and controversial. Conducting a CEA comparing cascade genetic testing following newborn screening with cascade genetic testing following the genetic testing of a child already displaying a CMP phenotype may provide useful information as to whether CMP should be added to the list of conditions for which infants are routinely tested for when they are born.

Chapter 5:
Conclusion

Cascade genetic testing and clinical screening in the families of children with CMP enables the identification of at-risk relatives and the initiation of surveillance protocols which may reduce morbidity and mortality in these individuals. This thesis is the first work to quantify the pattern and costs associated with cascade testing and screening triggered by genetic testing in a paediatric CMP proband in Canada. The results show that the cost of cascade health services offered per family are high, and they are most sensitive to changes in the unit price of the cascade genetic test. These findings are especially important as the use of genetic and genomic technologies in the clinical setting increases and more emphasis is placed on a family-centred approach to care.

Cascade effects are not currently incorporated in HTAs. Economic evaluations may therefore be underestimating both the cost and health benefits attributable to the implementation of a technology in a particular population. The findings of the retrospective cohort study in this thesis suggest that it may be important for health policy and funding decision makers to consider cascade costs and health outcomes when making health system- or population-level decisions about a technology. However, there are a number of challenges associated with incorporating cascade effects in HTAs, especially with regards to designing and conducting economic evaluations. One difficulty highlighted by this thesis was that identifying the cascade health services offered to patients' families may be challenging, especially when proband medical records are relied upon as the sole source of data. Information from these records is incomplete and does not necessarily reflect all of the offers of cascade health services made to relatives. Alternative data sources such as family members' records or administrative data should be explored. Overall, further research is needed to develop methodology to adequately include cascade health service costs and outcomes in HTA.

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Appendices

Appendix I: Scoping Literature Review Search Strategies

MEDLINE		
#	SEARCH TERMS	NUMBER OF RECORDS RETRIEVED
1.	exp Genetic Testing/	45,338
2.	exp Genotyping Techniques/	6,898
3.	exp Molecular Diagnostic Techniques/	17,355
4.	exp High-Throughput Nucleotide Sequencing/	30,574
5.	exp Sequence Analysis, DNA/	227,791
6.	1 or 2 or 3 or 4 or 5	306,241
7.	exp Chromosome Disorders/	70,419
8.	exp Genetic Diseases, Inborn/	629,872
9.	exp Genetic Predisposition to Disease/	135,715
10.	7 or 8 or 9	752,326
11.	6 and 10	55,006
12.	genetic testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	50,474
13.	genotyping techniques.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7,259
14.	molecular diagnostic techniques.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11,195
15.	high-throughput nucleotide sequencing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	30,367
16.	sequence analysis, DNA.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	157,917
17.	next generation sequencing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	33,868
18.	Sanger sequencing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	9,574
19.	single gene test.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	14
20.	gene panel.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism	1,798

	supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
21.	chromosome microarray.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	276
22.	gene sequencing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	9,876
23.	12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22	276,346
24.	chromosome disorders.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	20,616
25.	genetic disorders, inborn.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3
26.	genetic predisposition to disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	135,598
27.	genetic disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7,056
28.	genetic anomaly.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	216
29.	genetic condition.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,363
30.	chromosome anomaly.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	302
31.	chromosomal anomaly.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	567
32.	inherited disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2,707
33.	inherited condition.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	618
34.	hereditary disease.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2,123
35.	hereditary condition.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism	342

	supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	
36.	genetic abnormality.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,455
37.	chromosome abnormality.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,469
38.	chromosomal abnormality.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2,975
39.	24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38	174,652
40.	23 and 39	18,464
41.	11 or 40	57,951
42.	exp child/ or exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or exp infant/ or adolescent/ or exp pediatrics/ or child, abandoned/ or exp child, exceptional/ or child, orphaned/ or child, unwanted/ or minors/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre-term or preterm* or premature birth* or NICU or preschool* or pre-school* or kindergarten* or kindergarden* or elementary school* or nursery school* or (day care* not adult*) or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or pre-pubesc* or prepubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.	5,035,026
43.	proband.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	11,129
44.	index patient.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,980
45.	index case.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3,854
46.	43 or 44 or 45	16,742
47.	42 and 46	11,141
48.	41 and 47	1,926
49.	exp Genetic Carrier Screening/	8,580
50.	exp Parents/	111,016
51.	exp Siblings/	11,057
52.	exp Grandparents/	354
53.	50 or 51 or 52	121,053
54.	49 and 53	128
55.	genetic carrier screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	8,611
56.	predictive testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	914

57.	preventive testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	24
58.	carrier testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	873
59.	predictive screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	118
60.	preventive screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	449
61.	carrier screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	9,253
62.	cascade testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	199
63.	cascade screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	353
64.	reverse cascade testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3
65.	reverse cascade screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	6
66.	familial testing.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	19
67.	familial screening.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	162
68.	familial mutation analysis.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1
69.	surveillance strategy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	622
70.	surveillance program.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	4,542

71.	55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70	17,107
72.	parent.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	156,899
73.	sibling.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	23,044
74.	grandparent.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	894
75.	family.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	985,994
76.	relative.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	838,242
77.	mother.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	119,746
78.	father.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	25,862
79.	brother.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7,337
80.	sister.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	327,115
81.	72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80	2,046,648
82.	at-risk.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	1,737,743
83.	81 and 82	26,461
84.	71 and 83	805
85.	54 or 84	923
86.	41 and 48 and 85	24
87.	limit 86 to (English language and yr="2000-Current")	14

Search line 42 is a filter to retrieve paediatrics articles in Ovid Medline developed at the University of Alberta (Tjosvold et al., 2016).

EMBASE		
#	SEARCH TERMS	NUMBER OF RECORDS RETRIEVED
1.	exp genetic screening/	85,207
2.	exp genotyping technique/	8,667
3.	exp genotype/	443,014
4.	exp molecular diagnosis/	18,580
5.	exp molecular diagnostics/	7,132
6.	exp high throughput sequencing/	28,898
7.	exp sequence analysis/	236,304
8.	1 or 2 or 3 or 4 or 5 or 6 or 7	768,725
9.	exp chromosome disorder/	66,157
10.	"genetic and familial disorders"/	68
11.	exp genetic predisposition/	157,593
12.	9 or 10 or 11	223,040
13.	8 and 12	58,561
14.	genetic screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	86,214
15.	genotyping technique.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	8,816
16.	genotype.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	462,838
17.	molecular diagnosis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	25,224
18.	molecular diagnostics.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	8,640
19.	high throughput sequencing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	33,832
20.	sequence analysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	197,762
21.	next generation sequencing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	66,788
22.	Sanger sequencing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	26,076
23.	single gene test.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	19
24.	gene panel.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4,736
25.	chromosome microarray.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	432

26.	gene sequencing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	13,570
27.	genetic testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	34,824
28.	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	848,027
29.	chromosome disorder.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	9,402
30.	(genetic and familial disorders).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	162
31.	genetic predisposition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	65,927
32.	genetic disease.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	10,457
33.	genetic anomaly.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	348
34.	genetic condition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2,081
35.	chromosome anomaly.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	506
36.	chromosomal anomaly.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,010
37.	inherited disease.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4,011
38.	inherited condition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	851
39.	hereditary disease.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3,416
40.	hereditary condition.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	541
41.	genetic abnormality.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2,349
42.	chromosome abnormality.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	2,290
43.	chromosomal abnormality.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	4,680
44.	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43	106,367
45.	28 and 44	25,287
46.	13 or 45	67,191

47.	juvenile/ or exp adolescent/ or exp child/ or exp postnatal development/ or (pediatric* or paediatric* or child* or newborn* or congenital* or infan* or baby or babies or neonat* or pre term or preterm* or premature birth or NICU or preschool* or pre school* or kindergarten* or elementary school* or nursery school* or schoolchild* or toddler* or boy or boys or girl* or middle school* or pubescen* or juvenile* or teen* or youth* or high school* or adolesc* or prepubesc* or pre pubesc*).mp. or (child* or adolesc* or pediat* or paediat*).jn.	5,256,135
48.	proband.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	15,018
49.	index patient.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3,131
50.	index case.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	5,895
51.	48 or 49 or 50	23,641
52.	47 and 51	11,850
53.	46 and 52	468
54.	exp heterozygote detection/	6,563
55.	exp family/	552,841
56.	54 and 55	477
57.	heterozygote detection.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	6,676
58.	predictive testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,417
59.	preventive testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	30
60.	carrier testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	769
61.	predictive screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	153
62.	preventive screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	577
63.	carrier screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,547
64.	cascade testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	361
65.	cascade screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	621
66.	reverse cascade testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3
67.	reverse cascade screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	9

68.	familial testing.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	32
69.	familial screening.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	328
70.	familial mutation analysis.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3
71.	surveillance strategy.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,017
72.	surveillance program.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	32,434
73.	57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72	45,102
74.	family.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,197,221
75.	first-degree relatives.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	14,006
76.	parents.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	235,532
77.	siblings.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	50,181
78.	grandparents.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	3,321
79.	relative.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	1,072,430
80.	father.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	50,952
81.	mother.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	235,020
82.	brother.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	14,727
83.	sister.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	41,891
84.	74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83	2,627,671
85.	at-risk.mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]	251,029
86.	84 and 85	40,384
87.	73 and 86	746
88.	56 or 87	1,185
89.	46 and 53 and 88	5
90.	limit 89 to (english language and yr="2000 -Current")	5

Search line 47 is a filter to retrieve paediatrics articles in Ovid Embase developed at the University of Alberta (Desmeules, 2018).

Appendix II: Critical Appraisal Checklists for Studies Included in Scoping Literature Review

The checklists below are adapted from (Scottish Intercollegiate Guidelines Network (SIGN)).

SIGN Critical Appraisal Checklist for Cohort Studies

Prior to completing this checklist, consider:

1. Is the paper really a cohort study? If no, do not use this checklist.

2. Is the paper relevant to the key question? If no, exclude from analysis.

	CRITERION	YES	NO	CANNOT SAY	DOES NOT APPLY
IN A WELL-CONDUCTED COHORT STUDY:					
1.	The study addresses an appropriate and clearly focused question.				
SELECTION OF SUBJECTS					
2.	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.				
3.	The study indicates how many of the people asked to take part did so, in each of the groups being studied.				
4.	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.				
5.	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed?				
6.	Comparison is made between full participants and those lost to follow-up, by exposure status.				
ASSESSMENT					
7.	The outcomes are clearly defined.				
8.	The assessment of outcome is made blind to exposure status. If the study is retrospective, this may not be applicable.				
9.	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.				
10.	The method of assessment of exposure is reliable.				
11.	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.				
12.	Exposure level or prognostic factor is assessed more than once.				
CONFOUNDING					
13.	The main potential confounders are identified and taken into account in the design and analysis.				
STATISTICAL ANALYSIS					
14.	Have confidence intervals been provided?				

Overall Assessment of the Study: How well was the study done to minimize the risk of bias or confounding? *High quality/acceptable/low quality*

SIGN Critical Appraisal Checklist for Economic Evaluations

Prior to completing this checklist, consider:

1. Is the paper an economic study (i.e., assessing the cost-effectiveness of something) or is it just a study of costs? If the latter is true, exclude from analysis.

2. Is the paper relevant to the key question? If no, exclude from analysis.

	CRITERION	YES	NO	CANNOT SAY	DOES NOT APPLY
IN A WELL-CONDUCTED ECONOMIC EVALUATION:					
1.	The study addresses an appropriate and clearly focused question.				
2.	The economic importance of the question is clear.				
3.	The choice of study design is justified.				
4.	All costs that are relevant from the viewpoint of the study are included and are measured and valued appropriately.				
5.	The outcome measures used to answer the study question are relevant to that purpose and are measured and valued appropriately.				
6.	If discounting of future costs and outcomes is necessary, it has been performed correctly.				
7.	Assumptions are made explicit and a sensitivity analysis was performed.				
8.	The decision rule is made explicit and comparisons are made on the basis of incremental costs and outcomes.				
9.	The results provide information of relevance to policy makers.				

Overall Assessment of the Study: How well was the study conducted? *High quality/acceptable/low quality*

Appendix III: Clinical Activity Form Pertaining to Cascade Health Service Use

Cascade genetic testing: family members

- ☐ None
- ☐ Mother
- ☐ Father
- ☐ Siblings
- ☐ Grandparents
- ☐ Uncles
- ☐ Aunts
- ☐ Cousins
- ☐ Other

Testing: Family member: Other (relationship), specify

_____
(Specify relationship to proband)

Total number of siblings [with any information on genetic testing and cardiac screening]

_____

Total number of grandparents [with any information on genetic testing and cardiac screening]

_____

Total number of uncles [with any information on genetic testing and cardiac screening]

_____

Total number of aunts [with any information on genetic testing and cardiac screening]

_____

Total number of cousins [with any information on genetic testing and cardiac screening]

_____

Cascade screening (cardiac) or testing (genetic): Other - specify

_____

Mitigating family member risk re: cardiac disease
Genetic Testing: Family members (relationship to proband)

	Testing not offered	Tested Prior	Testing recommended	To decide later	Testing refused	Testing in progress	Tested	No information
Mother	☐	☐	☐	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐	☐	☐	☐
Sibling1	☐	☐	☐	☐	☐	☐	☐	☐
Sibling2	☐	☐	☐	☐	☐	☐	☐	☐
Sibling3	☐	☐	☐	☐	☐	☐	☐	☐

Sibling4	☐	☐	☐	☐	☐	☐	☐	☐
Sibling5	☐	☐	☐	☐	☐	☐	☐	☐
Sibling6	☐	☐	☐	☐	☐	☐	☐	☐
Sibling7	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent1	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent2	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent3	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent4	☐	☐	☐	☐	☐	☐	☐	☐
Uncle1	☐	☐	☐	☐	☐	☐	☐	☐
Uncle2	☐	☐	☐	☐	☐	☐	☐	☐
Uncle3	☐	☐	☐	☐	☐	☐	☐	☐
Aunt1	☐	☐	☐	☐	☐	☐	☐	☐
Aunt2	☐	☐	☐	☐	☐	☐	☐	☐
Aunt3	☐	☐	☐	☐	☐	☐	☐	☐
Cousin1	☐	☐	☐	☐	☐	☐	☐	☐
Cousin2	☐	☐	☐	☐	☐	☐	☐	☐
Cousin3	☐	☐	☐	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐	☐	☐	☐

Family member genetic test result

	Tested prior - positive	Tested prior - negative	Tested prior - uncertain	Tested prior - unavailable	Tested - positive	Tested - negative	Tested - uncertain	Tested - unavailable
Mother	☐	☐	☐	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐	☐	☐	☐
Sibling1	☐	☐	☐	☐	☐	☐	☐	☐
Sibling2	☐	☐	☐	☐	☐	☐	☐	☐
Sibling3	☐	☐	☐	☐	☐	☐	☐	☐
Sibling4	☐	☐	☐	☐	☐	☐	☐	☐
Sibling5	☐	☐	☐	☐	☐	☐	☐	☐
Sibling6	☐	☐	☐	☐	☐	☐	☐	☐
Sibling7	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent1	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent2	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent3	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent4	☐	☐	☐	☐	☐	☐	☐	☐
Uncle1	☐	☐	☐	☐	☐	☐	☐	☐
Uncle2	☐	☐	☐	☐	☐	☐	☐	☐
Uncle3	☐	☐	☐	☐	☐	☐	☐	☐
Aunt1	☐	☐	☐	☐	☐	☐	☐	☐
Aunt2	☐	☐	☐	☐	☐	☐	☐	☐
Aunt3	☐	☐	☐	☐	☐	☐	☐	☐
Cousin1	☐	☐	☐	☐	☐	☐	☐	☐
Cousin2	☐	☐	☐	☐	☐	☐	☐	☐
Cousin3	☐	☐	☐	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐	☐	☐	☐

Family member genetic testing type - familial mutation (FM) or specify type If different test for different member, then specify	☐ Familial mutation ☐ Other ☐ Unavailable
Family member genetic testing type - Other If different test for different member, then specify {e.g., Family member1 - xx test Family member2 - cc test}	_____
Cardiac screening: family members	☐ None ☐ Mother ☐ Father ☐ Siblings ☐ Grandparents ☐ Uncles ☐ Aunts ☐ Cousins ☐ Other

Cardiac Screening : Family member (relationship to proband)

	Screened prior	Recommended	To be screened	Screened	Refused	Unavailable	Screen - ECG/EKG	Screen - Echo	Screen - Other	Frequency - other
Mother	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Father	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling5	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling6	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Sibling7	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Grandparent4	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Uncle1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Uncle2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Uncle3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Aunt1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Aunt2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Aunt3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cousin1	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cousin2	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Cousin3	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐
Other	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

Screen Mother: Other: specify	_____
Screen Mother: Frequency Other: specify	_____
Screen Father: Other: specify	_____
Screen Father: Frequency Other: specify	_____
Screen Sibling: Other: specify	_____
Screen Sibling: Frequency Other: specify	_____
Screen Grandparents: Other: specify	_____
Screen Grandparents: Frequency Other: specify	_____
Screen Uncles: Other: specify	_____
Screen Uncles: Frequency Other: specify	_____
Screen Aunts: Other: specify	_____
Screen Aunts: Frequency Other: specify	_____
Screen Cousins: Other: specify	_____
Screen Cousins: Frequency Other: specify	_____
Screen Other: relationship to proband	_____
Screening type: Other specify	_____ (Specify member and the type of screening recommended)
Screening Frequency: Other specify	_____ (Specify member, the type & frequency of screening recommendation)
Comments / Notes:	_____

Appendix IV: General Pattern of Cascade Health Services Offered in Secondary Analysis

Pattern of Cascade Genetic Testing Offered to All First-Degree Relatives in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL FIRST-DEGREE RELATIVES					
		TOTAL NUMBER OF RELATIVES PER PROBAND		CASCADE GENETIC TESTING			
				NUMBER OF RELATIVES PER PROBAND OFFERED CASCADE GENETIC TESTING		NUMBER OF CASCADE GENETIC TESTS PER FAMILY	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	2.83	0.75	1.33	1.03	1.33	1.03
	HCM (n=9)	4.00	1.66	1.56	1.42	1.56	1.42
	RCM (n=1)	3.00	NA	2.00	NA	2.00	NA
	LVNC (n=3)	3.00	0.00	2.00	1.00	2.00	1.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**3.42**	**1.30**	**1.58**	**1.17**	**1.58**	**1.17**
INCONCLUSIVE	DCM (n=4)	4.75	1.71	2.00	2.83	2.00	2.83
	HCM (n=10)	2.70	0.67	1.50	1.08	1.50	1.08
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	3.00	1.41	1.00	0.00	1.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**3.25**	**1.34**	**1.56**	**1.55**	**1.56**	**1.55**
NEGATIVE	DCM (n=4)	5.00	1.63	1.00	2.00	1.00	2.00
	HCM (n=10)	3.20	0.79	0.10	0.32	0.10	0.32
	RCM (n=1)	2.00	NA	0.00	NA	0.00	NA
	LVNC (n=2)	2.50	0.71	0.50	0.71	0.50	0.71
	ARVC (n=1)	4.00	NA	2.00	NA	2.00	NA
	ALL (n=18)	**3.50**	**1.29**	**0.44**	**1.04**	**0.44**	**1.04**
TOTAL (n=53)		3.40	1.29	1.19	1.35	1.19	1.35

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

Pattern of Cascade Clinical Screening Offered to All First-Degree Relatives in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL FIRST-DEGREE RELATIVES															
		CASCADE CLINICAL SCREENING															
		TOTAL NUMBER OF RELATIVES PER PROBAND		NUMBER OF RELATIVES PER PROBAND OFFERED CASCADE SCREENING		NUMBER OF CASCADE ECGs PER FAMILY		NUMBER OF CASCADE ECHOs PER FAMILY		NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER FAMILY		NUMBER OF CASCADE CARDIAC MRIs PER FAMILY		NUMBER OF CASCADE STRESS MIBIs PER FAMILY		NUMBER OF CASCADE FETAL ULTRASOUNDS PER FAMILY	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	2.83	0.75	2.33	1.21	0.00	0.00	1.83	1.47	0.00	0.00	0.00	0.00	0.00	0.00	0.17	0.41
	HCM (n=9)	4.00	1.66	3.67	1.73	0.89	1.83	3.33	1.94	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	3.00	NA	3.00	NA	0.00	NA	3.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=3)	3.00	0.00	2.33	1.15	2.00	1.73	2.33	1.15	0.33	0.58	0.67	1.15	0.67	1.15	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**3.42**	**1.30**	**3.00**	**1.53**	**0.74**	**1.52**	**2.68**	**1.70**	**0.05**	**0.23**	**0.11**	**0.46**	**0.11**	**0.46**	**0.05**	**0.23**
INCONCLUSIVE	DCM (n=4)	4.75	1.71	4.75	1.71	3.50	2.38	4.75	1.71	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	2.70	0.67	2.40	1.17	0.10	0.32	2.10	1.37	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	3.00	1.41	2.00	2.83	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**3.25**	**1.34**	**2.94**	**1.77**	**0.94**	**1.88**	**2.50**	**2.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
NEGATIVE	DCM (n=4)	5.00	1.63	3.25	1.26	3.25	1.26	3.25	1.26	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	3.20	0.79	2.70	1.06	0.80	1.48	2.40	1.35	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	2.00	NA	2.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=2)	2.50	0.71	1.50	2.12	0.00	0.00	1.50	2.12	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=1)	4.00	NA	2.00	NA	0.00	NA	2.00	NA	3.00	NA	0.00	NA	0.00	NA	0.00	NA
	ALL (n=18)	**3.50**	**1.29**	**2.61**	**1.20**	**1.17**	**1.69**	**2.33**	**1.46**	**0.17**	**0.71**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
TOTAL (n=53)		3.40	1.29	2.85	1.49	0.94	1.67	2.51	1.69	0.08	0.43	0.04	0.27	0.04	0.27	0.02	0.14

ARVC: *arrhythmogenic right ventricular cardiomyopathy*
DCM: *dilated cardiomyopathy*
ECG: *electrocardiogram*
Echo: *echocardiogram*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
MRI: *magnetic resonance imaging*
MIBI: *myocardial perfusion imaging test*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

Appendix V: Relation-Specific Pattern of Cascade Health Services Offered in Secondary Analysis

Pattern of Cascade Genetic Testing Offered to Each Proband's Mother in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	MOTHERS					
		NUMBER OF MOTHERS PER PROBAND		CASCADE GENETIC TESTING			
				NUMBER OF MOTHERS PER PROBAND OFFERED CASCADE GENETIC TESTING		NUMBER OF CASCADE GENETIC TESTS PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	1.00	0.00	0.67	0.52	0.67	0.52
	HCM (n=9)	1.00	0.00	0.22	0.44	0.22	0.44
	RCM (n=1)	1.00	NA	1.00	NA	1.00	NA
	LVNC (n=3)	1.00	0.00	0.67	0.58	0.67	0.58
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.00**	**0.00**	**0.47**	**0.51**	**0.47**	**0.51**
INCONCLUSIVE	DCM (n=4)	1.00	0.00	0.50	0.58	0.50	0.58
	HCM (n=10)	1.00	0.00	0.70	0.48	0.70	0.48
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	0.00	1.00	0.00	1.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.00**	**0.00**	**0.69**	**0.48**	**0.69**	**0.48**
NEGATIVE	DCM (n=4)	1.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.10	0.32	0.10	0.32
	RCM (n=1)	1.00	NA	0.00	NA	0.00	NA
	LVNC (n=2)	1.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=1)	1.00	NA	1.00	NA	1.00	NA
	ALL (n=18)	**1.00**	**0.00**	**0.11**	**0.32**	**0.11**	**0.32**
TOTAL (n=53)		1.00	0.00	0.42	0.50	0.42	0.50

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

Pattern of Cascade Screening Offered to Each Proband's Mother in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	MOTHERS															
				CASCADE CLINICAL SCREENING													
		NUMBER OF MOTHERS PER PROBAND		NUMBER OF MOTHERS PER PROBAND OFFERED CASCADE SCREENING		NUMBER OF CASCADE ECGs PER PROBAND		NUMBER OF CASCADE ECHOs PER PROBAND		NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER PROBAND		NUMBER OF CASCADE CARDIAC MRIs PER PROBAND		NUMBER OF CASCADE STRESS MIBIs PER PROBAND		NUMBER OF CASCADE FETAL ULTRASOUNDS PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	1.00	0.00	0.67	0.52	0.00	0.00	0.50	0.55	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=9)	1.00	0.00	0.89	0.33	0.11	0.33	0.78	0.44	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	0.00	NA	1.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=3)	1.00	0.00	0.67	0.58	0.67	0.58	0.67	0.58	0.00	0.00	0.33	0.58	0.33	0.58	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.00**	**0.00**	**0.79**	**0.42**	**0.16**	**0.37**	**0.68**	**0.48**	**0.00**	**0.00**	**0.05**	**0.23**	**0.05**	**0.23**	**0.00**	**0.00**
INCONCLUSIVE	DCM (n=4)	1.00	0.00	1.00	0.00	0.75	0.50	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.90	0.32	0.00	0.00	0.80	0.42	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	0.00	0.50	0.71	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.00**	**0.00**	**0.88**	**0.34**	**0.19**	**0.40**	**0.75**	**0.45**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
NEGATIVE	DCM (n=4)	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.90	0.32	0.20	0.42	0.80	0.42	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=2)	1.00	0.00	0.50	0.71	0.00	0.00	0.50	0.71	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=1)	1.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	ALL (n=18)	**1.00**	**0.00**	**0.61**	**0.50**	**0.11**	**0.32**	**0.50**	**0.51**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
TOTAL (n=53)		1.00	0.00	0.75	0.43	0.15	0.36	0.64	0.48	0.00	0.00	0.02	0.14	0.02	0.14	0.00	0.00

ARVC: *arrhythmogenic right ventricular cardiomyopathy*
DCM: *dilated cardiomyopathy*
ECG: *electrocardiogram*
Echo: *echocardiogram*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
MRI: *magnetic resonance imaging*
MIBI: *myocardial perfusion imaging test*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

Pattern of Cascade Genetic Testing Offered to Each Proband's Father in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	FATHERS					
		NUMBER OF FATHERS PER PROBAND		CASCADE GENETIC TESTING			
				NUMBER OF FATHERS PER PROBAND OFFERED CASCADE GENETIC TESTING		NUMBER OF CASCADE GENETIC TESTS PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	1.00	0.00	0.67	0.52	0.67	0.52
	HCM (n=9)	1.00	0.00	0.33	0.50	0.33	0.50
	RCM (n=1)	1.00	NA	1.00	NA	1.00	NA
	LVNC (n=3)	1.00	0.00	1.00	0.00	1.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.00**	**0.00**	**0.58**	**0.51**	**0.58**	**0.51**
INCONCLUSIVE	DCM (n=4)	1.00	0.00	0.50	0.58	0.50	0.58
	HCM (n=10)	1.00	0.00	0.70	0.48	0.70	0.48
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.00**	**0.00**	**0.56**	**0.51**	**0.56**	**0.51**
NEGATIVE	DCM (n=4)	1.00	0.00	0.25	0.50	0.25	0.50
	HCM (n=10)	1.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	0.00	NA	0.00	NA
	LVNC (n=2)	1.00	0.00	0.50	0.71	0.50	0.71
	ARVC (n=1)	1.00	NA	0.00	NA	0.00	NA
	ALL (n=18)	**1.00**	**0.00**	**0.11**	**0.32**	**0.11**	**0.32**
TOTAL (n=53)		1.00	0.00	0.42	0.50	0.42	0.50

ARVC: arrhythmogenic right ventricular cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
LVNC: left ventricular non-compaction cardiomyopathy
RCM: restrictive cardiomyopathy
SD: standard deviation

Pattern of Cascade Screening Offered to Each Proband's Father in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	FATHERS															
				CASCADE CLINICAL SCREENING													
		NUMBER OF FATHERS PER PROBAND		NUMBER OF FATHERS PER PROBAND OFFERED CASCADE SCREENING		NUMBER OF CASCADE ECGs PER PROBAND		NUMBER OF CASCADE ECHOs PER PROBAND		NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER PROBAND		NUMBER OF CASCADE CARDIAC MRIs PER PROBAND		NUMBER OF CASCADE STRESS MIBIs PER PROBAND		NUMBER OF CASCADE FETAL ULTRASOUNDS PER PROBAND	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	1.00	0.00	0.83	0.41	0.00	0.00	0.50	0.55	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=9)	1.00	0.00	0.78	0.44	0.11	0.33	0.56	0.53	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	0.00	NA	1.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=3)	1.00	0.00	1.00	0.00	0.67	0.58	1.00	0.00	0.00	0.00	0.33	0.58	0.33	0.58	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.00**	**0.00**	**0.84**	**0.37**	**0.16**	**0.37**	**0.63**	**0.50**	**0.00**	**0.00**	**0.05**	**0.23**	**0.05**	**0.23**	**0.00**	**0.00**
INCONCLUSIVE	DCM (n=4)	1.00	0.00	1.00	0.00	0.75	0.50	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.80	0.42	0.00	0.00	0.70	0.48	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	0.00	0.50	0.71	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.00**	**0.00**	**0.81**	**0.40**	**0.19**	**0.40**	**0.69**	**0.48**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
NEGATIVE	DCM (n=4)	1.00	0.00	0.25	0.50	0.25	0.50	0.25	0.50	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	1.00	0.00	0.90	0.32	0.20	0.42	0.80	0.42	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=2)	1.00	0.00	0.50	0.71	0.00	0.00	0.50	0.71	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=1)	1.00	NA	0.00	NA	0.00	NA	0.00	NA	1.00	NA	0.00	NA	0.00	NA	0.00	NA
	ALL (n=18)	**1.00**	**0.00**	**0.67**	**0.49**	**0.17**	**0.38**	**0.56**	**0.51**	**0.06**	**0.24**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
TOTAL (n=53)		1.00	0.00	0.77	0.42	0.17	0.38	0.62	0.49	0.02	0.14	0.02	0.14	0.02	0.14	0.00	0.00

ARVC: *arrhythmogenic right ventricular cardiomyopathy*
DCM: *dilated cardiomyopathy*
ECG: *electrocardiogram*
Echo: *echocardiogram*
HCM: *hypertrophic cardiomyopathy*
LVNC: *left ventricular non-compaction cardiomyopathy*
MRI: *magnetic resonance imaging*
MIBI: *myocardial perfusion imaging test*
RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

Pattern of Cascade Genetic Testing Offered to Each Proband's Siblings in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL SIBLINGS					
		NUMBER OF SIBLINGS PER PROBAND		CASCADE GENETIC TESTING			
				NUMBER OF SIBLINGS PER PROBAND OFFERED CASCADE GENETIC TESTING[a]		NUMBER OF CASCADE GENETIC TESTS PER PROBAND[a]	
		MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	0.83	0.75	0.00	0.00	0.00	0.00
	HCM (n=9)	2.00	1.66	1.29	1.50	1.29	1.50
	RCM (n=1)	1.00	NA	0.00	NA	0.00	NA
	LVNC (n=3)	1.00	0.00	0.33	0.58	0.33	0.58
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.42**	**1.30**	**0.67**	**1.18**	**0.67**	**1.18**
INCONCLUSIVE	DCM (n=4)	2.75	1.71	1.00	2.00	1.00	2.00
	HCM (n=10)	0.70	0.67	0.17	0.41	0.17	0.41
	RCM (n=0)	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	1.41	0.00	NA[b]	0.00	NA[b]
	ARVC (n=0)	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.25**	**1.34**	**0.45**	**1.21**	**0.45**	**1.21**
NEGATIVE	DCM (n=4)	3.00	1.63	0.75	1.50	0.75	1.50
	HCM (n=10)	1.20	0.79	0.00	0.00	0.00	0.00
	RCM (n=1)	0.00	NA	NA	NA	NA	NA
	LVNC (n=2)	0.50	0.71	0.00	NA[b]	0.00	NA[b]
	ARVC (n=1)	2.00	NA	1.00	NA	1.00	NA
	ALL (n=18)	**1.50**	**1.29**	**0.27**	**0.80**	**0.27**	**0.80**
TOTAL (n=53)		1.40	1.29	0.46	1.05	0.46	1.05

ARVC: *arrhythmogenic right ventricular cardiomyopathy*
DCM: *dilated cardiomyopathy*
HCM: *hypertrophic cardiomyopathy*
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RCM: *restrictive cardiomyopathy*
SD: *standard deviation*

[a]Includes only those probands with known siblings.
[b]There was only one proband with this combination of genetic test result and CMP subtype who had siblings. Therefore, it was not possible to calculate the subsample standard deviation.

Pattern of Cascade Screening Offered to Each Proband's Siblings in Secondary Analysis

PROBAND GENETIC TEST RESULT	PROBAND CMP SUBTYPE	ALL SIBLINGS															
		NUMBER OF SIBLINGS PER PROBAND		CASCADE CLINICAL SCREENING													
				NUMBER OF SIBLINGS PER PROBAND OFFERED CASCADE SCREENING[a]		NUMBER OF CASCADE ECGs PER PROBAND[a]		NUMBER OF CASCADE ECHOs PER PROBAND[a]		NUMBER OF CASCADE 24-HOUR HOLTER MONITORS PER PROBAND[a]		NUMBER OF CASCADE CARDIAC MRIs PER PROBAND[a]		NUMBER OF CASCADE STRESS MIBIs PER PROBAND[a]		NUMBER OF CASCADE FETAL ULTRASOUNDS PER PROBAND[a]	
		MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD	MEAN	SD
POSITIVE	DCM (n=6)	0.83	0.75	1.25	0.50	0.00	0.00	1.25	0.50	0.00	0.00	0.00	0.00	0.00	0.00	0.25	0.50
	HCM (n=9)	2.00	1.66	2.57	1.40	0.86	1.57	2.57	1.40	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	1.00	NA	1.00	NA	0.00	NA	1.00	NA	0.00	NA	0.00	NA	0.00	NA	0.00	NA
	LVNC (n=3)	1.00	0.00	0.67	0.58	0.67	0.58	0.67	0.58	0.33	0.58	0.00	0.00	0.00	0.00	0.00	0.00
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=19)	**1.42**	**1.30**	**1.73**	**1.28**	**0.53**	**1.13**	**1.73**	**1.28**	**0.07**	**0.26**	**0.00**	**0.00**	**0.00**	**0.00**	**0.07**	**0.26**
INCONCLUSIVE	DCM (n=4)	2.75	1.71	2.75	1.71	2.00	2.45	2.75	1.71	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	0.70	0.67	1.17	0.41	0.17	0.41	1.00	0.63	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	1.00	1.41	2.00	NA[b]	0.00	NA[b]	0.00	NA[b]	0.00	NA[b]	0.00	NA[b]	0.00	NA[b]	0.00	NA[b]
	ARVC (n=0)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	ALL (n=16)	**1.25**	**1.34**	**1.82**	**1.25**	**0.82**	**1.66**	**1.55**	**1.44**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
NEGATIVE	DCM (n=4)	3.00	1.63	3.00	1.63	3.00	1.63	3.00	1.63	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	HCM (n=10)	1.20	0.79	1.00	0.50	0.44	0.73	0.89	0.60	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	RCM (n=1)	0.00	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
	LVNC (n=2)	0.50	0.71	1.00	NA[b]	0.00	NA[b]	1.00	NA[b]	0.00	NA[b]	0.00	NA[b]	0.00	NA[b]	0.00	NA[b]
	ARVC (n=1)	2.00	NA	2.00	NA	0.00	NA	2.00	NA	2.00	NA	0.00	NA	0.00	NA	0.00	NA
	ALL (n=18)	**1.50**	**1.29**	**1.60**	**1.24**	**1.07**	**1.53**	**1.53**	**1.30**	**0.13**	**0.52**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
TOTAL (n=53)		1.40	1.29	1.71	1.23	0.80	1.42	1.61	1.30	0.07	0.35	0.00	0.00	0.00	0.00	0.02	0.16

ARVC: arrhythmogenic right ventricular cardiomyopathy
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