Preliminary Validation of a Novel Genetic Knowledge Scale for Familial Hypercholesterolemia: Evaluation of Face Validity and Core Concepts

By

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ABSTRACT

Facilitating patient-informed decision making is a central part of the genetic counselling process. The Multidimensional Model of Informed Choice (MMIC) was developed to evaluate informed decision making in the context of genetic testing. A need has been identified for validated MMIC measures specific to inherited cardiac conditions, including familial hypercholesterolemia (FH). FH is a common genetic condition that can cause premature atherosclerotic cardiovascular disease (ASCVD) if left untreated. Studies have shown that patients who receive a genetic diagnosis for FH are more likely to comply with treatment and inform family members of their condition than those who do not receive a genetic diagnosis.

The primary aim of this study was to initiate the validation of an 8-item knowledge scale specific to FH. The secondary aim of this study was to explore the key factors that influenced how participants decisions about genetic testing for FH. Once validated, this knowledge scale can be used as part of an MMIC measure to evaluate patient informed choice in the context of genetic testing for this condition.

This study used semi-structured cognitive interviews (N = 10) paired with a traffic light coding system was used to assess the face validity of the items in the knowledge scale, along with the importance of their associated concepts. Conventional content analysis of the interviews was used to identify the key factors that influenced participants' decision regarding genetic testing for FH.

The items in the knowledge scale were interpreted correctly by all participants. Minor revisions were made based on participant feedback to improve the clarity of six items. Most participants (n = 9) considered the concepts covered by the knowledge scale to be either helpful or necessary to decide about genetic testing for FH. Conventional content analysis revealed three common motivations to pursue genetic testing which include family, insight into medical management, and the opportunity for patient empowerment. Importantly, participant responses highlighted a lack of awareness of genetic services among this patient population, along with the positive impact genetic counselling can have for those who are offered genetic testing for FH.

The development and validation of a FH-specific MMIC measure aims to be used in research targeted at maximizing informed choice among this patient population. Additionally, we foresee that these findings will serve to highlight the importance of genetic testing among this patient population and inform appropriate pre-test counselling for this condition.

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LIST OF ABBREVIATIONS

AB: Alberta
APOB: Apolipoprotein B
ASCVD: Atherosclerotic Cardiovascular Disease
CCS: Canadian Cardiovascular Society
EAS: European Atherosclerosis Society
FH: Familial Hypercholesterolemia
GCOS: Genetic Counselling Outcome Scale
GNA: Genetic Non-Discrimination Act
HDL: High Density Lipoprotein
HeFH: Heterozygous Familial Hypercholesterolemia
HoFH: Homozygous Familial Hypercholesterolemia
LDL: Low Density Lipoprotein
LDLR: Low Density Lipoprotein Receptor
LDLRAP1: Low Density Lipoprotein Receptor Adaptor Protein 1
MB: Manitoba
MMIC: Multidimensional Model of Informed Choice
NSGC: National Society of Genetic Counsellors
PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9
PI: Principal Investigator
SDM: Service Delivery Model
VUS: Variant of Uncertain Significance

CHAPTER 1: INTRODUCTION & LITERATURE REVIEW

1.1 INTRODUCTION

Familial hypercholesterolemia (FH) is an autosomal codominant genetic disorder that affects lipoprotein metabolism, resulting in elevated serum low-density lipoprotein (LDL) cholesterol in the blood. As a result, affected individuals are at an increased risk of developing premature atherosclerotic cardiovascular disease (ASCVD) (Varghese, 2014). As of 2020, the global prevalence of FH is estimated to be 1 in 313 individuals, making FH one of the most common genetic conditions worldwide (Beheshti et al., 2020). Despite available treatment options, FH is historically an underdiagnosed and undertreated condition (Nordestgaard et al., 2013). The underdiagnosis and underutilized treatment for FH calls for the implementation of increased screening measures for at risk individuals. Studies have shown that individuals who receive a genetic diagnosis for FH are more compliant to adhering to recommended treatment and are more likely to recommend genetic screening to family members (Marchand et al., 2021; Umans-Eckenhausen et al., 2001).

Patient-informed choice is an essential component of the patient experience that health care providers must consider when providing high quality and ethical healthcare. Guidelines for genetic testing emphasize the need for patients to understand the benefits, risks and limitations of genetic testing to promote voluntary consent and patient-informed choice (Godard et al., 2003). Clear communication of key information pertaining to the disease in question, along with the benefits, risks, limitations and implications of genetic testing are essential to obtaining informed consent from a patient (Ormond et al., 2021).

The Multidimensional Model of Informed Choice (MMIC) is a measure designed to assess whether patients are making informed decisions about genetic testing. Previous measures of informed choice were strictly one dimensional and considered patient knowledge as the primary determinant of informed decision making. The MMIC measure is a three dimensional model that considers knowledge, attitudes, and behaviour, to better reflect the multidimensionality of making an informed decision (Michie et al., 2002). This measure was initially implemented in the context of prenatal screening, where preliminary data supported this as being an effective model to measure informed choice (Marteau et al., 2001).

Since then, MMIC measures specific to other areas of genetic testing, such as hereditary cancer and Fragile X syndrome carrier testing have also been developed (Ames et al., 2012; Rager et al., 2022).

Currently, there are a lack of MMIC measurements specific to inherited cardiac conditions, including FH. Therefore, the goal of this study is to initiate the validation process of an 8-item true or false knowledge scale that is specific to FH. In doing so, the key factors that influence a patient's decision to proceed with genetic testing for FH will also be explored for the purpose of identifying additional information that should be included in the knowledge scale. This knowledge scale will be used as part of the MMIC measure to evaluate patient informed choice in the context of genetic testing for FH.

1.2 FAMILIAL HYPERCHOLESTEROLEMIA

This section of the literature review will define the prevalence, genetic etiology, diagnostic criteria, clinical features, management recommendations and available treatment options for this condition.

1.2.1 Prevalence of Familial Hypercholesterolemia

The world prevalence of heterozygous FH (HeFH) in the general population is estimated be 1 in 313 individuals (Beheshti et al., 2020). Historically, a rare form of homozygous FH (HoFH) has been estimated to be found in approximately 1 in 1 million people however, more recent studies suggest that the prevalence could be as high as 1 in 160 000 to 1 in 300 000 (Cuchel et al., 2014). Higher rates of HeFH are observed among certain populations including French Canadian (1 in 260), Lebanese (1 in 85), South African/Afrikaner (1in 72), and South African/Ashkenazi Jewish (1 in 67) cohorts (Austin et al., 2004; Moorjani et al., 1989; Seftel et al., 1989; Steyn et al., 1996). It is hypothesized that this is due to founder effects within these populations (Bétard et al., 1992; Singh & Bittner, 2015).

1.2.2 Genetic Contributions of Familial Hypercholesterolemia

The majority of monogenic FH diagnoses are the result of loss of function variants in the low-density lipoprotein receptor (*LDLR*) and the apolipoprotein B *(APOB*) genes, along with gain of function variants in the proprotein convertase subtilisin/kexin type 9 (*PCSK9*). *LDLR* disease variants are implicated in approximately 60-90% of monogenic FH. In contrast, disease causing variants in *APOB* and *PCSK9* are less prevalent, and account for 5-10% and 1-3% of FH diagnoses, respectively (Rogozik et al., 2024).

LDLR encodes the low-density lipoprotein receptor (LDLR). The function of LDLR was first characterized by Brown and Goldstein in 1986, who proved that this receptor facilitates the uptake and degradation of LDL cholesterol in the LDL-receptor pathway (Brown & Goldstein, 1986; Soutar & Naoumova, 2007). Disease causing variants in the *LDLR* gene have variable impacts on protein function that are dependent on the type and location of the variant. As such *LDLR* variants can be categorized into five different subgroups: defective ligand binding, defective transport, defective internalization, defective recycling and complete absence of LDLR protein (Singh & Bittner, 2015).

APOB encodes the apolipoprotein B-100 (apoB-100) and apolipoprotein B-48 (apoB-48) proteins (Rodríguez-Jiménez et al., 2023). Notably, disease causing variants in *APOB* that affect the function of the apoB-100 protein have been implicated in FH pathogenesis. ApoB-100 plays a major role in lipoprotein metabolism. It facilitates the transport and uptake of LDL cholesterol in the blood by hepatocytes, acting as the ligand for the LDL receptor (Rodríguez-Jiménez et al., 2023)..

Disease causing variants in *PCSK9* were implicated in FH pathogenesis following the classification of FH-specific variants in the *LDLR* and *ABOP* genes (Abifadel et al., 2003). The *PCSK9* gene codes for a human subtilase-neutral apoptosis-regulated convertase (NARC-1). NARC-1 is highly expressed in the liver, and plays an essential role in cholesterol homeostasis (Abifadel et al., 2003). PCSK9 proteins bind to LDLR and facilitate the internalization and lysosomal degradation of the LDLR protein. Notably, loss of function variants in *PCSK9* have been associated with hypocholesterolemia due to an increased presence of LDLR on cellular surfaces and may have a protective role in hyperlipidemia.

Although *LDLR, APOB* and *PSCK9* are the genes most commonly implicated in monogenic FH, they are not the sole genetic contributors for this condition. The potential for polygenic inheritance is estimated in more than 80% of cases where clinical FH is present, but a known pathogenic or likely pathogenic variant in *LDLR, PCSK9* or *APOB* cannot be identified (Futema et al., 2015; Khera et al., 2016; Talmud et al., 2013). Alternatively, bi-allelic pathogenic variants in *LDLRAP1* have been identified as causative for the rare autosomal recessive form of FH (Garcia et al., 2001). Heterozygotes for pathogenic variants in *LDLRAP1* have not been reported to be affected. The presence of pathogenic variants in *APOE, ABCG5/8* and *LIPA* have been identified in cases that are phenotypical of FH, but are not found to have a pathogenic

variant in a known FH-associated gene (Chora et al., 2017; Marduel et al., 2013; Rios et al., 2010). Emerging research into the genetic contributions of FH is ongoing and will contribute to efforts aimed at improving the identification and management of this condition in the population (Futema et al., 2021)

1.2.3 Clinical Characteristics of Familial Hypercholesterolemia

FH is inherited in an autosomal co-dominant manner. Therefore, the clinical presentation of this condition is dependent on the underlying genetic etiology, which can influence the severity and onset of the condition (Varghese, 2014). Heterozygous individuals are known to have a milder clinical presentation than those who are found to be homozygous or compound heterozygous for a pathogenic variant in the same gene (Cuchel et al., 2014; Varghese, 2014).

Individuals with HeFH often present with total and LDL-cholesterol levels over the 95th percentile which, in combination with a strong family history for premature cardiovascular disease is typically the first indication of FH (Varghese, 2014). Individuals identified to have a variant causative of FH have a 5- to 22-fold increased risk of developing premature ASCVD (<55 years in men; <65 years in women) due to prolonged exposure of elevated LDL-cholesterol (Brunham et al., 2018; Pearson et al., 2021). Additional clinical features of HeFH may include xanthomas in the cornea, eyelids and connective tissue surrounding extensor tendons (Yuan et al., 2006).

Individuals with HoFH present with a more severe clinical phenotype. The age of onset is typically within the first decade of life and disease severity is dependent on the level of LDL receptor activity (Pisciotta et al., 2006). In the vast majority of patients with HoFH, elevated LDL cholesterol levels are detectable at birth, resulting in cholesterol deposit accumulation in the tendons, cutaneous tissue and cardiovascular tissue over time (Raal & Santos, 2012). Unlike HeFH, individuals who are homozygous for an FH-associated pathogenic variant are more likely to experience a cardiac event much earlier in life. In severe cases, where LDL receptor activity is less than 2%, patients may succumb to intrauterine death as a result of coronary atherosclerosis (Varghese, 2014).

1.2.4 Diagnostic Criteria

Numerous criteria for establishing a diagnosis of FH have been developed over time. Most notable are the Dutch Lipid Network Criteria, the Simon Broome Criteria and the simplified Canadian definition of FH (Austin et al., 2004; Civeira, 2004; Ruel et al., 2018). In

general, the diagnostic criterion categorizes patients into having either possible, probable or definite diagnosis of FH (Rogozik et al., 2024).

Among all three models, the finding of a pathogenic variant confers a definite diagnosis of FH however, not all individuals with FH will receive genetic testing. Additional factors are considered when establishing a clinical diagnosis, such as the family history, total cholesterol and LDL-cholesterol levels and the presence of xanthomas or arcus cornealis upon physical examination. The diagnostic criteria models for HeFH are summarized below, in Tables 1 - 3. Diagnostic criteria for HoFH follows the guidelines set by the European Atherosclerosis Society, which were recently updated in 2023. A summary of the updated criteria for diagnosing HoFH has been outlined in Table 4.

Table 1: Dutch Lipid Clinic Network diagnostic criteria for Familial Hypercholesterolemia; adapted from Austin et al. (2004).

Dutch Lipid Clinic Network Criteria	Points
Family History	
First-degree relative with known premature* coronary and vascular disease, OR a first degree relative with known LDL-C level above the 95th percentile.	1
First-degree relative with tendinous xanthomata and/or arcus cornealis, OR children aged <18 years with LDL-C level above the 95th percentile.	2
Clinical History	
Patient with premature* coronary artery disease	2
Patient with premature* cerebral or peripheral vascular disease	1
Physical Examination	
Tendinous xanthomata	6
Arcus cornealis prior to the age of 45 years	4
Cholesterol levels mg/dL (mmol/L)	
LDL-C ≥ 330 mg/dL (≥ 8.5 mmol/L)	8
LDL-C 250-329 mg/dL (6.5-8.4 mmol/L)	5
LDL-C 190-249 mg/dL (5.0-6.4 mmol/L)	3
LDL-C 155-189 mg/dL (4.0-4.9 mmol/L)	1
DNA Analysis	
Functional mutation in *LDLR, APOB or PCSK9*	8
Diagnosis (based on the total number of points obtained)	
Definite Familial Hypercholesterolemia	>8
Probable Familial Hypercholesterolemia	6-8
Possible Familial Hypercholesterolemia	3-5
Unlikely	<3

*Premature: Men aged <55 years; woman <60 years

Table 2: Simon Broome diagnostic criteria for Familial Hypercholesterolemia; adapted from Austin et al. (2004).

Simon Broome Criteria	Diagnosis
Total cholesterol level of 290 mg/dL and LDL-C of 190 mg/dL in adults OR total cholesterol of 260 mg/dL and LDL-C of 155 mg/dL in children AND:	
1. DNA mutation	Definite FH
2. Tendon xanthomas in the patient or in a first- or second-degree relative	Probable FH
3. Family history of myocardial infraction <50 years in a second-degree relative or <60 years in a first-degree relative OR family history of total cholesterol > 290 mg/dL in a first- or second-degree relative	Possible FH

Table 3: Canadian definition for a clinical diagnosis of Familial Hypercholesterolemia; adapted from Ruel et al. (2018).

FH Screening Criteria	Diagnosis
LDL-C level ≥ 5.0 mmol/L (≥ 40 years) OR LDL-C level 4.5 mmol/L (18-39 years) OR LDL-C ≥ level 4.0 mmol/L (<18 years)	
Major Criteria	
DNA mutation* OR tendon xanthomas OR LDL-C level ≥ 8.5 mmol/L	Definite FH
Minor Criteria	
First degree relative with high LDL-C OR proband or first degree-relative with ASCVD (<55 years in men; <65 years in woman)	If yes: probable FH If no: severe hypercholesterolemia

Table 4: Diagnostic criteria for homozygous familial hypercholesterolemia; adapted from Cuchel et al. (2023).

Diagnostic Criteria for Homozygous Familial Hypercholesterolemia	
Clinical Criteria	**LDL-C Criteria:** - Untreated LDL-C >10mmol/L is suggestive of HoFH requiring further investigation to confirm the diagnosis **Additional Criteria:** - The presence of cutaneous or tendon xanthomas <10 years AND/OR untreated elevated LDL-C levels consistent with heterozygous FH in both parents (in digenic form, one parent may have normal LDL-C levels and the other may have LDL-C levels consistent with HoFH).
Genetic Criteria	Genetic confirmation of bi-allelic pathogenic/likely pathogenic variants on different chromosomes at the *LDLR, APOB, PCSK9* or *LDLRAP1* genes OR ≥2 such variants at different loci.

1.2.5 Treatment and Management Recommendations

Regarding the treatment and management of FH, emphasis is placed on early identification, intervention and implementation of therapeutic interventions to reduce plasma LDL-cholesterol and lower the risk for ASCVD. In general, all individuals who receive a diagnosis of FH are advised to make lifestyle modifications, including the incorporation of a heart-healthy diet, regular exercise, avoidance of smoking and alcohol, and aggressive treatment of co-morbidities such as hypertension and diabetes (Anderson et al., 2016). For the majority of patients, modifications to diet and exercise alone are not sufficient to lower LDL-cholesterol levels, and lipid lowering medication is required.

Heterozygous Familial Hypercholesterolemia

The Canadian Cardiovascular Society (CCS) recommends a therapeutic goal of LDL-cholesterol levels < 2.5 mmol/L or non HDL-cholesterol levels < 2.5 mmol/L (Anderson et al., 2016). The first line of lipid lowering treatment indicated for FH patients are statins, which target the production of LDL cholesterol by the liver. The use of statin medication for treatment of FH is based on the historical cohort data from the Netherlands FH registry, and landmark trials in non-FH populations showing that statins are the most effective medication for reducing LDL-cholesterol in patients with an increased risk for ASCVD (Brunham et al., 2018; Versmissen et al., 2008). Statin medication can be prescribed as early as 8-10 years of age. In addition, Nordestgaard et al. (2013) claim that individuals who display LDL-cholesterol levels within a normal range, but are known to carry a pathogenic variant that is causative of FH should be offered statin medication to lower their lifetime risk of premature ASCVD.

For individuals who are not responsive to statin therapy, or who experience severe side-effects due to these medications, alternative lipid lowering medications may be used in combination with low-dose statin therapy to lower LDL-cholesterol levels (Brunham et al., 2018). For example, ezetimibe is commonly prescribed in combination with a low-dose statin as an alternative to statin monotherapy (Brunham et al., 2018). More recently, PCSK9 inhibitors have shown promise as a therapeutic alternative to statin medication for reducing LDL-cholesterol levels and reducing the risk for ASCVD. In Canada, two PCSK9 monoclonal antibodies, alirocumab and evolocumab, have been approved for treatment among FH patients who did not achieve therapeutic goals with maximally tolerated doses of statin medication with ezetimibe (Brunham et al., 2018; Hovingh et al., 2017; Kastelein et al., 2015). For pregnant

individuals, statin therapy is not indicated due to teratogenicity. In these cases, patients are advised to stop statin treatment at least one month prior to a conception, and switch to treatment with bile sequestrants or therapeutic lipoprotein apheresis (Brunham et al., 2018).

Homozygous Familial Hypercholesterolemia

For individuals with HoFH, severely elevated LDL-cholesterol levels can result in the development of premature ASCVD within the first two decades of life, and therefore requires specific considerations for treatment (Cuchel et al., 2014). The European Atherosclerosis Society (EAS) recently published a consensus statement on the treatment for HoFH, which emphasizes the importance of early diagnosis and prompt intervention that is guided by the severity of the clinical phenotype (Cuchel et al., 2023). Therapeutic goals for HoFE patients involve an LDL-cholesterol level <1.8 mmol/L among adult patients, and LDL-cholesterol levels <3 mmol/L among pediatric patients, with lower goals for those with existing ASCVD (Cuchel et al., 2023).

Similar to HeFH, low rates of diagnosis and a delay in the ages of diagnosis are both major concerns. Therefore, when a diagnosis of HoFH is made, patients are often recommended to undergo a baseline cardiovascular evaluation to determine the status of ASCVD, which may include a low-dose computed tomography (CT) and echocardiogram (Cuchel et al., 2023). A combination of lipid-lowering therapies, including pharmacologic interventions and lipoprotein apheresis, in combination with lifestyle modifications are foundational for the treatment of HoFH, and are recommended to begin as early as 8 years of age for optimal intervention (Cuchel et al., 2023; Mach et al., 2020). In contrast to HeFH patients who begin with statin monotherapy, individuals with HoFH are recommended to begin treatment with a high-intensity statin, such as mipomersen or lomitapide, and ezetimibe (Cuchel et al., 2023; Rader & Kastelein, 2014). However, the majority of these patients will require additional interventions to achieve therapeutic goals which may include supplementation with PCSK9 inhibitors or LDLR-independent therapies (Cuchel et al., 2023).

In summary, the clinical management and treatment of FH is lifelong and highly personalized process, where early detection and intervention are essential for lowering the risk of premature ASCVD. The Canadian Cardiovascular Society recommends that the development of treatment plans should be a collaborative process between the patient and their health care provider, where variables such as age, cardiovascular risk factors, psychosocial and

socioeconomic factors, along with personal and family preferences should be considered (Brunham et al., 2018).

1.3 CONSIDERATIONS FOR THE INCLUSION OF GENETIC SERVICES INTO CLINICAL CARE FOR FAMILIAL HYPERCHOLESTEROLEMIA

FH has been described as an ideal target for genetic screening due to a comprehensive understanding of the underlying genetic etiology, along with the availability of effective treatment for this condition (Umans-Eckenhausen et al., 2003). The Canadian Cardiovascular Society has recognized genetic testing as an alternative method for establishing a diagnosis of FH, particularly among cases where a clinical diagnosis is 'probable' or not 'definite' (Brunham et al., 2018). Similarly, the National Lipid Association and European Atherosclerosis Society support the implementation of genetic testing for FH for the purpose of providing patients with a definitive diagnosis and facilitating cascade genetic testing for at-risk family members (Brown et al., 2020; Mach et al., 2020). European countries such as the Netherlands and Norway have high rates for uptake of genetic services for FH, likely due to the implementation of cascade genetic screening programs in these regions (Nordestgaard & Benn, 2017). In comparison, the uptake of genetic services (i.e. genetic testing and/or genetic counselling), along with the diagnostic rate is much lower in regions without a national screening program. For example, a genetic diagnosis is made in <5% and ~15% of cases in the United States and Canada, respectively (Nordestgaard & Benn, 2017).

This section of the literature review will explore the current state of genetic testing for FH in Canada, the benefits and limitations of genetic testing for FH, genetic counselling considerations for FH, and finally patient perspectives on genetic testing for this condition.

1.3.1 The Current State of Genetic Testing for Familial Hypercholesterolemia in Canada

As described, there is a consensus in support of implementing genetic testing for FH to assist in diagnosis, however, this is not reflected in the current state of genetic testing for of this condition across Canada. Recently, Kramer et al. (2024) explored this discrepancy, and characterized the availability and use of genetic services for FH across eight Canadian provinces: British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia and Newfoundland & Labrador.

Clinical genetic testing for FH is offered among all provinces included in this study with the exception of British Columbia, where testing is primarily facilitated through research

initiatives (Kramer et al., 2024). The provinces differ in which health care specialties (other than medical genetics) are able to request genetic testing for FH. In Manitoba, genetic testing for FH may only be ordered by medical genetics (Kramer et al., 2024). With regards to genes that are included in the gene panel, six of the seven provinces offer a 4-gene panel. In Manitoba, this panel includes: *LDLR*, *APOB*, *PCSK9* and *LDLR1*. Ontario recently introduced an 8 gene panel, which is now the standard for clinical genetic testing for FH in this province (Kramer et al., 2024). A genetic counsellor is available across all seven provinces to provide clinical genetic testing and counselling for FH, however the rates of referral to genetic counselling services are low, ranging from <1 to ≥4 referrals per month. Provinces differed in the availability of other health care professionals to provide pre-test counselling for this condition, which may explain the observably low rates of referral to genetics (Kramer et al., 2024).

Notably, the eligibility criteria for clinical diagnostic testing differed across provinces, with the most common criteria being the simplified Canadian Definition, accepted in five of the seven provinces that offer clinical genetic testing (Ruel et al., 2018). Kramer et al. (2024) highlight that a more consistent approach to the availability of genetic services and clinical diagnostic criteria across Canada may increase the rates of diagnosis, along with subsequent treatment and identification of at-risk family members through cascade screening. Additional research is needed to determine the existing barriers which prevent patients from accessing genetic services for FH, along with the state of genetic testing for FH among the provinces and territories not included in this study.

1.3.2 The Benefits and Limitations of Genetic Testing for FH

Genetic testing for FH offers numerous benefits which includes the opportunity for a definitive diagnosis, cascade genetic testing for family members and a positive impact on medical management (Berberich & Hegele, 2023; Sturm et al., 2018). Despite these benefits, genetic testing invokes an additional level of complexity to clinical care that may limit this approach.

Definitive Diagnosis & Risk Stratification

Genetic testing for FH can provide patients with a definitive diagnosis based on their genotype, rather than a probabilistic diagnosis of FH based on clinical criteria and patient phenotype. Indeed, the sensitivity of the clinical diagnostic criteria for FH is limited with respect to the detection of physical findings such as xanthomas or corneal arcus, which are detected in

less than 30% of cases (Ahmad et al., 2016; Perez de Isla et al., 2016). Additional factors such as incomplete penetrance, inaccurate measurements of baseline LDL cholesterol due to lipid lowering therapy and limited knowledge of family history can significantly impact how a patient is assessed for FH based on clinical diagnostic criteria (Sturm et al., 2018).

Furthermore, genetic testing can accurately distinguish patients with HeFH from those with homozygous or compound heterozygous forms, providing important information with respect to prognosis, disease management and risk information for family members. Indeed, individuals with biallelic forms of FH can develop premature ASCVD within the first two decades of life, making early detection and the implementation of appropriate treatment an essential aspect of clinical care (Cuchel et al., 2014).

It should also be noted that carriers of a pathogenic variant associated with FH are at a significantly increased risk of premature ASCVD in comparison to those who display clinically significant LDL cholesterol levels in the absence of a pathogenic variant. For example, when compared to a control group of individuals with a normal LDL cholesterol level (<130 mg/dl), individuals with LDL cholesterol levels ≥190 mg/dl in the presence of a pathogenic variant were reported to have a 22-fold increased risk for cardiovascular disease (Khera et al., 2016). In comparison, individuals with an LDL cholesterol ≥190 mg/dl in the absence of a pathogenic variant were at an increased risk for cardiovascular disease by a factor of six (Khera et al., 2016). It is hypothesized that the differences observed between these groups with respect to the risk for cardiovascular disease are likely due to prolonged exposure to LDL cholesterol particles among individuals who carry a pathogenic variant.

Medical Management

Increased interest, uptake and adherence of treatment recommendations are observed following a genetic diagnosis of FH (Marchand et al., 2021; Umans-Eckenhausen et al., 2001). Indeed, population data from national screening programs in Europe have provided evidence to support that individuals who receive a genetic diagnosis of FH are more likely to adhere to the recommendations for lipid lowering therapy in order to manage LDL cholesterol levels (Leren et al., 2004; Umans-Eckenhausen et al., 2001, 2003).

Furthermore, a genetic diagnosis of FH can provide access to novel or costly therapies, such as PCSK9 monoclonal antibodies and evinacumab, an effective but costly treatment for homozygous FH (Berberich & Hegele, 2023; Mohamed et al., 2021). There is also evidence to

suggest a patient's genotype can impact their response to certain pharmacological therapies, such as PCSK9 inhibitors. Santos et al. (2020) identified that individuals with HoFH who have null-variants in *LDLR* (i.e. <2% LDL receptor activity) are not responsive to PCSK9 inhibitor therapy. In comparison, individuals who have at least one copy of a receptor-defective variant (i.e. 2-30% LDL receptor activity) in *LDLR* displayed a mean cholesterol reduction of 20%. Therefore, an additional benefit of genetic diagnosis may be to assist with access to appropriate pharmacological treatment based on patient genotype.

It is proposed that the impact of genetic testing on the clinical management of this condition will continue to become more significant. Fu et al. (2022) recently reviewed the current state of gene therapy development for FH, highlighting several clinical trials that explored the potential for novel adeno-associated virus (NCT02651675) and exome-mediated (NCT05043181) therapies, along with the use of CRISPR-Cas 9 technology in animal models to target *PCSK9* in the liver (Musunuru et al., 2021).

Cascade Genetic Testing for At-Risk Relatives

As FH is an autosomal codominant condition, there is a 50% chance for all first-degree relatives of a proband to inherit this condition. Therefore, a key benefit of genetic testing for FH is the ability to perform targeted cascade genetic testing among at-risk relatives following the identification of a pathogenic variant in the family.

Although cascade screening for FH can be performed through cholesterol testing, patients with FH can have overlapping LDL cholesterol levels with individuals who do not have FH, making this a more ambiguous approach (Knowles et al., 2017). Indeed, approximately 20% of individuals with a pathogenic variant associated with FH will go undetected based on LDL cholesterol screening alone (Umans-Eckenhausen et al., 2001). Furthermore, cascade genetic testing has been identified as the most cost effective way to facilitate the identification of affected family members in comparison to other diagnostic strategies, such as cholesterol screening (Nherera et al., 2011). When cascade genetic testing is implemented in combination with appropriate pre- and post-test counselling, this also allows family members to have access to information, which can contribute to their overall understanding of the condition.

Importantly, cascade genetic testing can allow for early identification of FH among at-risk relatives. As FH often goes undetected in the absence of ASCVD, cascade genetic testing allows for the identification of affected family members, at a time when medical intervention is

most effective. Additionally, as treatment for FH can begin as early as childhood, cascade genetic testing includes younger members of the family who would not routinely receive bloodwork to assess cholesterol levels (Knowles et al., 2017).

Limitations of Genetic Testing for FH

The major limitations of genetic testing for FH include detection rate and variant interpretation. Pathogenic variants in *LDLR, APOB* and *PCSK9* are the most common monogenic forms of FH. However, in the patient population, an FH-causing variant is found in only 40-50% of cases within cohorts with a clinical diagnosis of FH (Mariano et al., 2020). Among the variants identified in *LDLR, APOB* and *PCSK9*, approximately 8%, 58% and 46% have been designated as a variant of uncertain significance (VUS), respectively (Iacocca et al., 2018). Additional data is needed to determine the clinical significance of the reported VUSs among these genes in order to provide patients with clarity and potential management recommendations following genetic testing. Currently, a working group has been tasked with creating guidelines for classifying *LDLR* variant pathogenicity in order to standardize genetic diagnoses of FH (Chora et al., 2022). Similar approaches for *APOB* and *PCSK9* variant interpretation have yet to be established, however, numerous independent functional studies are improving what is known about the genetic contributions of *APOB* and *PCSK9* variants on FH pathogenesis (Hsu et al., 2022; Rodríguez-Jiménez et al., 2023).

Limitations also exist regarding communication of genetic test results and the coordination of follow up care. It is imperative that genetic test results are interpreted accurately, ensuring that patients understand the significance of both a positive and inconclusive genetic test result. This is particularly important for those who meet the criteria for a clinical diagnosis of FH, but molecular analysis did not identify a causative variant, as a negative genetic test result does not rule out a diagnosis of monogenic FH. Furthermore, issues can arise in the clinical management following a genetic diagnosis. Huijgen et al. (2010) reported that approximately one fifth of a sample of patients (n = 781) identified through a Dutch genetic screening program did not start medication following a genetic diagnosis, with 56% of these individuals having been discouraged by a physician to do so. Additionally, it was found that within a sample of 207 pediatric patients identified through this program, 62% received lifestyle advice upon contacting their primary care provider, while only 26% were prescribed pharmacological treatment (Avis et al., 2012). These findings underscore that even in the presence of a genetic screening program

with a high degree of patient participation, increased education is essential for both patients and physicians regarding the implications and management recommendations for this condition following genetic testing.

1.3.3 Genetic Counselling Considerations

Genetic testing for any condition invites a new level of complexity, in terms of understanding the clinical, psychological and familial impact of the diagnosis. As such, the availability and uptake of genetic counselling services is an important consideration for conditions like FH, where a genetic diagnosis must be interpreted in the context of both the patient and their family members. The Canadian Cardiovascular Society, National Lipid Association, and European Atherosclerosis Society recommend that genetic counselling services should be used in both the pre- and post-test counselling for FH, when available (Brown et al., 2020; Brunham et al., 2018; Nordestgaard et al., 2013).

Sturm (2014) identifies that genetic counselling plays an essential role for patients who are considering genetic testing for FH. This process begins even before the test has been ordered and results have been returned, ensuring that the patient understands the implications of genetic testing for themselves and their family members, promoting informed decision making (Resta et al., 2006). The conversation between a genetic counsellor and their patient during the pre-test counselling session involves a comprehensive discussion that includes, but is not limited to, an assessment of the personal and family history, the benefits, risks and limitations of genetic testing, possible results that can be obtained from testing, and the clinical, familial and psychosocial implications of receiving a diagnosis. During result disclosure, genetic counsellors play a key role in the interpretation and translation of genetic test results. Should a pathogenic variant be identified, genetic counsellors have the responsibility of informing patients of the heritability of the condition, along with the risk to family members to help facilitate the process of cascade screening. Furthermore, genetic counsellors have the training to provide the psychosocial support that may be required for patients who are receiving a diagnosis, and begin the process of connecting patients with the appropriate clinical resources to manage their condition (Sturm, 2014).

1.3.4 Patient Attitudes on Genetic Testing for FH

Several qualitative studies have explored perspectives from the FH patient population on the utility of genetic testing, and how genetic services have impacted their overall experience of

the condition. These insights are an essential contribution to the growing evidence supporting the integration of genetic testing into clinical care for this condition.

Hallowell et al. (2017) conducted a qualitative study to explore the value of genetic testing for FH from the perspective of patients who had received a positive or inconclusive genetic test result. The majority of participants indicated that a genetic diagnosis provided an opportunity to re-frame how they thought about their personal history and family history of elevated cholesterol, as a positive test result provided an explanation for the underlying etiology of their condition. In addition, a positive genetic test result challenged previous beliefs that elevated cholesterol levels were the result of lifestyle factors such as diet or exercise. For some participants, this alleviated feelings of guilt or shame surrounding their condition. This is in contrast to individuals who received an inconclusive result and were disappointed by the fact that they could not dismantle the stigma surrounding their personal history of elevated cholesterol. Finally, many participants reported that a positive genetic test result allowed for the identification of at-risk family members, with an emphasis placed on the value of this information for younger members of the family.

Similarly, Pettit et al. (2024) conducted a qualitative study exploring the perspectives of patients and clinicians on the approaches to clinical care for FH. Although the focus of this study was not centred around patient views of genetic testing, their findings provide valuable insight into factors that motivate patients to participate in genetic testing. Consistent with the conclusions from Hallowell et al. (2017), participants were largely motivated to receive genetic testing to clarify risk information for family members. Additional knowledge related to one's health and a general sense of curiosity were identified as other common motivations among participants.

From a Canadian perspective, Marchand et al. (2021) also explored patient perspectives on genetic testing for FH using an online questionnaire. Among a sample of 183 participants, the majority of respondents (64.4%) did not yet know their genetic test result, 20.7% had a positive result and 14.8% had a negative result. Individuals who received a positive genetic test result were more likely to view genetic testing for FH as 'very important', in comparison to the two other groups. As a group, participants with a positive genetic test also reported higher motivation to take lipid lowering medications compared to those with negative results or those who were still awaiting results. In contrast, responses were more evenly distributed across each group with

respect to whether or not they would recommend genetic testing to family members, with >70% of participants from each group indicating that they would. An important outcome of this study was the finding that self-reported knowledge of FH did not improve following a genetic diagnosis, whereas a personal or family history of elevated cholesterol and cardiovascular disease did. These findings support the notion that adequate counselling in required in addition to genetic testing to ensure that patients are aware of the implications of this condition.

Interestingly, literature surrounding the negative impacts of genetic screening for FH from the patient perspective is extremely limited. While there is evidence to support the possibility of harmful psychological outcomes following the diagnosis of an inherited cardiovascular condition, this phenomenon has not been reported among the FH patient population (Ingles, 2020). It is possible that this is the result of when genetic testing typically takes place for individuals with FH, as the majority of patients have already received a clinical diagnosis or have been offered genetic testing due to the identification of a pathogenic variant in the family. This may also be explained by the availability of treatment options, which are highly effective in managing the symptoms of this condition even in the absence of genetic testing.

Research on the perspectives of the FH patient population on genetic testing is slowly evolving. However, there are aspects of this topic that remain to be explored. As genetic testing becomes more widely available for the FH patient population, additional exploration of patient perspectives regarding these services would be valuable to contribute to the overall understanding of the clinical utility of genetic screening for FH, and the impact on patient care. Furthermore, additional knowledge is required to understand how this patient population experience burdens to care, genetic service delivery, along with clinical management and support following disclosure of a genetic test result (Jones et al., 2018).

1.4 THE MULTIDIMENSIONAL MODEL OF INFORMED CHOICE

The MMIC is an instrument designed to measure the rates of informed choice among varying patient populations. The development of the MMIC was guided by O'Connor & O'Brien-Pallas' (1989) definition of an effective decision, where "an informed choice is one that is based on relevant knowledge, consistent with the decision maker's values and behaviourally implemented." Previous models of informed choice were strictly one dimensional and only considered patient knowledge as the key factor for making an informed decision. Whereas, the

MMIC is a three-dimensional model that considers knowledge, attitudes and behaviour, to better reflect the multidimensionality of making an informed decision (Marteau et al., 2001).

The MMIC measure was initially implemented in the context of prenatal screening, where preliminary data showed evidence supporting the MMIC as an effective model to measure informed choice (Marteau et al., 2001). The application and validation of the MMIC in the context of reproductive screening has been extensively reviewed by Ames et al. (2015). MMIC measures specific to other areas of screening, such as hereditary cancer and Fragile X syndrome carrier screening have also been developed (Ames et al., 2012; Dormandy et al., 2007; Steckelberg et al., 2011).

This section of the literature review will explore different approaches to knowledge scale development and validation, the functionality of the MMIC measure as a three-dimensional model, the approaches taken to validate the MMIC measure, along with the application, adaptations and limitations of this instrument.

1.4.1 Knowledge Scale Development and Validation

In the context of the MMIC, patient knowledge is measured using a knowledge scale or questionnaire that is unique to the condition for which testing is being offered. Marteau et al. (2001) note that different approaches can be used to identify the required information for patients to make an informed decision. Professional guidelines of informed consent for screening and the opinion of specialists in the field are often referred to as a starting point for the generation of a knowledge scale. A second approach may involve gathering opinions from the population for which genetic testing is being offered in order to refine the relevant information to be included in the knowledge scale. Michie et al. (2003) note that items included in a measurement of knowledge scale should be representative of differing levels of difficulty and if possible, items should be selected in relation to objectively defined criteria. The authors note that this may be particularly difficult in a healthcare setting, where ‘good knowledge’ is not well defined and may be subjective in nature, dependent on the opinions of health care professionals or values of the patient. Therefore, it is recommended that a combination of these approaches is applied when creating a novel knowledge scale, where professional guidelines along with patient values are equally considered (Marteau et al., 2001; Michie et al., 2003).

Best Practices in Knowledge Scale Development & Validation

Knowledge scale development and validation is known to be a time-consuming, complicated and costly process. Furthermore, approaches to the development and validation of knowledge scales are highly variable, as standardized methods of validation are not common practice. Boateng et al. (2018) have created a primer for the best practices in knowledge scale development and validation, based on a broad review of the available technical literature that relates to scale theory. As such, this primer has been selected as the guide for this study, in the development of a novel genetic knowledge scale that is specific to FH.

Item Development

The first phase of knowledge scale development is 'Item Development', which involves generating a preliminary set of questions that are relevant to the study domain, or topic that is to be assessed. Boateng et al. (2018) have selected the guidelines proposed by McCoach et al. (2013), who identify several approaches to domain identification. Importantly, it should be noted whether another instrument already exists that can evaluate the chosen study domain. Additionally, it should be determined whether the definition of the domain needs to be established *a priori* (based on existing theory and established framework) or *a posteriori.* The establishment of a defined study domain sets the stage for the process of item generation and content validation, which are central to the first phase of knowledge scale development.

Item generation can occur using either inductive or deductive methods however, it is considered to be best practice to use a combination of both approaches. Items can be generative inductively through the process of qualitative exploration, which considers the responses of individuals who are directly related to the study domain (Morgado et al., 2017). Deductive item generation can occur through the process of a literature review, where existing research within the study domain guides the process of item development (Raykov & Marcoulides, 2011). Furthermore, the readability of the items, along with the types of responses they are designed to elicit should be considered in their development. Boateng et al. (2018) emphasize that all items should be worded simply and unambiguously. This is especially the case for items that are designed to have dichotomous responses, such as true or false statements. Importantly, one should avoid the use of offensive or biased phrasing in item development with regards to race, gender, ethnicity, sexual orientation or socioeconomic status (Schinka et al., 2012).

Content Validity

Once the preliminary items have been generated, the process of content validity must take place. Content validity can be defined as the 'adequacy with which a measure assesses the domain of interest" (Hinkin, 1995). Notably, establishing content validity also ensures that the items included in the knowledge scale are capable of describing the experience of the target population for the study domain in question (Boateng et al., 2018). Content validity is best assessed through evaluation by expert judges within the study domain, along with members of the target population. Evaluation of proposed items by expert judges can be achieved using various statistical methods. Boateng et al. (2018) recommend using Cohen's co-efficient kappa (*k*) for measuring the degree of agreement among experts, as this method was found to be the most efficient (Cohen, 1960). Alternatively, the validity of proposed items can also be assessed using the Delphi method, where a consensus is required among all judges on which items should be included (Linstone & Turoff, 1975).

The primary purpose of evaluating items among the target population is to establish face validity, a subset of content validity, which can be defined as "the degree that respondents or end users judge that the items of an assessment instrument are appropriate to the targeted construct and assessment objectives" (Haynes et al., 1995). For the purposes of scale development, face validity is best assessed through a series of cognitive interviews (Boateng et al., 2018). Cognitive interviewing is a well-established method used to understand how participants interpret a questionnaire and its content, and allows for the identification and revision of misunderstood items (Beatty & Willis, 2007; Boateng et al., 2018). Best practices of cognitive interviewing for the purposes of questionnaire development includes a range of 5-15 interviews, which are conducted over 2-3 rounds, or until thematic saturation is reached (i.e. revision of the items is no longer required) (Beatty & Willis, 2007). Ultimately, face validity aims to decrease the likelihood that items will be misinterpreted by the target population, affecting the ability of the scale to accurately measure the construct (i.e. knowledge) in which it is intended to measure.

Scale Evaluation

The final phase of knowledge scale validation can be defined as scale evaluation, where the dimensionality, reliability and the overall validity of the scale is assessed (Boateng et al., 2018). Tests of dimensionality may include confirmatory factor analysis, bifactor modeling and

measurement invariance to determine the overall dimensionality (unidimensional vs multidimensional) of the items included in the scale.

Reliability refers to the degree of relatedness between the items within a scale, along with the ability of a scale to perform consistently in identical circumstances across different time points (Boateng et al., 2018). Inner item reliability is most often established using Cronbach's alpha, where an alpha coefficient of 0.70 is considered to be an acceptable threshold for reliability. In contrast, test-rest methods are employed to determine the ability of the scale to produce consistent outcomes in similar situations at different time points.

Finally, scale validity refers to the overall ability of the scale to accurately measure the construct in which it is intended to measure. Validity has already been considered in the previous steps of scale development, through the approaches to item development and content validity. However, the validity of a scale can be further established following administration to a target population, using criterion and construct validity. Criterion validity can be further broken down into predictive validity and concurrent validity. In other words, the ability of the scale to predict a future outcome (predictive validity) and the performance of a scale in comparison to the 'gold standard', or a similar measurement (Boateng et al., 2018). Similarly, construct validity can be separated into convergent validity and discrimination validity, differentiation by known groups and correlation analysis. Taken together, these assessments can indicate the efficacy of a scale to assess a given construct in comparison to similar or related constructs and in the context of real-world applications.

1.4.2 The MMIC as a Three-Dimensional Model: Considering Patient Knowledge, Attitudes and Behaviour

It is known that knowledge is not the sole factor in determining the uptake of screening. In a systematic review, Jepson et al. (2000) found that knowledge about risk, predicted uptake in approximately two in 11 studies. Similarly, knowledge about screening was found to predict uptake in approximately one in six studies. Recently, Lofters et al. (2018) explored the effect of cancer screening awareness on the uptake of cancer screening in a Canadian population consisting of 1683 participants. The majority of participants were found to have poor knowledge of cancer screening. However, this was not significantly associated with screening uptake. Although sufficient knowledge about a test is necessary to ensure patients are making an informed decision, additional factors must also be considered.

In the initial development of the MMIC, Marteau et al. (2001) note that their definition of informed choice involves not only an assessment of patient knowledge, but also an assessment of patient values, to measure whether a patient is making an informed decision. It is assumed that patient attitudes are reflective of their values as the decision maker and as such are said to contribute to the patient's ability to make an informed choice. A benefit to measuring a patent's specific attitude towards undergoing a screening test is the belief that a single attitude will encompass multiple values of the patient (Marteau et al., 2001). The MMIC uses an attitude scale based on the Theory of Planned Behaviour, a well validated model which considers the patient's attitude towards performing a behaviour, influence from external factors and perceived barriers (Ajzen, 1991; Michie et al., 2002). Multiple items are used in the assessment of patient attitude in order to obtain sufficient reliability. These scores are then summed in order to classify each patient as having either a positive or a negative attitude towards testing (Marteau et al., 2001).

The three dimensions of the MMIC measure are combined to classify patients who are offered a screening test as having made an informed or uninformed decision. In total, there are eight possible outcomes that are representative of a spectrum of informed and uninformed choices, according to knowledge (good vs poor), attitude (positive vs negative) and uptake. It should be noted that behaviour is defined as patient uptake of the screening test, and is either reported as 'yes' or 'no' (Marteau et al., 2001). Uptake may be self-reported by the patient or may be confirmed by laboratory records. According to the MMIC, an informed choice is said to be made when the patient has good knowledge towards a test, has a positive attitude towards the test, and proceeds with testing. Conversely, a patient is also considered to have made an informed choice when they are knowledgeable about the test, have a negative attitude towards testing and do not proceed with the test (Marteau et al., 2001). When a patient is found to have poor knowledge, or when attitudes towards the test are not reflective of their behaviour, the choice is considered to be uninformed. The unique typology of the MMIC allowed for the ability to compare the rate of informed versus uninformed choices across different health care delivery services. Furthermore, this method of categorization allows its users to identify the distinct ways in which patients may be making uninformed choices, guiding which aspects of a service require alternation in order to increase rates of informed decision making (Marteau et al., 2001).

1.4.3 Validation of the MMIC Measure

Marteau et al. (2001) emphasize the need for reliable and validated measures of informed choice in order to assess the ability of wide-scale screening programs to elicit informed choice from their patient populations. The authors note the requirement for additional means of validation of the MMIC measure among larger participant cohorts and suggest the possibility of adapting this model to measure informed choice beyond the prenatal setting.

The initial development of the MMIC was prompted by the expansion of pregnancy screening programs in the United Kingdom, where increased rates of screening called for an assessment of the rate of informed choice among the patient population (Marteau et al., 2001). In the preliminary study conducted by Marteau et al. (2001), the MMIC was used to assess the rate of informed choice among pregnant individuals who were offered first trimester screening for Down syndrome. A knowledge scale specific to screening for prenatal screening for Down syndrome was developed based on professional guidelines regarding information that is thought to be essential for patients to understand prior to screening. This information was corroborated further by the patient population through two sets of focus groups (Marteau et al., 2001).

Interviews were conducted among 33 participants in order to validate the knowledge and attitude scales developed for this model (Marteau et al., 2001). Additionally, face validity of the knowledge scale was piloted among the patient population, and was deemed comprehensible (Marteau et al., 2001). The internal reliability and construct validity were assessed for both the knowledge and attitude scales. The alpha coefficient of reliability was found to be 0.82 and 0.83 for the knowledge and attitude scales, respectively. Construct validity was assessed by comparing the scores on the knowledge and attitude scales with the responses from open-ended questions designed to elicit information regarding the participants' understanding and attitudes towards the screening test.

Given the limited sample size used to pilot the MMIC, Michie et al. (2002) performed a validation study to assess the reliability and validity of the MMIC among a larger patient cohort. A total of 225 pregnant individuals from two separate hospitals in the United Kingdom completed the MMIC prior to testing, and the Ottawa Decisional Conflict Scale six weeks after testing was complete. The knowledge and attitude scales were found to be internally consistent, with alpha values of 0.68 and 0.78, respectively (Michie et al., 2002). Evidence of predictive validity was supported by the Ottawa Decisional Conflict Scale, where participants who were

classified as having made an informed choice according to the MMIC also self-reported their decision as supported and informed compared to those who were classified as having made an uninformed choice by the MMIC (Michie et al., 2002). Additionally, construct validity of the MMIC was demonstrated, where an association was found between informed choice and decision outcome, but not feelings of anxiety among participants (Michie et al., 2002). Finally, knowledge and attituded were assessed independently for their impact on informed decision making. Attitudes towards undergoing the test was found to be predictive of decision outcome, whereas knowledge did not appear to be as informative of informed choice. The results of this study further support the basis of the MMIC, which assumes that there is a multidimensionality to making an informed decision.

The knowledge scale was further validated by Michie et al. (2003), where items in the knowledge scale were evaluated for range of difficultly and perceived importance among health care professionals (n = 152) and the target patient population (n = 345). Using an item characteristic curve which plots the probability of a correct response to each item against the knowledge score for each item, the authors demonstrated that with the exception of a single item, the knowledge scale represented a range of difficulty and was able to discriminate between individuals who completed the questionnaire. Additionally, all items included in the knowledge scale were rated as either essential or helpful by the patient population and antenatal healthcare providers. The results from this study conclude that the items included in the knowledge scale represent an appropriate range of difficulty for the target patient population and that each items holds justifiable importance for continued use in the scale (Michie et al., 2003). Similar to previous investigations, this particular study also found that knowledge was not a strong predictor of uptake, whereas patient attitude was. This further emphasizes the importance of considering both patient knowledge and attitudes in the assessment of informed choice (Michie et al., 2003).

1.4.4 Applications of the Original MMIC Measure

The MMIC measure has shown to be a valuable tool in the assessment of informed choice among a variety of different patient populations since its initial development and validation. Dormandy et al. (2005) used the antenatal MMIC measure to assess rates of informed choice for Down syndrome screening among minority ethnic and socioeconomic disadvantaged groups. Importantly, the researchers wanted to determine whether the observed low rates of

uptake for pregnancy screening was due to an overall negative attitude towards the test among these individuals, or due to a greater inconsistency between uptake and attitude, which would be reflective of lower rates of informed choice (Dormandy et al., 2005). Using the MMIC, the authors concluded that lower uptake was not associated with negative attitudes towards testing but rather lower rates of informed choice, where pregnant women were demonstrating a positive attitude towards screening which was not reflective in the overall uptake of the test. Importantly, an updated version of both the knowledge and attitude scales resulted from this study, with two items being added to each measure (Dormandy et al., 2005).

Validation of a translated version of the MMIC measure was conducted by Gourounti & Sandall (2011), conferring a cultural adaption of the initial MMIC to suit a Greek population. A total of 135 pregnant individuals awaiting prenatal screening for Down syndrome were recruited from a hospital in Athens, Greece. An updated version of the MMIC, modified by Dormandy et al. (2005) was used for the basis of translation, consisting of a 10-item knowledge scale (previously eight items) and a six item attitude scale (previously four items). Following translation, the knowledge scale was piloted through a series of cognitive interviews among the patient population to remove problematic wording or language that may result in ambiguity in the completion of the questionnaire. Similar to previous approaches to validating the MMIC, Gourounti & Sandall (2011) assessed the internal reliability and validity of the Greek-translated measures. The alpha coefficients for the translated knowledge and attitude scales were found to be 0.64 and 0.76, respectively. Construct validity was determined based on a significant positive association between the MMIC and global screening decision certainty (Gourounti & Sandall, 2011). The Greek-translated model of MMIC was found to be appropriate for the assessment of informed choice in a Greek population.

1.4.5 Adaptations of the MMIC Measure

A handful of studies have focused on the alteration of the MMIC measure to accommodate diverse patient populations, establishing the groundwork for making this measure applicable to a wider breadth of applications. Efforts have been made to facilitate the adaptation of the MMIC model to accommodate low literacy populations. The authors argue that adapted measures are important to consider, as there is evidence to suggest lower rates of health literacy and informed choice among individuals from minority ethnic groups and individuals with lower socioeconomic status (Dormandy et al., 2005; Rowe et al., 2004; Sepassi et al., 2023).

For example, Dormandy et al. (2007) developed a revised MMIC measure about antenatal screening for sickle cell and thalassemia. This cross-sectional study included 46 women with higher education levels alongside 33 women with lower education levels. Simplified versions of the standardized knowledge and attitudes scales were presented to both groups of women. The standardized knowledge scale was first developed based on professional guidelines for informed consent to screening, whereas the attitude scale was derived from the initial MMIC, developed by Marteau et al. (2001). Simplified versions of both questionnaires were developed through alterations made to improve readability, sentence size, and font size. Additionally, pictograms were added to each item in the questionnaires (Dormandy et al., 2007).

Both readability and validity of the simplified questionnaire were assessed. The simplified questionnaires were able to distinguish between women with good vs poor knowledge, along with positive vs negative attitudes towards screening. No observable differences in rates of informed choice were identified between the standardized and simplified questionnaires. Importantly, women with lower levels of education found the simplified versions of the questionnaires easier to comprehend, while women with higher levels of education found no difference between the two versions, making the simplified questionnaire suitable for use in both populations (Dormandy et al., 2007).

The development of a modified MMIC specific to assessing patient informed choice in the context of Fragile X carrier screening was conducted by Ames et al. (2012). This was the first adaptation of the MMIC to be used in the context of preconception genetic carrier screening. Items in the knowledge scale were developed based on a brochure provided through the clinic offering preconception carrier screening for Fragile X. These items were then reviewed by several experts in the field and piloted among several staff and patients of the clinic to establish both the face and content validity of the questions. In contrast to the original MMIC, which assessed knowledge through a series of multiple-choice questions, the Fragile X knowledge scale was designed as a true or false questionnaire. Additionally, modifications were made to the original attitude scale developed by Marteau et al. (2001) to include a fifth additional item. Once again, the modified attitude scale was assessed for both content validity and readability. Cronbach's alpha was used to quantify internal consistency for both the knowledge and attitude scales, resulting in an alpha of 0.70 and 0.73, respectively (Ames et al., 2012).

Finally, the MMIC has been adapted to assess patient informed choice in the context of cancer screening, which has proven to be particularly useful in the assessment of patient decision aids and informational brochures. Wakefield et al. (2008) assessed the impact of patient decision aids on rates of informed choice among individuals offered genetic testing for breast and ovarian cancer risk. Similarly, Steckelberg et al. (2011) used an adapted version of the MMIC model to assess patient informed choice in the context colorectal cancer screening, where the initial instrument was adapted to assess rates of informed choice among a German population. Rates of informed choice were measured among patients who had received the official information package provided by the German colorectal cancer screening program and compared to that of patients who had received a brochure containing evidence-based risk information on colorectal cancer screening. In both cases, the MMIC proved to be a useful instrument for evaluating the impact of patient decision aids and patient education material on rates of informed choice across different patient populations.

1.4.6 Limitations of the MMIC Measure

The MMIC has been proven to be a robust measure of informed choice across various contexts, demonstrating adequate internal reliability and construct validity among previously validated models. However, several limitations have been identified with respect to the efficacy of this instrument in the evaluation of informed choice. Although the MMIC is a three-dimensional model designed to encapsulate the complex process of patient decision making, it is still not capable of detecting all nuances that contribute to this experience (Lewis et al., 2016). Similarly, the MMIC alone is not capable of identifying situations where a patient is said to have made an 'uninformed choice' based on discordance between attitude and behaviour when the behaviour is not implemented for practical reasons, and not a true reflection of the patient's individual decision without barriers (Lewis et al., 2016). To address this, Lewis et al. (2016) suggest a mixed methods approach, where assessment of patient informed choice by the MMIC is accompanied by individual interviews where patients can elaborate on their experience of making a decision.

Another limitation of the MMIC is the quantification of 'good knowledge' as determined by a patient's score using the knowledge scale. There is not standard measurement of what constitutes 'good knowledge' across all contexts of health care, resulting in a subjective assessment of patient knowledge based on criteria set by clinical guidelines or expert opinions in

the development of the knowledge scale. In each version of the MMIC measure, 'good knowledge' may vary depending on the style of the questionnaire, the expert opinion of those who developed the knowledge scale or the overall performance of the knowledge scale among the patient population (Ames et al., 2012; Marteau et al., 2001).

To improve the sensitivity of the MMIC measure, it has been proposed that extensive qualitative research is required for an in-depth exploration of the ways in which a particular patient population makes a decision in order to encapsulate the complexity of this process (Ames et al., 2012). Doing so may inform additional methods of MMIC development which can then be adapted and implemented to accurately assess patient informed choice across a wider range of patient populations.

1.5 STUDY RATIONALE

Updated guidelines for FH support the clinical utility of genetic testing to facilitate early diagnosis, intervention, and cascade screening given the risk for premature ASCVD in this patient population. The pivotal role of genetic services has been highlighted throughout the literature, where genetic testing and counselling can provide patients with a comprehensive understanding of the implications of their condition for both themselves, and their family members. Given the high prevalence of FH, genetic testing may be offered at the frontline, where cardiologists, endocrinologists, and internal medicine practitioners facilitate testing directly. To support informed decision making, it is essential that the benefits, risks and limitations of genetic testing are communicated to patients in order to make an informed choice (Godard et al., 2003).

The MMIC has been identified as a valuable model to measure informed choice and a need has been identified, by the genetic counselling community, for validated measures of informed choice that are specific to inherited cardiac conditions, including FH. This study initiates the validation process of an 8-item knowledge scale specific to FH, to be used as part of an FH-specific MMIC measure to assess patient informed choice in the context of genetic testing for this condition in a Canadian population.

1.6 RESEARCH QUESTIONS AND OBJECTIVES

This study aimed to answer the following research questions:

1. Are the items included in the FH knowledge scale understood by participants?
2. What information is required for patients to make an informed choice about genetic testing for FH?

To answer these research questions, the objectives of this study are two-fold:

1. *Primary aim* – To evaluate the face validity and core concepts of an 8-item true or false knowledge scale specific to FH.
2. *Secondary aim* – To explore participant views regarding key factors that influenced their decision to pursue genetic testing for FH.

CHAPTER 2: METHODOLOGY

2.1 STUDY DESIGN

This study followed a qualitative approach, where a series of 10 interviews were conducted to achieve the primary and secondary aims. A qualitative methodology was selected for this study given its capacity to deepen the understanding of individual experiences, and provide insight into topics that are understudied in the literature (Creswell & Poth, 2017). This methodology was essential for understanding how participants interpreted the items included in the knowledge scale, the importance of the associated concepts, and the key factors that contribute to how individuals made a decision about genetic testing for FH. This study received ethics approval from the University of Manitoba Bannatyne Research Ethics Board (HS26404) and the University of Alberta Health Research Ethics Board (Pro00142282).

2.2 THEORETICAL FOUNDATIONS

Constructivism was selected as the primary framework for this study, which guided the approach to data collection, analysis, and interpretation. In the context of healthcare research, a constructivist framework can be used to discern the meanings behind patient experiences and inform healthcare practices (Burns et al., 2022). At its essence, constructivism does not assume a single truth but rather multiple and subjective realities, which are inclusive of the both the researcher and participants (Charmaz, 2014). In the context of this study, we aimed to explore the realities of how a proportion of the FH patient population perceive the items included in the knowledge scale and the factors that impacted their decision to pursue genetic testing.

2.3 DEVELOPMENT OF THE GENETIC KNOWLEDGE SCALE FOR FAMILIAL HYPERCHOLESTEROLEMIA

The FH knowledge scale was initially developed by a team of genetic counsellors who specialize in cardiogenetics and scale development (Christian, S; Borle, K; Mostafavi, R; Wand, H; Slamon, J; Biesecker, B). The items in the knowledge scale cover three broad domains of patient knowledge including their understanding of FH, the management implications following a diagnosis of FH, and genetic testing for FH. The order of the items in the knowledge scale was guided by the findings of Christian et al. (2025), who recently conducted a similar study to validate a genetic knowledge scale for inherited heart disease. Additionally, the true or false response system was selected based on the assumption that these types of questions allow items to be written in plain language, effectively reducing the overall cognitive burden and completion

time among patients (Frisbie, 1973). This style of response system has been widely used across other MMIC measures published in the literature (Ames et al., 2015). Prior to this study, the FH knowledge scale was revised based on feedback from key stakeholders within the field, including members of the Dyslipidemia working group within the National Society of Genetic Counsellors (NSGC) cardiovascular special interest group.

2.4 PARTICIPANT ELIGIBILITY AND RECRUITMENT

Individuals were eligible to participate in this study if they were ≥18 years and were seen by a genetics clinician for an indication of FH at either the Shared Health Genetics clinic in Winnipeg, Manitoba or the Medical Genetics Clinic in Edmonton, Alberta within the last 2 years. A comprehensive list of the inclusion and exclusion criteria for this study can be seen in Table 5.

Table 5: Inclusion and Exclusion Criteria for Participants

Inclusion Criteria Participants were eligible to participate in this study if they:	**Exclusion Criteria** Participants were not eligible to participate in this study if they:
1. were seen by a genetics clinician (genetic counsellor or medical geneticist) since January 2022 for an indication of FH 2. were offered genetic testing for FH since January 2022 3. were ≥ 18 years of age 4. were proficient in reading and speaking in English 5. had access to zoom	1. were seen by a genetics clinician (genetic counsellor or medical geneticist) before January 2022 for an indication of FH 2. were offered genetic testing for FH prior to January 2022 3. were ≤ 18 years of age 4. were not proficient in reading and speaking in English 5. did not have access to Zoom

Participants were recruited prospectively from both clinical sites through clinician referral to the study, following a clinician recruitment script (Appendix I). Recruitment was conducted using a combination of convenience sampling and later, purposeful sampling. Purposeful sampling was implemented to ensure diversity with regard to age, gender, and education level. Verbal consent was obtained from patients who were interested in learning more about the study using a consent to contact form (Appendix II). Completed contact forms were received by the student principal investigator (PI), who then reached out to participants using their preferred method of contact to provide additional information about the study and to coordinate an interview date.

Participants were also recruited retrospectively through the Shared Health Genetics Clinic in Winnipeg, MB. Eligible participants were identified through a clinical database query conducted by a Shared Health staff member, using the study eligibility criteria. A letter of

invitation to the study was sent to all individuals who met the eligibility criteria (Appendix IV). Individuals who expressed interest in learning more about the study were invited to contact the student PI via telephone or email. If they decided to participate, an interview date was then scheduled by the student PI.

This study aimed to recruit 10-15 participants. Sample size was determined based on recommendations made in the literature for the best practices in tool validation studies (Boateng et al., 2018). Recruitment took place from May 2024 to January 2025. All participants were offered a $25.00 honorarium to either Tim Horton's or Amazon as a thank you for their participation in this study.

2.5 DATA COLLECTION

2.5.1 Interview Guide Development

A semi-structed interview guide was developed for this study focusing on eliciting participants' understanding of the questions included in the knowledge scale and their perception of the importance of their associated concepts (Appendix VII). The interview guide also included questions at the beginning and end of the interview to explore key factors that influenced how participants made a decision about genetic testing for FH. The placement of these questions was intentional, to ensure that participants were not influenced by the items in the knowledge scale when sharing their motivations for genetic testing. The interview guide was developed following the approaches outline by Beatty and Willis (2007), where a combination of think-aloud approaches and follow up probes were included to facilitate the process of cognitive interviewing. Probes used during the interviews included a combination of both anticipated probes included in the interview guide, and emergent probes developed by the student PI in response to statements made by participants over the course of each interview.

The interview guide was reviewed by the research committee, consisting of a qualitative research expert (KM) with experience in cognitive interviewing methodology, a developmental biologist (JW) who specializes in cardiovascular science and a certified genetic counsellor (CCL) with experience in qualitative research. The interview guide was also piloted with the patient partner (AY), where revisions were made to improve the clarity of the interview questions. Additional probes were added to the interview guide based on feedback from the patient partner to allow for deeper exploration of participants' experiences making a decision about genetic testing for FH.

2.5.2 Interview Procedure

Interviews were conducted by the student PI and took place virtually over Zoom. Prior to the interview, each participant was emailed a copy of the interview consent form (Appendix VI). The consent form was then verbally reviewed in detail with each participant on the interview date, and consent was obtained by the student PI prior to the start of the interview. Once the interview recording was stopped, demographic information was collected verbally from participants and documented by the student PI in a confidential Master List.

2.5.3 Cognitive Interviewing

Cognitive interviewing was selected as the method to guide data collection based on the primary aim of this study, which was to evaluate the face validity and importance of core concepts of the items included in the FH knowledge scale. Cognitive interviewing prompts participants to provide a verbal retelling of their mental processes as they examine information and incorporates a combination of open-ended questioning and follow up probes to elicit detailed information. This style of interviewing is useful to understand how participants interpret a questionnaire and its content, and is broadly used in scale development (Beatty & Willis, 2007; Boateng et al., 2018). As such, this method of interviewing was best suited for assessing how participants perceive the items included in the knowledge scale and allowed for the identification of items in the knowledge scale that required revision to either the phrasing or content of the questions.

During each interview, participants were guided through a PowerPoint presentation containing the 8 items included in the knowledge scale, and their associated concepts (Appendix VIII). Participants were asked to discuss their initial interpretation of each item and describe in their own words what they think the question is asking. Following the interview guide, follow up probes were asked by the student PI to elicit additional information from the participants on their understanding of the items. Following this phase, the concept associated with each item was shared with the participant, where they were then asked to rate the concept as necessary, helpful, or not important to make a decision about genetic testing for FH. Once again, follow up questions were asked by the student PI to elicit additional information regarding the participants choice in ranking. For example, if a participant stated that they felt a concept was necessary, the interviewer asked, “why did you choose necessary instead of helpful or not important?”. At the end of the interview, participants were provided with an opportunity to make additional

comments regarding their experiencing deciding about genetic testing for FH or additional comments about the knowledge scale.

2.5.4 Transcription

All interviews were audio/video recorded and transcribed using the transcription feature on Zoom. Transcripts were audio verified by the either the student PI or a student volunteer (EC) following each interview to ensure accuracy and confidentiality. Transcripts were deidentified to maintain participant confidentiality through the removal of participant identifiers from interview transcripts such as names, clinic names, clinician names and locations. In replacement of their name, each participant was assigned a unique study ID number.

All interview recordings were saved to secure drive on a computer located on the University of Manitoba Bannatyne campus in the Basic Medical Science Building. Files saved to this computer are password protected and protected under the Personal Health Information Protection Act. All study data will be deleted from this drive following a period of at least 5 years after the completion of the study.

2.6 DATA ANALYSIS

The interview data was analyzed using two different approaches, which were selected according to the primary and secondary aims of this study. A traffic light coding scheme was used to address the primary aim of this study, in order to assess the face validity and importance of items included in the knowledge scale. Conventional content analysis was used to address the secondary aim of this study, which explored the key factors that affected participant decision making when deciding about genetic testing for FH.

2.6.1 Traffic Light Coding

Few guidelines are available for the analysis of cognitive interviews for the purpose of questionnaire revision and instrument design. However, there is a common understanding that the primary goal of cognitive interview analysis is to identify whether or not a question poses problems for participants (Beatty & Willis, 2007; Knafl et al., 2007). A traffic light system was used as the coding scheme for analysis of interview responses pertaining to the face validity and importance of concepts of the items in the knowledge scale. With respect to assessing face validity, problematic responses indicating a poor understanding of an item were coded as red, positive responses indicating a good understanding of an item were coded as green, and neutral or ambiguous responses were coded as yellow (Connell et al., 2018). Following this coding

scheme, if a problematic response (coded red) to an item included in the knowledge scale appeared in at least one interview, it was flagged and considered for revision. With respect to assessing the importance of core concepts, participant responses were highlighted as green if a concept was considered to be necessary to make a decision about genetic testing, yellow if the concept was considered to be helpful and red if the concept was rated as not important. Any concept coded as not important by three or more participants would be considered for removal from the scale.

Participant responses were analyzed in duplicate by the student PI and the supervisor (SC) following the process outlined by Knafl et al. (2007), who provide a step by step guide to the analysis of cognitive interview data for the purpose of identifying problematic responses and making revision to the content. Coding was performed independently and then compared between the student PI and the supervisor following each interview to resolve discrepancies and ensure consistency.

2.6.2 Knowledge Scale Revision

Following the first five interviews, preliminary results pertaining to the face validity and importance of core concepts was presented by the student PI to the team of genetic counsellors who were involved in the initial development of the knowledge scale. As such, all revisions to the items in the knowledge scale were made in collaboration between the student PI, the supervisor and this team of collaborators. Items that elicited suggestions from participants to improve the clarity of the questions were reviewed by the group and revised based on participant feedback. These revisions were subsequently presented to the patient partner for additional review by a relevant stakeholder. Upon final approval by the research team and patient partner, the revised version of the knowledge scale was implemented for the remainder of the interviews.

2.6.3 Conventional Content Analysis

Conventional content analysis was selected as the method to analyze data associated with the secondary aim of this study, which explored the key factors that influenced participants' decisions to pursue genetic testing for FH. The think-aloud tactic that is central to cognitive interviewing was conducive to this analytical approach, as conventional content analysis is most effective when open-ended questions and probes are presented to participants (Hsieh & Shannon, 2005). Conventional content analysis is best suited to describe a phenomenon, where existing literature on the topic is limited (Hsieh & Shannon, 2005). As such, this method of analysis

follows an inductive approach, where preconceived ideas of potential categories were avoided to allow for conclusions to flow directly from the data.

As described by Hsieh & Shannon (2005), conventional content analysis begins with the researcher immersing themselves in the interview data to obtain a broad understanding of the phenomenon that is to be investigated. As such, each interview transcript was thoroughly reviewed by the student PI, prior to the conception of codes and categories. Following this, interview transcripts were coded by student PI in sequential order (i.e. beginning with the first interview and ending with the final interview), to facilitate the development of a codebook. To facilitate this secondary analysis, transcripts were coded using Dedoose software, version 9.2.22 (Dedoose, 2024).

Codes were developed using three different strategies which included in vivo coding, descriptive coding and value-based coding (Richards, 2009). In vivo coding uses the participant's own words for code development. For example, if a participant mentioned the word 'medication' or 'family', this was coded verbatim. Descriptive coding was used to summarize participant responses that were lengthier and required interpretation by the student PI to summarize the essence of the data using a single code. Finally, value-based coding was applied to participant responses that were related to their values, attitudes, beliefs and worldviews. This type of coding is best suited for responses that begin with "I feel", "I think", or "I need". Once an initial code book was developed, another round of analysis was conducted to promote consistency between the codes that were identified across all interviews.

Following code development, categories were generated based on how individual codes were related or linked to one another. Codes were considered for category development based on the number of times that they appeared across interviews, consistent with the approaches taken for content analysis (Hsieh & Shannon, 2005). Codes that appeared in more than one interview were considered to be significant and therefore included in category development. If a code was only present in a single interview, it was not included in a category.

Participant responses were taken into consideration during revision of the knowledge scale, with consideration of the possibility for new concepts to emerge from the data that were not included in the initial knowledge scale.

2.6.4 Data Saturation

Saturation for this study was defined based on the primary aim, which sought to assess the face validity and importance of core concepts across the items included in the knowledge scale. Saturation was considered to be reached when a minimum of three consecutive interviews were conducted that did not elicit problematic responses from participants, and revisions to the knowledge scale were no longer required (Beatty & Willis, 2007; Boateng et al., 2018; Strauss & Corbin, 1990).

2.7 TRUSTWORTHINESS IN QUALITATIVE RESEARCH

In qualitative research, trustworthiness refers to the level of rigor that exists in the overall design and methodology used to investigate a research question in order to produce meaningful results that are reflective of participants experiences (Ravitch & Carl, 2020). The trustworthiness of a study can be assessed through four distinct criteria: credibility, transferability, dependability and confirmability (Ahmed, 2024; Guba, 1981).

Credibility refers to the ability of the research findings to accurately reflect the experiences of participants, and can be established through prolonged engagement with research participants (Guba, 1981). The use of semi-structed cognitive interviews allowed for in-depth exploration of participants interpretations of the knowledge scale and their experiences deciding about genetic testing for FH. Credibility in qualitative research can also be established through triangulation, which refers to the integration of multiple sources and feedback from relevant stakeholders throughout the research process (Ahmed, 2024). This was achieved through consistent communication with the committee members and patient partner throughout the research process to review the student PI's approach to interpreting the data. Peer debriefing between the student PI and main supervisor was conducted throughout the process of data collection and analysis to review emerging insights the student PI had while conducting interviews and resolve inconsistencies in the approach to traffic light coding. Finally, credibility was further established through the verification of interview audio files and transcripts by the student PI and a student volunteer.

Transferability refers to the extent of which the research findings can be applied broadly, beyond of the context of the research study (Guba, 1981). The transferability of the findings from this study was taken into consideration in the development of the recruitment strategy. Purposeful sampling was used to increase the diversity of the study sample in the second round

of interviews, where gender, age and education background were taken into consideration to broaden the scope of perspectives reflected in the data. Transferability of qualitative research can also be achieved through the collection of 'thick' and descriptive data, providing other researchers with sufficient information to critically apply the research findings to alternative contexts (Ahmed, 2024). This was conducted through the maintenance of detailed field notes and study documentation, outlining the student PI's approach to data interpretation and analysis.

Dependability, often thought of as reproducibility, refers to the ability for the study to be repeated in a separate context and is contingent on the availability of detailed documentation of the study design and methodological approaches (Guba, 1981). Dependability was considered in this study through the generation of detailed documentation pertaining to the methods used for data collection and analysis, along with the maintenance of records reflecting the student PI's approach to analyzing the data.

Finally, confirmability refers to the level of impartiality and objectivity of the research findings (Guba, 1981). In qualitative research, it is imperative that a reflexive and collaborative approach is taken when drawing conclusions from the data in order to limit the bias that is inflicted by the researcher's personal beliefs, values and experiences (Morse, 2015). In this study, the student PI frequently consulted members of the research team along with external stakeholders, such as the patient partner and genetic counsellors who were responsible for the development of the FH knowledge scale to review the findings from the primary and secondary aims of this project. Additionally, the student PI maintained a reflexive approach when interacting with the study data and was conscious of how their personal experiences may have impacted their approach to data collection and analysis.

2.8 POSITIONALITY STATEMENT AND REFLEXIVITY

The student PI is a genetic counselling student who has gained prior experience counselling patients on inherited cardiovascular conditions, including FH. As such, the student PI is knowledgeable of FH and has a thorough understanding of the concepts covered by the knowledge scale evaluated in this study. The student PI's clinical training in genetic counselling provides them with a familiarity of the factors that commonly motivate or deter patients from pursuing genetic testing, which was a topic explored in this study. Altogether, these factors may have influenced the way the student PI engaged with participants during interviews, along with their interpretation of participant responses to items in knowledge scale and their experience

making a decision about genetic testing. To mitigate these factors, the student PI practiced reflexivity by deliberating on the primary objectives of this study, their role as a researcher, and their personal experiences that may have influenced how they interacted with participants or the study data. Following each interview, the student PI documented field notes reflecting on the ways their personal biases may have influenced the interview, or their approach to data analysis. Finally, the student PI is a white, cisgender, heterosexual female, and was known to the participants as a genetic counselling student. As such, participants' outward perception of the student PI's identity may have affected their responses during the interview process.

CHAPER 3: RESULTS

3.1 PARTICIPANT DEMOGRAPHICS

A total of 67 individuals were contacted to participate in this study (53 retrospective, 14 prospective). Thirteen individuals expressed interest in this study, and three participants were lost to follow up. A total of 10 participants were interviewed for this study. The interviews ranged from 22-62 minutes in length, with an average interview time of 40 minutes. Eight participants were recruited prospectively through clinician referral, while two were recruited retrospectively through a mailed letter of invitation (Appendix IV). An equal number of participants were recruited from both the Winnipeg and Edmonton genetic clinics. A schematic diagram depicting the process of recruitment is shown in Figure 1.

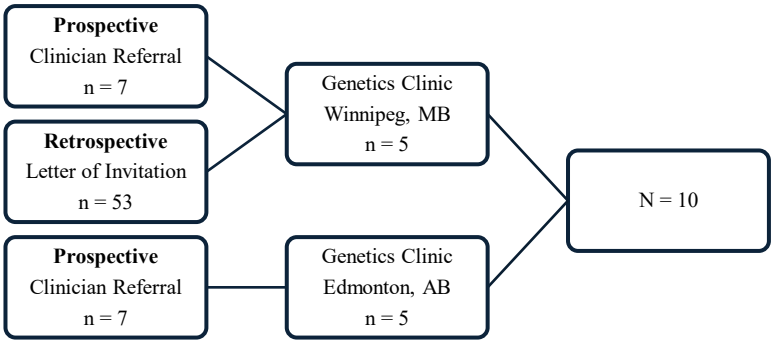

Figure 1: Recruitment Flow Chart

The majority of participants (n = 6) did not know their genetic status for FH, as results were still pending. Eight participants in this study were the first to receive genetic testing for FH in their family, while two participants received cascade genetic testing as the result of a previously identified familial variant. Four participants had a confirmed molecular diagnosis at the time of the interview. Two of these participants recalled that they were found to be heterozygous for a disease-causing variant. The age of participants ranged from 21-69, with the median age being 41.5 (mean age 43.2). Education levels of participants varied from high school level to post graduate degrees. Three participants identified as male, and seven participants identified as female. The majority of participants identified as white (n = 7), with one participant identifying as Hispanic/Latino/a, another participant identifying as Black and a third participant

identifying as mixed race as mixed race (Black/Indigenous). Three participants were reported to live in rural locations, while the remaining seven lived in urban centres. A complete summary of participant demographics is shown in Table 6.

Table 6: Participant Demographics

Characteristic	Number of Participants (N = 10)
Clinical Site	
Winnipeg, MB	5
Edmonton, AB	5
Proband vs At Risk Family Member	
Proband	8
At Risk Family Member	2
Method Of Recruitment	
Prospective	8
Retrospective	2
Confirmed Molecular Diagnosis Of FH	
Pending	6
Yes	4
No	0
FH Genotype	
Unknown	8
Heterozygous for disease-causing variant	2
Homozygous for disease-causing variant	0
Age	
18 - 35	3
36 - 53	4
54 - 70	3
Education Level	
High School	3
Trade/Technical/Vocational School	1
Some College	1
College	1
Bachelor's Degree	2
Post Graduate Degree	2
Race	
White	7
Black or African American	1
Hispanic or Latino/a	1
Mixed Race (Black/Indigenous)	1
Gender	
Female	7
Male	3
Non-Binary	0
Two Spirit	0
Transgender	0
Prefer not to respond	0
Residential Area	
Urban	7
Rural	3
Canadian Northern/Remote	0
Reserve	0

3.2 ASSESSING THE FACE VALIDITY OF FH KNOWLEDGE SCALE

The face validity of the items in the knowledge scale was assessed over the course of 10 interviews. Revisions to six of the eight items in the knowledge scale were made following the first round of interviews (n = 5). The revised knowledge scale was then repiloted over the course of an additional five interviews, which did not reveal any additional problematic responses. However, two additional revisions were made following the second round of interviews based on participant preferences regarding specific terminology used in the knowledge scale.

Participant responses in the first round of interviews were coded as either green or yellow, as all items in the knowledge scale were interpreted appropriately. However, some participants provided feedback on how Items 2, 4, 5, 7, and 8 could be reworded to improve the clarity of the questions. These responses were coded as yellow (Figure 2). Notably, four out of five participants provided feedback to improve the clarity of Item 7, which was initially written as "*for someone who has FH, genetics causes high cholesterol*". The majority of participant feedback suggested that this item was not specific enough for an individual to provide an accurate response, even if they had received adequate counselling on the condition. Interestingly, once participants were shown the initial concept related to this item, "*FH cholesterol levels cannot be fully managed by exercise and diet alone. Medication is usually needed to reach a healthy cholesterol level*", they expressed that this information should be included in the question itself. A summary of participant feedback from the first round of interviews is outlined in Table 7.

Table 7: Participant Feedback from the First Round of Interviews (Interviews 1–5, Items 2, 4, 5, 7 & 8)

Item	Response
Item 2: FH treatment in childhood does not have long-term benefits. (False)	**P001:** I would use a term that is definitely more specific. For example, I don't know. It's beneficial to the to the continuation of the of the family, or it's beneficial to the offspring of the participant, or something like that, something more specific, like giving one benefit in in a specific.
Item 4: FH can lead to serious heart disease. (True)	**P004:** I guess FH can lead to serious outcomes, such as heart disease, stroke. I can't think of all the other outcomes of FH. I would probably elaborate more on it, and not just stick to heart disease.

Item 5: If FH is found early in life, actions can be taken to lower the chance of heart disease. (True)	**P004:** I guess early in life I would maybe try to be more specific so early in life as in… as a child or like in your twenties? Maybe I would be more specific there. Actions can be taken to lower...and then I would maybe be more specific as to what those actions are.
Item 7: For someone who has FH, genetics causes high cholesterol. (True)	**P001:** It's easy to understand. But it's not as specific enough for me to say that it's true, because it's a yeah. It's just a very general term. And the genetic, the genetical thing is just too big, too broad. **P002:** For someone who has FH genetics causes high cholesterol. It seems like a... rereading it. My slow brain is, it makes perfect sense, but it just seems like a difficult sentence to maybe like follow. **P003:** I do think actually, for the question... I think that it should be explicit for someone who has FH genetics causes high cholesterol, and cannot be fully managed by exercise and diet alone. I think that's what the whole statement should be. **P004:** For someone who has FH, genetics along with other contributing factors causes high cholesterol. So other contributing factors would be diet and exercise because that it can help with the treatment of FH. I this could be maybe a little bit misleading, because you might just try to put it all on the genetics piece, as to why you have high cholesterol. Do you know what I mean? I think it would probably be better to have other factors in there as well.
Item 8: Genetic testing is a reliable way to test family members for FH when a genetic cause is found in the family. (True)	**P003:** I think the concept statement is much clearer than the statement. So, the genetic testing is currently the best way to screen family members for FH is a much better statement than genetic testing is a reliable way to test family members for FH. When a genetic cause is found in the family. And for that statement, if it's going to be that original statement I would probably start with when a genetic cause is found in a family member, then genetic testing is a reliable way to test family members for FH.

Following the first round of interviews, revisions were made to six of the eight items included in the knowledge scale. All revisions were made in collaboration with the team of genetic counsellors who initially developed the knowledge scale. The revisions made to Items 2,

4, 5, 7, and 8 were based on solely on participant feedback. To note, Item 7 required significant revision which consisted of switching aspects of the question and concept to better reflect the knowledge that was intended to be assessed by this item. A revision was also made to Item 6 to establish consistency between the narration of items in the knowledge scale (i.e. to ensure all items are written in the first person). A summary of the revisions made to the knowledge scale following the first round of interviews is shown in Table 8.

Flesh-Kincaid readability scores were used to determine the grade level for each item included in the knowledge scale (Kincaid et al., 1988). All revisions were made with the intention of items being scored between a 5th grade – 8th grade reading level. With respect to Item 7, the revised question (*medication is often needed to lower cholesterol for people with FH*) was ranked at a college reading level, which exceeded the maximum 8th grade reading level according to the Flesh-Kincaid readability score. As such, participants were asked to share their preference on the term 'medication' versus alternative terms that would lower the reading level ('drugs') or simplify the language used in this context ('medicine') in the next round of interviews.

Table 8: Summary of the Revisions to the FH Knowledge Scale (Interviews 1-5)

Original Statement	Revised Statement	Concept
Item 1: It is possible to have FH and not know that you have it. (True) **Flesh-Kincaid Score:** 5th grade	N/A	Incomplete penetrance
Item 2: FH treatment in childhood does not have long-term benefits. (False) **Flesh-Kincaid Score:** 8th/9th grade	FH treatment in childhood does not reduce the risk of heart attacks. (False) **Flesh-Kincaid Score:** 6th grade	Treatment for FH should start as early as possible to lower the chance of heart attack
Item 3: A negative genetic test means that you do not have FH. (False) **Flesh-Kincaid Score:** 7th grade	N/A	Limitations of genetic testing
Item 4: FH can lead to serious heart disease. (True) **Flesh-Kincaid Score:** 6th grade	FH can lead to health problems such as heart attacks. (True) **Flesh-Kincaid Score:** 5th grade	People with FH have a much higher chance of heart attacks
Item 5: If FH is found early in life, actions can be taken to	If you have FH, steps can be taken to lower your risk of heart attacks. (True)	There are ways to lower the chance of heart attack due to FH

lower the chance of heart disease. (True) **Flesh-Kincaid Score:** 7th grade	**Flesh-Kincaid Score:** 5th grade	
Item 6: If someone has FH, it is unlikely that their family members have it. (False) **Flesh-Kincaid Score:** 8th/9th grade	If you have FH it is unlikely that your family members have it. (False) **Flesh-Kincaid Score:** 7th grade	FH runs in families
Item 7: For someone who has FH, genetics causes high cholesterol. (True) **Flesh-Kincaid Score:** college	Medication is often needed to lower cholesterol for people with FH. (True) **Flesh-Kincaid Score:** College (*Replacing the word 'medication' with 'drugs' lowers this score to 8th/9th grade)	FH cholesterol levels cannot be fully managed by exercise and diet alone. Medication is usually needed to reach a healthy cholesterol level. **REVISED TO:** For someone who has FH, genetics causes high cholesterol
Item 8: Genetic testing is a reliable way to test family members for FH when a genetic cause is found in the family. (True) **Flesh-Kincaid Score:** 10th – 12th grade	If you are found to have a genetic cause for FH, genetic testing is the best way to screen your family members. (True) **Flesh-Kincaid Score:** 8th/9th grade	Genetic testing is the best way to screen family members.

The revised version of the knowledge scale was then re-piloted over the course of an additional five interviews. All participants demonstrated a good understanding of the revised items with the exception of one participant, whose response to Item 2 was coded yellow due to ambiguity. This item was not found to require additional revision upon consultation with the study team. During the second round of interviews, participants were also asked about their preferences towards specific terms used in Items 3 and 7. Item 3, which focuses on the limitations of genetic testing, states '*A negative genetic test means that you do not have FH*'. Participants were asked if they prefer 'normal (negative)" versus "negative (normal)" in this context. Ultimately, the majority of participants (n = 4) preferred the term "normal (negative)" when describing a negative genetic test result. These preferences have been incorporated into the final version of the knowledge scale.

With respect to Item 7, 'medication' remained the preferred term among the majority of participants (n = 4), compared to 'medicine' or 'drugs'. Therefore, no additional revisions were made to Item 7 in the final version of the knowledge scale. A summary of the codes applied to

each item in the knowledge scale is depicted in Figure 2. The final version of the FH knowledge scale is shown in Figure 4.

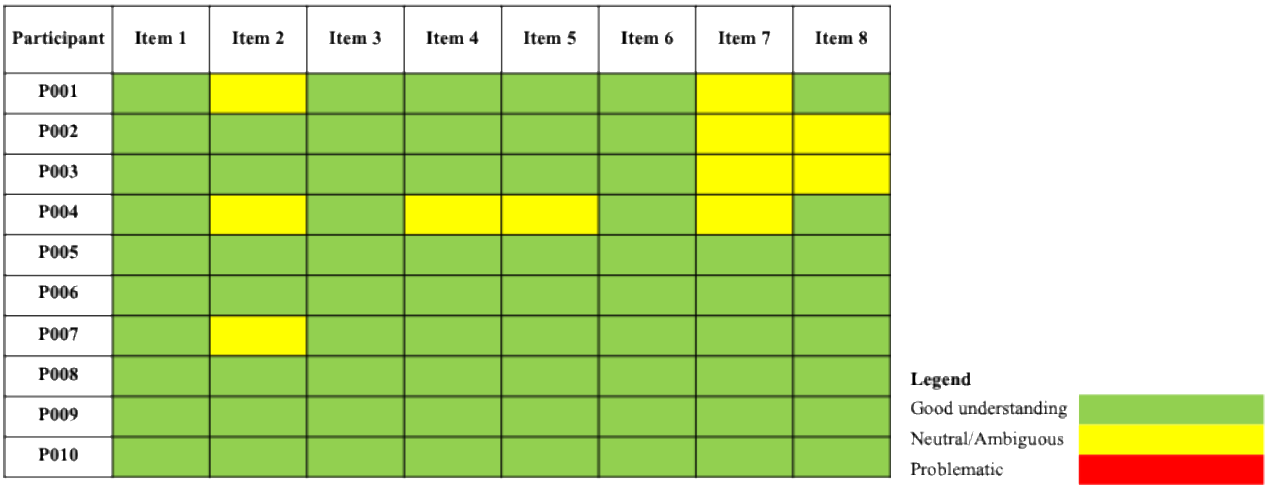

Figure 2: Face Validity of the Items Included in the FH Knowledge Scale

3.3 VALIDATION OF THE CONCEPTS IN THE FH KNOWLEDGE SCALE

Participants were asked to rank the concepts associated with each item in the knowledge scale as necessary, helpful or not important to consider when making a decision about genetic testing for FH. Almost all participants (n = 9) considered the concepts covered by the items in the knowledge scale to be either helpful or necessary. In general, participants were more likely to consider a concept as necessary if it was associated with health concerns seen with FH, treatment options, or implications for family members. In comparison, concepts associated with the genetic aspects FH, such as incomplete penetrance and the limitations of genetic testing, were more likely to be reported as helpful or, in one case, not important. The codes applied to demonstrate participant rankings of the importance of the concepts in the knowledge scale are shown in Figure 3.

Figure 3: Participant's Scoring of the Core Concepts Included in the FH Knowledge Scale

Concept 1: Incomplete penetrance

Overall, seven participants ranked the concept of incomplete penetrance as helpful rather than necessary or not important to decide about genetic testing. The predominate reasoning for this ranking was due to other factors, such as informing medical management, were considered to be more important when making a decision about genetic testing.

> "It's helpful, because it might influence someone who doesn't experience on paper, high cholesterol, or some sort of condition. But it might influence them in that direction if they know that they have a history in their family, but they don't themselves suffer." (P005, proband, 25 years old)

Additional responses suggested that this concept may be more meaningful to healthcare professionals who are more familiar with genetic concepts. However, for patients who are more concerned about their personal and family history, this concept was not viewed as necessary to make their decision.

> "Well, probably because I'm not really a scientist or a doctor, and I don't want to go really too far to an extreme. […] I mean, obviously 'not important' would be completely off my list. I would waver between the helpful and the necessary." (P007, proband, 61 years old)

Concept 2: Treatment for FH should start as early as possible to lower the chance of heart attack

Eight out of 10 participants considered this concept to be necessary to make a decision about genetic testing, while the remaining two participants ranked this concept as helpful. The majority of participants felt strongly that the concept was necessary for individuals to understand for the purposes of preventing adverse health outcomes associated with FH.

> "It's definitely necessary. It's not even, it's not even something in between. It's definitely necessary because some people don't know that you might have a heart attack even when you're so little, or even if your child has it, they don't know that they have that risk." (P001, at-risk family member, 21 years old)

> "I think it's necessary so that people can make decisions earlier in their life to decrease their risk exposure." (P002, proband, 41 years old)

Concept 3: Limitations of Genetic Testing

Five participants considered knowing the limitations of genetic testing as a necessary concept to understand prior to making a decision about genetic testing. The majority of responses in this category emphasized that it would be important for patients to know that a negative genetic test result does not rule out a diagnosis of FH, and that some individuals with a negative genetic test result will still require treatment.

> "I think that this has to be very clear to someone that this is not an absolute, that they will know absolutely but that that it's going to remain uncertain unless it comes out to be positive, and that they will still need to have treatments, even if it's negative. […] So instead of setting up the expectation for reliance and absolute certainty, you set up the expectation that this is science and it's a process." (P003, proband, 69 years old)

In contrast, four participants viewed this concept as helpful information rather than a necessary factor to make a decision about genetic testing. Finally, one participant felt that this concept was not important, stating that this information would only be useful in a post-test counselling scenario if the test result was reported as negative.

> "Personally, if I went through genetic testing and I came back normal, I would question whether or not the test was done correctly. It's like, okay, I don't know if that would change precisely how I treated my symptoms having, you know my lab work to back up my personal issue with high cholesterol. I don't know if that would lead to a more specific, you know, testing of the genes above those basic ones that you start with. But for my first interview with [the genetic counsellor], I think it would be not important." (P010, proband, 42 years old)

Concept 4: People with FH have a much higher chance of heart attacks

Nine out of 10 participants found this concept to be a necessary factor to consider when making a decision about genetic testing for FH. Many participants shared that individuals would be more likely to pursue genetic testing if they understood the heath concerns associated with this condition.

> "Necessary. The degree of understanding if you have a FH, and you understand that it's a much higher chance of having a heart attack, it would probably influence someone's decision." (P002, proband, 41 years old)

> "Prior to making decision about testing, I think this information is necessary. Someone might not know the seriousness of their condition, and I think this really emphasizes it." (P005, proband, 25 years old)

Some participants went on to express that this information is also necessary because it is actionable, and it may motivate individuals with FH to seek cholesterol-lowering treatment following their diagnosis.

> "Well, I mean, I guess I would like to know if I had the possibility of having a heart attack, say, in like my thirties or forties. And it would be necessary because it would encourage me to stay on treatment, be consistent with follow ups and watch for signs of possibly having a heart attack, possible signs of heart attack. Precursors probably would

make me choose a healthier lifestyle, diet. All that kind of stuff." (P004, proband, 39 years old)

"I would say necessary, especially with the younger… I wish I had had this information when I was younger, I may not have hesitated to start medication so soon or so late." (P010, proband, 42 years old)

Concept 5: There are ways to lower the chance of heart attack due to FH

Seven out of 10 participants considered this concept to be necessary to know when making a decision about genetic testing for FH. The remaining three participants ranked this concept as helpful. Similar to the responses for concept 4, participants who ranked this concept as necessary justified their ranking based on the availability of treatment options, which may motivate someone to pursue genetic testing.

"Again necessary. It's making decisions about intervention and testing. Sooner is always better." (P002, proband, 41 years old)

"If the person is aware that they can lower their chance of a heart attack, why wouldn't they seek that testing and genetic counseling and information? So, I feel like, that's definitely important." (P004, proband, 39 years old)

Participants also commented on the fact that understanding this information is valuable, as it may influence someone to explore treatment options and pursue genetic at a younger age.

"As I mentioned earlier, people that have this information, they're going to take action right away instead of just waiting for the for the condition, let's say, to get more critical and if they have this kind of information that they're going to take action quicker, and they're going to get treatment right away." (P001, at-risk family member, 21 years old)

"Yeah, I think it's I think it's helpful information because it might motivate someone to get their genetic testing done sooner rather than later. But I don't think it's going to make

them decide whether to or not to get genetic testing done. I think it just might get them to do it sooner." (P005, proband, 25 years old)

Concept 6: FH runs in families

Six out of 10 participants ranked this concept of necessary, while four participants ranked this concept as helpful. Among those who ranked this concept as necessary, their primary reasoning was due to the fact that family members should be informed that they may be at risk and should therefore have access to cascade screening.

"Necessary because it would impact, it could impact their decision similar to mine, because my decision is not just for myself. It is also... it could have future implications for people in my family that I care about." (P002, proband, 41 years old)

Among the participants who ranked this concept as helpful, they justified their reasoning by claiming that the majority of individuals who are pursuing genetic testing for FH would likely be aware of their family history, and the fact that FH is an inherited condition.

"'I'm going to say helpful, because I think a lot of people who have family members with heart problems already are aware of that. They might not know exactly that it's FH, but they probably have a sense that they have some sort of a genetic situation going on in their family." (P005, proband, 25 years old)

Concept 7: FH cholesterol levels cannot be fully managed by exercise and diet alone. Medication is usually needed to reach a healthy cholesterol level / For someone who has FH, genetics causes high cholesterol

Half of the participants ranked this concept as necessary, while the other half ranked this concept as helpful. It should be noted that this concept was revised following the first five interviews, based on feedback from participants. For the first five interviews, this concept read "FH cholesterol levels cannot be fully managed by exercise and diet alone. Medication is usually needed to reach a healthy cholesterol level". Two participants ranked this concept as necessary, while three ranked this concept as helpful.

> “Necessary, because otherwise one spends a lot of time trying to manage it by exercise and diet alone. Take years, truly.” (P004, proband, 39 years old)

> “I would say it's necessary. And the reason I think that is because someone who has high cholesterol might not have it on their radar that it's caused by genetics, and this might influence them to seek genetic testing.” (P005, proband, 25 years old)

In the second half of the interviews, the concept was revised to read “For someone who has FH, genetics causes high cholesterol”. In this case, three participants ranked this concept as necessary, while two participants ranked this concept as helpful. Participants maintained similar justifications for their rankings between each round of interviews, relating the importance of the concept to the need for interventions beyond diet and exercise to control cholesterol levels.

> “Well, I would say necessary, if people don't understand already how that could have an impact right like, if they just think that they can manage it. You can't always. You just absolutely have to have medication. So then then this would be necessary.” (P008, at-risk family member, 42 years old)

> “It's helpful for someone to know that it could be genetics just because, so you don't associate it with diet. I think, okay, you're eating all the right diet and thinking you're good. So, it's helpful to know it could be genetically caused and not diet related.” (P009, proband, 35 years old)

Concept 8: Genetic testing is the best way to screen family members.

Seven out of 10 participants ranked this concept as helpful, while three participants ranked this concept as necessary. Among those who ranked this concept as helpful, their reasoning focused on the fact that this information would not be necessary to make a personal decision about genetic testing, but it would be helpful information for other family members.

> “I think it would be helpful for the family members just to decide whether they want to pursue genetic testing.” (P004, proband, 39 years old)

> “It's helpful to know so that way you're able to involve your other family members and have them screened for the gene.” (P009, proband, 35 years old)

Similar to the responses for concept 6, some participants alluded to the fact that this knowledge would already be known among the majority of patients who are considering genetic testing.

> “I want to say not important, not because I don't think it's important, just because I think that by the time you're deciding whether or not you're interested in getting genetic testing, you already know this information. That it might run in your family or something along those lines.” (P005, proband, 25 years old)

Interestingly, one participant commented that they did not view this concept as necessary. When this participant was asked to elaborate on why they ranked this concept as helpful, rather than necessary, they explained that many individuals in their family were aware of the family history of FH but had decided against genetic testing.

> “Well, I guess, based on my experience with the amount of sharing that we've done with family members, nobody's taken up the opportunity to get genetic testing. So, I guess it's not necessary because they're not doing it anyway.” (P008, at-risk family member, 42 years old)

In summary, the face validity and importance of core concepts of the items included in the FH knowledge scale was assessed over the course of 10 interviews. Revisions to six of the eight items in the knowledge scale were made following the first five interviews based on participant feedback. The revised items elicited positive responses from participants throughout the remaining five interviews and no further revisions were required. Therefore, a subsequent round of interviews was not required for further validation. The final version of the FH knowledge scale is shown in Figure 4.

1. It is possible to have FH and not know that you have it. (True)
    - *Incomplete penetrance*
2. FH treatment in childhood does not reduce the risk of heart attacks. (False)
    - *Treatment for FH should start as early as possible to lower the chance of heart attack*
3. A normal (negative) genetic test means that you do not have FH. (False)
    - *Limitations of genetic testing*
4. FH can lead to health problems such as heart attacks. (True)
    - *People with FH have a much higher chance of heart attacks*
5. If you have FH, steps can be taken to lower your risk of heart attacks. (True)
    - *There are ways to lower the chance of heart attack due to FH*
6. If you have FH, it is unlikely that your family members have it. (False)
    - *FH runs in families*
7. Medication is often needed to lower cholesterol for people with FH. (True)
    - *For someone who has FH, genetics causes high cholesterol*
8. If you are found to have a genetic cause for FH, genetic testing is the best way to screen your family members. (True)
    - *Genetic testing is the best way to screen family members*

Figure 4: Final Version of the FH Knowledge Scale

3.4 SECONDARY AIM OVERVIEW

The secondary aim of this study was to determine the key factors that participants considered when deciding about genetic testing. Participants were asked at the beginning of each interview to describe how they made a decision about genetic testing, and to elaborate on the factors that influenced their decision. Conventional content analysis revealed three common motivations, along with insights into participant's hesitancy towards genetic testing and overall experience of genetic services. A summary of these categories can be seen in Table 10.

Common motivations for genetic testing included family, gaining insight into medical management and an opportunity for advocacy and empowerment. Alternatively, hesitancy towards genetic testing included insurance implications, time constraints and the logistics of sample collection. Participant responses also revealed valuable insights into the experiences of this patient population with genetic counselling, highlighting a general lack of awareness of the availability of genetic services (i.e. genetic testing and/or genetic counselling), and the positive impact genetic counselling can have for those who are referred for FH. These categories were derived from the codes applied most frequently across interviews, summarized in Table 9.

Table 9: Summary of Code Development for Secondary Analysis

Code	Number of Interviews	Frequency
Informing family members	10	36
Advocating for self and others	8	16
Genetic testing may provide clarity	7	14
Hesitations: Insurance, time, sample collection	7	10
Access to medication	6	21
Prevention	6	12
Family history	6	10
Not aware of genetic testing and/or genetic counselling	5	10
Impact of genetic counselling	4	5

Table 10: Summary of Category Development for Secondary Analysis

Category	Family	Medical Management	Patient Empowerment	Experience with Genetic Services	Hesitations Towards Genetic Testing
Codes	Informing family members Family history	Access to medication Prevention Genetic testing may provide clarity	Advocating for self and others	Not aware of genetic services Impact of genetic counselling	Insurance Time constraint Sample collection

3.4.1 Motivation for Genetic Testing: Family

Providing Information to Family Members

The motivation to pursue genetic testing to provide risk information to family members was brought up by participants across all interviews. Participants acknowledged that their decision to undergo genetic testing held implications not only for themselves, but also for their family members. Many participants considered their children as the central aspect in this decision. For some, this consideration was the primary motivation to pursue genetic testing.

> "It's something that it's going to be helpful for the entire family. And I'm also including the future generation. […] That's the most important thing for me, because it gives me the necessary information and some of the resources to help the generation, the next

generations in my family. So yeah, that's the most important thing for me." (P001, at-risk family member, 21 years old)

"And then, of course, I thought about my kids right. And then my grandkids and I just thought you know what I just might as well get this done. I mean, it says information that you can use for somebody else down the line, or somebody else can pipe up and say, yeah, I'll do it. Well, here you go." (P006, proband, 57 years old)

"And I guess my biggest issue was that I have 3 children of my own, and now a granddaughter. So, if there is any kind of possibility that I can give them a medical history heads up, so to speak. That was my purpose of agreeing to the genetics." (P007, proband, 61 years old)

One participant was prompted to expand on their previous comments of informing future generations when they encountered Item 6 in the knowledge scale which, which refers to the implications of genetic testing for family members.

"I'm taking the test because one of the things that changed my mind was this statement right here. If I could prevent it for one of my children in the future, then I would like to have that information with me." (P001, at-risk family member, 21 years old)

Participant 5 discussed that family planning for the future was a factor that played into their decision making, as they did not yet have children. They shared that when this topic was brought up by their primary care provider, it influenced their decision to pursue genetic testing.

"I just don't know if I want to have my own family someday, for me when my doctor brought that up, it did make a difference for me. […] I was definitely motivated to get the test done after that, probably more than I would have been otherwise. I likely would have gotten it done anyways but for me, this is an important piece of information that I now need to know in order to make important future decisions, right?" (P005, proband, 25 years old)

Family History

In addition to their motivation to undergo genetic testing for the purposes of providing risk information to family members, some participants commented on aspects of their family history that also contributed to this decision. For example, two participants were presented with the option of genetic testing based on their family history, as an individual with FH had previously been identified in their families.

> "The counselor called my mom two weeks ago or three, and I was there in the house when my mom was talking to her and the results for the genetic testing got back. [The genetic counsellor] told her that my little brother has a gene that is not correct per se, and that's why he has…Well, she explained that he has two copies of that gene, but one of the copies is not entirely functional, and that's why he has high cholesterol, and that my mom could also get genetic testing. And me, because we think that the high cholesterol is from my mom's side of the family. So that's when I got in contact with the with the possibility of the genetic testing." (P001, at-risk family member, 21 years old)

> "My niece has FH severely, and so we all were given the option to see if we were carriers" (P008, at-risk family member, 42 years old)

Other participants were able to make meaningful connections about their family history during their genetic counselling appointment, recognizing that their family history of heart attacks and heart disease were consistent with FH.

> "My mother had a heart attack and survived it. My father did not survive his heart attack, and I thought that was about all that needed to be known was that there's a family history of heart attack." (P003, proband, 69 years old)

> "I think all of my dad's brothers either died or had heart disease. My dad had a quadruple bypass. My brother, my other brother, had a heart attack. So, I know there's a lot of heart disease in our family history." (P007, proband, 61 years old)

3.4.2 Motivation for Genetic Testing: Informing Management of the Condition

Access to Medication

Many participants believed that a positive genetic test result would have implications for medical management, which contributed to their motivation to receive genetic testing. Importantly, several participants identified that they were advised that genetic testing may be necessary in order to gain access to and funding for medication in the future.

> "I think I'm now answering your question. What was important to me was that it could lead... if I have the genetic markers it could lead to me getting Repatha and skipping the statins." (P003, proband, 69 years old)

> "But in my case, I guess I was just kind of at a point where I was like, well, I am getting older. What if you know the statin and the Ezetrol aren't effective anymore? And then I need option B. Then at least, I have this kind of in my back pocket. […] Say, if the current therapy I'm on right now is no longer effective. Then [the cardiologist] said that this would be one of the pieces that they would require for approval. So, I agreed to the testing." (P004, proband, 39 years old)

> "So, they wanted me on an injectable cholesterol medication, Leqvio, and they weren't sure with that approval if they would need genetic testing. So, they said, 'well, it might be a good thing to have anyways', just to know for down the road for my kids or any reason. So, I went for the interview with [the genetic counselor], and here we are." (P010, proband, 42 years old)

Prevention

For some participants, genetic testing was viewed as an opportunity to initiate preventative measures to decrease the risk for heart disease in the future. Primarily, participants expressed that a positive genetic test result would prompt alterations to certain lifestyle factors including diet, exercise, and adherence to lipid lowering medication. In some cases, genetic testing itself was viewed as a method of prevention, allowing for early detection among at risk family members.

> "As I mentioned earlier, people that have this information, they're going to take action right away instead of just waiting for the for the condition, let's say, to get more critical and if they have this kind of information that they're going to take action quicker, and they're going to get treatment right away." (P001, at-risk family member, 21 years old)

> "Going into the meeting with a genetic counselor, I kind of already knew I would be consenting for genetic testing, because I want to understand what the root cause is and try to work with all the medical team to help us, you know try to prevent and check all the boxes for prevention, and just ensure we're doing the right thing on our part to prevent any crisis or any health issues that could potentially happen in the future which is what I'm really fighting for." (P009, proband, 35 years old)

For Participant 7, a significant family history of heart disease was the basis for their interest in preventative measures. In this case, genetic testing was seen as a tool to support this endeavor.

> "With our family history, I'm 100% okay to try and figure out if there is some way of preventing, you know these heart attacks and heart disease from happening. Let's try and do that before it gets to everybody either needing quadruple bypasses or dying. […] If there is anything you can do ahead of time to protect your heart you should do it and I'm all for doing that for myself and my family." (P007, proband, 61 years old)

Gaining Clarity from Genetic Test Results

Participants also felt that genetic testing would be helpful to clarify aspects of their medical history that had previously been unexplained. Many participants shared the sentiment that it would be important for them to know if their cholesterol levels were the result of modifiable lifestyle factors, versus a genetic condition that they were born with. Participants 2 and 5 each commented that their underlying curiosity played a role in their decision to pursue genetic testing.

> "Just curious, I guess. Curiosity. Yeah, understanding if it is genetic, or if it was just something I did to my body at some point in my life through the perfect storm of supplements that I would take when I was exercising in my youth or hormone imbalances that created something. I'm just curious as to how my arteries got to the way that they were." (P002, proband, 41 years old)

> "To sort of find out more information about myself. To see like... I know, exercise is important in your everyday life, but I want to see, like, how much my lifestyle is going to affect my health, because I know that if I do have this condition it's going to be a contributing factor." (P005, proband, 25 years old)

Another participant commented that they saw genetic testing as an opportunity to provide them with answers for their longstanding history of elevated cholesterol levels, which had previously been a mystery. In doing so, a genetic diagnosis of FH provided them with a sense of acceptance of the condition.

> "Part of the reason was because I always was kind of like, why? I'm young, and I was relatively healthy in my twenties, and you know, to have such high levels of cholesterol… and you know my doctor retested me because he thought it was inaccurate. […] I'm actually happy I did the testing because it's kind of just given me some answers and some clarity as to like why. […] So, it kind of brought me a little bit of not comfort, but just acceptance to having FH." (P004, proband, 39 years old)

Towards the end of the interview, this same participant acknowledged that they were hoping genetic testing would also clarify gene status, and the long-term outcomes associated with being heterozygous or homozygous for a pathogenic variant associated with FH. This response was prompted by the participant's reflection of the concepts that were covered in the knowledge scale.

> "Obviously, I know high cholesterol can lead to complications in the future. But I think I really wanted to kind of nail down if it was like the heterozygous or the homozygous. I

didn't realize at the time that, and this was probably explained to me by [the genetic counsellor] but the conversation was so long ago, I didn't realize that a negative test wouldn't have necessarily meant that I didn't have FH. I didn't know until I saw that statement. But she did explain to me, that they would be testing for... and I don't know how the testing happens, but they would be trying to determine if I have heterozygous or homozygous. And at that time, I didn't realize that the homozygous was the more serious of the two. So that piece was kind of newer to me, and I was kind of like, oh my, yeah, that this could be more serious, I think, than I've kind of realized in a way." (P004, proband, 39 years old)

3.4.3 Motivation for Genetic Testing: Patient Empowerment

Some participants shared that genetic testing provided them with an opportunity to advocate for their health, along with the health of their family members. While many participants shared the sentiment that genetic testing was an opportunity to learn more about their personal health, Participant 9 and 10 discussed how knowing their gene status would enable them to seek the appropriate care for their children moving forward.

"I'm just all about, you know, keeping on top or staying on top of all this information, I'm still doing my own research. I know Dr. Google is not the best. But yes, I go to Dr. Google, and if I have any doubt, I reach out to the doctor just to clarify and get that assurance from them if it doesn't apply to us that's all well and good. But if I see anything or note anything, I'm not keeping quiet. I'm putting it out there and ensuring I'm getting the possible best care for my kids, for my husband, for myself." (P009, proband, 35 years old)

"And they can kind of take those preventative measures to help their families. Because, you know, I, knowing this information, I will be asking my GP to get my kids tested early on, instead of waiting for them to hit whatever benchmark the GPs usually wait for." (P010, proband, 42 years old)

Others felt a call to advocate for the FH patient population in a broader sense, reflecting on how participating in genetic testing may increase the overall awareness of this condition for individuals who are seeking a diagnosis.

> "If at all, in any way I would be able to be a voice or an advocate, or reason that some further testing might be done when somebody that goes in mountain bike races and does cross fit shows up with chest pain. I was kind of turned around after my stress tests and blood work and told I was a hundred percent fine after a stress test. Six years later I went back and saying, this is not going away. It's repeatable. And then to be told again, that it was anxiety, and then I can push through. You know, if there's any way that I can influence another box that needs to be checked, or if we don't see anything, what is the next step that we can take? Then yeah. I'm happy to be a part of that." (P002, proband, 41 years old)

> "I've always been a big proponent of any kind of research, and anything that moves the dial forward, right? Anything that can help out. So, to me that was a no brainer." (P007, proband, 61 years old)

3.4.4 Hesitations Towards Genetic Testing

A smaller proportion of participants expressed that they had concerns about genetic testing such as the impact of a positive result on insurance coverage, the process of sample collection and the time constraint associated with attending a genetic counselling appointment and going for a blood draw. Among the participants who expressed concerns about insurance, two individuals identified that this was something they had considered prior to consenting to genetic testing and was brought up during their appointment with the genetic counsellor.

> "My only kind of concern was like, I'm young. And so, we kind of had discussed life insurance and different things like that. How like the results could potentially impact that." (P004, proband, 39 years old)

> “I was concerned only about really the insurance piece that that was not going to impact getting a life insurance policy, for example, or, you know, a job or something along those lines.” (P007, proband, 61 years old)

In contrast, when Participant 10 was asked if they had any concerns about insurance coverage prior to receiving genetic testing, they shared that this was not a consideration for them as their insurance company was already aware of their high cholesterol.

> “I mean, I already have insurance, and I think that's how I found out I had high cholesterol from the very start, was, you know, my husband and I bought a house, and we bought life insurance, and we needed all the blood work checks. And I found out then that I had high cholesterol. So yeah, I don't know actually, if that wasn't brought up, I never thought about it.” (P010, proband, 42 years old)

Participant 2 expressed that they were interested in understanding the process of genetic testing prior to making their decision. They shared that a more invasive procedure, beyond a simple blood draw, would have influenced their decision.

> “Once I learned that it's simple drawing blood work that gets tested, then I'm kind of like, yeah. If it was going to be you know, like some kind of a biopsy or a high-risk procedure that requires some kind of recovery, then maybe that would have influenced my decision.” (P002, proband, 41 years old)

Finally, several participants discussed that although time constraints did not directly influence their decision about genetic testing, taking the time to attend a genetic counselling appointment was a consideration.

> “The only hesitation was like, not another appointment. And just like how relevant the genetic testing was to my treatment plan. You know, like I've just had too many appointments all since January for many things. So, the hesitation wasn't with the genetic

testing at all. If I had had time, the hesitation was with, how do I fit it in?" (P003, proband, 69 years old)

"It's costing extra time, you know, going through the different tests and counselling and doctor visits and all, but it's better to check in than not check out. So, I'll say it's not an experience I would have chosen if I was given a choice. But since this is where we are, it's okay to have that opportunity to have good resources that you can rely on, and that are willing to help, you know, navigate through different steps and the different faces, and I'm really hoping it all ends well." (P009, proband, 35 years old)

Participant 3 went on to express their experience of having to travel to a different location in order to have a blood sample drawn for testing following their genetic counselling appointment. This was compounded by the fact that their appointment with a genetic counsellor was not also integrated into their care with their cardiologist.

"So, you go in for genetic testing, and you talk to the genetic counselor. But you have to go and give your blood work somewhere else. […] What I would like very much is for all of these things to be integrated so that I don't have to chase everything down." (P003, proband, 69 years old)

3.4.5 Experience with Genetic Services

When asked about the factors that influenced their decision about genetic testing for FH, some participants reflected on their overall experience with genetic counselling and testing. In doing so, two commonalities were identified among participants which included an overall lack of awareness of genetic services and the role that genetic counselling could play in their understanding of this condition.

"I didn't know anything about this condition before. I wasn't surprised to hear that it existed. But it...this is all new to me." (P005, proband, 25 years old)

> “I didn't even know about the existence of it to be honest with you. The counsellor just told us about [genetic testing] and the doctor as well and I was like, wow we have that technology in our hands. I didn't… yeah, I didn't even know about it.” (P001, at-risk family member, 21 years old)

Some participants shared that prior to speaking with a genetic counsellor, they were given limited information regarding their referral to genetics, and the role that genetic testing might have in the context of their care.

> “I've never thought about pursuing genetic testing until my doctor presented it to me. It was always kind of like…[the doctor] always just said to me, ‘Oh, it's likely genetics. It's likely your genetics’. And I was like...okay, but I was never really given a reason as to why I should pursue genetic testing.” (P004, proband, 39 years old)

Participant 3 shared that they would have appreciated additional information prior to their appointment with the genetic counsellor.

> “My experience was the cardiologist said, ‘okay, we're going to do this this and this’, one of which was genetic testing. And so, I didn't really have a say. […] I would like to have known more about the benefits [of genetic testing], how simple the interview would be and that I would need blood taken for finding out the genetic markers for [FH]. And that my previous blood tests did not test for what was needed to be known.” (P003, proband, 69 years old)

Similarly, Participant 10 shared that they think patients should be aware of the opportunity for genetic testing as early as possible to assist with informed decision making.

> “I didn't even know this was an option…to test. So, I would say well it would be nice if you know [general practitioners] mention this kind of thing, because I think it is important for people to not shy away from it. To really get the answer that they need, so that they can make an informed decision.” (P010, proband, 42 years old)

Some participants followed this discussion with sentiments of how genetic counselling contributed to their overall understanding of FH and the purpose of genetic testing.

> "Honestly, I would not have tested or thought of testing my daughter in her teens unless the genetic counselor and [physician at the lipid clinic] had recommended that. […] Yeah, I probably wouldn't have pursued that for my daughter. That piece definitely was beneficial with the genetic testing and the counseling and stuff like that." (P004, proband, 39 years old)

> "You know, it was informative to go through the counseling and stuff like that. And it was a little intimidating, you know, having that interview with [the genetic counsellor]. I was a little worried like, why do I need to have an interview to do this genetic testing? […] But after speaking to [the genetic counsellor] …and she probably just wanted to make sure that it was a legit reason for getting the genetic testing, and you're not just doing it for everybody on the on the street but no, I felt it was it was good. Any more information is better than not. I learned some things." (P010, proband, 42 years old)

Participant 9 also commented on how speaking with a genetic counsellor prior to receiving genetic testing helped them adapt to the possibility of a genetic diagnosis of FH.

> "[The genetic counsellor] was very considerate in trying to ensure and kind of comfort for lack of a better word, just to ensure that, you know, we're able to navigate and still lead a normal life and it's nothing very life threatening, at least for now it's something that's manageable." (P009, proband, 35 years old)

Overall, this secondary analysis revealed valuable insights into the factors that influence how the participants in this study made a decision about genetic testing for FH. While genetic testing and genetic counselling can both lead to patient empowerment, they do so in different ways. The information gained from genetic testing (i.e. a genetic test result) in combination with the information gained by genetic counselling (i.e. knowledge of the benefits, risks and

limitations of genetic testing) can provide patients with sufficient knowledge regarding the implications for medical management moving forward and improving outcomes for family members. Additionally, both genetic testing and genetic counselling were found to have distinct barriers that can impact a patient's decision to pursue genetic services. Barriers to genetic testing involved time, sample collection and potential impact on insurance, whereas barriers to genetic counseling involved time and lack of awareness. We have combined the outcomes that emerged from the interview data into Figure 5, which serves as a visual representation of the relationship between genetic testing, genetic counselling and factors that positively and negatively influenced participants' decisions about genetic testing for FH.

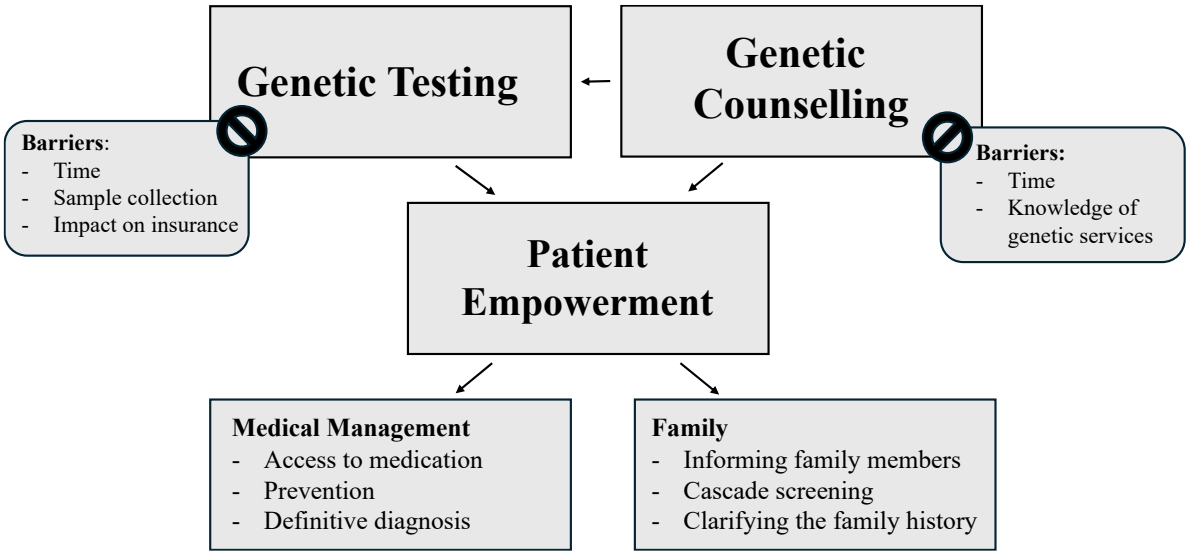

Figure 5: Summary of the factors that influence how participants made a decision about genetic testing for FH.

CHAPTER 4: DISCUSSION

4.1 OVERVIEW

This study initiated the validation of a novel genetic knowledge scale specific to FH, to be used as part of a larger measure to assess patient informed choice in the context of genetic testing for this condition. We evaluated the face validity of the items included in the knowledge scale, along with the importance of core concepts through a series of cognitive interviews with individuals who had previously been offered genetic testing for FH. Participant feedback was essential in guiding the revisions made to the knowledge scale and provided valuable insights into the key factors that patients consider when deciding about undergoing genetic testing for this condition.

4.2 VALIDATION OF THE FH KNOWLEDGE SCALE: FACE VALIDITY AND IMPORTANCE OF CORE CONCEPTS

4.2.1 Face Validity: Are the Items Included in the Knowledge Scale Understood by Participants?

An important aspect of scale validation is establishing face validity, which refers to whether the items included in a questionnaire are capable of eliciting intended responses among a target population (Boateng et al., 2018). As such, face validity of the items included in the FH knowledge scale was assessed through a series of cognitive interviews with members of the FH patient population, who varied in age, race, gender, and education level. Although none of the participants demonstrated significant difficulties in their comprehension of the items included in the knowledge scale, several participants provided feedback on how to improve the clarity of the questions.

Participants identified that certain terms used in the knowledge scale lacked specificity, which has the potential to impact the overall interpretation of the question. Therefore, items containing phrases such as ‘heart disease’ and ‘long term benefits’ were revised to better communicate the underlying construct that was intended to be assessed. This was particularly important for Item 7, which received feedback from four out of the five participants in the first round of interviews related to the ambiguity of this question. Removing ambiguity from the phrasing of items in the knowledge scale increases the likelihood that patient knowledge is measured accurately, and is not impacted by confusion in the way items are worded (Boateng et al., 2018).

Furthermore, the use of plain language consistent with a reading level that can accommodate a wide range of audiences was an important consideration in the development and subsequent revision of the items in the knowledge scale. In general, it is recommended that patient-facing material should be written at or below a sixth to eighth grade reading level, reflecting the average reading level among the general population (National Institutes of Health, 2025). A recent systematic review of readability assessment studies on patient-facing material identified that the majority of published material exceed this recommendation, demonstrating a significant lack of patient-friendly resources despite the availability of validated instruments designed to assess the difficulty of written material (Okuhara et al., 2025). In order to address this disparity, the Flesh-Kincaid readability formula was used to assess the reading level of each item in the knowledge scale to ensure that items were written clearly, allowing for fair interpretation by different members of the FH patient population. Although one item (Item 7) included in the final version of the knowledge scale was scored at a college reading level, it was correctly interpreted among our study participants, which includes individuals with a variety of educational backgrounds, ranging from high school to post graduate degrees.

Ultimately, face validity aims to maximize the clarity of how items are phrased in order to limit the cognitive burden required to read the items, thereby limiting the impact of poorly written items on the evaluation of patient knowledge. One consideration that has yet to be addressed in this study is the definition of ‘good knowledge’ in the context of assessing informed decision making using the FH knowledge scale. When a knowledge scale is applied in the context of the MMIC, a patient is only considered to have made an informed choice if they have adequate knowledge about the test (Marteau et al., 2001). In the development of the original MMIC measure which included an eight item knowledge scale about prenatal screening for Down syndrome, Marteau et al. (2001) used a median score of four, effectively dichotomizing knowledge scores into ‘good knowledge’ versus ‘poor knowledge’. The overall acceptability of this approach has been debated by other researchers who have since developed novel MMIC measures specific to other genetic conditions (Ames et al., 2012, 2015; Griffin et al., 2023).

Novel MMIC measures are variable in how they define ‘good knowledge’, and very few studies have validated a cutoff using data within a study sample, where the value is based on a comparison of scores collected from the target population (Ames et al., 2015). More often, a cutoff is defined based on professional consensus, since a universal benchmark defining ‘good

knowledge' ceases to exist as a reference (Ames et al., 2015; Griffin et al., 2023). In the context of the FH knowledge scale, 'good knowledge' was defined as a score of 75% or higher, by the team of genetic counsellors who were involved in its initial development. This is in keeping with the cutoff values assigned to other genetic knowledge scales that have been published in the literature (Ames et al., 2012; Lewis et al., 2016).

4.2.2 What Information is Important to Make a Decision About Genetic Testing for FH?

The core concepts covered by the items in the knowledge scale were selected based on a literature review and the expert opinion of genetic counsellors with experience in counselling on FH. Therefore, an important goal of this study was to evaluate the importance of each concept among the target population to justify their inclusion in the final version of the knowledge scale. Overall, each concept was perceived as necessary by at least one participant to make a decision about genetic testing for FH. Therefore, sufficient evidence was collected to support the inclusion of all eight concepts in the final version of the knowledge scale.

Notably, participants were more likely to rank a concept as necessary to decide about genetic testing if it was associated with the risk for health concerns related to FH, implications for treatment, or risks to family members. Research surrounding patient perceptions on genetic testing for FH is somewhat limited, however, these findings are consistent with that has been reported in the literature. Members of the FH patient population have previously reported that prognostic information, management implications and risks for family members were their primary motivations for undergoing genetic testing for FH (Hallowell et al., 2017; Pettit et al., 2024).

Strikingly, Item Four in the knowledge scale, which states that '*people with FH have a much higher risk of heart attacks'*, was rated as necessary by nine out of ten participants, more than any other item. It's possible that the term '*heart attack*' conveys a strong sense of urgency or severity, which may have influenced how participants perceived the overall importance of this concept. Similarly, Items Two and Five, which also contain the term '*heart attack*', received the most ratings for being necessary to make a decision about genetic testing for FH, following Item Four. Christian et al. (2025) reported that participants perceived the term '*sudden death*' as frightening in a similar study which aimed to validate a knowledge scale for inherited heart disease, where this term was included in a concept which states that '*inherited heart disease can lead to sudden death'*. Interestingly, less than half of their study sample rated this concept as

necessary to make a decision about genetic testing for inherited heart disease. Although '*heart attack'* and '*sudden death'* have similar connotations, the differences in how participants ranked the overall importance of these concepts may be due to the finality associated with '*inherited heart disease can lead to sudden death'*', versus the actionability of '*people with FH have a much higher risk of heart attacks'*(Item 4)*,* '*treatment for FH should start as early as possible to lower the chance of heart attack*' (Item 2), and '*there are ways to lower the chance of heart attack due to FH*' (Item 5).

In contrast, participants were more likely to rate concepts associated with the genetic aspects FH, such as *incomplete penetrance* (Item 1) and the *limitations of genetic testing* (Item 3), as helpful, and in one case, not important, to make an informed decision about genetic testing. The concept associated with Item 3, '*limitations of genetic testing'*, was the only concept to be perceived as not important by a single participant, who suggested that this concept may not be necessary to know prior to consenting to genetic testing, as its relevance is dependent on the outcome of the genetic test result. Nevertheless, this item was viewed as either necessary (n = 5) or helpful (n = 4) by the remaining participants, supporting its place in the final version of the knowledge scale.

Participant responses also brought awareness to the fact that the correct response to the Item 3, which addresses the limitations of genetic testing, differs for an index patient compared to an at-risk family member. For example, the correct response for someone offered targeted genetic testing for a previously identified familial variant, this question – '*A normal (negative) genetic test result means that you do not have FH'* - would be true. Referring back to the study conducted by Christian et al. (2025) two versions of the scale were developed in order to address the different implications of the limitations of genetic testing in the context of inherited heart disease. Therefore, it's feasible to suggest that a similar strategy could be employed for the FH knowledge scale to better assess knowledge of this concept in these distinct contexts, where '*a normal (negative) genetic test result means that you do not have FH'* would be considered a false statement for probands but a true statement for at-risk family members.

Additional support for the inclusion of the eight concepts in the FH knowledge scale has been reported in the literature. The Journal of the American College of Cardiology assembled a panel consisting of genetic counsellors, cardiologists and patient partners, among other relevant stakeholders to explore the utility of clinical genetic testing for FH. In doing so, Sturm et al.

(2018) developed a list of recommendations for information that should be discussed with patients prior to consenting to genetic testing for FH. These topics have been organized into five major categories, consisting of the benefits, risks, limitations, associated costs and familial implications of genetic testing. Although the concepts in the FH knowledge scale are largely consistent with these recommendations, a notable distinction is their inclusion of topics such as the psychosocial impact of a positive genetic test result, the possibility of variants of uncertain significance, the cost of genetic testing and genetic discrimination (Sturm et al., 2018).

The psychosocial impact of a genetic test result on both the individual and their family members is an important topic that is routinely explored in a genetic counselling session. Sturm et al. (2018) highlight that parental guilt (i.e. the guilt that parents may experience from passing on a pathogenic variant to their children) and survival guilt (i.e. the guilt that individuals may experience after receiving a negative genetic testing result when other family members are affected) may be particularly important for a patient to consider prior to providing consent for genetic testing for FH. Psychosocial topics such as these are personal and subjective and therefore cannot be adequately explored through an assessment of patient knowledge alone. However, the MMIC measure accounts for a patient's personal values through the inclusion of an attitude scale based on the Theory of Planned Behaviour, inclusive of questions regarding the patient's attitude towards genetic testing (Ajzen, 1991; Michie et al., 2002).

The possibility of identifying a variant of uncertain significance (VUS) is another topic recommended by Sturm et al. (2018) that was not included in the FH knowledge scale. As a VUS is a possible outcome of genetic testing, the inclusion of this concept in the knowledge scale should be considered. Christian et al. (2025) piloted two versions of a question in the context of inherited heart disease - one for probands (*you may receive an unclear genetic test result*) and another for at-risk family members (*your genetic test result will give you a clear answer about whether you inherited your family's heart disease*). Importantly, the majority (88%) of this study sample rated this concept as necessary to make an informed decision about genetic testing for inherited heart disease. Therefore, there is an opportunity to address this concept in the FH knowledge scale using a previously validated item.

Sturm et al. (2018) also indicate that the associated costs of genetic testing should be discussed with patients in a pre-test counselling session. This topic was intentionally excluded from the FH knowledge scale, as the cost of genetic testing is variable depending on the location

of the patient. For example, participants in this study were seen in two Canadian provinces where the majority of genetic testing is publicly funded by the provincial healthcare system, so long as an individual meets a pre-determined set of criteria which is often defined by their personal or family history. This is vastly different from other countries that do not have a universal healthcare system, where private pay or private insurance options may be more common for determining the cost of genetic testing. Attempting to include an item related to this concept would therefore limit the overall transferability and applicability of the FH knowledge scale in different contexts. The same is true for the concept of genetic discrimination, as there is no global policy for the protection of genetic information, and laws pertaining to the regulation of genetic discrimination are not consistent across every country (Joly & Dalpe, 2022). However, genetic discrimination was a concern raised by several participants in our study. Therefore, this topic is explored further in section 4.3.2.

In summary, these findings justify the inclusion of the concepts in the FH knowledge scale, as at least one participant viewed each concept as necessary to make an informed decision about genetic testing. Although concepts related to the genetic aspects of FH were considered to be helpful among our study sample, the majority of participants value personalized and actionable information when making a decision about genetic testing. When looking to the literature, several concepts were identified that were not included in the FH knowledge scale but can easily be integrated through the use of previously validated items that address these concepts (Figure 6).

Please indicate if each statement about familial hypercholesterolemia (FH) is true or false.

1. It is possible to have FH and not know that you have it. (true)
2. FH treatment in childhood does not reduce the risk of heart attacks. (false)
3. A normal (negative) genetic test means that you do not have FH. (false)*
4. FH can lead to health problems such as heart attacks. (true)
5. If you have FH, steps can be taken to lower your risk of heart attacks. (true)
6. If you have FH, it is unlikely that your family members have it. (false)
7. Medication is often needed to lower cholesterol for people with FH. (true)
8. If you are found to have a genetic cause for FH, genetic testing is the best way to screen your family members. (true)
9. You may receive an unclear genetic test result. (true)**

*The correct answer for at-risk family members is true

**The correct answer for at-risk family members is false

For each of the following five questions, please circle the number between 0 and 4 on the scale that best describes how you feel about genetic testing.

1.	For me, genetic testing would be:	Harmful	0	1	2	3	4	Beneficial
2.	For me, genetic testing would be:	Unimportant	0	1	2	3	4	Important
3.	For me, genetic testing would be:	A bad thing	0	1	2	3	4	A good thing
4.	For me, genetic testing would be:	Not reassuring	0	1	2	3	4	Reassuring
5.	For me, genetic testing would be:	Undesirable	0	1	2	3	4	Desirable

Which option did you choose regarding genetic testing for FH?

A) I chose to have genetic testing
B) I chose not to have genetic testing

Figure 6: Final Version of the MMIC Measure for FH

4.3 MAKING A DECISION ABOUT GENETIC TESTING FOR FH

Overall, the secondary analysis of this study revealed key factors that contributed to how participants made a decision about genetic testing for FH, providing additional evidence to support the inclusion of the concepts covered by the knowledge scale. Furthermore, participant responses indicated that personal factors along with logistical barriers have the potential to impact one's decision to pursue genetic testing, and their ability to access genetic services. Taken together, these findings help to illustrate a more comprehensive understanding of how this patient population experiences the process of making a decision about genetic testing for FH.

4.3.1 Motivations to Pursue Genetic Testing for FH

Family and Impact on Medical Management

The outcomes of the secondary analysis revealed that participants primarily considered their family members and the potential impact on medical management as the key factors that contributed to how they made a decision to pursue genetic testing for FH. These findings are consistent with how participants rated the importance of the concepts included in the FH knowledge scale and are reflective of what has been previously reported in the literature.

Many participants in this study discussed the benefits of identifying a familial variant in the context of facilitating cascade genetic testing and informing future generations of the condition. Umans-Eckenhausen et al. (2002) reported similar findings in their study that explored the attitudes of parents towards offering genetic testing for FH to their children, where 87% of parents indicated that they would want their children to undergo genetic testing. It is important to note that this perspective may be unique to individuals with FH, in comparison to other adult-onset genetic conditions that lack screening or treatment recommendations in childhood. In this same vein, participants from our study reported that aspects of their family history, such as a family history of heart disease, impacted their decision to pursue genetic testing. Similarly, Hallowell et al. (2017) explored patient perspectives on benefits of genetic testing for FH, reporting evidence to support the notion that genetic testing is seen as a tool to clarify the details of family history related to heart disease and provide risk information to family members.

The potential for genetic testing to impact medical management was also viewed as a motivator for genetic testing among many participants in this study. Subcategories related to this topic included providing access to medication, opportunities for prevention and gaining a sense of clarity on medical history. With respect to gaining access to medication, several of our participants noted that a positive genetic test result would be necessary to gain coverage for specific cholesterol-lowering medications, mainly PCKS9 inhibitors. Indeed, this aligns with the requirements for coverage of these medications in both the Manitoba and Alberta provincial healthcare systems, where a genetic test result is particularly useful for individuals who do not meet the traditional diagnostic criteria for FH (i.e. Simon Broome or Dutch Lipid Clinic Network Criteria). This specific motivation is less frequently reported in the literature and therefore may be more specific to patients who are treated in regions where these medications are readily available and where a positive genetic test result is required for insurance coverage.

Even so, there is evidence to suggest that a genetic diagnosis for FH can positively impact adherence to cholesterol-lowering medication by helping patients understand the underlying cause of their high cholesterol, and the importance of treatment (Pettit et al., 2024). Indeed, a subset of our participants reported that genetic testing was viewed as a means to provide clarity on their personal history of elevated cholesterol, which would ultimately justify the need for medical intervention rather than relying solely on lifestyle or dietary changes to manage cholesterol levels. The association between the confirmation of a genetic diagnosis and behavioural changes consistent with disease prevention has also been previously reported through data collected on the outcomes of population-wide screening programs for FH, where significant increases in uptake and adherence to cholesterol lowering medication was reported following the implementation of routine genetic testing (Umans-Eckenhausen et al., 2001, 2003).

Genetic Testing is Viewed as an Opportunity for Empowerment

An interesting outcome of the secondary analysis was the concept of patient empowerment, where participants reported that genetic testing was viewed as an opportunity to not only advocate for themselves, but also their family members and the broader FH patient population. Indeed, empowerment in a clinical context has been proposed to extend beyond self-advocacy, as patients who are empowered by health information often seek opportunities to share this knowledge with external entities (McAllister et al., 2008). Similar attitudes have been reported among patients who participated in a research-based screening initiative for FH, where individuals were partially motivated by altruistic factors and a desire to contribute to the evolving research on this condition (Pettit et al., 2024).

The topic of patient empowerment as a primary outcome of genetic services has been well described in the literature by McAllister et al. (2008), through the development of the Genetic Counselling Outcome Scale (GCOS). The GCOS is a validated patient reported outcome measure, designed to assess patient empowerment as an outcome of genetic services. In this context, empowerment is defined by five distinct dimensions including: decisional control (informed decision making), cognitive control (an understanding of the underlying cause of the condition), behavioural control (the ability to take action), hope for the future of the individual and their family members (including future generations) and emotional regulation (the ability to adapt to the diagnosis of a genetic condition) (McAllister et al., 2008, 2011). Importantly, the dimensions included in McAllister's definition of empowerment are not only reflected across

participant responses directly related to this category in our study, but also among the responses related to the perceived impact of genetic testing for FH on family members and medical management.

Evidence to support the impact of genetic services on patient empowerment among the cardiovascular patient population has been demonstrated by Ison et al. (2019). GCOS scores indicated a statistically significant increase in patient empowerment ($p < 0.0001$) after patients received genetic counselling for inherited cardiovascular disease. Ison et al. (2019) was the first study to employ the GCOS in the context of cardiogenetic counselling, contributing to the evidence that supports the role of genetic services among this patient population.

4.3.2 Hesitations and Barriers Impacting the Decision to Pursue Genetic Testing for FH

While only a small proportion of participants shared that they had hesitations towards genetic testing, our secondary analysis identified a few barriers that have the potential to influence patient decision making, and the uptake of genetic testing. These included the impact of a positive genetic test result on insurance coverage, the time constraints associated attending a genetic counselling appointment and blood collection, and a limited awareness of genetic services.

Genetic Discrimination

Genetic discrimination can be defined as the misuse of genetic information to limit access to various social services, such as insurance coverage and employment opportunities. As such, the security of genetic information is an important consideration for individuals making a decision about genetic testing. In Canada, genetic information is protected under the Genetic Non-Discrimination Act (GNA), which prohibits the requirement for individuals to undergo genetic testing or disclose genetic test results for the purpose of accessing social services, such as insurance, education, and employment (Department of Justice Canada, 2017). It is important to note that this law has several limitations, as insurance companies are still able to inquire about medical and family history as part of their assessment. Indeed, one of our participants noted that their elevated cholesterol was first detected following blood work required for coverage.

A key aspect of the secondary aim of this study was to determine if concepts are missing from the knowledge scale that significantly impact how individuals make a decision about genetic testing for FH and should therefore be considered in the evaluation of informed choice. While the majority of participant responses were reflective of the existing concepts in the

knowledge scale, such as the ability for genetic testing to identify risk information for family members and inform aspects of medical management, the concept of genetic discrimination is not included.

While the potential for genetic test results to impact insurance coverage and employment is an important aspect to consider when making a decision about genetic testing, the regulation of genetic information is variable across global healthcare systems. While many countries have enacted laws that are similar to Canada, there is not a global standard for the privacy of genetic information (Joly et al., 2020; Joly & Dalpe, 2022). As such, it falls under the responsibility of the ordering healthcare provider to educate patients on the local legislation (or lack thereof) in place to protect genetic information. For these reasons, an item related to insurance implications and genetic discrimination was not included in the final version of the knowledge scale. However, it is essential that clinicians who offer genetic testing for FH are aware of the regulations in place to protect genetic information and prevent discrimination based on genetic test results.

Time Constraints and Gaps in Genetic Service Integration

A separate consideration raised by several participants in our study group was the time constraint and inconvenience associated with accessing genetic services. Similar to the majority of genetic conditions, FH requires an interdisciplinary approach to care, often combining lipidology, cardiology and medical genetics to address all aspects of the condition. In circumstances where these services are not integrated with one another, the responsibility often falls on the patient to coordinate separate appointments.

Notably, patients who were seen in a lipid clinic where genetic testing was incorporated into clinical care reported positive views regarding the efficiency and ease of their experience with genetic testing (Hallowell et al., 2011). Similarly, a participant of our study suggested that the integration of genetic services has the potential to decrease the burden that patients may experience when coordinating separate appointments for genetic counselling and sample collection. It stands to reason that addressing this barrier may also result in a greater uptake of genetic services for FH, allowing more patients and family members to have access to the benefits that these services provide.

Limited Awareness of Genetic Services

For some participants, the decision to undergo genetic testing for FH was influenced by a limited awareness of genetic services. Participants characterized the referral process as largely uninformed, typically facilitated by their healthcare provider—such as a cardiologist or primary care physician—without a clear explanation of the referral's purpose or impact. Consequently, participants expressed a desire for greater engagement in the referral process. They emphasized that additional information regarding the role of the genetic counsellor and the clinical significance of genetic testing would have been valuable in clarifying the intent and relevance of the referral.

Recently, Lenin et al. (2025) conducted a systematic review of the literature in order to identify factors that impact the uptake of genetic services for FH. Importantly, healthcare provider perceptions on the utility of genetic testing, familiarity with making a referral to genetic services and comfort discussing genetic concepts with patients have all been reported to impact uptake of genetic services among the FH patient population (Lenin et al., 2025). Furthermore, one study revealed that non-genetics providers are more likely to initiate genetic consultation if this is first prompted by the patient, if they had previously referred patients to genetics or ordered genetic testing, or if they felt confident in providing appropriate pretest counselling on genetic concepts (Klitzman et al., 2013).

Additionally, there is evidence to suggest that even when patients are aware of a personal and family history of high cholesterol, they often do not recognize that this could be associated with an underlying genetic condition. Indeed, Silva et al., (2022) interviewed 24 individuals who had genetic testing for FH and found that although all participants were aware of their personal and family history of high cholesterol, very few were familiar with FH itself. Therefore, these findings are important to consider as most patients, particularly probands, are not presented with the opportunity to access genetic services until the option is presented by their healthcare provider. Indeed, this was reflected in our study, where the only participant who indicated that they initiated the process of genetic testing received cascade screening following the identification of FH in a family member.

Taken together, these findings support that patient awareness of genetic services is largely dependent on their healthcare provider. As such, it is essential that non-genetics providers are aware of utility and availability of genetic services for the FH patient population, so that the

option of genetic testing can be communicated in a timely manner to maximize the benefits that patients and their families receive from these services.

To conclude, the majority of findings from our secondary analysis highlight the perceived benefits that motivated patients to undergo genetic testing, rather than the concerns or barriers that may have influenced or deterred this decision. For the majority of individuals, genetic testing for FH is prompted by a longstanding history elevated cholesterol levels. Therefore, in most cases a positive genetic test result provides a confirmation of a clinical diagnosis rather than revealing unexpected information. Hollands et al. (2012) found that patients who were interviewed following the disclosure of a positive genetic test result were not surprised by the outcome of the test, as it was expected based on their personal or family history. Furthermore, previous studies support the notion that individuals with FH perceive their condition as highly manageable, and view genetic testing as an 'unexceptional' or 'non-threatening' event (Hallowell et al., 2017; Jenkins et al., 2013).

4.3.3 Participant Experiences with Genetic Services

Although the secondary aim of this study was focused on exploring factors that influenced patients' decisions to pursue genetic testing, it is important to recognize that all participants received pre-test counselling from a certified genetic counsellor prior to consenting to genetic testing for FH. Therefore, this raises the question of whether genetic counselling had any influence on the responses related to the secondary aim of this study, particularly those reflecting patient empowerment. Indeed, several participants indicated that speaking with a genetic counsellor positively contributed to their understanding of the implications for family members and their ability cope with the possibility of a genetic diagnosis of FH. Ultimately, genetic testing and genetic counselling can both lead to patient empowerment, but they do so in different ways.

Genetic counsellors specialize in helping patients and their families understand and adapt to both the genetic and psychosocial aspects of a condition (Resta et al., 2006). Recommendations have been made by the Canadian Cardiovascular Society, The National Lipid Association and the European Atherosclerosis Society supporting the role of genetic counsellors in FH patient care (E. E. Brown et al., 2020; Brunham et al., 2018; Cuchel et al., 2023). Sturm (2014) highlights that genetic counsellors play an important role throughout the entire process of genetic testing for FH. The collection of a comprehensive family history in combination with

patient education on the inheritance of this condition equips patients and their families with the information needed to facilitate cascade screening. Furthermore, genetic counsellors can assist with discerning the meaning of molecular findings that stem beyond a positive test result, as negative or uncertain findings still require appropriate interpretation. For example, Hilgart et al. (2013) found that patients desired additional support to manage feelings of uncertainty and confusion following a negative genetic test result for FH.

Furthermore, Nomura et al. (2023) explored the efficacy of genetic counselling in addition to genetic testing. Following a period of 24 weeks, the LDL-cholesterol levels of patients who received genetic testing with genetic counselling compared to those who only received a standardized education on FH and no genetic testing. Ultimately, those who received personalized counselling on their risk for cardiovascular disease displayed a significantly greater reduction in LDL-cholesterol levels, compared to those who did not speak with a genetic counsellor at the time of genetic testing. These findings support the notion that while genetic testing benefits the FH patient population, genetic counselling offers additional opportunities for education and support that have a different impact on patient care.

Although genetic testing and genetic counselling are often tightly intertwined, the results of our secondary analysis reveal that participants perceive them as separate entities (Figure 6). While genetic testing can provide a definitive diagnosis, risk information for family members and clarity on management recommendations, in the absence of adequate counselling, patients may not know how to utilize or adapt to this information effectively. Ultimately, the results of our secondary analysis provide important evidence to suggest the important but distinct roles that genetic testing and genetic counselling play in the experience of the FH patient with genetic services.

4.4 APPLICATIONS OF THE FH KNOWLEDGE SCALE AND RESEARCH OUTCOMES

Overall, the outcomes of this study have informed the validation process of a novel genetic knowledge scale for FH. This scale was developed with the intention of evaluating patient knowledge as part an FH-specific MMIC measure. Furthermore, this study has provided valuable insights on key factors that patients consider when making a decision about FH, along with their overall experience of genetic services. Taken together, we foresee that these findings have the potential to benefit researcher, clinician and patient cohorts with respect to evaluating

rates of informed choice among the FH patient population and highlighting the importance of the availability of genetic services for this condition.

4.4.1 Researchers

In response to the increasing demand for genetic services among clinical settings, alternative service delivery models (SDMs) such as mainstreamed or group genetic counselling services, webinars, chatbots, and patient education videos are being implemented as methods of providing genetic counselling and patient education on a larger scale. Consequently, validated instruments that assess whether patients are receiving adequate information to make an informed choice about genetic testing are essential, but limited. Therefore, we propose the FH knowledge scale may be used for its intended purpose as part of an FH-specific MMIC to facilitate research targeted at maximizing patient informed choice (Michie et al., 2002).

A handful of studies have explored the current practices and logistics of implementing novel SDMs into the genetic counselling practice (Boothe et al., 2021; Christian et al., 2022; S. A. Cohen et al., 2013; Greenberg et al., 2020; Khan et al., 2021; Raspa et al., 2021). Genetic counsellors are in favour incorporating alternative approaches to service delivery into their practice, as this is viewed as a way to expand access to genetic services and address growing waitlists (Boothe et al., 2021). While common concerns related to the implementation of alternative SDMs include reimbursement for services, technical issues, a lack of institutional-level support and adequate funding, another important consideration is the efficacy of these approaches in providing patients with sufficient information to make informed decisions (Boothe et al., 2021; Khan et al., 2021).

The application and efficacy of MMIC measures to assess rates of informed choice in the context of alternative SDMs has been described in the literature. For example, Xian Lim et al. (2023) conducted a randomised control trial to explore the rates of informed choice between women who received traditional counselling (i.e. a consultation with a genetic counsellor) for aneuploidy screening in pregnancy versus those who watched an educational video on the topic. Using an adapted version of the MMIC measure consisting of validated questions related to first trimester screening (FTS), non-invasive prenatal screening (NIPS) and invasive testing, the authors were able to successfully compare rates of informed choice between the two patient cohorts, thereby validating the efficacy of the educational video to provide sufficient information for patients to make an informed choice. The authors note that the application of the MMIC

measure in this context is particularly relevant for conditions where molecular analysis is offered as a first-line screening test to large patient cohorts (Xian Lim et al., 2023).

Overall, the availability of measurements to assess the efficacy of novel SDMs is essential for their implementation into clinical practice. While other instruments have been developed that are able to assess patient outcomes in this context, the MMIC offers a simplistic and targeted way of measuring rates of informed choice that are specific to a disease in question. This allows for a direct comparison of the rates of informed choice between traditional and novel methods of service delivery.

4.4.2 Clinicians

As the availability and clinical utility of genetic testing increases, a key consideration is how to effectively integrate genetic testing at the forefront of clinical care. In 2018, an expert panel of cardiologists, endocrinologists, lipidologists and genetic counsellors, among others, released a position statement, highlighting the importance of integrating genetic testing for FH into routine clinical practice (Sturm et al., 2018). Similarly, various national organizations such as the Canadian Cardiovascular Society and European Atherosclerosis Society have recognized the utility of cascade genetic testing for FH following the identification of disease causing variant in a family (Brunham et al., 2018; Nordestgaard et al., 2013). Given the high prevalence of FH and the limited number of genetic specialists, genetic testing for FH will likely need to transition to the frontline, which require non-genetics providers to conduct pretest counselling for this condition.

Various studies exploring the perceptions of non-genetics providers towards the implementation of genetic testing into clinical care have been published in the literature. Mikat-Stevens et al. (2015) published a systematic review on this topic, where a perceived lack of knowledge of genetic concepts, low confidence in the ability to provide adequate counselling on genetic conditions, and limited time with patients were identified as major themes across published literature. Outcomes of this research support the need for standardized materials to support the integration of frontline genetic testing, with a focus on pre-test counselling, patient support and result disclosure (Christensen et al., 2016; Hauser et al., 2018; Klitzman et al., 2013; Mikat-Stevens et al., 2015; Platt et al., 2022). Given the low diagnostic rate for FH, Zimmerman et al. (2018) explored the perceptions of 173 primary healthcare providers on the barriers that impact effective diagnosis of this condition. With respect to FH screening practices, the majority

(92%) of respondents claimed that they play a major role in diagnosing FH however, self-reported knowledge of the genetic aspects of this condition was extremely limited. Only half of the study group could correctly identify the risk to first degree relatives, even fewer (3%) reported that they regularly incorporate a discussion about cascade screening for family members into clinical practice.

When asked about the specific barriers that limit the diagnosis of FH in primary care, difficulties combining lipid results and family history data (34%), discomfort with discussing genetic lipid disorders (12%) and limited access to genetic services or the belief that genetic testing was outside of the scope of practice (1%) were identified as major barriers from genetics standpoint (Zimmerman et al., 2018). Some providers made suggestions for how these barriers might be addressed in clinical practice, indicating that additional training on inherited lipid disorders, consultation with genetic experts and more time with patients would support the implementation of additional screening for FH (Zimmerman et al., 2018). Although this study was not focused on identifying barriers to implementing genetic testing specially, these results provide valuable insights into the barriers that limit genetic testing for FH in routine clinical practice.

Therefore, we propose that the concepts covered by the FH knowledge scale may serve as a reference for non-genetics providers to facilitate a discussion about the benefits, risks and limitations of genetic testing for FH. Furthermore, the knowledge scale may be used as a tool to assess gaps in patient knowledge prior to pretest counselling, which may help address the time constraints reported by primary care providers regarding the implementation of genetic testing into frontline clinical care. Indeed, there is research to support the use of educational tools and interactive decision aids in clinical encounters to reduce the overall time required for patient education, allowing for more time to spent on addressing complex concepts or patient-specific concerns (Bombard et al., 2020; Shickh et al., 2018). As research related to the perceptions of primary care providers on integrating genetic testing for FH into clinical practice is limited, additional research is required to assess the feasibility of this approach, along with the perceived importance of the concepts in the FH knowledge scale among non-genetics providers.

4.4.3 Patients

Often FH is a clinically silent disease, making it difficult for patients to comprehend the severity of this condition in the absence of cardiovascular disease (Marchand et al., 2021). In

Canada, approximately 90% of at risk individuals remain undiagnosed with FH (Brunham et al., 2018). Patients who receive a genetic diagnosis for FH are more likely to comply with recommended treatment and are more likely to inform family members of the condition for the purpose of cascade genetic testing (Marchand et al., 2021). Appropriate pre-test counselling is vital to ensure that patients are informed in their decision and understand the implications of a genetic diagnosis of FH for themselves and their family members.

Overall, this study was designed with the FH patient population as the centre of focus. As such, both the primary and secondary aims of this study were informed by the feedback and perspectives of individuals who have been previously offered genetic testing for FH. Participant responses were essential in guiding revisions to the FH knowledge scale, evaluating the importance concepts covered by the knowledge scale, and providing novel insights into the key factors that impact how members of this patient population make a decision about genetic testing. From a patient perspective, we propose that the outcomes of this study have the potential to contribute to the evidence in the literature suggestive of the importance of genetic testing among the FH patient population and provide a means of assessing patient informed choice in the context of genetic testing for this condition.

4.5 STUDY LIMITATIONS

This study contains several limitations which may impact the overall generalizability of our findings. A total of 10 individuals participated in the validation of the FH knowledge scale and provided perspectives on the key factors that influenced how they made a decision about genetic testing. Although this sample size is in keeping with the recommendations for scale development, it is not representative of the national or global FH patient population with respect to gender, age, race, geographical location or educational status. Although attempts were made to increase the diversity of the sample population included in this study, the limited sample size, recruitment strategy and overall scope of this project impacted the opportunity to include a broader range of perspectives. Importantly, participants were recruited from two clinical sites with similar healthcare systems, workflow and approaches to counselling on FH. Therefore, it is a likely possibility that certain perspectives reflected in the results of this study are the result of site-specific factors, such as a publicly funded healthcare system that covers the cost of genetic testing.

Another limitation that is important to address with respect to this study are the methods selected to facilitate the development and subsequent validation of the FH knowledge scale. The items included in the initial version of the knowledges scale were selected based on professional opinion rather, rather than employing methods suggested to be 'best practice' in the early stages of scale development, such as a Delphi method (Boateng et al., 2018). Furthermore, the process of scale validation was qualitative in nature and did not include the use of statistical analysis. Although this approach is in line with the recommendations for establishing face validity and the importance of core concepts, it could be argued that researcher biases impacted the perception and reporting of participant responses.

Finally, as saturation for this study was determined based on the primary aim of this study, it is likely that additional interviews would have been required to reach thematic saturation with respect to the secondary aim of this study exploring the key factors influencing the decision to pursue genetic testing. Therefore, although we report findings that are consistent with the literature, it is possible that additional factors were not identified due to an insufficient number of interviews.

4.6 NEXT STEPS OF KNOWLEDGE SCALE VALIDATION AND FUTURE DIRECTIONS

To the best of our knowledge, this was the first study to initiate the validation of a genetic knowledge scale for FH, to be used as part of an FH-specific MMIC. As the complexity and availability of genetic testing continues to expand, the development of validated measures of genetic knowledge will continue to play an important role in assessing patient informed choice in this capacity. It is essential that future research addresses the inconsistencies in validation approaches, thereby improving the overall accuracy, applicability, and effectiveness of these tools in the evaluation of informed decision-making.

A recent review of measurements designed to assess genetic literacy identified that only 40% of measures were described as being validated (Daly & Kaphingst, 2023). Face validity and content validity, which were both addressed in this study, were identified as the most common methods of validation among published measures. Moving forward, the next steps of validation should aim to establish the reliability, criterion validity and construct validity of the FH knowledge scale in the context of its intended purpose of evaluating patient informed choice as part of the FH-specific MMIC.

Reliability refers to the ability of a measure to deliver similar or consistent responses over time (Boateng et al., 2018). Oftentimes, the reliability is assessed using test-retest scenarios, where the measure is administered to the same group over several different time points in order to determine the consistency of responses (Boateng et al., 2018; Daly & Kaphingst, 2023). As such, reliability of FH knowledge scale could be established among a patient cohort who completes the scale at two separate time points (i.e. one week and six weeks following a pre-test counselling appointment). Consistency between the number of correct responses following each counselling session would provide evidence to support the reliability of the knowledge scale.

Criterion validity refers to the ability of a scale to preform effectively in comparison to the 'gold standard' for the domain of which knowledge is being measured (Boateng et al., 2018). In this case, a gold standard has not been developed for the purposes of assessing the knowledge required for patients to make an informed decision about genetic testing for FH, which is not uncommon in the field of scale development. Therefore, researchers use previously validated measures that assess similar constructs for comparison. For example, patient-reported outcome measures such as the Decisional Conflict Scale and the Decision Regret Scale have been used to assess the criterion validity of previous MMIC measures, as one would expect an association between scores indicative of an informed decision with scores indicating low decisional conflict or regret, and vice versa (Ames et al., 2015; Brehaut et al., 2003; O'Connor, 1995).

Construct validity refers to whether a scale is able to accurately measure the construct (i.e. knowledge of FH) of which it claims to measure. Oftentimes, construct validity is established through real-world applications of the measure, which allows for the opportunity to conduct differentiation by known groups, or hypothesis testing. For example, the FH knowledge scale may be used to evaluate patient knowledge of FH in different settings. One would expect that scale outcomes would perform differently among a group of individuals who received sufficient pre-test counselling from a genetics professional, compared to those who receive counselling from an alternative resource.

Finally, the process of validating the knowledge scale should include an evaluation of the efficacy of a true or false response system in evaluating patient knowledge about FH. While the knowledge scale developed for the first MMIC utilized a multiple-choice response format, the majority of novel MMIC measures have transitioned to using a true or false response format (Ames et al., 2015). This is based on the assumption that a true or false response system offers a

more simplified approach to item generation, allowing items to items to be written in plain language, effectively reducing the overall cognitive burden and completion time among end users (Frisbie, 1973). However, there is an opportunity to explore the option of adding 'I don't know' or a 5-point Likert scale to the response selection. This is a common strategy used to diminish the ceiling effect that can occur when individuals have a high probability of guessing the answer to an item correctly (Langer et al., 2017).

Apart from the next steps required to validate the FH knowledge scale, additional research is necessary to investigate the feasibility of using the concepts covered by the knowledge scale as a guide for non-genetics providers to facilitate pretest counselling for FH. This may include an exploration of provider perspectives on the importance of the concepts included in the knowledge scale, how these topics may differ from their current approaches to providing pre-test counselling on FH, and how this information can best be presented as a guide for efficient use in a clinical setting.

The secondary aim of this study provided valuable insights on the key factors that influence how individuals make a decision about genetic testing for FH. As saturation for this study was based on the primary aim (i.e. establishing face validity and importance of core concepts), additional exploration on the topic may be necessary to substantiate these findings. Future research with this patient population may focus on expanding what is known about how genetic services facilitate opportunities for patient empowerment, along with an investigation of the barriers that limit patient access to these services. Additional insights into the experiences of this patient population may contribute to the growing evidence in support of the integration of genetic testing into routine clinical care for this condition.

Finally, as the availability of clinical genetic testing continues to expand for a broad range of conditions, the development of novel and validated MMIC measures capable of assessing informed choice is an important area of research. As each MMIC measure requires the development of a knowledge scale specific to the condition for which testing is being offered, a future challenge may be adapting these measures to assess informed choice in the context of large-scale genetic tests such as genome or exome sequencing, where multiple clinically significant findings are a possibly.

CHAPTER 5: CONCLUSION

The MMIC measure is a valuable resource for evaluating patient informed choice through the assessment of patient knowledge, attitudes and behaviours. Based on the lack of validated MMIC measures that are specific to inherited cardiac conditions, this primary aim of this study was to initiate the validation of a novel genetic knowledge scale for FH to be used as part of an FH-specific MMIC. The secondary aim of this study was to explore the key factors that influenced participants' decisions to pursue genetic testing for FH, for the purpose of identifying novel concepts that were not included in the initial FH knowledge scale.

A total of 10 semi structured cognitive interviews were conducted with individuals who had previously been offered genetic testing for FH. The items in the knowledge scale demonstrated adequate face validity among all participants. However, several responses informed revisions to the knowledge scale to improve the clarity of the questions. Additionally, participant responses confirmed that the concepts covered by the knowledge scale are important for patients to understand when making a decision about genetic testing for FH, and therefore justify their inclusion in the final version of the knowledge scale.

The secondary aim of this study revealed three primary motivations to pursue genetic testing for FH which included family, informing medical management and providing an opportunity for patient empowerment. Hesitations towards genetic testing included the time required to access genetic services, insurance implications and the process of sample collection. Additionally, a common barrier reported by multiple participants was a lack of awareness of genetic services. Finally, participant responses highlighted the positive impact that genetic counselling can have among those who are offered genetic testing for FH, by providing patients with personalized and actionable information.

Overall, the outcomes of this study have guided the preliminary validation of a novel knowledge scale about FH. This knowledge scale can be used as part of an FH-specific MMIC measure to assess patient informed choice in the context of genetic testing for this condition. Furthermore, this study provided novel insights into the considerations that impact how a subset of the FH patient population made a decision about genetic testing for FH, along with their experience of genetic services. Taken together, these findings may contribute to future research targeted at maximizing patient informed choice and help to inform appropriate pre-test counselling on this condition.

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APPENDIX

Appendix I: Clinician Recruitment Script

Clinician Recruitment Script

Clinician: Based on what we have discussed during this appointment, you are eligible to participate in a research study that is being conducted at the University of Manitoba. The purpose of this study is to evaluate 8 knowledge questions about familial hypercholesterolemia, and to explore what how patient's make a decision about genetic testing for this condition.

The study will involve a one-on-one interview between yourself and the Student Researcher, Emily Moss. The interview will take place over Zoom and will be approximately 60 minutes.

Participation in this study is completely voluntary. If you choose not to participate in this study, it will not impact the care that you receive from this clinic in any way.

Are you interested in learning more about this study?

[Yes] Clinician is to provide the consent to contact form to the patient.

[No] Thank you for your time.

Appendix II: Consent to Contact Form

Consent to Contact

Dear potential participant,

You have been identified as eligible to participate in a research study which aims to learn if a series of 8 knowledge questions regarding familial hypercholesterolemia are asking what the research team wants them to ask, and if they are important to make an informed choice about genetic testing. This study will also explore your individual experience in making a decision on whether or not to receive genetic testing for familial hypercholesterolemia.

Participation in this study is voluntary. If you would like to learn more about the study, you may fill out the contact form below to give the Student Principal Investigator, Emily Moss, permission to contact you at either the email or telephone number provided. Filling out this form does not mean you have consented to participate in the study. You may decide to participate in the study after talking to Emily.

Do we have permission to contact you? □ Yes □ No

Full name: _____

Phone number: _____

Email address: _____

How do you prefer to be contacted? □ Phone □ Email □ No preference

When is the best time to contact you? □ Morning □ Afternoon □ Evening

Signature: _____ **Date:** _____

Witness signature: _____ **Date:** _____

If verbal consent obtained:

Clinician's Name Signature:_____ **Date:** _____

Appendix III: Email of Invitation

Invitation Email

SUBJECT: Invitation to participate in research study at the University of Manitoba

Hello (insert name from consent to contact form),

My name is Emily Moss and I am a MSc Genetic Counselling student at the University of Manitoba. I am reaching out because you have indicated that you would like to learn more about my study titled "**Preliminary validation of a novel genetic knowledge scale for familial hypercholesterolemia: evaluation of face validity and concept validity"**. Please see a summary of the study below. This study is part of my MSc Genetic Counselling thesis project. If you are interested in taking part in the study, please provide potential times that would work for you to set up a Zoom call.

Study Description: The purpose of this study is to learn if a series of 8 knowledge questions about familial hypercholesterolemia are asking what the research team wants them to ask, and if they are important to make an informed choice about genetic testing. This study will also explore your individual experience in making a decision on whether or not to receive genetic testing for familial hypercholesterolemia.

Why am I being asked to participate in this study?

You are being asked to participate in this study because you were recently seen by a genetics clinician for an indication of familial hypercholesterolemia and was offered genetic testing for familial hypercholesterolemia at this appointment. Please note, to participate in this study, you must be18 years of age or older, you must be comfortable reading and speaking in English and you must have access to Zoom.

What does participation in this study involve?

If you volunteer to participate in this study, you will be asked to complete a one-on-one interview with the Student Principal Investigator, Emily Moss. The interview will take place over Zoom and will be approximately 60 minutes in length. Before completing the interview, Emily

will go through the consent form and obtain your verbal consent to participate in the interview. The verbal consent will take approximately 15 minutes to complete. During the interview, Emily will guide you through a series of 8 knowledge questions about familial hypercholesterolemia. Each question will be associated with an underlying concept that has been

identified as being important when making a decision about genetic testing. You will be asked to share in your own words what each question means to you. The goal is **not** to assess your knowledge, but rather how well the question is worded. You will also be asked to elaborate on if you think each concept is important to consider when making an informed choice about genetic testing. Finally, Emily will ask you to discuss your personal experience in making a decision about genetic testing for familial hypercholesterolemia.

Who can I contact for more information?

If you have any questions about the study, please do not hesitate to contact the Student Principal Investigator, Emily Moss. This study has been approved by the University of Manitoba Health Research Ethics Board.

Thank you for taking the time to consider participating in this study.

Sincerely,

Emily Moss

Appendix IV: Letter of Invitation

Letter of Invitation

Dear potential participant,

You have been identified as eligible to participate in a research study which aims to learn if a series of 8 knowledge questions about familial hypercholesterolemia are asking what the research team wants them to ask, and if they are important to make an informed choice about genetic testing. This study will also explore your individual experience in making a decision on whether or not to receive genetic testing for familial hypercholesterolemia.

Completing this study is **voluntary** and you do not have to participate if you do not wish do. If you require more information about the study, you can contact the Student Principal Investigator, Emily Moss, whose contact information is listed above.

This study is being conducted by Emily Moss, a Genetic Counselling Trainee at the University of Manitoba. The supervisor for this study is Dr. Susan Christian, a genetic counsellor with Alberta Precision Laboratories and Alberta Health Services.

Why am I being asked to participate in this study?

You are being asked to participate in this study because you were previously seen by a Genetics clinician at the Shared Health Genetics clinic since January 2022 for an indication of familial hypercholesterolemia, was offered genetic testing for familial hypercholesterolemia and are over the age of 18. Please note, to participate in this study, you must be comfortable reading and speaking in English.

What does participation in this study involve?

If you volunteer to participate in this study, you will be asked to complete a one-on-one interview with the Student Principal Investigator, Emily Moss. The interview will take place over Zoom and will be approximately 45-60 minutes in length. Before completing the interview, Emily will go through the consent form and obtain your verbal consent to participate in the interview. The verbal consent will take approximately 15 minutes to complete. During the interview, Emily will guide you through a series of 8 knowledge questions about familial hypercholesterolemia. Each question will be associated with an underlying concept that has been identified as being important when making a decision about genetic testing. You will be asked to share in your own words what each question means to you. The goal is **not** to assess your knowledge, but rather how well the question is worded. You will also be asked to elaborate on if you think each concept is important to consider when making an informed choice about genetic testing. Finally, Emily will ask you to discuss your personal experience in making a decision about genetic testing for familial hypercholesterolemia.

Who can I contact for more information?

If you are interested in learning more about the study, please contact Emily Moss at *email* or *phone number*. This study has been approved by the University of Manitoba Health Research Ethics Board.

Thank you for taking the time to consider participating in this study.

Sincerely,

Emily Moss

Appendix V: Recruitment Script

Recruitment Script

Hello, my name is Emily Moss. I am a genetic counselling student at the University of Manitoba. I am calling you because I:

- Received a permission to contact form indicating I had permission to contact you to discuss this research study.
- **OR** was contacted by you after you received a letter of invitation to this study in the mail indicating you wished to learn about this study.

I am conducting this research as part of my graduate school training. This research study is about how individuals make an informed choice about genetic testing for familial hypercholesterolemia.

Are you still interested in learning more about this study?

[Yes] Is now a good time or should I call back?

[No] Thank you for your time.

1. Study Overview

The purpose of this study is to evaluate 8 knowledge questions about familial hypercholesterolemia. We want to know if these questions are worded in a way that they are asking what we want them to ask. We also want to know if the topics covered in each question are important to consider when making a decision about genetic testing. Finally, we want to look at the key factors that contribute to making a decision about genetic testing.

You are being asked to take part in this study because you were previously seen in the genetics clinic and were offered genetic testing for familial hypercholesterolemia.

Before we continue, this study requires you to have access to a computer and a Zoom account to complete a virtual interview. Is this possible for you?

[Yes] Thank you for confirming. Continue to study procedures.

[No] Unfortunately, you will not be able to participate in this study without access to Zoom. I apologize for the inconvenience. Thank you for your time.

2. Study Procedures

Do you have any questions so far?

Completing this study is completely voluntary and you do not have to participate if you don't want to. If you volunteer to participate in this study, you will be asked to complete a one-on-one interview with me that will take approximately 60 minutes.

Before the interview, I will go over the consent form and obtain your verbal consent to participate. The consent form will be emailed to you prior to the date of the interview. The verbal consent process will take about 15 minutes. During the consent process, we will talk about things like confidentiality, as well as the potential benefits and risks of participating in the study.

During the interview, I will share a PowerPoint presentation consisting of 8 knowledge questions about familial hypercholesterolemia. I will ask you to share in your own words what each question means to you. The goal is not to assess your knowledge, but to determine how well the question is worded. I will also ask you to identify if you think the topic covered in each question is necessary, helpful, or not important to consider when making a decision about genetic testing.

Finally, I will ask you to discuss your personal experience of making a decision about genetic testing for familial hypercholesterolemia.

Once the interview is complete, a $25 electronic gift card to either Tim Hortons or Amazon will be sent to your email as a thank you for your time.

Do you have any questions about the study procedures?

Are you interested in participating in this study?

[Yes] If participant wishes to participate in the study, schedule a date and time to complete the verbal consent and interview. Confirm the email address in the consent to contact form with the participant. If an email address was not listed in the consent to contact form, or the participant was recruited via mail, ask the participant to provide their email.

[No] Thank you for taking the time to speak with me today.

Appendix VI: Interview Consent Form

CONSENT FORM FOR PARTICIPANT

Individual Interview

Title of Study: Preliminary validation of a novel genetic knowledge scale for familial hypercholesterolemia: evaluation of face validity and concept validity

Student Principal Investigator: Emily Moss

Student Supervisor: Dr. Susan Christian

You are being asked to take part in a research study that will involve a one-on-one interview between you and the Student Principal Investigator, Emily Moss. Please take your time to review this consent form. This consent form will be reviewed with you in detail before the interview, where you will have the chance to ask any questions you may have before you make your decision. Please ask the study staff to explain any information you do not clearly understand in this form.

The Student Investigator for this study is Emily Moss, an MSc student in the Genetic Counselling Program at the University of Manitoba. This research study is being completed as part of the student investigator's MSc Program. The Student Supervisor is Dr. Susan Christian, a board-certified genetic counsellor at Alberta Precision Laboratories and Alberta Health Services.

PURPOSE OF STUDY

The purpose of this study is to learn if a series of 8 knowledge questions about familial hypercholesterolemia (FH) are asking what the research team wants them to ask, and if they are important to make an informed choice about genetic testing. This study will also explore the

experience of participants in making a decision on whether or not to receive genetic testing for FH.

PARTICIPANT SELECTION

You are being asked to participate in this study because you were previously seen by a Genetics clinician for an indication of familial hypercholesterolemia at either the Shared Health Genetics clinic in Winnipeg, MB or the Medical Genetics Clinic in Edmonton, AB. A maximum of 15 individuals will be asked to take part in this study.

The table below outlines the eligibility criteria for this study:

You are eligible to participate in this study if:	You are NOT eligible to participate in this study if:
6. you were seen by a genetic clinician (genetic counsellor or physician) since January 2022 for an indication of FH 7. you were offered genetic testing for FH since January 2022 8. you are ≥ 18 years of age 9. you are proficient in reading and speaking in English 10. you have access to Zoom	6. you were seen by a genetic clinician (genetic counsellor or physician) before January 2022 for an indication of FH 7. you were offered genetic testing for FH prior to January 2022 8. you were not offered genetic testing for FH 9. you are ≤ 18 years of age 10. you are not proficient in reading and speaking in English 11. you do not have access to Zoom

STUDY PROCEDURES

- The interview will take place over the University of Manitoba Zoom account (UM Zoom) and will be conducted by the Student Principal Investigator, Emily Moss. The interview will be approximately 60 minutes in length.
- During the interview, you will be guided through a series of 8 knowledge questions about FH. You will be asked to explain what each question is asking in your own words and share if you feel that the information covered in the question is necessary, helpful, or not important to make an informed decision about genetic testing. You will also be asked to discuss your experience of making a decision about genetic testing for FH. Your responses to the interview questions will help us make changes to the knowledge scale and to better understand key factors that contribute to making a decision about genetic testing.
- At the end of the interview, you will be asked questions about your age, gender, ethnicity, educational background, and genetic diagnosis of FH (if you received one).
- Interviews will be audio recorded. Audio recordings will be transcribed word-for-word by the Student Principal Investigator, or by a confidential transcription service (Transcript Heroes) to ensure accurate reporting of the information that you provide. No personal identifiers will be included in the interview transcript.
- The transcription service will sign a form stating that they will not discuss any information included in the audio recording with anyone other than the study staff.
- Individual results and interview transcripts will not be provided to you.

POTENTIAL RISKS

There are very few risks to participating in this study. It is possible that talking about your experience with FH might be upsetting, emotional, or distressing for you. You do not have to answer any question that makes you feel uncomfortable or that is upsetting. Additionally, as the interview will be conducted through UM Zoom, the Student Principal Investigator cannot guarantee complete privacy of the data collected through this medium.

BENEFITS

There will be no direct benefit to you from participating in this study. However, we hope the results from this study will help us learn about what information is needed to make an informed choice about genetic testing. This information may benefit others in the future.

COSTS

There is no cost to you to participate, aside from the time it takes to conduct the interview.

PARTICIPANT HONORARIUM

Once the interview is finished, you will be offered with a $25.00 electronic gift card to either Tim Hortons or Amazon as a thank you for your time. You will be asked to provide your email so that the research team can send you the gift card.

SAFETY

Your confidentiality may be broken if you describe one of the following:

- You say something about harming yourself or others
- You tell me about the abuse or neglect of a child
- You report inappropriate or incompetent practice of a healthcare professional

CONFIDENTIALITY

We will do everything possible to keep your personal information confidential. Your name will not be used in the published records of this study. All participant information will be kept in a secure file in case we need to contact you about the study. All identifying information (names, pronouns, clinic name) will be removed during the transcription process of your interview. Please note that although you will not be identified as the speaker, your words may be used to highlight a specific point. Collection and access to personal information will comply with provincial and federal privacy legislations.

All study records, including audio recordings, transcripts, interview notes, screening questions, and contact information, will be labelled with a coded ID number, which will be assigned to you upon enrolment into the study. All electronic files (audio recordings, typed notes) will be saved in a secure password-protected computer drive at the University of Manitoba. Only the Student

Principal Investigator and study staff will have access to the study records. All electronic materials will be permanently deleted from the University of Manitoba hard drive within 5 years following the completion of the study.

All paper records will be kept in a locked office and filing cabinet located in the Department of Biochemistry and Medical Genetics. All paper materials will be destroyed within 5 years following the completion of the study.

Some people or groups may need to check the study records to make sure all the information is correct. All of these people have a professional responsibility to protect your privacy. These people or groups are:

- The Health Research Ethics Board of the University of Manitoba, which is responsible for the protection of people in research and has reviewed this study for ethical acceptability
- Quality assurance staff of the University of Manitoba who ensure the study is being conducted properly

VOLUNTARY PARTICIPATION AND WITHDRAWAL

Your decision to participate in this study is voluntary. You may refuse to participate or withdraw from the study at any time. Refusing to participate or withdrawing from the study will not affect any health care you receive from the Shared Health Genetics clinic in Winnipeg, MB or the Medical Genetics Clinic in Edmonton, AB. If you withdraw from the study, all data you provided will be destroyed.

QUESTIONS

If you have any questions or concerns about the study, you may contact the Student Principal Investigator, Emily Moss, at *email* or *phone number*. You may also contact the Student Supervisor, Dr. Susan Christian, at *email* or *phone number*.

If you have questions about your rights as a research participant, you may contact the University of Manitoba Bannatyne Research Ethics Board by phone at 204-789-3255 or by email at bannatynereb@umanitoba.ca. Please feel free to print a copy of this consent page to keep for your records.

CONSENT SIGNATURES

1. I have reviewed all pages of the consent form with the Student Principal Investigator.
2. I understand what this study entails, and I have had the opportunity to ask questions, all of which have been answered to my satisfaction.
3. I understand that my participation in this study is voluntary, and I do not have to participate in this study if I do not wish to.

4. I understand that any information collected about me during this study may be viewed by the Student Principal Investigator, Emily Moss, or a member of the study team, as well as the University of Manitoba Research Ethics Board.
5. I understand that by consenting to participate in this study, I am consenting to be audio recorded for the duration of the interview.
6. I understand that I may withdraw from the study at any time and my data may be withdrawn prior to publication.
7. I understand that by providing my verbal consent to participate in this study, I have not waived any of my legal rights.
8. I understand I will be provided with a copy of the consent form for my records.
9. I am providing verbal consent to the researcher to sign on my behalf.
10. I agree to participate in the study.

Participant name: _____ Date _____ (day/month/year)

Participant email address: _____

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has knowingly given their verbal consent.

Name: _____ Date _____ (day/month/year)

Signature: _____ Role in the study: _____

Appendix VII: Interview Guide

Interview Script

Thank you for taking part in our study. My name is Emily Moss, and I am the student researcher for this study. Our research team has created eight questions to better understand if patients have enough knowledge to make an informed choice about genetic testing. There are two goals for this study. The main goals is to learn if these questions are asking what we want them to ask and if these questions cover information that is key to you in making an informed choice. The second goal of this study is to better understand the key factors that played a role in your decision to either have or not have genetic testing.

To begin, I am going to ask you to walk me through your experience of having genetic counselling for FH. I would like you to try to remember how you came to a decision on whether or not to have genetic testing. Following this, I am going to show you 8 questions one by one. I

would first like you to think aloud and share what you think each question is asking. I would then like you to share if you feel that the information included in each question is important when making a decision about genetic testing.

This interview will audio recorded, and you have the option of turning off your camera if you prefer. The interview will likely be about 45-60 minutes long. Do you have any questions?

Start [audio recording]

Part 1 – Exploration of key factors that influenced the decision-making process about genetic testing

Question: "Can you walk be through your experience of being offered genetic testing for familial hypercholesterolemia?"

Probe: "What was going through your mind? How did you feel during the appointment?"

Question: "What were you told about the test?"

Probe: "Was any of the information presented in the appointment surprising to you?"

Question: "How did you make your decision to have/not have genetic testing?"

Probe: "Did you decide before/during the appointment? Did you make a pros/cons list? Did you speak to someone about genetic testing before the appointment? Did any of the information presented in the appointment influence your decision?"

Question: "Thinking back, what do you think was your main motivation to have/not have genetic testing?"

Question: "Was there any additional information you wish you had prior to making your decision?"

Interviewer: "Thank you for sharing. We will now move on to the second part of the interview. As a reminder, I am going to walk you through 8 questions about familial hypercholesterolemia one by one. I would first like you to think aloud and share what you think each question is asking. I would then like you to share if you feel that the information included in each question is important when making a decision about genetic testing. You do not need to answer whether or not each question is true or false."

Part 2 – Evaluation of face and concept validity of the knowledge scale

[Interviewer to share screen with the first question of the knowledge scale]. [Interviewer to read the question aloud.]

Question: "Can you share in your own words what the questions is asking?"

Probe: "Are there any words in the question that others may find confusing?" Or "Can you think of a better way to ask the question to make it more clear?"

[Interviewer to update the slide to reveal the first concept]. [Interviewer to read the concept aloud.]

Question: "Do you think this information is important (i.e. essential/necessary/critical), helpful or not important" "Kind of think of it as a scale."

Probe: "Can you explain why you think this information is important/not important"

Repeat process through all questions and associated concepts in the knowledge scale

[End of PowerPoint]

Question: "Is there any other information that you feel is important for people know before having genetic testing?"

Question: "After working through these 8 questions, can you tell me if any of the information was helpful in your decision-making process?"

Probe: "What information did you find to be the most important? What information was least important?"

Question: "Do you have any other comments you would like to share about your experience receiving genetic testing? Do you have any other comments about the 8 questions?"

[Stop recording]

Collect demographic data.

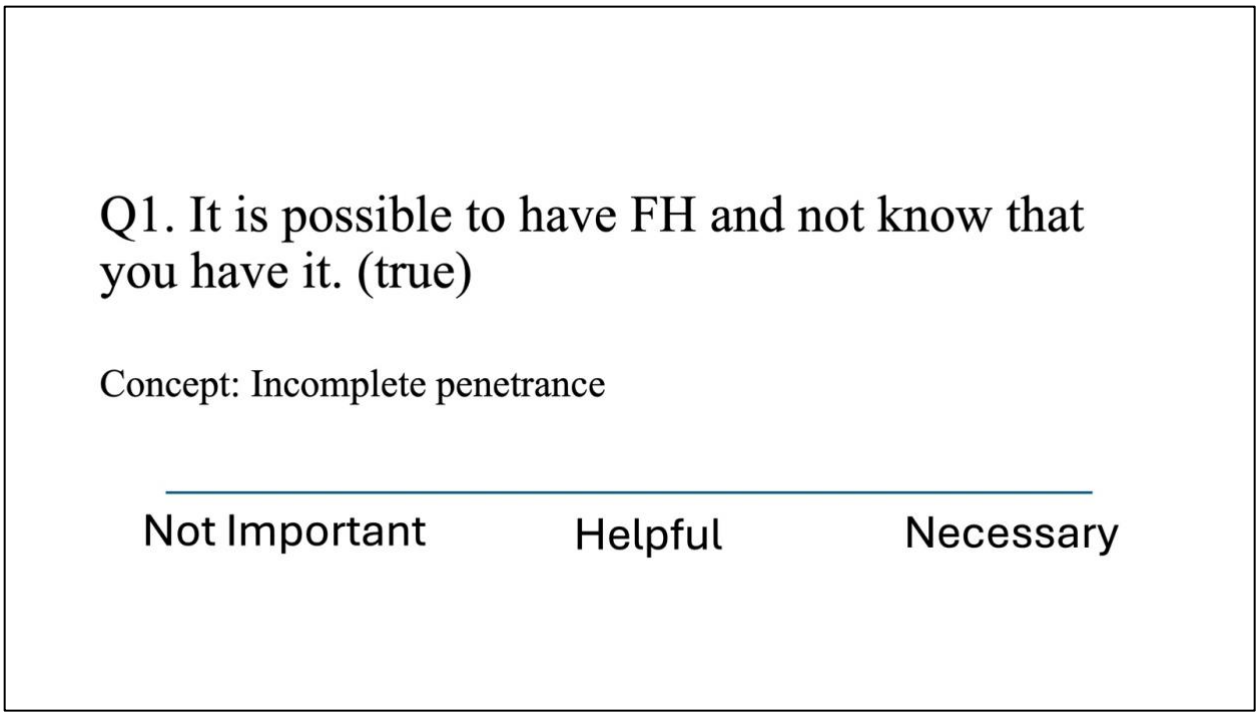
1. Do you have the condition or is it in your family?
2. If yes to question 1: Do you recall your genetic test result?
    a. Homozygous for a disease-causing variant in: *LDLR, ApoB, PCSK9*
    b. Compound heterozygous for a disease-causing variant in: *LDLR, ApoB, PCSK9*
    c. Heterozygous for a disease-causing variant in: *LDLR, ApoB, PCSK9*
    d. Unknown
3. How old are you?
4. What is the highest level of school you have completed or the highest degree you have received? {Let them answer, and then clarify as needed based on the choices.}
    a. Grade school/junior high
    b. Some high school
    c. High school graduate
    d. Trade/technical/vocational school
    e. Some college
    f. College graduate /bachelor's degree
    g. Post graduate work or graduate degree
    h. Prefer not to answer

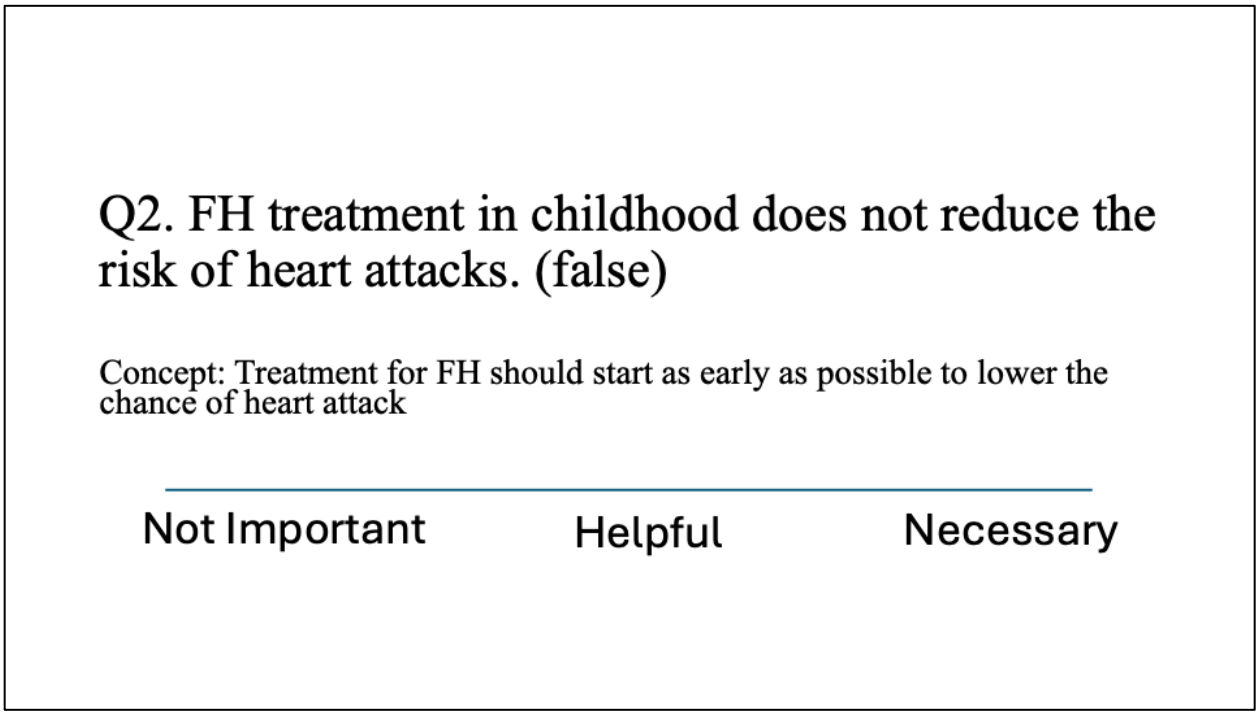
5. Are you an Indigenous Person from the lands or territories in what is now known as Canada?
    a. Yes
    b. No
    c. Prefer not to answer
6. With which Indigenous group(s) or peoples do you identify? Please select all that apply.
    a. First Nations
    b. Métis
    c. Inuit
    d. Prefer not to answer
7. Which of the racial designations below best describes you? Please select all that apply.
    a. Biracial/Multiracial
    b. Black
    c. East Asian
    d. South Asian
    e. Southeast Asian
    f. Middle Eastern
    g. Hispanic, Latino/a
    h. White
    i. Other (specify) _____
8. Gender identity if the personal concept of and expression of one's own gender(s). Do you self-identify as:
    a. Woman
    b. Man
    c. Intersex
    d. Trans or transgender
    e. Transfeminine
    f. Transmasculine
    g. Non-binary
    h. Two Spirit
    i. Prefer to self-describe
    j. Prefer not to answer
    k. (if self-describe was chosen) Please describe your gender: _____
9. Which setting best describes where you reside
    a. Rural
    b. Reserve
    c. Canadian Northern/Remote
    d. Urban
    e. Other (please specify: _____

Interviewer: "Thank you. That concludes the interview."

[End of Interview]

Appendix VIII: FH Knowledge Scale Interview Presentation





Q3. A negative (normal) genetic test means that you do not have FH. (false)

A normal (negative) genetic test means that you do not have FH. (false)

Concept: Limitations of genetic testing

Not Important Helpful Necessary

Q4. FH can lead to health problems such as heart attacks. (true)

Concept: People with FH have a much higher chance of heart attacks

Not Important Helpful Necessary

Q5. If you have FH, steps can be taken to lower your risk of heart attacks. (true)

Concept: There are ways to lower the chance of heart attack due to FH

Not Important Helpful Necessary

Q6. If you have FH, it is unlikely that your family members have it. (false)

Concept: FH runs in families

Not Important Helpful Necessary

Q7. Medication is often needed to lower cholesterol for people with FH. (true)

Concept: For someone who has FH, genetics causes high cholesterol.

Not Important Helpful Necessary

Q8. If you are found to have a genetic cause for FH, genetic testing is the best way to screen your family members. (true)

Concept: Genetic testing is the best way to screen family members.

Not Important Helpful Necessary

Appendix IX: Participant Infographic

Thank You for Your Participation!

Study: Preliminary validation of a novel genetic knowledge scale for familial hypercholesterolemia: evaluation of face validity and core concepts

Study Team: Emily Moss, Dr. Susan Christian, Dr. Jeffrey Wigle, Dr. Kim Mitchell, & Claudia Carriles Landry

Why did we conduct this study?

The purpose of this study was to....

1. Evaluate the clarity and importance of 8 true or false knowledge questions about familial hypercholesterolemia (FH)
2. Explore the factors that impact a patient's decision to have genetic testing for FH

Your Feedback

Your feedback was an essential part of ensuring the questions in the FH knowledge scale are written clearly, and that the concepts covered by the knowledge scale are important for patients to understand before making a decision about genetic testing.

We learned that genetic testing **and** genetic counselling for FH can empower patients with useful information about their health, and the health of their family members. We identified that common barriers are time, awareness of genetic services, and the potential impact of a genetic test result on insurance. These barriers can limit patient access to genetic testing for FH. (Figure 1)

Research Impact

The FH knowledge scale will be used as part of a larger survey to assess whether patients are making informed decisions about genetic testing for FH.

Overall, the outcomes of this study showcase the experiences of the FH patient population with genetic services, and will contribute to future research supporting value-based and informed decision making.

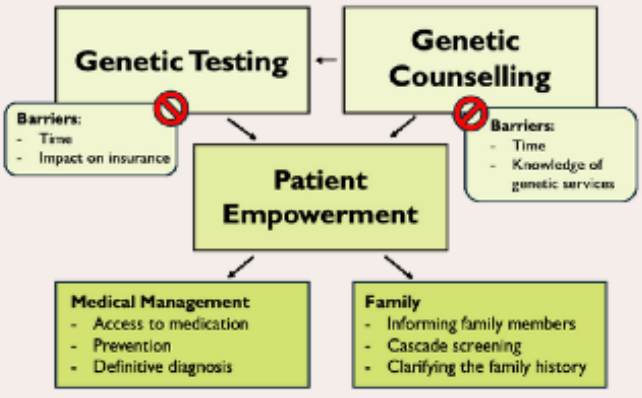


Figure 1: Summary of the key factors that impacted how participants made a decision about genetic testing for FH