Exploring the Diagnostic Journey of Individuals and Families with Mitochondrial Disease

by

Maria Vas

A Thesis submitted to the Faculty of Graduate Studies of
The University of Manitoba
in partial fulfilment of the requirements of the degree of

MASTER OF SCIENCE

Genetic Counselling Program
Department of Biochemistry & Medical Genetics
Max Rady College of Medicine
Rady Faculty of Health Sciences
University of Manitoba

ABSTRACT

Mitochondrial diseases (MtD) are amongst the most common inherited metabolic disorders, affecting approximately 1 in 5,000 individuals. The MtD diagnostic journey is often long and arduous due to the clinical and genetic heterogeneity of these conditions. Previous research on rare diseases shows that education, emotional support, and access to services are important to those navigating the diagnostic process. However, no studies to date have collectively assessed these needs specifically for MtD. Therefore, this study aimed to describe the diagnostic experience and explore in-depth the informational, psychological, and social needs of individuals and parents/caregivers of children with confirmed MtD. This study followed an embedded mixed-methods design, where participants completed surveys to detail their diagnostic journey and semi-structured interviews to delve deeper into these experiences. Seventeen affected individuals and parents/caregivers completed a survey, and twelve of these participants completed an interview.

The diagnostic journey was conceptualized to unfold in stages, with the number of specialists consulted and time to diagnosis being less than initially anticipated. Providers, the Internet, and personal networks were key sources of information and support, while support organizations and groups were found to be the least accessed. Participants described needing more information and support throughout the diagnostic process. Information and support resources for MtD understandably became more available upon diagnosis. However, the general lack of knowledge surrounding MtD meant uncertainty remained post-diagnosis. Psychological consequences of the journey were significant and heavily intertwined with the desire for an answer. Social needs extended beyond the medical setting and were systematically unmet. Overall, participant needs evolved throughout the diagnostic journey and continued to change post-diagnosis. Foundational to the experiences and needs identified was the patient-provider relationship, mainly with genetics and neurology providers, which played a central role in how the journey was remembered and the extent to which participants felt supported.

This study describes the complexities of the MtD diagnostic journey and highlights gaps in informational, psychological, and social supports. To improve the provision of MtD care, participant-driven recommendations focusing on assessment of needs and meaningful inclusion of patients and families in discussion and decision-making are presented.

ACKNOWLEDGEMENTS

I would like to express my sincerest appreciation to the participants. Thank you to each of you for your trust in sharing your journey with me. Your openness, resilience, and commitment to furthering knowledge on this topic are admired and appreciated.

To my supervisor, Jessica Hartley, thank you for your unwavering support, dedication, and mentorship, which have been instrumental in my growth as a researcher and a clinician. You reminded me to see the forest when I was stuck in the trees, for which I am grateful beyond measure. I would also like to extend my deepest gratitude to my committee members. To Dr. Gayle Halas, thank you for your thoughtful feedback and encouragement throughout this process, which inspired an abject appreciation for qualitative research. To Dr. Patrick Frosk, thank you for sharing your knowledge and encouraging me to think beyond the box; I have enjoyed learning from you throughout this program. To Dr. Susan Christian, I am grateful for your research expertise and for prompting me to consider the translational piece of this work.

Thank you to those who took an interest in this research and contributed in immeasurable ways. To Dr. Samantha Marin, for your expertise and guidance and for introducing me to the Mito community. To Gisèle Hansen, for sharing your insights and advising on this research. To Kate Murray and MitoCanada, for your partnership and dedication to raising the voices of patients and families with mitochondrial disease. To Devin Shuman, for taking the time to provide feedback and for your overall guidance.

I would also like to express my gratitude to Scarlett Chappell for volunteering her time to review charts, Loring Chuchmach for his assistance with quantitative data analysis, and Carrie Costello for her pivotal feedback early on the development of this project.

To Narin and Katherine, your friendship and support have meant the world. I would not have wanted to go through this process with anyone else. To our second years, Cassie, Dorothy, and Natasha and our first years, Michaela, Michelle, and Alyssa, I am beyond thankful to have shared this experience with all of you. And to Spencer, Tis, and Liumei, thank you for sharing in the moments that made Winnipeg feel like home.

To my family and friends back home, thank you for cheering me on from afar; knowing I had your unwavering support made this possible. And finally, to Marco, who reminded me that I was capable, first from across the country and then across the globe. Thank you for your unconditional love and for believing in me when I needed it most.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

CMC	Cognitively mature child
CoQ10	Coenzyme Q10
CPEO	Chronic progressive external ophthalmoplegia
IPA	Interpretative phenomenological analysis
GETs	Group experiential themes
KSS	Kearns-Sayre syndrome
KT	Knowledge translation
LHON	Leber hereditary optic neuropathy
MCN	Mitochondrial Care Network
MELAS	Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes
MERRF	Myoclonic epilepsy with ragged red fibres
MIDD	Maternally-inherited diabetes and deafness
MMS	Mitochondrial Medicine Society
MNGIE	Mitochondrial neurogastrointestinal encephalopathy
MtD	Mitochondrial disease(s)
mtDNA	Mitochondrial DNA
NARP	Neurogenic muscle weakness, ataxia, and retinitis pigmentosa
nDNA	Nuclear DNA
PCP	Primary care provider
PETs	Personal experiential themes
PI	Principal investigator
RD	Rare disease
SNHL	Sensorineural hearing loss

CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 INTRODUCTION

Mitochondrial diseases (MtD) are amongst the most common inherited inborn errors of metabolism, affecting approximately 1 in 5,000 individuals (Parikh et al., 2015). The diagnosis of MtD is challenging due to the clinical and genetic variability seen within this group of conditions (Chinnery, 2021). As a result, individuals are known to endure a lengthy and onerous diagnostic journey (Grier et al., 2018). Given that establishing an MtD diagnosis is complex, it is essential to understand how to best provide support throughout the diagnostic journey. Few studies have addressed this topic; however, studies within the rare disease realm have shown that education and psychological support, as well as access to support services, are important to individuals and families who have undergone the diagnostic process (Anderson et al., 2013; Lewis et al., 2010; Zurynski et al., 2017). Additionally, the ways in which healthcare providers communicate with patients during diagnosis are critical (Merker et al., 2021). While there are likely similarities between the MtD diagnostic experience and that of other rare diseases, how MtD are situated within the rare disease literature has not been previously investigated. It is important to consider that the MtD experience may not necessarily be aligned with that of the rare disease community, as depicted by previous studies which found that participants affected by MtD had poorer psychological wellbeing and coping efficacy compared to participants impacted by other chronic conditions (Senger et al., 2016a, 2016b; van de Loo et al., 2020).

Currently, there is a gap in the knowledge pertaining to the experiences and needs of patients and families throughout the MtD diagnostic journey. Therefore, this study aimed to appreciate the diagnostic experiences and explore in-depth the informational, psychological, and social needs of individuals and parents/caregivers who have received an MtD diagnosis in Manitoba in order to improve care for those navigating this journey. To our knowledge, this study was the first in Canada to explore the diagnostic experiences of patients and parents/caregivers with a molecular diagnosis of MtD, in the timeframe from the decision to seek care to receipt of a final diagnosis.

1.2 MITOCHONDRIAL DISEASES

1.2.1 Overview of Primary Mitochondrial Disease

MtD are a group of clinically and genetically heterogeneous disorders that arise from disruptions in cellular energy production (Chinnery, 2021). Although rare individually, collectively, they are amongst the most common inborn errors of metabolism (Schlieben & Prokisch, 2020). Though MtD are approximated to affect 1 in 5,000 individuals (Parikh et al., 2015), their prevalence is likely underestimated due to the challenges associated with establishing a diagnosis (Saneto, 2020). Mitochondrial dysfunction can be primary or secondary. Primary mitochondrial disease is caused by pathogenic and likely pathogenic variants that impact the structure and or function of mitochondria. In contrast, secondary mitochondrial dysfunction can be inherited or acquired and does not directly impact the process of oxidative phosphorylation (Niyazov et al., 2016).

Pathogenic and likely pathogenic variants in both nuclear and mitochondrial genes can give rise to MtD. As such, multiple patterns of inheritance are possible including, maternal, autosomal recessive, autosomal dominant, X-linked, or *de novo* occurrences (Chinnery, 2021). Interpretation of variants in mtDNA is complicated by heteroplasmy. Heteroplasmy refers to the proportion of wildtype and abnormal mitochondria in a cell (Alston et al., 2017; Stewart & Chinnery, 2015). Heteroplasmy level is thought to impact the severity of MtD, although this concept is poorly understood (Chinnery, 2021; Stewart & Chinnery, 2015). It is generally accepted that a heteroplasmy level greater than 60-80% is necessary for the clinical manifestation of MtD (Chinnery, 2021; Stewart & Chinnery, 2015). However, the threshold at which abnormal mtDNA causes disease is not well characterized and several exceptions exist (Schlieben & Prokisch, 2020). Furthermore, studies have identified mtDNA heteroplasmy to be quite common amongst the general population, arising as somatic variants over the life course (Sondheimer et al., 2011). This finding further challenges efforts to define a heteroplasmy threshold for pathogenicity.

To date, pathogenic variants in over 400 genes have been associated with MtD, mainly those that function in oxidative phosphorylation biogenesis, mitochondrial metabolism and homeostasis, and mitochondrial DNA replication and expression (Schlieben & Prokisch, 2020). Despite associations between these numerous genes and MtD, it is not well understood how

several of these genes contribute to disease and whether they are associated with primary mitochondrial dysfunction, leading to inconsistencies in annotation and reporting (Falk et al., 2020; Frazier et al., 2019; S. Rahman, 2020). These inconsistencies showcase the limited understanding of MtD genetics which, in addition to the phenotypic overlap and lack of reliable biomarkers to guide clinical recognition of MtD, lead to challenges in diagnosis (Stenton & Prokisch, 2020). Our understanding of MtD genetics is further convoluted by unclear genotype-phenotype correlations and pleiotropy (Schlieben & Prokisch, 2020). For instance, the mtDNA genotype m.3243A>G in the *MT-TL1* gene has been associated with MELAS, CPEO, and MIDD phenotypes (Nesbitt et al., 2013). Therefore, while remarkable advances have been made in the molecular era of MtD, it is unlikely that next-generation sequencing alone can improve MtD ascertainment as there is still much to be elucidated regarding the genetics of MtD (DaRe et al., 2013).

As with genetic etiology and inheritance, the associated age of onset, pattern of symptoms, and progression of MtD are variable. MtD can begin at any age; however, onset tends to be observed in infancy/childhood and adolescence/adulthood, suggestive of a bimodal distribution (Chinnery, 2021). While it was previously thought that pediatric-onset MtD are most often caused by nDNA variants and adult-onset MtD by mtDNA variants, recent evidence suggests the opposite phenomenon to be true (Chinnery, 2021). With regard to symptom pattern, MtD are highly variable in their clinical presentation, as illustrated by Figure 1.1. MtD can affect multiple systems, with organs and tissues that are highly dependent on aerobic metabolism tending to be impacted or, less commonly, be confined to a single organ or tissue, such as the eye in Leber Hereditary Optic Neuropathy (LHON; Chinnery, 2021). Common clinical manifestations of MtD include myopathy, exercise intolerance, sensorineural hearing loss (SNHL), diabetes mellitus, cardiomyopathy, stroke-like episodes, ataxia, pigmentary retinopathy, and external ophthalmoplegia (Chinnery, 2021). The majority of these manifestations are non-specific, and the associated differential diagnosis for these symptoms is broad, contributing to the difficulty in their clinical recognition (Paik et al., 2019). Despite the clinical variability of MtD, there are a handful of well-described syndromes, the features of which are outlined in Table 1.1.

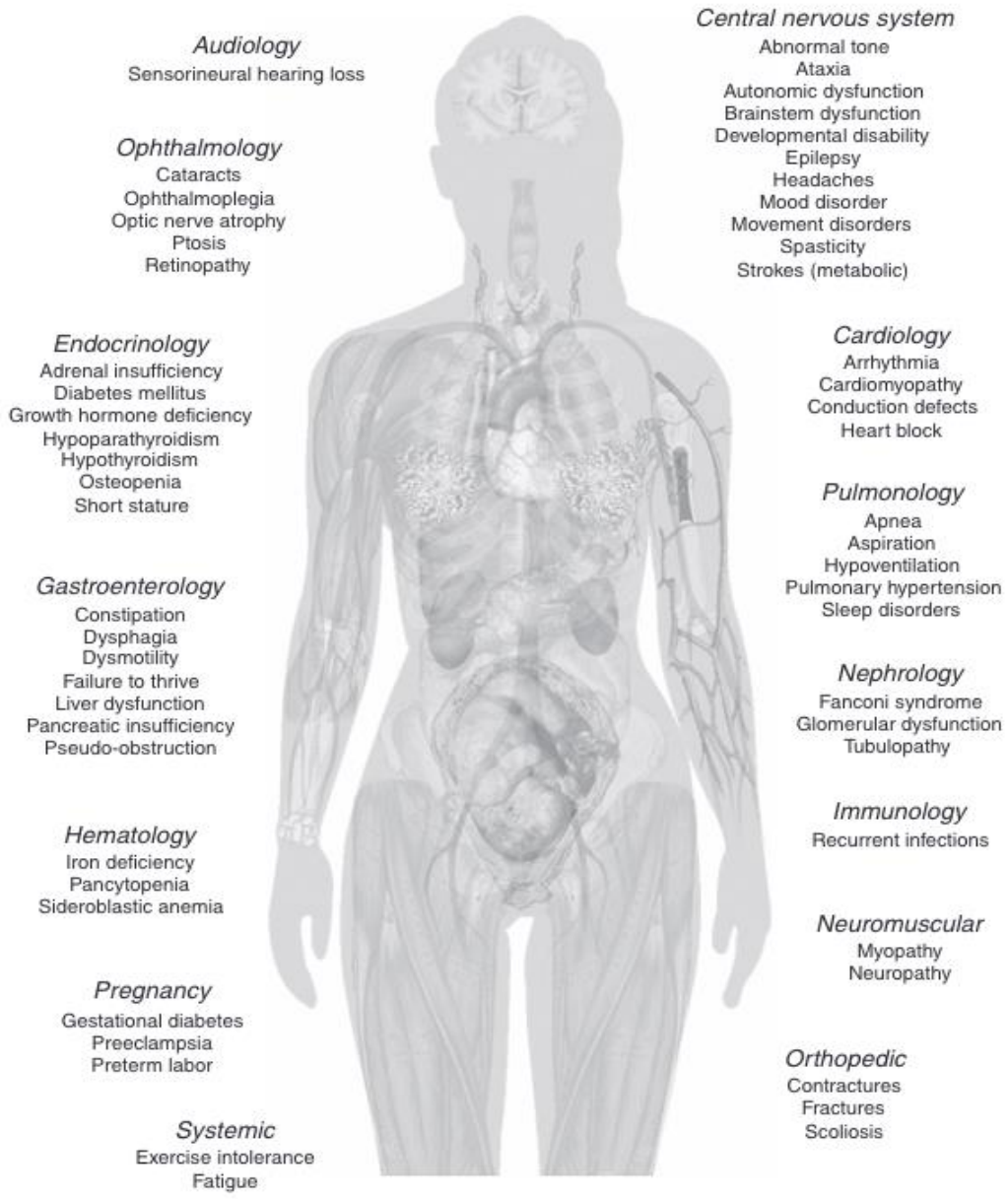

Figure 1.1. Overview of affected systems in MtD © S. Parikh et al., 2017. Used with permission from Elsevier.

Table 1.1. Features of well-described MtD syndromes. Adapted from *Table 1. Classical mitochondrial syndromes due to mtDNA- and nuclear-encoded variants* © R.P. Saneto, 2020. CC BY 4.0. Features updated with information from Chinnery, 2021; El-Hattab et al., 2018; Goldstein & Falk, 2019; S. Rahman, 2020; Thorburn et al., 2017; Velez-Bartolomei et al., 2021; Yu-Wai-Man & Chinnery, 2021.

Syndrome	Primary Features	mtDNA/nDNA	Age of Onset
Pearson syndrome	Exocrine pancreatic dysfunction, sideroblastic anemia	mtDNA	Infancy
Kearns-Sayre syndrome	Progressive external ophthalmoplegia, ptosis, retinitis pigmentosa, cardiac conduction abnormality	mtDNA	Childhood
CPEO	Ophthalmoplegia, ptosis, myopathy	mtDNA/nDNA	Adult
LHON	Optic atrophy	mtDNA	Adolescence / Adult
Leigh syndrome	Subacute necrotizing encephalomyelopathy, psychomotor regression, seizures	mtDNA/nDNA	Infancy / Childhood
NARP	Retinitis pigmentosa, peripheral neuropathy, ataxia	mtDNA	Adolescence / Adult
MELAS	Stroke-like episodes, encephalopathy with seizures and/or dementia, migraines, myopathy, vision loss, SNHL, peripheral neuropathy	mtDNA	Adolescence / Adult
MIDD	Diabetes mellitus, SNHL	mtDNA	Adolescence / Adult
MERRF	Myoclonus, seizures, myopathy, ataxia, ragged red fibres in muscle biopsy	mtDNA	Adolescence / Adult
Alpers-Huttenlocher syndrome	Seizures, hepatopathy, psychomotor regression, peripheral neuropathy	nDNA	Infancy / Childhood
Barth syndrome	Dilated cardiomyopathy, cyclic neutropenia, myopathy	nDNA	Adult
MNGIE	Leukoencephalopathy, gastrointestinal dysmotility, ophthalmoplegia, ptosis, cachexia, peripheral neuropathy	nDNA	Adolescence / Adult

SNHL: Sensorineural hearing loss. CPEO: Chronic progressive external ophthalmoplegia. LHON: Leber hereditary optic neuropathy. NARP: Neurogenic muscle weakness, ataxia, and retinitis pigmentosa. MELAS: Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes. MIDD: Maternally-inherited diabetes and deafness. MERRF: Myoclonic epilepsy with ragged red fibres. MNGIE: Mitochondrial neurogastrointestinal encephalopathy.

1.2.2 Diagnosis of MtD

In 2013, the Mitochondrial Medicine Society (MMS), an international group working towards advancements in mitochondrial medicine (Mitochondrial Medicine Society, 1998), published two articles reporting results from a series of surveys completed by MtD physicians across North America (Parikh et al., 2013, 2014). The primary goal of this research was to better understand the landscape of MtD care in the hope of developing consensus guidelines. This research found that while there was overlap in approaches to diagnosis, treatment, and management of MtD, the lack of standardized care guidelines resulted in variability in practice patterns. Since these findings were published, the MMS has developed consensus statements for the diagnosis, management, and care of those with MtD (Parikh et al., 2015, 2017).

Consensus guidelines for MtD diagnosis outline comprehensive biochemical testing of blood, urine, and cerebral spinal fluid, genetic testing, pathology and biochemical testing of tissue, and neuroimaging (Parikh et al., 2015). Previously, biochemical testing in tissue, most often skeletal muscle, was considered the gold standard for diagnostic testing (Parikh et al., 2015). However, with advancements in genetic and genomic technologies, genetic testing has become the gold standard for MtD diagnosis (Parikh et al., 2015). Genetic testing for MtD is advantageous because it is non-invasive and current next-generation sequencing technologies permit both mtDNA and nDNA to be sequenced in a rapid and cost-effective manner (Saneto, 2020). In fact, depending on the methodology, heteroplasmy can now be detected at levels as low as 1-2% (Saneto, 2020). Despite this progress, there are caveats, particularly when it comes to detecting pathogenic variants in mtDNA as different tissues may have varying degrees of heteroplasmy (Saneto, 2020). Therefore, DNA derived from blood may not be informative, warranting follow-up testing in other tissues or in urine (Parikh et al., 2015).

In Manitoba, the diagnostic testing approach for MtD begins with biochemical testing in blood and urine, in line with published guidelines (P. Frosk, personal communication, December 2021). Genetic testing is phenotype-driven and may be requested concurrently or as a second-tier approach. This testing begins with either mtDNA sequencing in urine or blood, a panel of nDNA genes in blood, or a combination of both approaches. If biochemical and targeted genetic testing is unrevealing, but a mitochondrial condition is highly suspected, whole-exome sequencing may be requested.

1.2.3 Treatment and Management of MtD

Currently, there is no cure or specific treatment for MtD. The most recent Cochrane review on this subject concluded that there is insufficient evidence that any of the MtD treatments proposed to date are efficacious (Pfeffer et al., 2012). Current therapies are limited to the mitochondrial "mito" cocktail, endurance exercise therapy, and symptom-based treatment, including for acute stroke and catabolic illness (Parikh et al., 2015).

The "mito cocktail" is a combination of vitamins and cofactors. Common agents prescribed as part of this cocktail include Coenzyme Q10 (CoQ10), L-carnitine, creatine, alpha-lipoic acid, B vitamins, vitamin C, and vitamin E (Parikh et al., 2015). Empiric evidence regarding the efficacy of various components of the mito cocktail is limited or lacking altogether due to the paucity of informative biomarkers to measure therapeutic effect and limitations of previously conducted clinical trials (Pfeffer et al., 2012). A few placebo-controlled, double-blinded clinical trials for CoQ10 have been conducted, but no significant clinical improvements were reported (Pfeffer et al., 2012). Furthermore, endurance exercise therapy has shown some promise for mitochondrial myopathies (Parikh et al., 2015, 2017; Pfeffer et al., 2012). Clinical trials investigating exercise therapy for MtD showed an increase in mitochondrial content, antioxidant and muscle mitochondrial enzyme activity, oxygen uptake, as well as muscle strength (Parikh et al., 2015). Notably, no adverse findings, such as elevated creatine kinase or musculoskeletal injury, were seen as a result of exercise therapy (Parikh et al., 2015).

Despite the dearth of current efficacious treatments for MtD, several clinical trials for emerging therapies are ongoing (J. Rahman & Rahman, 2018). In the meantime, treatment for these conditions remains largely supportive. In 2017, the MMS's Consensus Criteria Committee released standards for the care of patients with MtD (Parikh et al., 2017). These standards outline thorough screening guidelines to be followed for patients at the time of diagnosis and subsequently every one to two years, or as needed, depending on the presentation. Additionally, this publication provides guidance on medication contraindications and illness, anesthesia, and stroke management (Parikh et al., 2017). Overall, there is variability in approaches to the diagnosis, treatment, and management of MtD. While there have been several consensus statements published regarding MtD care, there remains a need for stronger evidence on which to base these recommendations.

1.2.4 Challenges in MtD Care

The clinical and genetic heterogeneity of MtD makes it challenging to apply a standardized approach to the care of those living with these conditions. As such, the practice patterns of MtD providers across North America reflect variability in approaches to care. For instance, in a recent survey of Canadian physicians providing MtD care, 75% of respondents completed genetic testing as part of the work-up, and 30% indicated utilizing genetic testing as a first-line test for most of their patients (Paik et al., 2019). These physicians described two significant barriers in making a diagnosis: recognition that non-specific symptoms are due to MtD (71%) and accessing funding for genetic testing (at least 50%). Another study of physicians in the United States and Canada found that different combinations of therapeutic agents are prescribed as part of the mito cocktail (Parikh et al., 2013). Sixty-three percent of respondents were found to prescribe three to six agents, and 69% indicated prescribing a unique combination of vitamins and cofactors. In Canada specifically, 49% of physicians recommended the mito cocktail to patients but again, there is variation in the agents recommended (Paik et al., 2019). Overall, while MtD care was in line with published consensus statements, these variations appear to be representative of the lack of underlying evidence on which to base MtD diagnosis and management (Paik et al., 2019).

The need for coordinated multidisciplinary care for MtD has resulted in the development of the Mitochondrial Care Network (MCN) across various sites in the United States (Karaa et al., 2019a, 2019b). Patients, parents/caregivers, and physicians were engaged as stakeholders in the conception of this network. MCN priorities identified by patients and parents/caregivers included a multidisciplinary team led by a geneticist or neurologist (indicated by 100% of respondents), care coordination (68%), social support (47%), education about MtD (42%), and accessible information and services (42%). The majority of physicians (93%) surveyed were in support of the establishment of an MCN, and all physicians agreed that a multidisciplinary team was necessary. Thus, the MCN was established in 2018 and today, there are 18 MCN sites and three affiliate sites (Mitochondrial Care Network, 2018). These sites strive to be “centres for excellence” in MtD care, with multidisciplinary teams involved in the clinical care of affected adults and children, as well as in MtD research endeavours (Karaa et al., 2019a).

Several patient registries have been developed to better understand the genetic and clinical features of MtD and, in turn, address gaps in the diagnosis, treatment, and management of these conditions. The United Mitochondrial Disease Foundation’s “Mitochondrial Disease Community

Registry" is an international patient registry launched in 2014 that aims to collect data from the patient community (United Mitochondrial Disease Foundation, 2014; Zilber & Yeske, 2020). In 2017, the Rare Disease Clinical Research Network introduced the "North American Mitochondrial Disease Consortium Patient Registry and Biorepository" to facilitate MtD research through ready access to clinical data (North American Mitochondrial Disease Consortium, 2017). Recently, MitoCanada launched its "Patient Contact Registry" to elicit the needs and experiences of Canadian patients with MtD and advance research efforts in this context (MitoCanada Foundation, 2021). Overall, it is evident that there are significant efforts underway to progress our understanding of MtD and, in turn, improve MtD care. Until then, challenges remain for patients and families navigating the diagnostic journey. Therefore, the rest of this chapter will explore what is known about the experiences and needs of those on this journey for both MtD and rare diseases in general.

1.3 OVERVIEW OF MITOCHONDRIAL DISEASE LITERATURE

1.3.1 The MtD Diagnostic Journey

While it is generally known that the journey to an MtD diagnosis is long and arduous, there is a dearth of research on this topic. A handful of previous studies have sought to elucidate the practice patterns of physicians providing MtD care across the United States and Canada (Paik et al., 2019; Parikh et al., 2013, 2014). However, to date, only one article characterizing the patients' experience of the diagnostic journey has been published. Grier et al. (2018) conducted a cross-sectional survey-based study of 210 patients and parents/caregivers enrolled in the Rare Disease Clinical Research Network's contact registry who were self-reported to have a biochemical deficiency or MtD diagnosis. Participants indicated that they consulted numerous specialists (average 8.19), received conflicting diagnoses (54.6% received ≥1 other diagnosis), and underwent extensive testing along the diagnostic journey. It was most common for participants to consult their primary care provider (PCP) about symptom onset, and the most commonly reported initial symptoms were weakness (62.4%) and fatigue (56.2%). With respect to testing, participants reported having received blood tests (84.8%), a muscle biopsy (71%), neuroimaging (60.5%), urine organic acid testing (38.6%), mtDNA sequencing (39.5%), nDNA sequencing (19%), and whole-exome sequencing (11.4%). Most participants received their diagnosis from a neurologist (55.2%), followed by geneticists (18.2%), and metabolic specialists

(11.8%). This landmark paper from Grier and colleagues provided a general overview of the MtD diagnostic journey. This study's survey questions were targeted and close-ended, which improved data quality and reduced ambiguity. Moreover, a favourable sample size was achieved. Despite the strengths, there are limitations in the generalizability of these findings. For instance, as the registry data was self-reported, recall bias is possible, as is the potential for misreported information. Additionally, this study was unable to report the time to diagnosis as intended. Similarly, genetic etiology was not collected, nor was the study limited to primary mitochondrial disease.

No additional studies have yet been published on the diagnostic journey specifically for MtD. However, demographic information collected by Senger et al. (2016b) as part of a quantitative study on stress and coping of parents of children with MtD reported some features of the journey. Parents in this study reported that their children had an average of six organs involved in their clinical presentation and saw an average of seven different specialists prior to receiving a diagnosis. The mean age of symptom onset was two years, and the mean age at diagnosis was six years, resulting in a mean time to diagnosis of four years for this cohort. However, the diagnosis was not definitive in some cases. Overall, this research shows that investigations into the diagnostic journey for MtD are significantly lacking, particularly within a Canadian context.

1.3.2 Psychological and Social Needs of Families with MtD

Only five studies to date have investigated the experiences and needs of children and parents/caregivers with MtD. Most of the studies on this topic have been quantitative and focused on the psychological impacts and manifestations of the MtD experience.

1.3.2.1 Psychological Functioning and Diagnosis in Children

One study investigated psychological functioning in 122 children with a suspected MtD diagnosis using validated scales to measure the pediatric quality of life, child behaviour, parental stress, and parental social reliance (van de Loo et al., 2020). The scales were administered at two timepoints: during the diagnostic process and upon receipt of a diagnosis. This study found that children being worked up for MtD reported a lower quality of life compared to the general population and more physical issues than those who are chronically impacted by other

conditions. Similarly, children were found to have more behavioural issues and internalizing problems (i.e. low self-esteem, depression, and anxiety) compared to the general population. After the diagnostic work-up, 6% of children received a molecular MtD diagnosis, 26% received an inconclusive muscle biopsy result, 54.9% remained undiagnosed, and 13.2% were diagnosed with a different condition. Interestingly, regardless of whether a diagnosis had been received, there were no significant differences in pediatric quality of life and behavioural issues. However, increased internalizing problems were reported in children without a diagnosis. These findings highlight the importance of providing support along the diagnostic journey regardless of whether a final diagnosis is established, as undiagnosed children may be particularly susceptible to psychological impacts due to persistent uncertainty.

1.3.2.2 Psychological Consequences in Parents/Caregivers

The MtD parental experience has been more frequently studied than the experience of children. Parents of children who were undergoing investigation for MtD reported increased stress in comparison to the general population (van de Loo et al., 2020). These parents also reported needing more social support than both those in the general population and those with children with rheumatoid arthritis. Furthermore, parents identified that the social support that they did receive was insufficient.

Senger et al. (2016b) investigated the stressors and coping strategies of parents of children with MtD. Using a quantitative questionnaire, which included demographics and two validated psychological scales, this research found that MtD parents experienced significant levels of stress. These stress levels were higher compared to parents of children with other chronic conditions such as cancer, diabetes, bladder exstrophy, sickle cell disease, and irritable bowel syndrome. Parents who coped using familial and social support had lower stress scores than those who coped by seeking to understand healthcare information. This finding is interesting as it raises the question of whether an emotion-focused coping style may be more adaptive than a problem-focused coping style in the context of MtD, possibly given that the lack of information on MtD may result in increased stress for parents who cope through information-seeking.

Another study, which worked with the same cohort, examined the parental experience of caring for a child being investigated for MtD (Senger et al., 2016a). Once again, demographic characteristics and responses to two validated scales were collected. Findings exhibited that not

only did parents experience high levels of illness-related feelings of guilt, worry, sorrow, anger, and long-term uncertainty but also that these levels were significantly correlated with parental stress. These scores were higher than for parents of children with other chronic conditions. As well, parents reported they had significantly fewer emotional resources to cope with stress compared to parents of children with other chronic conditions. This sister study demonstrated the psychological toll and increased stress associated with living with MtD.

Finally, an Australian study developed a survey using validated tools to assess health service use and needs for psychological support and social services among families living with a rare pediatric metabolic condition (Anderson et al., 2013). Twelve of the 30 study participants (40%) had a diagnosis of MtD. The study found that receiving the final diagnosis resulted in moderate to high psychosocial impact, as measured by validated tools. Thirteen percent of participants reported feeling the final diagnosis was delivered in an insensitive manner and indicated the desire for further informational and psychological support. Notably, this study also found that the majority of families (87%) wanted information about peer support groups, but only 43% received this information.

1.3.2.3 Familial Spillover Effects

A recent study aimed to estimate the parental health spillover effects of rare pediatric conditions, including MtD (Wu et al., 2020). Spillover effects are the "health-related quality of life effects for caregivers and family members of [those who are ill]" (Wittenberg et al., 2019, p. 475). Wu et al. (2020) measured pediatric and parental health-related quality of life using a series of validated scales. Parents were found to have a significantly lower health-related quality of life compared to the general population. There was a positive association between parental and child health, indicating the existence of significant health spillover from child to parent. While this study was not specific to children with MtD, it did emphasize the importance of addressing the family as a whole to improve the diagnosis and management of children with rare conditions. Although only a portion of study participants had MtD, it could be hypothesized that familial spillover holds true for families with MtD.

1.3.3 Informational Needs of Families with MtD

Currently, only one study has aimed to explore the informational and educational needs of MtD parents. A sequential exploratory mixed-methods pilot study at four stages along the diagnostic journey: 1) initial specialist referral or hospitalization, 2) examinations and investigations, 3) undergoing diagnostic testing (muscle biopsy exclusively due to the year of study), and 4) the period until the final diagnosis was received (Noorda et al., 2007). Noorda and colleagues (2007) found that the attitude and availability of physicians were most important in the provision of information with a central individual or place available to direct any questions. Also, parents preferred to receive information both in oral and written form. In this study, findings from focus group interviews and surveys suggested that the informational needs of parents increased throughout the phases of the diagnostic journey. This study concluded that there is a gap in information provision for parents of children with MtD along the diagnostic journey. Despite the authors calling for further study into the needs and issues of patients and their families to improve quality of life and MtD care over a decade ago, no additional studies have investigated this topic.

In summary, the research investigating the experiences and needs of children with MtD and their parents/caregivers highlights the psychological toll of MtD but is largely focused on psychological impacts on parents/caregivers rather than on children. While this is understandable given the clinical features and severity of certain pediatric-onset MtD, this illuminates a gap in the literature. The few published articles that exist on this topic have found parents of children with MtD to have increased levels of stress, negative feelings related to illness, and lower health-related quality of life. Additionally, there is some evidence to suggest that emotion-focused coping may be more adaptive amongst parents/caregivers of children with MtD than problem-focused coping, specifically information-seeking. Further, the informational needs of the MtD patient population are understudied.

1.3.4 Experiences and Needs of Adults with MtD

The adult MtD patient population has been significantly less studied than the parent/caregiver population. There is little known about the specific needs and experiences of affected adults throughout the diagnostic journey and beyond. In fact, only four studies have been published in the last 20 years on this topic. These studies have focused on the patient-

provider relationship (PPR), access to medical and social support, and issues in adjusting to an MtD diagnosis.

1.3.4.1 The Importance of the Patient-Provider Relationship

Recently, Zilber & Yeske (2020) published preliminary data collected from the initial four years of the Mitochondrial Disease Community Registry project. This report highlighted the most important needs during diagnosis and clinical care as identified by patients. A total of 1,428 participants completed a non-validated survey containing both closed and open-ended responses. Participants identified the PPR to be the most significant part of the experience, including throughout diagnosis. Additional diagnostic and clinical needs identified by participants included further research into effective MtD treatment, an appreciation for the impacts of the condition beyond the medical context, and shifting the medical focus to enhancing patient quality of life. The authors advocated for future studies to identify ways in which patients can be better supported and relationships with healthcare providers improved.

To elucidate how adults with MtD construct knowledge within the context of the PPR, O'Riley (2003) interviewed 13 participants. Participants described the responsibility of educating healthcare providers and the general public on their condition due to limited knowledge on MtD. Interestingly, participants constructed knowledge about their needs based on their lived experiences to advocate for validation from healthcare providers and navigate unpleasant feelings such as uncertainty, vulnerability, and frustration.

1.3.4.2 Perceived Barriers to Social Support

Krieg et al. (2016) conducted a comparative study to determine whether there were perceived differences in access to social and medical supports between adults with and without a genetic confirmation of their diagnosis. This cross-sectional study surveyed 201 participants (55 with genetically-confirmed MtD and 146 with non-genetically confirmed MtD) using both closed and open-ended questions. Quantitative findings revealed that both groups felt that medical and social supports were lacking. However, those without a genetic confirmation for their condition perceived there to be fewer medical and social supports available compared to those with genetic confirmation. Additionally, both groups indicated that they felt somewhat included within MtD support communities but the group without genetic confirmation felt

significantly less included. Four problem areas emerged from the qualitative data across both groups: 1) barriers to accessing medical treatments exist, 2) lack of knowledge of MtD gives rise to uncertainty, 3) lack of appropriate supports, particularly for adults, and 4) invalidation of symptoms and the disease experience. Participants in both groups identified their main source of support as their family. Conversely, participants in both groups turned to support/advocacy groups for support the least. This work showed that there is a lack of effective and specific resources for adults with MtD and that offering pan-MtD supports may not be sufficient given the heterogeneity among this group of conditions. Regardless of genetic confirmation of diagnosis, there is a need for improved resources for medical, informational, and social support for adults with MtD.

1.3.4.3 Experiences of Living with MtD

A qualitative study was conducted with the adult MtD population, which aimed to explore issues experienced by this group (Noorda et al., 2012). Sixteen participants with clearly defined MtD (i.e. MELAS, MERRF, Leigh syndrome) were interviewed, and a central theme of continued loss was revealed. Namely, loss of energy, loss of independence/autonomy, loss of social participation, loss of personal identity, loss of dreams and future, lack of healthcare, and difficulties in coping and adjustment. The authors theorized that the physical, psychological, social, and spiritual consequences of the MtD experience pave the way to a sense of continued and overwhelming loss as individuals adjusted to their diagnosis. They proposed that awareness of these issues could improve MtD care and outcomes for those affected. This study was the first and only qualitative study which sought to appreciate the challenges that adults with MtD face.

1.3.5 Summary

Ultimately, the literature regarding the needs and experiences of those with MtD is scarce. Existent research highlights the psychological toll of MtD but is largely focused on psychological impacts in parents/caregivers rather than in children and in adults. Therefore, within this body of literature, the adult experience and the voices of children are substantially underrepresented compared to the parental experience. While it is important to understand the parental experience, it is likely that children and adults with MtD construct different understandings of the MtD journey and likely have divergent needs. These needs have not been

characterized at present. Lastly, the majority of the studies summarized above have been quantitative in nature, with only a handful seeking to understand the experience of patients through qualitative methods.

1.4 OVERVIEW OF RARE DISEASE LITERATURE

Given the challenges with the diagnosis and management of MtD, it is imperative to understand how individuals and families can be better supported by healthcare providers in their experiences with MtD. However, due to the scarcity of MtD literature on this topic, it may be helpful to turn to the wider rare disease (RD) literature to offer guidance on possible shared needs and experiences. Thus, this section will review key studies characterizing the diagnostic experience within the realm of RDs. Then, RD literature investigating the informational and educational, psychological, and social needs along the diagnostic journey will be summarized.

1.4.1 Perceived Delays in RD Diagnosis

Several studies have documented the shared experiences along the RD diagnostic journey and living with a rare condition. Generally, patients and families consult with numerous healthcare providers before receiving a diagnosis, resulting in an odyssey characterized by numerous specialist consultations, investigations, and several perceived diagnostic delays (Anderson et al., 2013; Blöß et al., 2017; Zurynski et al., 2017). Another study found that 38% of parents of children with an RD reported consulting three to five physicians prior to diagnosis, and 14% reported consulting six to ten (Anderson et al., 2013). Forty-three percent of parents thought that the diagnostic process was “delayed”, meaning that they felt the diagnosis could have been made sooner. A similar study reported that 38% of parents of children with RD met with six or more physicians prior to diagnosis, and 37% perceived a diagnostic delay (Zurynski et al., 2017). Consequences of perceived diagnostic delays included anxiety, frustration, stress, loss of reproductive confidence, disease progression, and delays in treatment or inappropriate treatment (Zurynski et al., 2017).

1.4.2 Psychological and Social Needs of Families with RDs

Shared psychological experiences have been reported within the context of RDs. For example, patients and parents/caregivers have described feeling dismissed by healthcare

providers throughout the diagnostic journey and feeling as though they do not have a central healthcare provider to whom they can turn to address questions (Bendixen & Houtrow, 2017; Blöß et al., 2017). Similarly, a systematic review looking at qualitative literature on the topic of living with RDs noted three common themes across the 21 studies identified: 1) physical and psychological consequences, 2) social aspects, and 3) healthcare experiences (von der Lippe et al., 2017). Physical and psychological consequences included how patients' lives had been impacted by their conditions, negative and positive emotions that accompany the RD experience, from depression to gratitude, and the diverse coping strategies that patients utilize to adapt to a new normal. Social aspects described the various ways in which patients and families decide to communicate their diagnoses to those in their lives, the stigma associated with having an RD, and receipt of emotional support from family and friends. Healthcare experiences included the lack of understanding about individual RDs and the inevitability of becoming the "expert patient." The theme of "expert patient/caregiver" who is responsible for coordinating care and sharing their understanding of the condition is prevalent within the RD literature, given the lack of knowledge surrounding rare conditions (Baumbusch et al., 2018; von der Lippe et al., 2017).

All in all, these studies showcase that despite the heterogeneity of conditions, there are shared experiences among patients and families living with RDs. As such, there is a need to examine whether these experiences are apparent among those living with MtD. When looking at the MtD and RD literature and drawing generalizations, there are several factors to consider. For instance, most participants in MtD and RD studies are White mothers of higher socioeconomic status, who likely with better access to resources and higher health literacy. Additionally, similar to the MtD literature, much of the RD studies presented focus on the experience of parents/caregivers of children, although there are significantly more studies that characterize the experiences of adults. Once again, children are underrepresented among RD study populations.

1.4.3 Challenges of Living Without a Diagnosis

Significant medical, psychological, and social challenges have been identified for those living without a diagnosis (Lewis et al., 2010; McConkie-Rosell et al., 2018; Spillmann et al., 2017; Yanes et al., 2017). For instance, parents of undiagnosed children were found to have higher rates of anxiety and depression as well as fewer perceived social supports, and poorer coping self-efficacy than parents of children with a diagnosis (McConkie-Rosell et al., 2018;

Yanes et al., 2017). Furthermore, parents described feeling fearful, worried, and frustrated when there was seemingly no explanation for health issues that their child was facing (Lewis et al., 2010). This "inner emotional experience" outlined by parents was accompanied by the "outer sociological experience" that was characterized by relationships with healthcare providers, access to support networks, adequate education for their children, as well as housing and insurance (Lewis et al., 2010). The experience of awaiting a diagnosis varied amongst adults and parents/caregivers (Spillmann et al., 2017). Using narrative analysis, Spillmann and colleagues (2017) found that among those without a diagnosis, affected individuals struggled to feel believed and validated in their experiences. Conversely, the main worry of parents of undiagnosed children was the chance that important details were being missed that may affect their child's medical management. Therefore, these two groups may have different needs when it comes to the provision of care and support by healthcare providers throughout this experience. Additionally, this research underscored the importance of providing support for those along the diagnostic journey when uncertainty, and the emotions that accompany it, are heightened.

1.4.4 Significance of a Diagnosis

There are numerous perceived benefits to receiving a diagnosis as described by patients and families. A diagnosis can reduce feelings of uncertainty and inform treatment and management options (Lewis et al., 2010; Pelentsov et al., 2016). Having a diagnosis has been viewed as a means of personal acceptance for patients and families. That is, patients and families reported a sense of validation that came with receiving a diagnosis (Carmichael et al., 2015), as well as improved coping and communication with others, including healthcare providers (Rosenthal et al., 2001; Withers et al., 2021). As well, the diagnosis has been viewed as a means of social acceptance that reduces barriers to accessing financial and social services and support resources (Carmichael et al., 2015; Lewis et al., 2010; Rosenthal et al., 2001; Withers et al., 2021). The label of a diagnosis has also been found to provide parents with direction in decision-making and facilitate access to services and specialists that were otherwise unavailable (Carmichael et al., 2015; Withers et al., 2021).

1.4.5 Persistent Uncertainty of RD

Though receiving a diagnosis has many perceived benefits, uncertainty remains, particularly in the case of RDs, as there is generally a dearth of information regarding the natural history of conditions and or limited treatment options available (Withers et al., 2021). This theme of evolving uncertainty is seen throughout the RD literature (Baumbusch et al., 2018; Donegan et al., 2021; Spillmann et al., 2017; von der Lippe et al., 2017; Withers et al., 2021) and seems to be a pillar of the RD diagnostic experience. While uncertainty tends to be linked to negative feelings, poor psychological wellbeing, and low coping efficacy (McConkie-Rosell et al., 2018; Yanes et al., 2017), the ability to tolerate uncertainty has been associated with better cognitive, emotional, and behavioural wellbeing (Strout et al., 2018; Withers et al., 2021). Although, it should be noted that studies of high methodological quality indicate the strongest association to be between uncertainty tolerance and better emotional wellbeing (Strout et al., 2018). The various ways in which people cope with the uncertainty and other challenges as part of the RD diagnostic experience have been studied (von der Lippe et al., 2017). Coping strategies include attempts to normalize or renormalize life through self-management, negotiating control through information-seeking, and downward comparison, a theory in which individuals cope by comparing their experiences to those who are perceived to be less fortunate (von der Lippe et al., 2017; Wills, 1981).

1.4.6 Needs Along the RD Diagnostic Journey

Information, psychological support, access to services and resources, as well as a strong PPR are eminent needs for patients and families at the time of diagnosis and throughout the process leading up to it. Much of the literature is focused on the time of diagnosis as opposed to the diagnostic process and experience. At the time of diagnosis, 72.1% of adults with RD indicated that they received limited or no information (Molster et al., 2016). Both adults with RD and parents/caregivers of children with RD indicated dissatisfaction with how the diagnosis was delivered (Anderson et al., 2013; Molster et al., 2016; Zurynski et al., 2017). The most commonly cited reasons for this dissatisfaction included little to no information provided about the condition or how to access relevant and available support services (Anderson et al., 2013; Molster et al., 2016; Zurynski et al., 2017), communication issues with healthcare providers (Anderson et al., 2013), and a lack of psychological support such as empathy (Anderson et al.,

2013; Zurynski et al., 2017). In one study, the majority of parents/caregivers felt that psychological support was necessary when delivering the diagnosis (Zurynski et al., 2017). Studies have advocated for genetic counselling for those navigating an RD diagnosis, as well as psychology and counselling referrals as necessary (Merker et al., 2021; Zurynski et al., 2017).

Patients report that receiving education about a condition, including etiology, natural history, prognosis, treatment and management, at the time of diagnosis is important (Merker et al., 2021). Furthermore, patients report that psychological support, including discussion of coping as well as trust, collaboration, and social-emotional rapport, is also a pertinent aspect of diagnostic communication with healthcare providers. These findings were echoed by Donegan and colleagues (2021), who piloted a patient education program for adults with a pituitary adenoma. After the program, participants had reduced anxiety scores as measured by validated scales and reported high satisfaction. Follow-up interviews with a subset of participants revealed that patient-provider communication and feeling included by healthcare providers in these discussions were key for improving the diagnostic experience. Furthermore, participants expressed a need for condition-specific information and the ability to discuss information accessed online with a healthcare provider to assess reliability.

1.4.7 Summary

Overall, the experiences and needs surrounding diagnosis have been well characterized within the RD literature. The RD diagnostic journey is lengthy and challenging, with perceived diagnostic delays and associated psychological and emotional consequences. For many, a diagnosis signified the ability to begin treatment and gain access to disease-specific information and supports. However, in many instances, uncertainty remained beyond the diagnosis due to the lack of knowledge on most RDs. Similar to what is known of the MtD diagnostic journey, it is evident that those with RDs also face challenges in obtaining a diagnosis. The RD literature has aimed to uncover the value that individuals and families place on the diagnosis and has identified informational, psychological, and social challenges associated with this process. It is likely that there is a significant overlap in the MtD and RD diagnostic experiences. However, this overlap has not yet been investigated.

1.5 KNOWLEDGE GAPS AND STUDY RATIONALE

Due to the clinical and genetic heterogeneity of MtD, patients and families may face a long and arduous diagnostic journey. There is a paucity of research characterizing this journey, and the few studies that have engaged this patient population to better understand the challenges and needs throughout diagnosis have had limitations in their scope pertaining to sample selection, inclusion criteria, and methods. While existing literature has strengthened our understanding of the impacts of MtD, it has yet to explore, in-depth, the psychological consequences of navigating the MtD diagnostic journey from the perspective of patients and families. Similarly, the informational and social needs of this population are understudied and appear to be insufficiently addressed overall. In contrast, there is a substantially larger body of literature on the diagnostic experiences in the context of RDs. This research has found that information, psychological support, and access to services are important to those navigating the diagnostic process for RDs. Although there appear to be commonalities between the MtD experience and the wider RD experience, namely shared experiences surrounding lack of knowledge on conditions, persistent uncertainty, the importance of the PPR, and a scarcity of social support, it is unknown how the MtD experience is situated within the RD experience. Despite these similarities, it is likely that the MtD experience is unique, and support tailored to this population is necessary. However, to date, no studies have explored the experiences and specific needs along the MtD diagnostic journey, representing a significant gap in the knowledge about how patients with MtD and their parents/caregivers can be best supported in the time leading up to a diagnosis.

1.5.1 Research Question and Aims

The goal of this study was to understand the experiences and needs of individuals and families during their diagnostic journey for mitochondrial disease. The study aims were three-fold:

1. To explore the diagnostic journey of individuals and parents/caregivers of children with a known MtD diagnosis,
2. To identify the informational, psychological, and social needs of individuals and parents/caregivers throughout this experience, and
3. To identify ways in which individuals and families felt supported by providers[1] throughout the MtD diagnostic journey.

[1] In this study, "provider(s)" will refer to healthcare professionals involved in the medical care of patients and families with MtD. These individuals include but are not limited to primary care physicians and nurses, specialist physicians such as geneticists/metabolic specialists and neurologists, and allied health professionals such as genetic counsellors, therapists (physical, occupational, speech), and dietitians.

CHAPTER 2: METHODOLOGY AND METHODS

2.1 STUDY DESIGN

This study followed a mixed-methods design, a research methodology defined by the incorporation of both quantitative and qualitative components in a study (Creswell & Plano Clark, 2018). Mixed-methods research is driven by the notion that quantitative and qualitative approaches together are necessary to answer particular research questions in their entirety (Creswell & Plano Clark, 2018). An embedded mixed-methods approach was followed, wherein predominantly quantitative surveys were nested within qualitative semi-structured interviews, with an emphasis on the qualitative component (Creswell & Plano Clark, 2011; Figure 2.1). This approach was chosen to allow for survey responses to inform and tailor the follow-up interview to each participant's experience. The survey component acquired a breadth of information regarding the diagnostic journey, such as the number and specialty of providers seen, services accessed, and additional diagnoses obtained. From there, the interview component acquired a depth of information regarding the diagnostic experience and identified previously described and novel needs throughout the journey. The two datasets were integrated following a triangulation protocol to assess convergence, complementarity, silence, and divergence between trends and themes (Farmer et al., 2006).

There are many advantages to mixed-methods study design, which include the application and integration of both positivist and interpretivist paradigms to provide further depth and rigour and more completely answer a research question (Dawadi et al., 2021). However, there are challenges with this approach. For instance, the integration of qualitative and quantitative datasets can be difficult and incongruent findings may draw into question the reliability and validity of the research if integration is done haphazardly (Dawadi et al., 2021). To mitigate this issue, the survey and interview guide were developed in close consideration of the research question and structured around the study aims. Further, a previously described triangulation protocol guided data integration (Farmer et al., 2006). These considerations allowed for more meaningful integration of datasets, including points of divergence in the data. Though critics of mixed-methods research argue that qualitative and quantitative approaches are innately incompatible due to their conflicting epistemological positions, many researchers recognize the substantive advantages of carefully executed mixed-methods studies (Ravitch & Mittenfelner

Carl, 2020). Given our research question, study design, and integration framework, we maintain that a mixed-methods approach would establish validity and depth in this research to appreciate the complexity of the MtD diagnostic journey.

This study received approval from the University of Manitoba's Bannatyne Campus Research Ethics Board (approval number HS24923, H2021:195) and the Shared Health Approval Committee for Privacy, Impact and Access in Research (approval number SH2021:090).

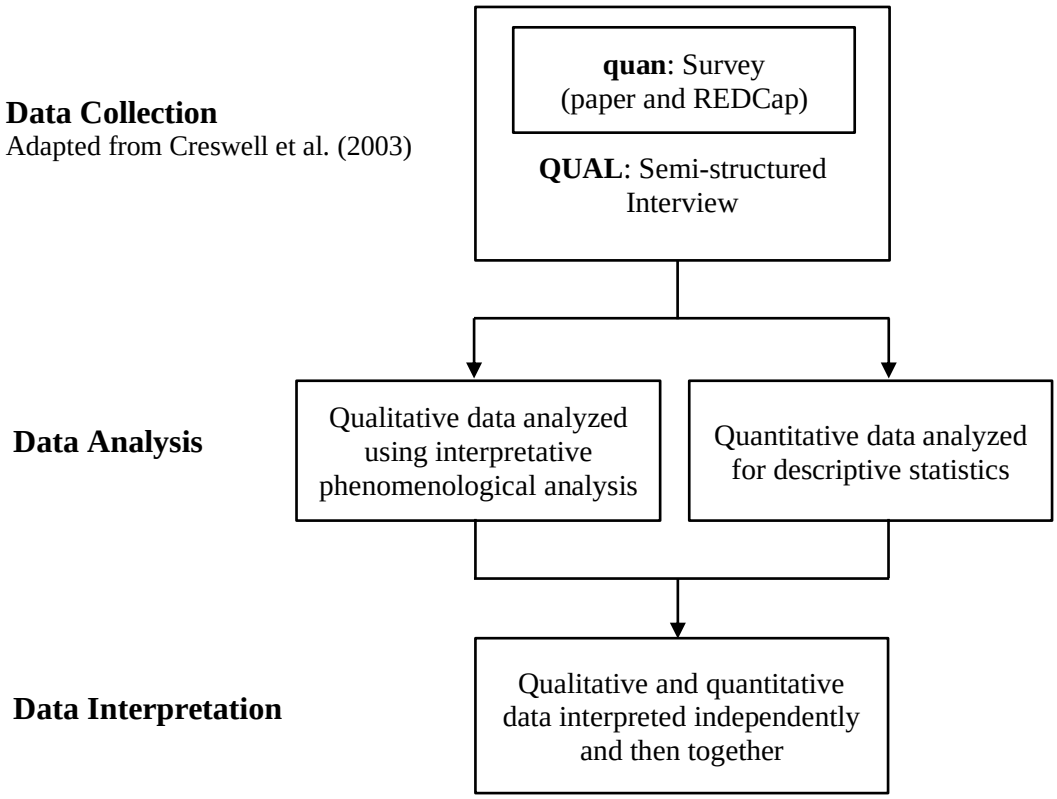

Figure 2.1. Embedded mixed-methods study design

2.2 THEORETICAL FOUNDATIONS

While mixed-methods research can be viewed as a methodology in itself, the quantitative and qualitative components of mixed-methods studies are each guided by their own philosophical underpinnings, namely ontology and epistemology, which impact the approach to each individual component. Ontology is the theory and study of being, and epistemology is the theory and study of knowledge (Ravitch & Mittenfelner Carl, 2020). The quantitative portion of

this research was grounded in a positivist paradigm. Ontologically, positivism maintains that there is a singular objective truth to be uncovered in response to the research question (Ravitch & Mittenfelner Carl, 2020). Epistemologically, positivism upholds the notion that knowledge is derived from the outside and that the researcher is an objective, external observer whose role is to uncover facts about a subject (Ravitch & Mittenfelner Carl, 2020).

The qualitative interview component of this study was guided by interpretivism and informed by hermeneutic phenomenology (Larsen & Adu, 2021; Schwartz-Shea & Yanow, 2020). The interpretivist paradigm maintains that people construct their realities and knowledge based on their lived experiences (Schwartz-Shea & Yanow, 2020). That is, how people understand a phenomenon, such as the MtD journey, is subjective and unique to the individual. Interpretivism also views researchers as co-creators of knowledge in partnership with participants, who cannot separate themselves from the research process, unlike with positivism. Thus, overall, the quantitative component was guided by the belief that each participant's account of their MtD diagnostic journey should be understood from their perspective, as interpreted by the researcher, whereas the positivist quantitative survey component of this work assumed that there was a "true" answer to each question. The qualitative piece was further informed by hermeneutic phenomenology, particularly during data collection and analysis. Hermeneutic phenomenology is a philosophy that focuses on the way that individuals make meaning of their lived experiences (Smith et al., 2022). In other words, hermeneutic phenomenology suggests that there is no universal experience of the MtD diagnostic journey. Instead, participant accounts hold meaning both individually and as a whole. Together, these philosophies guided this research in the selection of methods, development of data collection instruments, and the process of data collection, analysis, and interpretation.

2.3 ELIGIBILITY AND RECRUITMENT

This study sought out a sample of participants based on the age of symptom onset and a confirmed genetic (nDNA or mtDNA) diagnosis of MtD, in accordance with the criteria detailed in Table 2.1 and the eligible gene list established by the research team. This study included individuals who presented with symptoms prior to age 45 years, as those with later-onset MtD typically have less severe symptoms or symptoms restricted to a single organ. Therefore, it is suspected that these older individuals likely have a diagnostic journey that is different compared

to their younger counterparts. Both parents of a child with MtD were eligible to participate in this study, as were cognitively mature children (CMC). The eligible gene list was established based on a genetic testing panel routinely used in the investigation of MtD in Manitoba (GeneDx, Inc., 2018; P. Frosk, personal communication, January 2021). The student principal investigator (PI) worked with members of the research team (JH, PF, SM) to develop this list. Conditions not considered to be associated with primary mitochondrial disease were excluded (e.g. urea cycle disorders, organic acidemias, and sideroblastic anemia). Although rare, those with a reversible mitochondrial dysfunction were also excluded as their diagnostic experiences would likely have been different compared to those with non-reversible MtD. Additionally, pyruvate carboxylase deficiency was excluded due to the presence of a founder variant in the Manitoba population that follows a unique diagnostic process compared to other MtD.

Table 2.1. Study eligibility criteria

Inclusion Criteria
✓ They have/their child (living or deceased) has a diagnosis of primary mitochondrial disease AND
✓ They have/their child has diagnostic variants in an eligible gene AND
✓ They/their child had an appointment for diagnosis or management of primary mitochondrial disease in the past 5 years AND
✓ They/their child had symptoms that began before or at 45 years of age AND
✓ They are at least 13 years of age AND
✓ They are able to speak and read English

Eligible participants must also have been seen for follow-up within the last five years in one of two provincial clinics: Shared Health Program of Genetics and Metabolism or the Pediatric Mitochondrial Disease Clinic at the Winnipeg Children's Hospital. The Shared Health Program of Genetics and Metabolism provides services to over 5,000 patients per year, located in Manitoba, northwestern Ontario, and western Nunavut (Hartley et al., 2011; Winnipeg Regional Health Authority, n.d.). Patients and families with suspected or confirmed MtD are consulted through the multidisciplinary metabolic service comprised of geneticists/metabolic specialists, genetic counsellors, genetic assistants, a dietitian, and clinic support staff (Hartley et al., 2011; Winnipeg Regional Health Authority, n.d.). The Pediatric Mitochondrial Disease Clinic provides services to all children with MtD in the province (S. Marin, personal communication, January 2021). This clinic is offered by a pediatric neurologist who is an expert in MtD and is operated

through the Department of Pediatric Neurology at the Winnipeg Children's Hospital. The Shared Health Program of Genetics and Metabolism and the Pediatric Mitochondrial Disease Clinic work closely in the care of pediatric patients with MtD (P. Frosk, personal communication, May 2021). As these clinics are the exclusive sites for MtD care in the province, recruitment through these clinics ensured that all patients with MtD in Manitoba and the surrounding catchment were sampled.

We aimed to recruit 10-15 participants to complete a survey followed by an interview as this number is recommended to reach saturation of themes (Fugard & Potts, 2015). A larger sample size was not sought for the survey component as it was intended to describe the study population and inform the interview component and not to draw conclusions about the larger MtD population. Participants were recruited to the survey component of this study through two strategies. Potential participants either received a recruitment package that contained a study invitation letter (Appendix A.1) and a paper survey (Appendix A.2) mailed by our partner clinics or through an introduction by MtD clinicians, who completed a consent-to-contact form on behalf of the eligible patient (Figure 2.2). To enroll in the interview component, participants indicated their interest in being contacted for this purpose in the final section of the survey. Alternatively, the student PI's contact information was provided in the survey for the participant to reach out about arranging an interview.

All participants received an honorarium for taking part in this study. Those who completed a survey and interview received a $20 Tim Hortons gift card, and those who completed the survey component alone received a $5 Tim Hortons gift card.

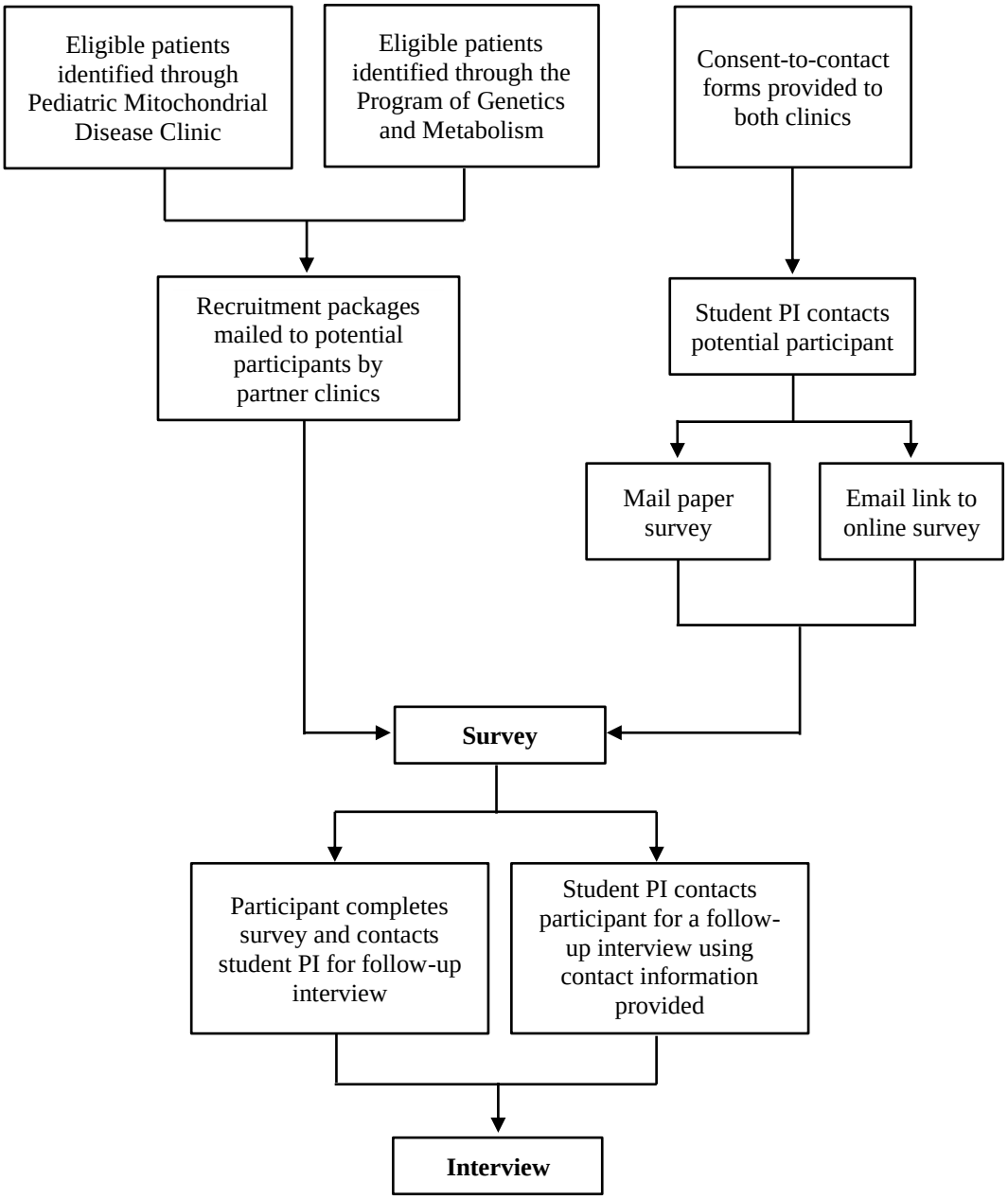

Figure 2.2. Study recruitment strategy

2.4 COMMUNITY ENGAGEMENT AND KNOWLEDGE TRANSLATION

Throughout the project, a MitoCanada community partner with lived MtD experience collaborated on study design, instrument piloting, data contextualization, and knowledge translation (KT). This study was fortunate to have several collaborating members and knowledge-users. A pediatric neurologist and MtD expert (SM) advised on the inclusion of a community partner, eligibility criteria, instrument development, piloting, recruitment. MitoCanada's chief executive officer (KM) has advised on what is known about the MtD community in Canada and partnered in KT efforts. A certified genetic counsellor and United Mitochondrial Disease Foundation advocate (DS) piloted the interview guide, advised on available support groups for the MtD community, and partnered in KT efforts.

In the last decade, KT activities have aided in translating clinical research into healthcare practice (Grimshaw et al., 2012). Therefore, we developed an end-of-grant KT plan (Canadian Institutes of Health Research, 2012) using available resources (Barwick, 2008) to ensure the study findings are shared. For the scientific and professional communities, participant-driven recommendations will be shared by way of knowledge-users and collaborators, and this work will be shared via conference presentations and peer-reviewed publications. Furthermore, in partnership with MitoCanada, the research team plans to develop KT tools, such as an infographic or a short-form video to be shared with the MtD community and the study participants.

2.5 SURVEY

2.5.1 Instrument Development

The quantitative component of this study was a survey (Appendix A.2), completed on paper or online through the secure web-based application Research Electronic Data Capture (REDCap) hosted at the University of Manitoba (Harris et al., 2009). This survey sought to obtain information about the experiences and educational, psychological, and social needs of those who navigated the MtD diagnostic process, including 1) salient features of the diagnostic journey (e.g. presenting symptoms, specialists encountered, time to diagnosis, time of treatment initiation), 2) sources of information and support throughout the diagnostic journey, 3) sources of information and support at the time of diagnosis, and 4) relationships with providers. The survey

included demographic questions, novel questions developed by the research team, and questions sampled from an instrument created by Grier et al. (2018) to facilitate comparison of the features of the diagnostic journey in our study and the study by Grier and colleagues. The majority of survey questions were closed-ended, specifically multiple choice, and multiple answer (select all that apply). Two questions asking about the impact of the diagnosis and perceived helpfulness of communities of support, if applicable, were open-ended.

2.5.2 Piloting

The paper and online versions of the survey were reviewed and piloted to reduce ambiguity, assess completion time, and improve the clarity and readability of the survey. This was completed by members of the student PI's advisory committee (SC, GAH, JH), our community partner (GH), study collaborator (SM), and the patient engagement coordinator (CC) at the Children's Hospital Research Institute of Manitoba Research Support Unit (Children's Hospital Research Institute of Manitoba, 2022), and five individuals from the student PI's personal network who were unfamiliar with MtD. The organization, flow and phrasing of questions, as well as ambiguity in instructions, were revised in accordance with the feedback. The survey was estimated to take 20-25 minutes to complete. Readability was assessed pre and post-pilot using the Flesch-Kincaid Grade Level test (Kincaid et al., 1988) and was improved from a Flesch-Kincaid grade level 10-11 to a grade level 8-9 following the pilot testing.

2.5.3 Quantitative Data Analysis

Statistical analysis of quantitative data was completed using Microsoft Excel (Microsoft Corporation, 2018) in consultation with a biostatistician (LC) from the George and Fay Yee Centre for Healthcare Innovation. Descriptive statistics such as frequencies and counts were visually summarized to identify patterns emerging across the dataset. The two open-text responses were analyzed along with interview data as described in section 2.6.3.

2.6 INTERVIEWS

The qualitative component of this study was a semi-structured interview, aligning with the hermeneutic phenomenology framework, which guided this component of the research. Semi-structured interviews are advantageous in their ability to delve deeper into each participant's

feelings and beliefs about and experiences with a particular topic. The interview approach allowed for flexibility in follow-up and probing questions to explore unique concerns (Ravitch & Mittenfelner Carl, 2020). This parallels the survey goals, allowing for a more complete exploration of the research question. The interview guide prompted participants to reflect on 1) navigating the diagnostic process, 2) resources, supports, and education received along the way, 3) the impact of the final diagnosis, 4) their relationships with providers, 5) what was particularly helpful, and 6) what could have been done differently (Appendix A.3).

2.6.1 Interview Guide Development

The interview guide was developed by adapting certain questions pertinent to our study from a publication that investigated the PPR and informational and psychological needs associated with the diagnosis of schwannomatosis (Merker et al., 2021). Questions were intentionally open-ended to better capture the participants' experiential perceptions. The interview guide was reviewed with a member of the student advisory committee (GAH) and piloted with our community partner (GH) and study collaborator (DS).

2.6.2 Interview Procedure

All interviews were conducted by the student PI and offered by telephone or videoconference. The student PI received guidance and feedback on interviewing and probing techniques from an expert committee member (GAH). At the beginning of each interview, the student PI obtained informed consent using the appropriate consent form(s) in Appendix A.4. The student PI reviewed each participant's survey responses prior to the interview to inform the interview approach. For instance, if the student PI noted that a participant indicated they were aware of support communities but did not participate in these, the reason for this could be explored to enhance data richness. To promote rigour, once three interviews were conducted, the student PI reviewed data elicitation techniques with members of the advisory committee (JH, GAH) and incorporated feedback moving forward. This feedback included improvement in responses and paraphrasing, but the content of the guide remained the same.

2.6.3 Qualitative Data Analysis

Interviews were audio recorded and transcribed verbatim by either the student PI or a confidential transcription service (*Transcript Heroes*, 2015). Transcripts underwent audio verification by the student PI to contribute to rigour (Tracy, 2010). Each interview participant was assigned a study ID to maintain confidentiality. Further, as MtD are rare and the MtD community is relatively small, items like names, places, pronouns, and specific diagnoses were removed from excerpts to encourage confidentiality.

Qualitative data, comprised of interview transcripts and open-ended survey questions, were analyzed using interpretative phenomenological analysis (IPA) as outlined by Smith et al. (2022). IPA was chosen for analysis as it is idiographic and focuses on how individuals with lived experience understand a phenomenon (Smith et al., 2022). Each transcript was read and re-read to ensure analysis was focused on the participant's narrative. Next, transcripts were annotated with descriptive, linguistic, and conceptual exploratory comments, which remained closely linked to the participants' explicit meaning. Exploratory comments were then used to develop personal experiential themes (PETs) per transcript. Once PETs were developed for all transcripts, these were compared across transcripts to identify group experiential themes (GETs). To be classified at a group level, themes were not required to be observed in the majority of participant narratives as themes are not solely based on prevalence within the context of IPA and instead consider the richness of themes (Smith et al., 2022). Three transcripts were co-annotated by the student PI and the thesis supervisor (JH) to ensure trustworthiness. Members of the research team met with the student PI at different stages of analysis, particularly to review exploratory comments for initial transcripts (GAH, JH) and to review PETs (JH) and GETs (GAH, JH). Final GETs were also reviewed with our community partner (GH) and a study collaborator (DS) for data contextualization.

Data saturation was achieved in the development of PETs and in GETs. For GETs, data redundancy was observed by the ninth interview, and the student PI anticipated no further novel GETs to emerge (Fugard & Potts, 2015; Guest et al., 2006). Due to the analytical depth of IPA, a sample size of three to five participants is generally sufficient for a good IPA study (Smith et al., 2022). However, a larger sample is generally preferred in qualitative research to improve validity. As this study worked with a larger sample size, the analysis focused more prominently on broader and shared experiences and less so on idiographic detail and case-level divergence

(Smith et al., 2022). Regardless, the analysis and findings remained grounded within the narrative of the participants, in keeping with the philosophy of IPA.

2.6.4 Validity and Reflexivity

Validity, or trustworthiness, in qualitative research refers to the quality and rigour of a study (Ravitch & Mittenfelner Carl, 2020). In other words, the ways in which researchers can be confident that findings are reflective of the participants' true experiences. There are four constructs of validity: credibility, transferability, dependability, and confirmability (Ravitch & Mittenfelner Carl, 2020).

In this study, various strategies were applied in the study design, data collection, analysis, and integration to contribute to validity. Credibility and dependability were achieved through strategic sequencing of events and data triangulation. That is, the survey was completed first to inform the interview component, and multiple data collection methods were used to provide context and more completely answer the research question. Credibility was further ensured through the consideration of divergences in the data during the integration process. As well, engagement with the thesis supervisor, advisory committee members, partners, and collaborators at various stages of data collection and analysis to discuss challenges and potential for improvement contributed to credibility. Transferability was achieved by positioning findings within the contexts that they were initially described to allow the reader to appreciate how these findings can apply to other contexts while understanding that generalizability is not a goal of qualitative research (Ravitch & Mittenfelner Carl, 2020). Additional strategies that contributed to research rigour and described earlier in this chapter included interview guide piloting, data elicitation assessment, co-annotation of transcripts, discussion of final GETs, and record-keeping for each stage of data analysis to provide an audit trail (Levitt et al., 2018; Smith et al., 2022).

Reflexivity was structured within the research design through memoing to promote confirmability. Reflexivity is the critical reflection of how a researcher's "identity, positionality, biases, assumptions, values, and subjectivities" influence their research (Ravitch & Mittenfelner Carl, 2020, p. 13). After each interview, the student PI reflected on her communication style, listening skills, presentation of questions, and decision to probe about certain topics. The student PI also noted how her perceptions and feelings impacted the data collection process. As more interviews were conducted, memos captured emerging trends or patterns across participants.

Positionality was important to consider in this context as well. The student PI was drawn to this research topic as she has personal experience with challenges of the diagnostic process, although unrelated to MtD and other rare diseases. This previous experience may have influenced the research process, specifically in how interviews were conducted and how participant concerns were received. At the same time, as an individual completing a Master's degree in a healthcare field directly related to the research topic and training clinically with providers involved in the care of participants, the student PI held viewpoints of the diagnostic process in this context. These viewpoints likely impacted the understanding of the participants' experiences, particularly in IPA, due to its double interpretation process whereby participants make sense of an experience and then the researcher attempts to make sense of their interpretation (Smith & Osborn, 2015). In addition, the student PI is a White able-bodied woman in her 20s. This indirect self-disclosure may have influenced how participants shared their experiences in a variety of ways, particularly in the context of their social locations and identities. Finally, while the student PI was not involved in the care of any participants, there is a power dynamic that exists within both patient-provider and participant-researcher relationships that may have been compounded in influencing how participants depicted their experiences.

2.7 INTEGRATION OF QUANTITATIVE AND QUALITATIVE FINDINGS

Quantitative and qualitative data were analyzed separately, and once finalized, both sets of findings were laid out in a matrix and areas of convergence, complementarity, silence, and divergence were highlighted (Farmer et al., 2006; O'Cathain et al., 2010). Emphasis was placed on the qualitative findings as the primary approach in this embedded mixed-methods study. Upon integration, qualitative findings provided context, nuance, and depth to the quantitative component.

CHAPTER 3: SURVEY RESULTS

3.1 PARTICIPANTS AND RESPONSE RATE

A total of 56 patients who met inclusion criteria were identified through the Program of Genetics and Metabolism and the Pediatric Mitochondrial Disease Clinic and mailed a recruitment package. As several eligible patients were family members at the same residence, some recruitment packages containing multiple surveys were sent to the same address. Thus, 36 recruitment packages were mailed to these 56 potential participants, of which one was returned to sender. Eight participants responded to the mailed survey. Eleven participants, included in the 56 eligible patients identified above, were concurrently recruited through personal invitation by each clinic. Nine of these patients expressed interest and were enrolled in the study. When the student PI followed up with potential participants, one patient declined to participate, and the student PI was unable to reach the remaining eligible patient. Eight participants completed a paper version of the survey, while nine participants completed the electronic version through REDCap. An overview of recruitment can be seen in Figure 3.1. The response rate for this study was approximately 30% (17/56), which was in line with similar studies conducted with the Manitoba patient population (Bonnell, 2020; Casalino, 2020; Dinchong, 2019).

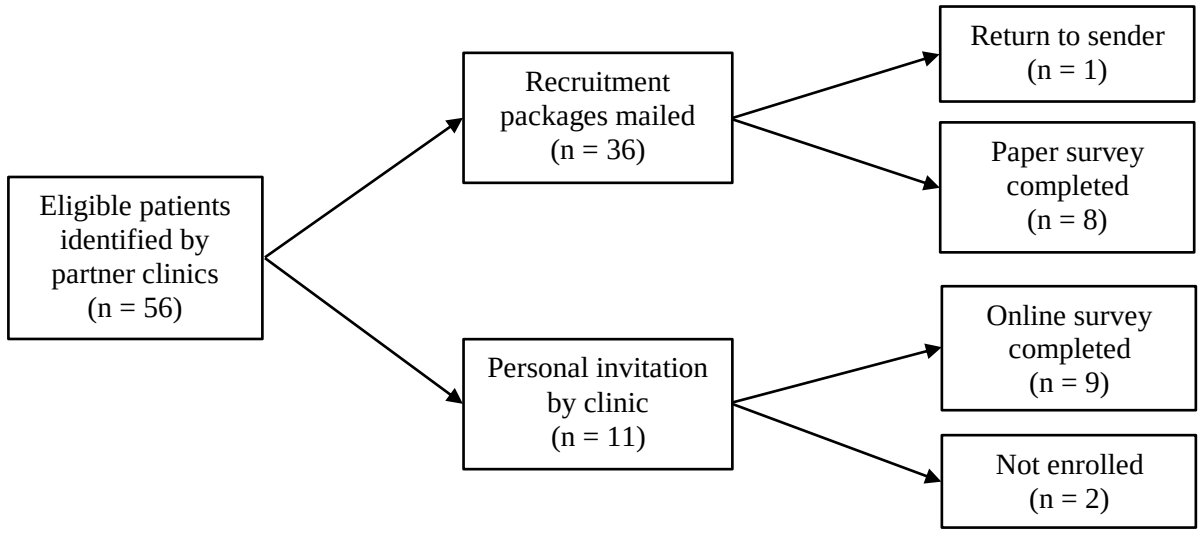

Figure 3.1. Overview of study participant recruitment. The number of recruitment packages is inequivalent to the number of eligible patients as a portion of potential participants were family members with the same address. Personal invitation by the clinic was a concurrent recruitment strategy that used consent-to-contact forms.

3.2 DEMOGRAPHIC CHARACTERISTICS

The demographic characteristics of survey participants are presented in Table 3.1. Seventeen participants completed the survey during the data collection period (August 2021-February 2022), and 12 of these participants completed a follow-up interview. Of the 17 survey participants, nine (52.9%) were individuals with MtD and eight (47.1%) were parents/caregivers of children with MtD. There were two participants who completed two surveys each. The first participant is a parent who completed a survey on behalf of each affected child's diagnostic experience. The second completed an individual survey describing their own experiences of the diagnostic journey and another on behalf of their affected child. Therefore, while there were 17 participants, 15 individuals responded to the surveys. The results presented consider each completed survey independently.

The majority of participants were aged 30 or above (15/17, 88.2%), identified as women (12/17, 70.6%), held an undergraduate degree (7/17, 41.2%), were of European ancestry (10/17, 58.8%), and lived in Winnipeg (10/17, 58.8%) where provincial health services and MtD care providers are exclusively located. In terms of specific MtD diagnosis, four participants (4/17, 23.5%) had a mitochondrial deletion syndrome, with the most common syndrome being KSS. Five participants (5/17, 29.5%) were impacted by MELAS, four participants (4/17, 23.5%) with Leigh syndrome or Leigh-like syndrome, and four participants (4/17, 23.5%) with a rare pediatric-onset MtD. The rare MtD were grouped together to safeguard participant confidentiality.

When compared to the Manitoba population with respect to age, education, gender, or ethnic origin, this study sample was not representative. According to 2016 census data available through Statistics Canada (2017a; 2017b), 63% of the Manitoba population was aged 30 and above, and 14% of the population held an undergraduate degree. Sixty-seven percent of the population was of European ancestry, while 18% and 14% of the population were of Indigenous and Asian ancestry, respectively. However, 55% of Manitoba's population lived in Winnipeg in 2016, which is comparable to this study sample. It is difficult to compare gender statistics from this study to the provincial population as the 2016 census reported binary sex, unlike the demographic question posed in this survey which inquired about gender. Nonetheless, it is clear that women were overrepresented in this study.

Table 3.1. Demographics of survey participants

	Total (n = 17)		Individual (n = 9)		Parent/Caregiver (n = 8)	
	n	%	n	%	n	%
Age						
13-17 years old	1	(5.9)	1	(11.1)	0	(0)
18-29 years old	1	(5.9)	0	(0)	1	(12.5)
30-39 years old	7	(41.2)	1	(11.1)	6	(75.0)
40-49 years old	3	(17.6)	2	(22.2)	1	(12.5)
50-59 years old	4	(23.5)	4	(44.5)	0	(0)
≥ 60 years old	1	(5.9)	1	(11.1)	0	(0)
Gender Identity						
Woman	12	(70.6)	5	(55.6)	7	(87.5)
Man	4	(23.5)	3	(33.3)	1	(12.5)
Non-binary	1	(5.9)	1	(11.1)	0	(0)
Condition						
Mitochondrial deletion syndrome	4	(23.5)	4	(44.4)	0	(0)
MELAS	5	(29.5)	4	(44.4)	1	(12.5)
Leigh/Leigh-like syndrome	4	(23.5)	0	(0)	4	(50.0)
Rare pediatric-onset MtD	4	(23.5)	1	(11.1)	3	(37.5)
Education[a]						
Some high school	3	(17.6)	2	(22.2)	1	(12.5)
Graduated high school	3	(17.6)	3	(33.3)	3	(37.5)
Some college/university	2	(11.8)	1	(11.1)	1	(12.5)
Undergraduate degree	7	(41.2)	2	(22.2)	5	(62.5)
Graduate degree	1	(5.9)	0	(0)	1	(12.5)
Other Ways of Knowing	2	(11.8)	1	(11.1)	1	(12.5)
Prefer not to answer	1	(5.9)	1	(11.1)	0	(0)
Ethnic Identity[b]						
Asian origins	4	(23.5)	2	(22.2)	2	(25.0)
European origins	10	(58.8)	5	(55.6)	5	(62.5)
Indigenous	2	(11.8)	1	(11.1)	1	(12.5)
Prefer not to answer	1	(5.9)	1	(11.1)	0	(0)
Geographic Location						
In Winnipeg	10	(58.8)	6	(66.7)	4	(50.0)
< 1 hour	2	(11.8)	0	(0)	2	(25.0)
1 hour	2	(11.8)	1	(11.1)	1	(12.5)
1.5 hours	2	(11.8)	1	(11.1)	1	(12.5)
5 hours	1	(5.9)	1	(11.1)	0	(0)
Interview						
Yes	12	(70.6)	7	(77.8)	5	(62.5)
No	5	(29.4)	2	(22.2)	3	(37.5)

[a.] Total does not sum to 100% as participants could select more than one option (e.g. Some high school and Other Ways of Knowing). [b.] Categories for ethnic origins were applied as developed by Statistics Canada (2017a).

3.3 THE DIAGNOSTIC JOURNEY

To better understand the salient features of the diagnostic journey, survey respondents were asked a series of questions about symptoms and age of symptom onset, specialist referrals, genetic and non-genetic testing, misdiagnoses, time to milestones, and initiation of treatment. On average, participants reported experiencing four to five different symptoms. Weakness (11/17, 64.7%) and fatigue (10/17, 58.8%) were the most commonly reported symptoms that prompted participants to seek medical consultation (Figure 3.2). Participants indicated that symptoms onset most commonly in infancy (0-3 years; 6/17, 35.3%) or mid-adulthood (31-45 years; 5/17, 29.4%). The first specialist to whom participants were referred was most often a neurologist (10/17, 58.8%) and or a geneticist/metabolic specialist (7/17, 41.2%) (Figure 3.3A). Half of participants (8/16, 50.0%) indicated that they met with a specialist within six months of seeking initial consultation (Figure 3.3B). Along the diagnostic journey, participants met with an average of two to three different specialists, although it was most common to meet with four different specialists prior to obtaining an MtD diagnosis (Figure 3.3C). The diagnosis of MtD was first mentioned by either a neurologist or a geneticist/metabolic specialist (6/17, 35.3% each) (Figure 3.4).

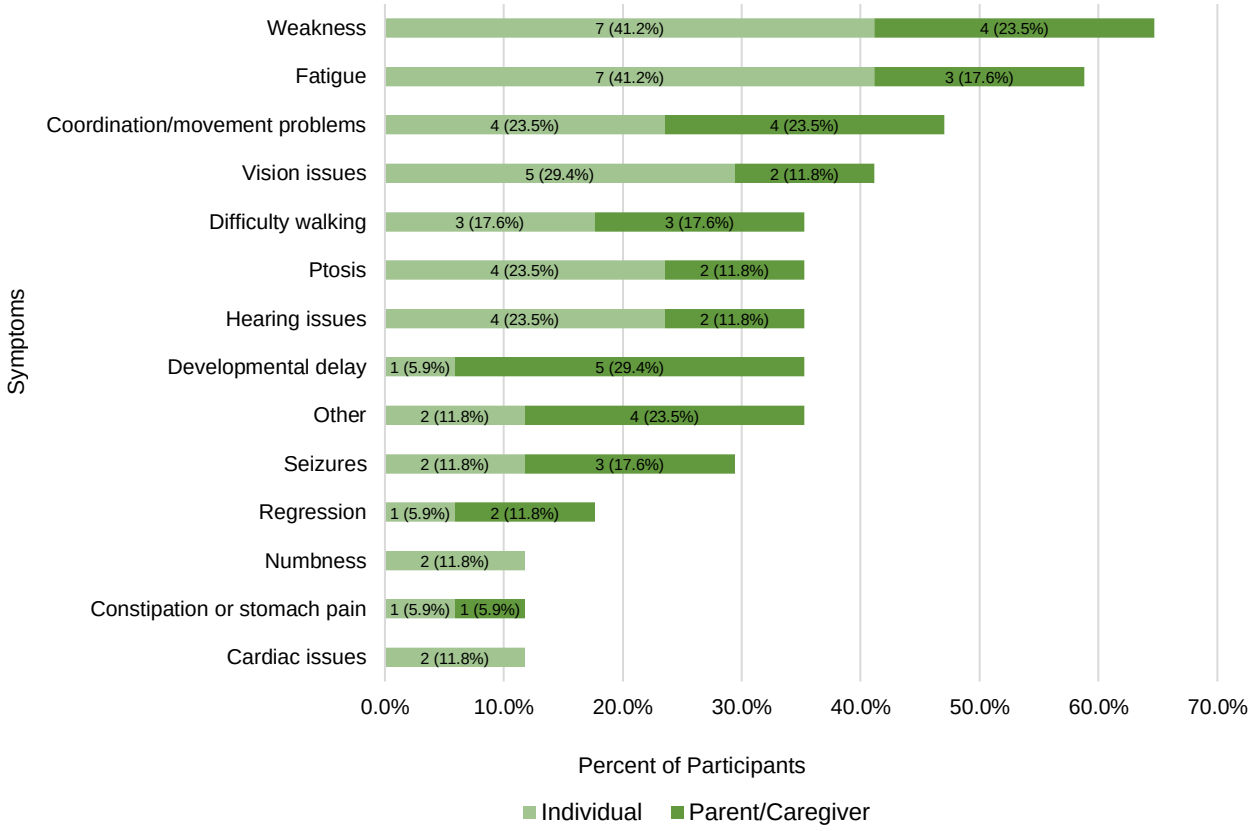

Figure 3.2. Initial symptoms prompting medical consultation. Other symptoms included weight gain, weight loss, migraines, poor feeding, vomiting, and positive on newborn screen. Participants could select all that applied.

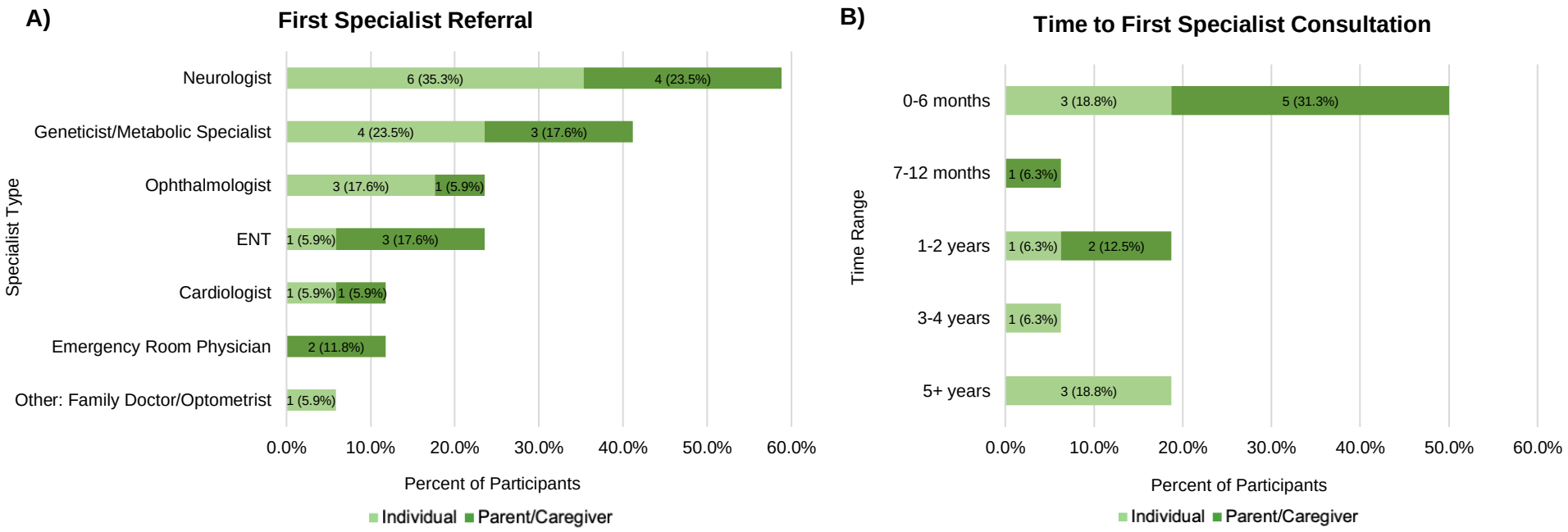

Figure 3.3. Providers along the diagnostic journey. A) First specialist referral received by participants. Participants could select all that applied. B) The amount of time that passed from symptom onset to meeting with the first specialist to whom participants were referred. C) The number of different specialists participants met prior to receiving a final MtD diagnosis.

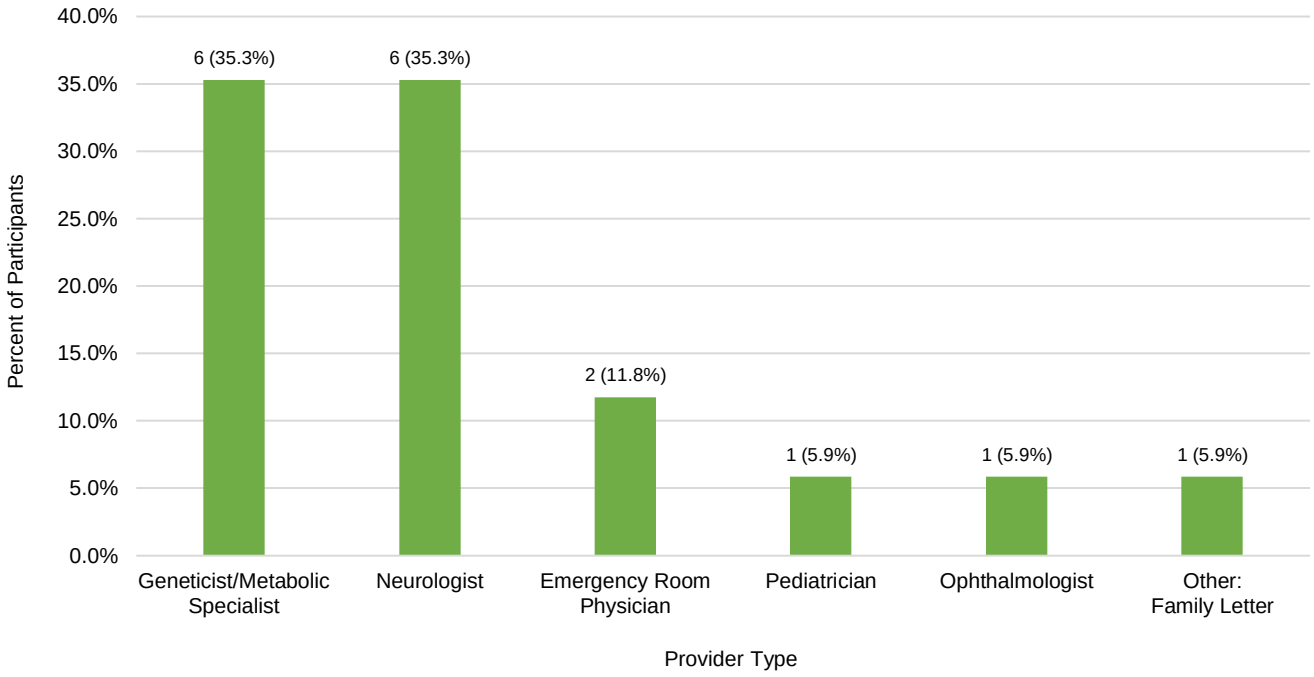

Figure 3.4. Providers who first suggested MtD to participants

Participants underwent non-genetic and genetic testing along the diagnostic journey. They identified neurologists (8/17, 47.1%), geneticists/metabolic specialists (6/17, 35.2%), and family doctors/nurse practitioners (5/17, 29.4%) as the providers who most often explained non-genetic testing while genetics providers (geneticists/metabolic specialists (11/17, 64.7%); genetic counsellors (7/17, 41.2%)) and neurologists (7/17, 41.2%) most often explained genetic testing (Table 3.2). The majority of participants (11/17, 64.7%) were not previously familiar with genetic testing. Also, as expected, genetic providers were most often reported to deliver genetic test results (15/17, 88.2%) (Figure 3.5). Before genetic testing, most participants reported understanding the reason(s) and logistics for testing (13/17, 76.4% and 14/17, 82.4%, respectively), as well as the possible results (9/17, 52.9%) (Figure 3.6). However, only four of 17 (23.5%) participants indicated understanding the benefits and risks involved (Figure 3.6). Interestingly, while all participants had genetic confirmation for their diagnosis, only five (5/17, 29.4%) recalled the gene involved. In terms of treatment, 16/17 (94.1%) participants were taking a mito cocktail of various vitamins and supplements, with 13/16 (81.3%) starting the regimen after their diagnosis.

Table 3.2. Providers reported to have explained testing. Testing included both non-genetic and genetic testing along the diagnostic journey.

Explained Non-Genetic Testing	**Total Frequency (%)**
Neurologist	8 (47.1)
Geneticist/Metabolic Specialist	6 (35.2)
Family Doctor/Nurse Practitioner	5 (29.4)
Pediatrician	3 (17.6)
Genetic Counsellor	2 (11.8)
ENT	2 (11.8)
Ophthalmologist	1 (5.9)
Emergency Room Physician	1 (5.9)
Neonatologist	1 (5.9)
No one	1 (5.9)
Only had genetic testing	1 (5.9)
Explained Genetic Testing	**Total Frequency (%)**
Geneticist/Metabolic Specialist	11 (64.7)
Genetic Counsellor	7 (41.2)
Neurologist	7 (41.2)
Other: Clinical Trials Team	1 (5.9)
Other: Family Letter	1 (5.9)
No one	0 (0.0)

Note: Columns do not sum to 100% as participants could select all that applied.

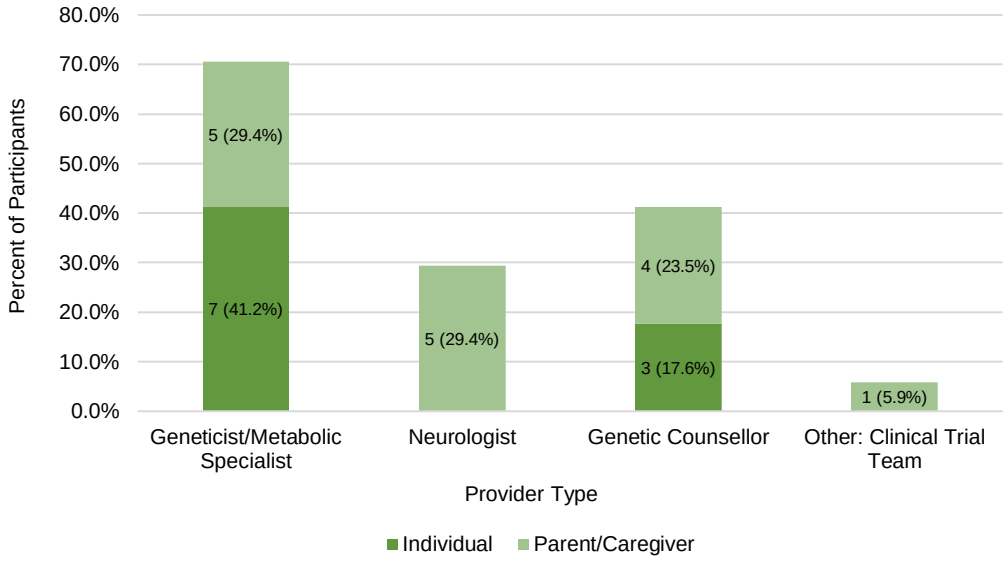

Figure 3.5. Providers who delivered genetic test results. Participants could select all that applied.

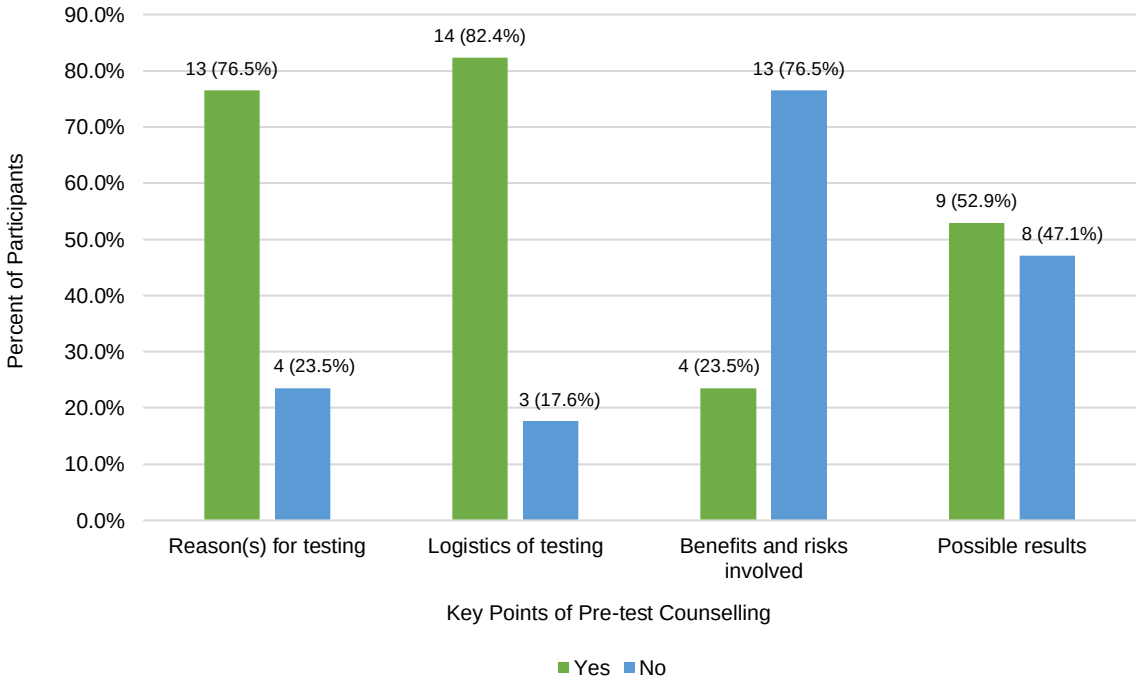

Figure 3.6. Recall of pre-test counselling for genetic testing. Participants were asked to recall whether their discussion of genetic testing included reasons for testing, logistics, benefits and risks as well as possible results.

The survey elicited the time to diagnosis, information that has not been well characterized within the MtD patient population. The majority of participants (13/17, 76.5%) indicated that a final MtD diagnosis was received within two years of seeking medical care (Figure 3.7). The time to diagnosis was variable between groups (Figure 3.7). Just over half of survey participants (9/17, 52.9%) indicated receiving at least one misdiagnosis prior to the final MtD diagnosis. Misdiagnoses included multiple sclerosis, dystonia, and pyruvate dehydrogenase deficiency.

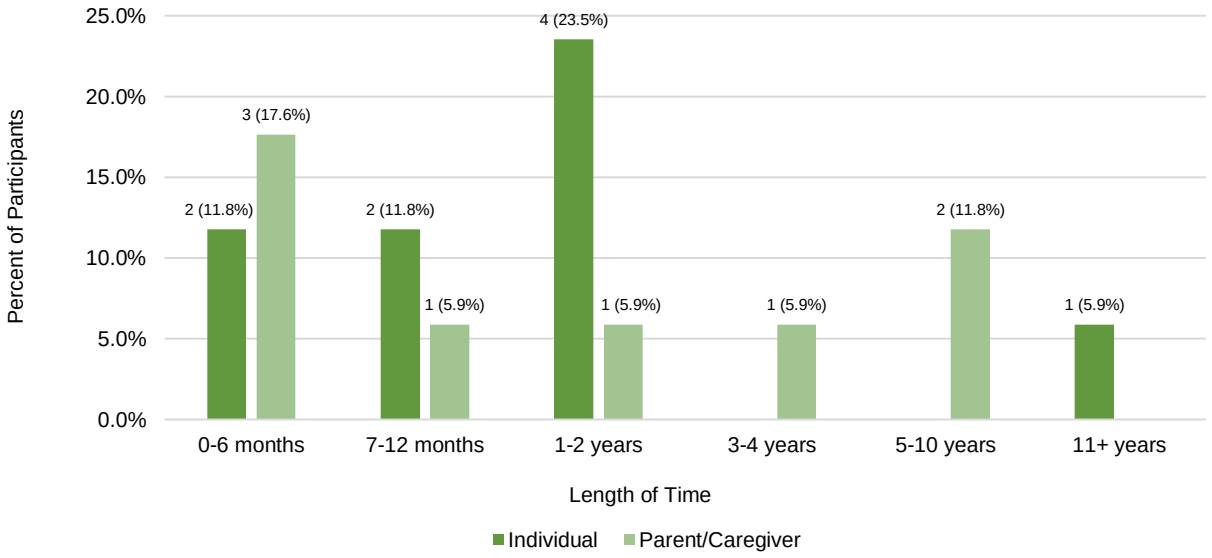

Figure 3.7. Time to diagnosis. Participants indicated the length of time that passed from symptom onset to receiving the final diagnosis of MtD.

3.4 THE PATIENT-PROVIDER RELATIONSHIP

Participants were asked to rate how often they felt included in decision-making by their providers, how often they felt they could trust their providers, and the quality of communication with their providers in a series of Likert questions. Generally, inclusion, trust, and communication quality were rated favourably (Figure 3.8). Eleven of 17 (64.7%) participants indicated that they either often or always felt included by providers, and 16/17 (94.1%) participants rated the communication quality as average, good, or very good (Figure 3.8A, 3.8B). Interestingly, when it came to feelings of trust, more variability was seen in the range of responses, though the majority of participants (10/17, 58.8%) indicated they felt they could trust their providers either often or always (Figure 3.8C).

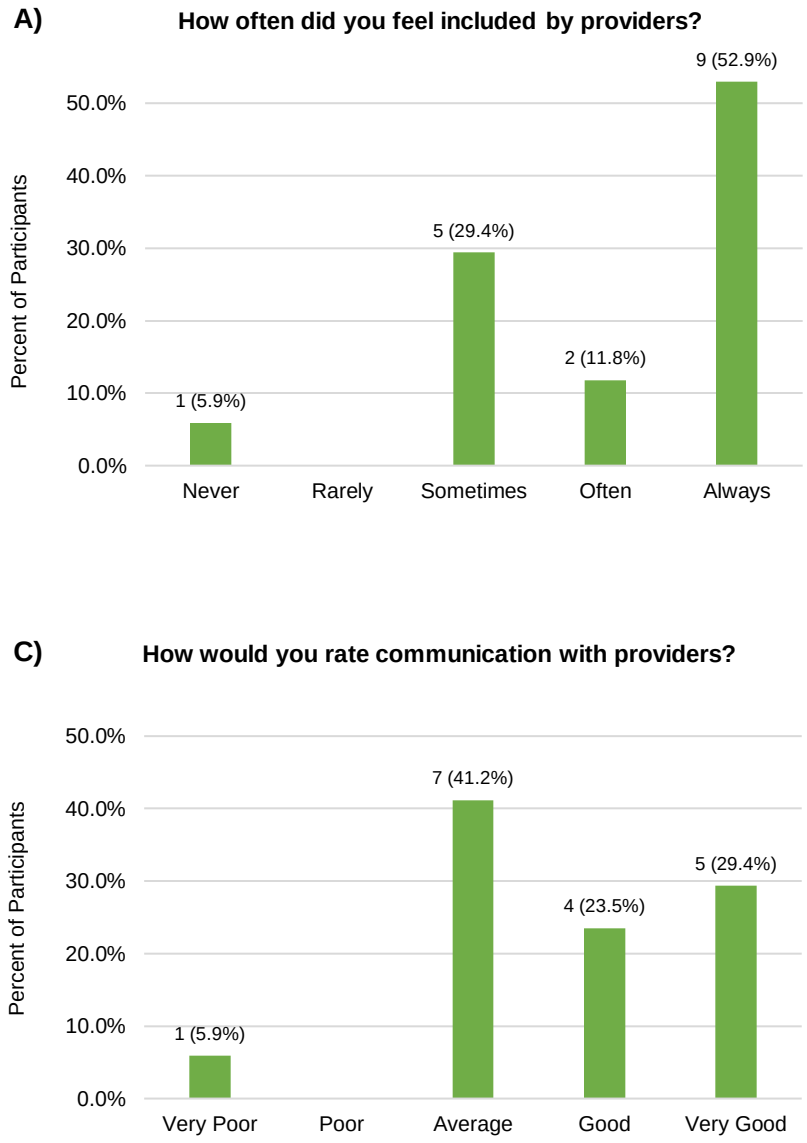

Figure 3.8. Inclusion, trust, and quality of communication in the patient-provider relationship. A) How often participants felt included by their providers. B) How often participants felt they could trust their providers. C) The quality of patient-provider communication.

Additionally, participants were asked about the different types of support provided throughout the diagnostic journey by various providers. Types of support included education (e.g. *'I learned about mitochondrial disease'*), support & communication (e.g. *'I felt like my providers cared about my opinions, feelings, concerns'*), and access to support services (e.g. *'I was told about or referred to services available to me'*). Geneticists/metabolic specialists and neurologists consistently provided the most education, support & communication, and access to support services for participants (Table 3.3). While genetic counsellors provided significant education to participants along the diagnostic journey, they provided less support & communication as well as facilitated less access to services (Table 3.3). The opposite trend was observed for primary care providers (Table 3.3).

3.5 INFORMATION AND EMOTIONAL SUPPORT

Participants reported on a Likert-style scale where they received the least to most amount of information and support along the diagnostic journey. Geneticists/metabolic specialists, neurologists, genetic counsellors, and the Internet were sources of the most information (i.e. ranked 4 or 5) (Figure 3.9A). Primary care providers, support groups and organizations, and family/friends were sources of the least information (i.e. ranked 1 or 2) (Figure 3.9A). A similar trend was noted for support (Figure 3.9B). Healthcare providers, family/friends, and the Internet provided the most support (i.e. ranked 4 or 5), while support groups and organizations provided the least support (i.e. ranked 1 or 2) (Figure 3.9B).

Table 3.3. Providers reported to have offered education and various support along the diagnostic journey (n=16)

Education	**Total Frequency (%)**
Geneticist/Metabolic Specialist	11 (64.7)
Genetic Counsellor	9 (52.9)
Neurologist	8 (47.1)
Family Doctor/Nurse Practitioner	2 (11.8)
Other: ENT	2 (11.8)
Support and Communication	**Total Frequency (%)**
Geneticist/Metabolic Specialist	10 (58.8)
Neurologist	8 (47.1)
Family Doctor/Nurse Practitioner	7 (41.2)
Genetic Counsellor	6 (35.3)
Other: ENT	2 (11.8)
Access to Services	**Total Frequency (%)**
Geneticist/Metabolic Specialist	7 (41.2)
Neurologist	5 (29.4)
Family Doctor/Nurse Practitioner	5 (29.4)
Other: ENT	2 (11.8)
Genetic Counsellor	1 (5.9)
Internet	1 (5.9)

Note: Examples were provided to participants for each category. Education: e.g. I learned about mitochondrial disease and how it can be passed down in families. Support and Communication: e.g. I felt like my healthcare providers cared about my opinions, concerns, and feelings. I felt included in decisions about my health. Access to Services: e.g. I was told about or referred to services that were available to me. These services could have included support/advocacy groups, support organizations, counselling, or other mental health services.

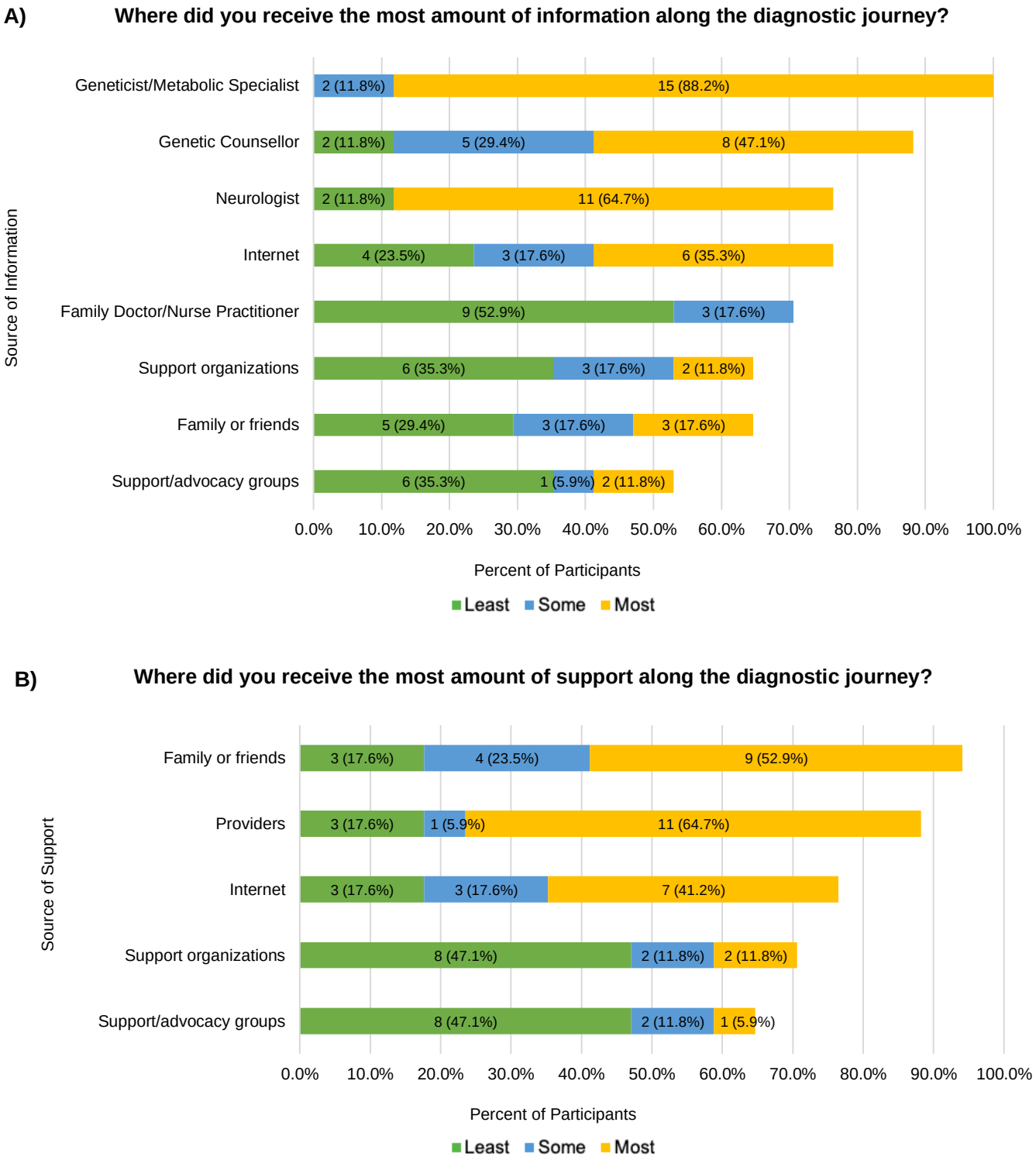

Figure 3.9. Sources of information and support. A) Sources of information along the diagnostic journey. B) Sources of support along the diagnostic journey. Participants answered a Likert-style question with least amount = 1 or 2, some amount = 3, and most amount = 4 or 5. Participants were asked to leave the question blank if they did not receive any information or support from the sources listed.

Participants were asked about the information they received prior to genetic testing compared to information received at the time of diagnosis. During pre-test counselling, most participants indicated having received information about MtD (9/17, 52.9%) and why these conditions are challenging to diagnose (12/17, 70.6%), inheritance and recurrence risk (11/17, 64.7%), and impacts on daily life (9/17, 52.9%) (Figure 3.10A). Survey responses were somewhat split on whether participants were given or wished to have been given information pertaining to symptom tracking, where to access health information, what to expect in the future, and psychological services (Figure 3.10A). A significant portion of participants wished they were given information on support/advocacy groups (9/17, 52.9%) and support organizations (8/17, 47.1%) (Figure 3.10A). While accounting for only a small proportion, some participants indicated that they were not interested to know certain types of information such as what to expect in the future (1/17, 5.9%), where to access health information (1/17, 5.9%), and information on psychological services (3/17, 17.6%), support/advocacy groups (2/17, 11.8%), and support organizations (2/17, 11.8%) (Figure 3.10A).

At the time of diagnosis, the majority of participants received information about the condition (14/17, 82.4%), inheritance and recurrence risk (14/17, 82.4%), what to expect in the future (12/17, 70.6%), and impacts on daily life (11/17, 64.7%) (Figure 3.10B). Also, many participants wished they had received information on support organizations (10/17, 58.8%), support/advocacy groups (8/17, 47.1%), and psychological services (7/17, 41.2%) (Figure 3.10B). As expected, survey respondents felt that they received the most information at the time of diagnosis. Somewhat surprising is the extent of information given prior to genetic testing by providers, particularly about the challenges associated with the diagnostic process. However, possible confusion around the difference between the information provided prior to diagnosis compared to the time of diagnosis cannot be discounted.

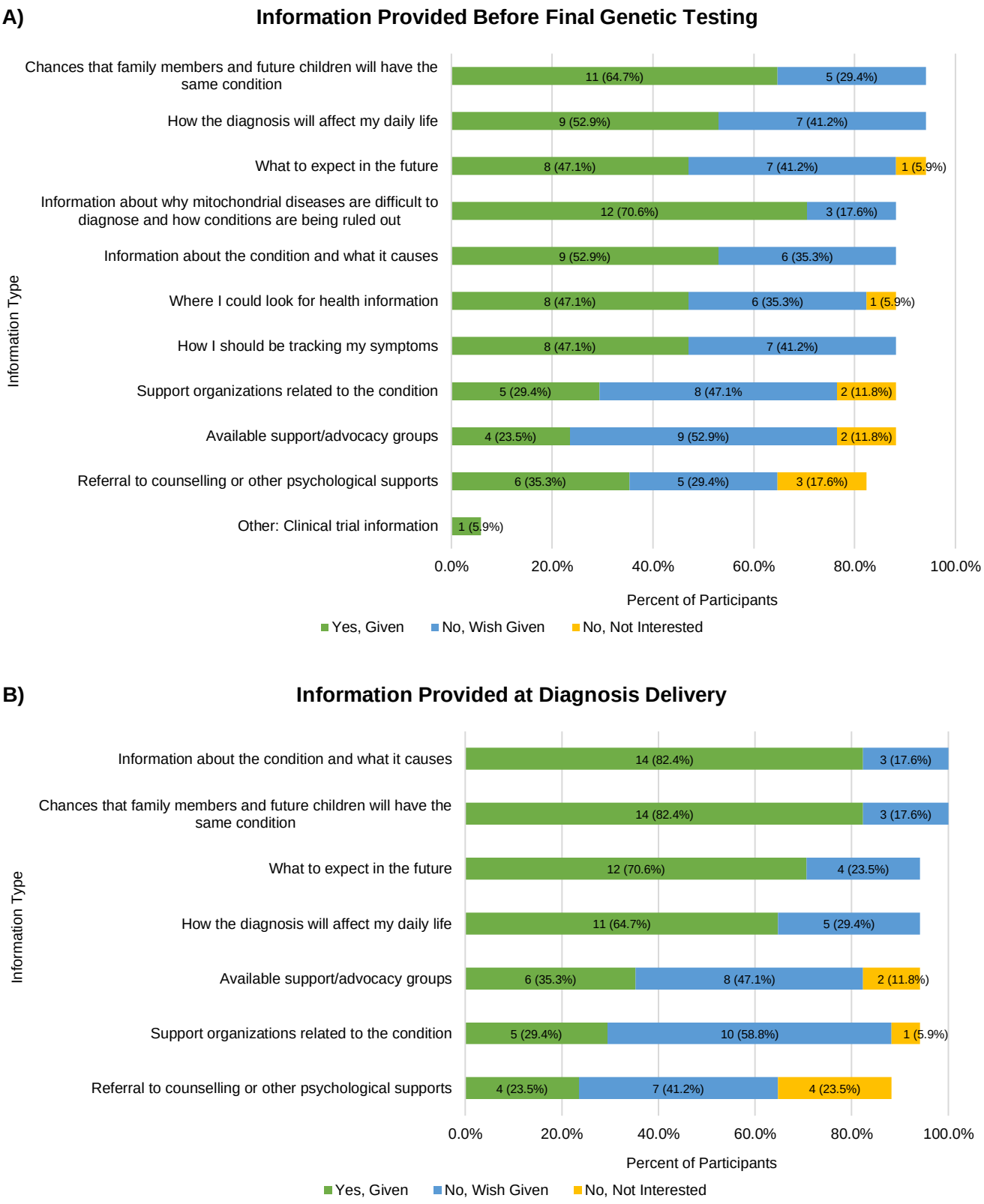

Figure 3.10. Information provision before and after the MtD diagnosis. A) Information provided before the genetic testing that conferred a diagnosis. B) Information provided when participants received the genetic test result that conferred an MtD diagnosis. Stacked bars do not sum to 100% in cases where respondents left the question blank.

3.6 ENGAGEMENT WITH SUPPORT COMMUNITIES

The survey elicited participants' engagement with various support communities such as support/advocacy groups, support organizations, Facebook groups, and online message boards. Most participants had heard of at least one support community (14/17, 82.3%) (Table 3.4). Of the 14 respondents who had heard of at least one support community, nine (64.3%) indicated having heard about this from a provider (Figure 3.11). Additionally, four respondents (28.6%) heard of support communities through the Internet (Figure 3.11). Taking a closer look, it is noteworthy that parents/caregivers responding to the survey represent the majority of those who had heard about these communities from a provider (Figure 3.11). In fact, one specific pediatric provider was responsible for sharing information on these communities with all nine respondents (two individuals and seven parents). Amongst the individual cohort, it was more common for respondents to have heard about these groups from the Internet (Figure 3.11). No participants heard about these communities from other patients or families living with MtD (Figure 3.11).

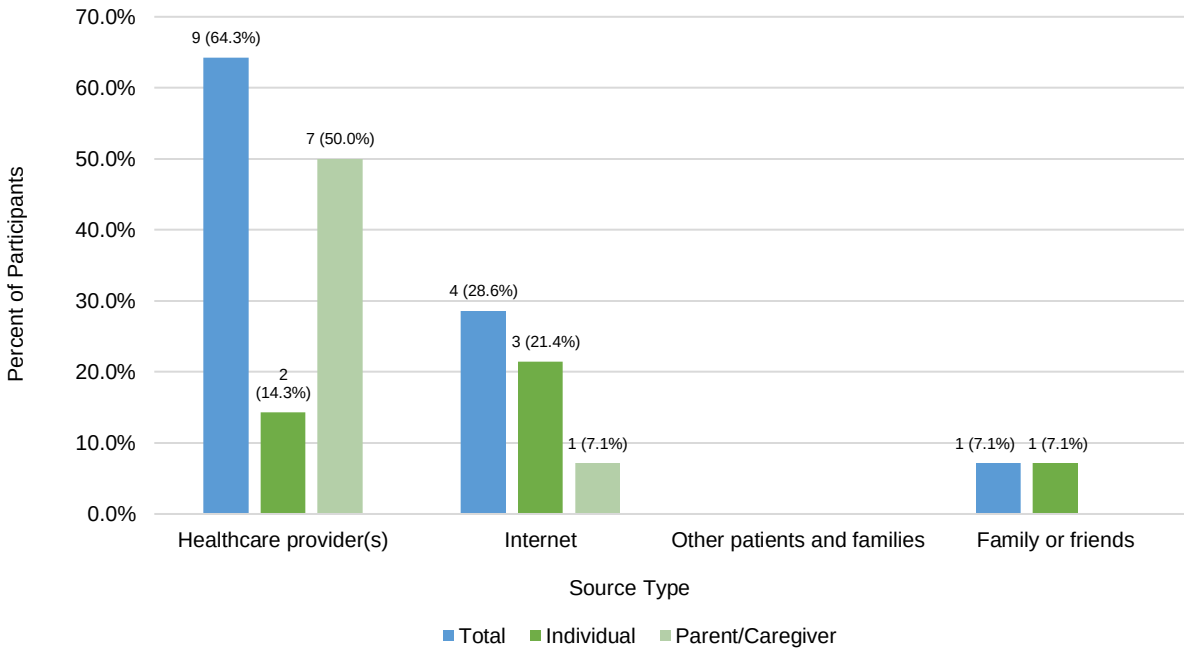

Figure 3.11. Sources of awareness about support communities. Participants could select all that applied.

Despite several participants having heard of support communities, only a portion were actually involved (7/17, 41.2%) (Table 3.4). Of note, a proportion of participants (6/17, 35.3%) wished they were informed about Facebook groups, support organizations, and online message boards (Table 3.4). As discussed above, participants noted in the survey that they accessed the least support and information from support/advocacy groups and support organizations throughout the diagnostic journey.

Table 3.4. Engagement with support communities

	Aware Frequency (%)	**Involved Frequency (%)**	**Wish Informed Frequency (%)**
Total	14 (82.3)	7 (41.2)	6 (35.3)
Individual	6 (66.7)	3 (33.3)	5 (55.6)
Parent/Caregiver	8 (100.0)	4 (50.0)	1 (12.5)

Note: Columns and rows do not sum to 100% as participants could select all that applied. Denominators are n=17 (total), n=9 (individual), n=8 (parent/caregiver).

Of the participants who reported being a part of one or more support communities, five of six (83.3%) reported these to be helpful, and the remaining participant left this question blank (Table 3.5).

Table 3.5. Perceived helpfulness of support communities

Helpful?	**Total Frequency (%)**	**Individual Frequency (%)**	**Parent/Caregiver Frequency (%)**
Yes	5 (83.3)	2 (66.7)	3 (100)
No	1 (16.7)	1 (33.3)	0 (0)
Total	**6 (100.0)**	**3 (100.0)**	**3 (100.0)**

An open-text response allowed participants to elaborate on the perceived helpfulness of these communities. Survey Participant 8 shared that these communities were helpful in gaining insight into how others were managing their conditions:

> "*[It] helps reading other people's experience and symptoms. What they do to manage daily life. Different treatments." (Survey-P8)*

Additionally, Survey Participant 17 highlighted how these communities act as a safe place to share their feelings and experiences:

> "*[It is] somewhere to vent. I don't have to pretend everything is okay. Hearing from other parents/caregivers who battle this disease with their child." (Survey-P17, parent/caregiver)*

The single survey participant who did not find involvement helpful shared their ambivalence and noted the importance of processing matters before moving forward:

> "*Apart from a brief introduction I wrote on the [Facebook page], I've not engaged with other members yet as I didn't know what to say without a concrete diagnosis. Will I become more active now? I can't say with any certainty as I'm still processing matters as we speak." (Survey-P1)*

CHAPTER 4: INTERVIEW RESULTS

4.1 PARTICIPANTS AND DEMOGRAPHIC CHARACTERISTICS

In the previous chapter, survey findings described the features of the diagnostic journey, relationship with providers, and sources of information and support. To further understand the diagnostic journey, semi-structured interviews were conducted by telephone or videoconference with 12 participants, all of whom had previously completed a survey. Interviews varied in length from 44-116 minutes, with the average interview time being 69 minutes. Interview participant demographics are summarized in Table 4.1 and are similar to the survey participant demographics presented in chapter 3. Again, certain groups were over-represented in this sample. The majority of participants were aged 30 or above (11/12, 91.7%), identified as women (10/12, 83.3%), were of European ancestry (8/12, 66.7%), and lived in Winnipeg (7/12, 58.3%) where provincial health services and MtD care providers are exclusively located. A notable proportion of participants held an undergraduate degree (5/12, 41.7%). In terms of MtD, four participants (4/12, 33.3%) had a mitochondrial deletion syndrome, with the most common syndrome being KSS. Three participants (3/12, 25.0%) were impacted by MELAS, two participants (2/12, 16.7%) with Leigh syndrome or Leigh-like syndrome, and three participants (3/12, 25.0%) with a rare pediatric-onset MtD. Rare pediatric-onset MtD were not specified to protect participant confidentiality.

Table 4.1. Demographics of interview participants

	Total (n = 12)		**Individual (n = 7)**		**Parent/Caregiver (n = 5)**	
	n	%	n	%	n	%
Age						
13-17 years old	1	(8.3)	1	(14.3)	0	(0)
18-29 years old	0	(0)	0	(0)	0	(0)
30-39 years old	3	(25.0)	0	(0)	3	(60.0)
40-49 years old	3	(25.0)	2	(28.6)	1	(20.0)
50-59 years old	4	(33.3)	3	(42.9)	1	(20.0)
≥ 60 years old	1	(8.3)	1	(14.3)	0	(0)
Gender Identity						
Woman	10	(83.3)	6	(85.7)	5	(100.0)
Man	1	(8.3)	1	(0)	0	(0)
Non-binary	1	(8.3)	1	(14.3)	0	(0)
Condition						
Mitochondrial deletion syndrome	4	(33.3)	4	(57.1)	0	(0)
MELAS	3	(25.0)	2	(28.5)	1	(20.0)
Leigh/Leigh-like syndrome	2	(16.7)	0	(0)	2	(40.0)
Rare pediatric-onset MtD	3	(25.0)	1	(14.3)	2	(40.0)
Education[a]						
Some high school	3	(25.0)	2	(28.6)	1	(20.0)
Graduated high school	2	(16.7)	2	(28.6)	0	(0)
Some college/university	1	(8.3)	1	(14.3)	0	(0)
Undergraduate degree	5	(41.7)	1	(14.3)	4	(80.0)
Graduate degree	0	(0)	0	(0)	0	(0)
Other Ways of Knowing	2	(16.7)	1	(14.3)	1	(20.0)
Prefer not to answer	1	(8.3)	1	(14.3)	0	(0)
Ethnic Identity[b]						
Asian origins	2	(16.7)	1	(14.3)	1	(20.0)
European origins	8	(66.7)	5	(71.4)	3	(60.0)
Indigenous	1	(8.3)	0	(0)	1	(20.0)
Prefer not to answer	1	(8.3)	1	(14.3)	0	(0)
Geographic Location						
In Winnipeg	7	(58.3)	4	(57.1)	3	(60.0)
< 1 hour	1	(8.3)	0	(0)	1	(20.0)
1 hour	1	(8.3)	1	(14.3)	0	(0)
1.5 hours	2	(16.7)	1	(14.3)	1	(20.0)
5 hours	1	(8.3)	1	(14.3)	0	(0)

[a.] Total does not sum to 100% as participants could select more than one option (e.g. Some high school and Other Ways of Knowing). [b.] Categories for ethnic origins were applied as developed by Statistics Canada (2017a).

4.2 OVERVIEW OF THEMES

Five key group experiential themes were identified through IPA of qualitative data (Figure 4.1). All themes were present across at least half of the participant accounts (Table 4.2). The first theme, “The diagnostic journey unfolds in stages,” conveys the sequential phases in which participants recalled their diagnostic journey and how these were situated within the overall MtD experience. The second theme, “The patient-provider relationship influences the diagnostic journey,” highlights the elements participants felt to be integral to an effective PPR and how this relationship underscored the journey. The third theme, “‘We’re all asking for prayers’: Psychological significance of the diagnostic journey,” offers insight into the unpleasant feelings and evolving uncertainty that seemed to transcend the journey, as well as how participants made sense of, and coped with, their experiences throughout this process. Theme four, “‘Knowledge is the key to everything’: Information as support,” encompasses the complexity of how information was viewed and negotiated by participants in the context of the MtD diagnostic journey. Finally, theme five, “‘The way of life changes dramatically’: Impacts on life and unmet social needs,” illustrates how social challenges and stressors of the diagnostic journey extended beyond the medical setting. Although these five themes are presented separately, it is important to note that these themes are intricately interconnected and influence each other in ways unique to each participant. Therefore, these themes represent shared experiences despite each participant making sense of their journey in their own way. Excerpts from the data are presented with study identifiers; responses are from individuals with lived experience of MtD unless noted as parent/caregiver.

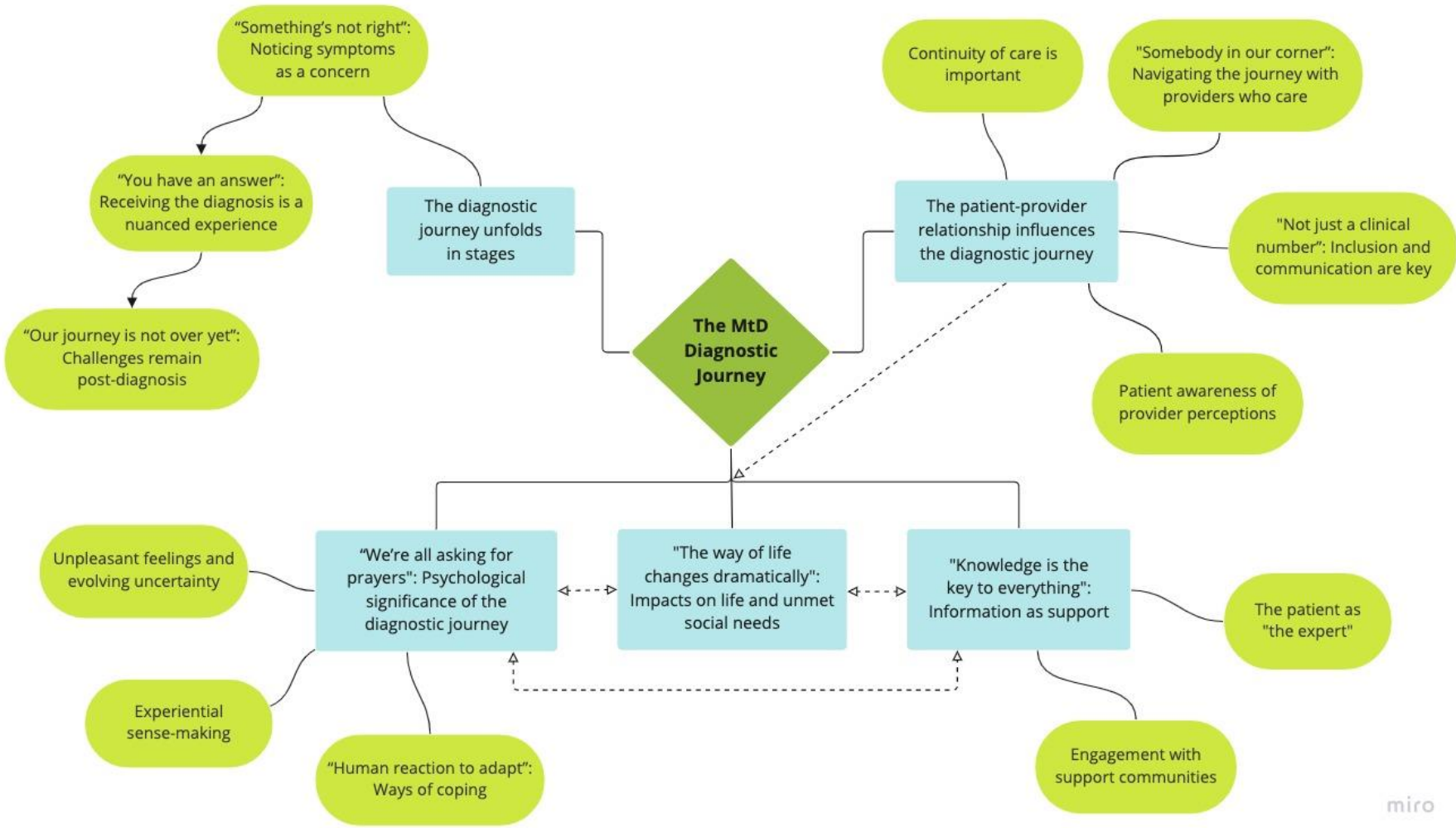

Figure 4.1. Group experiential themes and sub-themes resulting from IPA of qualitative data. Dashed arrow lines represent connections between themes that influence one another, and arrowheads indicate the directionality of this connection.

Table 4.2. Recurrence of group experiential themes across participants

Group experiential theme	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	Half of sample?
The diagnostic journey unfolds in stages	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	NO	YES
The patient-provider relationship influences the diagnostic journey	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
"We're all asking for prayers": Psychological significance of the diagnostic journey	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES	YES
"Knowledge is the key to everything": Information as support	YES	YES	YES	YES	NO	YES	NO	YES	YES	YES	YES	YES	YES
"The way of life changes dramatically": Impact on life and unmet social needs	YES	YES	YES	YES	YES	YES	YES	NO	NO	YES	YES	NO	YES

4.3 THEME 1: THE DIAGNOSTIC JOURNEY UNFOLDS IN STAGES

As participants shared their diagnostic experiences, they described a sequence of events that unfolded. These events allowed for the conceptualization of stages from participant accounts to help understand the diagnostic journey. These stages included noticing that something was wrong and seeking consultation, receiving the diagnosis, and adapting to life post-diagnosis.

4.3.1 "Something's not right": Noticing Symptoms as a Concern

Participants described the diagnostic journey beginning with the perception that "something's not right" (P11, parent/caregiver). This perception was not necessarily linked to the first instance that symptoms were experienced. For example, several participants reflected on the moment that they perceived symptoms as a problem for themselves or their child. Evidently, it was not until symptoms reached a threshold where life was impacted that participants began to worry and perceive notable changes as an issue requiring attention:

> *"I didn't notice anything really over the first year. [Child] started [experiencing symptoms], but it wasn't weird…so that wasn't even on my radar…I started noticing that [they weren't] hearing as well as I thought [they] were, and [their] speech was probably the biggest thing I noticed, it was super garbled. Like [they] would try to speak, but I couldn't understand anything that [they] said." (P3, parent/caregiver)*

For others, though they sensed something might be wrong, they waited until they were sure of this perception to insist on further investigation:

> *"I noticed that [child] is not moving [in utero] at least 17 times in a day, so I went to call my OB about the concern and, at first, [the OB] was hesitant…So I called my OB again that I'm 100 percent sure I'm counting and [they're] not moving as many times as [they] should during this third trimester compared to my other kids." (P7, parent/caregiver)*

While these participants began to notice symptoms as a concern before others in their lives, Participants 1 and 12 both noted that it was other people who perceived their symptoms to be an issue before they considered these to be serious themselves. Upon reflection of this experience, these participants recalled that symptoms likely started before they recognized them as a concern:

> *"I would hold my hand up, and my index finger was kind of crooked downwards and so my friends kind of made fun of me like, 'Oh, something is going on there,' and I never really paid any mind, you know? I didn't think anything of it, then the flesh in my hand kind of eroded away, and I started suddenly noticing that I couldn't do things with my fingers as nimbly as I could before, so it kind of just, the thing is I didn't really think, I just sort of adapted…That's where, now looking back at this last 20-30 years, the real mitochondrial disease symptoms started probably when I was like, probably like 21-22, I think." (P1)*

> *"I do remember when I was in kindergarten, I think, so five [years old], I had a lot of issues with balance. I remember my dad told me to stand up still. And I couldn't stand straight…So I remember it was confusing. And I remember I was like, I remember being, I think, a bit scared. I guess, just because no one else had like these balance issues, so why do I kind of thing?…I feel like I might have gotten more concerned about it because my parents noticed it and were like, 'Hey, this might be an issue.' So you know if your parents say it's an issue, oh, no." (P12)*

In hindsight, some participants noted that symptoms related to MtD were originally addressed on a standalone basis. It was not until the condition progressed and impacted their lives more significantly that they realized something more was going on. For instance, one participant had been Deaf since childhood but did not begin the diagnostic process until they began experiencing fainting episodes:

> *"I was having a lot of fainting experiences…First of all, I'm Deaf. [My] hearing aid would fall off or something [during a fainting episode]. I would be completely deaf. So it was terrifying. And also, my mind, I didn't know what was happening. It was very scary for me. And well, the worst thing was not being able to recognize when my husband and daughter came to me, I had no idea who they were. So it was just scary." (P5)*

Overall, these accounts highlighted the different ways in which participants perceived their symptoms as being a concern, whether these had a significant impact on their life or someone else took notice. This perception was what prompted participants to seek medical consultation, marking the beginning of the diagnostic journey.

4.3.2 "You have an answer": Receiving the Diagnosis is a Nuanced Experience

Most participants reflected on receiving the diagnosis as a pivotal event in their journeys. However, there was variability in what the diagnosis meant for participants. For instance, many participants described profound emotions in response, while others noted an

incongruence between expectation and reality when it came to the initial impact and what this meant for management moving forward. Participant 11 (parent/caregiver) struggled to describe the depth of their emotions both then and now:

> *"It was devastating. I was, this will sound so dramatic, I was, I don't even know what I was when I received the diagnosis. I was scared, I was worried. I didn't think then that I had much time with [my child]. I guess again, you always sorta jump to the worst at the beginning. I went outside the Children's Clinic, and I just bawled." (P11, parent/caregiver)*

In contrast, another participant described the diagnosis as a relief, as there was better direction for treatment following receipt of the diagnosis:

> *"I actually take every diagnosis I get as a relief, no matter how good or bad it is…I see it as, well, okay, if it's good, it's a relief because it's not bad. If it's bad, I see it as a relief because then now we can move forward with a treatment to correct the problem. And that's – that's pretty much for like a general blanket belief." (P10)*

However, for both Participants 10 and 1, the diagnosis was not described as a definitive answer but rather as a step in the overall journey:

> "*It [the diagnosis] just hadn't really taken prominence in the discussion I don't think, as I recall, I could be mistaken, but I don't remember it being like, 'that's our answer so far, that's kind of what we're thinking it might be,' it was sort of just it was mentioned that it could be that." (P1)*

For many participants, the diagnosis seemed to provide a sense of validation for what they had been experiencing. Some participants described the diagnosis as a moment of clarity, where they received an explanation for symptoms that they had experienced for some time. However, several participants described the validation of a diagnosis in slightly different ways. For instance, for Participant 4, while the diagnosis provided validation, it did not change their lived experience or priorities in that moment:

> *"When they actually diagnosed [spouse] with [MtD], we were all in the room. I remember [their] brothers being there, myself, my children. And yeah, when they said that [they] had [MtD], it was, I mean, it's what they had assumed [they] had…it was a confirmation that it was in fact [MtD]. So it was like, we were dealing with it already by that point, right? And as long as [they] hadn't had any more seizures, we were doing good." (P4)*

Unlike Participant 4's experience, Participant 10 noted that the diagnosis not only provided validation for present symptoms but also connected various issues experienced throughout their life:

> *"One thing that was kind of a relief was after hearing about a lot of these symptoms, it was a complete aha moment, like oh, that explains that, or that explains this. It was like you finally saw the full picture, like the full puzzle, but still missing some pieces rather than looking at the puzzle as individual pieces, it's now like a complete picture." (P10)*

For others, the diagnosis relieved uncertainty by providing, for the first time, some semblance of a concrete answer:

> *"It was just nice to be able to actually have a diagnosis at the end of that and not have more questions. I didn't want to be the question case. You know, 'It's kind of like this, but it's not completely, and it's kind of like this, but not completely,' and you're – you really wanted to [hear], 'This is what it is kind of thing.' So that was reassuring, when we finally had that." (P8, parent/caregiver)*

One participant conveyed that the diagnosis marked their ability to move forward or make progress in the journey. It was not until a diagnosis was received that meaningful action could be taken:

> *"…as much as the diagnosis that we got wasn't what we wanted, at least then you have an answer, and you know what you're dealing with, and you can do something about it, right? You can start – as much as there isn't treatment, you can start taking action and precautions and things like that. So, getting to that diagnosis is probably the number one thing we needed." (P9, parent/caregiver)*

Notably, despite the importance of a diagnosis, these excerpts impart an overall sense of incompleteness, as though the diagnosis could have provided more. This lingering feeling alluded to by participants likely related to the lack of understanding in the field of MtD and the uncertainty that veiled this group of conditions.

While receiving the diagnosis was a significant experience, it was also a complicated one. As noted in Participant 4's excerpt above, the diagnosis did not necessarily alter the ways in which symptoms were being managed. Instead, the diagnosis seemed to illuminate what to expect in the future and allowed participants to transition into the post-diagnosis stage, where they allowed themselves to process the significance of a diagnosis and move forward:

> *"…it [the diagnosis] doesn't really change much, they were still the same today as they were the day before they got the diagnosis, but it took a lot of worry out of our minds and it just let us focus our priorities." (P3, parent/caregiver)*

> *"When [child] was finally diagnosed, officially diagnosed, then that's when we were a little bit open to accepting that [they're] really sick…So we had to kind of accept and start to prepare ourselves for the worst." (P7, parent/caregiver)*

In summary, the diagnosis was described as a significant moment for participants. However, while this moment signified the resolution of the diagnostic journey, it seemed to be a milestone rather than a denouement in the overall MtD journey for participants.

4.3.3 "Our journey is not over yet": Challenges Remain Post-Diagnosis

Participants noted that numerous challenges remained post-diagnosis due to the lack of understanding surrounding treatment and management for MtD, signifying that "[their] journey is not over yet" (P4). One participant articulated the profound weight of this reality:

> *"And I think the missing pieces to that would be the fact that there is no end to this. Until the day that they come up with a cure for it, or treatment that is effective to everybody, there is no end in sight. And I think it's that empty hole that makes it, well, anxiety-inducing, really." (P10)*

Prior assumptions were made that the diagnostic journey would conclude at the receipt of a diagnosis; however, the experiences of participants suggested that the journey continues long afterward. The post-diagnosis stage was marked by persistent uncertainty about the future and symptom progression. For instance, Participant 1 noted the sense of progress with the management of another condition they experienced in childhood and how that compared to MtD:

> *"I now sort of have this answer, it's still kind of sort of like, 'Okay, now it's this,' it's not as satisfying as I thought it would be because there's no treatment option. Like, with [treatable condition]…it was like, 'Okay it's this and so now we're gonna talk to [providers] and we're gonna get some treatment ideas, things are going to move forward, things are going to get solved.' There was hope, there was progress." (P1)*

Similarly, Participant 6 shared their concern that their condition had worsened since diagnosis and how it may continue to do so, highlighting the notion that uncertainty remained following a diagnosis:

> *"So that hasn't made it any easier because over the past four years things have gotten progressively harder…I am already experiencing some of the worst things. They're not the worst things that are going to happen, but I also don't know what to expect in the future." (P6)*

Understandably, it seemed there was a general expectation that receiving a diagnosis would result in actionable next steps. Several participants compared MtD to other conditions with better-defined management and surveillance recommendations. This comparison showcased the unique challenges that participants navigate with an MtD diagnosis. For instance, this uncertainty affected how Participant 1 negotiated expectations about their future:

> *"I remember having a conversation trying to ask about progression because that's another huge sticking point I've been trying to get some concrete information on like how will this progress. What will my life be like in 2 years? 5 years? 10 years? 'Cause, say, if I'm going to be in a wheelchair in 5 years, should I be living my life differently now?" (P1)*

Interestingly, for Participant 2, the uncertainty of MtD appeared to be more difficult than the idea of having a diagnosis. That is, they seemed to accept living with a chronic illness but not the associated ambiguity in management, which spoke to how pervasive uncertainty is in the post-diagnosis stage:

> *"I was talking to [brother] on the phone one day and I said, 'You know, I really wish I had MS.' And he took that to mean that I wished I was seriously ill. But what I was actually saying is I wish I had MS because it was more understood and researched and had treatments for instead of the orphan disease…I would have preferred a different diagnosis, only because it would have been better understood." (P2)*

Despite the interview focusing on the reflection of past experiences, participants inevitably found themselves drawn to the present day living with MtD. This pull to the present may have signified the dynamic and evolving nature of the MtD experience that did not conclude at diagnosis as anticipated.

4.4 THEME 2: THE PATIENT-PROVIDER RELATIONSHIP INFLUENCES THE DIAGNOSTIC JOURNEY

While there were conceptualized stages of the journey that were elucidated through the accounts of interview participants, it was simultaneously evident that other relationship factors underlie the diagnostic journey, such as experiences with providers. The PPR is a hallmark of

clinical care. As such, providers are inseparable from the participants' experiences of the diagnostic journey. When asked about their providers, participants reflected on factors that both helped and hindered the PPR. Four sub-themes emerged, as a result, highlighting the importance of provider continuity, a genuine investment in patient care, meaningful inclusion in decision-making and communication, and positive regard in the PPR.

4.4.1 Continuity of Care is Important

Though participants had divergent experiences with providers, several noted that a lack of continuity hindered the ability to fully develop the PPR. For example, Participant 9 (parent/caregiver) described the struggle of having to rebuild trust with providers while navigating the difficulties of the journey:

> *"So we met with a genetic counsellor throughout the process multiple times and I think my biggest frustration was the turnover…I mean a lot of those conversations were fairly sensitive. I think I cried in a couple of them. So, always meeting with somebody new, and, you know, you've had conversations with one person, and now you're meeting with somebody completely different to talk about the same or similar things…you're always sort of rebuilding that relationship. I think some of those conversations would have been easier if it was consistent." (P9, parent/caregiver)*

For Participant 10, this lack of continuity resulted in a responsibility to continuously educate providers about their experiences, which was perceived to delay care:

> *"It's just disheartening when you do get pushed over to yet another specialist and have to go through square one again to catch them up…you can only then start with their procedures and such." (P10)*

In these accounts, participants shared that a lack of consistency impacted the ability to maintain rapport and deepen the PPR. In turn, this inconsistency necessitated the rebuilding of the relationship with new providers and perhaps lessened feelings of support along the journey.

4.4.2 "Somebody in our corner": Navigating the Journey with Providers Who Care

Participants felt most supported by providers who were perceived to "be in [their] corner" (P9, parent/caregiver). Many participants emphasized the lack of general knowledge around MtD but did not fault providers for the uncertainty they experienced along the journey. Instead, it was

important for participants to feel as though they had a provider who genuinely cared about them/their family:

> *"…they [specialist providers] did the best that they could, I felt like I was heard. I felt like I could call people if I had any questions. People [specialist providers] were very open to answering them. I didn't feel shut down or talked over or condescended to or anything like that. So, overall, I mean, if I have to have the experience, it wasn't horrible." (P8, parent/caregiver)*

Another participant similarly recalled the provider wanting them to be *"informed as much as I can be even though [they're] not there to talk to me about all this stuff."* (P11, parent/caregiver).

Similarly, a few participants recalled the moment in which they met with a provider who shared some of their burden of navigating the journey alone. One parent shared that *"knowing that [a particular specialist provider] was just on the journey with us was just a huge relief."* (P3, parent/caregiver).

Provider advocacy and reassurance were helpful throughout the diagnostic process as well. Participant 4 noted receiving reassurance from providers helped ease worry about worsening symptoms and the condition progressing:

> *"So and I get that confirmation from the doctors, right? So the doctors are all telling us [husband]'s doing really well. And as long as I hear that, I'm okay." (P4)*

Other participants recalled the specific providers who were involved in facilitating or advocating for testing to be the most helpful during the journey:

> *"[The] genetic counsellor who advocated for [child] to get the funding that [they] need[ed] for the diagnosis…because they needed to advocate to get this test done because it's fairly expensive, I was told…so the genetic counsellor helped us to get the test…and then [the specialist provider] who advocated [for child] to be tested..." (P7, parent/caregiver)*

Participants felt that this act conveyed a genuine investment in their care:

> *"[Specialist provider] was the one who sort of championed for the genetic testing, [they] really seemed to take an interest in [child]'s case…like I felt [they were] really pushing to find the answer there." (P8, parent/caregiver)*

In contrast, sharing information in an insensitive way negatively affected the PPR moving forward. Participant 6 recalled how one provider ruptured the PPR in the way that they explained diagnosis, which resulted in their emotional disengagement from care:

> *"So that made it difficult to deal with [specialist provider] for the next five years to the point where I didn't want to go to my appointment, but I did anyways. Because that's not how you put something if you are dealing with a person, because that's not very sympathetic or kind or caring. It was very harsh for [provider] to say that to me and that's always stuck in my mind that one doctor said that to me." (P6)*

A strong PPR fostered feelings of resilience and empowerment for participants when faced with additional challenges along the journey. For instance, one participant described the experience of finding out they were pregnant during their child's diagnostic journey and how the associated fear and anxiety of recurrence were eased by their established connection with a care team:

> *"We at least knew what to look for. And we already had a team…there was a little bit more of a comfort knowing that I had had a team of people I could contact if there was an issue as opposed to with [child who is affected], when we were like, we don't know what the heck's going on...So there was a little bit more of a comfort there knowing that we wouldn't have to start from scratch, you know?" (P8, parent/caregiver)*

Conversely, some participants discussed a perceived lack of urgency from providers and how this undermined the PPR. Participant 1 noted how they began to lose trust in their provider due to delays in care and how a lack of diagnostic progress exacerbated this frustration:

> *"So, I'm thinking a week, two weeks, three weeks max, I'll get a notice about my rescheduled appointment. I get a notice in the mail it was for [months later]! And so I'm just so frustrated and so annoyed and maybe if things were a bit more settled or more productive on the diagnostic side maybe I wouldn't have been acting as I did but…this was just like, something too far, a push too far…" (P1)*

Participant 9 (parent/caregiver) described how a lack of communication was perceived as a lack of urgency and associated progress with this process:

> *"…the [specialist] doctor was good to deal with, but we weren't getting answers, and it felt like were just constantly, you know, doing testing that wasn't resulting in anything." (P9, parent/caregiver)*

Similarly, Participant 10 remembered the dismay felt when they presented to their PCP with a family history of MtD and testing was not facilitated in a timely manner:

> *"…the actual process of going from not knowing to knowing, I had zero support. The lack of urgency from my family doctor at the time when I told [them]…" (P10)*

In addition, several participants shared experiences in which they felt dismissed by providers, which fostered feelings of distrust and self-doubt. In some cases, there was a perceived reluctance of providers to investigate patient concerns, resulting in feeling dismissed:

> *"Unfortunately, most doctors don't like the idea of a patient telling them, well, I know there's something wrong, I need your help to find out what it is. And especially…if they don't see an obvious answer, it's like, well, you're a medical miracle, or a mystery, have a nice day." (P10)*

Further, Participant 11 (parent/caregiver) spoke about the providers their family had met along the diagnostic journey and how trust was lost in providers' ability to address their needs over time:

> *"Honestly, I felt like telling them [providers] off [laughs]. [My child] even, like [they] got to the point where [they] didn't want to go see the doctors. [They] w[ere] telling them off to me even. 'I'm not going to another doctor's appointment,' [they] even still now say like, 'Another doctors?' Because like [they've] just lost trust in them as well…" (P11, parent/caregiver)*

Overall, the diagnostic process can be distressing, and participants emphasized that being accompanied by providers who show genuine caring and investment in their care can make a significant difference in how patients perceive this journey.

4.4.3 "Not just a clinical number": Inclusion and Communication are Key

It was important to participants that patients be seen as partners in healthcare and that ongoing communication be maintained between these groups throughout the diagnostic process. Multiple participants shared the desire to be included in discussions about how best to approach care and for providers to consider their perspectives:

> *"I've always been under the impression that the doctors are supposed to work…with the patients, not work for, or be in control of, [the patients]." (P10)*

Participants valued when providers meaningfully included them in discussing changes to their care, rather than superficially moving through the motions:

> *"Like [specialist provider] talking to me about why and what they want to switch [for treatment] and [they've] never left me out of the loop or talked too medical for me that I didn't understand. [They] made sure that I understood exactly what was going on and why." (P11, parent/caregiver)*

Likewise, making an effort to engage their child in their care was impactful for Participant 8 as a parent:

> *"So I always remember the ones that include [child] in [discussions about the diagnostic process] instead of talking over them, because they are quite sensitive to it and it's happening to them." (P8, parent/caregiver)*

The child of this participant was also interviewed and echoed the desire to feel included in discussions with providers during their diagnosis:

> *"I do remember, my [parent] has told me a couple times where nurses and doctors were talking over me. And so…I was like, 'Hey, it's about me, right? So why aren't you talking to me?' I'm pretty sure they listened after that one." (P12)*

Overwhelmingly, participants wanted to feel as though someone was invested in their care, alluding to the possibility of the diagnostic process being dehumanizing. Two participants specifically referred to the value of being viewed as a person rather than a clinical number. It was providers viewing the patient as a person and taking the time to listen that added an important human element to the care received:

> *"… for the most part, as long as I felt heard, if that makes sense…you don't want to just become a number, a clinical number, especially since a lot of this mito stuff is new and there is a lot of learning." (P8, parent/caregiver)*

> *"Because they [providers] showed interest in me as a person, not me as a number, or just a body on a table. And they're – it almost has that sense of where they're actually trying to make a concerted effort to take my healthcare seriously. It's stressful for me having to go through all these tests, and be the human guinea pig, and taking all my blood, and everything, but at least they're making that effort to stay on top of things." (P10)*

As this journey was a new experience for most participants, they expressed the desire for more communication to understand how and why the process was unfolding. For instance, some participants shared that it would have been helpful to have more updates on the progress of investigations as opposed to restricting communication to whether an answer had been identified:

> *"It would be nice to have the final information in writing, but even throughout it would be really cool just to say, 'We've done this test, we're looking for this,' and then when the results come, 'We couldn't find this so we're going to test this.' Just to, obviously speaking in person is nice and all, but it's a disorienting process, you know? You're dealing with some heavy issues, you don't know how you're going to react." (P1)*

While Participant 9 (parent/caregiver) echoed this need for more updates on diagnostic progress, they noted an awareness that this approach may not be universally requested, alluding to the importance of providers eliciting the informational needs of each patient and family:

> *"But I think having that heads up of…we had ruled out this original diagnosis that they had suspected and then there was no kind of, 'Okay, well, now we're looking at this spectrum of conditions,' and like this is what it could mean, which I get some people maybe wouldn't want that information, because maybe then they would start to panic, but I think at least having some idea of what was being considered would have been helpful." (P9, parent/caregiver)*

At times along the diagnostic journey, various providers did not communicate the reasoning behind their decision-making, leaving patients feeling confused:

> *"Most of [providers] say, 'Well, we're doing this' and walk out the door, but you didn't really tell me why. Why are we doing this? You know, end up leaving with more questions than when you went in." (P11, parent/caregiver)*

Other participants described feeling as though providers did not consider both their emotional and information needs – beyond establishing a diagnosis – and how this negatively influenced the PPR. Participant 1 recalled how a provider missed the opportunity to address their underlying emotions, which left them feeling alone in processing the information being shared:

> *"So, I'm trying to ask about progression and [specialist provider's] saying, 'Well, we don't really know 'cause it's such an ill-understood disorder so I really can't tell you,' so my head's spiralling off trying to fathom how am I gonna move forward with that kind of uncertainty, and he's still going on about the intricacies about what the tests entail, you know?" (P1)*

Participant 4 shared how difficult it was to communicate with providers who did not accommodate the communication needs of their spouse, which subsequently excluded them from conversations about their management:

> *"It was the fact that [spouse] could not hear. So I had to be there a lot of the times and say, listen, you're talking to [them] like [they] can hear you, [they] cannot hear you. So…it's been a big, a very big turmoil of emotions and things that go with that. And frustrating for [them] as well, because [they're]…only hearing half a conversation." (P4)*

As described by participants in the previous subtheme, a strong PPR can improve perceived support. Inclusion of patients in decision-making and healthcare, elicitation of patients' informational and emotional needs, and open communication are key elements of the PPR that participants in this study identified as being helpful along the diagnostic journey.

4.4.5 Patient Awareness of Provider Perceptions

Several participants noted an awareness of being positively or negatively perceived by providers as a patient or parent/caregiver, as well as the importance of being believed. One participant described an avidity to remain an agreeable patient while still trying to advocate for their needs:

> *"And the thing is, I feel shitty about it too because I'm like, 'Am I being a difficult patient? Am I being unreasonable? Am I being melodramatic?' Maybe…because of my state of mind and the experience I'm going through, but kind of work with me, don't make me seem like an asshole." (P1)*

Another participant alluded to the desire to avoid being labelled as an anxious parent when communicating concerns about their child's hearing to their PCP. This awareness led to participants doubting their perception of the situation:

> *"So I ended up taking [child] to our family physician, who, really that was kind of the frustrating part because I told [family physician] I really don't think [child's] hearing well and [they] kind of walked behind [child], [child] saw [them] do it, and [they] clapped behind [child]'s head and [child] turn to look at [them] and [they] said, 'Well, see, [child] can hear fine,' and didn't really take that seriously…So, then I was like fine okay I thought maybe I was just being... noticing things that weren't true..." (P3, parent/caregiver)*

Another parent reiterated the worry of being perceived as an anxious parent and how this influenced their approach to communication with providers:

> *"I don't want to be that person that's just like, 'I understand healthcare better than you'. And it's like, I just know that I know my kid." (P8, parent/caregiver)*

Within and beyond the PPR, the importance of being believed throughout the diagnostic journey emerged as a key finding. Particularly, participants highlighted the significance of compassion, accommodation, and understanding when navigating the MtD diagnosis. The invisibility of living with a chronic illness impacted relationships beyond the PPR for Participant 10:

> *"'Oh, why can't you do this? Why are you always tired? Why are you always sore? If you didn't want to come out, why didn't you just say so?' I've even heard, 'It's convenient that…you were fine up until your diagnosis.' And it's like, well, no, I wasn't, but that's one thing about this, is that it's degenerative. It doesn't get better. You may have good days, but it's not gonna get better. It's only going to progressively get worse." (P10)*

Similarly, Participant 12 recalled that while they had improved their ability to self-advocate once a diagnosis was received, learning to communicate their needs was difficult when first navigating the diagnostic process:

> *"I wish that there were more accommodations, I guess…like if I suggested, 'Hey, I'm feeling really tired. Can I sit down?' it was kind of more believed. Because now it is [believed] because I understand it, I can explain like, I get really tired easily. Where, at the time, I couldn't explain it." (P12)*

Overall, the relationship between participants and providers influenced the diagnostic journey in significant ways. An effective PPR founded on open communication, meaningful inclusion in decision-making, genuine care, and positive regard resulted in patients feeling supported and less alone.

4.5 THEME 3: "WE'RE ALL ASKING FOR PRAYERS": PSYCHOLOGICAL SIGNIFICANCE OF THE DIAGNOSTIC JOURNEY

In addition to the diagnostic journey seemingly unfolding in stages, there were accompanying psychological components that affected the wellbeing of participants.

Specifically, three sub-themes were identified. First, unpleasant feelings and evolving uncertainty were present throughout this experience. Second, participants recounted their journey through the lens of their unique life experiences. Lastly, participants reflected on the various ways in which they coped with stressors during the process. These sub-themes occurred throughout diagnosis and were embedded within the diagnostic stages.

4.5.1 Unpleasant Feelings and Evolving Uncertainty Along the Diagnostic Journey

Numerous emotions and psychological processes characterized the diagnostic journey and contributed to the experiences and needs of participants. Overwhelmingly, participants expressed the ubiquity of waiting and a constant but evolving sense of uncertainty. While waiting was an expected part of the diagnostic process, participants emphasized the agonizing aspects of awaiting answers:

> *"So, they said it's gonna be about 3-4 months because they said they need to culture the sample for about a month and then send it off, so I was like okay, fine, you know what, I'll wait, I'll wait. So, then it was March, April, May, June, waiting, waiting, waiting." (P1)*

When discussing the entirety of the journey, it was not the initial symptoms, diagnosis, or even lack of management implications that was the most impactful, but "*it was just basically the waiting, I think, that was the hardest part."* (P3, parent/caregiver).

Tying into the PPR described in the preceding theme, Participant 9 (parent/caregiver) highlighted how constant communication with the care team alleviated the psychological impacts of waiting:

> *"I mean we knew what they were doing, and the conversations that were happening. So, it was good to sort of be involved, and not just kind of waiting in limbo, waiting for things to happen." (P9, parent/caregiver)*

Waiting was accompanied by uncertainty, evident by the fact that all participants described living with uncertainty in some way. Furthermore, not only was uncertainty present throughout the journey but it was also appreciated by participants in various ways. For instance, some participants described uncertainty while undergoing investigations and awaiting a diagnosis, while others illustrated the uncertainty both at and following a diagnosis. One participant

portrayed the inability to move forward without answers and how this negatively impacted their psychological state:

> *"I was talking to my friend way back in [month] about how this is ruining my psychological wellbeing and he's like, 'Well…you can do two things, you can stew and kind of succumb to the despair and anguish or you can kinda try to move on,' and I'm like, 'I would love to do that but without an answer, it's just this unrelenting uncertainty, you know?'" (P1)*

Alleviating uncertainty was conveyed as the most impactful factor for one participant, and they recalled the most difficult part of their family's journey was when the uncertainty was most heightened:

> *"..the year of not really knowing what it was, was almost harder than…since knowing what it is, and trying to get used to all the medications and stuff like that, because at least we have a diagnosis…I know they're still learning about the whole thing but…it still was easier than going, 'What is this?'" (P8, parent/caregiver)*

Of note, although the experience of uncertainty is presented here within the context of a sub-theme, it is clear from several excerpts shared in this chapter that this element is intertwined throughout the journey and thus inseparable from the MtD experience.

Furthermore, it became apparent that the diagnostic journey evoked powerful emotions. When reflecting back on the early stages of the journey, Participant 3 (parent/caregiver) described feeling helpless while awaiting referrals and testing to move forward with the diagnostic process for their child:

> *"And you know the process of getting [diagnostic test] was the worst because there wasn't anything I could do. I knew [child] couldn't hear me, [they] w[ere] behind in things, and there wasn't anything I could physically do to make it better." (P3, parent/caregiver)*

It was apparent that the psychological consequences of the diagnostic journey went beyond just a hope for answers and represented the helplessness felt in trying to care for a sick child, as described by Participant 11 (parent/caregiver):

> *"You know, we all try and be chipper and pretend everything's great. And then, you know, all of us are asking for prayers, because you know, there're [children] in the hospital again. I just feel there's no hope. And I guess being a rare disease that has no cure, there is no hope." (P11, parent/caregiver)*

Participant 10 shared the waves of fear that they experienced while receiving the diagnosis and coming to terms with the associated familial implications:

> *"…as soon as the [provider] mentioned that it was passed down from mother to child, then the fear flooded in again, because I have a [child]…I was praying to any God you choose that [they didn't] come up positive." (P10)*

One participant shared how their child was emotionally affected by the journey and reflected on whether their child's behaviour change was a response to this trauma:

> *"And so for [child], it was, I think it really put like, they didn't cry with tears for two years. They cry, like, they were upset that they didn't produce tears for a couple of years. It was the weirdest thing, because they were quite emotional and expressed their emotions very openly up until that point. And then after, I don't know if it was after…hospital stays, but definitely after the first one, it was like a trauma response. I think." (P8, parent/caregiver)*

These excerpts highlight the psychological complexity and toll the diagnostic journey takes for patients and families. Many participants expressed feelings of worry, anxiety, fear, helplessness, or confusion. Moreover, looking back on the diagnostic journey elicited feelings of loss, grief, and regret. Once again, these feelings were seen throughout the diagnostic journey and were not confined to a single stage. For example, Participant 1 illustrated the ways in which grief was all-encompassing while awaiting the diagnosis:

> *"There was a lot of times where like spontaneous crying about weird things, at a television series or something unprovoked, like I could be…sitting here and just overcome with a wave of grief. And it's far more severe than just mere melancholy…You know what it was? What else it also is? The diminishing of any ideas of the future I thought I had." (P1)*

For Participants 7 and 11 (parents/caregivers), regret manifested in different ways. This regret was closely linked to the anticipated grief of losing a child. Participant 7 (parent/caregiver) shared their most significant regret was in the final months of their child's life:

> *"I'm still working fulltime…my [spouse] still works part time so it took us a long time to finally bring [child] home. It's just one of my regrets because it took us a while to bring [them] home and take care of [them] at home." (P7, parent/caregiver)*

For Participant 11 (parent/caregiver), the anticipated grief was associated with the profound fear of having little remaining time with their child. They wished that they had done more to support their child in the activities they enjoyed before their condition progressed:

> *"Now looking back, I wish I had done a lot more if I had known this was how this disease was going to be there, and how it was going to affect [child] so fast. I just would have spent my last dime…I would have done so much so different no matter what the cost was." (P11, parent/caregiver)*

Overall, participants experienced unpleasant emotions and marked uncertainty throughout the MtD diagnostic journey. The unpleasant feelings and uncertainty that participants recalled along the diagnostic journey played a role in how they made sense of the experiences that were unfolding, further supporting the notion that the diagnostic journey is a complicated process that participants experienced uniquely despite areas of convergence.

4.5.2 Experiential Sense-Making

While all participants had received an MtD diagnosis, some were more recently diagnosed than others. The process of reflecting on their diagnosis provided participants with the opportunity to share how they made sense of this journey. Interestingly, participants tended to do so within the context of their lived experiences and beliefs. For instance, one participant discussed how previous experiences with illness impacted the real-time processing of their MtD diagnosis:

> *"I've dealt with sickness for long enough and had felt the limitations of the mitochondrial disease for twenty years to know there was no denying the facts as they came to light." (P1)*

Participant 2 referred to themselves as a zebra, referencing the medical teaching, "When you hear hoofbeats, think horses, not zebras" (Dr. Theodore Woodward, 1940s). The purpose of this phrase is to remind physicians to consider the most likely scenario over a possibly rare occurrence. This participant used this analogy to describe how they had experienced several "rare" medical occurrences throughout their life and that this influenced their expectations that the MtD symptoms they had started to experience would likely also be rare and significant:

> *"And again, I wasn't unaware or uncomfortable. And I would say I really didn't seem to have great expectations that it would be resolved quickly, or that it wasn't*

going to be serious and did not – well, I was pretty sure, once again, I was gonna be a zebra." (P2)

Participant 9 (parent/caregiver) alluded to the shock that accompanied the possibility of illness for their child as part of their sense-making. This participant highlighted that the moment when they began to worry was discordant with when providers first showed concern, noting just how unexpected this information was:

"[Specialist provider] seemed surprised that I wasn't almost like breaking down crying. I think [they've] probably had some difficult conversations in the past that haven't gone well…but as a first-time parent, you don't realize. I think if [child] had been my second, I probably would have known sooner that something was off, but you kinda are very hopeful for the best with your first, so…" (P9, parent/caregiver)

Another participant, spoke about their experience as a child on the diagnostic journey and how they did not begin to process the idea of a diagnosis until years later:

"I'm pretty sure at the time, I was like, 'Okay, so I can't walk very good, that's cool.' Or at least that's how I interpret it now, but I didn't know what a diagnosis was…I couldn't really understand, like, getting that [a diagnosis] and not getting it kind of thing. So it was more…I don't actually remember when I got diagnosed. I thought that I got diagnosed way earlier than I actually did." (P12)

As well, it seemed that the perception of symptoms as concerning, as noted in the first theme, influenced the perceived severity and significance of the diagnostic journey. For instance, Participant 5 shared that they had been living with symptoms their entire life, and so the diagnosis did not impact how they were living:

"I just learned to live with it, because to me, it was normal. I don't know what normal actually is for a normal person. But for me, because I've had this all my life, it was normal…That's all." (P5)

Therefore, it was clear from these accounts that participants conceptualized their diagnostic journeys in unique ways constructed within the context of their own lived experiences.

4.5.3 "Human reaction to adapt": Ways of Coping

Given the psychological components of the diagnostic journey and the degree of uncertainty as illustrated above, participants noted using emotion-focused and problem-focused

ways of coping, as described by Lazarus and Folkman (1984). Emotion-focused coping aims to minimize the emotional aspects associated with a stressor, whereas problem-focused coping seeks to eliminate the stressor.

Various emotion-focused strategies were described by participants. For instance, some participants discussed attempting to maintain a sense of normalcy despite the dysregulating events of the diagnostic process:

> *"It [diagnostic process] was overwhelming, because I know that talking about it too much in front of [child] added to their stress. So a lot of it was just trying to maintain some kind of regular normal stuff for them as much as possible in that time." (P8, parent/caregiver)*

Others sought to escape or avoid the reality of the situation through distraction while awaiting updates:

> *"…I spent all my time just trying to occupy myself, occupy my brain with like TV series. I actually kept a list for a while of how much TV I was watching because it was just series after series after series just to kind of keep my mind off of it. And even now when I'm watching something, or if, well it's just reruns, I'll be okay, I don't really think about things but say I pause to go grab a drink from the kitchen, the whole time the whole walk there to is just a screaming stream of negative thoughts." (P1)*

For some participants, managing expectations about the journey or taking a fatalistic approach to understanding the situation were adaptive ways of coping. For instance, Participant 3 (parent/caregiver) shared that providers giving anticipatory guidance helped manage their expectations regarding the receipt of a diagnosis:

> *"…[providers] really prepared us for it saying, 'You know, we probably won't ever find out what's wrong and a lot of kids in these Facebook, you know these [symptom-specific] groups for kids, a whole lot of people don't ever find out.' It's kind of a rarity I guess that people do have a concrete answer, so I didn't, I went into it without expectations to be honest." (P3, parent/caregiver)*

Additionally, Participant 5 shared how they coped with persistent symptoms while awaiting an MtD diagnosis, implying that it was unproductive to stress about what they could not change:

> *"So there's not much you can do. I have to accept it. I was annoyed at it, yes. But there's not much I could do." (P5)*

For Participant 6, the diagnostic experience caused existential questions, which they coped with through acceptance and focusing on each day as it came:

> *"So it just makes you wonder, like, you kind of say, "Why did this happen to me?" but in the same regard, it's just like I can't change it, there's no cure, and those are the only things I'm learning from the doctors. So I'm just trying to take it one step at a time, day-by-day." (P6)*

Notice that in the excerpts of Participants 3 and 6 above, the PPR influenced coping strategies, highlighting that this relationship is foundational in the experience along the diagnostic journey.

Similarly, multiple participants discussed the role of faith and religion in coping. When asked about coping, Participant 2 described their relationship with God and the role this played in abating worry that MtD would impact their ability to care for their young children:

> *"Actually, it wasn't a person per se. I would say that although I'm not a, let's quote verses in the Bible, convert you Christian, it was my faith. I've had a long conversation, or a million, with God. I remember asking God, and the doctors, I said, 'I need,' and I did this in [year], I said, 'I need 10 years.' Because in 10 years, my children will be out of my home and in post-secondary school…" (P2)*

A few participants noted personal coping strategies that they were aware could exacerbate rather than alleviate stressors, and thus, intentionally avoided coping in these ways. Both Participants 8 and 9 (parents/caregivers) shared that they did not information seek online throughout the diagnostic process, even when they had an idea of what the diagnosis might be:

> *"My [spouse] did a bit more extensive research on it like [MtD] and stuff like that. [They] looked into that a little bit more in depth. I-part of me is afraid to know too much because if I know too much, I could look into symptoms and stuff and fear-based diagnose." (P8, parent/caregiver)*

> *"So, I'm not a Googler. I am not a self, you know, diagnosing kind of person, so I had nothing to do with that. I wanted nothing to do with that. The doctors would deal with it and tell us what we needed to know." (P9, parent/caregiver)*

Another means of emotion-focused coping was turning to personal support networks throughout the diagnostic journey. Participant 4 shared how important it was to have family members with whom to share the responsibility of care during the taxing processes of diagnosis:

> *"…we all talk to each other every single day. And, you know, two of my [children] at the time were living with us. So it was easier for, you know, [them] to be there for me as well. But at the same time, it was all to do with [spouse], right? Like, let's get [parent] home safe and sound, right?" (P4)*

Having friends and family as sources of support was helpful to cope along the diagnostic journey for several participants, such as Participant 8 (parent/caregiver), who shared:

> *"I have a pretty strong support system. I'm definitely a talk it out type person. So between my best friend and my mom and my sister and my [spouse], we all were able to kind of process it out loud. And so, having that was made it a lot easier to kind of abate the fears until we actually got a diagnosis." (P8, parent/caregiver)*

In contrast, some participants described feeling alone as they navigated the journey. Two participants captured this shared sentiment in different ways. Participant 6 described a sense of abandonment from providers and their personal network resulting from the diagnostic journey:

> *"…it can be very, I guess, isolating or lonely going through this and you feel like nobody cares and nobody – you don't want to be a burden to anybody so you just feel like you're all alone. Or I do, anyways." (P6)*

However, while some participants identified themselves as having personal support, they still described that the struggles of the diagnostic journey were beyond what their networks could support:

> *"I think the biggest factor for us was there is no one in our family that is willing enough to be trained [to assist in caring for child]. They were just not comfortable enough caring for [them] so we couldn't find another support person to help us take care of [them] to bring [them] home, so that's just the biggest thing that…we were facing because I think they [care team] initially wanted us to find at least two or three more support persons, but unfortunately, I couldn't find one." (P7, parent/caregiver)*

Interestingly, despite the difficulties of the diagnostic process, there was a sense of gratitude and understanding amongst participants when reflecting on their experiences, with one participant noting that *"I feel like we got like the lucky end of the stick with mitochondrial disease."* (P3, parent/caregiver). Perhaps situating the self in relation to how events could have unfolded, known as downward comparison (Wills, 1981), was also a means of coping:

> *"…I mean, obviously, you go back and you're like, 'Well, I wish we could have been diagnosed sooner.' But if they didn't know what it was, you got to answer all the questions, right? You don't want to rush anything. And I am grateful that they didn't just jump to that first diagnosis. And that [specialist provider] just wanted to do the genetic testing, just to be clear. Like when [they] suggested that we were like, 80% sure it was something else. And [they] just w[ere] like, 'I want to rule it out, just to be sure.' And that actually got us more into the mito stuff." (P8, parent/caregiver)*

Alternatively, problem-focused strategies described by participants included focusing on immediate needs and addressing symptom(s) that impacted life most significantly in an attempt to resolve the underlying stressor. Participant 2 spoke of a former PCP who refused to believe that their symptoms may be due to something other than the non-MtD condition that was initially proposed. This participant outlined how they coped in this situation:

> *"Well, like I said, this doctor was old…[they] w[ere] the family doctor when I was a child. And I kind of landed in [their] office by accident because I wanted the [diagnostic test]. So what I did, I changed doctors." (P2)*

As a result of feeling like their symptoms were dismissed by providers, Participant 10 described coping by learning to address symptoms in their own way:

> *"…that's how I managed to fine-tune my perception of my body and my health, is, I didn't have somebody else to help me look after it, so I had to get to know it as best as possible. So, even today, to this day, if I feel something different, I know something is up." (P10)*

When another participant's child was experiencing progressive symptoms that providers did not investigate further, they went to another province for answers:

> *"And it was so frustrating. Frustrating enough that I packed up a car one day…and drove to [another province] to see if anybody would help us. They said no, I drove to [another city]. They said no, not without referrals. So I drove back and was quite defeated." (P11, parent/caregiver)*

Furthermore, multiple participants used information to cope, such as through self-research. One participant described starting supplementation for MtD prior to diagnosis resulting from self-research that they conducted based on an inconclusive test report:

> *"They sent me a copy of that report and it was, obviously it was all technical medical language, I didn't really understand a lot of it. I reviewed it as best I could, and I came across this one bit about mitochondria on there and so I googled and researched myself and came across two articles here and there. One said to boost I guess production of mitochondria was to take Coenzyme Q10, so I thought oh what the hell, I'll give it a go until I hear otherwise. So, I started taking those...because it was a supplement, it wasn't really a medication." (P1)*

Information-seeking coping strategies offered a perceived sense of control. For instance, Participant 3 (parent/caregiver) viewed information as a way to abate the feelings of helplessness earlier described:

> *"I mean it was really a no-brainer for us, I really just thought, whatever information we could have as parents, let's do whatever we can so we can help the kids." (P3, parent/caregiver)*

Several other participants referred to information-seeking to remedy the lack of informational support received from providers:

> *"I guess what I've been doing is trying to read what I can about it online when I have the energy and can see well enough to do that, because I'm not getting a lot of answers. I don't feel like I get enough out of the doctor's appointments…" (P6)*

In summary, all participant accounts had some mention of coping. There did not appear to be a notable difference in coping strategies between affected individuals and parents/caregivers. Participants were not necessarily confined to a single coping strategy and described several strategies that were put into effect as their needs and stressors along the journey evolved. Overall, participants described the nuanced psychological consequences of the diagnostic journey, highlighting challenges intrinsic to the diagnostic journey and showcasing their resilience.

4.6 THEME 4: "KNOWLEDGE IS THE KEY TO EVERYTHING": INFORMATION AS SUPPORT

Information was a key part of participants' recollection of the diagnostic journey. This theme portrays how participants viewed and negotiated information as experts in their care as well as how they engaged with support communities.

4.6.1 The Patient as "The Expert"

As a result of the persistent uncertainty and in some cases, the lack of provider continuity that accompanied the diagnostic process, participants were often placed in the position of educating those in the healthcare system about their symptoms and investigations, placing them in the role of "the expert":

> *"The new [providers] I have at the [clinic] have all looked at me and said, '[Name], you know more about this than I do. Teach me.' So, you know, I do. Like they understand the science but, you know, they don't know the words and things it can do…" (P2)*

This also held true after diagnosis, as participants spoke about the lack of knowledge and awareness on MtD amongst providers and the public. Participant 1 shared how limited information available for MtD hindered the ability to make decisions about care:

> *"…when you look up what should you be eating for a diet or what vitamins should you take or whatever there's not a lot of knowledge, even on the Internet for this stuff. So it's kind of a catch-22, what do I do? What don't I do? What can I do?" (P1)*

As a result, several participants identified increasing awareness of MtD to be of importance in remedying the lack of knowledge on these conditions and improving the diagnostic journey:

> *"…the more that people are aware of what can happen…the more awareness is the best thing ever. So education, that's the main thing…knowledge is the key to everything." (P4)*

> *"I mean, getting the information about the disease out there is a big thing, so people can understand it. I mean, even if there's no cure…just getting the information about the disease out there and educating people." (P11, parent/caregiver)*

When asked about what would have been helpful along the diagnostic journey, participants spoke about information and what this represented. One participant suggested that providing patients and families with information throughout the process could relieve some degree of uncertainty:

> *"I'd say, give more information than you think is necessary. Like, if you think you're becoming a nuisance with all the information you're sending, do it, don't worry, flood that inbox, or that mailbox, just send it because people have questions, people have questions, they need answering, you know? I think it's a harrowing experience*

> *and information is like a salve, it's a balm, it helps when you're facing this looming question mark if you can make it a little smaller, it's helpful." (P1)*

Another participant described that they viewed information as a means of preparing for the future and seemed to credit this for improvements in their child's condition:

> *"So having that information I think is really helpful, and has helped us to keep [child] safe, so that [they're] able to develop, and to improve, and to continue to…exceed all the doctors' expectations…so I think information is key and having that is really helpful." (P9, parent/caregiver)*

In a way, this desire for further knowledge represented the hope that participants have for improved treatment, management, outcomes, and ultimately, a cure for MtD. Indeed, applying hope and positive thinking were coping strategies in themselves. However, it also seemed to move beyond coping. With a lack of tangible answers, it was understandable that participants advocated for ways to advance awareness of MtD and further knowledge that would provide these answers.

Furthermore, participants sought and received information from multiple sources, including providers, support organizations, social media, and the Internet. Navigating information online came with challenges that were exacerbated by a lack of diagnosis or a lack of available and or accurate information for MtD. Participant 6 spoke about the difficulty of appraising information online when trying to understand MtD inheritance patterns:

> *"So, I don't really know what to follow because on the Internet there's umpteen things you can read about the same subject and you don't know what's right or wrong, so that makes it difficult." (P6)*

Similarly, making sense of information related to possibly contraindicated medications was troublesome for other participants. Previously described ruptures in the PPR impacted one participant's ability to trust information received in the clinic, thus underscoring the importance of providers sharing their reasoning when it came to novel information:

> *"Well, and even worse is that there's so much conflicting information online…my [provider]…gave me a website – like the topic at hand was medications that people of mitochondrial disease should avoid. Okay, well, there was things on there that on previous lists that I had acquired said was an absolute no, you should not take these. And now, oh yeah, no, it's fine. Well, which is it? Is it okay for me to take this? Am I*

> *gonna die if I take this? Because a small handful of doctors said it was okay? Like – it's a huge rabbit hole online trying to figure out information." (P10)*

Interestingly, participants who alluded to challenges within the PPR also discussed relying more heavily on the Internet for information. For instance, Participants 6 and 10 above both described these challenges in the context of a lack of guidance from providers. while having a positive PPR does not eliminate challenges with navigating MtD information online, it may alleviate some of the responsibility expressed by participants to self-appraise information.

4.6.2 Engagement with Support Communities

When asked about sources of support, several participants mentioned support communities available through social media and the Internet. Differences existed in how participants heard about these groups, engaged with these groups, and weighed their benefits and limitations. For instance, although it was helpful for some participants to hear about the experiences of those with similar symptoms or diagnoses, the variability in these experiences evoked a sense of hope, countered by anxiety and fear:

> *"I joined…a [MtD parent] Facebook group…just to get some perspectives on things, which some days made it harder, and some days made it better. 'Cause the group has both spectrums with, you know, there's families that are losing their one-year-olds to the condition, and then there's other families that their kids are turning 30. So, it's a good thing, bad thing, I think." (P9, parent/caregiver)*

Notably, there was a sense of reciprocity in support communities. For example, Participant 9 (parent/caregiver) also noted the desire to give back to those still navigating their diagnostic journey:

> *"…in the last couple of years we've connected with MitoCanada, and we've done a lot of local kind of supports and fundraising events, and things like that to help support the organization too. So that's been a nice way to just feel like you're connected and helping in some way." (P9, parent/caregiver)*

It was apparent that motivations and timing for becoming involved in these communities varied among participants. Participants connected with these groups at different stages in the journey, with most participants accessing MtD-specific groups once a diagnosis was received.

This disparity is understandable given that a lack of diagnosis acted as a barrier, as highlighted by one participant:

> *"I also contacted the [non-MtD organization] for help, and they were very nice there as well, they said they need a concrete diagnosis before they can proceed with like any assistance, they might be able to provide." (P1)*

Others discussed accessing symptom-specific groups to obtain information before a diagnosis was received:

> *"…so I would just basically google symptoms, so I started to become a part of [symptom] groups on Facebook. I started to crowdsource information…ask about, has anybody had kids with these…random things." (P3, parent/caregiver)*

Interestingly, it was Participant 3 (parent/caregiver)'s provider who, during the diagnostic journey, mentioned Facebook as a means for crowdsourcing symptom-specific information:

> *" [The] genetic doctor…[they] had said the best information you're probably honestly going to find is on Facebook." (P3, parent/caregiver)*

In addition, there seemed to be an initial hesitancy amongst some participants about the appropriate time to join these groups once a diagnosis was received. After diagnosis, Participant 1 reflected on their wariness to join peer support groups as potentially being linked to their unique experiences with two rare conditions over the course of their life and their worry that others affected by MtD may not understand the entirety of their experience:

> *"I should avail myself to peer groups or forums or I don't know why I'm sort of hesitant about that…it's just like such a weird, strange life, it's been 33 years of unrelenting illness and that's a nightmare. If I speak to someone else, will they be able to understand it? I don't know, maybe to a certain point I guess I could speak to people who might have an idea of what I'm going through, but it's just weird." (P1)*

Participant 12 suggested that providers engage patients and families in ongoing discussions about support communities as their needs evolve throughout the diagnostic process:

> *"So kind of keep [available support groups] mentioned kind of thing. Because a seven year old isn't going to want to talk to a bunch of other seven year olds with balance issues. Not at the time, at least." (P12)*

Along the same thread of timing and hesitancy, one participant discussed navigating support groups as a parent and the importance of involving their child in this decision:

> *"We haven't involved ourselves personally with any sort of mito groups…And that's mostly because [child] is a little bit, I think they – there's a disconnect from recognizing they have this disability and disease to becoming actively involved...So I'm kind of letting them lead if they want us to contact a family with another child that has mito disease…then I will, but I don't want to push them into it." (P8, parent/caregiver)*

Furthermore, participant accounts were instrumental in offering insight into certain disparities between adult and pediatric care. Generally, adults tended to describe receiving less information and support compared to those in the pediatric setting. For instance, several adult participants would have liked the option to connect with others affected by the same condition to share experiences and offer encouragement and understanding:

> *"Well, I just would like to share my experiences with another person's experiences… [provider] says that I'm not the first person to be diagnosed with that. So I couldn't ask [them], 'Well, can I have contact with the person?' Because that's against the rules for [them]. But…I would like to find out if they're experiencing the same thing. Maybe give advice on how to live with it, or they can give me advice, stuff like that." (P5)*

> *"I think if somebody is diagnosed with something it would be beneficial for them to be connected to other people or groups or other, I don't even know how to put it, something that would help them ease through it, feel like they aren't alone, that they're safe." (P6)*

This trend became apparent throughout the analysis. However, one participant who had a point of reference for MtD care in both the adult and pediatric settings alluded to concerns about this disparity in the context of their child transitioning into adult care:

> *"These [pediatric] doctors have made themselves available – really available by phone quite easy. And I don't see the adult side doing this, you know, being as easily accessible. I just feel like we're starting over…[child's] not going to have the hands on medical-medical care that [they] did as a teenager once [they] w[ere] diagnosed. I find it scary but we'll have to just see, I guess." (P11, parent/caregiver)*

Altogether, participants discussed information in the context of their MtD diagnostic journeys. Many participants valued knowledge throughout the diagnostic process and viewed information as a means of hope and support. Each participant accessed the resources available in

a way that suited their unique needs. These needs evolved throughout the diagnostic journey and continued to develop beyond receipt of the diagnosis.

4.7 THEME 5: "THE WAY OF LIFE CHANGES DRAMATICALLY": IMPACT ON LIFE AND UNMET SOCIAL NEEDS

The MtD diagnostic journey was contextualized by several social factors, including navigating employment, schooling, housing, financial aid, and healthcare costs. Participants described how their needs extended beyond the medical and psychological aspects of the diagnostic journey. For instance, managing symptoms associated with MtD introduced financial difficulties in various direct and indirect ways. One participant detailed experience with stigma when job-seeking:

> *"…with me needing to find a job, how do I explain that I've been on a sabbatical for…three years, four years, to look into my health, and to like get my health conditions under control? And, well, they're gonna look at me and say, 'Well, if you're broken, like what makes you not a liability?' And I mean out of over 200 résumés that I pumped out, I had, what, four interviews, and all of which, as soon as they…heard the word 'health issues', they never called me back." (P10)*

Participant 7 (parent/caregiver) was required to move to accommodate the at-home care needs for their child and recounted how gruelling this was to manage with little support on top of financial and time constraints:

> *"…so we have to move [out of our apartment]…and then, because of the time constraints that we have to find it as soon as possible, so we have to look for a house. The house was our next option and it's very costly." (P7, parent/caregiver)*

Living with a chronic illness and undergoing diagnostic investigations resulted in financial challenges for several participants, and they expressed the desire to be made aware of available social resources to help navigate these concerns:

> *"But it would be nice to know that if there were clinics or help for people like me, whether it's through the government, that would be really nice to be a little more aware because some of us with stuff like this are struggling to pay our own bills and there's no help for us." (P6)*

In terms of treatment needs, participants reported barriers in accessing the various components of the mito cocktail as several supplements were not recognized or funded as medications:

> *"I think more so it's the medications part of it that I found to be very frustrating. Because L-arginine is not recognized as a medicine. It's only a vitamin. Q10 is only recognized as a vitamin. And these are significant medications…vitamins are one thing, but when they're used to keep your health in check, you need these and they need to be recognized as a medicine." (P4)*

Participant 7 (parent/caregiver) echoed the financial challenges associated with purchasing medication and how this was compounded by their struggle to find additional childcare, reflecting on how support with these items could ease the burden:

> *"…my [spouse] has to work to be able to afford those medications, so yeah, it's very, very stressful – stressful and challenging which, looking back from now to those years, if only we were maybe financially stable, we have the support that we need for an extra support person it would have been easier." (P7, parent/caregiver)*

Nutrition and diet support were also identified as important for several participants once they had been diagnosed with MtD:

> *"…it would have been nice to get nutritional information like I was doing intermittent fasting…but I was reading online…it's like mitochondrial disease patients should avoid fasting, so I was like, that would have been good to know! Like these are things that should be told, like send me to a nutritionist, dietician, send me nutritional information, you know? Like at least try to help me." (P1)*

Often, the diagnostic journey is viewed primarily through a medical lens with a secondary appreciation for the psychological component. However, participants chronicled a lack of recognition for how drastically their lives were altered as they embarked on this journey and adjusted to life with the condition. For example, one participant shared:

> *"Like, this is all stuff that has had to happen, and it has affected our lives tremendously. But at the same time, it's like, the doctors see the doctors' aspect of things, but they don't see the actual person's way of living after…The way of life changes dramatically." (P4)*

When discussing social needs, some participants described barriers that existed in accessing necessary medical care. For instance, one participant recognized how their privilege reduced these barriers and likely improved their ability to cope as a result:

> *"I mean I was just privileged to be able to cut back on work and seek therapy and that wouldn't happen for some parents. Like I definitely had privilege to be able to do the stuff that I did and to live near Winnipeg." (P3, parent/caregiver)*

Therefore, while there were gaps in informational and social support, as expressed by several participants, there was also a described need to consider and assess the various social factors beyond the medical setting that influence the diagnostic journey.

The themes presented can be conceptualized into a framework of the MtD diagnostic journey. Figure 4.2 illustrates the conceptualized stages of the diagnostic journey and provides an overview of these stages as modelled by the Aristotelian arc. The inciting incident, in this case, is the onset of symptoms that participants made sense of. This sense-making is in the context of something being wrong and requiring medical attention, which represents the rising action. From there, receiving the MtD diagnosis is akin to the climactic event that precedes falling action and a denouement. However, for our participants, there was no clear denouement as participants adapted to life post-diagnosis wherein challenges remained. Surrounding the arc are the factors that participants discussed as being constant yet dynamic throughout the journey and reflect the remaining themes.

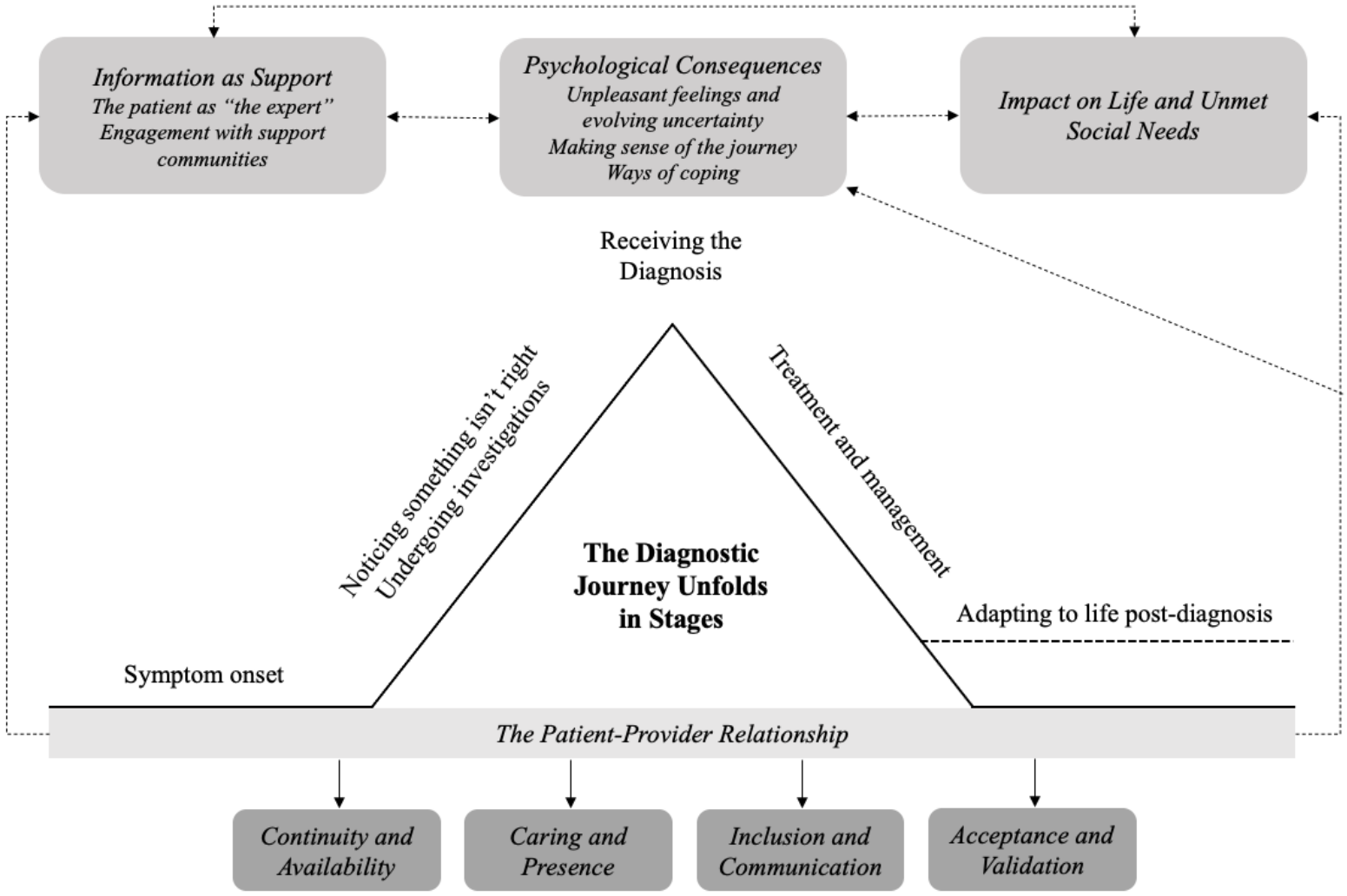

Figure 4.2. Conceptual framework of the diagnostic journey. The diagnostic journey unfolds in stages that mirror the schema of narrative structure, also known as the Aristotelian arc. The dashed line of the arc signifies that the journey continues post-diagnosis and does not reach a resolution or denouement. Dashed arrow lines represent influences, and arrowheads indicate their directionality.

4.8 SUMMARY

In conclusion, participants reflected on the experiences of the diagnostic journey. Their accounts resulted in the emergence of themes that encompassed the conceptual stages of the diagnostic journey as well as the psychological, informational, and social needs throughout this process. Interestingly, the diagnostic journey was found to be a piece of a larger overall MtD journey that participants navigated. As mentioned previously, none of the themes described here exist in isolation. Instead, they are interconnected in unique ways which illustrate how participants understand their experiences. These themes, taken together, illuminate the shared aspects of this journey that can inform how MtD diagnostic care is offered.

CHAPTER 5: INTEGRATION OF QUANTITATIVE AND QUALITATIVE RESULTS

5.1 OVERVIEW

This study's survey and interview components furthered the understanding of the experiences and needs along the diagnostic journey for MtD. In many instances, survey data provided an outline of the diagnostic journey, and the interview data offered context and meaning from the perspectives of participants. However, there were areas of divergence that illuminated the complexity of the diagnostic journey. In this chapter, the ways in which datasets were convergent, complementary, and divergent will be described.

5.2 THE DIAGNOSTIC JOURNEY

Most features of the diagnostic journey were complementary between surveys and interviews, although there was some divergence. Survey data provided valuable information on the number and type of initial symptoms, number and type of specialists encountered, familiarity with genetic testing and counselling, treatment, and time to milestones, while interview responses provided depth and context for these items. Surveys identified that participants underwent several tests along the diagnostic journey and encountered various providers who discussed these processes. During interviews, participants recalled experiences that held particular meaning, such as noticing something was wrong, receiving a diagnosis, or adjusting to the impacts of the condition. While testing and investigations were a part of this recollection, they were not its focus. Additionally, survey data revealed that symptoms most commonly began in infancy and mid-adulthood for this cohort. However, for adults, it became apparent in interviews that symptoms likely began long before participants were prompted to seek medical consultation. This divergence suggests that there is variability in how the "diagnostic journey" is defined and how participants view their journeys.

Both survey and interview data highlighted that receiving a diagnosis was validating and seen as a means to moving forward with treatment and management. However, interviews allowed for a more nuanced understanding of the thoughts, feelings, and emotions that accompanied receiving the diagnosis. The majority of survey participants (13/17, 76.5%) described being unaware of the possible benefits and risks of genetic testing, while interview participants alluded to an understanding of benefits and risks, in other words, suggesting that

these items may have been discussed but not explicitly introduced (i.e. using words “risks” and “benefits”). Finally, as the survey was focused on the space leading up to the diagnosis, it did not capture the challenges that remained post-diagnosis that were important for participants in the reflection of their experiences.

5.3 THE PATIENT-PROVIDER RELATIONSHIP

The PPR was found to influence the perception of the diagnostic journey for interview participants. Participants noted that provider continuity, having providers who care, inclusion in decision-making and communication, and being believed were key aspects of a strong PPR. Interestingly, nearly all survey participants (16/17, 94.1%) indicated that they felt included in decision-making either sometimes, often, or always and that communication with providers was average or better (16/17, 94.1%). While this was reflected in the interview experience for many interviewees, it was revealed that some providers ranked higher than others in these measures, and this nuance was not captured by the survey. Similarly, although ratings of trust were generally positive, there was more variability among participants despite positive ratings of inclusion and communication. Interviews shed some light on these findings. For instance, several interview participants had negative experiences with previous providers, either relating to MtD or in other medical contexts, and this resulted in a hesitancy to trust.

According to survey data, genetics and neurology providers were most consistently involved in information giving, support and communication, and service referrals. However, in terms of support and communication and access to services, PCPs were the providers to whom patients turned. These data were consistent with interview findings, although it was elaborated that while these various providers were involved, it did not necessarily mean that the education and supports provided were in keeping with participants’ needs. For example, as noted in chapter 4, some participants felt that communication was disparate, while others would have preferred updates and information in both written and oral form. Moreover, several participants felt pleased with the support they received from specialist providers, particularly when it came to both patient and inter-provider communication. Interestingly, genetic counsellors provided the least access to services despite being involved in the education of many survey participants. This finding could possibly be attributed to the lack of provider continuity or the fact that most

individuals affected with MtD did not recall meeting with a genetic counsellor, as this was more common within the parent/caregiver group.

Lastly, interviews found that participants are mindful of the ways in which they are perceived by providers. That is, participants described the desire to appear agreeable and be viewed as a "good" patient or parent/caregiver. This was not explored in the survey component and would not have been revealed without the opportunity for participants to share their experiences in an open-ended way.

5.4 INFORMATIONAL NEEDS

Survey and interview findings together provided an enriched understanding of the role of information along the MtD diagnostic journey. The survey inquired primarily about where participants received or accessed information at different time points (i.e. before and at the time of diagnosis), whereas the interview explored this topic more openly. Survey data indicated that most participants received information from geneticists/metabolic specialists, genetic counsellors, neurologists, and the Internet. The least information was received from support organizations, support/advocacy groups, and their personal networks. Understandably, the survey found that more information was available at diagnosis, which was consistent with interview results. However, interview participants expressed that there is a lack of information specific to MtD and that information is needed at all points of the diagnostic journey, rather than just at the time of diagnosis. The lack of information was particularly challenging for several participants who coped through information-seeking. Interestingly, what the survey could not capture was that information could be viewed as a means of hope when it came to MtD as these conditions entail significant uncertainty. Therefore, while many participants indicated receiving a variety of information prior to genetic testing and upon delivery of the diagnosis, the lack of concrete knowledge on MtD complicated participants' relationship with this information and its perceived utility. Finally, a small proportion of survey participants indicated they were not interested in receiving certain information before and at the time of diagnosis. This was divergent compared to interview participants who tended to want further information, although this was not a universally shared sentiment as participants also expressed being pleased with the level of information received. This nuance emphasized the importance of person-centred care and inquiring with participants regarding the timing of information-sharing.

5.4.1 Information Specific to Support Communities

As mentioned above, survey participants reported accessing the least support from support organizations and groups, although many wished they had received more information about these options throughout the journey. It was unclear whether participants had received little information to begin with or if the sources themselves were not as helpful in obtaining the information participants sought. Interviews allowed for further exploration of this topic, as participants mainly received these resources at the time of diagnosis, while others had not heard of these at all. This lack of information resulted in interview participants feeling a need to become the experts in their diagnosis.

There was a disparity seen both in surveys and interviews in the amount of information about support communities that adults received compared with parent/caregivers, with the former receiving less. However, survey findings were discordant in that the majority of participants indicated that they wished they had been given support community information before and at the time of diagnosis despite 14 (82.3%) participants indicating that they were aware of at least one support community (e.g. support group, Facebook group, support organization). Similarly, while survey participants wanted more information on support communities, those who were aware of communities generally had low engagement. The interview described the different ways that participants engaged with support communities, including hesitancy regarding the optimal timing. This finding is not discordant with the desire to obtain more information about support communities. Instead, it underscores the need for a person-centred approach to sharing this type of information.

5.5 PSYCHOLOGICAL NEEDS

Psychological needs were discussed primarily in the interview component of this study, allowing for exploration in the MtD context. Differences existed in the experience of affected individuals and parents/caregivers in terms of needing support and awareness of support communities. While there were unpleasant feelings and evolving uncertainty along the diagnostic journey for both groups, several parents/caregivers described the positive psychological effects of feeling supported along the diagnostic journey, whereas adults tended to describe feeling alone throughout the process. It was elucidated through interviews that the psychological needs of participants are influenced by their experiential sense-making. That is, how participants made

sense of a situation, psychological consequences, and resulting needs were unique. Overall, applying a person-centred approach, whether that be through the provision of information, communication about the diagnostic process, inclusion in decision-making, and or being believed, can in turn address the psychological components of the journey.

5.6 SOCIAL NEEDS

Survey data reported participants' needs concerning the provision of social supports and services. Similar to information needs, survey participants received the least support from support organizations and groups. Once again, participants shared in interviews that the reason for this was a lack of awareness about these supports existing, as well as the caveat that MtD-specific groups were mainly discussed once a diagnosis was received. Participants described ways that they accessed support before obtaining a diagnosis. For instance, some participants reached out to non-MtD support organizations and groups, while others turned to social media. One participant noted seeking symptom-specific groups through social media after a provider shared this as an option, highlighting the role of the PPR in the discussion of support options. Interviews were complementary to the survey dataset in the sense that they illuminated the extent of social needs beyond support organizations and support/advocacy groups. That is, social needs went beyond social support and encompassed the drastic ways in which life was impacted by the MtD diagnostic journey. Unmet social needs for participants included challenges with obtaining employment opportunities, adequate housing, managing healthcare costs, and obtaining disability insurance.

In summary, qualitative and quantitative datasets in combination provided an in-depth contextualized understanding of the experiences and needs of the MtD diagnostic journey. Survey questions acted as a starting point for exploration and elaboration of participants' experiences during the interview component introduced novel aspects. In combination, these results portrayed the complexity of this journey and highlighted opportunities for improved person-centred information, psychological, and social understanding and support from providers along the diagnostic journey.

CHAPTER 6: DISCUSSION

6.1 OVERVIEW

The aim of this study was to describe the experiences and explore in-depth the needs of individuals and families who had undergone the diagnostic process for MtD to identify ways in which patients could be better supported throughout this journey. Affected individuals and parents/caregivers of children with a confirmed MtD diagnosis completed a survey about their diagnostic experiences, and a portion completed a follow-up interview. Findings showed that this group had unmet needs while navigating this journey and that support could be improved. This study contributed to a significant gap in the knowledge by characterizing the MtD diagnostic journey. Specifically, this study conveyed the psychological consequences, relationships with providers, and informational and social needs of those with MtD and described participant-driven recommendations for MtD diagnostic care.

6.2 CHARACTERIZING THE DIAGNOSTIC JOURNEY

Characteristics of the diagnostic process identified in this study included when initial symptoms prompted medical consultation, age of onset, initial specialist referral(s), number of specialists consulted, and time to diagnosis.

6.2.1 Symptom Onset

Participants experienced an average of four to five symptoms, with weakness and fatigue being the most common, consistent with previous literature on this topic (Grier et al., 2018; Noorda et al., 2012). The average number of symptoms has not been well characterized; however, one study in a pediatric population found that, on average, six organs were affected (Senger et al., 2016b). As for the age of onset, MtD occurred largely in either infancy or mid-adulthood, in keeping with a bimodal mode of distribution (Chinnery, 2021), although interviews revealed that, in retrospect, adults contemplated that they likely experienced symptoms prior to their medically documented age of onset. This divergence between datasets may suggest possible variability in how participants understood their diagnostic journey, which was likely influenced by experiential sense-making. Additionally, when considering the bimodal mode of distribution

identified in this study, it is important to note that individuals with symptoms that onset after age 45 years were excluded to improve experiential heterogeneity in our sample.

6.2.2 Specialties Involved in MtD Care

Genetics/metabolism and neurology were the specialties most often involved in the care of this study population, which is in keeping with standards of care and past studies (Chinnery, 2021; Grier et al., 2018; Paik et al., 2019; Parikh et al., 2014). Most study participants were first referred to a neurologist and or a geneticist/metabolic specialist and typically had an appointment within six months of referral. An average of two to three different specialists were seen before receiving the final diagnosis, although four specialists were most commonly encountered. Grier et al. (2018) previously reported that the participants in their study consulted an average of approximately eight specialists, though one to five specialists was most common.

Interestingly, in this study, the number of specialists seen is towards the lower end of the spectrum in comparison. This divergence could reflect a difference in the experiences of the patient populations sampled by Grier et al. (2018) and this study. Grier et al. included those with self-reported biochemical deficiencies and secondary mitochondrial dysfunction, whereas this study worked with participants with a known MtD diagnosis. As a result, it is possible that the participants in this study may have had a more recognizable MtD condition that facilitated a more appropriate referral and thereby required fewer specialist consultations. In addition, this divergence could reflect that the participants in this study received healthcare in Canada, whereas those in the Grier and colleagues study were in the United States. Thus, it is possible that the healthcare landscape and referral procedure may differ between our study cohorts. Alternatively, the unique aspects of the Manitoba healthcare system could further explain this finding. For instance, healthcare is centralized in the province, and therefore, all patients referred for possible MtD are referred to a single centre for genetics/metabolism and neurology. As such, the providers in these specialties may, in turn, have more familiarity with this group of conditions, resulting in fewer specialists encountered.

6.2.3 The Time to Diagnosis

An MtD diagnosis was received by the two-year mark for just over half of participants. This time to diagnosis was shorter than anticipated, as one study previously indicated the time to

diagnosis to be approximately four years within their pediatric cohort (Senger et al., 2016b). Thus, to our knowledge, the present study was the second to report a time to diagnosis for MtD and the first to do so within the adult population. A shorter time to diagnosis could be explained by the fact that most participants were referred to the most appropriate specialist and were seen in a relatively timely manner. Again, this experience could be reflective of the landscape of provincial health services in that MtD providers in a single centre were consulted appropriately, which resulted in a timelier diagnosis. Similarly, the specific MtD diagnoses of study participants may have been better characterized and therefore resulted in a shorter diagnostic journey. In that case, if testing for MtD was completed shortly after initial presentation to hospital or a PCP, the time to diagnosis could be the result of waiting for a specialist consultation and or the turnaround for genetic diagnostic testing. In addition, it is possible that the overall younger age of onset of our participants played a role in the likelihood of being referred to specialty care, therefore facilitating the time to diagnosis. Longer wait times for referrals regarding non-specific symptoms, particularly in the adult setting, may have been a factor in longer diagnostic journeys. The possibility that this survey question was interpreted differently by participants cannot be discounted.

6.2.4 Recollection of Genetic Testing

Notably, prior to genetic testing, most survey participants indicated they did not recall receiving information about the benefits and risks associated with testing. In contrast, during interviews, some participants portrayed an understanding of these associated benefits and risks. With our awareness that all patients should undergo a consent process for genetic testing in Manitoba, an explanation for this discrepancy may be that the information shared in the clinic was not presented to patients using these specific terms. That is, while the patient may have understood the benefits and risks involved with genetic testing, they did not recall the information in this way.

6.2.5 The Meaning of a Diagnosis

The experience of receiving a diagnosis was nuanced for participants. Many hoped it would serve as a turning point in the journey that would allow for clarity in treatment and management, which was not always necessarily the reality. For others, it was a moment of

validation and relief. It is unlikely that participants wanted MtD to be the final diagnosis; however, once there was an awareness that something was wrong, it is possible that a diagnosis represented a sense of hope and a means to abate feelings of fear and uncertainty, similar to previous studies about the emotional impact of undiagnosed conditions (Lewis et al., 2010; Withers et al., 2021; Yanes et al., 2017).

The impact of the diagnosis has not been well characterized in the MtD population. One MtD study found that having a genetic confirmation of diagnosis was perceived to reduce barriers in access to medical and social supports (Krieg et al., 2016). Relevant literature, which included participants with MtD, has investigated the level of satisfaction with the delivery of the diagnosis but not how this affected participants holistically (Anderson et al., 2013; Zurynski et al., 2017). Our study was the first to explore in-depth the personal meaning of the diagnosis for people with MtD. In keeping with the RD literature, participants within this study echoed the perceived benefits associated with a diagnosis, such as reducing feelings of uncertainty, informing treatment decision-making, improving accessibility to services and specialists, and serving as a means of personal and social acceptance (Carmichael et al., 2015; Esquivel-Sada & Nguyen, 2018; Lewis et al., 2010; Pelentsov et al., 2016; Rosenthal et al., 2001; Withers et al., 2021). Therefore, the significance of the MtD diagnosis for our participants appeared to be aligned with the receipt of an RD diagnosis in general. However, the participants in our study seemed to place equal emphasis on the post-diagnosis stage and the additional challenges that were introduced thereafter. This finding is significant as it indicates that the journey for MtD does not end at diagnosis and that patients and families require continued support thereafter.

6.2.6 The Stages of the Diagnostic Journey

Overall, the diagnostic journey seemed to unfold in stages similar to the Aristotelian arc wherein the inciting incident was the onset of symptoms, the rising action was the recognition of something being wrong followed by various investigations, leading to the climax of a final diagnosis; the falling action was the effort made by participants to adjust to their diagnosis (Figure 4.2). In this sense, participants recalled the diagnostic journey similarly to a story. Although interviews were focused on the past, participants showcased a pull to the present, post-diagnosis stage and the challenges that they continued to navigate. There was seemingly no clear denouement to the MtD journey as uncertainty remained post-diagnosis, and the MtD journey

continued. This phenomenon signified that the MtD journey does not end with diagnosis, fitting with one study that identified gaps in the post-diagnosis management of those with MtD (Long et al., 2021). Similar to the study conducted by Long and colleagues, our participants spoke of a lack of knowledge to guide MtD management following diagnosis and the general lack of support in adapting to the psychological and social challenges, which included how to advocate for needs outside of a medical setting and managing mental health. Literature on how people recall their diagnostic stories is absent, though one study developed a framework for the phases of the diagnostic journey (Geng et al., 2019). While this framework noted the emotional and financial challenges associated with a diagnostic odyssey, it was established from a medical lens and focused on the first medical encounter followed by referrals and subsequent evaluations. Comparatively, our proposed stages focus on factors important to patients and families, such as informational, psychological, and social consequences of diagnosis. This perspective is important as it contextualizes the diagnostic journey outside of the medical scope and prompts providers to understand how to holistically and meaningfully support patients, especially when external factors, such as the lack of information on MtD, are currently beyond control.

6.3 THE PATIENT-PROVIDER RELATIONSHIP

A significant finding of this study was that the PPR influenced participants' perceptions of the diagnostic experience. While it is unrealistic to expect providers to absolve patients of the psychological and emotional hardships that accompany the diagnostic process, there is an opportunity for providers to mitigate these challenges by supporting patients and families through meaningful relationship-building and person-centred counselling.

6.3.1 Hallmarks of the Patient-Provider Relationship

Most participants in this study viewed communication with providers favourably and reported feeling included in decision-making. While the majority of participants were at least somewhat trustful toward providers, there was more variability in participants' ratings of trust as compared to the inclusion and communication ratings. Interviews provided context on how participants perceived trust, inclusion, and communication in the PPR through exploration what helped and hindered this relationship. Factors that influenced the PPR included provider continuity, sharing the diagnostic burden, inclusion in decision-making, and open

communication. Despite a recent study noting that adults and parents/caregivers with MtD identify the PPR to be the most important part of the diagnostic journey (Zilber & Yeske, 2020), there is a gap in the MtD literature investigating the hallmarks of this relationship. Therefore, this study is the first to elicit the opinions of patients and parents/caregivers on this topic.

Taken together, our results suggest that trust is built over time and is not guaranteed even with efforts to include patients in decision-making and maintain open communication. Studies investigating the PPR have noted that trust, knowledge and education, regard, loyalty, empathy, and compassion are integral to this relationship and have an impact on patient outcomes (Chipidza et al., 2015; Ha & Longnecker, 2010; Merker et al., 2021; Sinclair et al., 2016). In fact, even without effective treatment or a cure, the PPR can positively influence the wellbeing of patients and families (Awdish & Berry, 2019). Furthermore, it has been found that informal factors such as human connectedness, transparency, availability, being supportive of patient concerns, and showing sensitivity and empathy, precede formal factors in meaningfully establishing trust in this context (Gómez-Zúñiga et al., 2019; Wolf et al., 2017). The PPR has been found to be particularly influential for RDs as the general lack of treatment and management options following diagnosis necessitates increased support from providers compared to more prevalent conditions that have tangible next steps (Budych et al., 2012). Similarly, parents of undiagnosed children have expressed open communication and collaboration to positively impact the PPR with their genetics providers in particular (Levenson, 2015). Participants in our study echoed the importance of a strong PPR in feeling less alone at every stage of their experience. Specifically, our study identified meaningful inclusion, communication, acceptance and validation, presence and caring, as well as continuity to be key elements of the PPR. These findings offer insight into prominent characteristics of the PPR for MtD.

6.3.2 Theoretical Approaches to Person-Centred MtD Care

Participants in this study underlined the importance of being recognized and accepted by providers involved in their diagnostic care. For instance, participants described their awareness of how they were perceived by providers as well as their desire to be validated. These results are reminiscent of the Rogerian approach to client-centred therapy, which is founded on the belief that congruence, unconditional positive regard, and empathy are central to the PPR, and key for

therapeutic effect (Rogers, 1951). Certainly, the expressed desire of participants to feel included holistically in their care, as well as the desire to be believed and accommodated, are in line with these principles. Building off the dogma of client-centred therapy the Reciprocal Engagement Model of Genetic Counselling Practice poses five central tenets that could be applied in consideration of the needs of the MtD patient population (McCarthy Veach et al., 2007). These tenets maintain that to adequately address patient concerns, 1) sufficient information must be provided, 2) patient autonomy must be supported, 3) resilience must be recognized, and 4) emotions should be taken into account. The final tenet is central to the model and maintains that the PPR is integral to the ascertainment of the preceding tenets. Currently, there is no literature on the role of genetic counsellors in supporting those with MtD as they navigate the diagnostic journey, outside of recommendations for approaches on information giving and general counselling (Poulton et al., 2017; Vento & Pappa, 2013). Our study was the first to seek out what participants may need along the diagnostic journey and could act as a foundation for further studies to investigate the role for various providers in MtD care. For instance, as these theoretical approaches are in line with the key elements of the PPR noted above, training of relevant providers such as geneticists/metabolic specialists and neurologists could be considered. Additionally, given that these elements are in line with the skills of genetic counsellors, there may be a more prominent role for these providers in MtD care. Overall, these research findings highlight the significance of the PPR and the potential of providers to offer support to patients and families along the diagnostic journey.

6.4 PATIENT NEEDS AND SUPPORT

6.4.1 Informational Needs and the Patient as "The Expert"

Generally, the informational needs of the MtD population within this study are comparable to research conducted with other RD cohorts that found the provision of information to be lacking throughout diagnosis (Bryson et al., 2021; Donegan et al., 2021; Molster et al., 2016; Zurynski et al., 2017). Study participants conveyed wanting more information than was provided at each stage of the diagnostic process. Informational needs were person-specific, further underscoring the need for a person-centred approach to information given by providers. For our participants, the most information was received from specialist providers, particularly geneticists/metabolic specialists, genetic counsellors, and neurologists. Moreover, informational

needs seemed to evolve over the journey, which is somewhat consistent with existent literature, which found that parents/caregivers of children with MtD tended to need more informational support throughout the diagnostic journey (Noorda et al., 2007). Our findings did not specifically describe these needs as increasing but rather changing over time as participants moved through the conceptual phases of the diagnostic journey. For example, during the initial stages of the journey, participants described a need for information about the investigations initiated and diagnoses being considered. At the time of diagnosis, participants generally desired information on the condition itself and what to this diagnosis meant for daily life. During the post-diagnosis stage, informational needs included long-term disease management and outcomes, adapting to symptoms, and available social supports. Furthermore, two participants in our study described the desire for information both in oral and written form to facilitate an understanding of how the diagnostic process was progressing, which is similar to participants in the study conducted by Noorda and colleagues (2007).

While there is a gap in knowledge regarding the informational needs of the MtD patient population, this gap is wider still within the adult patient population. Our study identified that adults advocated for more information compared to parents/caregivers in this cohort. There are several reasons why this may have been the case. In Manitoba, there is a provider specializing in MtD care who works primarily in the pediatric setting but no official “equivalent” expert provider in the adult setting. This imbalance likely contributed to the gap observed. A contributing factor may also be that, generally, adults receive less support throughout the diagnostic experience due to the focus on self-management in adult care compared to pediatric care (Gray et al., 2018; Mahan et al., 2017), which may have necessitated an increased need to cope through information amongst adults. Finally, it is possible that the informational needs of adults differ from those of parents/caregivers of affected children. For example, perhaps the key concerns diverge between these groups based on where they are situated (carer or affected) in the diagnostic journey. Investigating the differences in information needs between these two groups was beyond the scope of this study, but further research into this possibility is warranted.

Another key finding from this study was that participants felt there was significant uncertainty when it came to the natural history, diagnosis, prognosis, treatment, and management of MtD. Therefore, the need for information was likely heightened within this population due to the lack of this knowledge in the medical field. This phenomenon has been previously described

in both the MtD (Krieg et al., 2016; Noorda et al., 2012; O'Riley, 2003) and the RD literature (Baumbusch et al., 2018; von der Lippe et al., 2017). As a result, patients and parents/caregivers found themselves taking on the role of being "the expert" in their care, fitting with past literature on this topic (Baumbusch et al., 2018; von der Lippe et al., 2017). In our study, being an expert involved educating not only the general population but also providers. Again, these results are in support of what is known from other MtD patient populations (Karaa et al., 2019a, 2019b). In order to become the expert, participants described information-seeking online and keeping medical libraries to track investigations along the diagnostic journey.

6.4.2 Information-Giving and Support Without a Diagnosis

An unexpected finding was that participants shared receiving the least information and support from patient support organizations and support/advocacy groups. Through interviews, it was revealed that several participants were unaware of these groups, while others primarily heard about or accessed these only once they received a diagnosis. The idea of the lack of a diagnosis as a barrier to accessing information and support has been previously described, mostly within the RD literature (Carmichael et al., 2015; Krieg et al., 2016; Lewis et al., 2010; Rosenthal et al., 2001; Withers et al., 2021). There were a handful of participants who self-sought access to support groups and organizations prior to diagnosis. For instance, one participant shared that they attended a group for a misdiagnosed condition before their MtD diagnosis, another participant shared accessing symptom-specific groups on social media, and another reached out to an MtD organization as the diagnosis was high on the differential. Therefore, while these findings suggest that providers need to share support resources and communities both during the diagnosis journey and at the time of diagnosis, the access to support in the former timepoint is particularly lacking.

The need for additional support may have implications for the way providers offer education to patients with MtD. Past research has identified that physicians providing MtD care in the United States almost exclusively provided patient education during office consultations and supported the development of a shared repository for patient education resources (Parikh et al., 2013). This same study found that the patient support groups most often shared with patients were MitoAction (MitoAction, 2005) and the United Mitochondrial Disease Foundation (United Mitochondrial Disease Foundation, 1996). Our study did not ask participants to identify any

sources of information or support by name, although several interview participants discussed MitoCanada and MtD groups on Facebook. Some participants in this study noted accessing the Internet and social media for information and support throughout the diagnostic journey, and some participants highlighted the advantages and limitations of these outlets. Our findings mirrored existent literature stating that there are barriers in accessing resources without a diagnosis and that social media groups can be helpful for crowdsourcing information but may also be emotionally challenging and anxiety-provoking (Deuitch et al., 2021). Of note, in our study, concerns about privacy and data sharing online did not arise as they have in others (Deuitch et al., 2021).

Interestingly, participants described the desire to have more information about support organizations, groups, and services prior to diagnosis, in accordance with the finding that information itself was viewed as a means of support. Currently, there are few networks for those who are undiagnosed, and many are focused on research efforts to confer a diagnosis (e.g., Care4Rare, 2011; Canadian Prairie Metabolic Network, 2021; The Undiagnosed Diseases Network, 2008) rather than solely on the provision of support to patients and families. In fact, to our knowledge, one of the only initiatives dedicated to the provision of support is a non-profit based in Australia called Syndromes Without A Name (Syndromes Without A Name, 2012). However, several support groups for undiagnosed illnesses do exist on Facebook. All in all, support and resources for those who are navigating the diagnostic journey are few and far between. These findings highlight that it is imperative for MtD providers to engage in ongoing discussion with patients about their informational and support needs to facilitate access/referral to the most appropriate resources at different stages of the diagnostic journey.

6.4.3 Beyond the Healthcare Setting: Social Aspects of the Diagnostic Journey

The social context of the MtD diagnostic journey extended beyond support organizations and groups and even beyond the medical and psychological space, which was unanticipated. Social challenges accompanying the diagnostic process included difficulties navigating diet, exercise and supplementation, employment and schooling, adequate housing, healthcare costs, and financial assistance. These findings are consistent with other studies (Baumbusch et al., 2018; Krieg et al., 2016; Pelentsov et al., 2016; Zilber & Yeske, 2020) and provide further evidence to support the need to assess the social concerns of patients and families with MtD

along the diagnostic journey. Of note, challenges with accessing vitamins and supplements due to costs and the required quantities were apparent in our results. The financial burden of treatment and management has been described in this population, albeit in an American setting (Cohen et al., 2018; Parikh et al., 2009). However, even in a Canadian setting, financial challenges associated with accessing the mito cocktail have been noted (S. Marin, personal communication, January 2021). It is possible that these challenges provide an explanation for why the vast majority of participants in our study began the mito cocktail post-diagnosis, despite its components being benign if not medically indicated. Overall, this study further evidenced the social needs that move beyond the medical setting and impact the day-to-day lives of patients and families seeking an MtD diagnosis and was the first to do so in a Canadian context.

6.4.4 Psychological Consequences of the Journey

Three key findings relating to psychological consequences were identified in our study. First, the diagnostic journey is accompanied by unpleasant feelings and evolving uncertainty. Second, experiential sense-making affects the ways in which participants remember their journeys. Third, participants coped in various ways throughout the diagnostic process. The psychological toll of MtD has been well-established within the literature (Kim et al., 2010; Klein et al., 2021; Senger et al., 2016b, 2016a; van de Loo et al., 2020), particularly for the parent/caregiver population. The present study contributed to the field by depicting the psychological consequences of MtD within both parents/caregivers and affected individuals. Additionally, the qualitative nature of these findings provided experiential depth and contextualized the current literature in this area which is predominantly quantitative. For instance, while this study did not assess psychological wellbeing or coping efficacy quantitatively, it allowed participants to discuss how their lives were affected by emotional states such as anxiety, worry, fear, and agony over awaiting an answer. Additionally, participants were able to share how they addressed these feelings during that time. The expression of unpleasant feelings and everlasting uncertainty is in keeping with other descriptions of the experience of adults with MtD (Noorda et al., 2012), suggesting this experience may be quite common within this population even before a diagnosis is conferred. There is a body of literature on the ubiquity of uncertainty within MtD (Krieg et al., 2016; Noorda et al., 2012; O'Riley, 2003; Senger et al.,

2016a; van de Loo et al., 2020) and RD in general (Baumbusch et al., 2018; Donegan et al., 2021; Spillmann et al., 2017; von der Lippe et al., 2017; Withers et al., 2021).

6.4.4.1 Power of Addressing Emotions in Healthcare

Uncertainty in healthcare is commonplace, and providers navigate discussions around this fact frequently. However, there is still a general reluctance to acknowledge uncertainty amongst providers, despite its documented ability to improve patient outcomes (Simpkin & Armstrong, 2019). Furthermore, addressing emotional and social stressors associated with health has been found to strengthen self-esteem, optimism, and mastery amongst patients and improve health-related quality of life (Adler et al., 2008). An empathetic approach to care has been associated with several positive outcomes, including improved patient and provider satisfaction, even in the absence of treatment options (Decety & Fotopoulou, 2015). Taken together, this knowledge may suggest the need for a shift in healthcare goals from fixing problems to a focus on helping patients address and adapt to psychological and social concerns. While much of this evidence has been within the context of psychotherapy, research assessing outcomes of genetic counselling has found this process to lead to an improved sense of personal control, positive health behaviours, and decreased anxiety and decisional conflict (Madlensky et al., 2017, p. 1). Overall, our findings indicate an opportunity for providers to improve patient support by exploring and acknowledging uncertainty and unpleasant emotions experienced by patients and families with MtD navigating diagnosis.

6.4.4.2 Ways of Coping

This study found that emotion-focused and problem-focused coping strategies were employed by participants throughout the diagnostic journey. Emotion-focused strategies included escape-avoidance to allow for distance from stressors, fatalism to foster acceptance, and seeking support from personal networks and faith. Problem-focused strategies included focusing on addressing immediate needs and information-seeking through self-research. Coping strategies were used simultaneously and were context-dependent throughout the diagnostic journey, similar to what has been previously described for adults living with MtD post-diagnosis (Noorda et al., 2012). Our study subsequently showcased that coping applied in the pre-diagnosis stage of the journey as well. Interestingly, another study within the MtD parent/caregiver population found

that those who coped by attempting to understand healthcare information, a problem-focused strategy, had higher stress scores compared to those who coped through emotion-focused means (Senger et al., 2016b). This finding suggests that focusing on emotions in an MtD context may be beneficial, regardless of the lack of medical knowledge on these conditions. While it is unknown if this finding applied to our cohort, it is a possibility given that several participants expressed frustration around the lack of available information and how this impacted their emotional state and psychological wellbeing. Lastly, participants spoke about positive aspects of their experiences, specifically feelings of gratitude regarding how processes and events unfolded. This sense of gratitude could be indicative of downward comparison, as is seen in the RD literature, whereby individuals cope through comparison to those who are perceived to be more significantly affected by an event (von der Lippe et al., 2017; Wills, 1981).

6.4.4.3 Potential for Far-Reaching Effects in Provision of Psychological Support

Unlike some of the needs previously described, the psychological consequences seem to blanket the entirety of the MtD diagnostic journey. Participants in our study highlighted their resilience in adapting to these experiences. Nonetheless, there is a gap in how best to address psychological impacts along the diagnostic journey. Our study provided some evidence to suggest that providers could engage in discussion about psychological challenges and personal coping strategies to better support patients throughout the diagnostic journey. It has been evidenced that parents/caregivers of children with MtD have reduced psychological wellbeing and coping efficacy compared to parents/caregivers of children with other chronic conditions (Senger et al., 2016a, 2016b; Sofou, 2013). Additionally, health spillover effects from child to parent have been documented in the setting of rare pediatric metabolic conditions (Wu et al., 2020). Therefore, assessing and addressing the psychological concerns of the patient has the potential to improve not only the patient experience but also the familial experience, given these previously documented spillover effects. No research to date has described spillover effects associated with adults with MtD and signifies an opportunity for future research. However, it is likely that family members, partners, caregivers and others within an affected adult's personal network may be privy to effects from such an approach as well.

6.5 PARTICIPANT-DRIVEN RECOMMENDATIONS

The findings from this study, as well as the discussion above, have portrayed the experiences and various needs of patients and families navigating the diagnostic journey for MtD. The participant-driven recommendations outlined below are proposed based on these findings.

1. **Apply principles of person-centred care to elicit and address psychological and emotional concerns pertinent to the uncertainty of the diagnostic journey.** Principles include empathy, congruence, and unconditional positive regard (Rogers, 1951). In practice, these principles may include taking time in a consultation to ask about patient wellbeing, listening and responding to concerns raised by the patient, and acknowledging and validating their experiences, particularly the uncertainty associated with the MtD diagnostic journey.

2. **Assess the social needs of patients and families along the diagnostic journey to identify relevant referrals.** Assessment of social needs may include inquiring about adequate housing, food security, financial concerns, access to medications, and social support with the goal of facilitating referrals to relevant agencies such as social work or advocacy clinics. Screening tools for assessing social needs in a primary care setting have been published and may be used to guide this assessment in other care settings (O'gurek & Henke, 2018).

3. **Assess and accommodate the informational needs of patients and families throughout the diagnostic process.** As preferences for information sharing are person-specific, it is recommended to discuss with the patient the ideal depth and amount of information and preferred mode of sharing, such as in written or oral form. Processing information may be challenging in the moment, and thus, applying these strategies may allow patients to understand and share information at their own pace.

4. **Engage patients and families in ongoing discussion about sources of support.** Topics of discussion include but are not limited to, how patients access social media, the Internet, and support organizations and how these needs change along the way. Discussion should include the benefits and limitations of these resources.

5. **Include patients and families as members of the healthcare team by maintaining open communication as decisions are made about their diagnostic management.**
   Open communication may include, but is not limited to, discussion of the differential diagnosis, tests being conducted, how conditions are being ruled out, steps that plan to be taken, and most importantly, why different approaches and diagnoses are being considered.

6.6 PRACTICAL IMPLICATIONS

There are several practical implications of this study. The overarching implication of this work is that while currently, there may not be a way to resolve the entirety of the challenges of the diagnostic journey, there are tangible ways in which providers can support patients and families through this process to improve MtD care. This study also draws into question whether there is an opportunity for expansion of the MtD care team to better accommodate patient needs. Data published to support the establishment of MCN in the United States revealed that patients and families desired to have a multidisciplinary care team for MtD (Karaa et al., 2019a, 2019b). Respondents envisioned these teams being led by geneticists/metabolic specialists and or neurologists with additional members including genetic counsellors, clinical coordinators, social workers, nutritionists or dietitians, and therapists (occupational, physical, speech) (Karaa et al., 2019a, 2019b). Manitoba has an MtD expert who is consistently involved in the care of pediatric patients but is not part of a multidisciplinary clinic.

Participants spoke to the benefits of having providers who specialize in MtD, with many identifying these providers to be amongst the most helpful components of the diagnostic process. The reason these providers were helpful was because they relieved some of the burden participants felt in needing to be the expert and coordinating their own care. Therefore, our research findings could offer evidence to endorse appropriate resource allocation for expanding the MtD care team, and possibly establishing an MCN centre in Manitoba. In an ideal MCN centre, various providers meeting gaps in MtD patient care needs would operate in a multidisciplinary team headed by a geneticist/metabolic specialist and a neurologist or have pathways embedded in MtD care to facilitate referrals to these specialties as needed. In keeping with our study findings and the previously published preferences of patients and families with MtD (Karaa et al., 2019a, 2019b), additional providers in the MCN centre would likely include

genetic counsellors, social workers, clinical psychologists, dietitians, pharmacists, and a clinical coordinator to oversee operations.

It is worth noting that all participant-driven recommendations presented are well-aligned with the practice goals of genetic counsellors. The National Society of Genetic Counselors' Definition Task Force (2006) defines the profession as "the process of helping people understand and adapt to the medical, psychological, and familial implications of genetic contributions to disease." Genetic counsellors are trained in medical genetics and counselling techniques and are skilled in assessing the psychological and social concerns of patients within the context of communicating and tailoring information to patients and families. Consequently, genetic counsellors are known to play a particularly important role in supporting patients with MtD beyond education, such as by discussing psychological and social concerns and identifying effective coping strategies to manage uncertainty (Vento & Pappa, 2013). One participant in our study noted explicitly the benefits of having a genetic counsellor who happened to be involved in their care. While genetic counsellors in Manitoba are not necessarily routinely involved in the diagnostic care of all patients with MtD (P. Frosk, personal communications, May 2021), they were most often encountered by study participants in the context of family planning. Therefore, having this role embedded within an MCN centre would enable patients and families to have access to this service not just in the context of family planning.

While genetics professionals and neurologists may address the medical and short-term psychological needs of patients, clinical psychologists may be best suited to address the significant psychological aspects of the MtD diagnostic journey and beyond (Canadian Psychological Association, 2016). Additionally, there were several unmet social needs described by our participants. To attend to systematic issues surrounding finances, housing, employment, and schooling that influence health and wellbeing, incorporating a social worker into the MCN team could be ideal (Canadian Association of Social Workers, 2020). For identified barriers and concerns around nutrition and diet, as well as mito cocktail supplementation and symptom-specific medication, dietetics and pharmacy could be most suited, respectively (Canadian Pharmacists Association, 2021; College of Dietitians of Manitoba, n.d.). Finally, to organize the daily operations of the MCN centre and facilitate communication between patients and providers, a clinical coordinator would be most beneficial in ensuring that providers are working at the top of their scope. Although various professionals could act in this role, recent research

suggests that genetics assistants as clinical coordinators contribute to increased efficiency of genetics-based care and improved service delivery, making them a particularly good fit within this context (Pirzadeh-Miller et al., 2017).

Although further consideration of the responsibilities and limitations of the scope of practice of various specialties is required, we suggest that, together, these providers could holistically address the needs of the MtD patient population. Thus, while there remains a need for further investigation into the feasibility and implementation of an MCN centre in Manitoba, we hope this work will serve as a launch pad for future investigations on this topic.

6.7 STUDY LIMITATIONS

This study had several limitations which, taken together, may impact the ability to generalize findings beyond our cohort. This was a small group of participants who were diagnosed with MtD. Therefore, the experiences and needs of those without genetic confirmation of MtD were not captured. Additionally, no parent/caregiver participants in this study were fathers, which may draw into question the completeness of the parental experience. As well, survey and interview demographic characteristics revealed that our sample was not representative of the Manitoba population (Statistics Canada, 2017a; 2017b). That being said, it is unclear whether the Manitoba population is representative of the MtD patient population or how existing health and social inequities influence who is diagnosed with MtD. Further, patients with MtD in Manitoba and surrounding catchment areas were sampled due to convenience and resource availability. As such, the experiences of participants are not necessarily representative of the entire MtD patient population or even the MtD patient population in Canada, given that healthcare is mandated at the provincial and territorial levels.

Also, participants self-selected into this study may have had particularly positive or negative experiences and may have been more motivated to participate, which could have introduced bias into the data. However, this limitation is mitigated in part by the use of IPA, which is grounded in understanding phenomena from the perspective of the individual, whatever that perspective may be. There were also limitations surrounding the breadth of experiences captured in this study. MtD experts are not equally available in other provinces, which likely influenced participants' healthcare experiences. Also, surveys and interviews were only available in English, and therefore, only English-speaking individuals were included in this study. Of note,

the COVID-19 pandemic did not alter study plans; however, one participant's diagnostic journey unfolded in this setting, delaying the diagnostic process in a way that may not have been representative of the journey otherwise. Next, because our research question required participants to reflect on their past experiences of the diagnostic process, this study was subject to possible recall bias, which could have impacted data accuracy. Further, while the inclusion of affected individuals and parents/caregivers was a strength of this study that addressed a gap in the literature, it did impact sample homogeneity. To address this limitation, IPA was chosen for qualitative data due to its idiographic nature. Despite limitations in generalizability, many of our findings parallel existent literature and, therefore, likely provide further context to current research and could be applied as local practice improvements.

Finally, there were limitations specific to the survey component of this study, which was intended to be conducted as a complementary method to interviews to provide descriptive statistics about our study population and not for inferential statistics. Therefore, the survey findings should only be used in the context of better understanding the interview data. As well, it became clear during quantitative data analysis and interpretation that there was ambiguity in certain survey questions, which may hinder the reliability and validity of these data. This ambiguity is reflective of the lack of previous research on this topic that necessitated a broader approach to instrument development. Lastly, while the survey was assessed for readability, it is important to note that the Flesch-Kincaid Grade Level test does not necessarily inform the understandability or coherence of a text, nor is there an appreciation for context such as the reader's previous knowledge (Jindal & MacDermid, 2017). Additionally, grade level scoring and readability formulae may be inconsistent depending on the software used (Jindal & MacDermid, 2017). Despite these steps taken to improve reliability, this survey was not validated. Therefore, it is unclear how accurately this survey measured the experiences and needs of the diagnostic journey. Survey validation was beyond the scope and aims of this study.

6.8 FUTURE DIRECTIONS

This study was the first to explore the experiences and needs along the MtD diagnostic journey in individuals and parents/caregivers using both quantitative and qualitative approaches. The findings of this study pave the way for several avenues of future research. First, adult participants in this study discussed a general lack of guidance along the MtD diagnostic journey,

which is unsurprising given the lack of literature on the experiences and needs of this patient population and even among adults with RD. While our study furthered understanding of this topic, additional research is required to establish the concerns specific to this patient population.

In addition, the survey developed in this study may serve as a pilot that can be amended and distributed on a national level to gain a better understanding of the diagnostic journey across Canada. The interview component of this research identified the psychological and social consequences of the MtD diagnostic journey to be significant. As such, validated questions inquiring about psychological wellbeing, coping efficacy, and social resources may be added to our survey to assess these factors. Nonetheless, a qualitative component, whether through open-ended questions or follow-up interviews, is recommended in the broader Canadian population due to the lack of qualitative research within this field.

Furthermore, study participants described the uncertainties and challenges associated with management and other day-to-day impacts that remained post-diagnosis. Further research is needed to characterize these challenges and explore life after the MtD diagnosis to ensure that patients and families are supported at all stages of their journey. Similarly, the present study identified that the MtD diagnostic process results in social needs that extend beyond the medical setting. Strategies for addressing the majority of these social needs are beyond the scope of this study due to their systematic nature. However, future studies may seek to characterize these social needs with the aim of developing evidence-based recommendations to enact policies that better support patients and families in meeting these needs.

Finally, this study highlighted the desire for increased support and information for those seeking a diagnosis and recommended that an effective PPR and a multidisciplinary team can address these needs. Future research on the role of genetic counsellors, social workers, and other professionals in MtD care is needed, as well as research investigating the feasibility of establishing a multidisciplinary MtD care centre for both adult and pediatric populations. This research could entail eliciting the opinions of patients and families with MtD, as well as providers, on the best approaches to such an endeavour.

CHAPTER 7: CONCLUSION

The little that is known about the diagnostic journey for MtD suggests that this process is long and arduous for patients and families, featuring consultations with numerous specialists, multiple investigations, and an overall sense of uncertainty. This study aimed to retrospectively explore the experiences and informational, psychological, and social needs of patients and parents/caregivers during the MtD diagnostic journey. Surveys were used to identify the salient features of the diagnostic journey, and interviews further explored the needs and experiential sense-making of those navigating this journey.

The diagnostic journey was found to unfold in stages, with the number of specialists consulted and the time to diagnosis being significant but less than initially anticipated, which could reflect differences in the diagnostic process in Manitoba compared to other centres. Information and support for MtD understandably became more available upon diagnosis. However, the general lack of knowledge on these conditions meant ambiguity remained. Participants described needing more information and support during the process leading to diagnosis and that evolving uncertainty and unpleasant feelings were heavily intertwined with the desire for an answer during this journey. As a result, participants expressed coping in several different ways, including through information-seeking, which represented seeking a means of hope. As well, results showed that the social needs associated with the diagnostic journey extended beyond the medical space and were insufficiently met on a systematic level. The PPR underscored the experiences and needs of participants and was found to be key in how the journey was recalled and the extent to which participants felt supported.

The results from this study provide insight into the complexities of the MtD diagnostic journeys and the need for improved informational, psychological, and social support, particularly within the adult patient population. Providers involved in the care of patients with MtD are ideally situated to provide this support to mitigate the challenges and stressors of the diagnostic process and improve MtD care. Therefore, participant-driven recommendations were developed to guide MtD providers in addressing the needs of patients and families. Our findings warrant further investigation into the possibility of establishing a multidisciplinary care team for MtD in the province, similar to existent MCNs in the United States. Overall, this study provided valuable insights that will support future research into the MtD diagnostic journey.

REFERENCES

Adler, N. E., Page, A. E., & Setting, I. of M. (US) C. on P. S. to C. P. in a C. (2008). Consequences of Unmet Psychosocial Needs. In *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*. National Academies Press (US). https://www.ncbi.nlm.nih.gov/books/NBK4008/

Alston, C. L., Rocha, M. C., Lax, N. Z., Turnbull, D. M., & Taylor, R. W. (2017). The genetics and pathology of mitochondrial disease. *The Journal of Pathology*, *241*(2), 236–250. https://doi.org/10.1002/path.4809

Anderson, M., Elliott, E. J., & Zurynski, Y. A. (2013). Australian families living with rare disease: Experiences of diagnosis, health services use and needs for psychosocial support. *Orphanet Journal of Rare Diseases*, *8*, 22. https://doi.org/10.1186/1750-1172-8-22

Awdish, R. L. A., & Berry, L. L. (2019, May 9). Putting Healing Back at the Center of Health Care. *Harvard Business Review*. https://hbr.org/2019/05/putting-healing-back-at-the-center-of-health-care

Barwick, M. A. (2008). *Knowledge Translation Planning Template*. Ontario: The Hospital for Sick Children. https://www.sickkids.ca/en/learning/continuing-professional-development/knowledge-translation-training/knowledge-translation-planning-template-form/

Baumbusch, J., Mayer, S., & Sloan-Yip, I. (2018). Alone in a Crowd? Parents of Children with Rare Diseases' Experiences of Navigating the Healthcare System. *Journal of Genetic Counseling*. https://doi.org/10.1007/s10897-018-0294-9

Bendixen, R. M., & Houtrow, A. (2017). Parental Reflections on the Diagnostic Process for Duchenne Muscular Dystrophy: A Qualitative Study. *Journal of Pediatric Health Care: Official Publication of National Association of Pediatric Nurse Associates & Practitioners*, *31*(3), 285–292. https://doi.org/10.1016/j.pedhc.2016.09.002

Blöß, S., Klemann, C., Rother, A.-K., Mehmecke, S., Schumacher, U., Mücke, U., Mücke, M., Stieber, C., Klawonn, F., Kortum, X., Lechner, W., & Grigull, L. (2017). Diagnostic needs for rare diseases and shared prediagnostic phenomena: Results of a German-wide expert Delphi survey. *PloS One*, *12*(2), e0172532. https://doi.org/10.1371/journal.pone.0172532

Bonnell, E. V. (2020). *Exploration of genetic counselling service provision to rural patients using Telehealth at a single tertiary centre*. https://mspace.lib.umanitoba.ca/xmlui/handle/1993/34775

Bryson, B., Bogart, K., Atwood, M., Fraser, K., Locke, T., Pugh, K., & Zerrouk, M. (2021). Navigating the unknown: A content analysis of the unique challenges faced by adults with rare diseases. *Journal of Health Psychology*, *26*(5), 623–635. https://doi.org/10.1177/1359105319828150

Budych, K., Helms, T. M., & Schultz, C. (2012). How do patients with rare diseases experience the medical encounter? Exploring role behavior and its impact on patient-physician interaction. *Health Policy (Amsterdam, Netherlands)*, *105*(2–3), 154–164. https://doi.org/10.1016/j.healthpol.2012.02.018

Canadian Association of Social Workers. (2020). *CASW Social Work Scope of Practice*. Canadian Association of Social Workers. https://www.casw-acts.ca/en/what-social-work/casw-social-work-scope-practice

Canadian Institutes of Health Research. (2012). *Guide to Knowledge Translation Planning at CIHR: Integrated and End-of-Grant Approaches*. Canadian Institutes of Health Research Government of Canada. https://cihr-irsc.gc.ca/e/45321.html

Canadian Pharmacists Association. (2021). *Scope of Practice*. https://www.pharmacists.ca/advocacy/scope-of-practice/

Canadian Prairie Metabolic Network. (2021). *Children's Hospital Research Institute of Manitoba*. https://www.chrim.ca/cpmn-overview/

Canadian Psychological Association. (2016). *Psychologists Practicing to Scope: The Role of Psychologists in Canada's Public Institutions*. https://cpa.ca/docs/File/Position/PracticingtoScopePaper_June2016_Final.pdf

Care4Rare. (2011). *The CareForRare Programs*. http://care4rare.ca/

Carmichael, N., Tsipis, J., Windmueller, G., Mandel, L., & Estrella, E. (2015). 'Is it going to hurt?': The impact of the diagnostic odyssey on children and their families. *Journal of Genetic Counseling*, *24*(2), 325–335. https://doi.org/10.1007/s10897-014-9773-9

Casalino, S. (2020). *Decisions surrounding risk-reducing salpingo-oophorectomy (RRSO): Experiences of BRCA-positive women*. https://mspace.lib.umanitoba.ca/xmlui/handle/1993/34779

Children's Hospital Research Institute of Manitoba. (2022). *Children's Hospital Research Institute of Manitoba*. https://www.chrim.ca/research-support-unit/

Chinnery, P. F. (2021). Primary Mitochondrial Disorders Overview. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, G. Mirzaa, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1224/

Chipidza, F. E., Wallwork, R. S., & Stern, T. A. (2015). Impact of the Doctor-Patient Relationship. *The Primary Care Companion for CNS Disorders*, *17*(5), 10.4088/PCC.15f01840. https://doi.org/10.4088/PCC.15f01840

Cohen, B., Balcells, C., Hotchkiss, B., Aggarwal, K., & Karaa, A. (2018). A retrospective analysis of health care utilization for patients with mitochondrial disease in the United States: 2008–2015. *Orphanet Journal of Rare Diseases*, *13*(1), 210. https://doi.org/10.1186/s13023-018-0949-5

College of Dietitians of Manitoba. (n.d.). *Professional Standards*. Retrieved 12 June 2022, from https://www.collegeofdietitiansmb.ca/about-dietitians/professional-standards/

Creswell, J. W., & Plano Clark, V. L. (2011). *Designing and Conducting Mixed Methods Research* (2nd ed.). SAGE Publications, Inc. https://us.sagepub.com/en-us/nam/designing-and-conducting-mixed-methods-research/book241842

Creswell, J. W., & Plano Clark, V. L. (2018). *Designing and Conducting Mixed Methods Research* (3rd ed.). SAGE Publications, Inc. https://us.sagepub.com/en-us/nam/designing-and-conducting-mixed-methods-research/book241842

DaRe, J. T., Vasta, V., Penn, J., Tran, N.-T. B., & Hahn, S. H. (2013). Targeted exome sequencing for mitochondrial disorders reveals high genetic heterogeneity. *BMC Medical Genetics*, *14*, 118. https://doi.org/10.1186/1471-2350-14-118

Dawadi, S., Shrestha, S., & Giri, R. A. (2021). Mixed-Methods Research: A Discussion on its Types, Challenges, and Criticisms. *Journal of Practical Studies in Education*, *2*(2), 25–36. https://doi.org/10.46809/jpse.v2i2.20

Decety, J., & Fotopoulou, A. (2015). Why empathy has a beneficial impact on others in medicine: Unifying theories. *Frontiers in Behavioral Neuroscience*, *8*, 457. https://doi.org/10.3389/fnbeh.2014.00457

Deuitch, N. T., Beckman, E., Halley, M. C., Young, J. L., Reuter, C. M., Kohler, J., Bernstein, J. A., Wheeler, M. T., Undiagnosed Diseases Network, Ormond, K. E., & Tabor, H. K. (2021). 'Doctors can read about it, they can know about it, but they've never lived with it': How parents use social media throughout the diagnostic odyssey. *Journal of Genetic Counseling*. https://doi.org/10.1002/jgc4.1438

Dinchong, R. (2019). *Reducing the psychosocial impact of a false positive newborn screen for inborn errors of metabolism*. https://mspace.lib.umanitoba.ca/xmlui/handle/1993/34019

Donegan, D., Gowan, T., Gruber, R., Cottingham, A., Flanagan, M., Erickson, D., & Imperiale, T. F. (2021). The Need for Patient-centered Education Among Patients Newly Diagnosed With a Pituitary Tumor. *Journal of the Endocrine Society*, *5*(6), bvab061. https://doi.org/10.1210/jendso/bvab061

El-Hattab, A. W., Almannai, M., & Scaglia, F. (2018). MELAS. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, & A. Amemiya (Eds.), *GeneReviews*®. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1233/

Esquivel-Sada, D., & Nguyen, M. T. (2018). Diagnosis of rare diseases under focus: Impacts for Canadian patients. *Journal of Community Genetics*, *9*(1), 37–50. https://doi.org/10.1007/s12687-017-0320-x

Falk, M. J., Shen, L., & Gai, X. (2020). Chapter 2 - Mitochondrial Disease Genes Compendium: Connecting with knowledge in the Mitochondrial Disease Sequence Data Resource (MSeqDR). In M. J. Falk (Ed.), *Mitochondrial Disease Genes Compendium* (pp. 17–23). Academic Press. https://doi.org/10.1016/B978-0-12-820029-2.00002-4

Farmer, T., Robinson, K., Elliott, S. J., & Eyles, J. (2006). Developing and implementing a triangulation protocol for qualitative health research. *Qualitative Health Research*, *16*(3), 377–394. https://doi.org/10.1177/1049732305285708

Frazier, A. E., Thorburn, D. R., & Compton, A. G. (2019). Mitochondrial energy generation disorders: Genes, mechanisms, and clues to pathology. *The Journal of Biological Chemistry*, *294*(14), 5386–5395. https://doi.org/10.1074/jbc.R117.809194

Fugard, A. J. B., & Potts, H. W. W. (2015). Supporting thinking on sample sizes for thematic analyses: A quantitative tool. *International Journal of Social Research Methodology*, *18*(6), 669–684. https://doi.org/10.1080/13645579.2015.1005453

GeneDx, Inc. (2018). *GeneDx, Inc*. https://www.genedx.com/test-catalog/disorders/mitochondrial-encephalopathy/

Geng, L. N., Sum-Ping, O., & Geng, Y.-J. (2019). *Phases of the Diagnostic Journey: A Framework*. https://doi.org/10.23937/2643-4466/1710013

Goldstein, A., & Falk, M. J. (2019). Mitochondrial DNA Deletion Syndromes. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, & A. Amemiya (Eds.), *GeneReviews®*. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1203/

Gómez-Zúñiga, B., Pulido Moyano, R., Pousada Fernández, M., García Oliva, A., & Armayones Ruiz, M. (2019). The experience of parents of children with rare diseases when communicating with healthcare professionals: Towards an integrative theory of trust. *Orphanet Journal of Rare Diseases*, *14*(1), 159. https://doi.org/10.1186/s13023-019-1134-1

Gray, W. N., Schaefer, M. R., Resmini-Rawlinson, A., & Wagoner, S. T. (2018). Barriers to Transition From Pediatric to Adult Care: A Systematic Review. *Journal of Pediatric Psychology*, *43*(5), 488–502. https://doi.org/10.1093/jpepsy/jsx142

Grier, J., Hirano, M., Karaa, A., Shepard, E., & Thompson, J. L. P. (2018). Diagnostic odyssey of patients with mitochondrial disease. *Neurology: Genetics*, *4*(2). https://doi.org/10.1212/NXG.0000000000000230

Grimshaw, J. M., Eccles, M. P., Lavis, J. N., Hill, S. J., & Squires, J. E. (2012). Knowledge translation of research findings. *Implementation Science*, *7*(1), 50. https://doi.org/10.1186/1748-5908-7-50

Guest, G., Bunce, A., & Johnson, L. (2006). How Many Interviews Are Enough?: An Experiment with Data Saturation and Variability. *Field Methods*, *18*(1), 59–82. https://doi.org/10.1177/1525822X05279903

Ha, J. F., & Longnecker, N. (2010). Doctor-Patient Communication: A Review. *The Ochsner Journal*, *10*(1), 38–43.

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap): A metadata-driven methodology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics*, *42*(2), 377–381. https://doi.org/10.1016/j.jbi.2008.08.010

Hartley, J. N., Greenberg, C. R., & Mhanni, A. A. (2011). Genetic Counseling in a Busy Pediatric Metabolic Practice. *Journal of Genetic Counseling*, *20*(1), 20–22. https://doi.org/10.1007/s10897-010-9324-y

Jindal, P., & MacDermid, J. C. (2017). Assessing reading levels of health information: Uses and limitations of Flesch formula. *Education for Health*, *30*(1), 84. https://doi.org/10.4103/1357-6283.210517

Karaa, A., Goldstein, A., Balcells, C., Mann, K., Stanley, L., Yeske, P. E., & Parikh, S. (2019a). Harmonizing care for rare diseases: How we developed the mitochondrial care network in the United States. *Molecular Genetics and Metabolism*, *127*(2), 122–127. https://doi.org/10.1016/j.ymgme.2019.05.012

Karaa, A., Goldstein, A., Balcells, C., Mann, K., Stanley, L., Yeske, P. E., & Parikh, S. (2019b). Primary mitochondrial disease in the US: Data from patients and physicians' perspective on health care delivery. *Data in Brief*, *25*, 104343. https://doi.org/10.1016/j.dib.2019.104343

Kim, K. R., Lee, E., Namkoong, K., Lee, Y. M., Lee, J. S., & Kim, H. D. (2010). Caregiver's burden and quality of life in mitochondrial disease. *Pediatric Neurology*, *42*(4), 271–276. https://doi.org/10.1016/j.pediatrneurol.2009.11.012

Kincaid, J., Braby, R., & Mears, J. E. (1988). *Electronic authoring and delivery of technical information*. https://doi.org/10.1007/BF02904998

Klein, I.-L., van de Loo, K. F. E., Smeitink, J. A. M., Janssen, M. C. H., Kessels, R. P. C., van Karnebeek, C. D., van der Veer, E., Custers, J. A. E., & Verhaak, C. M. (2021). Cognitive functioning and mental health in mitochondrial disease: A systematic scoping review. *Neuroscience and Biobehavioral Reviews*, *125*, 57–77. https://doi.org/10.1016/j.neubiorev.2021.02.004

Krieg, E., Calderwood, L., Campion, M., & Krepkovich, K. E. (2016). Confirmed versus suspected: The social significance of a genetic or non-genetic diagnosis of mitochondrial disease. *Mitochondrion*, *28*, 60–66. https://doi.org/10.1016/j.mito.2016.03.008

Larsen, H., & Adu, P. (2021). *The Theoretical Framework in Phenomenological Research: Development and Application*. https://doi.org/10.4324/9781003084259

Lazarus, R. S., & Folkman, S. (1984). *Stress, Appraisal, and Coping*. Springer Publishing Company.

Levenson, D. (2015). Respectful communication by geneticists important for parents of children with undiagnosed disorders. *American Journal of Medical Genetics Part A*, *167*(7), viii–ix. https://doi.org/10.1002/ajmg.a.37196

Levitt, H., Bamberg, M., Creswell, J., Frost, D., Josselson, R., & Suárez-Orozco, C. (2018). Journal Article Reporting Standards for Qualitative Primary, Qualitative Meta-Analytic, and Mixed Methods Research in Psychology: The APA Publications and Communications Board Task Force Report. *American Psychologist*, *73*, 26–46. https://doi.org/10.1037/amp0000151

Lewis, C., Skirton, H., & Jones, R. (2010). Living Without a Diagnosis: The Parental Experience. *Genetic Testing and Molecular Biomarkers*, *14*(6), 807–815. https://doi.org/10.1089/gtmb.2010.0061

Long, J. C., Best, S., Hatem, S., Theodorou, T., Catton, T., Murray, S., Braithwaite, J., & Christodoulou, J. (2021). The long and winding road: Perspectives of people and parents of children with mitochondrial conditions negotiating management after diagnosis. *Orphanet Journal of Rare Diseases*, *16*(1), 310. https://doi.org/10.1186/s13023-021-01939-6

Madlensky, L., Trepanier, A. M., Cragun, D., Lerner, B., Shannon, K. M., & Zierhut, H. (2017). A Rapid Systematic Review of Outcomes Studies in Genetic Counseling. *Journal of Genetic Counseling*, *26*(3), 361–378. https://doi.org/10.1007/s10897-017-0067-x

Mahan, J. D., Betz, C. L., Okumura, M. J., & Ferris, M. E. (2017). Self-management and Transition to Adult Health Care in Adolescents and Young Adults: A Team Process. *Pediatrics in Review*, *38*(7), 305–319. https://doi.org/10.1542/pir.2016-0074

McCarthy Veach, P., Bartels, D. M., & LeRoy, B. S. (2007). Coming Full Circle: A Reciprocal-Engagement Model of Genetic Counseling Practice. *Journal of Genetic Counseling*, *16*(6), 713–728. https://doi.org/10.1007/s10897-007-9113-4

McConkie-Rosell, A., Hooper, S. R., Pena, L. D. M., Schoch, K., Spillmann, R. C., Jiang, Y.-H., Cope, H., Palmer, C., & Shashi, V. (2018). Psychosocial Profiles of Parents of Children with Undiagnosed Diseases: Managing Well or Just Managing? *Journal of Genetic Counseling*, *27*(4), 935–946. https://doi.org/10.1007/s10897-017-0193-5

Merker, V. L., Plotkin, S. R., Charns, M. P., Meterko, M., Jordan, J. T., & Elwy, A. R. (2021). Effective provider-patient communication of a rare disease diagnosis: A qualitative study

of people diagnosed with schwannomatosis. *Patient Education and Counseling*, *104*(4), 808–814. https://doi.org/10.1016/j.pec.2020.09.029

MitoAction. (2005). *MitoAction*. Mito Action. https://www.mitoaction.org/

MitoCanada Foundation. (2021). *MitoCanada Patient Contact Registry*. MitoCanada. https://mitocanada.org/patient-contact-registry/

Mitochondrial Care Network. (2018). *Mitochondrial Care Network—Centers*. Mitochondrial Care Network. https://www.mitonetwork.org/centers

Mitochondrial Medicine Society. (1998). *About the Mitochondrial Medicine Society*. Mitochondrial Medicine Society. http://www.mitosoc.org/about

Molster, C., Urwin, D., Di Pietro, L., Fookes, M., Petrie, D., van der Laan, S., & Dawkins, H. (2016). Survey of healthcare experiences of Australian adults living with rare diseases. *Orphanet Journal of Rare Diseases*, *11*, 30. https://doi.org/10.1186/s13023-016-0409-z

National Society of Genetic Counselors' Definition Task Force, Resta, R., Biesecker, B. B., Bennett, R. L., Blum, S., Hahn, S. E., Strecker, M. N., & Williams, J. L. (2006). A new definition of Genetic Counseling: National Society of Genetic Counselors' Task Force report. *Journal of Genetic Counseling*, *15*(2), 77–83. https://doi.org/10.1007/s10897-005-9014-3

Nesbitt, V., Pitceathly, R. D. S., Turnbull, D. M., Taylor, R. W., Sweeney, M. G., Mudanohwo, E. E., Rahman, S., Hanna, M. G., & McFarland, R. (2013). The UK MRC Mitochondrial Disease Patient Cohort Study: Clinical phenotypes associated with the m.3243A>G mutation--implications for diagnosis and management. *Journal of Neurology, Neurosurgery, and Psychiatry*, *84*(8), 936–938. https://doi.org/10.1136/jnnp-2012-303528

Niyazov, D. M., Kahler, S. G., & Frye, R. E. (2016). Primary Mitochondrial Disease and Secondary Mitochondrial Dysfunction: Importance of Distinction for Diagnosis and Treatment. *Molecular Syndromology*, *7*(3), 122–137. https://doi.org/10.1159/000446586

Noorda, G., Hermans-Peters, M., Smeitink, J., van Achterberg, T., Kemps, H., Goverde, W., & Schoonhoven, L. (2007). Mitochondrial disease: Needs and problems of children, their parents and family. A systematic review and pilot study into the need for information of parents during the diagnostic phase. *Journal of Inherited Metabolic Disease*, *30*(3), 333–340. https://doi.org/10.1007/s10545-007-0426-0

Noorda, G., van Achterberg, T., van der Hooft, T., Smeitink, J., Schoonhoven, L., & van Engelen, B. (2012). Problems of adults with a mitochondrial disease - the patients' perspective: Focus on loss. *JIMD Reports*, *6*, 85–94. https://doi.org/10.1007/8904_2011_121

North American Mitochondrial Disease Consortium. (2017). *Patient Registry and Biorepository*. North American Mitochondrial Disease Consortium. https://www1.rarediseasesnetwork.org/cms/namdc/Get-Involved/Studies/7401

O'Cathain, A., Murphy, E., & Nicholl, J. (2010). Three techniques for integrating data in mixed methods studies. *BMJ*, *341*, c4587. https://doi.org/10.1136/bmj.c4587

O'gurek, D. T., & Henke, C. (2018). A Practical Approach to Screening for Social Determinants of Health. *Family Practice Management*, *25*(3), 7–12.

O'Riley, M. K. (2003). *How people with mitochondrial disorders construct knowledge within the health care relationship: A narrative inquiry*. [Unpublished Master of Arts Thesis]. University of British Columbia. https://doi.org/10.14288/1.0055927

Paik, K., Lines, M. A., Chakraborty, P., Khangura, S. D., Latocki, M., Al-Hertani, W., Brunel-Guitton, C., Khan, A., Penny, B., Rockman-Greenberg, C., Rupar, C. A., Sondheimer, N., Tarnopolsky, M., Tingley, K., Coyle, D., Dyack, S., Feigenbaum, A., Geraghty, M. T., Gillis, J., … Canadian Inherited Metabolic Diseases Research Network. (2019). Health Care for Mitochondrial Disorders in Canada: A Survey of Physicians. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *46*(6), 717–726. https://doi.org/10.1017/cjn.2019.240

Parikh, S., Goldstein, A., Karaa, A., Koenig, M. K., Anselm, I., Brunel-Guitton, C., Christodoulou, J., Cohen, B. H., Dimmock, D., Enns, G. M., Falk, M. J., Feigenbaum, A., Frye, R. E., Ganesh, J., Griesemer, D., Haas, R., Horvath, R., Korson, M., Kruer, M. C., … Chinnery, P. F. (2017). Patient care standards for primary mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, *19*(12), 1380–1380. https://doi.org/10.1038/gim.2017.107

Parikh S. et al. *Figure 1. Body systems affected by primary mitochondrial disease*. From Parikh, S., Goldstein, A., Karaa, A., Koenig, M. K., Anselm, I., Brunel-Guitton, C., Christodoulou, J., Cohen, B. H., Dimmock, D., Enns, G. M., Falk, M. J., Feigenbaum,

A., Frye, R. E., Ganesh, J., Griesemer, D., Haas, R., Horvath, R., Korson, M., Kruer, M. C., … Chinnery, P. F. (2017). Patient care standards for primary mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, *19*(12). https://doi.org/10.1038/gim.2017.107. Used with permission from Elsevier.

Parikh, S., Goldstein, A., Koenig, M. K., Scaglia, F., Enns, G. M., Saneto, R., Anselm, I., Cohen, B. H., Falk, M. J., Greene, C., Gropman, A. L., Haas, R., Hirano, M., Morgan, P., Sims, K., Tarnopolsky, M., Van Hove, J. L. K., Wolfe, L., & DiMauro, S. (2015). Diagnosis and management of mitochondrial disease: A consensus statement from the Mitochondrial Medicine Society. *Genetics in Medicine : Official Journal of the American College of Medical Genetics*, *17*(9), 689–701. https://doi.org/10.1038/gim.2014.177

Parikh, S., Goldstein, A., Koenig, M. K., Scaglia, F., Enns, G. M., Saneto, R., Anselm, I., Collins, A., Cohen, B. H., DeBrosse, S. D., Dimmock, D., Falk, M. J., Ganesh, J., Greene, C., Gropman, A. L., Haas, R., Kahler, S. G., Kamholz, J., Kendall, F., … Wolfe, L. A. (2013). Practice patterns of mitochondrial disease physicians in North America. Part 2: Treatment, care and management. *Mitochondrion*, *13*(6), 681–687. https://doi.org/10.1016/j.mito.2013.09.003

Parikh, S., Goldstein, A., Koenig, M. K., Scaglia, F., Enns, G. M., Saneto, R., Anselm, I., Collins, A., Cohen, B. H., DeBrosse, S. D., Dimmock, D., Falk, M. J., Ganesh, J., Greene, C., Gropman, A. L., Haas, R., Kahler, S. G., Kamholz, J., Kendall, F., … Wolfe, L. A. (2014). Practice patterns of mitochondrial disease physicians in North America. Part 1: Diagnostic and clinical challenges. *Mitochondrion*, *14*, 26–33. https://doi.org/10.1016/j.mito.2013.07.116

Parikh, S., Saneto, R., Falk, M. J., Anselm, I., Cohen, B. H., Haas, R., & Medicine Society, T. M. (2009). A modern approach to the treatment of mitochondrial disease. *Current Treatment Options in Neurology*, *11*(6), 414–430. https://doi.org/10.1007/s11940-009-0046-0

Pelentsov, L. J., Fielder, A. L., Laws, T. A., & Esterman, A. J. (2016). The supportive care needs of parents with a child with a rare disease: Results of an online survey. *BMC Family Practice*, *17*, 88. https://doi.org/10.1186/s12875-016-0488-x

Pfeffer, G., Majamaa, K., Turnbull, D. M., Thorburn, D., & Chinnery, P. F. (2012). Treatment for mitochondrial disorders. *The Cochrane Database of Systematic Reviews*, *4*, CD004426. https://doi.org/10.1002/14651858.CD004426.pub3

Pirzadeh-Miller, S., Robinson, L. S., Read, P., & Ross, T. S. (2017). Genetic Counseling Assistants: An Integral Piece of the Evolving Genetic Counseling Service Delivery Model. *Journal of Genetic Counseling*, *26*(4), 716–727. https://doi.org/10.1007/s10897-016-0039-6

Poulton, J., Finsterer, J., & Yu-Wai-Man, P. (2017). Genetic Counselling for Maternally Inherited Mitochondrial Disorders. *Molecular Diagnosis & Therapy*, *21*(4), 419–429. https://doi.org/10.1007/s40291-017-0279-7

Rahman, J., & Rahman, S. (2018). Mitochondrial medicine in the omics era. *Lancet (London, England)*, *391*(10139), 2560–2574. https://doi.org/10.1016/S0140-6736(18)30727-X

Rahman, S. (2020). Mitochondrial disease in children. *Journal of Internal Medicine*, *287*(6), 609–633. https://doi.org/10.1111/joim.13054

Ravitch, S. M., & Mittenfelner Carl, N. (2020). *Qualitative Research: Bridging the Conceptual, Theoretical, and Methodological* (2nd ed.). SAGE Publications, Inc.

Rogers, C. R. (1951). *Client-centered therapy; its current practice, implications, and theory* (pp. xii, 560). Houghton Mifflin.

Rosenthal, E., Biesecker, L. G., & Biesecker, B. (2001). Parental attitudes toward a diagnosis in children with unidentified multiple congenital anomaly syndromes. *American Journal of Medical Genetics*, *103*, 106–114. https://doi.org/10.1002/ajmg.1527

Saneto, R. P. (2020). Mitochondrial diseases: Expanding the diagnosis in the era of genetic testing. *Journal of Translational Genetics and Genomics*, *4*(4), 384–428. https://doi.org/10.20517/jtgg.2020.40

Saneto, R.P. *Table 1. Classical mitochondrial syndromes due to mtDNA- and nuclear-encoded variants*. Adapted from Saneto, R.P. (2020) Mitochondrial diseases: Expanding the diagnosis in the era of genetic testing. *Journal of Translational Genetics and Genomics*, *4*(4), 384–428. https://doi.org/10.20517/jtgg.2020.40. CC BY 4.0.

Schlieben, L. D., & Prokisch, H. (2020). The Dimensions of Primary Mitochondrial Disorders. *Frontiers in Cell and Developmental Biology*, *8*. https://www.frontiersin.org/article/10.3389/fcell.2020.600079

Schwartz-Shea, P., & Yanow, D. (2020). Interpretivism. In P. Atkinson, S. Delamont, A. Cernat, J. W. Sakshaug, & R. A. Williams (Eds.), *SAGE Research Methods Foundations*. SAGE Publications Ltd. https://doi.org/10.4135/9781526421036915455

Senger, B. A., Ward, L. D., Barbosa-Leiker, C., & Bindler, R. C. (2016a). Stress and coping of parents caring for a child with mitochondrial disease. *Applied Nursing Research: ANR, 29*, 195–201. https://doi.org/10.1016/j.apnr.2015.03.010

Senger, B. A., Ward, L. D., Barbosa-Leiker, C., & Bindler, R. C. (2016b). The Parent Experience of Caring for a Child with Mitochondrial Disease. *Journal of Pediatric Nursing*, *31*(1), 32–41. https://doi.org/10.1016/j.pedn.2015.08.007

Simpkin, A. L., & Armstrong, K. A. (2019). Communicating Uncertainty: A Narrative Review and Framework for Future Research. *Journal of General Internal Medicine*, *34*(11), 2586–2591. https://doi.org/10.1007/s11606-019-04860-8

Sinclair, S., Norris, J. M., McConnell, S. J., Chochinov, H. M., Hack, T. F., Hagen, N. A., McClement, S., & Bouchal, S. R. (2016). Compassion: A scoping review of the healthcare literature. *BMC Palliative Care*, *15*, 6. https://doi.org/10.1186/s12904-016-0080-0

Smith, J. A., Flowers, P., & Larkin, M. (2022). *Interpretative Phenomenological Analysis: Theory, Method and Research* (2nd ed.). SAGE Publications Ltd.

Smith, J. A., & Osborn, M. (2015). Interpretative phenomenological analysis. In J. A. Smith, *Qualitative Psychology: A practical guide to research methods* (3rd ed.). SAGE Publications, Inc.

Sofou, K. (2013). Mitochondrial Disease: A Challenge for the Caregiver, the Family, and Society. *Journal of Child Neurology*, *28*(5), 663–667. https://doi.org/10.1177/0883073813481622

Sondheimer, N., Glatz, C. E., Tirone, J. E., Deardorff, M. A., Krieger, A. M., & Hakonarson, H. (2011). Neutral mitochondrial heteroplasmy and the influence of aging. *Human Molecular Genetics*, *20*(8), 1653–1659. https://doi.org/10.1093/hmg/ddr043

Spillmann, R. C., McConkie-Rosell, A., Pena, L., Jiang, Y.-H., Undiagnosed Diseases Network, Schoch, K., Walley, N., Sanders, C., Sullivan, J., Hooper, S. R., & Shashi, V. (2017). A window into living with an undiagnosed disease: Illness narratives from the Undiagnosed

Diseases Network. *Orphanet Journal of Rare Diseases*, *12*(1), 71. https://doi.org/10.1186/s13023-017-0623-3

Statistics Canada. (2017a). *Census Profile, 2016 Census—Manitoba Province* [Data Table]. https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/page.cfm?Lang=E&Geo1=PR&Code1=46&Geo2=POPC&Code2=0618&Data=Count

Statistics Canada. (2017b). *Census Profile, 2016 Census—Winnipeg, City Census subdivision* [Data Table]. https://www12.statcan.gc.ca/census-recensement/2016/dp-pd/prof/details/page.cfm?Lang=E&Geo1=CSD&Code1=4611040&Geo2=PR&Code2=01&Data=Count&SearchText=4611040

Stenton, S. L., & Prokisch, H. (2020). Genetics of mitochondrial diseases: Identifying mutations to help diagnosis. *EBioMedicine*, *56*, 102784. https://doi.org/10.1016/j.ebiom.2020.102784

Stewart, J. B., & Chinnery, P. F. (2015). The dynamics of mitochondrial DNA heteroplasmy: Implications for human health and disease. *Nature Reviews. Genetics*, *16*(9), 530–542. https://doi.org/10.1038/nrg3966

Strout, T. D., Hillen, M., Gutheil, C., Anderson, E., Hutchinson, R., Ward, H., Kay, H., Mills, G. J., & Han, P. K. J. (2018). Tolerance of uncertainty: A systematic review of health and healthcare-related outcomes. *Patient Education and Counseling*, *101*(9), 1518–1537. https://doi.org/10.1016/j.pec.2018.03.030

Syndromes Without A Name. (2012). *SWAN Australia*. Https://Swanaus.Org.Au/. https://swanaus.org.au/

Thorburn, D. R., Rahman, J., & Rahman, S. (2017). Mitochondrial DNA-Associated Leigh Syndrome and NARP. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, & A. Amemiya (Eds.), *GeneReviews*®. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1173/

Tracy, S. J. (2010). Qualitative Quality: Eight "Big-Tent" Criteria for Excellent Qualitative Research. *Qualitative Inquiry*, *16*(10), 837–851. https://doi.org/10.1177/1077800410383121

Transcript Heroes Transcription Services. (2015). Retrieved 29 April 2021, from https://transcriptheroes.ca/

Undiagnosed Diseases Network. (2008). *Undiagnosed Diseases Network*. UDN. https://undiagnosed.hms.harvard.edu/

United Mitochondrial Disease Foundation. (1996). *United Mitochondrial Disease Foundation*. UMDF. https://www.umdf.org/

United Mitochondrial Disease Foundation. (2014). *MitoSHARE Registry*. United Mitochondrial Disease Foundation. https://www.umdf.org/mitoshare-registry/

van de Loo, K. F. E., Custers, J. A. E., Koene, S., Klein, I.-L., Janssen, M. C. H., Smeitink, J. A. M., & Verhaak, C. M. (2020). Psychological functioning in children suspected for mitochondrial disease: The need for care. *Orphanet Journal of Rare Diseases*, *15*(1), 76. https://doi.org/10.1186/s13023-020-1342-8

Velez-Bartolomei, F., Lee, C., & Enns, G. (2021). MERRF. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, & A. Amemiya (Eds.), *GeneReviews*®. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1520/

Vento, J. M., & Pappa, B. (2013). Genetic Counseling in Mitochondrial Disease. *Neurotherapeutics*, *10*(2), 243–250. https://doi.org/10.1007/s13311-012-0173-2

von der Lippe, C., Diesen, P. S., & Feragen, K. B. (2017). Living with a rare disorder: A systematic review of the qualitative literature. *Molecular Genetics & Genomic Medicine*, *5*(6), 758–773. https://doi.org/10.1002/mgg3.315

Wills, T. A. (1981). Downward comparison principles in social psychology. *Psychological Bulletin*, *90*(2), 245–271. https://doi.org/10.1037/0033-2909.90.2.245

Winnipeg Regional Health Authority. (n.d.). *Genetics and Metabolism*. https://wrha.mb.ca/genetics-and-metabolism/

Withers, C. M., Fleming, J., Wallingford, C. K., Gabbett, M. T., Peterson, M., Humphreys, L., & McInerney-Leo, A. (2021). Waiting for a diagnosis in Rubinstein-Taybi: The journey from ‘ignorance is bliss’ to the value of ‘a label’. *American Journal of Medical Genetics. Part A*, *185*(1), 105–111. https://doi.org/10.1002/ajmg.a.61920

Wittenberg, E., James, L. P., & Prosser, L. A. (2019). Spillover Effects on Caregivers’ and Family Members’ Utility: A Systematic Review of the Literature. *PharmacoEconomics*, *37*(4), 475–499. https://doi.org/10.1007/s40273-019-00768-7

Wolf, A., Moore, L., Lydahl, D., Naldemirci, Ö., Elam, M., & Britten, N. (2017). The realities of partnership in person-centred care: A qualitative interview study with patients and professionals. *BMJ Open*, *7*(7), e016491. https://doi.org/10.1136/bmjopen-2017-016491

Wu, Y., Al-Janabi, H., Mallett, A., Quinlan, C., Scheffer, I. E., Howell, K. B., Christodoulou, J., Leventer, R. J., Lockhart, P. J., Stark, Z., Boughtwood, T., & Goranitis, I. (2020). Parental health spillover effects of paediatric rare genetic conditions. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, *29*(9), 2445–2454. https://doi.org/10.1007/s11136-020-02497-3

Yanes, T., Humphreys, L., McInerney-Leo, A., & Biesecker, B. (2017). Factors Associated with Parental Adaptation to Children with an Undiagnosed Medical Condition. *Journal of Genetic Counseling*, *26*(4), 829–840. https://doi.org/10.1007/s10897-016-0060-9

Yu-Wai-Man, P., & Chinnery, P. F. (2021). Leber Hereditary Optic Neuropathy. In M. P. Adam, H. H. Ardinger, R. A. Pagon, S. E. Wallace, L. J. Bean, K. W. Gripp, G. M. Mirzaa, & A. Amemiya (Eds.), *GeneReviews*®. University of Washington, Seattle. http://www.ncbi.nlm.nih.gov/books/NBK1174/

Zilber, S., & Yeske, P. E. (2020). Mitochondrial Disease Community Registry: First look at the data, perspectives from patients and families. *Mitochondrial and Metabolic Medicine*, 19. https://doi.org/10.9777/mmm.2020.10001

Zurynski, Y., Deverell, M., Dalkeith, T., Johnson, S., Christodoulou, J., Leonard, H., Elliott, E. J., & APSU Rare Diseases Impacts on Families Study group. (2017). Australian children living with rare diseases: Experiences of diagnosis and perceived consequences of diagnostic delays. *Orphanet Journal of Rare Diseases*, *12*(1), 68. https://doi.org/10.1186/s13023-017-0622-4

APPENDIX

A.1 Study Invitation Letter

University of Manitoba

Rady Faculty of Health Sciences
Max Rady College of Medicine
Biochemistry and Medical Genetics

xxx – xxx Bannatyne Avenue
Winnipeg, Manitoba
Canada
Telephone (xxx) xxx-xxxx
Fax (xxx) xxx-xxxx
xxx@xx.ca

Dear Potential Participant,

You are receiving this letter as the [Program of Genetics and Metabolism, Shared Health OR Pediatric Mitochondrial Disease Clinic at the Winnipeg Children's Hospital] has agreed to forward this package to those who were seen in the clinic for mitochondrial disease. Your contact information has not been provided to our research team.

You are being asked to participate in a research study to learn more about the mitochondrial disease diagnostic process. The study title is "Exploring the diagnostic journey of individuals and families with mitochondrial disease". The responses to this survey will be used as a portion of an MSc Genetic Counselling thesis project at the University of Manitoba.

Study Description: The goal of this study is to raise voices of those with mitochondrial disease and better understand the experiences and needs in the journey to get a diagnosis. We hope the study results will help healthcare providers better support patients in the future.

Your Role: This survey will ask you a series of questions about your experience up to receiving a diagnosis and should take about 15-20 minutes. A paper version of the survey can be found in this package (next page). Please use the return envelope and postage provided to return completed surveys. Another option is to complete an online version of the survey through the web link: [REDCap URL].

Hearing about your experiences and impressions is important to us. At the end of the survey you will be asked if you are willing to have a 30-60 minute follow-up interview to help us better understand your diagnostic experience as a whole. You can do this by 1) providing your first name and phone number at the end of the survey for us to contact you or 2) phoning us. If you choose to participate in a follow-up interview, your survey responses will be linked to your interview by a confidential participant ID. This will allow us to review your survey ahead of the interview and possibly ask more about your survey answers during the interview. We will do everything possible to keep your personal information confidential.

Risk and Benefits: Your participation is completely voluntary. You may skip questions if you are uncomfortable or decide to stop at any time. Your decision whether or not to participate or to withdraw from the study will not affect your or your child's current and future healthcare. The risks of participating are low. It is possible that thinking about past experiences might be upsetting, emotional, or distressing for you. There will be no direct benefit for participation in this study. However, results from this study may help other people or family members getting testing for mitochondrial disease in the future. As a thank you, we are offering a $5 Tim Hortons gift card to those who complete the survey and a $20 Tim Hortons gift card to those who complete both the survey and interview.

If you have questions about this survey, need help filling it out, or would like to participate in a follow-up interview, please contact the student investigator, Maria Vas, at xxx-xxx-xxxx or xxx@xx.ca or the project supervisor, Jessica Hartley, at xxx-xxx-xxxx or xxx@xx.ca.

The study is funded by the University of Manitoba. This study and survey have been approved by the University of Manitoba Health Research Ethics Board. If you have questions about your rights as a research study participant, contact the University of Manitoba Research Ethics Board by at xxx-xxx-xxxx.

By continuing on to the back of this page and completing the survey, you are consenting to participate in this study.

Thank you for your participation!

Maria Vas, BSc
Genetic Counselling Student
Department of Biochemistry & Medical Genetics

Jessica Hartley, MS, CGC
Assistant Professor
Department of Biochemistry & Medical Genetics

SURVEY STARTS ON BACK OF THIS PAGE

A.2 Survey

Note: The parent/caregiver version of this survey is not included as, apart from changes to question wording to accommodate a parent/caregiver respondent, the survey content is the same.

SURVEY FOR INDIVIDUALS WITH MITOCHONDRIAL DISEASE

Thank you for taking the time to participate in this study. It is important to us to understand your diagnostic experience better because we hope to improve the journey to diagnosis for people with mitochondrial disease. We hope the study results will help healthcare providers better support patients in the future.

Please circle your response to the following questions. If you don't want to answer a question, please circle "Prefer not to answer" or leave the question blank.

Please send your completed survey to the Student Investigator, Maria Vas, by mail using the return envelope and postage in the package. By finishing and sending back this survey, you are consenting to participate in the study.

Introduction Questions

1. Do you have a diagnosis of mitochondrial disease?
    a. Yes, please specify name of condition: _____
    b. No

2. When did you first start having symptoms of mitochondrial disease?
    a. 0-3 years old
    b. 3-12 years old
    c. 13-18 years old
    d. 19-30 years old
    e. 31+ years old
    f. Not applicable

3. Did you have genetic testing that confirmed which gene change caused your mitochondrial disease?
    a. Yes, please specify gene name if you can recall: _____
    b. No
    c. I don't know

4. In the past 5 years (since January 2017), have you had a medical appointment for mitochondrial disease? A medical appointment would before managing symptoms or for a diagnosis/testing.
    a. Yes
    b. No
    c. I don't know

Diagnostic Journey: Signs and Symptoms

"The diagnostic journey" means your experience from when you first noticed signs or symptoms until you got a diagnosis of mitochondrial disease. "Getting a diagnosis" or "receiving a diagnosis" means when you received the genetic test result that confirmed your diagnosis of mitochondrial disease.

5. What signs or symptom(s) first motivated you to see a doctor? (Circle all that apply)

   a. Weakness
   b. Numbness
   c. Fatigue/tiredness
   d. Difficulty walking
   e. Coordination/movement problems
   f. Droopy eyelids
   g. Hearing problems
   h. Vision problems
   i. Seizures
   j. Developmental delay
   k. Loss of skills you had before
   l. Constipation or stomach pain
   m. Heart problems
   n. Other, please specify: _____

6. Approximately how long after these symptoms started did you first meet with a specialist doctor?

   a. 0-6 months
   b. 7-12 months
   c. 1-2 years
   d. 3-4 years
   e. 5+ years

7. What type of specialist doctor were you first referred to after you started having symptoms?

   a. Neurologist (brain/nervous system doctor)
   b. Gastroenterologist (digestive system doctor)
   c. Endocrinologist (hormone doctor)
   d. Geneticist/Metabolic Disease Doctor (genetics doctor)
   e. Cardiologist (heart doctor)
   f. Respirologist (lung doctor)
   g. Internist (internal organ doctor)
   h. Ophthalmologist (eye doctor)
   i. Ear, Nose, and Throat Doctor (Otolaryngologist)
   j. Emergency Room Doctor
   k. Other, please specify: _____

8. Was the doctor with whom you first discussed your symptoms the same doctor who suggested the diagnosis of mitochondrial disease?

   a. Yes
   b. No
   c. I don't know

9. If you answered “No” in question 8: What type of specialist was the doctor who suggested the diagnosis of mitochondrial disease?

    a. Family Doctor/Nurse Practitioner
    b. Pediatrician
    c. Neurologist (brain/nervous system doctor)
    d. Gastroenterologist (digestive system doctor)
    e. Endocrinologist (hormone doctor)
    f. Geneticist/Metabolic Disease Doctor (genetics doctor)
    g. Cardiologist (heart doctor)
    h. Respirologist (lung doctor)
    i. Internist (internal organ doctor)
    j. Ophthalmologist (eye doctor)
    k. Ear, Nose, and Throat Doctor (Otolaryngologist)
    l. Emergency Room Doctor
    m. Other, please specify: _____

10. Were you misdiagnosed with any other non-mitochondrial disease before getting your diagnosis?

    a. Yes
    b. No

11. If you answered “Yes” to question 10: What non-mitochondrial disease(s) were you misdiagnosed with?

    _____

12. Who offered and explained any <u>non-genetic</u> testing that you had <u>before</u> getting a diagnosis of mitochondrial disease? (Circle all that apply)

    This testing could include blood and pee testing, MRI, skin or muscle biopsy, EMG (a test that measures how well muscles respond to nerve signals).

    a. Family Doctor/Nurse Practitioner
    b. Pediatrician
    c. Neurologist (brain/nervous system doctor)
    d. Gastroenterologist (digestive system doctor)
    e. Endocrinologist (hormone doctor)
    f. Geneticist/Metabolic Disease Doctor (genetics doctor)
    g. Genetic Counsellor
    h. Cardiologist (heart doctor)
    i. Respirologist (lung doctor)
    j. Internist (internal organ doctor)
    k. Ophthalmologist (eye doctor)
    l. Ear, Nose, and Throat Doctor (Otolaryngologist)
    m. Emergency Room Doctor
    n. I only had genetic testing
    o. Other, please specify: _____

Diagnostic Journey: Relationship with Healthcare Providers

13. Throughout the journey to diagnosis, how often did you feel included by healthcare providers when making decisions about your health (e.g. testing, diagnosis, treatment)?

    a. Always
    b. Often
    c. Sometimes
    d. Rarely
    e. Never

14. Throughout the journey to diagnosis, how often did you feel you could trust your healthcare providers?

    a. Always
    b. Often
    c. Sometimes
    d. Rarely
    e. Never

15. Throughout the journey to diagnosis, how would you describe the quality of communication you had with your healthcare providers?

    a. Very Good
    b. Good
    c. Average
    d. Poor
    e. Very Poor

16. Please rate from 1 to 10 how helpful healthcare providers were in providing each option below throughout your diagnostic journey.

    1 = Not at all helpful and 10 = Very helpful

    If any of the options listed below do not apply, please leave that option blank.

    a. **Education** (e.g. I learned about mitochondrial disease and how it can be passed down in families.)

       1……2……3……..…4……5……6……7……8……9……10

    b. **Support & Communication** (e.g. I felt like my healthcare providers cared about my opinions, concerns, and feelings. I felt included in decisions about my health.)

       1……2……3……..…4……5……6……7……8……9……10

c. **Access to Support Services** (e.g. I was told about or referred to services that were available to me. These services could have included support/advocacy groups, support organizations, counselling, or other mental health services.)

1……2……3……..…4……5……6……7……8……9……10

d. **Other**, please specify: _____

1……2……3……..…4……5……6……7……8……9……10

Diagnostic Journey: Educational Needs and Source of Support

17. Which of the following were you provided with **during** your diagnostic journey, and by whom? Examples for each category can be found in question 16 above (Check all that apply)

	Family Doctor/ Nurse Practitioner	Geneticist/ Metabolic Disease Doctor	Genetic Counsellor	Neurologist	Other, please specify: _____
Education	○	○	○	○	○
Support & Communication	○	○	○	○	○
Access to Services	○	○	○	○	○
Other, please specify: _____	○	○	○	○	○

18. What information were you given, or would you have liked to have been given **during** your diagnostic journey (i.e. ***before*** you had a diagnosis)? (Check all that apply)

	Yes, I was given this information	No, but I wish I was given this information	No, but I didn't want this information
Information about why mitochondrial diseases are difficult to diagnose and how conditions are being ruled out	○	○	○
Where I could look for health information	○	○	○
How I should be tracking my symptoms	○	○	○
Information about the condition and what it causes	○	○	○
How the diagnosis will affect my daily life	○	○	○
What to expect in the future (e.g. treatment options, amount of medical care needed, how severe the condition is)	○	○	○
Chances that family members and future children will have the same condition	○	○	○
Support organizations for the condition	○	○	○
Available support/advocacy groups	○	○	○
Referral to counselling or other psychological supports	○	○	○
Other, please specify: _____ _____	○	○	○

19. Which of the following were sources of support for you throughout your diagnostic journey? Please rate each of the options below from 1 to 5.

    1 = Provided the least support and 5 = Provided the most support.

    If you did not receive support from any of the options listed below, please leave that option blank.

    a. Family or friends ……..…….1……2……3……4……5
    b. Healthcare providers ……1……2……3……4……5
    c. Other individuals and families ……..……..……1……2……3……4……5 with mitochondrial disease
    d. Internet resources (e.g. Facebook groups) ……1……2……3……4……5
    e. Support/advocacy groups …..……1……2……3……4……5
    f. Other, ……..……1……2……3……4……5 please specify: _____

Getting a Diagnosis: Genetic Testing

20. Who offered and explained the genetic testing that gave you a diagnosis of mitochondrial disease?

    a. Geneticist/Metabolic Disease doctor
    b. Neurologist
    c. Genetic Counsellor
    d. No one explained genetic testing to me
    e. Other, please specify: _____

21. Were you familiar with the idea of genetic testing before your genetic testing?

    a. Yes
    b. No

22. When your genetic test was ordered, what did you know about this? (Circle all that apply)

    a. Why genetic testing was being done
    b. How genetic testing was being done (e.g. blood test or using a sample the lab already had)
    c. The benefits and risks involved
    d. What the results of genetic testing could mean

23. Who shared the results of your genetic testing with you?

    a. Geneticist/Metabolic Disease doctor
    b. Neurologist
    c. Genetic Counsellor
    d. Other, please specify: _____

Getting a Diagnosis: Family

24. As far as you know, are you the first person in your biological family to be diagnosed with mitochondrial disease?

    a. Yes
    b. No

25. If you answered "No" in question 24: Who else in your family has a mitochondrial disease? (Circle all that apply)

    a. Immediate family member (i.e. brother/sister, parent, another child)
    b. Close family member (i.e. cousin, niece/nephew, aunt/uncle, grandparent)
    c. Distant family member

Getting a Diagnosis: Educational Needs and Sources of Support

26. What information were you given or would you have liked to have been given **at the time of your diagnosis**? (Check all that apply)

	Yes, I was given this information	No, but I wish I was given this information	No, but I didn't want this information
Information about the condition and what it causes	○	○	○
How the diagnosis will affect my daily life	○	○	○
What to expect in the future (e.g. treatment options, amount of medical care needed, how severe this condition is)	○	○	○
Chances that family members and future children will have the same condition	○	○	○
Support organizations related to the condition	○	○	○
Available support/advocacy groups	○	○	○
Referral to counselling or other psychological supports	○	○	○
Other, please specify: _____ _____	○	○	○

27. Where did you receive information about your mitochondrial disease? Please rate each of the options below from 1 to 5.

    1 = provided the least information and 5 = provided the most information.

    If you did not receive information from any of the options listed below, please leave that option blank.

    a. Family Doctor/Nurse Practitioner ……...1……2……3……4……5
    b. Geneticist/Metabolic Disease doctor……...1……2……3……4……5
    c. Neurologist……...1……2……3……4……5
    d. Genetic Counsellor……...1……2……3……4……5
    e. Internet (e.g. Google)...……...1……2……3……4……5
    f. Support groups……...1……2……3……4……5
    g. Other patients and families ……...1……2……3……4……5
    h. Family or friends……...1……2……3……4……5
    i. Other,……...1……2……3……4……5
       please specify: _____

Getting a Diagnosis: Reflecting on the Journey

28. About how many <u>different</u> doctors did you have appointments with during your diagnostic journey? Please include the doctor you saw when you first started having symptoms up until the doctor that gave you a diagnosis.

    (e.g. if you met with your family doctor who referred you to a neurologist and a geneticist/metabolic doctor = 3 doctors <u>OR</u> if you went to the hospital for symptoms and saw an emergency room doctor, 2 different neurologists, and a geneticist/metabolic doctor = 4 doctors)

    _____

29. How much time passed from the time when you first talked about your symptoms with a doctor and the time that you were given a genetic diagnosis of mitochondrial disease?

    a. 0-6 months
    b. 7-12 months
    c. 1-2 years
    d. 3-4 years
    e. 5-10 years
    f. 11+ years

30. In what ways did receiving the diagnosis of mitochondrial disease change the way you were managing your health issues/symptoms (if at all)?

    _____

    _____

Treatment

31. Do you take a "mitochondrial cocktail" for treatment of your mitochondrial disease (can include combinations of Coenzyme Q10 (CoQ10), Alpha-Lipoic Acid (ALA), L-Arginine, L-Carnitine, B-Vitamins, Vitamin C, Vitamin E, Creatine)?

    a. Yes
    b. No
    c. I don't know

32. If you selected "Yes" in question 31: Did you start this treatment before or after receiving a diagnosis of mitochondrial disease?

    a. Before
    b. After

Communities of Support

33. Which of the following groups or communities are you aware of and/or currently involved with? (Check all that apply)

	I have only heard of these groups	I receive information or am involved with these groups	No, but I wish I was given information on these groups	Not interested
Support/advocacy group (e.g. local rare disease support group, MitoAction weekly support calls)	○	○	○	○
Facebook group (e.g. MitoCanada Peer2Peer Facebook group)	○	○	○	○
Online message board (e.g. RareConnect message board, RareShare)	○	○	○	○

Support organization (e.g. MitoCanada, United Mitochondrial Disease Foundation)	○	○	○	○
Other, please specify: _____	○	○	○	○

34. If you selected any of the communities in question 33: How did you first come to know about these communities? (Circle all that apply)

    a. Healthcare provider(s), please specify who told you about these: _____
    b. Internet
    c. Other patients and families
    d. Family or friends
    e. Other, please specify: _____

35. If you selected any of the communities in question 33: Do you feel participation in this community has been beneficial to you and/or your family?

    a. Yes, please explain: _____
    b. No, please explain: _____

Demographic and Background Information

36. How old are you?

    a. 13-17 years old
    b. 18-29 years old
    c. 30-39 years old
    d. 40-49 years old
    e. 50-59 years old
    f. 60+ years old
    g. Prefer not to answer

37. What is your gender identity?

    a. Transgender
    b. Two-Spirit
    c. Woman
    d. Man

e. Non-binary
f. Another gender identity, please specify: _____
g. Prefer not to answer

38. What education do you have? (Circle all that apply)

a. Some high school, please specify grade: _____
b. Graduated high school or equivalent
c. Some college/university, no degree
d. Graduated college/university, trade/technical school
e. Graduated Bachelor's degree (e.g. BA, BSc, etc.)
f. Graduated Post-graduate degree (e.g. Master's or Doctoral degree)
g. Other Ways of Knowing
h. Prefer not to answer

39. What is your ethnic identity? (Circle all that apply). For more detail on each option, visit the Statistics Canada website.

a. Indigenous (Inuit, Métis, Status First Nations, Non-status First Nations)
b. European origins
c. Caribbean origins
d. Latin, Central and South American origins
e. African origins
f. Asian origins
g. Oceania (Pacific Islands) origins
h. Prefer not to answer

40. How far do you live from Winnipeg (where mitochondrial experts are)?

_____ KM or HOURS (circle one)

Follow-up Interview

As part of this study, we would like to ask you to join us for a 30-60 minute interview to explore your experience in greater depth. Participants who complete a survey and interview will be offered a $20 Tim Hortons gift card as a thank you.

Are you willing to participate in a 30-60 minute interview on your mitochondrial disease diagnostic journey?

a. Yes, the student investigator may contact me for an interview. Please specify your:

First name: _____Phone number: _____

Best time to contact you: _____

b. Yes, I will contact the student investigator by phone or email

Student Investigator: Maria Vas
Phone number: xxx-xxx-xxxx
Email: xxx@xx.ca

What is **your** first name? _____

Why are we asking for your name? So that we can link your survey responses to your interview and know which survey is yours. We are doing this so we can ask you more about some of your survey answers during your interview if you choose to have one. Your name and any contact information will be kept confidential.

c. No, I do not wish to be contacted for an interview

To thank you for completing this survey, we would like to offer you a $5 Tim Hortons gift card. If you would like to receive this gift card, please provide an email address to send this gift card to: _____

THANK YOU for doing this survey and for considering a follow-up interview.
Please mail this survey back to us in the provided envelope with postage.

A.3 Interview Guide

SEMI-STRUCTURED INTERVIEW GUIDE

Thank you again for participating in this interview. I will be asking you a variety of questions about your (your child's) diagnostic journey. Just as a reminder, the research is focused on your experiences *at the time of* the diagnostic journey, and not the present moment. I will be asking you to reflect back on that journey and what it was like for you then. Like with the survey, "the diagnostic journey" refers to your experience from when you first noticed signs or symptoms (for your child) until you (your child) received a diagnosis of mitochondrial disease. "Getting a diagnosis" refers to when you (your child) received the genetic test result that confirmed your (child's) diagnosis of mitochondrial disease. Please feel free to let me know if you would prefer to not answer a question, or if you would like to take a break at any time.

INTRODUCTION QUESTIONS [Optional].

1. You let me know you (your child) has a diagnosis of _____. How long have you (your child) had this diagnosis?
2. How long have you (has your child) been experiencing symptoms for? *(Probes: How are those symptoms today?)*
3. Does anyone else in the family have the same or similar diagnosis? *(Probes: Who is that? When were they diagnosed? How are they doing?)*

OPENING QUESTION. [Can move through next questions based on what is shared].

1. Tell me about your experience getting your diagnosis? (*I don't have personal experience with mitochondrial disease or this diagnostic journey. I'm very interested in hearing about your experience and what this was like for you.)*

BEFORE GETTING THE DIAGNOSIS. *I'd like to hear a bit about your experience* ***before*** *getting a diagnosis of mitochondrial disease.*

1. Tell me about how you came to the decision that a sign or symptoms was serious and required medical attention (for your child)? *(Probes: What was that decision like? How did you feel at that point?)*
2. Can you please tell me about some of the discussions you had with healthcare providers about the symptoms you were experiencing? *(Prompt: How were your concerns received or addressed?)*
    a. How were decisions made to proceed with [genetic] testing?
    b. How involved did you feel in these decisions/discussions?
3. What did you feel you needed most when seeking a diagnosis? *(Probe: Information, resources, supports)*

A MISDIAGNOSIS. [If previously misdiagnosed, will indicate in survey].

1. Could you tell me about your experience receiving a misdiagnosis of _____?
    a. Tell me about your thoughts and feelings when you were first told about this diagnosis? *(Probes: Did you have any doubts about the diagnosis when you were first told? Tell me more about why that was?)*

   b. When you found out the diagnosis was not accurate, how were you impacted by this information? *(Probe: What was it like between getting a misdiagnosis and your (child's) mito diagnosis?)*
   c. How did you cope during this time? *(Probe: what was it like adjusting to the mito dx)*
2. Looking back, what could have helped, or did help, you during this time? *(Probe: Information, resources, supports)*

THE MITO DIAGNOSIS

1. What was your experience like getting a diagnosis of mitochondrial disease? *(Probes: Can you walk me through that? Who did you speak to? What were you told about the condition and next-steps? What was recommended? What supports or resources were you offered?)*
   a. What was going through your mind (or how did you feel) when you got your diagnosis? *(Probe: How did you cope during this time?)*
   b. How did receiving the diagnosis impact you and your (child's) life? *(Prompt: How did this affect your day-to-day activities? Emotionally? Mentally?)*

LOOKING BACK ON THE EXPERIENCE

1. Could you tell me more about your relationship with your (child's) healthcare providers throughout your (child's) diagnostic journey for mitochondrial disease?
2. "Is there anything about your [(child's)] care during the diagnostic process that you wish had happened differently?"
3. "Was there anyone or anything that was helpful to you during the process of getting a diagnosis?" *(Probe: How were they/was it helpful?)*
4. "Is there anything else you think I should know to understand what it's like for [individuals (or parents/caregivers of children)] who are seeking a diagnosis of [mitochondrial disease]?"

Possible probes and prompts: *You mentioned _____, tell me more about that. Can you tell me more about that? What happened then? Can you describe what that felt like? Can you explain that a little bit more? Summarize what has been said as if asking a question. "How" statements.*

Thank you so much for participation in this interview. As a thank you we would like to send you a $20 Tim Hortons gift card. Is it alright to send this to you through email?

Would you be interested in receiving a summary of the findings or any infographics or videos that are developed as a result of this research study? Email: _____

If you have any other questions about this study or how the information you shared will being used, please don't hesitate to contact me by phone or email, my contact information is on the consent form. Thank you once again. Take care.

Reference: Merker, V. L., Plotkin, S. R., Charns, M. P., Meterko, M., Jordan, J. T., & Elwy, A. R. (2020). Effective provider-patient communication of a rare disease diagnosis: A qualitative study of people diagnosed with schwannomatosis. *Patient Education and Counseling*. https://doi.org/10.1016/j.pec.2020.09.029.

A.4 Interview Consent Forms

INTERVIEW CONSENT FORM FOR PARTICIPANT
Individual Interview

Study Title: *Exploring the diagnostic journey of individuals and families with mitochondrial disease*

Student Investigator: Maria Vas, BSc **Supervisor:** Jessica Hartley, MS, CGC

You are being asked to participate in a research study involving an individual interview. Please take your time to review this consent form and discuss any questions you may have with the study staff before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

The Student Investigator for this study is Maria Vas, a Masters 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 Project Supervisor for this study is Jessica Hartley, a board-certified genetic counsellor and the Program Director of the Genetic Counselling Program at the University of Manitoba.

PURPOSE OF STUDY
This research study's goal is to raise voices of people with mitochondrial disease, and better understand the experiences and needs in the journey to get a diagnosis. We hope the study results will help healthcare providers better support patients in the future.

PARTICIPANT SELECTION
You are being invited to participate because you or your child had an appointment with the Program of Genetics & Metabolism and/or the Pediatric Mitochondrial Disease Clinic within the last 5 years about your or your child's diagnosis of mitochondrial disease. You can participate in this interview if you speak English AND if you have OR you are the parent/caregiver of a child who has:

- ✓ A diagnosis of mitochondrial disease AND
- ✓ Genetic confirmation for your or your child's diagnosis AND
- ✓ Symptoms of mitochondrial disease that started at or before age 45

STUDY PROCEDURES
- The student investigator will ask you screening questions to determine if you qualify for this study. We are hoping a total of 10-15 participants will complete an interview.
- The interview will be conducted over the phone, video conference, or in-person by the student investigator, Maria Vas. The interview will be 30-60 minutes in length.
- You will be asked questions about your experience throughout the mitochondrial disease diagnostic journey, and what your perceived needs were during this time.
- These questions will help us better understand the needs of individuals and families with mitochondrial disease to improve support for those navigating this diagnostic journey.
- Interviews will be audio recorded and the audio recordings will be transcribed by the student investigator or by a confidential transcription service to ensure accurate reporting of the information that you provide. The student investigator may also take notes during your interview.
- The transcription service will sign a form stating that they will not discuss any item on the tape 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 experiences with diagnosis of mitochondrial disease might be upsetting, emotional, or distressing for you. You do not have to answer any question that makes you feel uncomfortable or that are upsetting. If you need any additional help or support, you may contact Klinic 24-hour Crisis Line (x-xxx-xxx-xxxx) or we will help you find other counselling help.

BENEFITS
There will be no direct benefit to you or your child for participation in this study, but the information gained may help other people or family members navigating the diagnostic journey for mitochondrial disease in the future.

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

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

PAYMENT FOR PARTICIPATION
You will receive a $20 Tim Hortons gift card as a gesture of appreciation for your participation. You will receive this gift card after completion of the interview. It will be mailed or emailed to you.

CONFIDENTIALITY
If you previously completed a survey, this will be linked to your interview by a confidential participant ID. This will allow us to review your survey ahead of the interview and possibly ask more about your survey answers during the interview. We will do everything possible to keep your personal information confidential. Your name or your child's name will not be used at all in the study records. A list of names and addresses of participants will be kept in a secure file in case we need to contact you with regards to the study. If the results of this study are presented in a meeting, or published, nobody will be able to tell that you were in the study. Please note that although you will not be identified as the speaker, your words may be used to highlight a specific point. To keep you anonymous, we will remove information from quotes like names, places, pronouns and specific diagnoses from all study reports. The 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 surveys, will be labelled with a confidential coded ID number, which will be assigned to you upon enrollment 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 study staff will have access to the study records. All paper records will be kept in a locked office and filing cabinet located in the Department of Biochemistry and Medical Genetics. Paper materials will be destroyed, and electronic materials will be permanently deleted from the University of Manitoba hard drive, 7 years following the completion of the study in Fall 2022.

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. If you withdraw from the study, all data you provided will be destroyed. Your decision not to participate or to withdraw from the study will not affect your or your child's current and future healthcare.

QUESTIONS

If you have any questions or concerns about the study, you may contact the student investigator, Maria Vas, at xxx-xxx-xxxx or xxx@xx.ca. You may also contact the student supervisor, Jessica Hartley, at xxx-xxx-xxxx or xxx@xx.ca.

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at xxx-xxx-xxxx.

CONSENT SIGNATURES

1. I have read all pages of the consent form.
2. I have had a chance to ask questions and have received satisfactory answers to all of my questions.
3. I understand that by giving my consent I have not waived any of my legal rights as a participant in this study.
4. I understand that my records, which may include identifying information, may be reviewed by the research staff working with the Principal Investigator and the agencies and organizations listed in the Confidentiality section of this document.
5. I understand that I may withdraw from the study at any time and my data may be withdrawn prior to publication.
6. I understand I will be provided with a copy of the consent form for my records.
7. I am providing verbal consent to the researcher to sign on my behalf.
8. I agree to participate in the study.

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

Participant phone number: _____

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:_____

INTERVIEW CONSENT FORM FOR PARENT/GUARDIAN OF COGNITIVELY MATURE CHILD PARTICIPANT

Study Title: *Exploring the diagnostic journey of individuals and families with mitochondrial disease*

Student Investigator: Maria Vas, BSc **Supervisor:** Jessica Hartley, MS, CGC

You are reviewing this form because your child is considered a cognitively mature child (CMC) and is being asked to participate in a research study involving an individual interview. Please take your time to review this consent form and discuss any questions you may have with the study staff before you make your decision. This consent form may contain words that you do not understand. Please ask the study staff to explain any words or information that you do not clearly understand.

The Student Investigator for this study is Maria Vas, a Masters 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 Project Supervisor for this study is Jessica Hartley, a board-certified genetic counsellor and the Program Director of the Genetic Counselling Program at the University of Manitoba.

PURPOSE OF STUDY

This research study's goal is to raise voices of people with mitochondrial disease, and better understand the experiences and needs in the journey to get a diagnosis. We hope the study results will help healthcare providers better support patients in the future.

PARTICIPANT SELECTION

Your child is being invited to participate because they had an appointment with the Pediatric Mitochondrial Disease Clinic and/or the Program of Genetics & Metabolism within the last 5 years about their diagnosis of mitochondrial disease. Your child can participate in this interview if they speak English AND if they have:

- ✓ A diagnosis of mitochondrial disease AND
- ✓ Genetic confirmation for their diagnosis AND
- ✓ Symptoms of mitochondrial disease

As a parent/guardian of a child with mitochondrial disease, you are also eligible to participate and can choose to complete your own independent interview regardless of whether your child completes an interview and whether you join your child in their interview.

STUDY PROCEDURES

- CMCs aged 13 and older will be provided with, and will sign, either an informed consent form or an age-appropriate assent form if they would like to participate. CMCs will only be enrolled in this study if you agree to their participation by signing this form.
- The student investigator will ask your child screening questions to determine if they qualify for this study. We are hoping a total of 10-15 participants will complete an interview. You can assist your child in answering any questions.
- The interview will be conducted over the phone or videoconference by the student investigator, Maria Vas. The interview will be 30-60 minutes in length.
- The interview can be completed on their own or with you present if that is the preference.
- Your child will be asked questions about their experience throughout the mitochondrial disease diagnostic journey, and what their perceived needs were during this time.

- These questions will help us better understand the needs of individuals and families with mitochondrial disease to improve support for those navigating this diagnostic journey.
- Interviews will be audio recorded and the audio recordings will be transcribed by the student investigator or by a confidential transcription service to ensure accurate reporting of the information that you provide. The student investigator may also take notes during your interview.
- The transcription service will sign a form stating that they will not discuss any item on the tape with anyone other than the study staff.
- Individual results and interview transcripts will not be provided to you or your child.

POTENTIAL RISKS
There are few risks to participating in this study. It is possible that talking about experiences with diagnosis of mitochondrial disease might be upsetting, emotional, or distressing for your child. Your child does not have to answer any questions that make them feel uncomfortable or that are upsetting. We will check in throughout the interview with your child to ask if they are still okay to continue or if they would like to take a break or end the interview. If you or your child need any additional help or support, you may contact Klinic 24-hour Crisis Line (x-xxx-xxx-xxxx) or we will help you find other counselling help.

BENEFITS
There will be no direct benefit to you or your child for participation in this study, but the information gained may help other people or family members navigating the diagnostic journey for mitochondrial disease in the future.

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

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

- Your child says something about harming yourself or others
- Your child tells me about the abuse or neglect of themselves or another child
- You or your child report inappropriate or incompetent practice of a healthcare professional

PAYMENT FOR PARTICIPATION
Your child will receive a $20 Tim Hortons gift card as a gesture of appreciation for your participation. They will receive this gift card after completion of the interview. It will be mailed or emailed to either yourself or your child.

CONFIDENTIALITY
If your or your child previously completed a survey, this will be linked to their interview by a confidential participant ID. This will allow us to review the survey ahead of the interview and possibly ask more about the survey answers during the interview. We will do everything possible to keep your child's personal information confidential. Your name or your child's name will not be used at all in the study records. A list of names and addresses of participants will be kept in a secure file in case we need to contact you with regards to the study. If the results of this study are presented in a meeting, or published, nobody will be able to tell that you were in the study. Please note that although your child will not be identified as the speaker, their words may be used to highlight a specific point. To keep them anonymous, we will remove information from quotes like names,

places, pronouns and specific diagnoses from all study reports. The 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 surveys, will be labelled with a confidential coded ID number, which will be assigned to your child upon enrollment 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 study staff will have access to the study records. All paper records will be kept in a locked office and filing cabinet located in the Department of Biochemistry and Medical Genetics. Paper materials will be destroyed, and electronic materials will be permanently deleted from the University of Manitoba hard drive, 7 years following the completion of the study in Fall 2022.

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 child's decision to participate in this study is entirely their own. If you, as the parent/guardian, wants the CMC to participate in the study but the CMC objects, the child's objection will be respected and they will not be enrolled in this study. They may refuse to participate or withdraw from the study at any time. If they withdraw from the study, all data they provided will be destroyed. Their decision not to participate or to withdraw from the study will not affect their current and future healthcare.

QUESTIONS

If you or your child have any questions or concerns about the study, you may contact the student investigator, Maria Vas, at xxx-xxx-xxxx or xxx@xx.ca. You may also contact the student supervisor, Jessica Hartley, at xxx-xxx-xxxx or xxx@xx.ca.

For questions about your rights as a research participant, you may contact The University of Manitoba, Bannatyne Campus Research Ethics Board Office at xxx-xxx-xxxx.

CONSENT SIGNATURES

1. I have read all pages of the consent form.
2. I have had a chance to ask questions and have received satisfactory answers to all of my questions.
3. I understand that by giving my consent I have not waived any of my legal rights as a participant in this study.
4. I understand that my child's records, which may include identifying information, may be reviewed by the research staff working with the Principal Investigator and the agencies and organizations listed in the Confidentiality section of this document.
5. I understand that my child may withdraw from the study at any time and their data may be withdrawn prior to publication.
6. I understand I will be provided with a copy of the consent form for my records.
7. I am providing verbal consent to the researcher to sign on my behalf.
8. I agree to my child participating in the study.

Parent/Guardian name: _____ Date _____
(day/month/year)

CMC Participant name: _____

Parent/Guardian phone number: _____

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

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

Signature: _____ Role in the study:_____

ASSENT FORM FOR CHILD PARTICIPANT
Individual Interview

Study Title: *Exploring the diagnostic journey of individuals and families with mitochondrial disease*

Student Investigator: Maria Vas, BSc **Supervisor:** Jessica Hartley, MS, CGC

Why you are here?
Our team wants to tell you about a study about people with mitochondrial conditions. A study is a way to better understand something to see if we can make it better. We want to see if you would like to be in this study. This form tells you about the study. If there is anything you do not understand, please ask your parent, your guardian, or the study staff.

Why are they doing this study?
We want to learn more about what type of support children and adults with mitochondrial conditions need while getting their diagnosis. We hope this study can help children and adults with similar health problems to you get more support from doctors and other medical people.

What will happen to you?
If you want to be in the study these things will happen:

- The interview will last about 30-60 minutes. It only happens one time. It happens after you finish a survey.
- You will be asked to talk over phone or video with a study investigator named Maria.
- Maria will ask you questions about what it was like to get a diagnosis of a mitochondrial condition. You do not need to answer questions you do not want to answer.
- Your interview with Maria will be recorded so the study staff can use it for study results. Only the study team and people working with the study team will hear this recording.

Will the study hurt?
We do not think the study will hurt. But it might make you feel sad or mad to talk about what it was like getting a diagnosis. If this happens, you can decide to stop the interview. If this happens, we can talk to your family, doctors, or other people in your life to help you with those feelings. You will not need any blood tests or other types of tests as part of this study. You will not need to take any medications as part of this study.

Will you get better if you are in the study?
This study won't make you get well or help your mitochondrial condition. But we might find out something that will help other children like you later.

Will you get anything for being in this study?
Yes, you will get a $20 Tim Hortons gift card to say thank you for being in this study. It will be emailed to you or to your parent/guardian to give to you. It will be emailed after the interview.

What if you have questions?
You can ask questions any time, now or later. You can talk to your family, your doctors, or someone else. You can talk to the study investigator Maria Vas too. Maria's phone number is xxx-xxx-xxxx and her email is xxx@xx.ca. You also can ask your parent/guardian to call or email Maria if you can't.

Who will know what you did in the study?
Any information you give to the study staff will be kept private. Your name will not be on any study paper and no one but the study staff and your parents/guardians will know that it was you who was in the study.

Do you have to be in the study?
You do not have to be in the study. No one will be mad at you if you don't want to do this. If you don't want to be in this study, just say so. We will also ask your parents/guardians if they would like you to be in the study. Even if your parents/guardians want you to be in the study you can still say no. The doctor will still take care of your mitochondrial condition. Even if you say yes now you can change your mind later. It's up to you.

ASSENT

I want to take part in this study. I know I can change my mind at any time.

_____ **Verbal assent given:** **Yes □**
Child Name

I confirm that I have explained the study to the participant to the extent compatible with the participants understanding, and that the participant has agreed to be in the study.

_____	**_____**	**_____**
Printed name and role of Person obtaining verbal assent	**Signature of Person obtaining verbal assent**	**Date**