Health Care Providers’ Perspectives of Uncertainty in Newborn Screening

by

Paul John Azzopardi

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ABSTRACT

There is a paucity of research exploring the issues of uncertainty in the context of newborn screening and metabolic care. This work explores these issues of uncertainty through qualitative description. Semi-structured telephone interviews were conducted with health care providers at specialized metabolic centers across Canada. Data was coded and thematically analyzed. This study found that health care providers experience personal, practical, diagnostic, prognostic, and therapeutic issues of uncertainty when managing the care of patients affected by mild hyperphenylalaninemia (MHP), very long chain acyl CoA dehydrogenase (VLCAD) deficiency, medium chain acyl CoA dehydrogenase (MCAD) deficiency, and partial biotinidase deficiency. Health care providers described nosological inadequacy as a source of uncertainty when managing 3-methylcrotonyl CoA (3-MCC) deficiency. Participants emphasized caution, while avoiding overmedicalization, when managing medical uncertainty. Providers indicated that greater communication and consensus is required across care centers, which may open a dialogue for a pan-Canadian newborn screening strategy.
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# Table of Contents

Acknowledgements ............................................................................................................... iii

Table of Contents ................................................................................................................ iv

Introduction .......................................................................................................................... 1

Background ............................................................................................................................ 2

Newborn Screening: An Evolving Paradigm .............................................................. 2

Rationale for the Screening of Inherited Metabolic Disorders .............................. 4

Hyperphenylalaninemia ............................................................................................... 5

Biotinidase deficiency .................................................................................................... 7

Fatty acid oxidation disorders .................................................................................... 8

3-Methylcrotonyl CoA carboxylase deficiency ...................................................... 10

Theoretical Background ............................................................................................... 11

Orienting Newborn Screening Research ............................................................... 11

Researchers’ Conceptualizations of Uncertainty .................................................. 12

Health Care Provider Conceptualizations of Uncertainty ...................................... 14

Analytic Forestructuring ............................................................................................... 16

Study Design and Methodology ............................................................................... 19

Study Question ............................................................................................................... 19

Qualitative Description ............................................................................................... 20

Sampling Considerations ......................................................................................... 21

Data Collection ............................................................................................................. 23

Data Analysis ............................................................................................................... 25

Findings ............................................................................................................................. 27

Contextualizing Uncertainty in Newborn Screening and Metabolic Follow-Up Care .................................................. 28

Mild hyperphenylalaninemia (MHP) ....................................................................... 31

Partial biotinidase deficiency ..................................................................................... 34

Fatty acid oxidation disorders: MCAD deficiency and VLCAD deficiency .......... 35

3-MCC deficiency ......................................................................................................... 37

Health Care Providers Are Cautious .......................................................................... 39

There is a Need for Consensus and Clear Communication in the Context of Uncertainty .......................................................................................................................... 41

Discussion ....................................................................................................................... 44
Introduction

This study seeks to develop a deeper understanding of physicians’ experiences with medical uncertainty related to variant and non-classic inherited metabolic disorders (IMDs) identified by newborn screening. For the purposes of this study, medical uncertainty is defined as a perceived lack of health-related knowledge (Han, Klein, & Arora, 2011). Medical uncertainty occurs in the absence of clear practice guidelines, professional consensus, evidence, or provider awareness of management strategies (Greenhalgh, Howick, & Maskrey, 2014). However, it is unclear how health care providers understand and manage care in the context of medical uncertainty pertaining to newborn screening. To navigate uncertainty, health care providers may withhold information to protect patients (Gerrity, Earp, Devellis, & Light, 1992), order more diagnostic tests (Alam et al., 2017), or simply wait and monitor patients for fluctuating signs and symptoms (Almond & Summerton, 2009). Providers’ strategies for communicating and reacting to uncertainty may influence whether confusion and anxiety is experienced by patients (Seaburn et al., 2005). However, uncertainty may also foster resiliency in patients and provide an opportunity to hope for optimistic outcomes (Newson, Leonard, Hall, & Gaff, 2016). Although medical uncertainty is not conceptualized as an inherently problematic facet of health care, it is not well understood how providers navigate uncertainty when managing patient care (Newson et al., 2016). The United States Centers for Disease Control and Prevention (CDC, 2011) consider newborn screening to be one of the ten great achievements in public health over the last decade. There is a need to better understand how providers navigate medical ambiguity, complexity, and unpredictability in the context of universal newborn screening.
Background

Newborn Screening: An Evolving Paradigm

The purpose of newborn screening is to prevent severe, uncommon, well-defined, and actionable outcomes through the early identification, diagnosis, and management of disease (Newborn Screening Ontario, n.d.). In the early history of newborn screening, disorders were added to panels with the introduction of expanded technical capability, often despite a lack of empirical evidence of screening benefit (Guthrie & Susi, 1963; Pourfarzam & Zadhoush, 2013). Several years later, the selection of conditions for screening was predominantly guided by the classical screening criteria proposed by Wilson and Jungner (1968, appendix A). These oft-cited criteria suggest that screened diseases should be significant, but treatable, diseases with suitable and acceptable screening tests and early symptomatic or latent stages of disease. In addition, the Wilson and Jungner (1968) principles suggest that the natural history of the target disorder should be understood, symptoms should be similar across cases, and there should be an agreed-upon policy to treat patients while balancing health care expenditures. However, technological change in newborn bloodspot screening, such as widespread use of tandem mass spectrometry (TMS), has allowed for earlier detection, treatment, and prognostication of a larger number of diseases with greater sensitivity (Millington, Kodo, Norwood, & Roe, 1990). As a result, many screening advisory committees are increasingly considering newborn screening as a tool to enhance reproductive decision-making for parents, avoid long diagnostic odysseys, and identify patients for therapy trials in early, asymptomatic stages of disease (Grob, 2008; K. Wilson, Kennedy, Potter, Garaghty, & Chakraborty, 2010). Additionally, clinical genome sequencing contributes to a complex and expanding body of knowledge that is relied upon by
health care providers. With an abundant array of technologies in the context of newborn screening, many programs are growing to include more conditions on their panel over time (Jansen, Metternick-Jones, & Lister, 2017). These advances, combined with an evolution in thinking about the goals of newborn screening, have hastened a paradigm shift from the classical principles of newborn screening to screening with broader purpose for a wider range of disorders.

In the wake of this paradigm shift, Jansen et al. (2017) discuss considerations for evolving newborn screening policies. Although Jansen et al. (2017) argue for a process of consensus-based selection of target disorders through evaluation of the best available evidence, many jurisdictions continue to rely on a more ad hoc approach. Pollitt (2006, p. 390) states, “Though all discussion is nominally founded on the ten principles laid down by Wilson and Jungner in 1968, there seems no generally accepted way of using these principles, or derived criteria, as objective decision tools”. There are many working and advisory committees that successfully apply best evidence to screening. However, there are also many snags when translating evidence into practice. For example, public pressure to include disorders on newborn screening panels is one challenge faced by independent working committees (Jansen et al., 2017). In the United States, the Secretary’s Advisory Committee on Heritable Disorders in Newborns and Children relies on evidence-based screening criteria and endorses a Recommended Uniform Screening Panel (RUSP) of 31 core disorders to be screened in infancy across all states (Kemper et al., 2014). Newborn Screening Ontario (n.d.) has adopted a similar approach by implementing an advisory council that evaluates disorders based on a process of evidence-based review. However, the absence of a pan-Canadian harmonized newborn
screening panel or associated national policy has led to interprovincial discrepancies. For example, Ontario offers universal blood spot screening for 28 core conditions, but infants born in Quebec are only offered 4 (Canadian Organization for Rare Disorders, 2015). The Health Council of Canada (2014) reports that screening variation between jurisdictions does not reflect informed consideration of local differences, but rather, unclear evidence and guidelines. This variation is catalogued in *appendices B* and *C*. This lack of harmonization across provincial screening programs may result in inequitable access to care, inconsistent management strategies, and substandard quality of care.

**Rationale for the Screening of Inherited Metabolic Disorders**

Inherited metabolic disorders (IMDs) are a heterogeneous group of monogenic conditions that result from a mutation in a gene that codes for an intermediary enzyme, cofactor, or transporter in a metabolic pathway. This typically results in dysfunctional metabolism or the accumulation of toxic intermediate metabolites (Pourfarzam & Zadhoush, 2013). Although individual diseases are relatively rare, the collective incidence of IMD has been estimated to be as high as 1 in 800 live births (Sanderson, Green, Preece, & Burton, 2006). In Canada, one estimate places the incidence of IMD at 1 in 2500 (Applegarth, Toone, & Lowry, 2000). Many IMDs can be treated through dietary alterations, oral supplementation of lacking metabolites, or elimination of toxic intermediaries (Mak, Lee, Chan, & Lam, 2013). However, missed or delayed diagnosis may result in neuropsychological dysfunction, moderate-to-severe intellectual disability, or mortality (Pourfarzam & Zadhoush, 2013). This study seeks to examine
management strategies for a sub-group of IMD associated with medical uncertainty; these disorders are described in greater detail in later sections (for a summary table, see appendix D).

It is also important to consider this uncertainty in the context of the complexities of a screening program. Screening results are often interpreted by comparing metabolite concentrations to established cut-off values (Mak et al., 2013). Metabolite concentrations exist on a continuum and can fluctuate; therefore, the distribution of a healthy population and diseased population can overlap. When establishing a cut-off value, there is a tradeoff between sensitivity and specificity: lowering the threshold increases the sensitivity of the test, but also decreases its specificity. In other words, lowering the established cutoff generates a greater number of true positive results, but also increases the return of false positive results. Screening and subsequent results from diagnostic tests do not always establish clear and absolute diagnoses. Rather, results need to be interpreted by providers in the context of other clinical cues. In addition, McHugh et al. (2011) write that some newborn screening programs have not yet identified true positive cases for 30-80% of the disorders that they are screening for. This increases uncertainty due to a lack of familiarity or experience with managing cases. For several IMDs, there is insufficient evidence or a lack of consensus to manage patient care (McHugh et al., 2011, appendix D).

**Hyperphenylalaninemia.**

Patients with plasma phenylalanine (Phe) concentrations above the normal threshold are labeled with hyperphenylalaninemia. The average Phe concentration in healthy individuals is approximately $58 \pm 14$ (SD) μmol/L (Blau, van Spronsen, & Levy, 2010; Scriver, 1989). At the
time of writing, patients were diagnosed with phenylketonuria (PKU) if their Phe concentration was greater than 600 μmol/L (van Wegberg et al., 2017). PKU is a rare IMD caused by deficiencies in phenylalanine hydroxylase, an enzyme that acts with a cofactor, called tetrahydrobiopterin (BH₄), to convert phenylalanine into tyrosine (van Wegberg et al., 2017). High Phe concentrations can lead to permanent intellectual disability, autistic features, seizures, developmental delay, and abnormal behaviour (van Wegberg et al., 2017). A variant screening result for hyperphenylalaninemia may persist if patients have a partial deficiency of phenylalanine hydroxylase, resulting in Phe concentrations between 360 and 600 μmol/L (van Spronsen, 2011). This condition is labeled ‘mild hyperphenylalaninemia’ (MHP). Historically, the Phe cut-off value that has been determined to be ‘safe’ has varied over time (Holtzman et al., 1986; Scriver, 1989; van Spronsen & Burgard, 2008).

Available guidelines for the management of hyperphenylalaninemia were recently proposed in Europe (van Spronsen et al., 2017). Even still, there is no unilateral consensus for managing patients with MHP. Van Wegberg et al. (2017) write that some patients may benefit from adjuvant sapropterin dihydrochloride supplementation, also known by the brand name, ‘Kuvan’ (or a prescription for biopterin, BH₄). Although van Wegberg et al. (2017) find that the evidence supporting treatment is suboptimal and the evidence supporting monitoring alone is of higher quality, the authors remark that they can make no definitive conclusions. Van Wegberg et al. (2017) propose an approach that advises providers to treat patients with MHP. Although these authors suggest that treatment errs on the side of caution, dietary restriction is not without risk and may result in some children developing unhealthy eating habits as they avoid protein-rich foods, such as dairy products, nuts, red meat, beans, poultry, and fish.
Dietary restrictions might result in stunted growth, vitamin B₁₂ and long-chain unsaturated fatty acid deficiency, or decreased bone density (van Spronsen, 2011). Moreover, overtreatment of phenylalanine-free diets may induce protein insufficiency causing erythematous and eczematous lesions, diarrhea, pitting edema, failure to thrive, and stunted hair growth (Pode-Shakked et al., 2013). For health care providers, this may present a grey zone of uncertainty when managing patients with MHP (Camp et al., 2014).

**Biotinidase deficiency.**

Biotinidase is an enzyme that binds with carboxylases to produce active biotin, or vitamin B₇, from macromolecules (Wolf, 2012). For this reason, biotinidase deficiency tends result in a lack of serum biotin and the accumulation of dicarboxylic acid in the urine. Mutation in the human biotinidase gene (*BTD*) on chromosome 3q25 may result in a wide range of clinical symptoms if left untreated (Wolf, 2012). For instance, profound biotinidase deficiency may result in hypotonia, seizures, respiratory problems, and cutaneous issues—such as eczematic rash (Wolf, 2012). This disorder can also result in irreversible neurological impairment, sensorineural hearing loss, and optic atrophy (Wolf, 2012). Lifelong oral biotin supplementation effectively treats this disorder (Jay et al., 2015). Unaffected individuals typically exhibit biotinidase activity of about 7.57 ± 1.41 (SD) μmol/min/L (Gannavarapu et al., 2015). However, it is unclear whether treatment is indicated for partial biotinidase deficiency, where screen results identify infants with 10-30% of mean normal serum enzyme activity. Wolf (2015) writes that some patients with partial biotinidase deficiency may develop symptoms. This has been observed in Ontario and Michigan (Gannavarapu et al., 2015; Jay et al., 2015). Therefore, Wolf
(2015) recommends biotin therapy as a preventative measure for such patients to err on the side of caution. Although biotin supplementation may prevent neurocognitive decline, alerting families to a positive screen result can also generate anxiety and stress (Wolf, 2015). This has raised some uncertainty about the ethics of managing patients with partial biotinidase deficiency.

**Fatty acid oxidation disorders.**

Medium-chain acyl CoA dehydrogenase (MCAD) catalyzes the first step in the β-oxidation of medium chain fatty acids (Soler-Alfonso, Bennett, & Ficicioglu, 2016). MCAD deficiency is the most common fatty acid oxidation disorder, with a prevalence of about 1 in 8750 (Touw et al., 2012). When screening for MCAD deficiency, programs typically assess octanoylcarnitine (C8) plasma concentration, C8 concentration as a ratio against decanoylcarnitine (C10) concentration, and the presence of disease-causing mutations (including the common c.985A>G point mutation) in the **ACADM** gene (Comeau, Larson, & Eaton, 2004). Patients with MCAD deficiency have impaired fatty acid oxidation producing ketone bodies and are instead dependent on glucose during times of fasting (Soler-Alfonso et al., 2016). The resultant hypoketotic hypoglycaemia may cause acute encephalopathy, coma, and even mortality (Soler-Alfonso et al., 2016). Prior to universal newborn screening, the mortality rate for MCAD was 20-30%, and approximately 21-40% of surviving cases resulted in developmental delay (Andresen et al., 2012; Iafolla, Thompson, & Roe, 1994). There are few signs or symptoms to help physicians predict whether patients will suffer a severe hypoglycemic episode (Soler-Alfonso et al., 2016). MCAD deficiency is typically treated through the avoidance
of fasting, for example, by frequent feeds or ingesting complex carbohydrates prior to sleep.

With newborn screening, the risk of mortality reportedly drops to approximately 4-5%, with the highest risk period being neonatally prior to the availability of newborn screening results (Ahrens-Nicklas, Pyle, & Ficicioglu, 2016; Wilcken et al., 2007). The impact of NBS in the context of MCAD deficiency is favourable, although “long-term outcome assessment after wide use of NBS is sparse” (Soler-Alfonso et al., 2016, p. 4). This may be attributable to the recency of expanded newborn screening in the mid-2000s. In the context of MCAD, fasting precautions generally lead to positive outcomes (Ahrens-Nicklas et al., 2016). Variant MCAD deficiency screening results include residual MCAD enzyme activity (greater than 10%) and/or patients with ACADM genotypes containing variants of unknown significance (Touw et al., 2012). Although it is commonly suggested that patients with variant results should receive treatment, Touw and colleagues (2012) identified subjects with variant ACADM genotypes and MCAD activity between 20 to 63% of normal activity. Such patients have more unpredictable prognoses, which may generate management uncertainty.

Like MCAD deficiency, very long chain acyl CoA dehydrogenase (VLCAD) deficiency is a fatty acid oxidation disorder that inhibits the β-oxidation of fatty acids. VLCAD deficiency is caused by mutations in the ACADVL gene (Diekman, Ferdinandusse, et al., 2015). This inherited metabolic disorder is further subdivided into three clinical phenotypes: an early onset type with severe cardiomyopathy, a later onset type with similar symptoms as MCAD deficiency following hypoketotic hypoglycemia, and an adult onset type causing muscular symptoms (Evans, Andresen, Nation, & Boneh, 2016). VLCAD deficiency is typically screened through C14/C16:1 acylcarnitine concentrations in newborns (Millington et al., 1990). However, Diekman et al.
write that a different screening test (C14:1/C2) is more sensitive, but less specific, generating more false positives. Due to the paucity of clinical cases - about 1 in 31,500 live births - there is insufficient data to generate evidence-based practice guidelines (Arnold et al., 2009). Arnold et al. (2009) developed a Delphi, or consensus-based, protocol for clinical practice, but failed to achieve consensus describing which infants are at risk for early onset, or severe, VLCAD deficiency. Moreover, this Delphi protocol did not reach consensus regarding the necessary degree of long chain triglyceride (LCT) dietary restriction and medium chain triglyceride (MCT) dietary supplementation for VLCAD deficiency. Dietary supplementation of MCT in a mouse model of VLCAD deficiency (VLCAD -/-) resulted in worsened outcomes, such as severe dilated cardiomyopathy (Tucci, 2017). Although there is consensus that infants should avoid fasting, there is very limited evidence for both the identification and treatment of infants with mild VLCAD deficiency (Marsden, 2009). Therefore, providers may experience prognostic uncertainty when attempting to classify the severity of VLCAD deficiency and management uncertainty when treating the disorder.

3-Methylcrotonyl CoA carboxylase deficiency.

3-Methylcrotonyl CoA carboxylase (3-MCC) deficiency is an inborn error of leucine catabolism that may result in symptoms including ketoacidosis, hypoglycemia, Reye syndrome, or intellectual disability (Arnold et al., 2008). 3-MCC deficiency has a prevalence between 1:2,400 and 1:68,300 (Rips et al., 2016). Although many newborn screening programs include 3-MCC deficiency, most patients diagnosed with the disorder appear to be asymptomatic (Jung et al., 2012; Lam et al., 2013). There is no consensus on the proportion of infants diagnosed with
3-MCC deficiency that develop symptoms, but this figure may be as low as 4-5% (Wilcken, 2016). Moreover, some newborn bloodspot screen positive results reflect asymptomatic maternal values of the screened metabolite (Lee & Hong, 2014). Although there is consensus that 3-MCC should be monitored in order to prescribe supplemental oral carnitine if the patient’s levels are low, there is a paucity of evidence with which to determine how to manage screen-positive patients (Arnold et al., 2008). Some physicians prescribe a restricted diet for asymptomatic patients with 3-MCC deficiency despite a lack of evidence and consensus (Arnold et al., 2008; Koeberl et al., 2003). For the above reasons, Ontario no longer screens for 3-MCC as of December 4, 2017 (NSO, 2017). A table is provided in appendix D to describe the evidence and uncertainties associated with these target conditions in greater detail.

Theoretical Background

Orienting Newborn Screening Research

Although over 1 million infants have been screened in Canada over the past 3 years alone, there is currently no pan-Canadian newborn screening strategy to coordinate which disorders should be screened or to recommend management guidelines for health care providers (Health Council of Canada, 2014). This study proposes to describe how health care providers across Canadian jurisdictions manage patient care despite medical uncertainty pertaining to MHP, partial biotinidase deficiency, MCAD deficiency, VLCAD deficiency, and 3-MCC deficiency. This project also seeks to describe the variation in health care providers’ experiences of managing care due to complex or ambiguous evidence. As discussed, newborn screening has experienced a paradigm shift from its classical roots. Wilson & Jungner (1968,
p.3) wrote, “in theory, screening is an admirable method of combating disease ... in practice, there are snags”. Recognizing that uncertainty is one such snag, this work strives to develop clinically relevant descriptions to inform both health care providers and health policy actors.

**Researchers’ Conceptualizations of Uncertainty**

The ambiguity of the word, ‘uncertainty’, has been a focal point for researchers that attempt to study this phenomenon. According to Han et al. (2011, p. 830), uncertainty is defined as “the subjective perception of ignorance”. Thus, those who research uncertainty can have a different understanding of the term than those who experience uncertainty. As this study generates a co-constructed account of the perceived sources and issues of uncertainty, it has been informed by the social constructionist school of thought. The following background information is provided to more explicitly operationalize the construct of uncertainty.

Uncertainty is contextualized by its relationship between known and unknown information and its relationship to probabilities, statistics, and quantified risk (Djulbegovic, Hozo, & Greenland, 2011). Renee Fox (1957) suggests that uncertainty stems from incomplete mastery of existing knowledge, limitation of current knowledge, or a combination of such factors. Likewise, McNeil (2001) purports that uncertainty is due to lack of clear evidence from clinical studies, lack of applicability of evidence at the bedside, and ambiguous data interpretation. Such definitions are Socratic, as they explicitly recognize the limitations of human knowledge. More broadly, the term ‘epistemic uncertainty’, has been used to refer to the grey zone between knowledge and the inadequate knowledge of a phenomenon (Colyvan, 2008; Regan, Colyvan, & Burgman, 2002). From an epistemic lens, uncertainty can also be
described in its relation to probability, statistics, and quantified risk (Djulbegovic et al., 2011). Ross Upshur (2013) discusses the role of probability in clinical medicine, which is categorically distinguished by three distinct interpretations. The mathematical theory of probability derives numerical procedures in entirely abstract terms with little relevance to the ‘real’ world of medicine (Upshur, 2013). Secondly, the frequency interpretation of probability allows for the generation of likelihood estimates if there is a well-defined class of possible events in an infinite or finite reference set (Upshur, 2013). Lastly, likelihood propositions are only as strong as the individual beliefs in the likelihood of an event occurring (Upshur, 2013). Therefore, likelihood statements only reflect reality as if intellectual constructs are accurately based. Upshur (2013) also observed that the language of probability obscures uncertainty through a veneer of scientific objectivity. Under the epistemic lens, uncertainty is a metaphysical idea related to the abstract concept of ‘knowing’. As such, a co-constructed account of uncertainty is a tincture of individual ontological and epistemological beliefs about what it means ‘to know’, whether there is ‘truth’, and whether ‘certainty’ is possible. Djulbegovic et al. (2011, p. 325) write, “most authors believe there is simply no better method of addressing uncertainty in individual cases but through using research evidence”. According to the epistemic lens, all clinical management strategies are informed by evidence; therefore, all medical actors are influenced by uncertainty. Thus, this lens is used to transfer and extrapolate the qualitative findings across multiple health care contexts.
Health Care Provider Conceptualizations of Uncertainty

In line with the methodology of qualitative description, existing literature is explored to analyze what is known about how providers experience the phenomenon of uncertainty. Early research on professional uncertainty in medicine is sociological in nature and focuses on the medical training of clinicians. Talcott Parsons (1951) acknowledged the limits to a physician’s control over and understanding of illness and disease. Later, Renée Fox (1979) found that health care providers strive for intellectual command to master probabilistic circumstances, mask awareness of the presence of uncertainty, or even employ gallows humour to confront the limitations of medical knowledge. Donald Light (1979) wrote that uncertainties of power are addressed by conforming to expectation, uncertainties of knowledge are addressed by specialization and conviction in a school of thought, and uncertainties of diagnosis are addressed by invoking clinical expertise for resolution. Light (1979) also found that some physicians strive to attenuate medical uncertainty in patients by exercising communicative control to restrict knowledge transfer. However, this method of coping with uncertainty at the locus of the health care professional may increase anxiety in patients (Waitzkin, 1985). Bosk (1980) found that medical residents cope with uncertainty by estimating probability, hedging assertions, consulting with other professionals, avoiding decision-making, and learning through the best available evidence. Atkinson (1984) discussed the problem of training medical students ‘for certainty’ with positivist and mechanistic thinking. Training for certainty may not translate well to the inevitable ambiguity and complexity experienced in general practice.

Various health care providers are likely to have a different understanding of medical uncertainty in the context of newborn screening. In this study, ‘understanding’ is defined as a
process of learning, consulting with others, invoking clinical expertise, and information seeking to navigate uncertainty. Providers may strive to better understand biological, psychosocial, and environmental factors or strive to minimize knowledge gaps to better navigate uncertain circumstances. Gerrity et al. (1992) report that more experienced physicians note feeling less stress due to uncertainty than physicians who have not been in practice for long. In addition, less experienced practitioners are more likely to discuss medical error with colleagues rather than patients (Nevalainen, Kuikka, & Pitkälä, 2014). Experienced providers have a greater breadth of circumstances from which to base their medical decision-making. Secondly, male providers have been found to experience less stress due to uncertainty than female providers (Gerrity et al., 1992). However, male providers tend to order more diagnostic tests when experiencing uncertainty (Schneider, Wubken, Linde, & Buhner, 2014). Moreover, specialized practitioners experience less stress due to uncertainty than general practitioners (Gerrity et al., 1992; Light, 1979). This may be because specialized providers have greater education and credible authority to understand and manage uncertainty (Mishel, 1988). Some general practitioners deny or fail to acknowledge the existence of uncertainty (Seaburn et al., 2005). These physicians may be less able to address patient concerns and engage in shared decision-making, while more often making premature diagnoses (Alam et al., 2017). Neuroticism in health care providers is correlated with stress due to uncertainty, reluctance to report uncertainty to patients, and reluctance to share medical errors with colleagues (Schneider et al., 2014). In summary, medical uncertainty may be better understood by perceiving health care providers as social actors that navigate complex, unpredictable, and ambiguous circumstances.
Health care providers must manage uncertainty based on their perceived lack of health-related knowledge. In this study, ‘management’ is operationally defined as decision-making and strategizing patient care in the context of medical uncertainty. This may involve the decision to communicate results to families. Over 75% of physicians report that they would not hesitate to share information on uncertain diagnoses with patients (Gerrity et al., 1992). However, Alam et al. (2017) write that many physicians withhold ambiguous information if they believe their patient will react unfavourably to uncertain news. In practice, it has been reported that uncertainty in decision-making is rarely discussed with patients (Braddock, Edwards, Hasenberg, Laidley, & Levinson, 1999). Secondly, physicians may order more diagnostic tests to reduce, rather than cope with, medical uncertainty (Alam et al., 2017). Building a network of trust with colleagues and applying the diagnostic ‘test of time’ were also seen as approaches to managing medical uncertainty. For instance, Almond and Summerton (2009) argue that diagnostic precision is not invariably necessary at initial assessment. These authors write that monitoring is a valid diagnostic method if the benefits of diagnostic delay outweigh its harms. The avoidance of invasive treatments and a lengthy diagnostic odyssey may outweigh the harms of a delayed diagnosis where there is no indication that rapid treatment is required.

**Analytic Forestructuring**

Brazil and colleagues (2005) advocate for the incorporation of theory in health services research to clarify methodology, provide more informative descriptions, and assist in the analysis of results. In line with the methodological paradigm of qualitative description, additional theorizing was conducted to foster analytic perspective.
Newson et al. (2016) challenge the assumption that uncertainty is necessarily problematic – something to be avoided, reduced, or rejected. Newson et al. (2016) suggests that uncertainty may also provide opportunity for optimism in patients with a severe, but uncertain, diagnosis. For instance, an equivocal diagnosis of cystic fibrosis allows physicians to communicate results to patients by framing them as an opportunity for hopeful outcomes (Tluczek, McKechnie, & Lynam, 2010). Additionally, Newson et al. (2016) suggest that resilient providers understand uncertainty with recognition and acceptance. By encouraging and facilitating the acceptance of information, providers may help patients navigate uncertainties. The indeterminacy of future outcomes may alleviate patients from being constrained by factors outside of their control. This idea suggests that uncertainty is not inherently negative and that it is important to fairly examine the sources, forms, and consequences of uncertainty in health care. For example, Babrow and Kline (2000) discuss the single-minded discourse of uncertainty reduction in breast self-examination and explore the potential harms of this bias on women’s health. Considering the possible benefits of uncertainty, reduction and avoidance of this phenomenon are not always appropriate goals. This position is examined during the reflexive process of data collection and analysis.

Mishel's (1988) uncertainty in illness theory provides a helpful sociological perspective to better describe and analyze how uncertainty subjectively affects individual patients. Mishel (1988) defines uncertainty as the inability to construct meaning, the absence of associated cues, or the inability to categorize events or predict outcomes with accuracy. This theory posits that uncertainty may present as ambiguous illness states, complex treatments and systems of care, lack of diagnostic information, and unpredictable prognoses. Mishel (1988) describes a
‘stimuli frame’ composed of symptom patterns, event familiarity, and event congruence. Symptom patterns occur when patients present consistent signs of illness, event familiarity allows patients to rely on previous experience to assign meaning to illness, and event congruence occurs when cases are similar and meet expectations. This theory specifies the contextual cues that individuals may rely on to navigate uncertain medical circumstances. Most recently, this theory has been applied to patients’ perspectives of equivocal newborn screening results for cystic fibrosis (Tluczek et al., 2010). This theory is sparingly examined, as it was intended for use at the locus of the patient. However, it is useful because the theory explains how uncertainty may be perceived through the observation of external cues. In addition, this theory suggests that health care providers can act as ‘structure providers’ who alleviate uncertainty by framing information for patients. According to Mishel (1988), providers’ success in navigating uncertainty depends on the extent of their education, social support, and credible authority.

Han and colleagues (2011) recently put forward a conceptual taxonomy for categorizing the sources, issues, and loci of medical uncertainty (appendix E). This 3-dimensional taxonomy claims to synthesize the theoretical and empirical literature on uncertainty in health care, as described in preceding sections. Firstly, the source of uncertainty may be unpredictability, ambiguity, or complexity. This translates to the idea that uncertainty is caused by the indeterminacy of future outcomes, a lack of reliable or adequate evidence, and inherent aspects of a phenomenon that make it difficult to understand. This widely mirrors the epistemic lens of uncertainty, which posits that uncertainty is contingent on a perceived lack of knowledge. Secondly, the issue of uncertainty may be scientific, practical, or personal. Thus,
uncertainty may relate to diagnosis, prognosis, causation, and management; relate to the structures and processes of care; or relate to individual psychosocial factors. Our work catalogues these issues of uncertainty by cross-referencing data to this taxonomic framework. 

In their later work on clinical genome sequencing, Han et al. (2017) note that uncertainty acts on specific stakeholders. This reflects the final axis, or the locus of uncertainty, which may be health care providers, patients, lab technicians, hospital administrators, and others. This study focuses on the locus of the health care provider. Following this project, two additional research studies will seek to explore the patient perspective and uncertainty at the locus of the newborn screening program representative. Han et al. (2017) developed and applied this framework within the context of clinical genome sequencing, however, many of the intricacies of genetic sequencing may not align with categories of uncertainty in the context of newborn screening and metabolic care. Thus, this project aimed to explore the salience of the 3-dimensional taxonomy in a novel context. In addition, this project tested the claim that Han et al.’s (2011) taxonomy consolidates and synthesizes descriptions of uncertainty in the literature.

**Study Design and Methodology**

**Study Question**

According to the United States Centers for Disease Control (CDC, 2011), newborn screening is one of ten great achievements in public health over the last decade. The vast majority of parents support expanded newborn screening, which is seen as a means to prevent future morbidity with minimal risk (Hayeems et al., 2015). However, Wilson and Jungner (1968) mused, “in theory, screening is an admirable method of combating disease ... in practice, there
are snags”. For example, newborn screening may result in invasive and resource-exhaustive follow-up procedures, strict dietary changes, false positive results, and overdiagnosis of untreated or asymptomatic diseases (Miller et al., 2015). Several IMDs were selected that appear to generate uncertainty, including mild hyperphenylalaninemia, MCAD deficiency, VLCAD deficiency, partial biotinidase deficiency, and 3-MCC deficiency. To explore these intriguing snags, the following research question was proposed: “How do health care providers manage care in the context of medical uncertainty generated by newborn screening?”.

**Qualitative Description**

This research was developed to generate clinically meaningful results, ever-mindful of “the tyranny of method” (Sandelowski, 2000, p. 334). Qualitative description allows researchers to explore methods with the primary purpose of developing an accurate account of the data. In other words, qualitative description is an “eclectic but reasonable and well-considered combination of sampling, and data collection, analysis, and re-presentational techniques” (Sandelowski, 2000, p. 337). Thus, qualitative description is a pragmatic and illustrative qualitative research paradigm that allows researchers to develop a design logic that is consistent with their research question and investigation. This methodological paradigm can be readily understood and assessed by non-qualitative researchers as it entails an analysis that stays closer to the data. To enhance the accessibility of our findings, this dissertation strives to present “the facts of the case in everyday language” (Sandelowski, 2000, p.336). Sandelowski (2010) identifies qualitative description as a ‘distributed residual category’ to explore various kinds of methods that may not conform to the more rigid qualitative paradigms. It is also
interesting that residual categories "can signal uncertainty at the level of data collection or interpretation under conditions where forcing a more precise designation could give a false impression of positive data" (Bowker & Star, 2000). This paradigm appears to be well-suited to studying the probability, ambiguity, and complexity that generate residual categories - such as whether 3-MCC deficiency can be categorized as a disease - in clinical practice.

**Sampling Considerations**

Through the applied qualitative paradigm of qualitative description, it was important to develop a coherent design logic to best answer the research question. It was useful to explore other qualitative paradigms for guidance on sampling and methodological strategies. For example, grounded theorists often employ theoretical sampling and constant comparative analysis (Breckenridge & Jones, 2009; Glaser & Strauss, 2017; Heath & Cowley, 2004). In grounded theory, saturation is defined as the replication of data until it is not possible to identify new themes to ensure completeness and adequacy of information (Charmaz & Belgrave, 2007; Glaser & Strauss, 2017; Morse, Barrett, Mayan, Olson, & Spiers, 2002). It seems clear that a larger sample size improves a researcher’s ability to capture variation and document complexity. Creswell (1998) notes that to achieve an appropriate degree of saturation, grounded theorists should conduct 20 to 30 interviews. Creswell (1998) also writes that phenomenologists should conduct 5 to 25 interviews to develop an accurate and coherent account. In practice, Mason (2010) observed that about half of grounded theory studies failed to meet Creswell's (1998) criteria, while one third of phenomenological studies failed to meet these criteria. Sandelowski (1995b, p. 183) writes:
“An adequate sample size in qualitative research is one that permits-by virtue of not being too large-the deep, case-oriented analysis that is a hallmark of all qualitative inquiry, and that results in-by virtue of not being too small-a new and richly textured understanding of experience”

Clearly, there is no perfect sample size for a qualitative study. However, it is not unreasonable to assume that the ability to generate meaningful patterns and descriptions is intrinsically linked with sample size.

In the context of this research, the logic of sample selection was pragmatic due to the small population pool of potential participants. There are fewer than 15 specialized metabolic treatment centres across Canada with an approximate total of 50 metabolic physicians at these centres, as the rarity of inherited metabolic disease limits the need for Canadian metabolic specialists. To achieve maximum saturation, it was necessary to engage potential participants within this small pool of health care providers. Researchers leveraged existing relationships with the Canadian Inherited Metabolic Disease Research Network (CIMDRN) to recruit metabolic specialists and other health care providers at specialized metabolic centres. CIMDRN is an established network of 14 Canadian IMD treatment centres that provides critical infrastructure for rare disease research (Potter et al., 2012). These participants share a greater breadth of experience and knowledge with regards to managing MHP, partial biotinidase, VLCAD, MCAD, and 3-MCC deficiencies. In contrast, the majority of primary care providers self-reported that they were not entirely comfortable discussing PKU and other rare disorders with families (Kemper, Uren, Moseley, & Clark, 2006). Eligible health care providers within the patient’s circle of care were invited to participate through an electronic invitation letter (appendix F). The invitation letter explains that participation involves completing a 30 minute semi-structured, qualitative interview and asks potential participants to reply to the study
coordinator if they are interested in participating or would prefer no further contact. Three reminder emails were sent to non-responding health care providers approximately 2 weeks apart. All study participants were required to read the consent form (appendix D) prior to participation to ensure they are fully informed of study goals, potential benefits and risks, and requirements. Verbal consent was obtained prior to conducting the interview. The extant literature indicated that it would be possible to achieve a response rate of approximately 40-50% (Cummings, Savitz, & Konrad, 2001; VanGeest, Johnson, & Welch, 2007). However, it is important to recognize that many participants lead busy lives - serving multiple roles as researchers, clinical chiefs, and newborn screening program directors. One invitation email and three reminder emails were sent to 34 metabolic specialists and 15 dieticians affiliated with the CIMDRN network. Snowball sampling was conducted to recruit participants within the patients’ circle of care, including nurses and genetic counsellors at these specialized metabolic centres.

Data Collection

Data collection took the form of semi-structured, open-ended, telephone interviews with metabolic specialists, a clinical nurse specialist, and a genetic counsellor. Although telephone interviews prevent the collection of non-verbal communication to supplement verbal data, such as facial expressions and gestures, the advantage of this method is that it allowed us to collect data from distant geographical locations in Canada without being as cost-prohibitive and time-consuming as traditional face-to-face interviews. All interviews were audio recorded and transcribed. Memos and fieldnotes were written during interviews to record contextual and non-spoken information (e.g. participant demeanor, extended silences, background noise),
which aided in elucidating participant meaning (Phillippi & Lauderdale, 2017). Computer files of
transcripts were backed up on a separate password-protected computer in a locked room. The
anonymity of participants was protected by de-identifying names and assigning a unique study
identification number at the time of transcription. Grinyer (2002) writes that study participants
may wish to have their contributions acknowledged and remarks that anonymity is not always
an ethical prerequisite. However, the literature suggests that a historical social expectation may
exist: that providers should practice with certainty (Atkinson, 1984). Thus, health care providers
may be more open to acknowledging and discussing uncertainties if protected from judgment
or reprisal through the provision of anonymity.

The analytic framework informed data collection through the development of an open-
ended interview guide (appendices G and H), which probed health care providers’ experiences
with (i.) understanding the biochemical, genotypic, and clinical meaning of medical uncertainty
pertaining to IMDs in newborn screening, (ii.) managing results, focusing on communication
with families, and (iii.) managing decisions, focusing on follow-up care in the presence of
uncertainty and in the absence of clear evidence- or consensus-based guidelines. Interview
guides also explored (iv.) health care providers’ perceptions of the clinical and policy relevance
of medical uncertainty. The initial interview guide did not reflect concrete, prefigured
categories with which to survey emergent themes. This is reflected by updates to the initial
interview guide. The guide was used to inform branching lines of questioning to saturate
themes in greater detail from a greater variety of perspectives. Under the taxonomy of
uncertainty generated by Han et al. (2011), attention was paid to contextualizing the sources of
uncertainty described by providers and the issues that providers perceive to arise as a result of
uncertainty. Mishel's (1988) uncertainty in illness theory was adopted to heighten awareness of contextual cues and to explore whether health care providers structure the experience of uncertainty on behalf of patients. Data collection and analysis occurred concurrently so that previous interviews could inform further lines of questioning and validate or invalidate emergent themes.

Data Analysis

Data were analyzed according to the principles of thematic analysis (Braun & Clarke, 2006) and Sandelowski's (2000) description of thematic survey. The qualitative computer software, NVivo 11, was applied at all stages of analysis. Although computer software required additional learning and has the potential to distance researchers from the data, NVivo was used to organize and store data, encourage line by line analysis during the initial coding phases, and develop relationships between codes to assign themes (Thorne, 2016). The first step of analysis involved reading transcripts several times to develop intuition and a broader understanding of the data. Following this stage, memos were recorded in fieldnotes and margins to reflect on the data. At a later stage in the research, thematic analysis was conducted to establish codes and interpret patterns in the data. The six steps of thematic analysis identified by Braun and Clarke (2006) were adhered to so as to develop familiarity with the data, develop codes, search for themes, and describe these themes to generate a thematic map of the data. Definitions and labels for themes were clarified and a final report was produced by providing examples to illustrate themes. Codes were checked by an additional researcher to increase the variety of analytical perspectives and insight that the data might yield. Thorne (2016) writes, “the ‘more
probable truths’ ... are those that we have arrived at using multiple angles of vision”. Bi-weekly meetings were held during the data analysis phase with a thesis supervisor to discuss developing findings. Initial interviews yielded more general data on uncertainty in the newborn screening process. Therefore, the interview guide was re-organized to gain more specific insight into the target metabolic disorders by specifically probing uncertainty in the context of MHP, partial biotinidase deficiency, VLCADD, MCADD, and 3-MCC deficiency. When coding, pattern identification was driven by a strong majority of similar responses indicating relevant data or a particularly intriguing code made by minority of respondents. This dissertation attempts to demonstrate a clear line of logical reasoning when describing these patterns. Transcripts were analyzed using a mixed coding approach - drawing upon prefigured themes established through the fore-structured framework as well as emergent themes that were inductively generated from the transcripts. Braun and Clarke (2006) remark that although “thematic analysis is not wedded to any pre-existing theoretical framework... it is important that the theoretical position of thematic analysis is made clear”. Aligned with the theoretical fore-structure developed in preceding sections of this dissertation, this study was informed by social constructionist ways of thinking. Therefore, these findings present medical uncertainty as a socially constructed phenomenon where a perceived lack of health-related knowledge exists. This work sought to develop codes and identify patterns by paying attention to the sources and issues of uncertainty at the locus of the health care provider (Han et al., 2011). However, this work also sought to develop inductive codes and themes, as described in the data, with a focus on informing clinical practice and health policy.
Findings

The study sample included a total of 12 participants, including 10 metabolic geneticists, 1 clinical resource nurse, and 1 genetic counsellor across British Columbia, Alberta, Manitoba, Ontario, and the Maritimes. Participants were recruited from a total of 9 specialized metabolic centres across Canada, including BC Children’s Hospital, Alberta Children’s Hospital, Edmonton Medical Genetics Clinic, Winnipeg Children’s Hospital, London Health Sciences Centre, McMaster Children’s Hospital, Sick Kids Hospital, Kingston General Hospital, and the IWK Health Centre. The clinical resource nurse and genetic counsellor were involved on the care teams at these specialized metabolic centres. In addition to their role as a clinician, many metabolic geneticists had served in a variety of roles such as program or clinic directors, associate professors, and researchers. Some participants had experience working in more than one province or specialized metabolic centre. Although all participants were recruited from urban care settings, many clinics served a large geographic area. Therefore, specialized metabolic centres tend to serve both an urban and rural patient demographic. In total, 7 participants were female, and 5 participants were male.

Throughout the iterative process of data collection and analysis, it was clear that health care providers experienced medical uncertainty related to the newborn screening process, both in general and in the context of the selected IMDs. Issues of uncertainty were described under Han et al.’s (2017) 3-dimensional taxonomy of uncertainty. In the context of newborn screening and metabolic care, clinicians described diagnostic, therapeutic, prognostic, and personal issues of uncertainty. Clinicians also described nosological inadequacy as a source of uncertainty when managing patients with 3-MCC deficiency. When navigating metabolic care in the context of
this uncertainty, clinicians tended to err on the side of caution through the medicalization of their patients. Clinicians expressed concern over the level of caution and vigilance required to appropriately manage the care of patients with indeterminate, mild, benign, or partial conditions. Lastly, participants highlighted the importance of collaborative decision-making with patients, colleagues, other specialized metabolic centres, and newborn screening programs in the context of this uncertainty to evaluate the best course of medical management. The following sections explore these themes in greater detail.

**Contextualizing Uncertainty in Newborn Screening and Metabolic Follow-Up Care**

Health care providers describe a common pattern of uncertainty from the initial moments of newborn screening. Many clinicians cite the positive predictive value of the screening test - or the probability that patients with a positive screen have the target disorder - as a common source of uncertainty. For example, one participant said, “there’s the standard uncertainty with screening results, you know, in terms of the positive predictive value of the, the test, so that’s the initial thing” (P4). This screening limitation was thought of as a more ‘standard’ or ‘usual’ form of uncertainty that is not specific to a single target disorder. For example, one clinician stated, “I mean every positive newborn screen has the potential of being a false positive and so, that creates some degree of uncertainty” (P5). To describe such findings, clinicians used words like ‘indeterminate’, ‘abnormal’, ‘benign’, and ‘borderline’.

Drawing on the taxonomy of uncertainty (*appendix E*), health care providers indicated that uncertainty due to indeterminate screening results became a *personal issue* at the locus of the family. One physician stated, “this leaves a lot of uncertainty with the family – some of
them can’t understand that concept of: it’s just a screen, it doesn’t mean the baby has the disease” (P1). However, repeated testing or confirmatory follow-up testing can lead to more persistent uncertainties. For example, another metabolic specialist remarked that “it was not unusual to get a finding that wasn’t clearly pathologic or clearly benign and therefore, led to uncertainty” (P3). Participants remarked that these abnormal findings resulted in both ‘usual’ and more persistent personal issues of uncertainty:

“It would be very disconcerting to hear about the baby having an abnormal newborn screen when the family doesn’t understand the language, doesn’t understand what you’re talking about, and didn’t even know their baby had a newborn screen” (P7)

“They’re kind of in a bit of a haze or a turmoil after having a baby, and so they figure ‘Okay – I do this test and then, you know, I get to go home and think nothing of it’… I think for many of them it’s a surprise and it’s often conditions that they hadn’t heard about before … they’ve probably never even heard of metabolic diseases. So I think it creates a lot of stress for them when we have that kind of uncertainty” (P2)

“For the parents that are more anxious, getting an indeterminate result can even add more anxiety because now, not only have we said they’re at risk for something, now we’re telling them, ‘well, we’re not sure what this means or how long we need to keep doing blood work’, so they can have more anxiety around that” (P1)

Further drawing on the taxonomy of uncertainty, uncertainty in the newborn screening process also resulted in **practical issues**. Participants frequently discussed how they would evaluate the infant’s risk of decompensation based on the screening results and weigh the urgency of following up with the family to prevent adverse outcomes. When it came to ‘critical’ findings, health care providers felt it was important to communicate the results to families as quickly as possible to reduce the risk of harm to the infant. One participant said:

“If we cannot identify who the family doctor is on the newborn screen card … we’ll contact the patient directly by phone. If we don’t get the patient and it’s a critical level, we would actually get the police or RCMP or Public Health to track the family down” (P7)
However, at one of the clinics serving a larger geographic area, a participant remarked, “If they’re one of these indeterminate results ... that’s a bit of a call to say, ‘are we going to bring them all the way back to talk about what that means?’” (P1). Another participant reflected, “Of course you cannot ask the family to drive 5-7 hours with a newborn in an ice storm in the middle of winter. So sometimes we try to see the families by TeleHealth” (P12). It appeared that the perceived urgency of follow-up also depended on the target disorder. For example, a metabolic specialist said:

“If the newborn screen is caught on a Saturday night, for example, and it’s something that can’t wait – like for a high phenylalanine level – we would just wait until Monday... but for MCADD ... the physician on call would contact the family” (P5)

There was variation across metabolic care centres as to whether bad news would be disclosed to the primary care provider, who could in turn, convey this information to the family. Several participants commented on this practical issue:

“The first thing that we do when there’s a screen-positive is call the family doctor and tell him or her about the results and then we don’t even give them the option, we just tell them that we will call the family to disclose the results ... there are things that the family doctors cannot explain. So for example: what’s the next step... where is the hospital, who am I going to meet, what type of blood work or urine tests are being done, what’s the turnaround time ... all of these are great questions that can be used to reassure the family that the family doctor, uh, cannot answer” (P12)

“We will contact the family doctor or the paediatrician immediately. If we’re not able to contact or, there’s no physician actually assigned to the baby, then we would call the patient directly” (P7)

This demonstrates some of the practical issues of uncertainty that arise from initial newborn screening. However, health care providers perceived medical uncertainty pertaining to metabolic follow up to be highly contextual; “each case is individual – especially in the uncertain category” (P10). Participants mentioned “uncertainty is very much a case by case
basis” (P8) and that, “there’s enough nuance in the different conditions that, our approach is, I’d say, fairly unique for each of them” (P4). In comparison to the initial uncertainty associated with newborn screening, the following sections contextualize the issues that persistent medical uncertainty generates pertaining to each of the five target cases of IMD.

Mild hyperphenylalaninemia (MHP).

In comparison to the personal and practical uncertainty generated by initial newborn screening, health care providers appeared to navigate diagnostic, therapeutic, and prognostic issues of uncertainty in the context of MHP. Following a screening result for elevated plasma phenylalanine that did not meet the criteria for a classic PKU diagnosis, many providers described variation in diagnostic follow-up. For example, one metabolic specialist said:

“I think there’s several layers of variation in practice, which is maybe where I’ll put the uncertainty to start with. Starting with whether or not to do a biopterin loading test in the neonatal period – there is a fair bit of variation there. Whether or not to do genotyping is another place where you see variation. If a kid does have a biopterin response and/or has a genotype consistent with Kuvan or biopterin responsiveness, whether or not to start a child on biopterin in the infancy period, as a treatment. If a child has mild to moderate elevation, there is variation in the practice of when to start a child on diet or when to watch” (P10)

Other providers also commented on variation in follow-up to find out why the neonate has elevated serum phenylalanine. Many participants commented on biopterin responsiveness testing on a case by case basis. Another participant reflected:

“If the phenylalanine, let’s say, is 500 but the tyrosine’s also elevated, you would look further and see ... maybe something else is going on... the tandem mass result really helps us to determine... whether it’s a true positive or a false positive... you just don’t know where the phenylalanine level’s going to be, and so you, you basically have to bring the baby in, you do more definitive study” (P7)
Health care providers appeared to weigh whether each infant had a ‘true’ or a ‘benign’
case of MHP, and follow-up cases accordingly. Providers said:

“Certainly for the people who have the kids who have clear levels that are, you know,
less than 360 micromoles per litre.... We just follow them for a period of time and that's
not a big, you know, dilemma. It’s the ones that are hovering up around, you know, 360
or above, to know what to do with them and ... really it’s just a case by case basis that
we deal with those ones” (P4)

“We don’t want to overmedicalize a condition that is benign like that and that may not
actually need any dietary changes. So in terms of follow-up on a long-term basis, it’s
very different.... we still want to follow them – not as frequently as someone with classic
PKU – but we still want to follow them” (P12)

Providers at some centres appeared to exercise a more cautious approach, such as
monitoring infants with slightly elevated hyperphenylalaninemia results that are less than 360
micromoles per litre (P4, P6, P7). Health care providers also indicated that they navigated
therapeutic issues of uncertainty, such as whether to administer biopterin:

“If it’s under 360 you can ignore it, at least in a male, for sure. Between 360 and 600 is
questionable whether you treat; greater than 600, probably mostly treat ... some would
consider sapropterin if they’re sapropterin responsive but because it’s so expensive and
not always covered ... I’m not sure that’s something that should be routinely done. So
that, again, is an uncertainty in the mild hyperphe” (P3)

“I have been a bit more strict compared to Sick Kids because Sick Kids was only treating
after 600 levels and we treat, in our clinic, we treat between 300 to 600, as well... So,
we’ve got a lot of patients on Kuvan. I like to see lower levels: 120 to 360 ... You have to
also make sure how they are doing clinically, because remember, this is only blood; I
don’t know what’s happening in the brain” (P6)

Health care providers seemed to voice doubts about whether MHP was associated with
negative clinical outcomes. This appears to be a prognostic issue of uncertainty in the context
of MHP. For example, one clinician said, “We’re calling it benign because we don’t have great
evidence that it’s not benign” (P10). It was not always clear what physicians meant by ‘benign’,

32
but this participant said, “it’s something you don’t have to worry about. It’s okay” (P10).

Another participant voiced a similar idea:

“If we’ve got the initial phenylalanine back and we know that we’ve confirmed that it’s a fairly low level, we talk about the fact that its likely a benign condition that would just require follow-up, but we always sort of leave the caveat in there that phenylalanine levels in the neonatal period do not necessarily translate to the lifelong phenylalanine levels and phenylalanine tolerance in the diet” (P4)

Another participant raised an interesting doubt:

“Not to be cynical, but especially after there’s a pharmacological product, there’s been a lot of debate as to whether it is truly benign or whether there was much more subtle things as to whether treatment, of some sort, might benefit – and of course, the drug company would argue that non-dietary treatment would be the way to go” (P10)

Lastly, health care providers appeared to guide their decision-making processes around clinically-available evidence. For example, many participants discussed the follow-up of females with MHP as they age to prevent future complications that have been indicated in pregnancy.

“For the females, we want to keep following them because if they become pregnant as young adults, we want to make sure that their levels are still staying in a safe range. But for the males … as they become teens and adults, should we stop following them at some time? And there’s not really good evidence one way or another in the medical literature” (P1)
Partial biotinidase deficiency.

Health care providers experienced therapeutic issues of uncertainty when managing the care of patients with partial biotinidase deficiency. In comparison to the uncertainty of dietary restriction and biopterin supplementation that providers described with MHP, many participants seemed to suggest that there was less uncertainty associated with partial biotinidase deficiency. One provider said, “I mean, I think we’re probably over-treating a lot, with pharmacologic doses of biotin, but it’s a pretty innocuous treatment” (P7). Another participant stated, “I think there’s some uncertainty about whether we treat … above 30%, most of us, I think, would treat because the treatment’s so benign” (P3). Another health care provider said:

“Compared to complete biotinidase deficiency where there’s no question that … these patients should be treated with biotin supplementation, for partial, the evidence is less clear, but we typically tend to advise treatment with biotin supplementation because it’s cheap, it’s safe, it’s effective, and it could potentially eliminate the risk of a complication associated with the disease” (P5)

However, not all participants treated all their patients with partial biotinidase deficiency with biotin supplements. Additionally, one participant seemed to suggest that selective treatment had resulted in negative outcomes for some patients:

“If it’s the partial, and especially the D444H homozygous, then I’m not very keen on pushing too much, most of these patients do quite well … but I’ve had a few patients who again, were not very much seen in the clinic and then when they got infections and things, their learning got affected, they were not doing as well in school. So I think the jury is still out … there were a couple of Mennonite patients that I have had who had partial biotinidase deficiency, who actually did quite poorly in their cognitive, sort of, issues” (P6)

Although several providers indicated that they do not treat patients with partial biotinidase deficiency on a case by case basis, they acknowledged that there was a small risk to
the infant when deciding not to prescribe biotin supplements. Therefore, there are therapeutic issues of uncertainty in the context of partial biotinidase deficiency, however, to a lesser extent than therapeutic uncertainty associated with MHP.

**Fatty acid oxidation disorders: MCAD deficiency and VLCAD deficiency.**

Drawing on the taxonomy of uncertainty, health care providers navigated *diagnostic* and *therapeutic issues* of uncertainty in the context of MCAD deficiency and VLCAD deficiency. Follow-up testing for these fatty acid oxidation disorders differs from MHP, which typically involved reassessing the serum concentration of screened analyte (phenylalanine). Repeat acylcarnitine profiles were not seen as a definitive way to resolve uncertainty – which providers said can fluctuate between the time of newborn screening and metabolic follow-up. In cases that were ‘intermediate’, ‘moderate’, or ‘mild’, molecular testing would typically resolve issues of diagnosis. In the case of MCAD deficiency and VLCAD deficiency, for instance, confirmatory testing involves, “a variety or a combination of enzyme testing, molecular testing, and [analyte testing] and then taking the presence or absence of any clinical manifestations into it” (P10). From the perspective of health care providers, this allowed them to “really reduce that uncertainty, but you’re still left with that concept of those kids with a variant who may have adult onset disease and how aggressively do you manage them” (P10). Another provider remarked, “I can think of ... one or just that MCADD really, that kind of dragged on; all the rest are – you usually get a pretty definitive answer with the follow-up or the genetic testing usually sorts it all out” (P2). One participant stated:
“By the time the time they see us, they can completely normalise their biochemical abnormalities. So, the concern really lies if we’re able to properly make a diagnosis – is it true MCADD or VLCADD, or, if they’re only carriers, or if it’s just a benign biochemical abnormality to begin with?” (P8)

Even once follow-up testing returns to health care providers, diagnostic issues of uncertainty linger. For example, one provider reflects on the limitations of follow-up testing:

“We do follow-up biochemical testing, which gives us sort of, equivocal results, where the diagnosis isn’t completely clear, and so, you know, we wonder about - for example, with VLCADD – the possibility that the baby’s actually a heterozygote for a mutation as opposed to affected. And so that can create some uncertainty with respect to how to manage the patients ... and contributes to [a] longer period for diagnosis” (P5)

In other cases, follow-up testing may provide normal results, but still result in lingering diagnostic issues of uncertainty:

“Sometimes we’ll order genetic testing – but if the results come back normal or not significantly elevated, it really questions the diagnosis, it puts a lot of doubt in your mind whether the newborn screening is just showing carrier status, or, as I said, benign biochemical abnormalities. So we may pursue genetic testing, sometimes we try to do enzyme testing which sometimes requires skin biopsies – it can be quite invasive for a little baby” (P8)

Although health care providers indicated that follow-up testing generally allows for a more definitive diagnosis, there were therapeutic issues of uncertainty associated with ‘benign’ cases of MCAD deficiency and VLCAD deficiency. For instance, one clinician described their experience in treating MCAD deficiency: “I’m not sure what the risk of sudden decompensation is and I’m not sure what degree to aggressively intervene in intercurrent illness” (P10). At other centres, guidelines were in place to maintain consistency of care if patients were seen by different providers. However, one provider said, “We are probably still over cautious – probably a lot of the mild MCADs we picked up don’t require any kind of, you know, illness protocols, but we still do it, regardless” (P4). In the context of VLCADD, one metabolic specialist stated:
“For VLCAD deficiency, for example, to have more clear guidelines about who needs treatment, what degree they need treatment, and correlations between the molecular enzyme activity and the metabolite levels, in terms of what we need to do, because I think the concern there is, are we over-treating some of these patients and taking undue or unnecessary precautions which are maybe overly – they’re just more than the patient needs” (P5)

Specialized metabolic centres and physicians varied in prescribing oral carnitine for MCADD due to limited evidence, generating therapeutic equipoise. One provider describes variation between providers at their clinic:

Participant: I put one or two kids on carnitine and you know I have a colleague who is on the side of never starting carnitine and we got into quite the argument. Right?

Interviewer: Really?

Participant: Oh yeah you know: “Why’d you do it!”; “I was on call and I had to deal with that!” [both laugh] Oh you know I’m not sure I’m comfortable with the kid with MCADD who’s having episodes of presenting to an emerge who’s total carnitine is sitting at five ... I know there’s no evidence that I’m going to decrease the probability of the life threatening – um, episode. I do know physiologically you do need carnitine; you do need to get long chain fatty acids into the mitochondria (P10)

In the context of these fatty acid oxidation disorders, health care providers navigated diagnostic issues of uncertainty to ascertain the patient’s ‘true’ disease status through metabolic follow-up and confirmatory testing. Health care providers also navigate therapeutic issues of uncertainty pertaining to the appropriate degree of treatment, especially for mild cases.

3-MCC deficiency.

The source of uncertainty in the context of 3-MCC deficiency is conceptual ambiguity due to nosological inadequacy – limitations in the classifications of diseases and phenotypes (Han et al., 2017). In the newborn screening context, health care providers describe 3-MCC
deficiency as a “so-called disease” (P1), a “real/not real disease” (P2), a “non-disease” (P3, P10), a “benign condition” (P4, P8), and a “nill pathological condition” (P10). The participants clearly indicated that, in their experience, patients labelled with 3-MCC deficiency were not symptomatic:

“So you know, when we first started screening for 3-MCC, we had a much more aggressive approach to working them up and treating and following them ... we would do things like fibreglass studies to prove that it was an isolated enzyme defect versus, you know, a multiple carboxylase defect ... we put people on, you know, carnitine, maybe .... Certainly we put in the illness protocols for all of them. And then over time, you know, as more and more cases were identified and nobody really got sick ... we pulled back on our recommendations” (P4)

“Most of the other conditions, you can see quite clearly why they’re on the screening panel... so it prevents death or it prevents disability, so that’s why we look for it, that’s why we stress them out, we know that it might identify carriers, it might all wind up being nothing, but at the same time, if we find it and it is real, then we have done something to change the course of disease. 3MCC – I’m not convinced that’s the case” (P2)

Participants clearly agreed with the Newborn Screening Ontario decision to remove 3-MCC deficiency from the provincial newborn screening panel, although one participant seemed to express some hesitation: “Well I have a lot of respect for the Newborn Screening Ontario program so, I mean I wouldn’t second guess their decisions ... They may do things differently from us, in a variety of ways, but that’s okay, if it works for them” (P7). Another participant expressed concerns about screening for other C5-OH disorders, such as HMG-CoA lyase. While the participants of this study indicated that 3-MCC was, by and large, a ‘benign condition’, they were well-aware of the nosologic controversy surrounding 3-MCC deficiency:

“Well, we dealt with criticism from the American Organic Acidemia Association, who were tweeting at us and that... there’s people at some centres who really do believe that this is a disease. Right? And treat their kids much more aggressively” (P10)
There may be the occasional patient, very occasional, who has a disease associated with 3-MCC, and there’s some controversy, if one speaks to different people, about whether it should or shouldn’t be included” (P3)

This provides a description of the uncertainty pertaining to five newborn screening target disorders and the variation in practices and ideas held by various health care providers.

‘We Would Err on Overtreating than Not Treating at All’: Health Care Providers Are Cautious

This section illustrates the common pattern of health care providers exercising caution in the context of the medical uncertainty to prevent harm to the infant. This theme departs from the pre-established framework and analytic scaffolding. Health care providers used monitoring as a tool to be able to act quickly if the child suffered a decompensating episode. For example, providers often communicate signs to watch out for to parents to extend medical surveillance into the patient’s home. One provider said she tells parents, “In the meantime, you’re going to have to keep an eye on your baby and make sure that he or she doesn’t do this list of things that we say is concerning” (P2). Even in instances where providers are not actively prescribing treatment, monitoring is still seen as an important precautionary measure. One health care provider said:

“This is not the classical type of the disease where we expect there to be significant problems .... [but] we still have to follow them, to monitor them, because in some situations, we may find out further information that does have a health impact on the child” (P1)

Applying this test of time, health care providers can ascertain whether the child is truly at risk of the disorder. However, clinicians frequently suggested that monitoring becomes less frequent as the patients age. One participant said, “If we’re not instituting therapy, it’s just
periodic monitoring of phenylalanine levels and as they get older, the period gets longer” (P4).

However, one participant worried about losing patients to follow-up:

“I’ll tell you why I am very particular, so, many years ago... we had a patient with hyperphe, I think her level was 300 or something, or less... I ran into her when she was 10 years of age and her levels were 1000 ... So after that, I am quite sensitized to it. So I feel that at least we should monitor by blood levels, even if we are doing nothing else” (P6)

Health care providers indicated that medical uncertainty exists while waiting for the results of confirmatory testing. Many providers employed a cautious approach during this period. One participant said, “we treat this as if the child has the condition until we can rule it out, but that we ... can’t predict for sure if they’re going to be a true positive or a true negative” (P1). One provider stated, “I think that we are trying to be cautious, to prevent morbidity and mortality in their child ... but in the meantime we are going to do things that err on the side of caution, to keep the baby safe” (P2). However:

“To some physicians, cautious means, erring on the side of over-treating... you’re over-emphasizing the benefits of treatment and under-emphasizing the potential harms of treatment in that situation” (P4).

“If we know that this child is at, perhaps, increased risk, we don’t want to take chances. And this is why we usually overtreat those individuals. You don’t want to take the chance that after 10 years you learn one of your mild cases - where you have said ‘no risk’ - has passed away” (P11).

In an ironic twist, participants described the dangers of caution. In the context of newborn screening, it was clear that caution could result in medicalization — in greater treatment costs, family anxiety, and potentially, a prolonged diagnostic odyssey.

Notably, participants said:

“What we usually tell parents is: ‘keep a very close eye on the baby... call us if the baby’s not feeding well, or not looking well’. So, you know, we put in that increased anxiety for them, to always be watching their baby” (P8)
“We have to be careful, cause we, we don’t consider it completely harmless to treat a child as affected if they don’t actually have the condition because there are potential harms associated with, you know, hospitalising kids during minor illnesses and that kind of thing; it’s not necessarily benign and certainly dietary changes are not necessarily benign interventions” (P5)

In general, participants were keen to suggest that while the principle of caution is integral to the process of newborn screening, perhaps it is possible to be overprescriptive:

“I tend to, I guess in general, err on the side of being cautious … rather than saying, ‘oh nothing to worry about, parents’, or the other extreme would be to be, very prescriptive about management and diet change, and so, I think caution without putting the fear of, excessive fear and worry into the parents” (P3)

“I think over time we need to get some bravery and decide to stop some of the follow-ups... because it’s really not driven by clinical observation and scientific evidence, but really, the angst of running in a situation where at some point ... you think you could have done this differently – could have saved someone” (P11).

There is a Need for Consensus and Clear Communication in the Context of Uncertainty

When navigating uncertainty in the context of these metabolic disorders, physicians appeared to provide structure to families’ experiences by supporting and informing families (Mishel, 1988). One provider commented on the importance of:

“Reassuring them that we’re not just sending them back with no support at all ... That we’re going to continue to follow them until we get a better understanding of what’s going on ... and also we usually give them our contact information, let them know that there’s a geneticist on call – someone that they feel like they can reach out to if there are concerns about their child or questions” (P1)

For these health care providers, it was important to help patients come to terms with the uncertainty:

“If you have someone that really has trouble with the uncertainty, then maybe you do end up taking a more prescriptive approach, right? ... Here’s the things that could happen – what we need to watch out for – and that’s why I’m going to be seeing your
child ... the communication style can be more certain – even when describing the uncertainty” (P10)

In the words of one participant, “There’s a little bit of an art to metabolic care, it’s not all strict science” (P2). This section maps the strategies that health care providers suggest for managing care in the context of medical uncertainty – specifically, being very clear and open when communicating with families and developing consensus within and across specialized metabolic care centres. Participants suggested that many families are anxious in the context of medical uncertainty. One health care provider said, “you can tell from the very first time you meet the family if they’re going to be very anxious about indeterminate results, or if they’re going to be very easy going” (P1). These specialists suggested that each case should be treated uniquely.

Participants suggested:

“Comfort with uncertainty or certainty is going to be highly variable between individuals. What will work with parent A to get them into a common understanding with you on what this might mean for their child might be a very different approach than for parent B” (P10)

“Some families are very easygoing and you can really communicate the uncertainty to them and they’re able to accept it and sort of just go with the flow; where, other families, the uncertainty is very anxiety provoking – [it] makes them really doubt the medical system” (P8)

In the absence of collaborative care, consistency, guidelines or consensus, physicians indicated that the uncertainty can be uncomfortable. Commenting on the absence of standardized care plans, one provider said:

“It can get disorienting, because we think, ‘Oh, did I do that last time? Or the time before?’, or, ‘how often should I be doing this?’, and ..., ‘why am I doing this? Why am I poking this child? Am I actually going to change things based on what I do? Is it going to make a difference? ..... Then, it depends on the condition too ... ‘Do I need to bring them in for an appointment? Does it matter? Does it not?’ , you know, ‘How diligent do I need to be about this?’” (P2)
Participants frequently highlighted the importance of making sure ‘everyone’s on the same page’, having ‘good communication’, and being ‘open and honest’ about uncertainty with families. For example, providers describe their approach to communicating with families:

“To me, being open about the evidence and the existence of medical uncertainty doesn’t mean I’m personally uncertain. Right? ... Doesn’t mean I have to present things as wishy-washy ... It doesn’t mean I’m presenting things with less confidence ... I’ll say, ‘The approach here is permissive. What does that mean? It means that I don’t believe your child absolutely does or absolutely doesn’t need something – that there is a grey zone ... let’s make a decision together’” (P10)

“I feel that being very honest with patients, or families – telling them what we think – being honest when we don’t know, guiding them with respect to when we get results, um, I feel that these are all key things to build up a good relationship and I feel that very often it helps to manage uncertainty and people’s anxiety” (P12)

“I think what works best is to be completely open and honest about our uncertainty and what we think is the best management plan, whether it be nothing, in some of the mild hyperphenylalaninemia patients, or mild protein restriction, for the MCADDs and VLCADDs, as I’ve said, caution when the children are unwell” (P3)

A common strategy that health care providers employed was reviewing policies and guidelines in place in other jurisdictions to translate those practices on a case-by-case basis. Several participants discussed guidelines that were intended for use in the United States, such as the ACMG ACT Sheets and Algorithms. For instance, one provider said:

“Canada hasn’t come up with a definitive statement on it, yet. So we kind of have to rely on the American, and you know, some other guidelines, but, the more, the most recent guidelines from the ACMG ... I think there’s been a slide towards being more aggressive in treating [mild hyperphenylalaninemia patients] who are sort of between that 360 and 600, because the American recommendations are pushing that” (P4)

Health care providers across Canada are striving to work together to find solutions. One participant said, “We’ve made our own care plans based on CHEO’s and other centres’” (P6), and, “We reach out to other clinics across the country and ask, what are you doing with your mild hyperphe?” (P1). Many providers engaged in collaborative decision-making within their
specialized metabolic centre. One participant said, “We’ve developed some in-house care plans. And so, and we try to be consistent amongst our group and then we also try to, we speak to other groups. And we see what they’re doing too” (P2). Participants indicate that there is a communication and consensus gap that could be filled at a national level. One participant said, “hopefully they can find a united screening, country-wide... that’d be my goal” (P9). Other health care providers said:

“I think it’s important that not every province has to reinvent the wheel every time they want to add new things to their newborn screen ... I think it’s helpful if there ... is good communication between various provinces, but perhaps if there’s somewhere where people can keep their protocols, that we shared, and keep things up to date... whether we having something similar like [the ACMG ACT Sheets], yeah, across Canada” (P1)

“There is not a lot of communication between the different newborn screening programs. And maybe that’s okay and maybe that’s how this was meant to be, but sometimes I feel that knowing what other people do or sharing our experience could be of some value ... We recently started screening for [several disorders]; I needed a little bit of guidance about how to proceed given the urgency of medical attention these babies need ... We are not the only one with these challenges ... I was able to have a 30 minute discussion with 4 other screening programs in Canada, which was so awesome because based on that I was able to write our own guidelines. So that is just so awesome and I felt so supported” (P12)

While participants emphasized the idea that uncertainty is uniquely contextualized on a case-by-case basis, clinically flexible guidelines allow health care providers to adopt generalizable management strategies to specific clinical circumstances.

**Discussion**

The goal of this dissertation was to explore how health care providers manage medical uncertainty pertaining to newborn screening and metabolic follow-up by exploring 5 IMDs: MHP, MCAD deficiency, VLCAD deficiency, partial biotinidase deficiency, and 3-MCC deficiency.
This section links the findings to relevant academic literature, discusses the implications of this research, and identifies several strengths and limitations of this work.

**Summary of Findings and Relation to the Literature**

This study included 12 total respondents, including 10 metabolic geneticists, 1 clinical resource nurse, and 1 genetic counsellor from 9 specialized metabolic centres across Canada. All study participants articulated specific issues of uncertainty, as catalogued under Han et al.’s (2017) taxonomy of uncertainty (see appendices E and I).

The first theme allowed for the contextualization of uncertainty in newborn screening and metabolic care. Participants discussed how initial newborn screening results commonly resulted in *personal issues* of uncertainty – “pertain[ing] to psychosocial and existential issues, including the effects and implications of .... test results for one’s own goals or outlook on life, personal relationships, sense of meaning or one’s future well-being and that of one’s family members or social groups” (Han et al., 2017, p. 921). For example, health care providers described the shock, surprise, and anxiety that a positive screening result generates for families – some of whom “didn’t even know their baby had a newborn screen” (P7). While this is a common finding in the United States, where the practice of informed consent is not the standard of care for newborn screening, it is perhaps more surprising in the context of provincial newborn screening systems in Canada, since all provinces require informed consent for blood spot testing (Hiller, Landenburger, & Natowicz, 1997). Etchegary et al. (2016) explored both patient and health care providers experiences in the consent process for newborn bloodspot screening in Canada. They found that “The process was highly routinized, sometimes
even described as being presented as compulsory” (p.1532). In a more extreme case, parents declined screening and recall being misinformed, “Well it’s the law, you have to get it done … it’s hospital policy that you have to get it done within this hospital before leaving” (Etchegary et al., 2016, p. 1532). Even if families are informed of newborn screening and told that results sometimes come back positive, this perhaps would not sufficiently prepare families for the more complex possibility of ‘benign’ or ‘indeterminate’ results. Language also appears to be very important – as ‘benign’ would imply that a condition is not pathological or disease causing, while ‘indeterminate’ alludes to ‘patients-in-waiting’ who are both sick and not sick - where their true condition might one day be established after a potentially lengthy diagnostic odyssey (Timmermans & Buchbinder, 2012). While Etchegary et al. (2016) suggest that there are a variety of ways to inform patients prior to newborn bloodspot testing, the work presented here suggests that there are different ways to frame newborn screening results. This may help to explain why families face personal issues of uncertainty on a case by case basis.

Health care providers also observed practical issues of uncertainty in newborn screening and metabolic follow-up; uncertainty relating to both the structures and processes of health care (Han et al., 2017). In terms of a structural issue, health care providers weighed non-medical factors when evaluating whether and when patients need to be ‘medicalized’ pending an indeterminate result – such as the patient’s distance from the specialized metabolic centre. This suggests that uncertainty may manifest differently when managing patients in remote areas. This is not traditionally emphasized in the literature on metabolic care. For example, Demirkol, Gičewska, Giovannini, and Walter (2011) write,

“The primary obstacles to better adherence are time constraints and stress associated with food preparation and record-keeping, and the restrictions imposed on social life.
Reasons of the failure of PKU treatment may be parents' inability to administer a low-Phe diet to their child because of family situations and backgrounds as well as barriers with language, psychological, and cultural communication” (p. S36).

In addition to these factors, this study suggests that structural barriers to accessing care – such as distance to a specialized metabolic clinic – may contribute to reduced adherence to treatment or follow-up. This holds true in the context of cancer care, where specialized care is centralized in urban centres (Payne, Jarrett, & Jeffs, 2000). However, in the context of mammography, travel time to clinics does not appear to affect stage of diagnosis or screening compliance (Henry et al., 2011; Kreher, Hickner, Ruffin IV, & Lin, 1995). There is a recognized need to improve screening in remote communities through Telemedicine – such as in the context of screening for hearing loss (Swanepoel et al., 2010). It may be possible to extend home monitoring of inherited metabolic disease, such as hyperphenylalaninemia, through mail-in, self-sampled dried blood spot or saliva specimens (Sakhi et al., 2015). Research is needed to explore whether geographic proximity and travel time affects adherence or access to metabolic follow-up care.

Clinicians described another practical issue of uncertainty: whether to inform the primary care provider so they might communicate positive screening results. While many participants explicitly identified the importance of informing the patient’s primary care physician, who in turn, could communicate results to the family, Kemper, Uren, Moseley, and Clark (2006) found that many family physicians are not comfortable managing initial counselling of positive newborn screens. For instance, 53.2% of family physicians self-reported that they lacked the competence to appropriately discuss PKU with families (Kemper et al., 2006). The idea of the clinician as a structure provider resonates in this context (Mishel, 1988). Likewise,
Light (1979) writes that health care providers with greater clinical expertise will better be able to navigate uncertainty.

Participants described diagnostic issues of uncertainty in the context of MHP, MCAD deficiency, and VLCAD deficiency, which tended to result in a lengthened period of follow-up testing. This is interesting because “early diagnosis is often identified as an important benefit of NBS, to avoid the so-called diagnostic odyssey” (Miller et al., 2015, p. e414). However, the findings presented here indicate that newborn screening has the potential to trigger, rather than avoid, a diagnostic odyssey. In the context of this prolonged diagnostic period, Carmichael and colleagues (2015) suggest that both invasive and non-invasive procedures cause distress for the child. Lenhard et al. (2005, p.173) write, “diagnostic uncertainty constitutes a strong independent determinant of long-lasting emotional burden for parents”. More work is needed to explore costs and consequences of the diagnostic odyssey in the context of inherited metabolic disease.

Participants described nosological inadequacy, or “limitations in the conceptual systems used to classify diseases and phenotypes”, as a source of conceptual ambiguity and uncertainty associated with 3-MCC deficiency (Han et al., 2017, p. 919). 3-MCC deficiency was assumed to be an extremely rare condition but blossomed in prevalence following the identification of cases via biochemical screening. However, most of these cases are asymptomatic (Jung et al., 2012). One participant describes this as an ascertainment bias which has led to the overmedicalization of many children. At the time of writing, Saskatchewan, Manitoba, Quebec, and most regions in Nunavut still screen for 3-MCC deficiency (Canadian Organization for Rare Disorders, 2015). Secondly, participants indicated that incidental findings in the context of 3-M

48
MCC deficiency are associated with ethical challenges in their practice. This finding aligns with reports in the literature that newborn bloodspot screen positive results for 3-MCC often reflect the values of the screened metabolite in an asymptomatic mother (Lee & Hong, 2014). Ross, Rothstein, and Clayton (2013) write, “testing for conditions beyond the scope of the original request is in conflict with key ethical principles of patient autonomy and shared decision making” (p. 368). This raises the ethical issue of whether such information should be conveyed to the family. In the case of 3-MCC deficiency, there are no specific ACMG guidelines to indicate whether such results should be disclosed (R. C. Green et al., 2013). Physicians may not convey secondary findings if they believe that families have a right to not know or if they think it may cause unnecessary anxiety. Conversely, other physicians have voiced concerns about the risk of legal liability due to non-disclosure (Ross et al., 2013).

Despite 50 years of newborn screening for hyperphenylalaninemia, this study reveals that there are still “deceptive snags” in the newborn screening process (Guthrie & Susi, 1963; J. Wilson & Jungner, 1968). While erring on the side of caution was perceived to benefit a child’s health, participants believed that excessive caution could lead to over-medicalization. This is a source of tension for health care providers that navigate uncertainty. Previous sections describing the literature in the field of medical uncertainty research suggested that female health care providers experience more stress due to uncertainty than male providers (Gerrity et al., 1992). Observing that most of the study participants in this project were female, one might speculate that this sample could have been more likely to emphasize a cautious approach. Secondly, Light (1979) suggested that specialized health care providers can invoke their clinical expertise to resolve uncertainty. Thus, participants in supportive health care roles, including the
genetic counsellor and clinical nurse, may also be more inclined towards using a cautious approach. Brennan, Eagle, and Rice (2010, p. 10) write, “Medicalization can be broadly defined as the redefining or reconceptualizing of nonmedical behaviors, experiences, or problems as medical in nature”. This can reduce the scope of what is considered ‘normal’ or ‘healthy’. For example, Phe cut-off values considered to be safe have lowered over time (Holtzman et al., 1986; Scriver, 1989; van Spronsen & Burgard, 2008). This has expanded the classification of disease status in the context of hyperphenylalaninemia. Pharmaceutical companies promote medicalization through medical research to narrow the cut-off value for ‘healthy’ status, to promote the therapeutic efficacy of a drug, or sponsor research to find that a condition is treatable (Brennan et al., 2010). Burgard et al. (2017, p. 682) state:

“overtreatment of a lifelong metabolic disease can have medical, psychological, social, and economic consequences that might outweigh any potential benefit... Compliance with recommendations for phenylketonuria has been shown to be poor, and setting targets that are too strict might result in decreased appointment compliance because patients will want to avoid getting repeated negative professional feedback”

In the context of MHP, providers expressed therapeutic uncertainty when prescribing bipterin. Van Wegberg et al. (2017) found that evidence supporting bipterin treatment is suboptimal and that of supporting monitoring alone is of higher quality. Uncertainty continues to present snags in the newborn screening process for hyperphenylalaninemia.

The data collected by this study appears to corroborate the epistemic lens of uncertainty, which holds that uncertainty results from a lack of evidence or knowledge. Target inherited metabolic disorders were selected because there was a paucity of research and consensus for managing patient care. In the context of VLCAD deficiency, for example, Arnold and colleagues (2008, p. 87) describe a lack of evidence: “the full range of
genotype/enzyme/phenotype correlation has not yet been described in infants ascertained through newborn screening”. In line with an epistemic lens of uncertainty, care providers in our study indicated that VLCAD deficiency was associated with diagnostic issues of uncertainty. The association between lack of evidence and lack of certainty is very apparent from the data produced by this study. Many management plans are affected by a paucity of evidence and consensus, which suggests that uncertainty is a complex and many-faceted phenomenon across multiple clinical contexts. Renowned Canadian physician, Sir William Osler, is commonly quoted as stating, “Medicine is a science of uncertainty and an art of probability”.

**Uniform Screening: Why Not in Canada?**

Due to the many indications that greater consensus and communication is required across newborn screening jurisdictions in Canada, this section discusses the potential for a national uniform newborn screening panel. Some would suggest that newborn screening lies at the intersection of administered health care services and public health (K. Wilson et al., 2010). However, Shah (2003) notes, “No common definition of public health is in use across Canada”. While provinces are largely responsible for the delivery of health services, K. Wilson et al. (2010) write that matters of public health – in essence, health protection and promotion - often fall under both federal and provincial responsibility. For example, the federal government created the National Advisory Committee on Immunization (NACI) because immunization is believed to be an aspect of public health. NACI published the Canadian Immunization Guide (CIG) to standardize vaccination schedules across provinces. These public health guidelines standardize care, while also allowing for provincial autonomy in the delivery of services. It is
not immediately clear why Canada has not attempted to standardize newborn screening across provinces. One explanation is the lack of precedence for the expansion of federal powers over matters of public health, except for cases that prevent risks spanning provincial boundaries (K. Wilson et al., 2010). In the case of immunization, federal government can intervene to prevent the transmission of communicable disease across borders. However, inherited disorders do not present this risk. Secondly, instituting such guidelines would likely require significant financial expenditure. In the United States, the Nixon administration passed the *National Sickle Cell Anemia Control Act* and distributed $85 million in grants to leverage individual states into screening for sickle cell disease (K. Wilson et al., 2010). In the United States, the successful implementation of the uniform screening panel has largely been attributed to the voices of powerful interest groups like the American Academy of Pediatrics (AAP) and the ACMG (Khoury, McCabe, & McCabe, 2003). Physician-led interest groups in Canada have not advocated for uniform newborn screening to the same extent. However, variation in newborn screening policy has the potential to influence a significant proportion of the Canadian population, since over one million infants have been screened in Canada over the last 3 years alone (Statistics Canada, 2017). Historically, technological capability to screen was sufficient justification for screening (Pourfarzam & Zadhoush, 2013). However, tandem mass spectrometry (TMS) has exponentially increased the number of disorders detectable via screening. Many of these disorders are untreatable or fail to present a significant health problem. To address this issue, jurisdictions rely on Wilson and Jungner's (1968) classical criteria for the inclusion or exclusion of disorders on provincial panels (*appendix A*). However, Pollitt (2006) states that there is no objective and accepted way to use these principles as criteria. Prior to the development of
national guidelines in the United States, Pollitt (2006) wrote, “The lack of even broad concordance at the level of national policy is extremely disturbing”. While this indicates that national newborn screening policy is needed, there is also the question of whether harmonization is desirable if uncertainty is managed uniquely on a case-by-case basis. It may be helpful to emphasize that clinical flexibility is a critical aspect of health guidelines. Grimshaw and Russell (1993) state, “Guidelines should identify exceptions to their recommendations and indicate how patient preferences are to be incorporated in decision making” (Grimshaw & Russell, 1993, p. 243). This allows for the flexibility of managing uncertainty on a case-by-case basis while having an available and generalizable management strategy.

Implications

This study generated the first pan-Canadian analysis related to providers’ management of medical uncertainty as a complex consequence of universal newborn screening. Communicating and collaborative-decision making while being open about the uncertainty appears to be the most effective method to navigating clinical care where there is a lack of evidence or consensus. This descriptive qualitative study suggests that uncertainty allows providers to navigate the tension between caution and medicalization. Therefore, the medical community should strive to develop best practices through evidence and consensus, rather than strive to eliminate or reduce uncertainty. While health care providers did not appear to be uncomfortable with uncertainty, they suggested that many families face personal issues of uncertainty through newborn screening and metabolic follow-up care. Through clear communication, information sharing, and collaborative decision making, clinicians can help
structure families’ experiences and provide emotional support. Due to the importance of communication in the context of uncertainty, stakeholders should use consistent terms that suit the message they are striving to convey. Terms such as ‘benign’, ‘intermediate’, and ‘borderline’ have different connotations for patients, labs, families, policy-makers, and other health care providers. In addition, this study captures some of the variation in newborn screening practices across Canada while highlighting a need for greater communication and collaboration across jurisdictions. Recognizing this need, it is important for policy-makers to consider national uniform screening guidelines that allow for sufficient clinical flexibility.

Prior to data collection and analysis, it was unclear whether uncertainty was something to be avoided, reduced, or rejected. For example, Newson et al. (2016) suggest that uncertainty provides an opportunity to build resilience and allow patients with dire conditions to hope for a positive recovery. In the context of newborn screening and metabolic care, uncertainty was expressed by providers when reconciling the tension between erring on the side of caution and overmedicalizing patients. Where a lack of evidence remains, consensus guidelines aimed to ‘reduce uncertainty’ could lead to routine medicalization of patients that do not necessarily require extensive treatment or follow-up. Although the concept of resilience, as suggested by Newson et al. (2016), did not resonate in this study, our findings do corroborate the idea that uncertainty has positive implications. For example, Seely (2013, p. 72) writes:

“Acknowledging uncertainty does not mean abandoning patients to their autonomy; it is the physician’s responsibility to manage the decision-making process in a fashion in keeping with each individual patient’s values and beliefs. By acknowledging uncertainty within patient care, the physician-patient relationship can be elevated to one of greater communication and shared decision-making”
Supporting patients and collaborative decision-making processes can allow health care providers to navigate uncertainty on a case-by-case basis to manage the balance between precaution and medicalization.

This study also applied the taxonomy of uncertainty developed by Han et al. (2011) within the context of newborn screening and metabolic care for the first time. This taxonomy was a useful framework for organizing uncertainty into various domains. However, the taxonomy has been much more extensively developed for researchers that study clinical genome sequencing (Han et al., 2017). When classifying the uncertainties pertaining to non-genetic screening and test results, the taxonomy was of limited value. It would be very useful to develop the taxonomy to a greater degree in non-genetic contexts, as uncertainty appears to affect health care across many disciplines (Alam et al., 2017). Diagnostic issues of uncertainty described by Han et al. (2017), such as gene-phenotype association, pathogenicity of variants, and phenotype-disease association are very specific to the context of clinical genome sequencing. At face-value, it appeared that their earlier and more general taxonomy of uncertainty helped to categorize uncertainties expressed by providers in the context of metabolic care (Han et al., 2011). In this study, health care providers described diagnostic, prognostic, therapeutic, personal, and practical issues of uncertainty. However, our data appears to fit classifications of uncertainty proposed by Djulbegovic et al. (2011) equally well. These authors describe ‘uncertainty about defining the disease’, ‘diagnostic uncertainty’, ‘uncertainty about treatment’, ‘uncertainty about prognosis’, and ‘uncertainty about eliciting patients’ values, preferences and risk attitudes’ (Djulbegovic et al., 2011). In many ways, these two frameworks appear to have redundant, overlapping categories. Recognizing that medical
uncertainty arises out of a *perceived* lack of knowledge, it follows that taxonomies of uncertainty are subjectively constructed. Han et al. (2017) also observed that multiple angles of vision may develop a more meaningful account of uncertainty in genome sequencing, and developed an interactive website to encourage discussion and expansion of the taxonomy (available at http://research.nhgri.nih.gov/taxonomy/). It may be beneficial to synthesize similar co-constructed taxonomies of uncertainty in other medical contexts, such as newborn screening and metabolic care.

As medical knowledge of inherited metabolic disease has improved, so too, have the knowledge gaps. This is reminiscent of a paradoxically liberating colloquialism that is often mis-attributed to Aristotle: ‘The more you know, the more you know you don’t know’. Over three decades ago, Atkinson (1984) suggested that medical residents were being trained for certainty despite the complexity and ambiguity of clinical practice. This study suggests that clinicians manage uncertainty on a case-by-case basis. This may lead one to speculate whether it is possible to train physicians for the art of managing a complex phenomenon in such unique clinical contexts. While there may be a myriad of uncertainties that influence clinical practice, the findings presented here corroborate with Waitzkin's (1985), who suggested that openness and honesty about the existence of uncertainty is the best management strategy for managing patient care. It may be possible to train clinicians to invoke the principles of honesty and openness in the context of managing medical uncertainty.

Future decades may bear witness to genotype-first newborn screening strategies, in contrast to the contemporary method of newborn blood spot screening or urine analysis (Stessman, Bernier, & Eichler, 2014). Some of the challenges associated with medical
uncertainty are expected to intensify with a shift towards clinical genome sequencing-based screening approaches. For example, Han et al. (2017) contextualize the nosological inadequacy associated with variants of unknown significance identified through genetic sequencing. In turn, clinical genome sequencing may increase the positive predictive value of screening. In the context of a screening program, one cost of certainty may be additional uncertainty. The data produced by this study will enable the newborn screening community, including health care providers and decision-makers, to understand clinical perspectives and develop evidence-based forward thinking and best practices in the context of uncertainty. It is hoped that this exploratory work will catalyze future research including the development and trial of educational resources for families and communication tools or management strategies for providers, as well as encourage the development of consensus or evidence-based guidelines for best practices related to screening, reporting, and medical surveillance of families that receive uncertain results.

Limitations and Strengths

Limitations.

Several limitations of this research have been identified. Firstly, this study does not make use of the principle of triangulation, which involves gathering multiple sources of data and employing multiple methods to converge on similar findings. However, Tracy (2010) remarks, “triangulation does not lay neatly over research from … paradigms that view reality as multiple, fractured, contested, or socially constructed”. Rather than striving for a singular, positivistic truth, this study aims to account for multivocality, or developing a diversity of
perspectives across health care providers by jurisdiction and provider type. Secondly, health care providers who have agreed to participate in this study may not be representative of their respective whole theoretical population, as they occupy key positions in specialized metabolic centres. However, it is expected that varied insight between jurisdictions will illuminate the range of experiences and strategies that exist. Thirdly, practical considerations necessitated telephone, rather than face-to-face, interviewing. This may have limited the ability to collect non-verbal data or develop more meaningful connections with participants. Lastly, retrospective interviewing techniques are subject to confirmation and recall biases. In line with the paradigm of qualitative description, this study developed an open and transparent analytic scaffolding with which to interpret results so that readers can evaluate whether the investigator’s preconceived notions have detracted from, or supplemented, data collection and analysis.

**Strengths.**

Data were collected by a single investigator that relied on the clinically-meaningful approach of qualitative description. Allegiance to this theoretical paradigm was maintained. No new codes were generated after the first eight interviews. Other authors have observed similar findings. For example, Guest, Bunce, and Johnson (2006) explored qualitative data from over 60 interviews across multiple African countries. They concluded that “a total of thirty-six codes were applied with a high frequency to the transcripts. Of these, thirty-four (94%) had already been identified within the first six interviews, and thirty-five (97%) were identified after twelve” (p. 73). Many authors seem to agree that data collection in later stages of the research process
has diminishing returns on new insight (Creswell, 1998; Guest et al., 2006; Thorne, 2016). In the context of our study, this was found to be the case. Therefore, it is proposed that themes were adequately saturated to provide a meaningful answer to the question, while acknowledging that there will always be more to learn and understand. In addition, intriguing points that present contrasting perspectives were presented – such as the concern that lowering cut-off values for hyperphenylalaninemia aligned with pharmacological interests. Morse et al. (2002) highlight the importance of reviewing negative responses and dissenting opinions when generating new codes. For example, while virtually all providers commented on the pervasiveness of uncertainty in the newborn screening process, one participant stated that there is no uncertainty. From this participant’s perspective, “physicians simply need to follow the protocols”. As Morse (1995) writes, this is not an outlier or an error, but could instead be the key to the puzzle. Perhaps clear protocols and clinical guidelines can reduce, if not eliminate, uncertainty for clinicians when choosing amongst management strategies. Although dissenting ideas were not patterns shared across participants and did not seem to represent overlying themes, these negative responses often reflected interesting and unique insights that would serve an important purpose in interpreting and discussing meaningful findings. Ultimately, the heterogeneity of the sample across multiple jurisdictions led to a greater variety of insight.

**Future Research, Knowledge Translation and Exchange**

This study intends to transfer research findings into clinical practice and policy according to the Knowledge to Action Process, proposed by Graham & Tetroe (2010). Following primary
knowledge inquiry regarding uncertainty at the locus of the health care provider, the research team aims to explore uncertainty at other loci – including the locus of the patient and family, as well as the locus of the newborn screening program representative. This three-armed approach hopes to capture multiple perspectives to better explore the phenomenon of uncertainty in the context of newborn screening and metabolic care. The study will be condensed and submitted to academic publications related to newborn screening, pediatric health care, and/or metabolic care. Academic publications will be distributed to CIMDRN and participating health care providers. In addition, it is hoped that findings might be distributed to the Newborn Screening Ontario Advisory Committee (NSO-AC) and annual symposium. As participants suggested that the US ACT Sheets and Algorithms were a valuable tool, the team is interested in developing similar tools for managing uncertainty in Canada.

Conclusion

In the context of newborn screening and metabolic care for MHP, MCAD deficiency, VLCAD deficiency, and partial biotinidase deficiency, health care providers experienced personal, practical, diagnostic, prognostic, and therapeutic issues of uncertainty. In the context of 3-MCC deficiency, health care providers described conceptual ambiguity when attempting to diagnose patients with a ‘disease/not disease’ – highlighting the nosological inadequacy associated with the disorder (Han et al., 2017). Participants emphasized the importance of managing care in the context of uncertainty with a degree of caution, however, expressed concerns over the overmedicalization of affected infants. In addition, health care providers suggested that there is a need for greater communication and consensus in the context of
uncertainty generated by newborn screening. Although more evidence is required to evaluate and develop management algorithms and protocols in the context of uncertainty, it is likely that all clinicians face a degree of uncertainty in their medical practice.

The findings of this dissertation contribute towards the extant literature in three significant ways. Firstly, the intended audience can develop a deeper understanding of specific issues of uncertainty in the context of a clinical program that has been described as “deceptively simple” (J. Wilson & Jungner, 1968). Secondly, this report challenges health care providers to consider whether they err on the side of caution in their clinical practice when navigating medical uncertainty and whether this strategy has led to an overmedicalization of certain patients. Lastly, this report suggests that greater communication and consensus is highly valued in the context of newborn screening. Policy-makers should consider whether a national newborn screening strategy could aide in this endeavor. Therefore, it is important for future researchers to understand and explore this uncertainty in greater detail across a variety of clinical settings.
Appendices

Appendix A: Wilson and Jungner (1968) Principles of Screening

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a “once and for all” project.

Appendix B: Variation in Newborn Screening within Canada

<table>
<thead>
<tr>
<th>Province/Territory</th>
<th>Fatty Acid Disorders</th>
<th>Organic Acid Disorders</th>
<th>Amino Acid Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CUD</td>
<td>LECHAD</td>
<td>MCAD</td>
</tr>
<tr>
<td>Newfoundland &amp; Labrador</td>
<td>A</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Prince Edward Island</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>New Brunswick</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Quebec</td>
<td>A</td>
<td>U</td>
<td>U</td>
</tr>
<tr>
<td>Ontario</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Manitoba</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Saskatchewan</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Alberta</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>British Columbia</td>
<td>A</td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

*Canadian Organization for Rare Disorders (2015): Demonstrates variation across Canada in newborn screening practices for core inherited metabolic disorders by province. Dot = screening for the condition is universally required by Law; A = universally offered but not yet required by law; B = offered to select populations or by request; U = screened through urine analysis.
Appendix C: Variation in Newborn Screening across Countries

Therrell et al. (2015). Proportion of total jurisdictions (n=158) screening for the disorder. Number of conditions screened per jurisdiction may have changed since publication.
## Appendix D: Table of Selected Inherited Metabolic Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Biochemical Profile</th>
<th>Natural History</th>
<th>Management Strategies</th>
<th>Uncertainty of Non-Classic Form</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mild Hyperphenylalaninemia (MHP)</strong></td>
<td>Residual phenylalanine hydroxylase activity; Plasma Phe concentration 360-600 umol/L; Possible pterin defect; Non-elevated tyrosine</td>
<td>May or may not be at higher risk of developing intellectual, neurologic, or neuropsychological impairment</td>
<td>No consensus on dietary restriction of Phe, no consensus on sapropterin prescription, varying plasma Phe levels considered to be ‘safe’</td>
<td>Diagnostic, therapeutic, and prognostic issues of uncertainty</td>
</tr>
<tr>
<td><strong>Phenylketonuria (PKU)</strong></td>
<td>Complete/near-complete deficiency of phenylalanine hydroxylase Type 1: Plasma Phe concentration &gt;1200 umol/L Type 2: Plasma Phe concentration 360-1200 umol/L Possible pterin defect; Non-elevated tyrosine</td>
<td>Without dietary restriction of phenylalanine most children develop profound and irreversible intellectual disability</td>
<td>Dietary restriction of Phe; Prescription of adjuvant sapropterin (tetrahydrobiopterin)</td>
<td></td>
</tr>
<tr>
<td><strong>Partial Biotinidase Deficiency</strong></td>
<td>Partial deficiency of biotinidase; residual enzyme activity 10-30%; Possible heterozygous mutation on gene 3q25</td>
<td>Rare/anecdotal occurrences of hypotonia, skin rashes, hair loss - appear more often during illness or active infection and other times of stress</td>
<td>Biotin supplementation generally recommended; lower dose at the discretion of the clinician</td>
<td>Therapeutic issues of uncertainty</td>
</tr>
<tr>
<td><strong>Profound Biotinidase Deficiency</strong></td>
<td>Complete/near-complete deficiency of biotinidase; residual enzyme activity &lt;10%; Possible homozygote for mutation on gene 3q25</td>
<td>Hypotonia; seizures; eczematous skin rash; alopecia; respiratory problems, conjunctivitis, candidiasis; ataxia; developmental delay; deafness, blindness</td>
<td>Biotin supplementation recommended at 5-10mg per day for life</td>
<td></td>
</tr>
<tr>
<td><strong>MCAD Deficiency</strong></td>
<td>Elevated C8 acylcarnitine; lesser elevations of C6 and C10; decarboxylic acid in urine; mutation in ACADM gene - varying severity</td>
<td>Lethargy, hypoketotic hypoglycemia, liver and brain damage. Prolonged periods of fasting may result in metabolic crises or death.</td>
<td>Educate parents on the importance of regular feedings; avoidance of prolonged fasting, ingesting complex carbohydrates prior to resting. Administer IV glucose when ill.</td>
<td>Diagnostic and therapeutic issues of uncertainty</td>
</tr>
<tr>
<td><strong>VLCAD Deficiency</strong></td>
<td>Elevated C14:1 acylcarnitine; VLCAD gene mutation; Unusual ratio of long-chain fatty acids (C10, C12, C14, C16)</td>
<td>May cause severe cardiomyopathy, fatty liver, skeletal myopathy, pericardial effusions, ventricular arrhythmias, and sudden death. May be fatal. Clinical presentation is heterogeneous and time of onset varies.</td>
<td>Administer IV glucose when ill. No clear consensus on long-chain or medium-chain fatty acid supplementation.</td>
<td>Diagnostic and therapeutic issues of uncertainty</td>
</tr>
<tr>
<td><strong>3-MCC Deficiency</strong></td>
<td>Mild to moderate persistent elevations of C5-OH acylcarnitine in blood; presence of 3-methylcrotonylglycine acid in urine; often reflects maternal analyte concentrations</td>
<td>As few as 4-5% of cases are symptomatic with ketoacidosis, hypoglycemia, Reye syndrome, or intellectual disability.</td>
<td>Prescribe oral carnitine if C5-OH levels are low, treat for acute illness. Lack of consensus for dietary modification.</td>
<td>Conceptual ambiguity due to nosologic inadequacy</td>
</tr>
</tbody>
</table>
Appendix E: The 3-Dimensional Taxonomy of Uncertainty

Uncertainty

Source
- Probability
- Ambiguity
- Complexity

Issue
- Personal
- Practical
- Scientific

Locus
- Health Care Providers
  - Diagnostic
  - Prognostic
  - Therapeutic

*Modified from Han et al. (2011)
Appendix F: Electronic Invitation Letter

[---Date---]

Dear [Formal Title; Provider Name]

As a health care provider for children with inherited metabolic disease, we are writing to tell you about a research study exploring how individuals understand and manage medical uncertainty generated by newborn screening (NBS). Led by Dr. Robin Hayeems at the Hospital for Sick Children, this study aims to explore how parents, health care providers, and newborn screening programs understand and manage uncertainty. The health care provider component of this study aims to reach providers across Canada.

We are asking those involved in caring for children with IEM to participate in a telephone interview. From a health care provider perspective, we would like to explore your approach to understanding these results, communicating results to families, and managing the child’s care.

Please be assured that you are under no obligation to participate. Participation involves taking part in one telephone interview. The interview should take approximately 30 minutes of your time. All information gathered will be kept strictly confidential.

If you do not wish to participate, please complete the enclosed response card and respond via email to our research team member, ________ [name], at ___________@sickkids.ca, to let the researchers know not to contact you further.

If we do not receive a response within two weeks, our Study Coordinator will follow up by telephone. At this time, you can indicate whether you are interested in learning more, are willing to participate or wish to decline participation.
Appendix G: Initial Interview Guide

Initial Interview Guide

OPENING

Hello, my name is __________ and I am [role & affiliation]. I would like to thank you in advance for your time. The purpose of this interview is to explore how clinicians manage medical uncertainty generated by newborn screening.

We have selected a few conditions that may be associated with medical uncertainty due to limited evidence or guidelines for managing care. These conditions include mild hyperphenylalaninemia (MHP), medium-chain acyl CoA dehydrogenase deficiency (MCADD), very long chain acyl-CoA dehydrogenase deficiency (VLCADD), 3-methylcrotnyl CoA carboxylase deficiency (3-MCCD), and partial biotinidase deficiency (Partial-BIO).

Participation in this study is entirely voluntary: you may leave the study at any time. The interview will be audio-recorded so that it can be analyzed as a written transcript. Identifying information will be anonymized so that transcripts will not include any information that reveals your patients’ or your own identity.

The interview is standardized and open-ended. We expect that the interview will take 30 minutes of your time. If you would like to get in touch with our team after this interview to find out more, you may reach us through email or telephone. Details can be found in the study invitation letter.

Do you have any questions before we begin the interview?

QUESTIONS

Do you agree to participate in this study knowing that you may leave the study at any time with no consequences to you?

1. How would you describe your role in newborn screening and caring for children with inherited metabolic disease?

2. Several variant or non-classic inherited metabolic diseases, such as MHP or MCADD, might be identified through newborn screening. Tell me about how you approach these variant screening results.

   Prompts:
   - How does your approach in managing variant screening results (e.g. MHP) compare to your approach in managing classic screening results (e.g. hyperphenylalaninemia)?
3. How would you describe your typical process for communicating or sharing variant or non-classic results related to your patients and their families?

**Prompts:**
- Who is involved in explaining the results?
- How else do you inform the patient? (e.g. counselling letters, emergency letters, other educational resources, parent-to-parent support, referrals)

4. How do you approach a care plan for infants with variant and non-classic results?

**Prompts:**
- Others have suggested that they use hospital protocols or localized professional guidelines. How do you feel about such strategies?
- Do practices vary among clinicians at your centre?
- To what extent are care plans influenced by families themselves?
- How does this care plan change as patients grow older?

5. How do parents respond to the recommended plan?

**Prompts:**
- What questions do they ask?
- What concerns do they share?
- To what extent do they follow the recommended care plan?

6. We have about three more questions left. When navigating uncertain results in your practice, what do you think works well and what do you think requires further consideration?

7. Ontario recently removed 3-MCCD from the provincial newborn screening panel. What are your thoughts on this decision?

**Prompts:**
- How might have medical uncertainty played in this decision?

8. Is there anything else that you would like to ask or discuss?

**CLOSING**

Thank you very much for your time. If you have any further comments, observations, or criticisms regarding my research, please do not hesitate to contact me at the email or telephone number provided in the study information letter. I will also follow-up by email. Once again, thank you kindly for your participation.
Appendix H: Interview Guide Rationale

Opening

Prior to the interview, participants are provided a study information sheet and a consent form that outline the potential risks, benefits, and goals of the study in greater detail. The opening discussion serves to: (1) introduce the interviewer; (2) communicate the interview’s purpose; (3) remind participants of study confidentiality and re-iterate voluntary participation; (4) briefly introduce the interview format; (5) re-affirm expectations for interview duration; (6) establish means for future communication; and (7) address any further questions (D. Turner, 2010). The purpose of these statements is to establish rapport, build trust with participants, and set a precedence for communication to allow interviewees to express their thoughts and experiences within ethical parameters (Qu & Dumay, 2011).

Questions

Question 1. Jacob & Furgerson (2012) suggest that researchers begin an interview with a relatively basic, open-ended question to build trust and establish context for future answers. The study sample includes key metabolic specialists affiliated with CIMDRN. Therefore, respondents are likely to be able to clearly articulate their role and situate themselves within the context of newborn screening.

Question 2. This question begins to explore the interviewees’ clinical strategy where the literature cites a lack of evidence and professional consensus for managing patient care (van Wegberg et al., 2017). Jacob and Furgerson (2012) suggest the phrase, “tell me about…”, to elicit memories, which enable the interpreters to weave a descriptive story out of the
participants’ experiences. The questions are asked chronologically to facilitate the interviewees’ narrative recollection of their experiences (Thorne, Kirkham, & MacDonald-Emes, 1997). The initial screen positive result marks the beginning of this clinical odyssey. The associated prompt seeks to stimulate the participant’s memory (Smith, 1992). It accomplishes this by situating an unusual disease context (MHP) within a more familiar, or common, disease context (classic hyperphenylalaninemia).

**Question 3.** This question continues the narrative chronology established in question 2, focusing on the communication aspect of managing the care of patients in the context of uncertainty. Green and Thorogood (2014, pg. 118) describe this type of question as a “verbal diary”, since it seeks to elicit the respondents’ perspective surrounding their experience. The associated prompts probe for more complete information and broaden the contextual picture of participants involved in the diagnostic process (Barriball & While, 1994).

**Question 4.** This question sets the tone for a discussion around follow-up care and management strategies in the context of prognostic uncertainty. The associated prompts aim to explore whether these strategies resonate with the theoretical background that informs the work. It is believed that uncertainty is due to the subjective perception of a lack of knowledge, which draws attention toward variation between health care providers and centres (Han et al., 2011).

**Question 5.** This question aims to explore whether the findings from this study resonate with the findings from a related study branch, which seeks to explore parents’ perceptions of uncertainty in newborn screening. The use of multiple data sets and perspectives to link findings aims to increase the rigor of the collective work (Morse, 2015). This question also has
the potential to inform a less experienced or unspecialized audience that might be interested in anticipating common patient concerns (Thorne, Kirkham, & O’Flynn-Magee, 2004). The associated prompts stem from a curiosity to understand how providers interpret patients’ reactions to ambiguous diagnoses.

**Question 6.** Harvey (2011) suggests that researchers inform respondents as to how much longer an interview will last to improve focus and avoid a seemingly unending stream of questions. This question strives to improve the transferability of the research by sharing commonly successful strategies that specialists utilize (“what do you believe works well”) and areas for future research (“what do you think requires further consideration”).

**Question 7.** This question attempts to determine how newborn screening policy decisions are interpreted in a clinical context. This question requires respondents to critically reflect on a recent policy change – which may lead to contentious opinions. Richards (1996, p. 203) suggests that researchers wait to ask such questions until “you have established a rapport with your interviewee and have been involved in discussion for a while”. Therefore, this question is situated near the end of the interview. Participants are likely to comment on the policy context due to their affiliative ties with CIMDRN and large specialized treatment centres (e.g. Hospital for Sick Children or the Children’s Hospital of Eastern Ontario).

**Question 7.** Harvey (2011) suggests that interviewers ask respondents for feedback and provide an opportunity to elaborate. Respondents are knowledgeable and may be able to inform questions for future interviews with other respondents. Similarly, Morse (2015) highlights the importance of flexibility and ending semi-structured interviews through open and reflexive dialogue.
Closing

Harvey (2011) writes that it is important to thank your interviewer as common courtesy and to help provide opportunities for future dialogue with respondents. Participants may also wish to reflect on their interview transcripts. The goal of member reflection is “not specifically to have the participants agree that this is the account they would have given, but rather to recognize themselves, their words and ideas”, while simultaneously recognizing the researchers’ ongoing interpretations (Press, 2005).
Appendix I: Target IMDs and Associated Uncertainty

- **Mild Hyperphenylalaninemia:**
  - Diagnostic, therapeutic, and prognostic issues of uncertainty

- **Partial Biotinidase Deficiency:**
  - Therapeutic issues of uncertainty

- **MCAD and VLCAD Deficiencies:**
  - Diagnostic and therapeutic issues of uncertainty

- **3-MCC Deficiency:**
  - Conceptual ambiguity due to nosologic inadequacy
## Appendix J: Newborn Screening Program Characteristics

<table>
<thead>
<tr>
<th>British Columbia Newborn Screening Program (BC Children's Hospital; Perinatal Services BC)</th>
<th>Babies Screened per Year</th>
<th>PKU</th>
<th>BIOT</th>
<th>MCAD</th>
<th>VLCAD</th>
<th>3-MCCD</th>
<th>Number of Cases per Year</th>
<th>Governance Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>44,000</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>About 40 affected infants identified per year³</td>
<td>Newborn screening advisory committee of BC responsible for scope and function of NBS</td>
<td></td>
</tr>
</tbody>
</table>

| Alberta Newborn Metabolic Screening Program (Alberta Health Services) | 56,000 | ✓ | ✓ | ✓ | ? | Between 2015-2016: 234 critical screen results and 30 borderline results. 68 with abnormal diagnostic outcome, 8 with unclear or unknown diagnostic outcome⁴ | Advisory structure appointed and maintained by Alberta Health and Wellness (AHW) |

| Newborn Screening in Saskatchewan (Saskatchewan Disease Control Laboratory; Roy Romanow Provincial Laboratory) | 17,000 | ✓ | ✓ | ✓ | ✓ | About 8-10 affected infants identified per year³ | Regulated by the Saskatchewan Ministry of Health |

| Manitoba Newborn Screening Program (Cadham Provincial Laboratory) | 17,000 | ✓ | ✓ | ✓ | ✓ | About 10-12 affected infants identified per year³ | Committee reports directly to the Public Health branch of the Manitoba Health, Healthy Living and Seniors, Government of Manitoba |

| Newborn Screening Ontario (Children's Hospital of Eastern Ontario) | 145,000 | ✓ | ✓ | ✓ | ✓ | Removed | About 200 affected infants identified per year² | NSO Advisory council reports to CHEO and the Ontario Ministry of Health and Long-Term Care. Solicits advice from Maternal Child Screening Advisory Committee |

| Québec's Neonatal Blood and Urine Screening Program (Centre Hospitalier Universitaire de Québec) | 84,000 | ✓ | ✓ | ? | | Urine | Unknown | Multi-disciplinary committee responsible for scope and function of NBS |

| Newfoundland and Labrador Newborn Screening (Provincial Medical Genetics Program) | 4,000 | ✓ | ✓ | | | Unknown | Notices and advisories provided by the Newfoundland and Labrador Medical Association |

| Maritime Newborn Screening Program (IWK Health Centre; Nova Scotia, New Brunswick, and Prince Edward Island) | 16,000 | ✓ | ✓ | ✓ | | About 26 affected infants identified per year⁴ | Advisory Committee responsible for scope, evaluation of diseases, & general program details. 5 working groups specific to each disorder comprised of clinical experts & stakeholders |

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8. Personal communication; April 30, 2018
Appendix K: Canadian Inherited Metabolic Disease Research Network (CIMDRN) Mailing List

<table>
<thead>
<tr>
<th>Program</th>
<th>Metabolic Specialists Affiliated with CIMDRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>British Columbia Newborn Screening Program</td>
<td>3</td>
</tr>
<tr>
<td>Alberta Newborn Metabolic Screening Program</td>
<td>6</td>
</tr>
<tr>
<td>Newborn Screening in Saskatchewan</td>
<td>0</td>
</tr>
<tr>
<td>Manitoba Newborn Screening Program</td>
<td>1</td>
</tr>
<tr>
<td>Newborn Screening Ontario</td>
<td>12</td>
</tr>
<tr>
<td>Québec’s Neonatal Blood &amp; Urine Screening Program</td>
<td>8</td>
</tr>
<tr>
<td>Newfoundland and Labrador Newborn Screening</td>
<td>1</td>
</tr>
<tr>
<td>Maritime Newborn Screening Program</td>
<td>3</td>
</tr>
</tbody>
</table>
Appendix L: Consent Form for Health Care Providers

Consent Form

Title of Research Project:
Health Care Providers' Understanding and Management of Medical Uncertainty in Newborn Screening

Investigator(s):
Principal Investigator:
Dr. Robin Hayeems, PhD, ScM

Co-Investigators:
Dr. Beth Potter, PhD: 613-562-5465
Dr. Pranesh Chakraborty, MD, FRCPC, FCCMG
Dr. Jonathan Kronick, MD, PhD, FRCPC
Dr. Fiona Miller, PhD
Dr. Andreas Schulze, MD, PhD, FRCPC
Dr. John Mitchell, MD, MSc, FRCP
Dr. Aziz Mhanni, MB, ChB, FRCP, FCCMG, FACMG, PhD
Dr. Cheryl Greenberg, MD, CM, FRCPC, FCCMG
Dr. Hillary Vallance, MD, FRCPC, FCCMG
Dr. Sylvia Stockler, MD

Team Members:
Viji Venkataramanan, MA
Ashley Wilson, BSc, CCRP
Paul Azzopardi, BHSc, MSc Candidate

Purpose of the Research:
As a health care provider for children with inherited metabolic disease (IMD), you have been asked to take part in this research study. The objective of this study is to advance capacity to manage diagnostic uncertainty generated by NBS for IMD for i) parents of infants who receive these results, ii) health care providers who care for families, and iii) NBS programs that deliver and govern this service. The health care provider component of this study aims to reach providers in all Canadian provinces. We hope to interview 10-12 health care providers.

Description of the Research:
This study involves taking part in one 30 minute interview with the study coordinator. The interview will take place at a time and place that is convenient for you. The interview will be audio-recorded so that it can be made into a written transcript for the purpose of analysis.
Transcripts of audiotaped interviews will not include any information that reveals your patient’s or your identity. You may refuse to answer any question.

**Potential Harms, Discomforts or Inconvenience:**

We do not anticipate any harm from taking part in this study. The interview will last about 30-60 minutes. The time commitment for these interviews may be an inconvenience.

**Potential Benefits**

You may not benefit directly from participating in this study. However, we will provide you with a summary of results, if you are interested, once the research is complete.

**Benefits to Society:**

This study will help us to understand parents’, health care providers’ and NBS programs’ experiences with newborn screening for IEM and in particular, how they respond to and manage diagnostic uncertainty. As the technology used to support newborn screening changes, it is important to consider the experiences of those who participate in, operate, and govern this program. We are expecting to publish the findings of this study, which will be publicly available.

**Confidentiality:**

We will respect your privacy. No information about you or your patients will be given to anyone or be published without your permission.

The data produced from this study will be stored in a secure, locked location. Only members of the research team (and maybe those individuals described above) will have access to the data. This could include external research team members. Following completion of the research study the data will be kept as long as required then destroyed as required by SickKids policy. Published study results will not reveal any participant’s identity.

**Participation:**

It is your choice to take part in this study. You can stop or leave the study at any time.

**Sponsorship:**

This research study is funded by the Rare Disease Foundation and the Hospital for Sick Children’s Centre for Genetic Medicine Catalyst Grant. The sponsors of this study are Dr. Robin Hayeems and The Hospital for Sick Children.
Conflict of Interest:

Dr. Hayeems and the other research team members have no conflict of interest to declare.

Consent:

By signing this form, I agree that:

1. You have explained this study to me. You have answered all my questions.
2. You have explained the possible harms and benefits (if any) of this study.
3. I know what I could do instead of taking part in this study. I understand that I have the right not to take part in the study and the right to stop at any time.
4. I am free now, and in the future, to ask questions about the study.
5. I understand that no information about who I am will be given to anyone or be published without my permission.
6. I agree, or consent, to take part in this study.
7. I have read, and understand pages 1-3 of this consent form.

____________________________________  __________________________
Printed Name of Participant  Participant’s signature & date

____________________________________
Printed Name of Person who explained consent

____________________________________
Signature of Person who explained consent & date

If you have any questions about this study, please call [study team member], at [SickKids-affiliated phone number], or email at [SickKids-affiliated email]

If you have questions about your rights as a subject in a study or injuries during a study, please call the SickKids Research Ethics Manager.
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