Reducing the psychosocial impact of a false positive newborn screen for inborn errors of metabolism

by

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ABSTRACT

Newborn screening (NBS) is standard practice for neonatal care in Canada and screens for over 20 inborn errors of metabolism (IEM). Education about NBS is meant to mitigate parental anxiety following an initial positive screen and reduce the inappropriate medicalization of children after a false positive result. Parents of 482 children who had NBS done by Cadham Provincial Laboratory in Winnipeg, MB between 2011-2017 and who screened positive for an IEM were invited to participate in an online survey and follow-up interview. Although only 21 online survey responses were completed (5.06% response rate), these data allowed for a more detailed understanding of the demographic characteristics of the interviewed sample. Eleven respondents completed semi-structured telephone interviews designed to identify how communication of a positive result and educational resources can be improved; explore how parents are accessing educational information about IEMs after being notified of their result; and determine when in the NBS process parents feel that they will benefit most from these educational messages. Overall, participants felt that clinicians downplayed the significance of their result and provided them with limited information about the IEM. Immediately after being notified, parents sought information online as a source of comfort and wanted to learn more about the likelihood of a false positive result, follow-up process, prognosis of the IEM, and management guidelines. In hindsight, parents felt unaware of the potential outcomes of NBS because of a lack of education about the program prior to being notified of their result. Additionally, parents indicated that their local healthcare providers, emergency departments, and medical laboratories had inadequate knowledge about NBS that led to multiple redraws and unnecessary challenges in follow-up. Based on interpretive description, evidence-based strategies for improving the experience of a positive NBS result for IEMs are described.

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INTRODUCTION

1.1 Overview

Newborn screening (NBS) is standard practice for neonatal care in Canada and across North America. NBS involves analysis of a dried blood spot card collected by a heel prick within the first five days of life. Analysis of biochemical markers provides pre-symptomatic detection for a variety of inborn errors of metabolism (IEMs) and other congenital conditions that will result in severe complications if they are not managed from birth. Inborn errors of metabolism (IEM) are a group of diseases that affect the way people break down or synthesize substances made by their body or consumed through their diet. They cause the disruption of a metabolic pathway, usually due to a defect in an enzyme or chemical transporter. This leads to toxic accumulation of upstream substrates, deficiency in downstream metabolites, and the production of abnormal compounds through metabolic pathways that are normally unused. Overall, preemptive management of these diseases through NBS has had an immensely positive impact on child health by reducing morbidity and mortality in newborns.

A false positive result means that NBS shows that the baby may have a disease, but follow-up testing proves that they do not. This type of result is relatively common and is not without significant psychosocial impact on the parents of the newborn. This thesis investigates the experiences of families with a positive NBS result so that genetic counsellors and geneticists can better understand how to support them during this difficult period. The goal of this study is to reduce the psychosocial impact of having a positive NBS result by recommending empirically

supported modifications to the content and dissemination of existing educational resources and health service delivery.

1.2 Principles of a screening program

NBS has been in effect for several decades throughout North America. Throughout this time, it has expanded from a targeted test for a single disease to detecting over thirty congenital disorders, the majority of which are IEMs (Cadham Provincial Laboratory, 2019). Before any condition is added to a population-wide screening program, it should meet the following criteria outlined by Wilson and Jungner (1969):

(1) "The condition sought should be an important health problem" (Wilson & Jungner, 1969). Although each individual IEM is rare, they are cumulatively common and have an overall incidence of 1 in 800 (Mak, Lee, Chan, & Lam, 2013). The IEMs included on NBS all have the potential to be severe if left untreated. When unmanaged, these diseases may cause sudden and rapid decompensation involving hyperammonemia, hypoglycemia, vomiting, lethargy, coma, and death within the first weeks of life (Claudius, Fluharty, & Boles, 2005). Other IEMs may result in severe neurologic damage and permanent intellectual disability.

(2) "There should be an accepted treatment for patients with recognized disease" (Wilson & Jungner, 1969). Effective management options exist for many IEMs and the majority of patients will be largely asymptomatic if treated from birth. For example, individuals with managed phenylketonuria (PKU) can have normal intellect and be in good overall health by simply following a protein restricted diet from birth and maintaining low plasma phenylalanine levels throughout their lifespan (Vockley et al., 2014). Breakthroughs in gene therapy, molecular chaperones, substrate reduction therapy, and enzyme replacement therapy offer promising

solutions to other IEMs that are not currently amenable to treatment (Kay, 2011). Many IEMs that are capable of being detected have been excluded from NBS until it can be justified that effective treatment exists.

(3) "Facilities for diagnosis and treatment should be available" (Wilson & Jungner, 1969). Although confirmatory algorithms vary by province and testing centre, positive results are all handled in a coordinated manner such that they are not lost to follow-up. Action Sheets provided by the American College of Medical Genetics (ACMG) describe possible differential diagnoses based on the abnormal analyte and recommended actions that the healthcare provider should perform following a positive NBS result (ACMG, 2001). Manitoba's specific NBS algorithm is described later in greater detail.

(4) "There should be a recognizable latent or early symptomatic stage" (Wilson & Jungner, 1969). The vast majority of infants with IEMs have a normal presentation at birth. Often, they first come to medical attention due to a sudden and rapid decompensation which may cause irreparable damage to their health.

(5) "There should be a suitable test or examination" (Wilson & Jungner, 1969). Newborn screening is currently performed using tandem mass spectrometry (MS/MS), which will be described later in greater detail. Analysis using MS/MS is a relatively simple and inexpensive procedure which can process over 400 bloodspot cards per day by a single laboratory (Pandor, Eastham, Beverley, Chilcott, & Paisley, 2004). Population-wide screening programs are designed to be highly sensitive in order to minimize false-negatives, thereby causing a compromise in specificity. The specificity of MS/MS is reported to be between 83-99% depending on the specific IEM and the biochemical marker used in screening (Pandor et al., 2004). Since newborn screening is not considered a diagnostic test, further confirmatory testing

must be performed to make a diagnosis. In addition to assessment by a metabolic geneticist, diagnostic testing may include enzyme assays, genetic testing, or further biochemical studies.

(6) "The test should be acceptable to the population" (Wilson & Jungner, 1969). Newborn screening for IEMs is minimally invasive and involves analysis of a dried blood spot sample collected by a heel prick.

(7) "The natural history of the condition, including development from latent to declared disease, should be adequately understood" (Wilson & Jungner, 1969). Common triggers of a metabolic crisis in a newborn may include feeding with breast milk that is indigestible to the newborn, long periods of fasting, or a common sickness that increases the newborn's energy demands beyond their metabolism's capacity. The underlying genetic cause, disease progression, and prognosis if untreated is well understood for all IEMs included on NBS.

(8) "There should be an agreed policy on whom to treat as patients" (Wilson & Jungner, 1969). Patients are identified through a positive newborn screen and continue to be managed by metabolic specialists if confirmatory testing establishes a diagnosis of an IEM.

(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" (Wilson & Jungner, 1969). A cost-effective analysis performed by ACMG demonstrated that the expenses incurred by untreated disease outcomes are greater than the cost of NBS programs (Watson, Mann, Lloyd-puryear, Rinaldo, & Howell, 2006). Thus, NBS reduces the financial burden on the provincial healthcare system while improving health outcomes (Watson et al., 2006).

(10) "Case-finding should be a continuing process and not a 'once and for all' project"(Wilson & Jungner, 1969). Developmental pediatricians and family doctors continue to

monitor patients for normal development and functioning over the course of their lifetime. If a patient has symptoms suggestive of an IEM, metabolic geneticists and genetic counsellors are available to provide expert assessment, treatment, and ongoing management.

It is evident that NBS has rapidly evolved since its inception, all the while maintaining these core principles outlined by Wilson and Jungner. What was once a simple test intended for a single disease has become a population-wide program implemented by countries across the world to screen for multiple congenital diseases.

1.3 History of newborn screening

Dr. Robert Guthrie is credited as being the father of NBS after demonstrating that phenylalanine levels in newborns could reliably screen for PKU by analyzing a dried bloodspot collected on filter paper (Guthrie & Susi, 1963). In 1962, only two years after the invention of the Guthrie card, Massachusetts became the first state in the United States of America to implement a population-wide screening program for PKU (Holtzman, Watson, & Paul, 1997). One year later, Prince Edward Island became the first province in Canada to do the same (Therrell & Adams, 2007). Within the next 10 years, all of the provinces in Canada implemented NBS for PKU, with each program being funded and regulated by their own provincial government (Haworth, Miller, & Scriver, 1974).

The success demonstrated by population-wide screening for PKU prompted additional initiatives across Canada to expand NBS. A pilot project in Winnipeg, MB evaluated the use of chromatographic methods for detecting galactosemia and select amino acidopathies. In 1969, Manitoba adopted this methodology over the Guthrie test (Fox, Hall, Haworth, Maniar, & Sekla, 1971). It wasn't until 1974, however, that a second condition, congenital hypothyroidism (CH),

was added to all NBS programs across North America after an assay was established by Quebec's program (Dussault et al., 1975). Adapting the established framework of the Guthrie card, Dussault developed an assay to quantify plasma T4 levels from the eluate of bloodspots (Dussault et al., 1975). Testing primarily for PKU and CH remained the universal standard in NBS for the next several decades, despite other efforts to screen for additional disease over that time.

Not all attempts at expanding NBS were successful, as evident by Manitoba's pilot program which screened for Duchenne Muscular Dystrophy (DMD) and Becker's Muscular Dystrophy (BMD) from January 1, 1986 to August 31, 1990 (Hildes et al., 1993). DMD and BMD are progressive, X-linked recessive, neuromuscular diseases caused by a defect in the dystrophin protein. DMD results in loss of mobility with symptoms typically starting at age four to five years and is usually lethal by the third decade of life due to associated cardiac and respiratory complications (Passamano et al., 2012). BMD is a milder phenotype with later onset of symptoms and a longer life expectancy than DMD (Passamano et al., 2012). NBS for both of these conditions was trialed by measuring creatine kinase concentrations from the dried bloodspot card. Elevated levels indicated a positive result and confirmatory testing was performed six weeks later by repeat testing, muscle ultrasound, muscle biopsy, and molecular studies of the DMD gene (Hildes et al., 1993). This pilot program highlights important challenges in expansion of NBS.

First, no treatment was available for DMD at the time of the pilot, thereby contradicting one of the essential principles of NBS. Instead, the pilot program aimed to provide early diagnosis of males with DMD in order to identify carrier mothers, reduce subsequent births of children with DMD through prenatal diagnosis, and reduce the overall frequency of the disease

in the general population (C. R. Greenberg et al., 1988). The approach of using NBS for reproductive benefit conflicts with the primary purpose of a screening program and may encourage eugenics and sex selection in the general population (Paul, 2018). Screening for DMD was unwarranted at the time based on lack of treatment and no difference in prognosis based on early diagnosis through NBS.

Second, the pilot program was ineffective in accomplishing its goal. Among 43,513 male newborns screened over the duration of the pilot program, eight children affected with DMD were identified (C. R. Greenberg et al., 1992). Follow-up with the families demonstrated that the pilot program did not decrease the number of repeat cases of DMD within families. Five of seven pregnancies that occurred subsequent to being identified as a carrier were not monitored through prenatal diagnosis and ultimately resulted in the birth of two affected males (Hildes et al., 1993). The program did not result in a decreased birth rate or reduced incidence of DMD in the general population.

Lastly, a false positive result for DMD led to the unintended diagnosis of an off-target and untreatable congenital myopathy. During the period of piloting, approximately 1 in 1000 children had a false positive initial result (C. R. Greenberg et al., 1992). Upon confirmatory testing, two incidents occurred where the individual did not have DMD but had persistently elevated creatine kinase levels. One had benign raised CK-BB isozyme and the other had hydrocephalus and congenital cataracts consistent with a diagnosis of Walker-Warburg Syndrome (C. R. Greenberg et al., 1992). The latter individual died at age eight months and no effective treatment was available (C. R. Greenberg et al., 1992). It was concluded that testing for DMD may detect other unintended forms of congenital muscular dystrophies. In summary, Manitoba's pilot program for DMD demonstrated that the utility of a true positive result and the

psychosocial impact of a false positive result needed to be more carefully considered in future attempts to expand NBS.

Additional tests for other congenital disorders that have been added to NBS throughout its evolution are summarized in Table 1.1. By far, the most rapid and successful expansion to NBS was facilitated by the integration of MS/MS in the analytic process (Denes et al., 2012). Although MS/MS was first introduced as a clinical chemistry tool in 1990, it was not used by NBS programs across Canada until the 2000s and is currently still in effect. Manitoba implemented expanded NBS in 2011, using MS/MS to screen for over 20 IEMs (Cadham Provincial Laboratory, 2019). These IEMs include aminoacidopathies, organic acidemias, and fatty acid oxidation defects. Ultimately, MS/MS has revolutionized the ability of clinicians to screen for a wide array of IEMs with a single multiplex test.

Table 1.1: Examples of disorders screened by NBS that are not detected by MS/MS [*]

Disorder	Test
CH - Congenital Hypothyroidism	↓ T4 ↑ TSH
CAH – Congenital adrenal hyperplasia	↑ 17-OHP
CF - Cystic Fibrosis	Immunoreactive trypsinogen (IRT) + IRT or DNA
BIOT - Biotinidase Deficiency	Biotinidase colourimetric assay
GALT – Galactosemia	Elevated galactose Decreased GALT enzyme activity
HL - Hearing Loss	Otoacoustic Emission Testing Auditory Brainstem Response Tests
SCID – Severe Combined Immunodeficiencies [±]	Absence of T-cell excision repair circles
Hemoglobinopathies [±]	Hb Electrophoresis
Critical congenital heart disease [±]	Pulse Oximetry
MPS1 – Muccopolysaccharidosis Type 1 [±]	Iduronidase enzyme activity
Pompe Disease (GSD Type 2) [±]	Alpha-glucosidase enzyme activity
XL-ALD – X-linked adrenoleukodystrophy [±]	↑ Very long-chain fatty acids
SMA – Spinal muscular atrophy [±]	Homozygous deletion of exon 7 in SMN1

[*] Adapted from Watson et al. Genet Med 2006:8 (Watson et al., 2006)
[±] Included on the ACMG Recommended Uniform Screening Panel (Watson et al., 2006) but not tested for by Newborn Screening Manitoba

1.4 Tandem mass spectrometry

MS/MS has become the standard technique for analyzing NBS bloodspot cards after being demonstrated to be highly effective at detecting IEMs (Millington, Kodo, Norwood, & Roe, 1990). MS/MS is a much more efficient technique for analysis of the newborn bloodspot card compared to the "one test – one condition" framework of previous analytic methods. Unlike past assays, MS/MS allows for multiple IEMs to be rapidly screened using a single automated run (Millington et al., 1990). MS/MS tests for abnormal biochemical analyte levels and the presence of unusual compounds to determine if the pattern is consistent with an IEM.

As the name suggests, tandem mass spectrometry involves the use of two mass spectrometer chambers connected by a collision cell (Banta-Wright & Steiner, 2004). In the first chamber, electrospray ionization is used to separate compounds based upon their mass-charge ratio (m/z) (Chace, Kalas, & Naylor, 2003). Smaller and lighter molecules move faster through the mass spectrometer than larger and heavier molecules. As the compound passes through the collision cell, a noble gas such as Argon is used to fragment the compound into smaller ionized molecules (Pandor et al., 2004). These components then pass through a second mass spectrometer that is able to qualitatively identify the component as well as quantify the amount of analyte present in the sample (Banta-Wright & Steiner, 2004). The output reported by a computer program is then compared to control values to determine deviations from normal (Banta-Wright & Steiner, 2004).

Samples may be flagged as a high-risk result for an IEM based upon the concentration and category of abnormal analyte identified. An abnormal concentration of one or more amino acids may be indicative of an aminoacidopathy, whereas an abnormal acylcarnitine profile may indicate an organic acidemia or a fatty acid oxidation defect (Banta-Wright & Steiner, 2004).

The conditions on NBS indicated by these abnormal analytes are summarized in Tables 1.2 and 1.3. Amino acids and acylcarnitines are both important for energy synthesis and metabolism making them ideal biochemical markers for IEMs. Amino acids are subunits of protein and may have a toxic effect if they are unable to be broken down or converted into a different form by an enzyme. Acylcarnitines are fat molecules composed of varying lengths of carbon chains attached to a transporter molecule, carnitine. Carnitines have an integral role in mitochondrial oxidation and transport of fatty acids (Hoppel, 2003). Overall, MS/MS is an important first-tier test that uses biochemical markers to identify individuals at risk of having an IEM.

After MS/MS identifies a positive result, second-tier testing is performed on the original bloodspot card. Second-tier testing screens for the presence of additional metabolites that may either support or refute a positive first-tier result (Chace et al., 2003). This additional step is important because it allows for more inclusive cut-off values for first-tier tests while eliminating results influenced by environmental and nutritional factors (Chace et al., 2003). Thus, it increases the specificity of NBS without compromising its sensitivity. Although more accurate, these tests are not the primary method of screening because they may be more expensive, complex, or time-consuming (Chace et al., 2003). Importantly, second-tier testing is performed before a positive NBS result is released. Confirmatory diagnostic testing is still required before a diagnosis of an IEM is made and may involve biochemical testing of blood and urine, enzyme assays, infection screening, and/or molecular testing.

Table 1.2: Aminocidopathies detected by Newborn Screening Manitoba [*]

Amino Acid Analyte	Change	Indication
Phe	↑	PKU - Phenylketonuria
Tyr	↑	TYR - Tyrosinemia
Met	↑	HCY - Homocysteinuria
Cit	↑	CIT - Citrullinemia ASA - Argininosuccinic acidemia
Leu Ile	↑	MSUD - Maple Syrup Urine Disease

[*] Adapted from ACMG (ACMG, 2001)

Table 1.3: Fatty acid oxidation defects and organic acidemias detected by Newborn Screening Manitoba [*]

Acylcarnitine Analyte	Change	Indication
C0	↓	CUD - Carnitine uptake defect
C0	↑	CPT-I - Carnitine Palmitoyl Transferase 1A Deficiency
C2 C3	↑	PA - Propionic acidemia MMA - Methylmalonic acidemia MCD - Multiple carboxylase deficiency
C4	↑	SCADD - Short chain acyl-CoA dehydrogenase deficiency
C4-DC		PA - Propionic acidemia MMA - Methylmalonic acidemia
C5	↑	IVA - Isovaleric acidemia
C5-DC C5:C8	↑	GA1 - Glutaric acidemia type 1
C5-OH	↑	3-MCC deficiency - 3-methylcrotonyl-CoA carboxylase deficiency HMG deficiency - 3-hydroxy-3-methylglutaryl-CoA lyase deficiency BKT deficiency - ß-Ketothiolase deficiency
C6 C8 C10:1	↑	MCADD - Medium chain acyl-CoA dehydrogenase deficiency
C10:2	↑	DE RED - 2,4-dienoyl-CoA reductase deficiency [±]
C12:1 C14 C14:1 C14:2	↑	VLCADD - Very long chain acyl-CoA dehydrogenase deficiency
C16	↓	CPT-I - Carnitine Palmitoyl Transferase 1A Deficiency
C16-OH	↑	LCHADD - Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency TFP deficiency - Trifunctional protein deficiency
C18:1	↓	CPT-I - Carnitine Palmitoyl Transferase 1A Deficiency

[*] Adapted from ACMG (ACMG, 2001)
[±] Secondary condition according to the ACMG Recommended Uniform Screening Panel (Watson et al., 2006)

Overall, MS/MS has facilitated the expansion of aminoacidopathies, organic acidemias, and fatty acid oxidation defects that can be detected by NBS. Currently, advances in molecular genetics and next-generation sequencing also promise to drastically revolutionize the way that NBS is performed. With this exciting future direction on the horizon, it is imperative to critically evaluate the benefits and limitations of each new test being added to NBS and consider challenges in expansion.

1.5 New tests and future directions for newborn screening

In the future, NBS has the potential to detect a wide array of Mendelian disorders through the use of molecular techniques such as targeted sequencing, multigene panels, and whole exome/genome sequencing. The list of conditions detected by NBS is continually expanding in an effort to keep up with these rapid advances in technology, but the limiting step continues to be suitability of these conditions for a population wide screening program. The Recommended Uniform Screening Panel (RUSP) is a list of disorders that have been systematically reviewed by experts and recommended to be included on all NBS programs (U.S. Department of Health Resources & Services Administration, 2018). Barring limitations in availability of resources between each independently state/provincially run NBS program, the RUSP attempts to minimize variability in NBS by standardizing what congenital conditions are screened across North America.

The RUSP is determined by the Advisory Committee on Heritable Disorders in Newborns and Children, which is composed of representative organizations like ACMG. Conditions that are being considered for addition to the RUSP must be nominated by a multi-disciplinary team then reviewed by a panel designated by the advisory committee (U.S.

Department of Health Resources & Services Administration, 2018). Advocacy groups, professional organizations, and individuals with a vested interest are usually the driving force of these efforts and have a heavy influence on what conditions are reviewed (U.S. Department of Health Resources & Services Administration, 2018). When a nominated condition is being evaluated, a quantitative score is calculated based upon how well it satisfies the principles of a screening program outlined by Wilson and Jungner (Wilson & Jungner, 1969). The highest possible score is 2100, with the weighting being evenly distributed between the natural history of the disorder, efficacy of the screening test, and suitability of available treatment (Goldenberg et al., 2016; U.S. Department of Health Resources & Services Administration, 2018; Watson et al., 2006). A systematic review of the literature is performed and each criterion that is satisfied adds to the cumulative score. If a condition surpasses the threshold of 1200, it is deemed appropriate to be added to the RUSP as a primary target for NBS (U.S. Department of Health Resources & Services Administration, 2018; Watson et al., 2006). Those that fall between 1000-1200 are suitable as secondary targets (U.S. Department of Health Resources & Services Administration, 2018; Watson et al., 2006). Lastly, conditions that score below 1000 are not included on the RUSP until further supportive evidence is available (U.S. Department of Health Resources & Services Administration, 2018; Watson et al., 2006). Stringent guidelines for RUSP approval ensure that as NBS continues to expand, all included conditions are amenable to the principles of a population-wide screening program.

Some recently approved tests utilize MS/MS and simply requires the inclusion of an additional analyte during analysis. For example, X-linked adrenoleukodystrophy (XL-ALD) was added to the RUSP in 2015 and uses very-long chain fatty acids as a reliable first-tier test (Kemper et al., 2017).

It is also becoming more common to directly measure enzyme activity as a first-tier test and follow-up with molecular studies to confirm the diagnosis. Pompe disease, which was added to the RUSP in 2013 (U.S. Department of Health Resources & Services Administration, 2018), is detected by assaying alpha-glucosidase enzyme activity. Similarly, mucopolysaccharidosis type 1 (MPS1) was approved in 2015 and is screened by iduronidase enzyme activity (U.S. Department of Health Resources & Services Administration, 2018). One potential challenge with enzyme based first-tier tests, such as seen with VLCADD, is interpretation of decreased enzyme activity in combination with poorly characterized variants of uncertain significance (Hesse et al., 2018). Similar challenges have been observed for Fabry disease, where pseudo deficiency of enzyme activity and decreased sensitivity for heterozygotes complicate interpretation of NBS results. Females with Fabry disease develop symptoms yet have residual enzyme activity that falls within the lower levels of normal in the general population. This overlap can cause approximately 80% of newborn females with Fabry disease to have a false negative result (Lu et al., 2018). Recurrent mutation panels as a first-test have been demonstrated to improve sensitivity of NBS for Fabry disease (Lu et al., 2018), however, it still has not received approval for the RUSP and highlights a difficult challenge in enzyme based screening.

In the future, there will likely continue to be a shift towards molecular methods as a first-tier test in NBS. For example, spinal muscular atrophy (SMA) was approved for the RUSP in July 2018 after being declined in 2008 (U.S. Department of Health Resources & Services Administration, 2018). Screening for SMA is performed by detecting a homozygous deletion of exon 7 in the SMN1 gene (Kraszewski et al., 2018). Pilot programs are also exploring the use of much broader molecular tests like whole exome sequencing (WES) for the purposes of NBS. The **N**ewborn **S**equencing **I**n **G**enomic medicine and public **H**eal**T**h (NSIGHT) Consortium

recently established a randomized clinical trial called the BabySeq Project (Holm et al., 2018). This complex pilot program is currently in progress and follows healthy and sick newborns who are randomly assigned to standard of care NBS with/without trio WES (Holm et al., 2018). The impact of WES on the newborn's health, psychosocial issues of parents, and economic burden on the healthcare system will be compared between each group (Holm et al., 2018).

Although this project is still many years away from influencing policy change, it may provide the basis of a new model which could reshape NBS. In their study design, every family meets with a genetic counsellor to discuss informed consent and is required to complete a survey demonstrating understanding of the salient implications of WES (Holm et al., 2018). Importantly, this test is in addition to, not in replacement of, the dried bloodspot card analysis using MS/MS. Each family then has a results session with a geneticist and/or genetic counsellor to disclose any positive results, carrier status, and pharmacogenomic variants (Holm et al., 2018). In total, 954 genes are reported based upon published guidelines for disclosing results of newborn genomic sequencing (Ceyhan-Birsoy et al., 2017). This new proposed model of NBS will require a tremendous amount of support from geneticists and genetic counsellors in order to be sustainable in the future.

The possible shift towards precision medicine in NBS over the next several decades presents many complex challenges that need to be carefully considered. Potential logistical challenges include the security of data, feasibility and duration of storage, ownership of health information, reporting and reclassification of variants of uncertain significance, reinterpretation of raw data, and cost of infrastructure. Other possible ethical and psychosocial challenges may include the conflict of carrier screening with the traditional goals of NBS, protection of this information from insurance companies, interpretation of poorly defined molecular variants and

uncertain prognosis in an otherwise healthy individual, and management of an incidental diagnosis in an asymptomatic or subclinical parent. Lastly, education of the general public and lack of informed consent have always been challenges with NBS and will continue to persist in the future. False positive or inconclusive results will only become more common as NBS becomes more complex. The impact of these results needs be addressed by healthcare providers and NBS programs.

1.6 The psychosocial impact of a false positive result

The newborn period, an already vulnerable time for most parents, is made even more difficult due to the psychosocial impact of a false positive NBS result. Throughout this thesis, the term 'psychosocial' refers to a combination of factors in response to health information, including an individual's emotional reaction, psychological defense mechanisms, and changes in social support and family dynamics. False positive results are common and occur in approximately one in every 300 infants (Schulze et al., 2003). In contrast, Cadham Provincial Laboratory reports that one in every 1000 babies born each year in Manitoba are diagnosed with an IEM (Cadham Provincial Laboratory, 2019), yet some estimates suggest that there are approximately eight false positives per true positive detected through NBS (Hewlett & Waisbren, 2006). This difference means that numerous families are faced with the uncertainty of a life-changing diagnosis within days of their child being born.

Until a diagnosis is established or ruled out, families with a false positive or inconclusive result may find themselves in the unique position of the "patient-in-waiting" – unsure if they are healthy or actually sick (Timmermans & Buchbinder, 2010). The patient-in-waiting undergoes extensive medical surveillance aimed at secondary prevention, even though they are unsure if

they truly have the disease (Timmermans & Buchbinder, 2010). Essentially, the individual is well enough that there is no tangible change in their health, yet they are treated as an at-risk individual that requires careful monitoring and/or treatment. It is possible that this contradiction could lead to difficulty believing that the risk is valid or difficulty accepting that they are no longer at risk once a diagnosis has been ruled out (Timmermans & Buchbinder, 2010). Consequently, the uncertainty surrounding their state of health may shape their personal identity and other aspects of their lifestyle, both in the interim and long-term (Timmermans & Buchbinder, 2010).

Many studies have demonstrated the significant psychological impact of a false positive result for NBS (Cavanagh, Compton, Tluczek, Brown, & M.Farrell, 2010; Dixon, Shackley, Bonham, & Ibbotson, 2012; Gurian, 2006; R.Z. Hayeems et al., 2017; Robin Z. Hayeems et al., 2017; Robin Z Hayeems, Miller, Barg, Bombard, & Kerr, 2016; Hewlett & Waisbren, 2006; Moody, Atkinson, Kehal, & Bonham, 2017; O'Connor et al., 2018; Perobelli et al., 2009; Siddiq et al., 2016; Tu, He, Chen, Shi, & Li, 2012). Quantitative studies (Cavanagh et al., 2010; Dixon et al., 2012; Gurian, 2006; R.Z. Hayeems et al., 2017; Robin Z. Hayeems et al., 2017; Robin Z Hayeems et al., 2016; O'Connor et al., 2018; Perobelli et al., 2009; Tu et al., 2012) have used validated measures such as the Parenting Stress Index (PSI) (Abidin, 1995) and Depression, Anxiety, and Stress Scale (DASS) (P. F. Lovibond & Lovibond, 1995) to demonstrate that parents of children with a false positive NBS result have a statistically significant increase in difference in anxiety and stress compared to those with a negative result. Qualitative studies (Dixon et al., 2012; Gurian, 2006; Hewlett & Waisbren, 2006; Moody et al., 2017; Perobelli et al., 2009; Siddiq et al., 2016) have further described this psychosocial impact and suggested possible difficulty of new parents bonding with their newborn. Other themes that have

commonly been reported across multiple studies include seeking information and seeking social support as a way of coping (Gurian, 2006; Hewlett & Waisbren, 2006; Schmidt et al., 2012). Additionally, studies have demonstrated that parents may think that their child has a health problem when they are actually healthy, as shown by higher rate of hospitalization for unrelated causes within the first year of life following resolution of a false positive NBS result (R.Z. Hayeems et al., 2017; Karaceper et al., 2016).

Parental education has been shown to be an effective means of reducing the psychosocial impact of a positive NBS result. An interview of mothers with a false positive result for an IEM showed that understanding the correct reason of why confirmatory testing was required was associated with less stress compared to mothers who did not know or could not remember this information (Gurian, 2006). Parents have a desire for information about NBS throughout the process (Ciske et al 2001) and it has been shown that half of mothers with a false positive result did not feel that important information about NBS was adequately explained to them (Clemens et al 2000). Despite several studies suggesting that further research is required on how to improve communication and education of NBS (Araia et al., 2012; Hewlett & Waisbren, 2006; Schmidt et al., 2012), recommendations for communicating this information have not been described in a Canadian population. This information is imperative in reducing the psychosocial impact of a positive NBS result. The NBS model in Manitoba, which also serves parts of Ontario, Nunavut, and Saskatchewan, provides an excellent opportunity to study health service delivery and quality of education given to parents whose child screens positive for an IEM.

1.7 Newborn screening in Manitoba

The NBS algorithm in Manitoba begins with collection of a dried blood spot sample within the first five days of birth after the baby's metabolism has been challenged. Consent for NBS is assumed meaning that parents must deliberately opt-out if they do not wish for their child to be screened. All bloodspot cards in Manitoba are processed though Cadham Provincial Laboratory and all positive results requiring a geneticist and/or genetic counsellor are facilitated through the Genetics & Metabolism Program at Health Sciences Centre in Winnipeg.

As shown in Figure 1.1, negative NBS results are not called out since the vast majority of families fall into this category. If there is a positive result, however, Cadham Provincial Laboratory will contact the retrieval site to notify the family. Parents of the child will then be called by either a geneticist and/or genetic counsellor from the Genetics & Metabolism Program in Health Sciences Centre, Winnipeg, or by their local nursing station in remote communities. Differences in which healthcare provider initiates contact are based upon geographic location, availability of resources, and urgency of the indication. Based upon this variability, it is possible that the explanation given to these families about the meaning and interpretation of a positive NBS result may differ depending on who delivered this information.

Parents may be instructed to bring their newborn to the Emergency Department immediately in order to treat or prevent a potential metabolic crisis. A thorough medical and family history is taken relating to the condition, and at the same time, they often stop breast feeding and begin dietary intervention until an IEM is ruled out. Importantly, the time between screening positive and having an IEM ruled out or diagnosed can take several weeks to months. There are three main outcomes to a positive NBS result. If a true positive result is established, the child continues being treated and receiving ongoing monitoring by a metabolic geneticist and

genetic counsellor. In the vast majority of cases, however, confirmatory testing indicates that the child is healthy and no longer requires follow-up. In these instances, the prior prophylactic management may be confusing to the parent. Very rarely, confirmatory testing may still be inconclusive. The patient continues to be treated and monitored as if they have the condition, but it is uncertain whether or not they are asymptomatic because of prophylactic treatment, because they do not actually have the disease, or because they have a mild genetic variant. This thesis explores the experiences of families with a positive result who met with the genetics team.

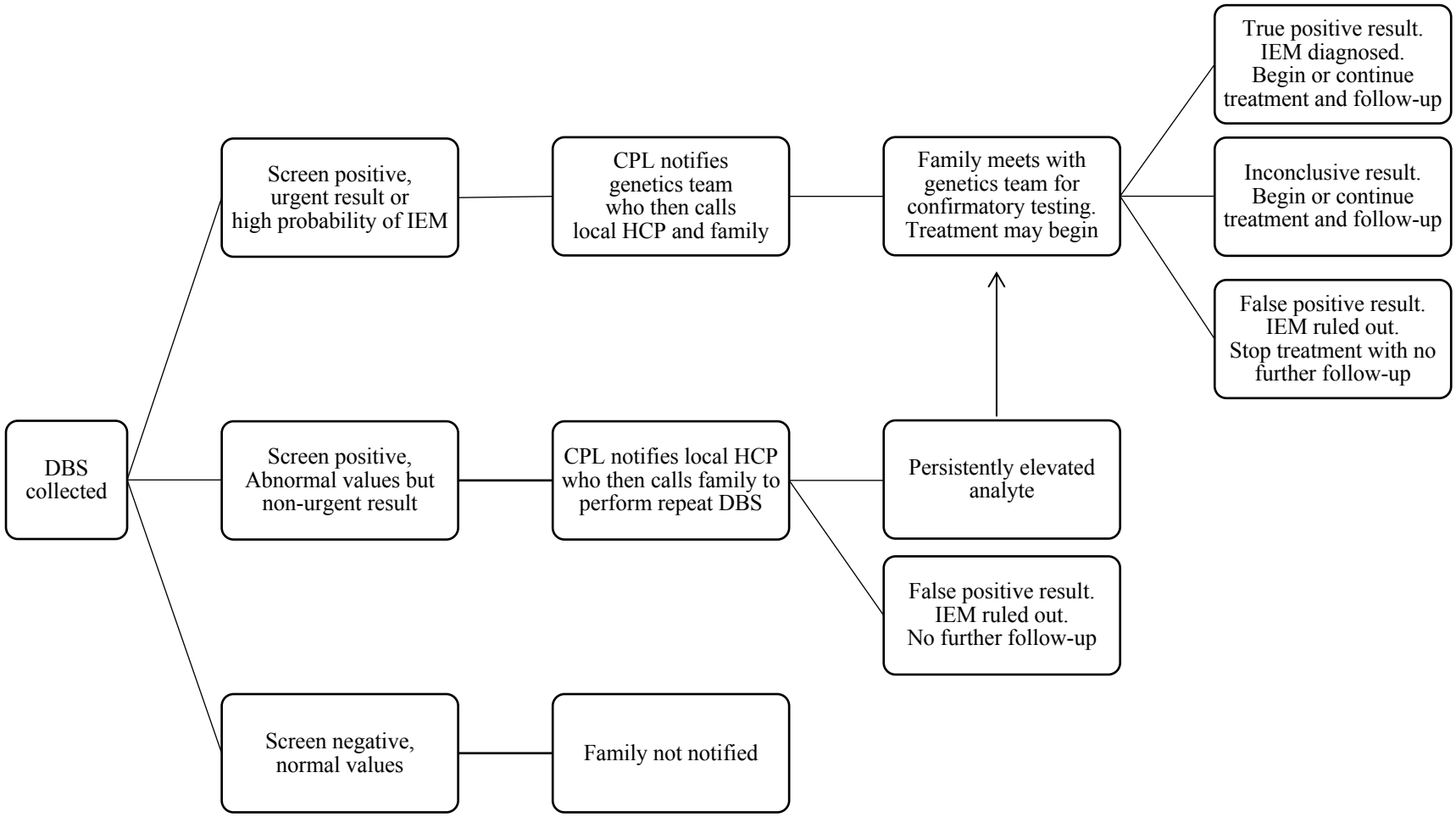

Figure 1.1: Manitoba's algorithm of newborn screening process for inborn errors of metabolism.
DBS – dried blood spot, CPL – Cadham Provincial Laboratory, HCP – healthcare provider, IEM – inborn error of metabolism

1.8 Thesis rationale

In studies that have described the psychosocial impact of a false positive NBS result, the authors make general claims that improved education of the NBS process is an important factor to mitigating these risks. There is a need for increased understanding of how families who screened positive for an IEM use and benefit from such educational resources.

Winnipeg Regional Health Authority (WRHA) has come up with its own resources to provide to these families to help them during this sensitive period. Other publicly available resources on the internet also exist, designed with the general population in mind. Many of these existing materials do not include key messages to educate the public on NBS for IEMs (Araia & Potter, 2011). In contrast, highly technical Action Sheets from the American College of Medical Genetics are available for physician reference but do not address the approach a clinician should take to counteract the potential psychological impact of receiving a positive NBS result (ACMG, 2001). The relative importance to parents of these key messages, congruence of information with the needs of these families, and recommendations for delivering this information have not yet been described in a Canadian population.

This current research aims to provide empirically supported directions for health service delivery and educational resources based on an expanded NBS program that has been in effect for several years. Chapter Two describes the research design and methodology for achieving this goal. In the first phase of this project, it was hypothesized that having an appointment with a geneticist and/or genetic counsellor following a false positive NBS result for an IEM was correlated with increased knowledge of NBS and decreased psychological impact. The results from this survey are presented in Chapter Three. The second phase of this project was exploratory and sought to provide qualitative directions to improve delivery of education on

NBS. The results from these interviews are presented in Chapter Four. Based on these findings, modifications to health service delivery of NBS and the content and dissemination of pre-existing educational resources are recommended in order to improve the follow-up care provided by geneticists and genetic counsellors. These proposed strategies are described in Chapter Five and Chapter Six details closing remarks.

CHAPTER TWO:

RESEARCH DESIGN & METHODOLOGY

2.1 Research design

Parents of children who had expanded NBS done by Cadham Provincial Laboratory in Winnipeg, MB between 2011-2017 were invited to participate in an online survey and telephone interview. Nine-hundred-and-four children had a positive NBS result for an IEM during this period, of which 482 met inclusion criteria. Participants met inclusion criteria if their child had (1) screened false positive and did not have an appointment with a geneticist/genetic counsellor, (2) screened false positive and had an appointment with a geneticist/genetic counsellor, or (3) screened true positive and had been diagnosed with an IEM by a geneticist/genetic counsellor. All screening results during this period were resolved and children either had a confirmed diagnosis or were determined to not have an IEM.

Inuit children who had a prevalent CPT1A DNA variant (n=420) were excluded from the study prior to generating a mailing list because they are handled differently than other positive NBS for IEMs. The p.P479L variant is common in the Inuit population of Canada and has a mutant allele frequency of 0.81 (C. Greenberg et al., 2009). This variant results in only a slight decrease in beta-oxidation activity despite a significant decrease in CPT1A enzyme activity in fibroblasts. This group would have been likely to skew survey results since such individuals are common in Manitoba and are expected to have transient biochemical changes that do not necessitate treatment or follow-up.

Clinicians with the WRHA Genetics & Metabolism Program were asked to forward the package of study materials to families whose child met inclusion criteria (n=482). The mailed-out package included an introduction letter with a link to the online survey, an interview consent form, and an unconditional incentive in the form of a one dollar lottery scratch card (see Appendix for study materials).

Participants who were interested in a follow-up telephone interview opted-in by contacting the researchers using the provided information in the mailed-out package and at the end of the online survey.

This study was approved by the Research Ethics Board at University of Manitoba (Approval number HS21863/H2018:133) and the Pediatric Research Coordinating Committee at Health Sciences Centre (Approval number 2018:065).

2.2 Survey

The survey was consistent across all groups. It included questions on parental demographic characteristics, understanding of the newborn screening process, and utility of NBS educational tools that had been previously accessed. Since we did not have access to participants' health information, all respondents self-selected their NBS outcome based upon their response to a clinical vignette and direct questions.

The survey was designed to take approximately 10-15 minutes to complete. It was piloted on a small group of staff from the WRHA Genetics & Metabolism Program using the Training Server in REDCap (Harris et al., 2009). Feedback was elicited to assess the amount of time required to complete answers and modify the survey in order to improve comprehension of questions. The final version of the survey, which was compatible with mobile devices, was

hosted using the Survey Server in REDCap (Harris et al., 2009). Data collection occurred from May 2018 – August 2018.

The short-form version of the Depression, Anxiety, and Stress Scale (DASS-21) was integrated as part of the online survey. This scale is a publicly available, validated quantitative measure of the emotional states of depression, anxiety, and stress and was used to quantify the psychosocial impact of a positive NBS result for an IEM (Henry & Crawford, 2005; P. F. Lovibond & Lovibond, 1995). The DASS-21 is a 21-item self-reported, short-form version of Lovibond & Lovibond's (1995) original DASS tool (S. H. Lovibond & Lovibond, 1995). The DASS-21 is an effective psychometric measure and can reliably discriminate between several emotional states using a tripartite model that includes increased negative affectivity, decreased positive affectivity, and physiological hyperarousal (P. F. Lovibond & Lovibond, 1995). Final scores and recommended cut-offs for conventional severity labels (normal, mild, moderate, severe, extremely severe) were calculated according to the recommended score guide (S. H. Lovibond & Lovibond, 1995).

2.3 Interviews

The interview explored the relative importance of messages to convey to parents in NBS educational tools; gathered information on an optimal delivery model for these educational tools; and provided insight as to when in the NBS process families would benefit most from this information. All recruited participants were provided with an interview consent form in the initial mail-out package and were invited to participate on an opt-in basis by contacting the researchers. All inquiries were responded to using a standardized email with minimal modification based on context of the original message. Seventeen participants provided their

information to be contacted for a semi-structured telephone interview. An effort was made to schedule interviews with all participants who provided their information, however, six of those individuals could not be reached despite multiple attempts at contact. Eleven participants completed the interview in order to achieve theoretical sufficiency, defined as a lack of significant emergent data from incoming interviews (Francis et al., 2010). All interviewed individuals were mailed a $10 Tim Horton's gift card as a show of appreciation for their time.

Pre-interview training was provided by a senior researcher (KR) with qualitative research expertise. Training followed best practices described by Glogowska et al (2011) and was necessary to practice role-plays, improve rigor, and gauge when sufficient information had been collected (Glogowska, Young, & Lockyer, 2011). Additionally, a practice interview was conducted with a colleague to rehearse questioning style and become familiarized with the recording software. Feedback was also elicited to improve interview style and assess the clarity of questions. Where necessary, the interview guide was deviated from in order to establish rapport, demonstrate responsiveness, and express regard for the interviewee (Drabble, Trocki, Salcedo, Walker, & Korcha, 2016). Examples of possible deviations included brief small-talk, orienting statements, active listening, probing questions, supportive vocalizations, validation, non-judgmental responses, and statements of appreciation for participation (Drabble et al., 2016). These strategies maintained a natural flow to the conversation while still following the structure of the interview guide.

Interviews were semi-structured and were an average of 54 minutes in length (minimum 39 minutes, maximum 66 minutes). All interviews were audio-recorded and were conducted by RD using BlueJeans Meeting software (Blue Jeans Network, Inc, 2019). This audio-only medium offered logistical advantages in comparison to face-to-face interviews given the large

coverage area for the Manitoba newborn screening program. A standardized reminder email was sent to interview participants 48 hours in advance of the scheduled interview time with instructions for accessing BlueJeans through their smart phone, tablet, or computer with microphone.

Interpretive description is one of the most widely used analytic strategies for health research and was used for analysis of interview data (Thorne, Kirkham, & MacDonald-Emes, 1997). This qualitative method is based on a constructionist framework and is intended to be flexible in its theoretical approach (Braun, 2011; Kahlke & Hon, 2014; Thorne, Kirkham, & Flynn-magee, 2004). Interpretive description assumes that the experiences reported by participants are subjective and that there is not one absolute truth (Kahlke & Hon, 2014). It allows researchers to explore experiences of a clinical phenomenon while providing commentary on why the observed themes may occur (Thorne et al., 2004).

Several steps were taken to ensure rigor and improve trustworthiness in the qualitative research process. A reflexivity journal was used before and after the interview and throughout the analytic process. This approach ensured consistency across interviews and promoted accountability in data collection. All interviews were manually transcribed by RD and checked against the recordings for accuracy. This process facilitated immersion in the data before beginning analysis. Coding was performed using Dedoose ("Dedoose Version 8.1.8, web application for managing, analyzing, and presenting qualitative and mixed method research data," 2019). The codebook was initially created by RD using inductive thematic analysis at a latent level. During first cycle coding, a list of codes was generated *in vivo* as they emerged in transcripts. The codebook was then revised by RD to refine codes and enhance organization. During second cycle coding, all transcripts were independently analyzed by two authors (RD and

PF) according to the revised codebook. Multiple coders ensure consistency and accuracy in qualitative analysis. Any discrepancies in coding were resolved through conversation.

CHAPTER THREE:

SURVEY RESULTS

3.1 Overview

Nine-hundred and four children had a positive NBS result for an IEM between 2011-2017, of which 482 met inclusion criteria and were mailed an invitation package. Seventy-one invitation packages were returned to sender or undeliverable (14.7%) because of an outdated or inaccurate last-known mailing address. Twenty-five individuals participated in the online survey during the data collection period but only 21 surveys were completed (5.1% response rate). Four survey results were excluded from analysis because the participants did not complete the vast majority of questions. A flowchart summarizing the study design is depicted in Figure 3.1. Due to the poor response rate, this survey was not sufficiently powered to make statistical comparisons. It did, however, allow for a more detailed understanding of the demographic characteristics of the interviewed sample. It also provided a limited understanding of respondents' knowledge of NBS and the psychological impact of a positive NBS result.

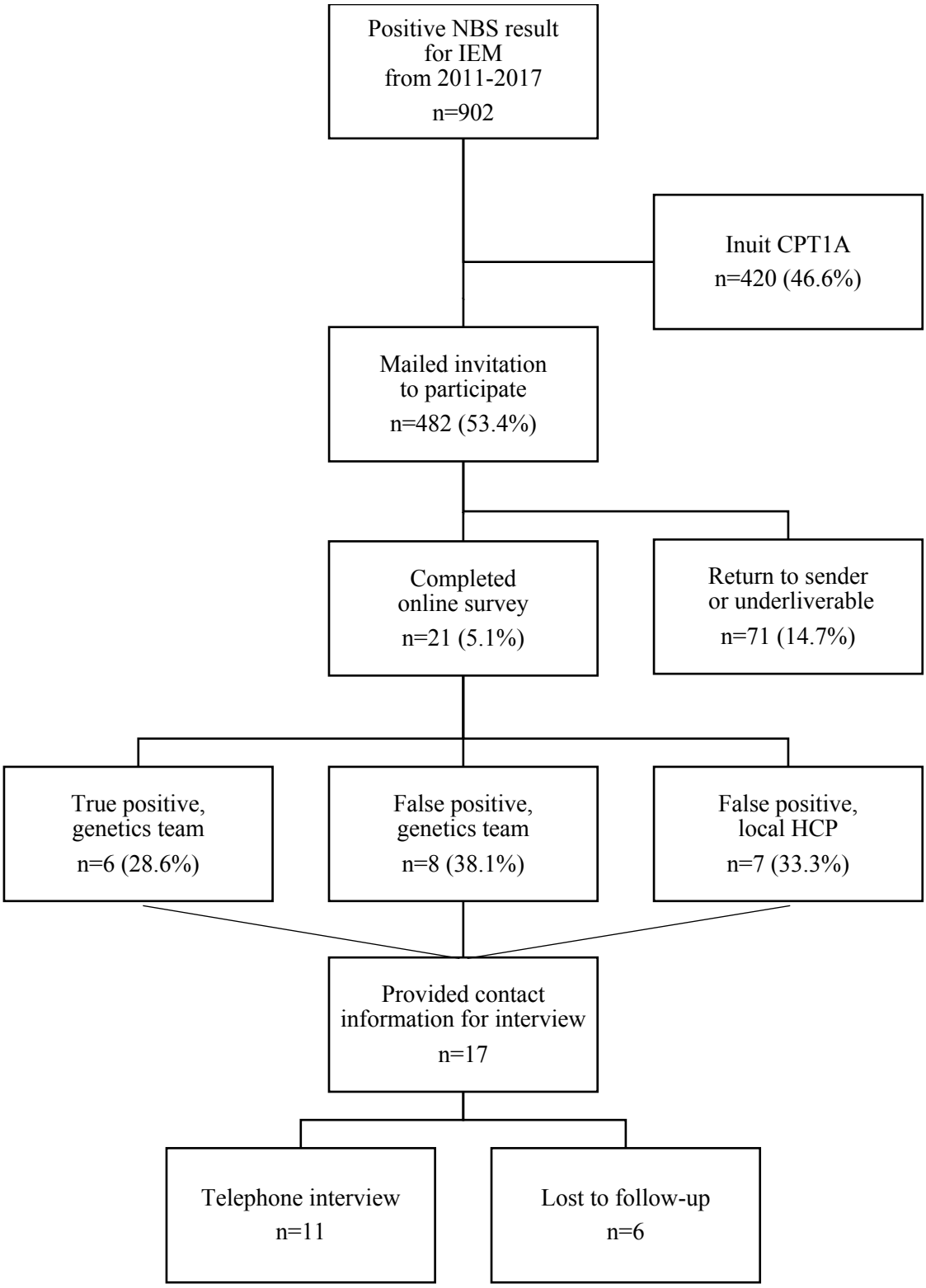

Figure 3.1: Flowchart of data collection

3.2 Demographic characteristics

The demographic characteristics of survey respondents are presented in Table 3.1. Respondents' newborn screening status was classified as true positive or false positive based on their response to the question, "Was your child later diagnosed with a genetic disease after the newborn screening result for which they are on a special formula, diet, medication, etc to prevent further complications". Their responses were also confirmed by having them select a scenario that best matched their outcome to the newborn screening process. Seven respondents (33.3%) had a true positive result and 14 respondents (66.7%) had a false positive result. In both groups, the year they reported receiving their NBS result was approximately evenly distributed.

The majority of respondents in both groups were from Manitoba with only one respondent in each group from Ontario. No respondents identified as living in Saskatchewan or Nunavut, although these provinces are included in the catchment area of Manitoba's newborn screening program. Eleven respondents with a false positive result (78.6%) and three respondents with a true positive result (57.1%) reported that their child with a positive screen was not their first born, indicating that they most likely had previous exposure to NBS in some capacity.

The sampled population was highly educated and tended to be in a higher income bracket. All but one respondent had received post-secondary education, with five individuals in each group having a graduate or professional degree (35.7% of those with a false positive result and 71.4% of those with a true positive result). Ten respondents with a false positive result (71.4%) and all respondents with a true positive result had a household income greater than $75,000 CAD. Twelve respondents with a false positive result (85.7%) and all respondents with a true positive result indicated that English was their native language.

Table 3.1: Demographic characteristics of survey respondents

	False Positive n = 14	True Positive n = 7
Characteristics	**n (%)**	**n (%)**
Province		
Manitoba	13 (92.9)	6 (85.7)
Ontario	1 (7.1)	1 (14.3)
Nunavut	0 (0)	0 (0)
Saskatchewan	0 (0)	0 (0)
City Size		
Urban	8 (57.1)	6 (85.7)
Rural	6 (42.9)	1 (14.3)
Year of NBS Result		
2011	1 (7.1)	1 (14.3)
2012	3 (21.4)	0 (0)
2013	1 (7.1)	1 (14.3)
2014	3 (21.4)	0 (0)
2015	1 (7.1)	2 (28.6)
2016	1 (7.1)	1 (14.3)
2017	4 (28.6)	2 (28.6)
Maternal Age		
≤ 25	3 (21.4)	0 (0)
26 – 30	2 (14.3)	5 (71.4)
31 – 35	7 (50.0)	2 (28.6)
36+	2 (14.3)	0 (0)
First Child		
Yes	3 (21.4)	3 (42.9)
No	11 (78.6)	4 (57.1)
Gestational Age at Delivery		
< 35 weeks	0 (0)	1 (14.3)
35+ weeks	14 (100)	6 (85.7)
Education		
Highschool or less	1 (7.1)	0 (0)
College or CEGEP	2 (14.3)	1 (14.3)
Undergraduate	6 (42.9)	1 (14.3)
Graduate or professional	5 (35.7)	5 (71.4)
Income		
< $75,000	4 (28.6)	0 (0)
$75,000+	10 (71.4)	7 (100)
Native Language		
English	12 (85.7)	7 (100)
German / Russian	1 (7.1)	0 (0)
Mandarin	1 (7.1)	0 (0)

3.3 Perceived understanding of newborn screening

Participants' perceived understanding of newborn screening is represented in Table 3.2. Respondents with a false positive NBS result were stratified by the healthcare provider who coordinated their follow-up care during the confirmatory testing period. Six respondents (42.9%) had follow-up care provided by a local HCP such as a family doctor, nursing station, or midwife, whereas 8 respondents with a false positive result (57.1%) were seen directly by a geneticist or genetic counsellor. All respondents who were seen by a local HCP selected fully understanding that NBS was being performed on their child. In contrast, of those seen by the genetics team, 71.4% who had a false positive result and 71.4% who had a true positive result fully understood this same message.

Although the majority of respondents in all groups either slightly or fully understood why NBS was being performed on their child, they mostly appeared to have a poor understanding of the details of their result when asked more specific questions. In total across all groups, 66.7% of participants had minimal to no understanding of the possible outcomes of NBS before testing was performed. Three respondents in both false positive groups (50% seen by local HCP, 37.5% seen by the genetics team) were unable to recall which IEM their child had a positive NBS result for, despite selecting from a list with the acronym and full names of all the IEMs tested for. Concerningly, one parent who had a true positive NBS result and was seen by the genetics team did not know what IEM their child was diagnosed with. Across all groups, selected IEMs included PKU, ASA, GA1, MCADD, VLCADD, and CUD.

Table 3.2: Participant understanding of newborn screening

	False Positive, Local HCP follow-up n = 6	False Positive, Geneticist / GC follow-up n = 8	True Positive, Geneticist / GC follow-up n = 7
	n (%)	n (%)	n (%)
I understood that newborn screening was being performed on my child			
Not at all	0 (0)	1 (14.3)	0 (0)
Minimally	0 (0)	0 (0)	0 (0)
Yes, slightly	0 (0)	1 (14.3)	2 (28.6)
Yes, fully	6 (100)	5 (71.4)	5 (71.4)
I understood the reason why newborn screening was being performed on my child			
Not at all	1 (16.7)	1 (12.5)	0 (0)
Minimally	0 (0)	0 (0)	1 (14.3)
Yes, slightly	0 (0)	4 (50)	2 (28.6)
Yes, fully	5 (83.3)	3 (37.5)	4 (57.1)
I understood the possible test results before screening was performed			
Not at all	2 (33.3)	2 (25)	1 (14.3)
Minimally	2 (33.3)	3 (37.5)	4 (57.1)
Yes, slightly	1 (16.7)	3 (37.5)	1 (14.3)
Yes, fully	1 (16.7)	0 (0)	1 (14.3)
IEM screened positive for			
I do not know	3 (50)	3 (37.5)	1 (14.3)
PKU	1 (16.7)	0 (0)	2 (28.6)
ASA	1 (16.7)	0 (0)	1 (14.3)
GA1	0 (0)	0 (0)	1 (14.3)
MCADD	0 (0)	1 (12.5)	2 (28.6)
VLCADD	0 (0)	1 (12.5)	0 (0)
CUD	1 (16.7)	3 (37.5)	0 (0)
I understood the specific genetic condition for which my newborn tested positive			
Not at all	2 (33.3)	4 (50)	6 (85.7)
Minimally	1 (16.7)	1 (12.5)	1 (14.3)
Yes, slightly	1 (16.7)	3 (37.5)	0 (0)
Yes, fully	2 (33.3)	0 (0)	0 (0)
I understood what this screening result meant			
Not at all	1 (16.7)	1 (12.5)	2 (28.6)
Minimally	2 (33.3)	3 (37.5)	3 (42.9)
Yes, slightly	1 (16.7)	4 (50)	1 (14.3)
Yes, fully	2 (33.3)	0 (0)	1 (14.3)

Abbreviations: PKU – Phenylketonuria, ASA – Argininosuccinic acidemia, GA1 – Glutaric acidemia type 1, MCADD - Medium chain acyl-CoA dehydrogenase deficiency, VLCADD – Very long chain acyl-CoA dehydrogenase deficiency, CUD - Carnitine uptake defect

Respondents had a poor understanding of the specific IEM that was being investigated in their child, as shown in Table 3.3. All respondents with a true positive result reported minimal to no understanding of the specific IEM that their child was diagnosed with following NBS. Likewise, of those with a false positive result, 50% who were seen by a local HCP and 62.5% who were seen by the genetics team had minimal to no understanding of the specific IEM. Participants had mixed responses for what their NBS result meant. Fifty percent of respondents in each false positive group and 71.9% of individuals with a true positive result had minimal to no understanding on this topic.

Educational resources are intended to help parents better understand the NBS process and their child's result. Almost all participants in each group had minimal to no understanding that these resources existed. Of those who were aware, over 50% learned of this through a clinician. Additionally, participants had mixed responses when asked if they found any resources to be useful. Of those who selected that resources were helpful to some degree, 50% of individuals accessed those resources online and searched for disease specific information. These findings are summarized in Figure 3.2.

Table 3.3: Patient access of newborn screening resources

	False Positive, Local HCP follow-up n = 6	False Positive, Geneticist / GC follow-up n = 8	True Positive, Geneticist / GC follow-up n = 7
	n (%)	n (%)	n (%)
I was aware that resources existed to help me understand the newborn screening process			
Not at all	3 (50)	4 (50)	1 (14.3)
Minimally	2 (33.3)	1 (12.5)	6 (85.7)
Yes, slightly	1 (16.7)	3 (37.5)	0 (0)
Yes, fully	0 (0)	0 (0)	0 (0)
I found the resources that I accessed to be useful			
Not at all	3 (50)	3 (37.5)	1 (14.3)
Minimally	0 (0)	3 (37.5)	3 (42.9)
Yes, slightly	3 (50)	2 (25)	3 (42.9)
Yes, fully	0 (0)	0 (0)	0 (0)

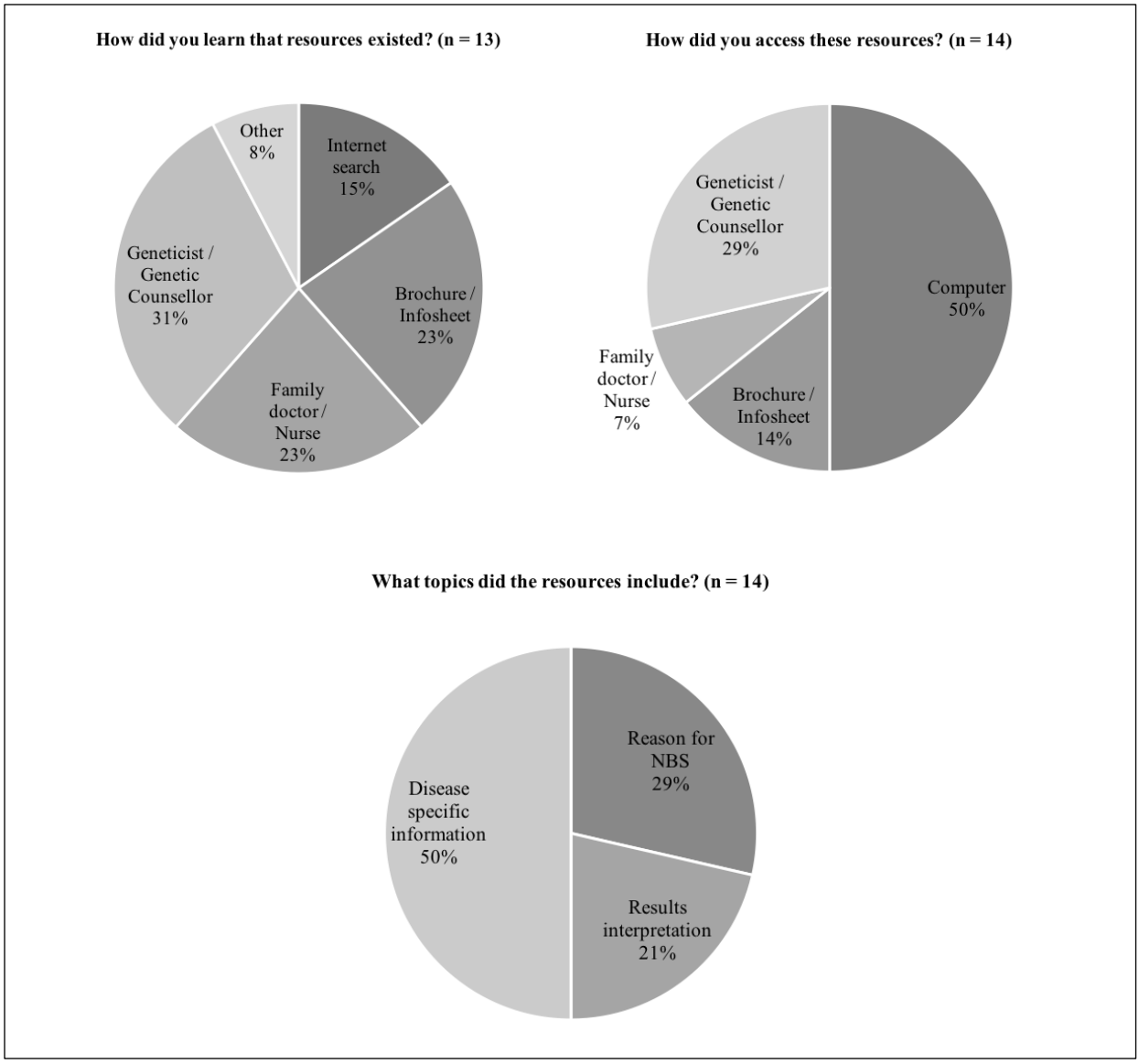

Figure 3.2: Patient access of NBS Resources

3.4 The psychological impact of a positive newborn screen

The psychological impact of a positive NBS result was assessed using the DASS21, a standardized measure of depression, anxiety, and stress. Final scores and recommended cut-offs for conventional severity labels (normal, mild, moderate, severe, extremely severe) were calculated according to Lovibond's score guide (S. H. Lovibond & Lovibond, 1995) and are summarized in Table 3.4. Although each outcome is unable to be accurately compared because of insufficient statistical power due to the small sample size, general trends between groups can be appreciated.

Individuals with a false positive NBS result who were seen in follow-up by the genetics team appeared to have slightly lower scores in all categories compared to those who were seen a by a local HCP. Participants with a false positive result seen by a local HCP scored normal/borderline mild for depression (μ=8.67, SD=9.52), normal/borderline mild for anxiety (μ=7.00, SD=9.61), and mild/borderline moderate for stress (μ=18.0, SD = 12.96). There was a large range of variability in each category within this group, with the minimum scores falling in the normal range and the maximum scores falling in the severe or extremely severe range. Participants with a false positive result seen by the genetics team scored normal for depression (μ=6.75, SD=5.23), normal for anxiety (μ=6.75, SD=7.70), and mild for stress (μ=16.5, SD=8.26). This group also had a large range of variability, with the minimum scores falling in the normal range and maximum scores falling in the moderate range for depression, extremely severe range for anxiety, and severe range for stress.

On average, individuals with a true positive result in which an IEM was diagnosed following NBS appeared to have higher scores in all categories compared to those with a false positive result. Participants with a true positive result scored mild for depression (μ=12.29,

SD=9.12), moderate for anxiety (μ=10.57, SD=8.46), and mild/borderline moderate for stress (μ=18.86, SD=10.70). There was also a large range of variability in each category, with the minimum scores falling in the normal range and the maximum scores falling in the extremely severe range. Across all groups, stress appeared to be the highest ranking score compared to anxiety and depression during the confirmatory testing period.

Table 3.4: DASS21 Scores

	False Positive, Local HCP follow-up n = 6				False Positive, Geneticist / GC follow-up n = 8				True Positive, Geneticist / GC follow-up n = 7			
	Mean	SD	Min	Max	Mean	SD	Min	Max	Mean	SD	Min	Max
Depression	8.67	9.52	0	24	6.75	5.23	0	16	12.29	9.12	2	30
Anxiety	7.00	9.61	0	22	6.75	7.70	0	22	10.57	8.46	0	24
Stress	18.0	12.96	4	40	16.5	8.26	4	30	18.86	10.70	4	36

CHAPTER FOUR:

INTERVIEW RESULTS

4.1 Overview

Of the 21 participants who completed the online survey, 17 provided their information to be contacted for a semi-structured telephone interview. An effort was made to schedule interviews with all participants who provided their information, however, six of those individuals could not be reached despite multiple attempts at contact. Eleven participants completed the interview in order to achieve theoretical sufficiency, defined as a lack of significant emergent data from incoming interviews (Francis et al., 2010). Descriptive information reported by participants that emerged throughout the interview are summarized in Table 4.1.

Thematic analysis identified seven main themes across interviews, as depicted in Figure 4.1. These themes included 1) Mixed opinions on when to introduce the topic of NBS, 2) Frustration with disclosure of the positive result, 3) Limitations of care during the confirmatory testing period, 4) Non-genetics providers being uninformed about NBS, 5) Ways of coping, 6) Patient-in-waiting, and 7) Mixed emotions in retrospect.

Table 4.1: Descriptive characteristics of interview participants

ID	IEM / Marker	Result	Year of NBS	Occupation	Notified by
P1	CUD	FP	2016	Dietitian	GP
P2	"Carboxylase"	FP	2017	Dietitian	GP
P3	MCADD	TP	2013	*	GC
P4	GALT	TP	2012	*	Midwife
P5	"PKU test"	FP	2012	RN in maternity ward	GC
P6	Unsure	FP	2014	NA, but mom is RN	Midwife
P7	Unsure	FP	2012	Social worker	NA
P8	MCADD	TP	2017	Pharmacist	GP
P9	MCADD	FP	2014	*	GC
P10	PKU	TP	*	Psychologist	GC
P11	C5-OH	FP	2013	*	GP

* Was not shared by participant in the interview
Abbreviations: CUD - Carnitine uptake defect, MCD - Multiple carboxylase deficiency, MCADD - Medium chain acyl-CoA dehydrogenase deficiency, GALT - Galactosemia, PKU – Phenylketonuria, C5-OH - acylcarnitine analyte, TP - true positive, FP - false positive, GP - general practitioner, GC - genetic counsellor

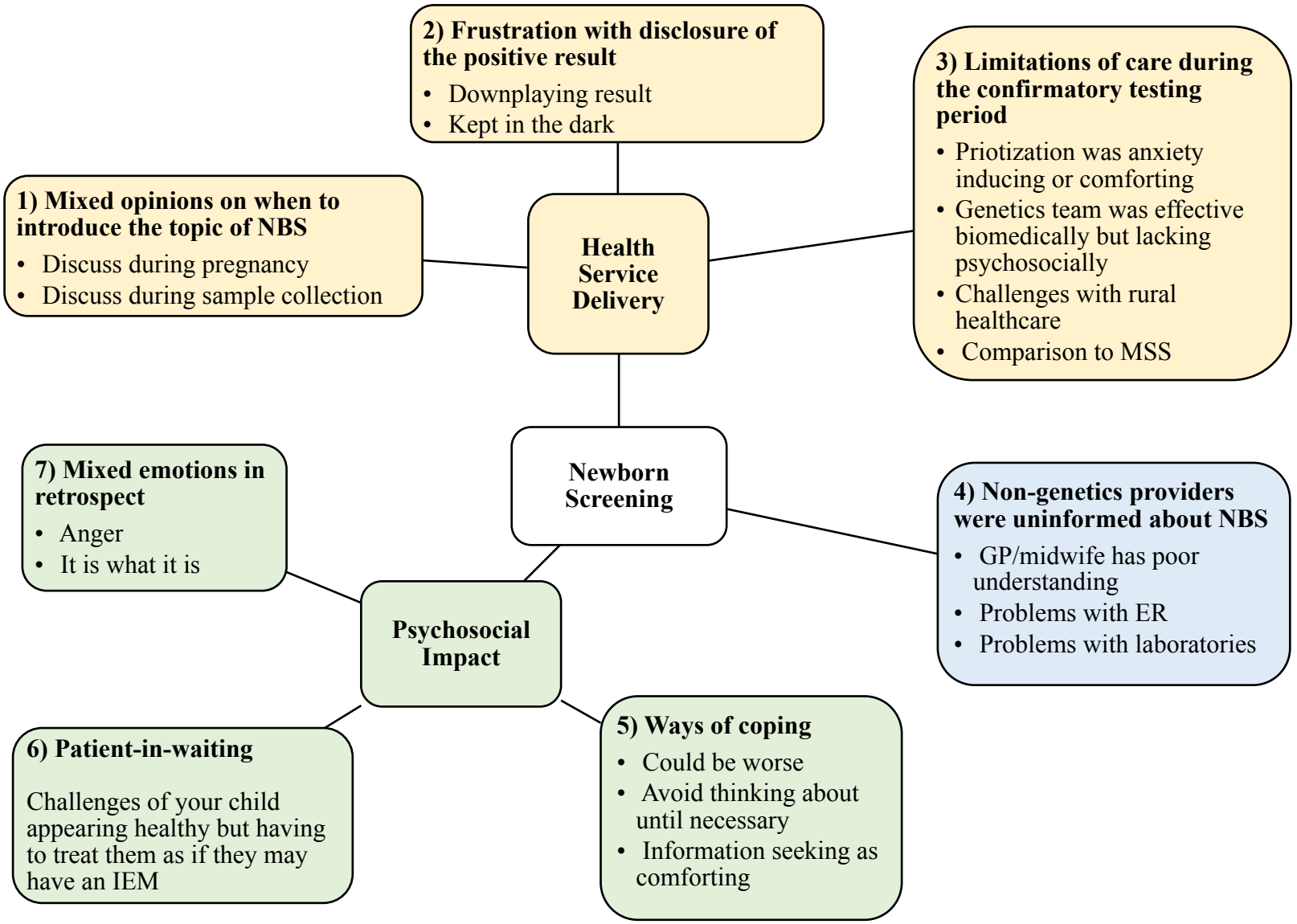

Figure 4.1: Thematic network. Qualitative analysis identified seven themes across interviews.

4.2 Mixed opinions on when to introduce the topic of newborn screening

When asked directly, all participants reflected that in hindsight they did not feel prepared for or aware of the possible outcomes of NBS before being notified of their result. The first theme was that participants had mixed opinions about when they would have preferred the topic of NBS to initially be introduced to them. They either felt that it was appropriate to discuss at the time of sample collection or thought it should initially be introduced towards the end of the pregnancy.

Participants who believed the conversation about newborn screening should occur at the time of sample collection thought that it was unnecessary to cause additional worry to parents by discussing it during the pregnancy. The majority of these individuals had a false positive result. They also expressed that at the time of sample collection, most parents do not pay attention or think it is unlikely their baby could be affected because the conditions included on NBS are so rare. They suggested that changes to the way information is presented to parents may modify their perception of the potential outcomes. First, they felt that including the brochure on NBS in an enveloped package with other information that they take home is not an effective means of distributing information. Numerous participants felt that nobody actually reads the brochure because the way it is presented makes it not seem important, so it is discarded or put aside never to be looked at. For example, one participant whose son died from MCADD before receiving his NBS result commented:

> It's my own fault that I didn't read it, but it was never suggested that I look up what these conditions are. No other information was given to me. So I mean, how is one supposed to know what the outcomes are of getting a positive result if you're never

> given the information? And I understand that you would be providing a lot of people with information that would not pertain to them, but geez, that one in 10,000 that might get that information that could save the baby would totally be worth it.
> - Participant 3, TP, MCADD

Furthermore, many participants did not feel like there was an actual conversation about NBS when their baby was taken away for sample collection. Consequently, they felt it was difficult to link the two events together. Apart from being told that testing is done on every baby, they did not receive additional information about why the testing is being performed or what they can expect. Participants who felt that NBS should be discussed at the time of sample collection suggested that nurses on the maternity ward should provide parents with more detailed information on NBS and then directly hand them a brochure on NBS to read while their baby is taken away for sample collection. For example, one participant who herself worked as a nurse on a maternity ward noted:

> It's important for the nurses that you have to relay that information to you. “This is what the test is for, this is what they're testing for, this is how they do it, and this is what you can expect.” I think after you have a result – like when they phone to tell us that we had to go back to the hospital for more blood work – that’s all they told us, was that we have to go back for more blood work because he's got… I don't even remember how they put it… that he had a positive result for PKU test?… That's the most anxiety-inducing part of the whole situation, is when your child has to go back

> for further testing and you don't really know why.
>
> - Participant 5, FP, “PKU Test”

On the other hand, participants who expressed that NBS should be discussed towards the end of their prenatal care thought that it provided the advantage of additional time to process the information in a less overwhelming environment. Both individuals with a true positive or false positive result thought that this timeline was more appropriate. They felt that parents would be more likely to retain information they were provided if their OB/GYN or midwife encouraged them to read more about it before the birth of their baby. At the time of sample collection, they described being in awe over their baby and distracted from the information because they were trying to learn how to breastfeed and had other concerns. When reflecting on the experience, one participant shared:

> I really think that it should be part of your prenatal care… I think that’s something that should be discussed – not in terms of creating fear, but providing information. I got lots of handouts about the various tests that they could offer you and what the different procedures were, and blood work, and urine tests, or whatever they do throughout your pregnancy and why it's done. I remember getting a lot of that. But there's really nothing about what to expect afterwards. A little bit of information about what kind of testing happens in the hospital on a routine basis with your baby, what they're testing for, how you find out that information would be helpful. Because I think, a lot of people I’ve spoken to, everybody expects that when you go home with the baby because they've discharged you, it means all clear. There was no part

> of me that was thinking that there were still tests that were still being run. I thought we were going home because everything that had been done had checked out.
>
> - Participant 10, TP, PKU

4.3 Frustration with disclosure of the positive result

Participants were asked to describe their experience with newborn screening starting at the beginning of the process. Parents expressed being initially notified of their child's positive NBS result over the phone by their general practitioner (GP), midwife, or a genetic counsellor (GC). All individuals reported feeling anxious, upset, and/or overwhelmed in response to the phone call. Participants focused their responses on the information that was explained or absent, the way in which it was described, and how they felt in response to this news. Overall, they described the theme of frustration with the disclosure of the positive result.

Regardless of the healthcare provider communicating the information, all participants commented on the subtheme of being "kept in the dark", referring to information being vague or withheld from them deliberately or unintentionally. This void often left them feeling frustrated, anxious, and/or confused about what the result meant, what the condition was, what the follow-up process included, and why it was necessary. Furthermore, the majority of participants expressed that they were discouraged from seeking additional information online in the time between the initial phone call and their follow-up appointment. Illustrating this point, one participant noted:

> I do remember them either at [the initial phone call] or some point just saying, "We don't want to go into details too much because what if it isn't so". We weren't

> provided much information because of that… I was frustrated, but I get it at the same time. We wanted to know more information. We wanted to know what the chances of it being a false positive were. But also, what if it wasn't, right? And how would that affect our daughter, and us, and our family. So, it was hard because we were really kept in the dark. But I guess everyone really was. And I also get that they didn't want us to worry about something if it wasn't so. But then with today's world you can look up things, right? So sometimes that's worse because you don't know if that information is accurate you're seeing online.
>
> - Participant 7, FP, Unsure IEM

As a result of being kept in the dark, every participant expressed that they felt uninformed about NBS in some capacity. They reported feeling unsure of potential outcomes, suggestive symptoms of IEMs, and the follow-up process to confirm or rule out a diagnosis. As previously described, every participant responded that they felt unaware of the potential outcomes of NBS when asked directly. Additionally, they also reported not knowing that testing was still pending once they left the hospital. Parents were under the assumption that once their newborn was discharged, they were cleared of all health issues. Thus, they were not anticipating a phone call with a positive NBS result that required urgent action. In the time between initial sample collection and meeting with the genetics team, participants were unsure of suggestive symptoms. For example, one parent expressed feeling helpless as her child died from MCADD before she had received his NBS result:

> The fact that his blood sugar was low. I wish I had known that that wasn't normal… I wish that I had known that the way that he's acting was lethargic – it wasn't just sleepy, it was beyond sleepy. And the fact that his heart rate was low - that wasn't normal. When nurses were saying these things to me I wish I had been more on the ball and said, "Why is this happening? Let's figure out what's going on". Or if I'd known more about these genetic conditions, I could have said "Hey, if this is a possibility, let's check into this more". I just wish that I had known more.
>
> - Participant 3, TP, MCADD

Although this unfortunate circumstance is not the typical outcome of NBS, many participants expressed similar thoughts of being unable to differentiate between what features are normal for a newborn and which are suggestive of an IEM. This information was not consistently discussed at the time of the initial phone call. Participants also expressed having unanswered questions about the follow-up period. They reported being unsure about why confirmatory testing needed to be performed, who they would be meeting with, what everyone's role was, how long the appointment would take, and why false positive NBS results can occur.

Additionally, participants felt that the importance of the NBS result was downplayed by the relaying healthcare provider. This subtheme of dissatisfaction with disclosure of a positive result was usually described in participants who were notified by their GP or midwife. One participant described:

> We had seen our pediatrician just for regular appointments and he had really downplayed [it], just saying like "Oh, those things never come back positive". He

> didn't… He wasn't worried about it at all. But at the same time, I also didn't really feel like he knew that much either. So, it was kind of hard to trust what he was saying
>
> - Participant 2, FP, "Carboxylase"

Participants' reactions to a downplayed result ranged from feeling comforted that the clinician did not appear overly concerned to feeling dismissed because they felt that the impact it had on them was being minimized or brushed off. Each individual's reaction also seemed to be influenced by how knowledgeable on the IEM they perceived their healthcare provider to be. For example, if their pediatrician said that results often come back as a false positive and they're sure it's nothing, participants questioned how much they truly knew about NBS in the first place. If a genetic counsellor did the same, however, they perceived that it was so unlikely that even the specialist was not concerned. For example, the same participant commented:

> I got the sense from the genetic counselor that she didn't know that much about it either because it was one of the very rare ones. [It was] a tiny bit comforting that it's that rare. But then [I] also [did] not really know where to go for questions.
>
> - Participant 2, FP, "Carboxylase"

In summary, the majority of participants wanted additional information at the time of the initial phone call. In particular, they wanted a brief description of the IEM, prognosis, and management, details on the follow-up process including who will be involved and what testing

will include, an indication of the positive predictive value of their NBS result, and online resources in case they sought additional information.

4.4 Limitations of care during the confirmatory testing period

Participants were asked what they did following the initial phone call and what the follow-up process was like for them. Their actions during this time are detailed under the theme 'Ways of Coping'. The theme of 'Limitations of care during the confirmatory testing period' describes shortfalls of the NBS program as reported by participants. In general, parents described feeling prioritized. Interestingly, different participants had different interpretations of this factor. Some participants found it anxiety inducing while others found it comforting. They also expressed the subtheme that the genetics team was effective from a biomedical standpoint but lacking in terms of psychosocial support. Additionally, participants living in a rural setting described additional challenges in their follow-up care because of their geographic location. Lastly, the subtheme comparing service delivery of NBS to maternal serum screening (MSS) is described.

While waiting to meet with the genetics team in follow-up, two participants described the waiting room as an anxiety-inducing experience. Being in the clinic not only made the experience of a positive NBS result feel more real, but it was emotionally upsetting for parents to be seen more urgently than other patients with visible disabilities or developmental delay. Since parents were unsure of the prognosis of the IEM, they thought the patients they were waiting with were now their patient cohort. This misconception led them to believe that their child would develop similar symptoms in the future. As a result, participants felt that they went in to the

appointment feeling incapable of receiving information because they were too emotional and distraught. One participant described:

> I think when you're waiting to get information or confirmation of the diagnosis, your mind just naturally goes to all these 'what if' worst-case scenarios. And so, when you're waiting in a space like that, where they're right in your face, and rationally you know that that child may not have anything remotely like what your child might have, it sort of just feeds into that anxiety about this could be my life. It feeds into the worst-case scenario… I remember crying before we even got into the clinic because it was an overwhelming experience to have that particular child in the same waiting room in the same space.
>
> - Participant 10, TP, PKU

Conversely, the majority of participants expressed that being seen as a priority was comforting and that they felt adequately cared for by the genetics team. Once participants had been seen in follow-up, they mostly described it as a positive experience. They felt that the genetics team was knowledgeable and the best source of information about their NBS result. For example, they felt that the genetics team was well equipped to translate complex information. They liked being provided with reputable websites that had been vetted by professionals, and most participants wanted more of these types of recommendations at the initial phone call. Overall, participants felt reassured by the genetics team and commented:

> We were with them for well over an hour and they just totally explained everything to us. And really reassured us and made us feel a lot more comfortable with the positive screening results. After we met with the metabolics team, we still felt crappy, but we felt a lot better. We felt like it was manageable and we would get through it… And honestly, from the time that we found out until we met with the metabolics team, I cried the whole time. And once we had more information, I felt like a weight was lifted off my shoulders and I felt like I could cope.
>
> - Participant 8, TP, MCADD

Participants also felt grateful that the genetics team was available in urgent situations but reported that there were long intervals without contact while awaiting confirmatory testing. They also described having difficulty with lengthy wait times for confirmatory testing. Furthermore, the majority of participants felt that there was a lack of psychosocial support provided during this period. One participant shared:

> While everybody on that team is supportive, and I can't really complain about anything that happened in terms of their approach to it, there's no psychologist, there's no social worker, so you get this bomb dropped on you and then you just leave with a bag of formula.
>
> - Participant 10, TP, PKU

Parents wanted a healthcare provider to be available who would inquire how they were coping emotionally following a positive NBS result. They often reported feeling like they were

alone or isolated during the confirmatory testing period when they needed the most support. Parents expressed that their family and friends did not understand the situation they were experiencing. Thus, participants described that a healthcare provider focused on psychosocial support would provide them with someone to vent to about the process and who would validate their emotions as a normal response to the circumstances. Some participants even suggested that resources of this nature would decrease the amount of time it took to recover emotionally from receiving a positive NBS result and help them to move on quicker.

As opposed to psychosocial support, participants described that the genetics team was occasionally apathetic when explaining the follow-up procedure. They believed that there was an overemphasis on the biomedical model and not enough focus on the impact on the family system. Parents speculated that this imbalance in content was because the genetics team had become desensitized to the impact of the result on patients. Illustrating this point, one participant described:

> It's kind of like a production line really… do this, this, and this. There wasn't really emotion attached. And they [genetics team] probably do it so often and see so many cases that are a false positive potentially or what have you, that's it's just like, "oh yeah, no big deal". And on the other side it's like "Yeah, this is the end of our lives as we know it."
>
> - Participant 7, FP, Unsure IEM

Participants who lived in a rural setting outside of Winnipeg experienced additional challenges related to their geographic location. All participants who shared that they lived

outside of the city reported that the travel required for a follow-up appointment with the metabolic team was an added stress. For example, one participant learned of her child's positive NBS result at 9pm at night and had to leave at 5am the next morning to travel three hours to be seen in Winnipeg. Multiple participants shared similar stories, often having to travel several hours only days after giving birth. Several participants commented that they believed this journey negatively impacted their recovery time from their delivery. Mothers reported feeling apprehensive about travelling long-distances with their newborn because they had to feed their child on the roadside. This task was described as challenging because they had not yet become comfortable with breastfeeding, especially in an unfamiliar environment. Other concerns with travel included needing a support person to assist with the drive and questioning how they would commute to Winnipeg on an ongoing basis if they had a true positive result. Beyond concerns with the distance to the metabolic clinic, participants commented that they had issues with getting to any hospital in a timely manner in case of an emergency with their newborn. Describing their struggled, one participant shared:

> I just didn't hear the alarm go off and then when I went to nurse him after the 7 hours of not feeding him he was not responding properly. We saw that he wasn't moving at all and reacting - he was just breathing - but we didn't know if he would survive or not. We didn't know. We got in the vehicle, we started to drive…we lived out in the country side, so we were worried that the ambulance wouldn't get to us. We started to drive as an instinct trying to get to the nearest hospital but then we called the ambulance on the way and they met us on the side of the highway. And then they

> brought him into emergency on the stretcher as a little three-month-old baby.
>
> - Participant 9, FP, MCADD

Lastly, three participants made the comparison of follow-up for NBS to prenatal screening for Down Syndrome. These two population-wide screening programs are both coordinated by the genetics team in Manitoba. They reported similar feelings of uncertainty following a positive result for either NBS or MSS. In contrast, MSS was described as more anxiety inducing because of the severity of Down Syndrome compared to the IEMs on newborn screening. They also commented on being provided a risk number in MSS such as "1 in X chance of Down Syndrome" versus not being told the positive predictive value of their NBS result. Furthermore, parents contrasted that they clearly understood that MSS was being performed but were unaware of NBS at the time of sample collection. One participant noted:

> When I went to my doctor when I was pregnant, I always knew, "This is what we're doing today, this is why we're doing it, this is when you'll get the results if there is a result to know about." I was never confused about any of that. As compared to [newborn] screening, which the mentality that I was picking up on is, "Don't worry about this. This is not very important because this doesn't happen to too many people. You don't need to know about it or worry about it because it doesn't happen." But it does happen.
>
> - Participant 10, TP, PKU

4.5 Non-genetics providers were uninformed about newborn screening

While sharing their experience, participants consistently described the theme that non-genetics providers were uninformed about NBS. A subtheme was that GPs and midwives had a lack of knowledge about IEMs included on NBS. Participants also reported unnecessary challenges during interactions with the emergency department and laboratories during the confirmatory testing period.

First, at the time of sample collection, participants felt mislead by nurses on the maternity ward because NBS was sometimes referred to as "the PKU test". They also recalled being told not to wake their child to feed if their newborn slept longer than four hours. Participants reported that this information should not be advised because they could not have known if their baby had a fatty acid oxidation disorder before receiving a positive NBS result, which occurred several days after discharge from the hospital. For example, one participant commented:

> I know they can't treat every baby like they have something like that but when you don't find out the results for many of those newborn screens for 4 or 5 days, you almost kind of do need to treat every baby like they do.
> - Participant 8, TP, MCADD

Second, when GPs or midwives initially called parents with the results, participants felt that the clinician did not always understand the meaning or urgency of confirmatory testing. The majority of individuals felt that their healthcare provider "didn't really know anything" about NBS and in some cases had never heard of the IEM before. One participant described:

> Even my family physician hadn't heard of it before because it's so rare. I felt like nobody really knew what was going on. Nobody could really reassure me but the genetic counsellor.
>
> - Participant 1, FP, CUD

Some participants also indicated that they were contacted by a receptionist with a brief note that their child needed to repeat bloodwork without further information why it was necessary. It was not until several weeks later when meeting with the genetics team in follow-up that they were explained that they had a positive NBS result and that an analyte was considered abnormal. Furthermore, if participants contacted their local healthcare provider during the follow-up period for NBS, they described that their clinician did not always know what testing they were referring to and didn't understand the details of the result. Participants were left with an impression that there was not enough training on NBS and IEMs as part of the medical school curriculum or family medicine residency programs. This subtheme was also reflected in participants reporting that they had difficulty finding a family doctor who would feel comfortable accepting their child as a patient because they had an IEM that they were unfamiliar with. Reflecting on this overall topic, one participant shared:

> Having no medical background trying to explain to a doctor what my son has, I would find it very frustrating in that moment. Them not knowing. But I don't know where it needs to be picked up. I don't know. Maybe more education needs to be provided on these [fatty acid oxidation defects] when they are medical students. Or maybe they need to do a round with a genetics team. Maybe that needs to be part of

> their residency.
>
> - Participant 3, TP, MCADD

Third, parents reported having issues with their local emergency department if they presented with a potential metabolic crisis during the confirmatory testing period. A subtheme of non-genetics providers being uninformed was that emergency staff were unfamiliar with NBS and unsure of whom to consult for more information about the indication. Parents reported feeling frustrated and unconfident that the emergency department would know how to handle their situation because they observed that staff did not know what symptoms were suggestive of an IEM. Thus, participants indicated that they needed to advocate for their child but did not feel prepared on how to educate the emergency department about their NBS result. Consequently, parents reported not being taken seriously when they presented and having to wait many hours without assistance. For example, one mother requested a glucose monitor to check for hypoglycemia when she was concerned about a potential MCADD crisis in her newborn, but her request was declined by the staff. Another parent described a similar struggle she encountered:

> Well one of the problems was that the people - the emergency room staff - had no idea what I was talking about. They had no idea like anything about these newborn screens or they never heard about this inborn error and so I felt a little bit silly… I felt a little bit lost. I guess I was trying to explain I was worried about my son. But nobody really knows what's going on except for the genetic counselor who wasn't there. She did try and help by calling across to the children's emerge and [geneticist] did come eventually, but then I ended up staying there for like 8 hours and just sort

> of like waiting and waiting. And the staff, they were kinda just ignoring me… That was pretty frustrating. And by the end I was crying, and they basically let me go home because I was really upset that we were just there and nobody was talking to us explaining why we are waiting or what we are waiting for.
>
> - Participant 2, FP, "Carboxylase"

Parents encountered similar challenges with laboratories, which was another subtheme. Some individuals indicated that the laboratory technician expressed being unfamiliar with how to complete the sample collection. Approximately half of participants described needing multiple redraws due to incorrect sample collection, incorrect labelling, or misinterpretation of the requisition. Consequently, parents were frustrated by the already lengthy turnaround time for confirmatory testing being further delayed. For example, one participant described:

> I got a call saying, "Unfortunately the results of the blood work that took so long to do - to try and get blood off the baby - they didn't do all the right tests" …or something like that. I think they hadn't gotten the requisition to do the special genetic testing? For some reason we need to go back and do more blood work… It was horrible! Watching them try and get the blood work plus we've been there all day. That was like really frustrating… So even getting all the testing done was just a lot of running around and it was very confusing.
>
> - Participant 2, FP, Carboxylase

Furthermore, participants described sample collection being a traumatic and emotionally upsetting experience because it required unnecessary additional attempts at venipuncture and urine collection. Participants reported being an active participant in sample collection and needing to restrain their child while still recovering from labour. Multiple parents expressed that this task was a challenging experience. One participant, whose child was delivered via an emergency Caesarean section only days prior, described:

> She wouldn't pee in the urine bag and it didn't matter where we positioned it, it kept going out. They said, "We're closing now, so you need to go home. We'll send you with a few of these bags and try to get a urine sample". Then we came home, and we were sitting there super stressed… we ended up just leaving her diaper completely off so that if I could see her peeing, I could try and hold the bag there to be able to catch the urine. And we finally got the urine sample, but when we called them, we found out again they were closing early … And the blood and the urine had to be within 24 hours. So, my husband got in the car – again, 125km away from [hospital] – and drove the urine to the lab so that they had the blood and the urine.
>
> - Participant 11, FP, C5-OH

This example highlights the difficult experience with sample collection and the obstacles parents faced with laboratory hours. They often reported challenges with laboratories not being able to send out the sample while it was fresh or being unsuccessfully redirected to the emergency department because the laboratory was closing. This subtheme was more likely to occur when the parent was notified of the positive NBS result towards the end of the day. Parents

expressed being distressed that they were sent on a roundabout journey because they were unable to complete confirmatory testing in the urgent timeline indicated by the genetics team. Some participants indicated that they felt afraid that their child might die or have a severe crisis because unforeseen circumstances delayed them from providing a sample by one or two days.

4.6 Ways of coping

During the time between the initial phone call and being seen in follow-up, participants described a variety of coping mechanisms that they used to reduce the psychosocial impact of a positive NBS result. Subthemes included a perceived hierarchy of IEMs, coping with uncertainty by avoiding information, and seeking information as a source of comfort. Participants also sought social support from peers in order to feel less lonely and more connected.

In order to cope with the upsetting news of a positive NBS result, parents expressed that the IEM they screened positive for "could have been worse". They reported having a preconceived idea of which diseases were the most severe and were worse to have than others. Participant 6 commented that there were "varying degrees of different illnesses and diseases". Their subjective rankings were based on a range of criteria, including if participants could continue to breastfeed, if frequent feeds were required, and if the IEM would affect other aspects of their child's lifestyle. Interestingly, some participants described PKU as their worst-case scenario whereas others thought that PKU was the least "scary" of the IEMs. Illustrating this idea, Participant 1 described PKU as sounding "horrible" because of the potential for impaired cognitive function, whereas Participant 5 thought that PKU wasn't scary because she knew it was treatable. Parents tried to remind themselves that there were worse things in the world that

could happen as an attempt to be grateful despite their circumstances. For example, one participant shared:

> I kept telling myself to be optimistic and telling myself that there's so many worse things out there – this is so mild compared to so many things that people are dealing with with their babies.
>
> - Participant 9, FP, MCADD

When parents had to cope with uncertainty during the confirmatory testing periods, they employed one of two opposite strategies. The first strategy was avoiding thinking about the positive NBS result and its implications until it was absolutely necessary. As one parent described, "what you don't know can't hurt you" (Participant 11, FP, C5-OH). Some parents felt that they did not need to know further information about the IEM because it was rare and statistically unlikely to affect them. In fact, Participant 5 described being less concerned about the NBS result because she knew there was a high chance that it would be false positive. Parents did not want to expend too much effort for this reason. Those who employed this strategy wanted to know if the result was a true positive before taking next steps. Participants also expressed that thinking about their positive result only made them worry more:

> I think it just gives you more things to be potentially scared about that maybe you don't even have to be scared about. Because it's all hypothetical until it actually happens. It's the same as What To Fear [Expect] When You're Expecting. If we give all this information based on fear, until you actually know what's happening, it's not

useful.

- Participant 6, FP, Unsure IEM

The other coping strategy employed by parents was information seeking as a source of comfort. These individuals felt that having more knowledge about a topic translated to having more control over the situation. They also described that the act of information seeking allowed them to focus their attention on the task, thereby reducing their anxiety. All participants who adopted this approach proceeded to conduct an Internet search for the name of the IEM immediately after the initial phone call. Their searches were directed at general websites about the IEM. Consequently, the majority of individuals did not encounter information relating to NBS and felt that there was a lack of information available online because they didn't know where to look. Additionally, many parents were unaware of information sheets from WRHA designed for parents with a positive result. Those who did read the WRHA information sheets thought that they were easily understandable, but too general, for the information they were seeking. Illustrating this point, one participant described:

I think it was the procedure of finding it that distracted me for my … So maybe it was the search for me that was comforting and hopeful. Because the harder it was to find, it showed that it was rare. And the more rare, there was still more of a hope that it could be not something.

- Participant 9, FP, MCADD

All parents who searched online reported looking for the same type of information. They wanted to know the probability that their result was a false positive result (positive predictive value) in order to have hope that their child would be healthy. They also wanted to learn more about the prognosis of the IEM and management guidelines. This information helped them to feel more prepared of what to expect in case the condition was actually diagnosed and provided them with comfort that their child could still lead a "normal" life as they originally envisioned.

> That's what I was looking for. Was just more detail in regard to what it was, and what we would have to do treatment-wise for him to be healthy… I like to know more information than less. So that's why I looked everything up. The more information I found, the better I felt about it.
>
> - Participant 5, FP, "PKU Test"

While seeking information, parents reported that the credibility of the source was important to them. As participant 4 described, "You can't always trust the internet". Participants indicated a desire for, but lack of, Canadian-based resources compared to American-based resources, and that the information differed between the two. Parents considered information to be reliable if it was replicated across multiple websites, originated from primary literature or an academic database, or if the educational resource was recommended to them by a healthcare professional such as the genetics team. Some parents expressed that the complexity of information was a barrier to their understanding and that they felt like they were reading a foreign language. The majority of participants thought that online forums were not a reliable

source of information but were helpful and reassuring. Illustrating this point, one participant described her research process:

> If I looked something up and I found information, I would always go to one of the reputable sites to see if I can find the information on there as well. And if I did, then I knew it was correct. And if I didn't, then it was this unknown of whether it was actually right or not
>
> - Participant 3, TP, MCADD

Parents openly acknowledged that content on forums are often worst-case scenarios or false information that does not apply in the majority of circumstances. They felt, however, that it was comforting to read that others had experienced how they were feeling and that their result was a false positive. They described that forums took something that felt rare and isolating and make it feel like they weren't alone and belonged to a community. For example, one participant noted:

> The forums probably weren't good. Because I knew they were just regular people commenting and that their information wouldn't be accurate. But it was kind of reassuring hearing someone else's experience about it and that it turned out okay. But I didn't read too much into what those people said on those websites.
>
> - Participant 1, FP, CUD

Apart from forums, participants also sought support from peers in other ways. Although they would seek comfort from their friends and family members, participants felt that they did not fully understand what they were going through. Parents either directly expressed that they would have benefitted from having a support group or described an experience where they received support from a similar type of interaction. The majority of participants felt that it was comforting to share their story with others who could relate to receiving a positive NBS result, regardless of the condition. They felt that this support helped them to feel less isolated and emotionally validated. One participant described social support she received from her peers:

> I used to be part of a breastfeeding group with a bunch of lovely ladies. And I went there every week. And I remember sharing that I got this call there. And they were quite supportive, but I mean they didn't know much to say. But it was nice to have that group of people… After we found out that it was a false positive, it was interesting to be on the other side of things because then there was another mom that came and was going through the same thing that we had… Sometimes just knowing that you're not alone is helpful in itself to hold on to that hope that things could still turn out to be just fine after all.
>
> - Participant 7, FP, Unsure IEM

4.7 Patient-in-waiting

The theme 'patient in waiting' refers to a parent's psychosocial challenges with having a potentially healthy child but having to treat them as if they may have an IEM while awaiting the results of confirmatory testing following a positive NBS result. Participants unanimously

expressed that the interim period was too long, describing it as “hell” (Participant 11, FP, C5-OH) and “seem[ing] like an eternity” (Participant 1, FP, CUD) or the “longest wait of [their] lives” (Participant 7, FP, Unsure IEM). Parents reported that the turnaround time for confirmatory testing ranged from 5 weeks to almost a year (in an extreme case where the baby was apparently a carrier for MCADD with two mutations in cis and a variant of uncertain significance in trans). During this lengthy period, parents often reported having minimal to no contact from the genetics team regarding the status of testing.

The majority of participants indicated that the initial time frame they were cited was delayed multiple weeks without anyone being sympathetic or acknowledging the impact it had on them. Furthermore, parents reported struggling to carry on with their life during this time because they felt anxious about the unknown. This uncertainty was described as being caught between a grieving process for losing the life they envisioned for their child and themselves, all the while still hoping that they would have a false positive result. This dynamic was further complicated by mother’s having “intuition” about whether or not their child was healthy based on their newborn’s observed development:

> If I'm looking at this baby, and everything inside me is telling me this baby is happy and healthy, am I wrong in thinking that? Is there something else happening? And I think, kind of when your mother’s intuition [kicks in] and you know how to give birth and you know how to breastfeed and you’ve conquered those kinds of things, to have that “Am I wrong? Is my intuition wrong here?” That was where the fear came from I think. And also scared that maybe my baby isn't healthy.
>
> - Participant 6, FP, Unsure IEM

The majority of parents described this theme, especially if they saw their child as healthy but had to feed them regularly or treat them as if they had an IEM. Parents initially felt confused about why their child needed to be managed as if they had a disease when, in their opinion, they appeared asymptotic and growing appropriately. For most participants, the theme of being a 'patient in waiting' ended once they received the final result of confirmatory testing. For one parent, however, she still could not definitively say whether or not her child had MCADD more than four years after NBS was completed. Although she and the genetics team are highly suspicious that her son is only a carrier, she still keeps a letter with an emergency protocol to treat her son as having MCADD in-case he has severe flu-like symptoms or a potential metabolic crisis. She shared that she's never allowed him to fast for more than a few hours because she does not want to test this theory.

4.8 Mixed emotions in retrospect

Participants reported a range of emotions throughout their NBS experience and described the theme of mixed emotions in retrospect. When reflecting back on the period, parents described the subthemes of anger or the sentiment of "it is what it is".

Individuals who felt anger in hindsight reported that it was hard for them to move on from the result because of gaps in psychosocial support provided throughout the process. Several participants commented that NBS was a repressed memory that they intentionally tried to block out because of how difficult the experience was. They also expressed anger at having to feel all of those emotions during the period only to have a false positive result in the end. One mother in particular felt like she was unable to bond with her newborn during this period because she was afraid she might die from the IEM she screened positive for:

> I honestly feel like I lost the entire first month of her life because I tried to stop myself from bonding with her, just in case. I was preparing myself or trying to not let myself love her too much. And that's a time in her life, in my life, in our life together than I can never get back…So that was the hardest part.
>
> - Participant 11, FP, C5-OH

In contrast, the majority of participants had "come to peace" with that time in their lives and did not feel scarred by receiving a positive NBS result. For example, Participant 7 described, "Once we got that call that it was a false positive we never looked back, right. Luckily that was the end of it for us". Although participants did feel a range of emotions during the immediate follow-up period, they commented that those feelings were mainly derived from the nature of the testing. They felt that tweaks to the follow-up process would reduce their psychosocial response and help parents to cope, but not eliminate negative emotions all together. Illustrating this point, one participant commented:

> Overall, I do feel like the process was good. I think anyone who gets a positive result for the screening is going to be overwhelmed. I don't… there's maybe a couple things, like having more information at the time. It could make it less stressful but it's stressful and overwhelming just because of what it is, not because of the process.
>
> - Participant 8, TP, MCADD

CHAPTER FIVE:

DISCUSSION

The aim of this project was to improve health service delivery of NBS in order to reduce the psychosocial impact of a positive result. Specifically, we sought to identify how communication of a positive result and educational resources could be improved; explore how parents were accessing educational information about IEMs after being notified of their result; and determine when in the NBS process parents will benefit most from these educational messages. Based on our findings, the following suggestions are made in order to improve the follow-up care provided by geneticists and genetic counsellors.

5.1 Introducing the topic of newborn screening to parents

5.1.1 Key messages to convey to parents when initially discussing newborn screening

Participants in this study described several key messages that they felt were important to know about NBS or were unanswered throughout their experience. They reported being unsure of the potential outcomes of NBS, what symptoms were suggestive of IEMs, and what follow-up may be involved if their child screened positive. They also expressed a desire to know the frequency of a false positive result, why confirmatory testing was necessary, and why a false positive result could have occurred. Not only were these messages important to our Manitoba-based sample, but they have also been described in a similar study based in Ontario (Araia et al., 2012). Parental satisfaction with NBS has been shown to be correlated with understanding the purpose and benefits of NBS, how they will be notified of results, and the interpretation of those

results (Araia et al., 2012). Furthermore, this information is an important factor in reducing the psychosocial impact of a positive result.

Parents who are uninformed about NBS have been shown to have a heightened psychological response in comparison to parents who are educated on these topics (Tluczek, D, Orland, Nick, & Brown, 2009). Education about NBS likely helps parents to be more psychologically prepared to receive a positive result (Araia et al., 2012; Manson, 2010) and working in the healthcare field has been associated with increased familiarity with NBS (Newcomb et al., 2013). Participants in this study expressed having poor knowledge on NBS despite being a highly educated population with a background in healthcare. The concerns they described makes one wonder if a less educated group would be less insightful and more accepting of their healthcare providers being uninformed about NBS. It is of concern that this group was so poorly informed, as it suggests that the majority of families in this situation would be even less informed. Therefore, it is crucial that information about NBS is disseminated by healthcare providers even though consent for NBS is not required in Canada.

5.1.2 Introducing the topic of newborn screening during the prenatal period

Participants expressed having mixed feelings of when to initially introduce the topic of newborn screening. A subtheme was the desire to introduce the topic of NBS during the prenatal period. Participants felt that this timing would have allowed them to absorb and retain information because they would not have been psychologically overwhelmed from the birth of their baby or physically recovering from labour. Previous studies have also shown that parents with a positive result desired to receive information about NBS during the prenatal period for the same reasons (Tluczek et al., 2009). Receiving information antenatally may allow parents to be

more thoughtful in asking questions. In fact, introducing this topic during the prenatal period has been shown to increase active information seeking and is correlated with increased parental understanding and satisfaction with NBS (Araia 2012). It is possible that participants in our study who expressed this desire were more likely to use information seeking as a source of comfort as their way of coping. It also appears that participants were more likely to suggest introducing NBS at this time if they had a true positive result. Their outcome could have affected their response to this question because they may have felt that their peers were unaware of NBS when they shared their positive result. Alternatively, their experience may have provided them with reinforcement of the importance of NBS and a desire to share that awareness with their community.

Although OB/GYNs have the ideal opportunity to discuss NBS with patients during the late third-trimester of pregnancy, it has been reported that almost two-thirds rarely or never introduce this topic (Little et al., 2009). A survey of prenatal care providers showed that they were not introducing information on NBS mainly because they felt it would be discussed by another healthcare provider postnatally, but also because they did not feel it was their duty or felt unprepared to discuss it with patients (Faulkner, Feuchtbaum, Graham, Bolstad, & Cunningham, 2006). In fact, only a minority of OB/GYNs reported feeling responsible to introduce NBS (Little et al., 2009). In contrast, a study performed in the United Kingdom found that midwives preferred providing information on NBS during the third-trimester of pregnancy instead of postnatally (Wright, Ulph, Lavender, Dharni, & Payne, 2018). Despite the benefit of introducing NBS during the prenatal period and parents' desire for this knowledge, OB/GYNs and midwives are not currently providing this information. Moving forward, it is advisable that more education

on NBS is provided to these clinicians and dissemination of this information is included as a required responsibility in their practice guidelines.

5.1.3 Introducing the topic of newborn screening at the time of sample collection

Conversely, the other subtheme was the desire to initially introduce the topic of NBS at the time of sample collection. Participants may have been more likely to express this opinion if they had a false positive result and used information avoiding as their way of coping with a positive NBS result. To this end, they expressed that it was unnecessary to cause parents worry by discussing NBS during the prenatal period. Interestingly, they often commented that they would have probably changed their opinion if they had a true positive result. Overall, introducing NBS during the prenatal period would allow parents who were information seeking to have time to acquire more information while parents who were information avoiding could choose not to pursue additional information. Therefore, we propose that the topic of NBS should be introduced during the prenatal period and education at the time of sample collection should be directed at reiterating important messages about NBS.

Participants expressed that nurses should hand parents an information sheet on NBS before they take the baby away for testing. Currently in Manitoba, information on NBS is provided inside of an envelope amongst many other information sheets. Parents receive this package upon leaving the hospital and participants reported never reading this information because it seems insignificant. In Ontario, tear-off information cards are included as part of the dried blood spot filter paper and nurses are required to hand this card to parents before obtaining a sample (Araia et al., 2012). One study showed that three-quarters of parents who received this information card knew that they would be contacted if their child had a positive NBS result

(Araia et al., 2012). Data from our interviews shows that participants were not as well-informed, suggesting that Manitoba should consider adopting a strategy whereby the information provided is directly linked to the sample taken in some way.

Adopting such a strategy may also ensure consistency and accountability of nurses to discuss information about NBS despite informed consent not being required. The majority of participants in our study reported that they did not feel like they received adequate information on NBS at the time of sample collection. It has been shown that nurses' and physicians' knowledge of NBS is an important factor in determining if they inform families about NBS (Little et al., 2009). Taken altogether, it appears that many nurses in Manitoba may have inadequate knowledge about NBS and thus avoid discussing this information with families. For example, one participant who used to be a nurse in a maternity ward described NBS as the "PKU test". Nurse educators have been suggested as a strategy for teaching nurses more about NBS (Deluca, Zanni, Bonhomme, & Kemper, 2013). Another potential solution may be presentations from genetic counsellors to nurses.

Participants also expressed other messages that they believed to be important to understand about NBS at the time of sample collection. They expressed a desire to be provided statistics on how often false positive and true positive results occur. They felt that this information would have made them pay closer attention to information about NBS instead of assuming that positive results were rare. Participants also wanted to be provided with information on what symptoms are suggestive of an IEM. They indicated that they would have paid more attention to subtle signs and may have brought their child to medical attention if there were concerns prior to receiving a positive result. They also felt it was important to know that children with an IEM can be asymptomatic initially, which is a concept they expressed difficulty

understanding. Lastly, it is essential that parents are informed that they will be contacted by telephone if they have a positive result. Participants thought that being discharged from the hospital meant that all tests on their baby were completed and their child was cleared of all health concerns. Psychological preparedness may be an important factor to help parents avoid being overwhelmed when receiving a positive NBS result. These important messages should be included on the information sheet that nurses will hand to parents at the time of sample collection. Overall, efforts to provide education on NBS should focus on OB/GYNs and nurses on the maternity ward because they are best suited to share this information with new parents.

5.2 Comparing delivery of population-wide screening programs: newborn screening versus maternal serum screening

It is interesting that while discussing introducing NBS prenatally, participants drew a connection between NBS and MSS. In Manitoba, MSS is a population-wide prenatal screening program for Down Syndrome, Trisomy 18, open neural tube defects, and Smith-Lemli-Opitz syndrome. This test is offered to pregnant women during their second-trimester and individuals with a positive screen are offered second-tier testing including non-invasive prenatal testing or an amniocentesis. Although NBS and MSS are similar in multiple aspects, there are several key differences in service delivery that are worth highlighting.

First, consent is assumed for NBS but is required for MSS. This difference is justified because MSS is informative solely for the purposes of pregnancy management whereas NBS reduces childhood morbidity and mortality through early intervention. Regardless of the need for consent, clinicians have a responsibility to provide information to parents (Manson, 2010). Participants in our study described that they were unaware that NBS was being performed but

understood that MSS was being completed because their OB/GYN clearly discussed it with them. A survey by Faulkner et al (2006) showed that prenatal care providers had a lack of knowledge on NBS and a lack of educational materials to provide to patients (Faulkner et al., 2006). It would be interesting to further explore the topic of why OB/GYNs seem to be more comfortable discussing MSS compared to NBS.

Second, despite both NBS and MSS providing population-wide screening for genetic indications, patients with a positive NBS result have unequal access to genetic counsellors compared to patients with a positive MSS result. Only a subset of individuals with a positive NBS result interact with a genetic counsellor whereas all individuals with a positive MSS result for Down Syndrome or Trisomy 18 have the option to meet in-person with a genetic counsellor. During prenatal appointments for MSS, patients meet with a genetic counsellor for at least 30 minutes to discuss what the genetic condition is, what the chances are for the pregnancy to be affected, what confirmatory testing options are available, and to explore psychosocial factors influencing their decision. In contrast, patients with a positive NBS result may not even receive a phone call from a genetic counsellor explaining their result. If they do, it is likely a brief conversation notifying them that their newborn screened positive for a metabolic disease and they need to have more testing. If all parents with a positive NBS result had the option to meet in-person or via telehealth with a genetic counsellor in the same way as MSS, it possible that this strategy may mitigate their psychosocial response. Dedicated laboratory and clinical newborn screening genetic counsellors would be required to meet the demand of this proposed model.

Third, confirmatory testing for NBS and MSS have significantly different turn-around-times. Individuals with a positive NBS result in Manitoba may have to wait several weeks, if not months before a diagnosis can be established or ruled out. In contrast, patients with a positive

MSS result typically have results from an amniocentesis within a week. Participants in our study unanimously expressed a desire for quicker turn-around-time for their results and described the confirmatory testing period as extremely challenging. This desire for shortened waiting times has also been reflected in the literature (Schmidt et al., 2012).

Steps should be taken to streamline the confirmatory testing process as much as possible in order to reduce the period of uncertainty where parents experience an adverse psychosocial response. An integrated model where the laboratory performing NBS also coordinates follow-up diagnostic testing may be a potential solution to decrease turn-around-times. Precedent has already been established by Newborn Screening Ontario and within Cadham Provincial Laboratory (CPL). CPL currently performs molecular testing for common mutations causative for MCADD and CPT1A. Further integration of the biochemical, enzyme, and molecular testing necessary to confirm a diagnosis of IEMs included on NBS would reduce avoidable delays that are incurred by applying for out-of-centre approval and utilizing third party laboratories outside of the province or country.

5.3 Coping with uncertainty in genetic counselling

Participants expressed a range of emotions during the confirmatory testing period which have also been observed in the literature. Depression, anxiety, and stress have been well described as a psychological response amongst parents with a false positive NBS result for cystic fibrosis (Cavanagh et al., 2010; R.Z. Hayeems et al., 2017; Robin Z. Hayeems et al., 2017; Robin Z Hayeems et al., 2016; Perobelli et al., 2009). Our data reflect these emotional aspects in the context of IEMs and also highlight coping mechanisms used by parents during the confirmatory testing period.

Participants described the theme of the "patient in waiting", which was first reported by Timmermans & Buchbinder (2010). When confirmatory testing is inconclusive, parents are not provided with closure and may be required to continue adhering to management protocols as a proactive measure. They may never receive a definitive explanation of why the analyte was abnormal and the genetics team may continue monitoring them indefinitely despite reassuring them that they are okay. Timmermans & Buchbinder (2010) described that this theme may also be applicable to other genetics patients who have predictive genetic testing for an adult-onset condition or a cancer predisposition syndrome. These patients continue to be surveilled and treated as if they have a disease even though they are asymptomatic. This contradictory action can be confusing for the parents of a newborn, as reflected in our data. Additionally, participants described having intuition about their child's wellbeing. This intuition is a conflicting sense of the participant feeling confident that they would be able to sense if something was wrong with their child yet doubting their intuition and wondering if they are missing warning signs of an IEM. This theme has been reported once before, although it was not described in detail at that time (Schmidt et al., 2012).

Participants in our study had several ways of coping when faced with uncertainty during the confirmatory testing period. Typical responses to difficult news can be categorized as problem-focused, emotion-focused, or a combination of both (Weil, 2000). Emotion-focused responses, which are usually observed when circumstances are static (Weil, 2000), were reported by participants in response to their positive NBS result. Their ways of coping included seeking social support, positive reappraisal, seeking information, and avoiding information. These strategies are also representative of psychosocial responses described in a broad range of genetic counselling encounters.

Seeking social support has been well defined as a coping mechanism in the field of genetic counselling and was discussed by participants in this study (McCarthy Veach, LeRoy, & Bartels, 2003; Weil, 2000). In contrast, a similarly designed study showed that parents with a positive NBS result were hesitant to share information about their result with others because they were unsure how they would react to this news (Schmidt et al., 2012). We hypothesize that a support group comprised of parents with current and previously positive NBS results may help to bridge this gap by providing parents with an outlet to share their feelings with others in a similar situation. Alternatively, another possibility may be a curated list of former parents who have experienced a positive result and are willing to take phone calls from parents going through the process. The logistics of such a strategy would be challenging. Hypothetically, a parent could be recruited to such a roster during a follow-up appointment once they have come to terms with their child's diagnosis and provided consent to share their contact information with a parent in a similar situation. Either of these social support systems may promote emotional wellbeing, validation, comfort, and role modeling of effective coping strategies amongst parents with a common set of circumstances (Weil, 2000).

Positive reappraisal is another established coping mechanism observed in genetic counselling and involves an individual trying to reframe their circumstances from a more optimistic perspective (McCarthy Veach et al., 2003; Weil, 2000). Participants in this study often expressed that the IEM or situation "could be worse", which suggests that they have a preconceived idea of which IEMs are more manageable than others. For example, it may be possible that individuals who viewed PKU as the most devastating IEM were afraid of intellectual disability or of changing their lifestyle because of the restricted diet involved, whereas those that viewed it as one of the least daunting IEMs may have been relieved that they

did not have to do frequent feeds or live in fear of a sudden metabolic crisis as may be the case in a child with a fatty acid oxidation disorder. The preconceptions about each disease relate to the Health Belief Model (Ulman, Schuette, & Yashar, 2009), by which an individual's fear or threat of a condition is influenced by the perceived severity of the disease, inconvenience of the follow-up, and the amount of effort required for management of the disease. When participants tell themselves to be grateful that their child is not at risk for a more severe IEM, whatever that disease may be, it seems that they are trying to find the positive in their circumstances in order to console themselves.

Applying the lens of positive reappraisal, it is interesting that the experience of the waiting room had enough of a memorable impact that some participants chose to bring up this topic organically in their interview. Naturally, waiting to be seen by a medical specialist can be anxiety inducing. The prompting factor for participants' distress, however, was the experience of seeing other genetics patients in the waiting room whom they thought were at a more advanced stage of the IEM for which their child screened positive. Participants who remarked on this situation did not express using positive reappraisal as a coping mechanism but rather reported experiencing a negative emotional impact. We hypothesize that this emotional reaction precludes positive reappraisal because observing other patients causes the parent to see a physical manifestation of their fears. This subtheme has been reported in other clinical populations. A survey of cancer patients showed that half of participants who were in a waiting-room amongst other cancer patients in a more advanced stage of their disease experienced a significant psychosocial impact as a result of observing them (Catania et al., 2011). The same study also showed that three quarters of the cohort expressed desire to have freedom to leave the waiting room by using a buzzer or similar device (Catania et al., 2011). This strategy could be useful for

NBS patients since it would allow parents to have the mobility to remove themselves from an emotionally triggering situation and thus, begin the appointment in a more positive and receptive frame of mind to receive information.

Information seeking as a source of comfort is a well-studied psychological adaptation seen in genetic counselling as a whole (Weil, 2000) and specifically within the context of NBS (Schmidt et al., 2012). This response seemed to be more common in participants who had a true positive result and in those who had more time to research about the IEM prior to the appointment. Information seeking has been shown to help individuals feel that they have more control over a situation (Schmidt et al., 2012; Weil, 2000). In extension to this concept, our findings add to the literature by showing that the act of information seeking itself can help patients to distract themselves because they are channeling their negative emotions into focusing on a cognitive task.

Conversely, information seeking may cause an exacerbated psychosocial response in some individuals. Thus, avoiding information can also serve as a form of self-protection (Schmidt et al., 2012; Weil, 2000). Our data suggests that a subset of patients use this strategy to delay themselves from acknowledging underlying distress until they have a confirmed reason to confront the situation. This coping mechanism seemed to be more common in participants who appeared to have a less anxious personality type and in those who sounded more trusting of the medical system in their responses.

5.4 Newborn screening educational resources

Participants of all coping styles expressed a desire for reliable information that was vetted by professionals. Unfortunately, the vast majority of participants were unaware that the WRHA

Program of Genetics & Metabolism website has fact-sheets designed for parents with information about each potential indication. Instead, they relied on performing an internet search using the name of the IEM. Participants indicated that they read general webpages of mixed quality about the IEM but very rarely encountered or thought to look for information related specifically to NBS. Those that did use these resources thought that it was easily understandable but still expressed having unanswered questions.

We performed an informal content review of the NBS fact-sheets provided by WRHA (Genetics & Metabolism Program, 2019). The individual Flesch–Kincaid Grade Level (Kincaid, Fishburne, Robert P., Richard L., & Brad S., 1975) of each fact-sheet is shown in Table 5.1. The average Flesch–Kincaid Grade Level was 9.98 and the median was 9.35 (minimum 8.2, maximum 15.0). Each fact-sheet generally discussed the purpose of newborn screening, the meaning of a positive result, the IEM and what causes it, additional testing that is required, why screening is performed for the specific IEM, how it is treated, the inheritance pattern, contact information for the department, and online resources for more information about the IEM. The content of these fact-sheets was mainly derived from Newborn Screening Ontario and the information did a good job of including the majority of key messages for NBS educational materials (Araia & Potter, 2011). This content answers the majority of topics requested by parents in our interviews. The link to additional online resources is also an excellent idea for patients who use information seeking as a way of coping. The link to reliable information discourages participants from performing their own search that may result in irrelevant, inaccurate, or worst-case information about the IEM. Additional online resources to potentially refer parents to during the phone conversation are detailed in Figure 5.1.

Table 5.1: Readability of NBS fact-sheets provided by the Winnipeg Regional Health Authority

WRHA Genetics & Metabolism NBS Fact-Sheet	Flesch–Kincaid Grade Level
Argininosuccinic Acidemia (ASA) or Citrullinemia (↑ citrulline)	12.0
Beta-Ketothiolase Deficiency (BKT) (↑ C5OH)	8.9
Biotinidase Deficiency	12.1
Carnitine Uptake Defect	8.2
Inuit Carnitine Palmitoyl Transferase 1A Deficiency Variant	15.0
Carnitine Palmitoyl Transferase 1A Deficiency	8.2
Cystic Fibrosis	9.6
Elevated C5OH	10.0
Galactosemia	11.8
Glutaric Acidemia Type 1 (↑ C5DC)	8.9
Homocystinuria (↑ methionine)	12.1
Isovaleric Acidemia (↑ C5)	9.6
LCHAD or TriFunctional Protein	8.2
Maple Syrup Urine Disease	8.6
Medium Chain Acyl CoA Dehydrogenase Deficiency (MCADD)	9.1
Phenylketonuria	8.7
Propionic Acidemia or Methylmalonic Acidemia (↑ C3 or ↑ C4DC)	9.6
Short Chain Acyl CoA Dehydrogenase Deficiency (SCADD) (↑ C4)	9.0
Tyrosinemia	11.5
Very Long Chain Acyl CoA Dehydrogenase Deficiency (VLCADD)	9.3

Figure 5.1: Online resources to refer parents to during the phone conversation

- Program of Genetics & Metabolism, Winnipeg Regional Health Authority http://www.wrha.mb.ca/prog/genetics/newborn-screening.php
- Newborn Screening Ontario https://www.newbornscreening.on.ca/en
- Screening, Technology and Research in Genetics (STAR-G) Project https://www.newbornscreening.info/
- Save Babies Through Screening Foundation: http://www.savebabies.org/
- Baby's First Test http://www.babysfirsttest.org/
- Genetic Home Reference http://ghr.nlm.nih.gov/

Possible changes to these fact-sheets are suggested based on our interview data. First, simplifying the language of these fact-sheets would help them to be easier to understand, especially because not all individuals have completed secondary education in science. Second, more detailed information about the follow-up process could be provided to help parents be more prepared for what to expect. For example, details about the need for venipuncture and urine bags may be preferable over a general statement that blood and urine testing is necessary. Third, management information could be more specific by including a typical diet or feeding schedule. Again, this information could help parents to feel like they are in control of the situation and capable of managing the IEM. Next, fact-sheets could include the frequency of a false positive result for each indication. This statistic may help to provide parents with hope during the confirmatory testing period.

Lastly, a change in WRHA's NBS webpage design is recommended to make it easier to navigate and more user-friendly. The information from these fact-sheets should also be included on CPL's website because it is the centralized source of information on NBS in Manitoba. A parent in a rural community may not think to look on WRHA's website since they are outside of the city limits. Furthermore, WRHA's website requires the user to click on several links before viewing a pdf version of the fact-sheet. In comparison, Newborn Screening Ontario's website has all information readily available and imbedded in the website. The WRHA webpage hosting the fact-sheets is difficult to find if one does not know where to look online. It would be useful for parents to be provided with the link to the website when they are notified of their result via telephone.

5.5 Strategies for communicating a positive newborn screen for inborn errors of metabolism

5.5.1 At the time of disclosing a positive result

Based on interview responses, several strategies are suggested at various timepoints to improve communication of a positive NBS result. At the time of initially notifying families, this information should always be communicated by a laboratory or clinical genetic counsellor. This should be the case regardless of whether the sample was collected incorrectly, if a repeat DBS was required for an abnormal analyte, or if there was a critically abnormal result. Genetic counsellors are more qualified than pediatricians or family doctors to discuss this information because they have expertise in medical genetics and psychosocial counselling. If participants are notified by their local healthcare provider's office, our data and previous literature show that this news may be delivered by a medical secretary who is unfamiliar with the interpretation of the result (Buchbinder & Timmermans, 2012). Accurate information and empathy provided by genetic counsellors at the time of disclosure will help to minimize the impact of the anchoring effect on negatively influencing the patient's risk perception (Tversky & Kahneman, 1974).

Although it has been shown that families would rather be notified of their result by a healthcare provider that they were familiar with, this desire only applied if the pediatrician was able to fully answer all of their questions (Buchbinder & Timmermans, 2012; Schmidt et al., 2012). A survey of pediatricians showed that approximately half felt less than prepared to discuss a positive NBS result for an IEM (Gennaccaro, Waisbren, & Marsden, 2005). Additionally, our survey data suggested a statistically insignificant trend towards lower scores of depression, anxiety, and stress for participants notified of their result by the genetics team compared to those seen by local HCP. This disparity was also observed in our qualitative data.

Minor changes to the way genetic counsellors disclose a positive result may help to reduce the psychosocial impact of a positive NBS result. First, genetic counsellors should not censor information. Participants were frustrated that information was withheld from them, regardless of whether or not they reported being information seeking or information avoiding. Interestingly, other qualitative interviews (Buchbinder & Timmermans, 2012; Salm, Yetter, & Tluczek, 2012) have reported verbatim the theme of "kept in the dark", which is a phrase we used directly from a participant's quote to describe censorship of information. These studies were based in California and had very similar results which provide support that theoretical sufficiency was achieved in our study. Our data also show that these findings are reproducible in a Canadian population. Although healthcare providers may think that withholding details prevents parents from being overwhelmed, an incomplete explanation has been shown to lead to parental dissatisfaction with the communication of the result (Buchbinder & Timmermans, 2012).

Admittedly, a challenge of providing full details of an NBS result is that an abnormal analyte may indicate a variety of IEMs, meaning that it would be difficult to discuss each possible scenario. Clinicians may also be reluctant to go into detail if the analyte is only a minimal deviation from the normal range and it is highly likely to be a false positive result. Nonetheless, attempts should be made to provide as detailed of information as possible within reason. Information should not be withheld even if the result is unlikely to be a true positive.

Participants reported that any information at the time of the initial phone call was helpful. Overall, they wanted a brief description of the IEM, an indication of the positive predictive value of their NBS result, a description of the prognosis with and without management, and details on the follow-up process. In particular, parents felt that a plan before the appointment would have

helped them to feel emotionally grounded and think more logically. They would have also been mentally prepared for the length of the appointment and that venipuncture and a urine bag would be necessary. Similar suggestions have also been previously made based on data from American and European cohorts (Davis et al., 2006; Schmidt et al., 2012; Tluczek et al., 2009).

When discussing the urgency of confirmatory testing, genetic counsellors should demonstrate acceptance and understanding if it cannot be completed immediately due to unforeseen circumstances. Participants felt helpless if the sample could not be sent-off immediately, particularly if they tried to provide a sample on a Friday afternoon. Additionally, those in rural communities expressed that it was extremely challenging to drive several hours to the collection site with less than 24 hours of notice.

Lastly, genetic counsellors should ask the parent how they cope with uncertainty. As previously described, parents have many different coping mechanisms. Regardless of whether or not they are information seeking or avoiding, participants should be directed to WRHA's online fact-sheets or another source of reliable information (Deluca et al., 2013). Studies have shown that parents searching up disease information online without suggestions of where to search can increase parents' distress (Dunn, Gordon, Sein, & Ross, 2012). By starting parents off with a reliable source of information, they can choose if they want to stop reading or do additional research. At a minimum, they will have accurate information to refer back to when they are less emotionally overwhelmed and will have a resource to share with their partner about what was discussed initially over the phone.

5.5.2 At the time of meeting with the family

At the time of meeting with the family, patients should be provided with a private area to wait prior to the appointment. A buzzer or similar device may be useful to allow participants the freedom to move from the waiting room, as previously discussed. When starting the appointment, the genetics team should ensure that the clinic space is large enough to accommodate the family and all members of the team. Ideally, all clinicians should be present at the beginning of the appointment to introduce themselves and define their roles. A clinical psychologist or social worker should be present at the appointment, not just available on-call. Parents, especially mothers who recently had a Cesarean section delivery, should not be expected to be active participants in restraining the baby during sample collection. At the end of the appointment, families should have the contact information of all clinicians involved. A team member, typically the genetic counsellor, should identify themselves as the primary contact person who will be in touch with the family during the confirmatory testing period. A general turn-around-time for the results should also be provided.

5.5.3 During the confirmatory testing period

At the time of providing a requisition for confirmatory testing at an external laboratory, the laboratory should be contacted by the genetic counsellor. The genetic counsellor should verbally provide them with instructions on how to collect the sample in order to minimize the likelihood of a repeat draw because of mishandling. While patients are awaiting results, they could be invited to be a participant in a support group that runs on a monthly basis for parents with a positive NBS result. This session could be facilitated by a nurse, psychologist, or genetic assistant. Lastly, if results are still pending after 1 month, families should be contacted at least

once to let them know their status. Unlike typical genetic testing, these parents are required to treat their child as if they have an IEM before receiving results. Families deserve to be notified with up-to-date information if results have not been received by the projected turn-around-time.

5.6 Suggested changes for Manitoba's newborn screening program

In summary, the following modifications to Manitoba's newborn screening program are suggested based on participants responses. These strategies at various timepoints are summarized in Figure 5.2. Newborn screening should be introduced to parents in the prenatal period beginning at 30 weeks gestational age. OB/GYNs and midwives should be prepared to discuss the purpose of NBS, potential outcomes, and the follow-up process for a positive result.
At the time of sample collection, nurses on the maternity ward should reinforce these concepts by discussing this information with parents. They should physically provide parents with an information sheet or tear-away card on NBS for them to consider while they perform the dried blood spot. Nurses should reinforce that positive results occur often but do not necessarily mean that the baby is affected. Parents should be informed that they may be contacted with a positive result when they are discharged from the hospital. The filter paper with the DBS should include the contact information of parents. These demographics would streamline the process of informing families of their result and avoid the unnecessary challenges of contacting doctors for the information of newborns who have not yet been registered as a patient at their practice.

All positive results should be disclosed by a laboratory or clinical genetic counsellor. CPL may benefit from hiring a laboratory genetic counsellor to call out all positive results that are not forwarded to the Genetics & Metabolism team. This change would ensure that all families have access to a genetic counsellor and receive accurate and detailed information about

Figure 5.2: Strategies for improving communication of a positive newborn screen for inborn errors of metabolism

At the time of the heel prick…

1. Hand parents an information sheet on newborn screening.
2. Provide statistics on how often false positive and true positive results occur.
3. Provide information on what symptoms are suggestive of an inborn error of metabolism.
4. Reinforce that affected children are asymptomatic initially.
5. Communicate that they will be contacted by telephone if they have a positive newborn screen.

At the time of communicating a positive result…

1. Genetic counsellors should be the healthcare provider notifying the family.
2. When expressing the urgency of completing confirmatory testing, demonstrate acceptance and understanding if it cannot be completed immediately due to unforeseen circumstances.
3. Outline the logistics of what will take place during the meeting with the genetics team, including how long the appointment will be, who they will be meeting with, and that several tests will need to be done (including the possibility of venipuncture and a urine bag).
4. Do not censor information.
5. Ask how they cope with uncertainty.
6. Provide website recommendations to patients.

At the time of meeting with the family…

1. Have them wait in a private area prior to the appointment.
2. Integrate clinical psychologists or social workers into the multidisciplinary team.
3. Clearly define the role of all healthcare providers on the team.
4. Identify who will be their primary contact person throughout the confirmatory testing period.

During the confirmatory testing period…

1. When sending a requisition to external laboratories for confirmatory testing, provide a coversheet that explains what newborn screening is and why a sample is necessary.
2. Host a support group on a monthly basis for families who have a positive NBS result.
3. If results are still pending after 1 month, contact families to let them know you still have not received results.

their result without placing extra burden on the clinical team. The laboratory genetic counsellor could also assist with designing educational material to be distributed to patients and other healthcare providers. A dedicated NBS clinical genetic counsellor should also be hired for the Genetics & Metabolism Program in order to ensure continuity between disclosing a positive result and meeting with the genetics team. The genetics team plays an essential role in educating

patients and other healthcare providers about NBS and adequate staffing is required to meet this demand. Patients should be directed to NBS fact-sheets created by the genetics team as a starting point for finding information online.

A clinical psychologist or social worker should meet with all parents with a positive NBS result who plan to be seen by the genetics team. This psychosocial support should be integrated as part of all initial NBS appointments. A support group or parent-to-parent support system should also be considered for parents with a positive NBS result. These suggestions could be coordinated by a clinical psychologist, social worker, genetic counsellor, or metabolic nurse.

Accurate sample collection for confirmatory testing is required to avoid unnecessary redraws which cause families psychosocial harm. This may involve more coordination between the NBS genetic counsellor, the site of sample collection, and the biochemical genetics laboratory performing the analysis. If a positive NBS is seen on a Friday, parents should be informed that their child will be okay over the weekend and sample collection can be performed on Monday. If a sample is collected from a rural laboratory on a Friday, it is unlikely to be received by the analyzing laboratory before the sample is spoiled. Since certain assays need to be performed in a time-sensitive manner from the time of sample collection, this poor planning may lead to uninterpretable test results and a repeated sample. Additionally, quicker turn-around-time for results would lessen the period of uncertainty during which parents experience an adverse psychosocial response. An integrated laboratory that also performs confirmatory testing would help in this regard.

Lastly, improved medical school curriculum with increased integration of genetics knowledge will help physicians from all specialties to be familiar with IEMs. This will facilitate

OB/GYNs, pediatricians, family doctors, and emergency physicians to be able to comfortably discuss these topics with patients who have a positive NBS result.

5.7 Limitations

This thesis is not without limitations. The survey results represented a small sample size which precluded statistically significant conclusions from being drawn. The small sample size was likely due to a variety of reasons, including inaccurate last known mailing addresses, lack of a reminder invitation, and exclusion of participants without access to internet services or a mobile device. First, an inaccurate last known mailing address is demonstrated by 71 surveys (14.7%) being returned to sender or undeliverable. It is possible that the Genetics & Metabolism Program had an inaccurate mailing address stored in their records, or that the intended recipient moved since their demographic information was last updated. Second, a lottery scratch card was used as incentive to complete the survey instead of a reminder invitation because of limited funds. A lottery scratch card has been shown to be more effective at improving response rate than a monetary incentive (Olsen, Abelsen, & Olsen, 2012) and an unconditional incentive has been shown to increase the response rate more than a reminder survey or a conditional incentive (Iglesias et al., 2002). Unfortunately, its implementation in this study did not mimic the literature. Third, the online survey also excluded participation of individuals without internet access, which may have inadvertently caused underrepresentation of the Indigenous population and members of rural communities. These groups comprise a significant portion of Manitoba's demographic.

Unfortunately, the conclusions from the survey were anecdotal because of the small sample size. The scale used to measure the psychosocial response in participants was appropriate

based on themes identified in the literature. In comparison to other well-established tools such as the Beck Depression Inventory and the Beck Anxiety Inventory, the DASS has a correlation of 0.81 and 0.74, respectively, and has a greater degree of separation between the various emotional states (P. F. Lovibond & Lovibond, 1995). The DASS-21 is highly precise in a non-clinical sample in comparison to the long-version of the DASS, with a reliability of 0.88 for depression, 0.82 for anxiety, 0.90 for stress, and 0.93 overall (Henry & Crawford, 2005). Thus, the DASS-21 was a suitable choice to be included in the survey design as it is a brief but reliable measure of the psychosocial response to a positive NBS result.

The methodology of the interviews may have also limited our analysis. Potential concerns associated with telephone interviews include data loss or distortion due to absence of non-verbal cues (Novick, 2008). This method was chosen because it was cost-effective and allowed for greater flexibility in scheduling. To its benefit, telephone interviews may minimize power imbalance between the interviewer and the interviewee by scheduling the interview based on respondents' preference (Glogowska et al., 2011). This method has been shown to improve the richness of information due to factors that cannot be achieved in face-to-face interviews (Drabble et al., 2016; Glogowska et al., 2011; Novick, 2008). These factors include privacy due to perceived anonymity, reduced self-consciousness from note-taking, and increased comfort due to an interview environment that is familiar to the respondent (Drabble et al., 2016; Glogowska et al., 2011; Novick, 2008). Overall, telephone interviews have been established as a robust method of gathering in-depth information on an individual's personal experiences and were the most suitable choice for this project.

Despite our best attempts to maintain rigor in the qualitative process, several factors may have influenced interview results. First, the interview sample was composed of highly motivated

individuals, as demonstrated by 17/21 (80.96%) survey respondents providing their contact information for a follow-up interview. It is possible that the sample reflects a skewed proportion of individuals who were more inclined to voice their experience because of a particularly traumatizing or good experience. Thus, responses may indicate opposite ends of the spectrum in terms of potential experiences with NBS.

Second, occupations in the healthcare field are overrepresented in the interview sample. This impact may be interpreted in two opposing ways. The challenges with NBS that highly educated participants encountered may be more pronounced in a less educated sample. A less educated sample may have poorer literacy to understand information related to NBS and less social supports to offset the psychosocial impact of a positive result. Conversely, it is also possible that individuals who work in the healthcare field are more prone to anxiety because they have observed poor health outcomes through their work. They may also tend to use information-seeking as their coping mechanism whereas other individuals in the general population may be less inclined to worry during the confirmatory testing period.

Lastly, the time that passed since the actual event of a positive NBS result may have impacted participants' perception of the experience compared to how they felt when it initially occurred. Some participants received their positive result as many as seven years ago. Since that time, it is possible they forgot the magnitude of emotions they experienced. It is also possible that they were more likely to respond because of a negative experience or that the experience was particularly memorable because it occurred close to a holiday or weekend. Similar studies have shown that learning of a positive NBS result around these times was associated with increased parental anxiety (Schmidt et al., 2012). If parents can still remember how they felt many years after receiving a result, it is likely that NBS stands out as a significant experience in

their mind. Parents may have also had a difficult time recalling their experience if it was a repressed traumatic memory.

5.8 Future Directions

Further research is needed to validate the hypotheses generated by these results. A repeated study using the survey on a prospective sample may allow for statistically significant conclusions to be drawn. Additionally, participants expressed the need for additional psychosocial supports and discussed the use of a support group, similar to those available for new moms that are breast feeding. A randomized controlled trial examining the efficacy of support groups for a positive NBS result may help to establish their benefit in reducing the psychosocial impact that parents experience and provide further evidence for the integration of support groups into NBS programs. Participants also felt that receiving a positive NBS result negatively impacted their recovery from the birthing process. This relationship, and the potential relationship with post-partum depression, is another interesting topic to be explored in the future. Lastly, the contrast of information seeking versus information avoiding when coping with uncertain results is an important area of research for genetic counselling. This topic is of great relevance to the profession as patients being seen for various indications may receive results with variants of uncertain significance or pathogenic mutations in genes with reduced penetrance.

Additional research is also necessary to explore how to refine the roles of various healthcare providers in delivery of NBS. Since some participants expressed that NBS should be introduced in the prenatal period, a survey delivered to the Society of Obstetricians and Gynecologists of Canada may be useful to elucidate receptivity and preparedness of OB/GYNs to discuss this content with their patients. Just as genetic counsellors provide pre-test counselling

for genetic testing, it is important that parents receive pre-test counselling for NBS in order to reduce the psychosocial impact of a positive initial result. Additionally, targeted education to nurses on the maternity ward, laboratory technicians, and emergency department staff may help to reinforce important messages about NBS. It is imperative that these groups have a proper understanding of what conditions are screened for, why screening is performed, and the possible outcomes of NBS because they are on the front-lines interacting with patients during sample collection or medical intervention during a metabolic crisis.

Further studies may also be needed to confirm that genetic counsellors should be the sole healthcare provider disclosing a positive NBS result. Currently in Manitoba, this task is a shared responsibility between family doctors, midwives, pediatricians, and genetic counsellors. A survey distributed to the professional associations of these healthcare providers may be useful to validate that genetic counsellors are the most equipped for performing this role. This research may also help to clarify which concepts of NBS healthcare providers have difficulty understanding and facilitate targeted supplementary education to these providers.

Lastly, broader questions regarding the overall model of NBS are likely to be of importance in the future. This includes examining if follow-up genetic counselling should be provided for all positive results and what the of role genetic counsellors should be in NBS if whole exome sequencing is used in replacement of or in addition to MS/MS.

CHAPTER SIX:

CONCLUDING REMARKS

In summary, parents whose children had a positive result for an IEM detected through Manitoba's NBS program from 2011-2017 were surveyed and interviewed. Survey results, despite not being statistically significant, suggested that participants were uninformed about NBS. Additionally, individuals with a false positive result that were notified by the genetics team tended to have lower scores on the DASS21 in all categories compared to those that were notified by their local care provider. In qualitative interviews, parents discussed when they would like information about NBS to be introduced, what messages they felt were important to include in educational resources, how they were accessing these resources, and when in the NBS process they would like to receive this information. Based on participant responses and previous literature, the topic of NBS should be introduced to patients in the prenatal period. Parents should be provided with additional information at the time of sample collection. Current educational resources are successful in addressing the majority of topics that parents desire to know, but suggested revisions include adding the frequency of a false positive result, symptoms suggestive of an IEM, and details for the follow-up process. Parents are unaware that these resources exist because they perform general internet searches unrelated to NBS, therefore, these resources should be made into user friendly websites that are more searchable online. Parents should be provided with a link directly to this information at the time of receiving a positive result, and this news should be communicated by a laboratory or clinical genetic counsellor specialized in NBS.

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APPENDIX

A.1 Invitation Letter

To Whom It May Concern,

You are invited to participate in a research study that is being performed at the University of Manitoba. The title of the graduate thesis project is, "Reducing the psychosocial impact of a false positive newborn screen for inborn errors of metabolism".

You are being asked to consider participation in a survey and interview study. Clinicians with the Department of Metabolism at Health Sciences Centre have been asked to forward this package to families whose child had a positive newborn screening result between 2011-2017. Your personal health information has not been accessed by anyone outside of your healthcare team.

This survey is being conducted to assess the educational and emotional impact of geneticists/genetic counsellors on patients whose child had a false positive newborn screening result for an inherited metabolic disease. Your participation is important to us and may help us provide guidelines for future educational resources on newborn screening for families who screen positive.

Your responses will be collected through completion of an online survey which will ask you a series of questions and should take about 10-15 minutes to complete. Please use the following link or QR code to access the online survey that is compatible with your mobile device or personal computer.

Link to online survey

Your participation is completely voluntary. As an expression of our gratitude, we are happy to enclose a scratch lottery ticket as a gift. The gift is yours whether or not you respond to the questionnaire.

You may only answer the questions you feel comfortable answering. The risks of participating are low. You may be requested to complete sensitive questions that may be upsetting. **You are not required to provide any personal information such as your name, address, or telephone number.** Your responses will be anonymous as we will not know who has completed the survey and it will not be linked to any other information about you.

The online survey will not record your e-mail address or IP (Internet protocol) address. If you agree to participate in the survey, please note that you must complete it in one sitting (in other words, the system won't let you save your survey responses and return to complete them later). Also, please note that when you submit your response you will not be able to withdraw them as we cannot link the survey responses back to you.

Additionally, if you are willing to be contacted for a telephone interview, please contact the graduate student conducting the study, **Rachelle Dinchong, at or by email at** . Your personal information will be handled separately for the purposes of being contacted about the interview and will not be linked to study responses. Participation is optional and participants who are selected for an interview will receive a $10 Tim Horton's gift card as a show of our appreciation for their time. Please find the interview consent form enclosed for your consideration.

If you have any questions about this study, please do not hesitate to contact Rachelle Dinchong at . Thank you in advance for your participation.

Sincerely,

Rachelle Dinchong, HBSc
MSc Genetic Counselling Candidate
Department of Biochemistry & Medical Genetics

Patrick Frosk, PhD, MD, FRCPC, FCCMG
Clinical Geneticist, Assistant Professor
Department of Pediatrics & Child Health

The study is funded by the University of Manitoba. This study and survey has been approved by the University of Manitoba Health Research Ethics Board and the HSC Pediatric Research Coordinating Committee. Completion of the online survey implies your consent for the purposes

A.2 Survey

Part 1: Demographic Characteristics

1. What province or territory do you live in?
    a. Manitoba
    b. Ontario
    c. Nunavut
    d. Saskatchewan
2. Do you live in an urban or rural community?
    a. Urban (a city environment)
    b. Rural (a small or isolated community)
3. What year was your child who most recently screened positive on the newborn screen born?
    a. 2011
    b. 2012
    c. 2013
    d. 2014
    e. 2015
    f. 2016
    g. 2017
4. How old were you at the time of this child's birth?
    a. 25 years old or less
    b. 26-30 years old
    c. 31-35 years old
    d. 36 years old or more
5. Was this your first child?
    a. Yes
    b. No
6. How many weeks into the pregnancy were you when this child was delivered?
    a. Less than 35 weeks
    b. 35 weeks or more
7. What is your highest level of education?
    a. High-school or less
    b. College/CEGEP
    c. Undergraduate
    d. Graduate or professional school
8. What is your combined household income?
    a. Less than $75,000
    b. $75,000 or more

Part 2: Newborn Screening Experience

Recall your newborn screening experience as you answer the following questions. There is no right or wrong answer. Do not spend too much time on each question.

1. Please select the scenario that most closely matched your outcome during the newborn screening process.
    a. My newborn baby had a heel prick test performed before leaving the hospital. A few days later, I received a phone call from my local nursing station. I was told that my baby had a positive newborn screen for an inherited metabolic disease. After seeing my local doctor for additional testing, I was told that my baby had a "false positive" result. In other words, my baby did not have the genetic condition and was actually healthy.
    b. My newborn baby had a heel prick test performed before leaving the hospital. A few days later, I received a phone call from a geneticist/genetic counsellor in Winnipeg. I

was told that my baby had a positive newborn screen for an inherited metabolic disease and I needed to come to Winnipeg to have an appointment with the Genetics department. After several weeks of waiting for additional testing to be done, I was told that my baby had a "false positive" result. In other words, my baby did not have the genetic condition and was actually healthy.

c. My newborn baby had a heel prick test performed before leaving the hospital. A few days later, I received a phone call from a geneticist/genetic counsellor in Winnipeg. I was told that my baby had a positive newborn screen for an inherited metabolic disease and I needed to come to Winnipeg to have an appointment with the Genetics department. After several weeks of additional testing, my baby was officially diagnosed with an inherited metabolic disease. My child is now on a special formula, diet, medication, or other management plan to prevent further complications.

2. Did a family doctor, nurse practitioner, or other local healthcare provider follow-up with you regarding your child's positive newborn screening result?
    a. Yes
    b. No
    c. I do not know

3. Did a geneticist or genetic counsellor follow-up with you regarding your child's positive newborn screening result?
    a. Yes
    b. No
    c. I do not know

4. Was your child later diagnosed with a genetic disease after the newborn screening result for which they are on a special formula, diet, medication, etc to prevent further complications?
    a. Yes
    b. No
    c. I do not know

5. What condition did your child screen positive for?
    a. I do not know
    b. PKU - Phenylketonuria
    c. TYR - Tyrosinemia
    d. HCY - Homocysteinuria
    e. CIT - Citrullinemia
    f. ASA - Argininosuccinic acidemia
    g. MSUD - Maple Syrup Urine Disease
    h. IVA - Isovaleric acidemia
    i. GA1 - Glutaric acidemia type 1
    j. HMG deficiency - 3-hydroxy-3-methylglutaryl-CoA lyase deficiency
    k. MCD - Multiple carboxylase deficiency

l. PA - Propionic acidemia
m. MMA - Methylmalonic acidemia
n. 3-MCC deficiency - 3-methylcrotonyl-CoA carboxylase deficiency
o. BKT deficiency - ß-Ketothiolase deficiency
p. 2,4-dienoyl-CoA reductase deficiency
q. SCADD - Short chain acyl-CoA dehydrogenase deficiency
r. MCADD - Medium chain acyl-CoA dehydrogenase deficiency
s. VLCADD - Very long chain acyl-CoA dehydrogenase deficiency
t. LCHADD - Long chain 3-hydroxyacyl-CoA dehydrogenase deficiency
u. TFP deficiency - Trifunctional protein deficiency
v. CUD - Carnitine uptake defect

Please use the rating scale below to answer the following questions.

0 Not at all
1 Minimally
2 Yes, slightly
3 Yes, fully

6. I understood that newborn screening was being performed on my child.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

7. I understood the reason why newborn screening was being performed on my child.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

8. I understood the possible test results before screening was performed.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

9. I understood the specific genetic condition for which my newborn tested positive.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

10. I understood what this screening result meant.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

11. I was aware that resources existed to help me understand the newborn screening process.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

a. How did you learn that these resources existed?
i. Internet search
ii. Brochure/Infosheet
iii. Family/friend
iv. Family doctor/nurse

v. Geneticist/genetic counsellor
vi. Other _____

b. What were these resources? _____

12. I found resources that I accessed to be useful.
0 (Not at all) 1 (Minimally) 2 (Yes, slightly) 3 (Yes, fully)

a. How did you access these resources?
i. Computer
ii. Smart phone
iii. Printed Brochure/Infosheet
iv. Family doctor/nurse
v. Geneticist/genetic counsellor
vi. Other _____

b. What topics did the resource include?
i. Reason for newborn screening
ii. Results interpretation
iii. Disease specific information
iv. Other _____

Part 3: DASS21

Please think back to the time between receiving a positive newborn screening result and receiving a definitive result (an actual diagnosis or being told your child is healthy). Please read each statement and rate how you felt during this period. There are no right or wrong answers. Do not spend too much time on any statement.

The rating scale is as follows:
0 Did not apply to me at all
1 Applied to me to some degree, or some of the time
2 Applied to me to a considerable degree or a good part of time
3 Applied to me very much or most of the time

1. (s) I found it hard to wind down.	0	1	2	3
2. (a) I was aware of dryness of my mouth.	0	1	2	3
3. (d) I couldn't seem to experience any positive feeling at all.	0	1	2	3
4. (a) I experienced breathing difficulty (e.g. excessively rapid breathing, breathlessness in the absence of physical exertion).	0	1	2	3
5. (d) I found it difficult to work up the initiative to do things.	0	1	2	3
6. (s) I tended to over-react to situations.	0	1	2	3
7. (a) I experienced trembling (e.g. in the hands).	0	1	2	3

8. (s) I felt that I was using a lot of nervous energy.	0	1	2	3
9. (a) I was worried about situations in which I might panic and make a fool of myself.	0	1	2	3
10. (d) I felt that I had nothing to look forward to.	0	1	2	3
11. (s) I found myself getting agitated.	0	1	2	3
12. (s) I found it difficult to relax.	0	1	2	3
13. (d) I felt down-hearted and blue.	0	1	2	3
14. (s) I was intolerant of anything that kept me from getting on with what I was doing.	0	1	2	3
15. (a) I felt I was close to panic.	0	1	2	3
16. (d) I was unable to become enthusiastic about anything.	0	1	2	3
17. (d) I felt I wasn't worth much as a person.	0	1	2	3
18. (s) I felt that I was rather touchy.	0	1	2	3
19. (a) I was aware of the action of my heart in the absence of physical exertion (e.g. sense of heart rate increase, heart missing a beat).	0	1	2	3
20. (a) I felt scared without any good reason.	0	1	2	3
21. (d) I felt that life was meaningless.	0	1	2	3

Thank you for completing in this survey. If you are willing to be contacted for a follow-up telephone interview which may take up to 1 hour in duration, please contact the lead researcher, **Rachelle Dinchong, at or by email at .** Your personal information will be handled separately for the purposes of being contacted about the interview and will not be linked to study responses. Participation is optional and participants who are selected for an interview will receive a $10 Tim Horton's gift card as a show of our appreciation for their time.

A.3 Interview Guide

Hello,

May I speak with _____? My name is Rachelle Dinchong, I am a researcher with the Faculty of Health Sciences at the University of Manitoba. You recently completed a survey on newborn screening and you previously emailed me indicating that you are willing to be contacted regarding a follow-up interview at this time. Is now an okay time for you to talk about this more? How are you doing today? *Establish rapport*

The purpose of this interview is to provide guidelines for future educational resources on newborn screening for families who screen positive. Through our interview today, we hope to learn more about what information is most important for families to know, how they'd like to receive this information, and when in the newborn screening process they would like to know this information. Participating in this interview is optional and may take up to 1 hour. There is a consent form that I need to review with you before beginning (it's the same one you would have received in the mail). Would you like to continue?

[Read Interview Consent Form]

[Begin interview after receiving verbal consent]

"Thank you again for agreeing to participate in this interview. I will be asking you a range of questions. Please feel free to let me know if you would prefer to not answer a question, or if you would like to take a break at any time."

1. I would like you to think back to your experience with newborn screening. What was your experience like?
    a. How did you feel when you received the phone call notifying you of the positive newborn screening result?
    b. What information were you told at this time?
    c. Who told you this information? (Genetic counsellor, nursing station, etc)
    d. Did you know any of this information already? How did you learn this?
    e. Did you feel the need for additional information? Why?
    f. What did you do next?
2. What information do you wish you had known at the time of the positive newborn screening result?
    a. If you had known that information, would it have made you feel any differently? Why?
    b. Thinking back to that time, were you more concerned about learning about the specific metabolic disease or the follow-up process to rule out a diagnosis?
    c. What information was not helpful to you at the time of the screen positive result? Why?
3. What method of accessing information would be the most accessible to you and why? For example, online, brochure from health care provider, etc.

    a. What do you think would be the best way to let others know that this information exists?
    b. Were there any barriers that made it more difficult for you to access this information?
    c. What search terms or websites did you use to find information online about your newborn screening result?
    d. If you knew this information was available to you in your desired format, would you have felt any differently or done anything differently?
4. At what point in the newborn screening process would you have benefitted most from this information and why? For example, during the pregnancy, before the heel prick, when contacted about result, etc.
    a. In what way would you like this topic to have been brought up?
    b. Would knowing about this information earlier change your emotional reaction to the initial phone call about the positive newborn screening result?
5. Is there anything else that you would like to add that would be helpful for us to know?

Examples of Affirmations:
"Thank you for sharing your experience. That sounds like it was a _____ experience for you"
"Mhm, right, ok, yup, etc" helps to show active listening

Examples of Probes:
- "Tell me more about that"
- "Can you give me an example of that"
- If still being vague after a few probes, move on (don't jeopardize rapport)

Examples of Wrap-Up:
- Wait for lull in conversation then interject
- Summarize and bring back to main point of what they're saying
- "Thanks for sharing that, just being mindful of time, the next question I wanted to ask you is"
- "Thanks for sharing that, I'm still looking forward to hearing your experience for the next question and would like to move on for the sake of time"

[Interview concludes]

Thank you very much for participating in this interview. We will mail you a $10 Tim Horton's gift card as appreciation for your time. What mailing address is best for us to use?

If you have any additional questions about this research study or how the information you provided is being used, please feel free to contact me, Rachelle Dinchong, at .
Thank you for your time.