# Analysis of Parent Perception of Newborn Screening for Lysosomal Storage Disorders

by

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## Abstract

Lysosomal storage disorders (LSD) are a family of rare metabolic disorders that include Pompe disease and Mucopolysaccharidosis Type 1 (MPS1). Pompe disease is caused by deficiencies in the lysosomal enzyme alpha-glucosidase (GAA). This diagnosis is generally divided into infantile and late onset, but can exist along a spectrum. The main feature of Pompe disease is progressive muscle weakness, and in the infantile onset form, cardiomyopathy is present as well. MPS1 results from a deficiency in the lysosomal enzyme alpha-L-iduronidase (IDUA). Features include progressive neurological disease, skeletal abnormalities, cardiac disease, corneal clouding, hearing loss and hepatomegaly. The diagnosis has been stratified into MPS1 or attenuated MPS1, and severity or development of symptoms is dependent on the type. Both Pompe disease and MPS1 were recently added to the newborn screening panel. With their addition, a number of challenges have occurred including negative psychosocial impact on parents of infants who have an abnormal newborn screening result. The purpose of this study was to examine the experience and perceptions of parents/caregivers of an infant who had a positive newborn screening result for Pompe disease or MPS1.

A survey was distributed via email and mailer, to parents and caregivers followed by the UPMC Children's Hospital of Pittsburgh and the Children's Hospital of Philadelphia. The survey consisted of questions specific to newborn screening of LSDs. Parent responses, were consistent with the literature, indicating that this period was categorized by stress and uncertainty. Of the five

respondents, 100% described initial disclosure of the newborn screening results as difficult. Responses suggest that negative emotions were fueled by lack of information provided about the results, and provider's lack of knowledge. Similar to published literature, this study indicated the majority of infants are not diagnosed with the most severe forms of the disorders. Results of this study may have implications for how genetic counselors care for these families and how they communicate with other providers. Likewise, it demonstrates public health relevance given the large scale in which newborn screening is utilized. This information can be used by providers in their own practice and may even influence standard of care.

## Table of Contents

**Preface** ..... x

**1.0 Introduction** ..... 1

**1.1 Specific Aims** ..... 3

**2.0 Literature Review** ..... 4

**2.1 Lysosomal Storage Disorders** ..... 4

**2.1.1 Pompe Disease** ..... 4

**2.1.2 Mucopolysaccharidosis Type 1** ..... 10

**2.2 Newborn Screening** ..... 17

**2.2.1 Methods of Testing** ..... 17

**2.2.2 Criteria for Newborn Screen** ..... 18

**2.2.3 Lysosomal Storage Disorders and Newborn Screening** ..... 19

**3.0 Manuscript** ..... 25

**3.1 Background** ..... 25

**3.2 Methods** ..... 29

**3.2.1 Participants** ..... 29

**3.2.2 Survey Development** ..... 30

**3.2.3 Data Collection** ..... 31

**3.3 Results** ..... 32

**3.3.1 Demographics** ..... 32

**3.3.2 Disclosure of Final Newborn Screening Results** ..... 33

**3.3.3 Initial Genetic Appointment and Diagnosis** ..... 35

**3.3.4 Perception of Newborn Screening** ..... 37

**3.3.5 Stress Scale** ..... **38**

**3.4 Discussion** ..... **39**

**3.4.1 Demographics** ..... **39**

**3.4.2 Disclosure of Final Newborn Screening Results** ..... **39**

**3.4.3 Initial Genetics Appointment and Diagnosis** ..... **41**

**3.4.4 Perception of Newborn Screening** ..... **42**

**3.4.5 Stress Scale** ..... **43**

**3.4.6 Study Limitations** ..... **44**

**3.4.7 Future Directions** ..... **45**

**3.5 Conclusion** ..... **47**

**4.0 Research Significance to Genetic Counseling and Public Health** ..... **49**

**Appendix A University of Pittsburgh IRB Approval** ..... **51**

**Appendix B Permission to Use Stress Scale** ..... **52**

**Appendix C Recruitment Email for the UPMC Children's Hospital of Pittsburgh** ..... **53**

**Appendix D Recruitment Mailer for the UPMC Children's Hospital of Pittsburgh** ..... **54**

**Appendix E Recruitment Email for the Children's Hospital of Philadelphia** ..... **55**

**Appendix F Survey** ..... **56**

..... **58**

**Appendix G Supplemental Figures** ..... **68**

**Bibliography** ..... **72**

## List of Tables

**Table 1 Demographics** ..... **33**

**Table 2 Results Disclosure** ..... **34**

**Table 3. Parent Perception** ..... **35**

**Table 4 Parent Perception and Actions** ..... **37**

**Table 5 Parent Perception of Newborn Screening** ..... **38**

**Table 6 Stress Scale Scores** ..... **38**

**Table 7 Additional Demographic Information** ..... **68**

**Table 8. Perception Toward Newborn Screening Results Disclosure** ..... **69**

**Table 9 Perception Post-Genetics Appointment** ..... **70**

**Table 10 Perception of Newborn Screening** ..... **70**

**Table 11 Stress Scale** ..... **71**

## List of Figures

**Figure 1 Confirmed Diagnoses ..... 36**

## Preface

I would like to extend my sincerest gratitude to the parents and patients within the Lysosomal Storage Disorders community, whose resilience and dedication was the inspiration for this study. With a special thank you to the parents who took time to participate in this study. Without their participation this study would not be possible. I also want to thank my entire committee for their support throughout this process. To Nadene, Dr. Ortiz, and Josh, thank you all for one of the best experiences of my graduate career. During my optional rotation, I was continuously impressed by your team's knowledge and care of these patients. I learned something new every day. You all made me feel supported and like one of the team, which only continued over these last few months. I would also very much like to thank Dr. Robin E. Grubs, who has been an incredible support system throughout my entire graduate career. Many a time I sought out your advice and you were always there. You read every document, gave wonderful feedback, and guided me through many decisions. Thank you to Dr. Todd Bear for lending his expertise. The survey was integral to this study, and so his knowledge was greatly appreciated. Thank you to all my family, friends, and mentors for their encouragement. Lastly, I would like to extend a huge thank you to my classmates. You all are all some of the most wonderful people and I am grateful to have experienced these two years with all of you.

## 1.0 Introduction

Lysosomal storage disorders (LSDs) are a group of over 50 rare inborn errors of metabolism. These conditions are categorized by impaired lysosome function that typically leads to multisystem health manifestations. Of the 50 conditions, two that have been well described are Pompe disease and Mucopolysaccharidosis Type 1 (MPS1). In recent years, the development of treatment as well as more efficient screening technology have made it possible for early detection of these conditions. For this reason, Pompe disease and MPS1 were added to the Recommended Uniform Screening Panel (RUSP) in 2015 and 2016.

Pompe disease, also known as glycogen storage disease type II, is an autosomal recessive condition that is estimated to occur in 1/40,000 live births (Hayley, Fragal, & Skrinar, 2003). This condition results from variants in the *GAA* gene, which ultimately leads to impaired functioning of the lysosomal enzyme alpha-glucosidase. When this enzyme is not working properly, glycogen builds up in the body resulting in multiple health problems (Leslie & Bailey, 2017). Diagnoses are categorized into two subtypes, infantile onset (IOPD) and late onset (LOPD). Individuals with IOPD have earlier presentations and more severe symptoms. The main systems impacted are the musculoskeletal and cardiovascular systems. In addition, patients may also experience respiratory complications, macroglossia, failure to thrive, and hepatomegaly (Van den Hout et al., 2003). LOPD is distinguished from IOPD by age of diagnosis (over the age of 12 months) as well as absent cardiac findings. Clinical features of LOPD are more variable amongst patients. For both groups of patients, care should be established with a multidisciplinary team. Likewise, when the individual's phenotype warrants it, initiation of enzyme replacement therapy (ERT) is also

recommended (Kishnani et al., 2016). Currently, ERT is the only FDA approved therapy for Pompe, however, research options may also be available.

MPS1 is an autosomal recessive condition that is caused by a deficiency of the lysosomal enzyme alpha-L-iduronidase (Clarke, 2002) and is due to variants in the *IDUA* gene. The incidence of MPS1 is estimated to be 1/100,000 live births (National Organization for Rare Disorders). As a result of impaired enzyme activity, an accumulation of glycosaminoglycans (GAGs) occurs in the body. In particular, GAG accumulation affects the skeletal system, neurologic functioning, cognitive and physical development, hepatic function, vision, and cardiovascular system. MPS1 is a highly variable condition and diagnoses are broadly placed into one of two categories, MPS1 and attenuated MPS1. In all cases, a multidisciplinary team is needed to manage the manifestations of this condition. Approved by the FDA in 2003, ERT has also become routine in the care of these patients. In the more severe cases, hematopoietic stem cell transplant (HSCT) may be utilized. Individuals may also enroll in research trials studying various other treatments such as gene therapy.

For both MPS1 and Pompe disease, the gold standard for diagnosis is an enzymatic assay specific to the deficient enzyme. Earlier detection of these disorders was of interest given that early intervention has been shown to improve clinical outcome (Wyatt et al., 2012). Key advancements in technology and therapies made it plausible for the addition of Pompe and MPS1 to the newborn screen. A key advancement came in 2001 when Chamoles *et al.* uncovered that lysosomal enzymes present in a dried blood spot (DBS) retain their activity. This was the first study that showed it was possible to test for lysosomal enzymes in a DBS sample. Finally, in 2015 and 2016 the US Secretary of Health and Human Services approved the addition of both conditions to newborn screening. The main justifications were the availability of treatment, ability to screen effectively,

and proven benefit of early treatment (Bodamer, Scott, & Giugliani, 2017; Donati, Pasquini, Spada, Polo, & Burlina, 2018). Nonetheless, their addition to newborn screening engendered controversy because it also elicits the detection of individuals with later onset forms, pseudodeficiencies, and variants of uncertain significance. Existing literature examining parental impact of newborn screening for Pompe disease and MPS1 is limited. However, studies on a variety of inborn errors of metabolism have suggested that the newborn screening period is a time of uncertainty and fear for parents (Pruniski, Lisi, & Ali, 2018). The goal of this study was to examine parents' and caregivers' experience during the newborn screening period for MPSI and Pompe disease. The information gained from this study has the potential to influence the way health care providers guide parents through the experience of receiving an abnormal newborn screen test result for these two conditions, and potentially other LSDs that are being considered for addition to the newborn screening panel. Understanding both the psychosocial and medical experience of these parents may allow for more competent care of families.

### 1.1 Specific Aims

**Specific Aim 1:** Recruit parents and caregivers of children identified through newborn screening to be at risk for MPS1 or Pompe disease

**Specific Aim 2:** Develop a survey specific for Pompe disease and MPS1 to elicit the experiences of parents and caregivers during the newborn screening process

**Specific Aim 3:** Use descriptive statistics to analyze and interpret qualitative and quantitative data

# 2.0 Literature Review

## 2.1 Lysosomal Storage Disorders

Lysosomal storage disorders (LSDs) are a group of over 50 different metabolic conditions that impact the function of the lysosome. In the general population, the incidence of lysosomal storage disorders is approximately 1/7700 live births and the carrier frequency is 1/100. These conditions are typically characterized by impaired activity of individual lysosomal enzymes. Alternatively, storage disorder phenotypes have also been reported in individuals with defects in lysosome biogenesis, impaired receptor activator proteins, defects in the membrane proteins, and transporter abnormalities (Parkinson-Lawrence et al., 2010). The altered metabolism leads to a build-up of toxic substrate within the cells, which ultimately leads to impaired cellular function (National Organization for Rare Disorders; Parkinson-Lawrence et al., 2010). As a result, impairment of multiple organ systems can occur. This literature review aims to focus on two particular lysosomal storage disorders, Pompe disease and Mucopolysaccharidosis Type 1, as these are the conditions of interest for the study.

### 2.1.1 Pompe Disease

#### *Clinical Features*

Pompe disease, also known as glycogen storage disorder type II, occurs due to a deficiency in the lysosomal enzyme alpha-glucosidase (GAA), which results in the buildup of glycogen in the body (Leslie & Bailey, 2017). It is estimated that the incidence of Pompe is 1/40,000 live births

(Hayley et al., 2003). Phenotypes are quite variable, however, two broad categories of diagnoses exist, infantile (IOPD) and late-onset (LOPD). The diagnoses are distinguished by age of onset, severity of symptoms, organs impacted, and the rate of progression (Kishnani et al., 2016).

The infantile form of the disease is typically characterized by an onset within the first months of life and cardiac impairment (Angelini & Semplicini, 2011). If glycogen build up is significant enough, then cardiac hypertrophy may begin in utero and continue to progress postnatally. Eventually, the excessive accumulation leads to cardiomegaly with subsequent left ventricular thickening (Hayley et al., 2003). Another key feature is the onset of progressive muscle weakness within the first four months of life (Kishnani et al., 2006). Infants with IOPD typically present with severe hypotonia or generalized muscle weakness. When left untreated, the muscles of the body will become progressively weaker, which can impede motor development and ambulation. Muscle weakness can also lead to complications such as difficulty breathing, impaired cough, feeding difficulties, blood gas abnormalities, and sleep apnea. Feeding difficulties are common in this patient population, and as a result, about 53% of patients have failure to thrive (Kishnani et al., 2006). Approximately 29% of patients with IOPD present with hepatomegaly and macroglossia (Van den Hout et al., 2003). Macroglossia may also contribute to airway obstruction and feeding difficulties (Staretz-Chacham, Land, LaMarca, Krasnewich, & Sidransky, 2009).

LOPD is characterized by onset any time between childhood to adulthood. This form of the disease is slowly progressive and clinical phenotypes tend to be much more variable. In both LOPD and IOPD the systems that are impacted are similar, however, the major distinction is the absence of cardiac findings in LOPD patients. The main clinical features include, proximal muscle weakness, respiratory complications, and delayed motor milestones. (Hayley et al., 2003).

Respiratory manifestations are common, occurring in approximately 1/3 of LOPD patients. Recurrent respiratory infections, and sleep-disordered breathing may be early manifestations of LOPD (Confalonieri et al., 2019). Failure to properly treat respiratory findings may lead to respiratory failure and subsequent early mortality (Merk, Wibmer, Schmann, & Hruger, 2009).

***Molecular Basis***

Pompe disease is caused by pathogenic variants in the *GAA* gene, which is located on chromosome 17 at 17q25.3. *GAA*, is responsible for coding the lysosomal enzyme acid alpha-glucosidase (U.S. National Library of Medicine). The gene contains 20 exons and spans a length of 20 kb (Dennis, Moran, & Healy, 2000; Giancarlo Parenti et al., 2013). Over 300 pathogenic variants have been identified in the *GAA* gene. One of the most common variants is the deletion of exon 18 c.2482_2646del (Ngiwsara et al., 2019). Many variants are common to various ethnic groups. The most common pathogenic variant in the Caucasian population with a frequency of 47% is c.-32-13T>G (Kroos et al., 1995). In the African American population, the most common IOPD variant is the R854X variant (c.2560C>T; p.Arg854Ter) (Becker et al., 1998). In the Taiwanese population, *Ko et al.*1999 were able to identify 7 different pathogenic variants by studying 11 unrelated families (Ko et al., 1999). The most commonly occurring were the p.D645E (p.Asp645Glu), p.G615R (p.Gly615Arg), and c.1411del4 (p.Glu471-shift).

***Inheritance and Recurrence risk***

Pompe disease is an autosomal recessive condition. For an individual to be affected, they must be homozygous or compound heterozygous for two disease-causing variants. In the event that each member of a heterosexual couple is a carrier for Pompe they would have a 25 % chance of having a child who is affected with the condition.

### *Genotype/ Phenotype correlation*

While a clear genotype/phenotype correlation has yet to be established for Pompe, generally, individuals who are homozygous for null variants which will produce no alpha-glucosidase activity have an infantile presentation (Hoefsloot LH, 1990). In comparison, patients with LOPD usually have a combination of pathogenic variants that lead to residual enzyme activity (Confalonieri et al., 2019). Nonetheless, variability of symptoms and presentation continues to pose a challenge to the effort of establishing a clear genotype/phenotype correlation. Multiple pathogenic variants have been reported in both forms of the conditions. For example, the exon 18 deletion has been reported in both LOPD and IOPD (Hule et al., 1994). In 2005, Wens *et al.* performed a study in which they identified 22 Dutch families comprised of two or three siblings diagnosed with Pompe disease (Wens et al., 2013). Of those 22 families, 11 of the sibling sets displayed a large variation in phenotype. This included a set of siblings in which one of the siblings was ventilator and wheelchair dependent and the other ambulant with no need for a ventilator. Notably, as well, 12 families with a shared genotype (c.-32-13T>G/c.525delT) had individuals who presented as infants and some who presented later in life.

### *Diagnosis*

The standard method for diagnosing Pompe disease is enzyme activity testing with the use of an assay. This testing approach has become popular due to the inexpensive cost, minimally invasive nature, and accuracy of results. The assay can be run on various samples including a dried blood spot, leukocytes, and fibroblasts. In the case of LOPD, muscle biopsies are sometimes used as a tool for diagnosis (Muscumeci, 2019), although if Pompe disease is included as part of the differential diagnosis then enzyme testing is less invasive. Molecular testing of the *GAA* gene can also be useful. (Leslie & Bailey, 2017).

***Management and Treatment***

Treatment of Pompe disease entails the involvement of a multidisciplinary team. Along with standard medications for heart disease and nutrition, initiation of enzyme replacement therapy is recommended when the individual's symptoms warrant it. In 2006 the American College of Medical Genetics (ACMG) published standard guidelines for treatment of patients (Kishnani et al., 2016). For infantile patients, care should be established with the following specialists: cardiology, pulmonology, neuromuscular, and a metabolic geneticist. Assessment of cardiac disease should begin with a baseline echocardiogram and electrocardiogram (EKG). Subsequent cardiac management may include the use of chest x-rays and various heart medications, such as ACE inhibitors. Other medications may exacerbate cardiac symptoms, and thus should be cautiously used. Respiratory function should be assessed regularly, both when the patient is awake and asleep. Testing such as gas exchange and chest radiographs may be utilized for this purpose. Infections should be treated aggressively in both LOPD and IOPD given the high risk for severe respiratory complications. Annual monitoring of neuromuscular disease is another important component of management. Progression of disease can be assessed using nerve conduction studies as well as electromyography (EMG) and developmental scoring.

Enzyme replacement therapy (ERT) was first approved for IOPD in 2006, and then later again in 2010 for LOPD. Commercially known as Myozyme™ (initially and outside of the US) and Lumizyme™ (same product but utilizes a larger bioreactor), the drug itself is a recombinant form of the human alpha-glucosidase enzyme (alglucosidase alfa). The drug is administered to the patient intravenously and is used to replace the absent or deficient enzyme so that it breaks down the accumulated glycogen and prevents future build up in the body. Response to the therapy tends to vary among patients since effectiveness of the treatment depends on a multitude of factors

including the clinical picture of the individual (Desai et al., 2018). Alternative therapies as well as therapies to use alongside ERT are under investigation given that ERT is not curative and response is variable (Bellotti et al., 2020). Another current therapy under study is chaperone therapy. This therapy is of particular interest given that chaperones have high bioavailability, can cross the blood brain barrier, and can be administered orally (Parenti, Generoso, & Valenzano, 2015). Kishnani *et al.* in 2017 conducted a phase II study in which they administered a chaperone (Duvoglustat) to individuals with Pompe (Kishnani et al., 2017). They found that after administration of both Duvoglustat and ERT increased total GAA activity, specifically muscle GAA activity, was increased.

While gene therapy is not yet available clinically for patients with Pompe disease, multiple studies are being conducted to study the efficacy of gene therapy as a potential treatment. The treatment would consist of the administration of a gene delivery vector into the bloodstream, muscle, or other tissues (Ronzitti, Collaud, Laforet, & Mingozzi, 2019). A study performed by Han *et al.* in 2019 utilized gene therapy on both adult and infant mouse models. Both the infant and adult mice showed significant improvement in both muscle tone and cardiac disease. Moreover, both sets of mice in the study showed biochemical correction, however these findings were much more significant in the adult population (Han et al., 2019). Lastly, due to the fact that there are nonsense variants in *GAA* known to be associated with Pompe, stop codon read through therapy has been considered, however, there is no evidence suggesting efficacy in treating Pompe (Bellotti et al., 2020).

***Prognosis***

Without intervention, the prognosis of individuals with IOPD is poor, with death occurring before the age of one. The most common cause of mortality in these patients is cardiac and/or

respiratory failure (Kishnani et al., 2009). In recent years, however, the introduction of ERT has changed Pompe disease outcomes. IOPD patients who receive ERT within the first few weeks of life have shown improvement in all clinical features including respiratory, cardiac, and muscle function. A study by Yang *et al.* (2016) found that patients who began treatment early were found to have lower levels of anti-rh acid alpha-glucosidase, antibodies indicating long-term effectiveness as a treatment method (Yang et al., 2016). Likewise, ERT administration over the course of multiple years has shown to reduce mortality and morbidity. Kishnani *et al* (2009) conducted a study in which 18 infants diagnosed with infantile Pompe disease were administered infusions of alglucosidase alfa every other week while being monitored over the course of three years (Kishnani et al., 2009). Results showed that the overall risk of death was decreased by 95% and risk for ventilation was reduced by 91%. Furthermore, ERT was found to improve cardiomyopathy and a majority of the patients maintained significant motor skills. In the case of LOPD, prognosis is more variable based on the severity of the disease. Typically, individuals with LOPD, who have experienced the disease for longer periods of time, have diminished quality of life and a shorter life span (Chan et al., 2017). Similar to IOPD, studies since 2010 have shown that adults with preexisting symptoms who are placed on ERT show significant improvement. In particular, ERT has a positive impact on respiratory function as well as laboratory markers (Merk et al., 2009).

### 2.1.2 Mucopolysaccharidosis Type 1

#### *Clinical Features*

Mucopolysaccharidosis Type 1 (MPS1), also known historically as Hurler/Hurler-Scheie/Scheie syndrome, is due to a deficiency in the lysosomal enzyme alpha-L-iduronidase

(Clarke, 2002). This enzyme is responsible for the breakdown of glycosaminoglycans (GAGs) in the body. Four categories of GAGs exist including, heparan sulfate, dermatan sulfate, keratan sulfate, and hyaluronan (Zhang, Zhang, & Linhardt, 2010). GAGs are thought to play a role in cell signaling (Casale & Crane, 2019). When there is not enough enzyme or it is not functioning properly, GAGs accumulate in the body and lead to significant health problems. Specifically, in individuals with MPS1, dermatan sulfate and heparan sulfate accumulate. The estimated incidence of MPS1 is approximately 1/100,000 live births (National Organization for Rare Disorders). At birth, infants usually do not present with any features but over time will present a progressive neurologic decline or worsening of physical features throughout childhood. Based on severity and age of onset, the diagnosis was historically classified into one of three broad categories, Hurler, Hurler-Scheie, and Scheie. Currently, however, it is organized/categorized into MPSI and attenuated MPSI.

The most severe form of the disorder referred to as MPS1 (MPS1-H). This form of the condition is characterized by early onset of neurological disease and death before the age of 10 (Matter et al., 2002). The effects of neurological disease typically appear around 12-24 months in the form of developmental delay. Early development may appear appropriate, however, skill development will usually cease and neurological decline will commence shortly after (Muenzer, Wraith, Clarke, & International Consensus Panel on the Managment and Treatment of Mucopolysaccharidosis, 2009). Hydrocephalus is another feature that may contribute to delayed neuromotor development. A patient's clinical course is also complicated by dysostosis multiplex. These skeletal findings can include a large skull, enlarged J-shaped sella, short stature, and deformities of the spine as well as the pelvis (Wendel, 2003). Corneal clouding is also noted in the majority of patients. Typically this clouding is progressive, which leads to severe visual

impairment (Clarke, 2002). Furthermore, most individuals have some degree of cardiac involvement. Most commonly, the GAG accumulation in the heart leads to thickening of the aortic and mitral valve (Wendel, 2003). Progression of cardiac findings and early-onset dementia are often contributors to mortality. Other common features include, coarse facial features, hepatomegaly, and hearing loss.

Attenuated phenotypes are categorized by a later age of onset and absent or mild intellectual disability (Terlato & Cox, 2003). The organ systems affected can be similar to MPS1-H, but the presentation and severity can be more variable.

***Molecular Basis***

MPS1 is caused by pathogenic variants in the *IDUA* gene, which is located on chromosome 4p16.3. *IDUA* is responsible for the production of the lysosomal enzyme alpha-L-idurondase. The gene contains 14 exons that span 19 kb (H. S. Scott, Giuo, Hopwood, & Morris, 1992). There have been 170 disease-producing pathogenic variants identified in the *IDUA* gene (Beesley et al., 2001). In the Caucasian population, the p.W402X and p.Q70X are two common pathogenic variants that account for 60% of disease alleles (Bunge et al., 1995). Other common pathogenic variants include p.P533R and p.L490 (Bunge et al., 1995; Gatti et al., 1997).

***Inheritance and Recurrence risk***

MPS1 is an autosomal recessive condition. For an individual to be affected with this condition, they must be homozygous or compound heterozygous for two disease-causing variants. In the event that each individual in a heterosexual couple are carriers for MPS1, their offspring would have a 25% chance of being affected.

### *Genotype/phenotype correlation*

Genotype/phenotype correlations are not well established for MPS1. However, recent analysis of the MPS1 registry has identified some correlations. In general, nonsense variants as well as variants that drastically disrupt protein function have been associated with little to no enzyme activity. Individuals who are homozygous or compound heterozygous for these types of pathogenic variants usually present with a more severe phenotype (Clarke et al., 2019). Both the p.W402X and p.Q70X variants are associated with absent enzyme activity. However, these variants have been identified in individuals with an attenuated phenotype as well. In most cases, these individuals were compound heterozygous for one of these null variants as well as a missense variant (Clarke et al., 2019). Missense variants tend to be associated with residual enzyme activity. The most common variants associated with an attenuated phenotype are p.P533R and p.L490. The p.P533R variant has been reported in individuals with variable disease severity (Terlato & Cox, 2003). This variability in phenotype is common in the presence of missense variants, and thus they continue to pose a challenge for prognosis and counseling.

### *Diagnosis*

An enzyme assay for alpha-L-iduronidase is the standard method for diagnosis of MPS1. This testing can be performed on cultured fibroblasts, isolated leukocytes, or dried blood spot cards. Although not diagnostic, urine studies are often used in the evaluation process to measure the amount of GAG accumulation that is present. Individuals with MPS1 will usually have higher levels of GAGs in their urine due to the defective enzyme activity (Cleary & Wraith, 1995; Sanofi Genzyme, 2017). Molecular analysis of the *IDUA* gene is also available for diagnostic purposes.

***Management and Treatment***

Management of MPS1 requires a multidisciplinary team to attend to the clinical manifestations of the disease. In addition to standard clinical care for each of the organ systems, enzyme replacement therapy is also available for administration when clinical manifestations warrant it. In more severe cases individuals may also undergo a hematopoietic stem cell transplant. The ACMG guidelines published in 2009 recommend that patients with MPS1 have evaluations from the following specialists: cardiology, ophthalmology, orthopedics, audiology, neurology, and gastroenterology (Muenzer et al., 2009). Evaluations should continue every 6-12 months to monitor disease progression. Annual neurology evaluations should include imaging of the brain and spine in addition to monitoring of head circumference. If hydrocephalus is suspected, then a lumbar puncture should be considered in order to evaluate cerebral spinal fluid pressure. When a patient is experiencing headaches or abnormal sleep behavior, shunting may alleviate these symptoms as well as the intracranial pressure. While cognitive impairment is typically recognized between 12-24 months, a baseline neurocognitive evaluation is warranted in order to monitor for decline. Developmental stimulation in early stages of the disease can also be helpful for retention of skills. Respiratory management is another important component. Patients with MPS1 are at increased risk for respiratory insufficiency. Pulmonologists should be consulted in order to guide treatment. In some cases, a tonsillectomy and/or adenoidectomy may be helpful, however, in severe cases a tracheostomy may be performed as a lifesaving method. An orthopedic surgeon should address skeletal manifestations of the disease. Surgery may be an option when skeletal deformities are detected early. These surgeries may include, spine fusions, osteotomy for hip dysplasia, and carpal tunnel release. Regardless of surgical status, physical therapy is recommended for maintenance of joint function and muscle strength.

The FDA approved enzyme replacement therapy with laronidase (brand name: Aldurazyme™) in 2003. The drug is a recombinant form of the human alpha-L-iduronidase and is administered intravenously. Recommended dosage for patients is 0.58 mg/kg on a weekly basis (Genzyme, 2010). When administered, the recombinant enzyme promotes the breakdown of GAGs as well as prevents further build up. Long-term administration has been shown to reduce the levels of urine GAGs and improves non-CNS manifestations (Wraith et al., 2004). Although there are benefits, the therapy does have limitations. ERT does not remedy the cognitive or neurological manifestations due to the fact that it does not cross the blood-brain barrier (Muenzer et al., 2009). Variations of ERT as well as alternative administration sites have been suggested in order to address this limitation. One alternative therapy suggested, which is similar to current practice, is intravenous ERT with fusion proteins. This therapy is another recombinant form of alpha-L-idronidase, however, the fusion protein has been modified so that the IgG domain targets blood barrier transporters (Kubaski et al., 2020). In 2018, Giugliani *et al.* studied the effects of the IgG-IDUA fusion protein (valanafusp alpha) on pediatric patients with MPS1 (Giugliani et al., 2018). Throughout the trial, researchers noted improvements of urine GAGs, liver and spleen volumes, and shoulder range of motion. This data suggested that the fusion protein is transported across the blood brain barrier, and thus has potential to improve neurological disease. Intrathecal administration of ERT has also been explored as a means to address cognitive impairment. Recently, studies have focused on the intrathecal administration used in conjunction with intravenous ERT and hematopoietic stem cell transplant (HSCT). In 2019, Eisengart *et al.* found that when all three methods were administered together there was a decrease in disease biomarkers, and increase in cognitive function (Eisengart et al., 2019 ).

In more severe cases, enzyme replacement therapy is used in combination with HSCT. HSCT alone has been shown to improve multi-system functioning, however, guidelines recommend the use of both ERT and HSCT for maximal efficacy and improved outcomes. The use of ERT administered before transplant has been shown to reduce mortality associated with HSCT due to the fact that ERT generally improves symptoms (Wynn et al., 2009).

A number of novel gene therapies are under investigation for MPS1. The therapy would involve the delivery of the *IDUA* gene to the patient via a vector. The theory is that the administration of the deficient gene would be able to address the health concerns that current therapies cannot address such as the neurological deterioration. Studies using MPS1 mice and gene therapy have resulted in increased IDUA activity as well as improved lysosomal function, indicating clinical effectiveness, and potential to translate to human disease (Schuh et al., 2018). Stop codon read through has also been suggested as a possible therapy given the prevalence of nonsense variants in certain populations (Kubaski et al., 2020). However, studies on various models have yet to prove any efficacy of this therapy (Kamei et al., 2014).

***Prognosis***

Historically, prognosis for patients with MPS1 (MPS1-H) has been poor. Unfortunately, even with the introduction or ERT and HSCT to the management of these patients, death still usually occurs within the first 10 years of life (Clarke, 2002; Zhou, Lin, Leung, & Wang, 2020). Mortality is most commonly a result of cardiorespiratory failure and progressive neurological disease (Muenzer et al., 2009). Combination therapy has been associated with a decrease in morbidity as well as enhanced (Eisengart et al., 2013; Eisengart et al., 2018). Patients with the attenuated form of the disease have a more variable outcome given the clinical variability seen amongst patients.

## 2.2 Newborn Screening

Newborn screening refers to the testing that each newborn undergoes during their first few days of life. It is a public health intervention for all newborns in the US in which the goal is to initiate treatment early for life threatening health conditions in order to decrease morbidity (Bradford et al., 2015). The work of Robert Guthrie led to the development of newborn screening in the 1960's. In his work as a microbiologist, Guthrie developed a bacterial inhibition assay used to study purine and pyrimidine metabolites. He was able to utilize this technology to detect phenylalanine, which lead to early detection of Phenylketonuria (PKU) (Pitt, 2010). Early detection was integral to the management of PKU because it allowed for regulation of phenylalanine intake before the excess of phenylalanine led to intellectual disability and other health problems caused by PKU. The utility of the screen was quickly realized, and many state newborn screening programs commenced during the 1960's.

### 2.2.1 Methods of Testing

In the United States, the newborn screen consists of multiple tests. Although this screen is used to detect individuals with various conditions, it is just a screening test. Further evaluations are necessary following an abnormal screen result to confirm a diagnosis. A hearing test is part of newborn screening. The test utilizes audiometry to assess the newborn's hearing. This test follows a two-stage protocol; all newborns are tested in the first stage and then for those who have failed the first stage they are tested again (Welzl-Mueller, 2001). Infants are also tested for congenital heart disease through the use of pulse-oximetry (Koppel et al., 2003). Through this method, oxygen saturation is measured in the blood in order to identify low levels of oxygen (Seelback-

Gobel, 2014). An abnormal test could indicate the presence of congenital heart disease. Lastly, the Guthrie card is utilized to screen for a variety of other conditions with known interventions. Typically, a heel stick is performed 48-72 hours after the infant is born and the blood is blotted onto a special card (Pitt, 2010). The sample is then analyzed using high performance liquid chromatography and/or tandem mass spectrometry (Wilcken, Wiley, Hammond, & Carpenter, 2003). This technology allows for the detection of metabolites in order to screen for various disorders such as inborn errors of metabolism (Fernandez-Lainez, Aguilar-Lemus, Vela-Amieva, & Ibarra-Gonzalez, 2012). This technology also allows for states to regulate which conditions they screen for. This is due to the fact that technology detects the metabolites by their specific mass and displays the results on a mass spectrum. Different metabolites can be blinded based on what each state has chosen to include in their screening panel.

### 2.2.2 Criteria for Newborn Screen

In 1968, Wilson and Jungner developed a set of criteria that would be used to establish guidelines for screening. Their goal was to guide the selection of conditions based on the ability to detect the condition in the early stages and the availability of treatment (Andermann, Blancquaert, Beuchamp, & Dery, 2007). Recently, the criteria have been updated in order to accommodate for advancement in technology. In 2006, the ACMG established basic principles to be used as a framework when creating criteria to evaluate conditions (Watson, Mann, Lloyd-Puryear, Rinaldo, & Howell, 2006). The criteria were divided into three main categories: (1) clinical characteristics of the conditions, (2) analytical characteristics of the screening test, and (3) diagnosis, treatment, and management. After their analysis, they identified 31 core conditions, or conditions in which screening should be mandated.

In the United States, it is the responsibility of each state to determine which conditions are included on newborn screening. However, the Recommended Uniform Screening Panel (RUSP) was adopted nationally as an effort to standardize the newborn screen across the country (National Institute of Child Health and Human Development). First developed in 2003 by the Advisory Committee on Heritable Disorders and the ACMG, the RUSP is the list of disorders that are recommended to be included on each state's newborn screen (Advisory Committee on Heritable Disorders in Newborns and Children, 2006). Currently, there are 35 conditions listed on the RUSP. The list has been organized into five main categories of disorders: hemoglobinopathies, organic acid disorders, amino acid disorders, fatty acid oxidation disorders, and miscellaneous disorders (American College of Obstetricians and Gynecologists, 2015). Based on the ACMG guidelines, for a condition to be added to the newborn screen it must at minimum meet the following three criteria: detection of the condition can occur within 24-48 hours of birth, there is an accurate test that is sensitive and specific, and there is benefit to early initiation of treatment (National Institute of Child Health and Human Development).

### 2.2.3 Lysosomal Storage Disorders and Newborn Screening

The recent addition of LSDs to the newborn screen was made possible by advancements in technology as well as treatment. In the past, limitations in knowledge of the natural history, treatment, and reliable testing methods made first tier screening unfeasible (Schielen, Kemper, & Gelb, 2017). In 2001, a significant breakthrough occurred when Chamoles and his colleagues, uncovered that lysosomal enzymes in a dried blood spot sample retain their activity (Chamoles, Blanco, & Gaggioli, 2001). Using fluorescence, they were able to successfully quantify enzyme activity in Fabry patients. Tandem mass spectrometry (MS/MS), a key advancement in newborn

screening, is an effective strategy for identifying LSDs via newborn screening. MS/MS utilizes specialized technology to electronically measure the mass of various molecules. The first successful use of MS/MS in the identification of a lysosomal enzyme was in 2005 by Wang *et al*. Subsequent studies using MS/MS for the detection of lysosomal enzymes reported positive predictive values as high as 95%, which supported the addition of LSDs to routine newborn screening (Scott et al., 2013). Advancements in therapies in the last two decades have also influenced the decision to include LSDs on newborn screening. Specifically, treatment with ERT has significantly impacted the natural history of these conditions. Longitudinal studies of patients treated with ERT provided evidence that early initiation as well as long-term treatment resulted in better clinical outcomes (Wyatt et al., 2012). Findings, such as these highlighted the importance of early detection and reinforced the need for appropriate screening.

#### 2.2.3.1 Pompe

The addition of Pompe disease to the RUSP was first suggested by the ACHDNC in 2013, and then approved by the US Secretary of Health and Human Services in 2015. The key justifications for the approval was the availability of enzyme replacement therapy and that its early initiation has proven benefits (Bodamer et al., 2017). In addition to treatment, the committee also determined that the addition of Pompe disease would have beneficial public health impact. Experts estimated that in the US each year, the newborn screen would identify 144 infants with the disease, which could prevent 19 deaths per year (US Secretary of Health and Human Services, 2015). Nonetheless, the addition of Pompe disease was controversial and remains that way today. Concerns related to screening for Pompe stems mainly from inevitable detection of individuals with late-onset Pompe disease, those with pseudodeficiencies or variants of unknown significance, and inability to predict reliably the onset of symptoms. Debate still surrounds the best course of

action for this cohort of individuals found to have LOPD, pseudodeficiencies, and VUS. However, the detection by newborn screen has the potential to save the patient from a diagnostic odyssey (Pruniski et al., 2018).

#### 2.2.3.2 MPS1

The addition of MPS1 to the newborn screen was first proposed in 2015 and then approved by the US Secretary of Health and Human Services in 2016. Inclusion of MPS1 was supported as a result of evidence indicating that early initiation of enzyme replacement therapy with laronidase (Aldurazyme™) improves clinical outcome as well as biomarkers (Donati et al., 2018). From a public health perspective, it was determined that screening all newborns in the US would detect about 44 infants with MPS1 per year, and prevent two deaths before 5 years of age each year (US Secretary of Health and Human Services, 2016). Parents of these children were also in support of the addition of MPS1 to the newborn screen. A study conducted by de Ru *et al.* in 2012 revealed that parents experienced considerable distress caused by delay in their child's diagnosis (de Ru, Bouwman, WIjburg, & van Zwieten, 2012). While these parents acknowledged the risks, the majority felt that the benefit of early diagnosis and treatment outweighed those risks. Nonetheless, challenges that were considered in this study have come about as a result of screening infants for MPS1. With a wide clinical spectrum, prediction of severity and onset remains difficult to determine. Another concern is the identification of variants of uncertain significance and pseudodeficiencies. Each of these cases can result in undue psychological and financial burden for the family (Parini et al., 2018). For this reason, the addition of MPS1 to newborn screening has not been without controversy.

#### 2.2.3.3 Pilot Studies

Since the addition of LSDs to the newborn screen, multiple pilot studies have been carried out in order to assess whether or not they are suitable as part of the newborn screen. In the United States, New York conducted a pilot study in which they reported the data from the newborn screening of 65,000 infants, making it one of the largest studies performed (Wasserstein et al., 2019). The study focused on five lysosomal storage diseases: Pompe, Fabry, Niemann Pick A/B, Gaucher, and MPS1. In the sample of 65,000 infants, sixty-nine positive screens were identified. Of the sixty-nine positive screens, twenty-three were found to be a true positive result. Further analysis of the twenty-three infants revealed that all were at risk for a late-onset presentation or had pseudodeficiency variant(s). Specifically, in the cohort identified to be at risk for Pompe disease, they found one late-onset patient, two heterozygote carriers, and three infants who were pseudodeficient. In the cohort identified to be at risk for MPS1, there were thirteen individuals. Four were heterozygote carriers and eight were pseudodeficient or had a benign variant. Based on this data, the researchers determined that newborn screening for lysosomal storage diseases is feasible, however, screening is more likely to identify infants at risk for late-onset disease and carriers than those who are affected with the more severe early onset disease.

#### 2.2.3.4 Impact on Families

While there is limited literature available about the impact of newborn screening for LSDs on parents, a number of studies have been conducted on the impact of screening for other metabolic conditions. Parents who have gone through the newborn screening process report increased levels of stress, long-term concern for the health of their child, and uncertainty regarding what the screening results meant for their own health (Waisbren et al., 2003). Interviews conducted via a single site study of thirty families revealed that the feelings of distress began with the initial shock

of receiving the abnormal results (DeLuca, Kearney, Norton, & Arnold, 2011). These feelings then carried through the entirety of the process and were exacerbated while waiting for the results of the diagnostic testing. Of note, some parents when asked to recall details of the child's condition even reported back inaccurate information. Similar findings were reported in a 2018 study in which parents of children diagnosed with Pompe disease were interviewed (Pruniski et al., 2018). The two most common themes amongst parents were uncertainty and fear. Parents of infants diagnosed with late-onset Pompe were particularly prone to this reaction when thinking how to best care for asymptomatic children. When asked about their overall view of newborn screening, parents of infants diagnosed with IOPD reported being grateful that their child was diagnosed early. On the other hand, parents of infants diagnosed with LOPD either felt that the screen prevented a future diagnostic odyssey for their child or that their child was a "guinea pig." Another concern is the impact of false positive results on parents. Currently, the specificity of the screen overall is poor and ability to establish a positive predictive value is difficult given the rarity of LSDs (Baerg et al., 2018). These problems can lead to costly follow up testing as well as psychological burden to the parents (Baerg et al., 2018). Studies have shown that false positive test results cause negative effects on parents both short term and long-term (Hewlett & Waisbren, 2006). Parents interviewed for a study in 2006 by Gurian *et al.* reported that stress level increase during the follow up testing needed in light of an abnormal screen. This study also suggested that false positives have an impact on how parents care for the child in the future. Children who received false positive results had twice as many hospitalizations for a variety of childhood symptoms as compared to children whose newborn screening did not result in a false positive (Gurian, Kinnamon, Henry, & Waisbren, 2006). Studies have suggested improvements to second tier testing as well as alternative metrics to amend this concern (Baerg et al., 2018; Gelb, 2018). These studies outline that understanding

the psychological impact is a vital component to care. Expanding health care providers understanding of the family's experience will allow for optimal care and adaptation as more infants are identified to be at risk for Pompe or MPS1 via newborn screening.

# 3.0 Manuscript

## 3.1 Background

Lysosomal storage disorders (LSD) constitute a group of over 50 metabolic disorders, with an approximate incidence of 1/7700 in the general population. Most often, these conditions are characterized by impaired lysosomal enzyme function. Less commonly, LSD phenotypes can result from biogenesis of the lysosome, impaired receptor activator proteins, deficits in the membrane proteins, and defects with transporters (Parkinson-Lawrence et al., 2010; R. Wang, Bodamer, Watson, & Wilcox, 2013). The defect in lysosomal function leads to an accumulation of toxic substrates in the cells, which ultimately impairs intracellular and extracellular function. As a result, multiple organ systems such as the cardiovascular, nervous, and musculoskeletal systems become compromised.

### *Pompe Disease*

Pompe disease, also known as glycogen storage disorder type II, is an autosomal recessive condition with an estimated incidence of 1/40,000 (Hayley et al., 2003). This condition is caused by pathogenic variants in the *GAA* gene that lead to a deficiency in the lysosomal enzyme alpha-glucosidase (GAA) (U.S. National Library of Medicine). Deficiencies in this enzyme result in glycogen build up in the body (Leslie & Bailey, 2017). Pompe disease is divided into two categories, infantile (IOPD) and late onset (LOPD). Diagnosis is differentiated based on age of onset, severity of symptoms, organ involvement, and rate of progression (Kishnani et al., 2016). Both IOPD and LOPD are diagnosed via an enzyme assay. Sequencing of the *GAA* gene can also

be performed for diagnostic purposes, and in the event that sequencing of *GAA* only reveals one pathogenic variant, deletion/duplication analysis may follow (Leslie & Bailey, 2017). Molecular analysis may also be warranted to confirm diagnoses in cases of LOPD (Kishnani et al., 2016).

IOPD is characterized by an onset of symptoms within the first few months of life and significant cardiac impairment, specifically cardiomegaly (Angelini & Semplicini, 2011). Additionally, the muscles of these infants are significantly impacted. Hypotonia or generalized muscle weakness becomes apparent within the first 4 months of life (Kishnani et al., 2006). Progressive muscle weakness can lead to breathing difficulty, issues with feeding, and sleep apnea. Other symptoms associated with IOPD are macroglossia, failure to thrive, and hepatomegaly (Van den Hout et al., 2003). Management for patients involves a multidisciplinary team as well as the utilization of enzyme replacement therapy (ERT). Care should be established with cardiology, pulmonology, neurology, and a clinical geneticist (Kishnani et al., 2016).

LOPD is characterized by onset of symptoms anytime between childhood to adulthood. Infants with LOPD may also present with symptoms, but the diagnosis is distinguished from IOPD by of the lack of cardiac involvement. While the majority of systems impacted in LOPD are similar to that of IOPD, clinical features are more variable in this group of patients. Generally, common features of LOPD include proximal muscle weakness, respiratory complications, and delayed motor milestones (Hayley et al., 2003). Similar to patients with IOPD, management for LOPD patients includes a multidisciplinary team and ERT (Kishnani et al., 2016).

### *Mucopolysaccharidosis Type 1*

Mucopolysaccharidosis Type 1 (MPS1) is a condition that is caused by a deficiency of the lysosomal enzyme alpha-L-iduronidase (Clarke, 2002). It is estimated to occur in approximately every 1/100,000 live births (National Organization for Rare Disorders). The condition is caused

by pathogenic variants in the *IDUA* gene, and is inherited in an autosomal recessive manner. When alpha-L-iduronidase is not functioning properly, glycosaminoglycans (GAGs) accumulate in the body, which ultimately leads to a variety of health problems. Due to the variability in phenotypes, MPS1 diagnoses have been divided into two broad categories, MPS1 and attenuated MPS1 (MPS1-H, MPS1-HS, MPS1-S). An individual's disease is placed into one of these categories based on severity of symptoms and age of onset (Clarke, 2002).

The most severe form of the disorder is MPS1 (MPS1-H). Typically individuals who fall into this category have early onset of neurological disease between 12-24 months. (Matter et al., 2002). With the attenuated forms, MPS1-HS and MPS1-S, neurological disease is typically diagnosed later in life or not at all (Terlato & Cox, 2003). Other hallmarks of MPS1 include, corneal clouding, dysostosis multiplex, coarse facial features, hepatosplenomegaly, hearing loss, and recurrent ear, nose, and throat infections. A diagnosis of MPS1 is often made using an enzyme assay specific to alpha-L-iduronidase. Individuals with MPS1 usually have higher traces of GAGs in the urine, and thus a urine analysis can be used as a screening tool (Cleary & Wraith, 1995). Molecular analysis of the *IDUA* gene is also available and should be part of the diagnostic work-up for patients. Management entails a multidisciplinary team. In 2009 the ACMG published guidelines that recommended individuals with MPS1 establish care with cardiology, ophthalmology, orthopedics, audiology, neurology, and gastroenterology (Muenzer et al., 2009). Enzyme replacement therapy and hematopoietic stem cell transplant (HSCT) are also established treatment approaches for MPS1.

### *Newborn Screening*

Developed by Robert Guthrie in 1963, newborn screening refers to the testing that nearly every newborn in the US undergoes within the first 48-72 hours of life (Pitt, 2010). The ACMG

and the Advisory Committee of Heritable Disorders developed criteria that a condition must meet at a minimum in order to be considered for the RUSP. These include: (1) detection of the condition can occur within 24-48 hours of birth, (2) there is an accurate test that is sensitive and specific, and (3) there is benefit to early initiation of treatment (National Institute of Child Health and Human Development). The US Secretary of Health and Human Services approved the addition of Pompe disease to the RUSP in 2015 and the addition of MPS1 in 2016. For both conditions, the main justification in favor of the addition was the availability of FDA approved therapies, proven benefits of early administration, and ability to screen effectively (Bodamer et al., 2017; Donati et al., 2018). Nonetheless, controversy still surrounds the addition of these conditions (Peake & Bodamer, 2017; Wasserstein et al., 2019). The screening is sensitive, and because of this, it has detected individuals with late-onset forms of these conditions, pseudodeficiencies, and variants of uncertain significance. While the debate currently continues regarding the best means of care for this cohort, there is a general consensus that screening for Pompe disease and MPS1 has the potential to save individuals from long diagnostic odyssey and improves clinical outcomes (Pruniski et al., 2018).

Parent and caregiver experience with newborn screening for various conditions has been explored in the literature in regards to inborn errors of metabolism (DeLuca et al., 2011; Pruniski et al., 2018). However, literature related to LSDs is limited. One study conducted by Pruniski *et al.* (2018), interviewed parents of children identified to be at risk for Pompe disease by newborn screening. Parents reported that fear and uncertainty about their child's health defined this time period. The goal of this study was to expand our knowledge and understanding of parents' and caregivers' experience with newborn screening. To achieve this goal, a survey was constructed to elicit various aspects of parents'/caregivers' experience, with a focus on the psychosocial impact.

Providers may use the results of this study to guide families through the complicated process of receiving an abnormal newborn screening result. Understanding the psychosocial impact on families may allow genetic counselors to better tailor their interactions to alleviate some of the emotional burden parents may experience. The results of this study may inform the way healthcare providers manage families as more infants are identified to be at risk.

## 3.2 Methods

### 3.2.1 Participants

The population of interest for this study were parents and caregivers, 18 years and older, who have infants identified to be at risk for Pompe disease or MPS1 via newborn screening. Before recruiting commenced, the study was approved by the University of Pittsburgh Institutional Review board (IRB) (Appendix A). The main study site was the UPMC Children's Hospital of Pittsburgh. Recruiting sites included the UPMC Children's Hospital of Pittsburgh as well as the Children's Hospital of Philadelphia. Families were identified at each institution via patient databases kept by the lysosomal storage disorders teams at each respective facility. At the UPMC Children's Hospital of Pittsburgh, parents and caregivers were contacted via email or mailer. Only an email was distributed by the Children's Hospital of Philadelphia to their families. Both the email and mailer were abbreviated versions of the formal consent located at the beginning of the survey. Both documents outlined that the survey was optional, there were no benefits to participating, minimal risk was associated with participation, information was collected anonymously, and there was no compensation for participating. The email then concluded with the

link to the survey, which the participant could click, and contact information for the lead researcher. The mailer contained the link to the survey, which the recipient would have to type in to their browser of choice in order to participate. Similar to the email, the mailer concluded with the contact information for the lead researcher. Formal consent was obtained directly at the beginning of the document prior to the start of the survey. The consent outlined in further detail the information in the email and mailer as well as described the study in more detail. Participants then had the option to select "Yes, I would like to participate" or "No, I do not wish to participate". If they chose "yes," then they were directed to the survey and if "no" was chosen, then they were taken to the end of the survey. Non-responses were categorized as "no," or not included in the dataset.

### 3.2.2 Survey Development

The survey consisted of 28 questions. Participants accessed the survey through a single web link. The survey was developed using the Qualtrics survey platform and consisted of five main sections. The first section developed by the lead researcher consisted of multiple-choice questions pertaining to demographics as well as questions about physical processes the parents and caregivers went through during this specific period of time. The second and third portion of the survey utilized a Likert scale. The questions in these portions were adapted from interview questions developed for a study by DeLuca *et al.* in 2011. The questions from the interview were modified to be specific for Pompe disease as well as MPS1. The fourth section of the survey consisted of an adapted version of the Perceived Stress Scale. Permission to use the scale was given by the lead developer of the scale, Sheldon Cohen (Appendix B). Questions in this section were adapted to pertain more specifically to stress related to the newborn screening process. The

last section of the survey was an open-ended question for the participants to add any comments about their experience which they did not feel was captured by the survey The survey used skip logic as well as branching in order to personalize the survey based on which condition the respondent's child was identified to be at risk for. A clinical geneticist, two genetic counselors, and a researcher with expertise in survey development reviewed the survey. (Appendix F).

### 3.2.3 Data Collection

The survey was open to participants from February 21st, 2020 to March 21st, 2020. Access to the survey was through a web link given to participants via an email or mailer. A reminder was sent to families on March 6th. Data was collected anonymously through the Qualtrics system.

Utilizing Microsoft Excel, descriptive statistics were performed on the data collected from the survey. Given the response rate, data specific to each condition was not analyzed separately. Responses were analyzed using Microsoft Excel. Since the Perceived Stress Scale was modified to fit the aims of this study, the scale developed to evaluate the original stress scale was not used for this specific data analysis. Instead a similar process was used to interpret the data in which an answer of "yes" was given 2 points, "sometimes" was given 1 point, and "no" was given 0 points. In the case of questions 2, 3, and 6 the scores were reversed to account for the positive statements. All questions were answered in full, so there was no need to remove partial responses.

## 3.3 Results

### 3.3.1 Demographics

The survey was distributed to approximately 40 families cared for by UPMC Children's Hospital of Pittsburgh or Children's Hospital of Philadelphia. The survey was distributed to families who had at least one infant identified to be at risk for Pompe disease or MPS1 by newborn screening. Of the estimated 40 families, five responded resulting in a response rate of 12.5%. Each participant completed the survey in full. The first set of questions asked the participants to identify their relationship to the child, what condition the child was identified to be at risk for, and if they had had any previous children with the same partner (Table 1). Of the 5 participants, 60% (n=3) had infants identified to be at risk for Pompe disease and 40% (n=2) had infants who were identified to be at risk for MPS1. Every participant identified themselves as the mothers of these children, with the average age being 34.8 years and a standard deviation of 5.1 years. Additionally, 100% (n=5) of participants identified themselves as Caucasian (Table 7, Appendix G). Education levels varied between all the participants. Each individual reported a different level of education including, an associate degree, some college, 4-year college degree, doctorate degree, and trade school (Table 7, Appendix G). The majority of the participants, 60%, had previous children with the same partner while 40% (n=2) reported that this was the first child between them and their partner (Table 1).

**Table 1 Demographics**

| Variable | Number of participants n=5 |
|---|---|
| Condition | |
| Pompe | 60% (3) |
| MPS1 | 40% (2) |
| Relation to Child | |
| Mother | 100% (5) |
| Father | 0% (0) |
| Grandparent | 0% (0) |
| Other | 0% (0) |
| Any previous children with the same partner | |
| Yes | 60% (3) |
| No | 40% (2) |

### 3.3.2 Disclosure of Final Newborn Screening Results

#### 3.3.2.1 Details of Disclosure

Participants answered questions that pertained to receiving the newborn screening results for the first time. The majority of patients reported that they had heard about newborn screening prior to receiving the results. Participants were asked how they were first told about the final newborn screening results, and 100% reported that they were told over the phone (Table 2). Three (60%) out of the 5 participants were first told about these results by the child's primary care physician (PCP), while the other 2 (40%) were told about the results by a genetic counselor (Table 2).

**Table 2 Results Disclosure**

| Variable | Number of participants n=5 |
|---|---|
| First provider to disclose the results of the final NBS results | |
| Primary Care Physician (PCP) | 60% (3) |
| Genetic Counselor | 40% (2) |
| Geneticist | 0% (0) |
| Means by which you were told about the final NBS results | |
| During a doctors appointment | 0% (0) |
| Over the phone | 100% (5) |
| Other | 0% (0) |
| Had you heard about newborn screening prior to this experience? | |
| Yes | 80% (4) |
| No | 20% (1) |

### 3.3.2.2 Perception of Newborn Screening Results Disclosure

Participants answered Likert scale questions that addressed their experience receiving the newborn screening results for the first time (Table 8, Appendix G). For both groups, questions were similar except when asked if the participants had heard of the particular condition that their child was identified to be at risk for. The majority of respondents (80%) strongly disagreed with this statement. When asked to respond to the statement, "It was difficult hearing the results of the newborn screen for the first time", 80% (n=4) strongly agreed while the other 20% (n=1) agreed (Table 3). In response to "I understood what the results meant for my child's health", answers were much more variable; 20% (n=1) strongly disagreed, 20% (n=1) disagreed, 20% (n=1) neither agreed nor disagreed, 40% (n=2) agreed (Table 3). Lastly when asked about the information the participants received from their provider, 40% (n=2) indicated that they strongly agreed that their

provider could have given them more information during that initial contact, while another 40% (n=2) agreed with the same statement (Table 3).

**Table 3. Parent Perception**

| Variable | Number of participants n=5 |
|---|---|
| I knew what Pompe/MPS1 was before this process | |
| Strongly Agree | 0% (0) |
| Agree | 20% (1) |
| Neither agree nor disagree | 0% (0) |
| Disagree | 0% (0) |
| Strongly Disagree | 80% (4) |
| It was difficult hearing the results of the newborn screen for the first time | |
| Strongly Agree | 80% (4) |
| Agree | 20% (1) |
| Neither agree nor disagree | 0% (0) |
| Disagree | 0% (0) |
| Strongly Disagree | 0% (0) |
| I feel like the health care provider who first told me the results could have given me more information | |
| Strongly Agree | 40% (2) |
| Agree | 40% (2) |
| Neither agree nor disagree | 20% (1) |
| Disagree | 0% (0) |
| Strongly Disagree | 0% (0) |
| I understood what the results meant for my child's health | |
| Strongly Agree | 0% (0) |
| Agree | 40% (2) |
| Neither agree nor disagree | 20% (1) |
| Disagree | 20% (1) |
| Strongly Disagree | 20% (1) |

### 3.3.3 Initial Genetic Appointment and Diagnosis

#### 3.3.3.1 Diagnoses

Urine and lab studies were used to determine the diagnoses of the infants. In the cohort of participants who had infants identified to be at risk for Pompe disease, 100% (n=3) of the parents self-reported that their infants were diagnosed with LOPD (Figure 1). Of the participants whom

had children identified to be at risk for MPS1, 50% (n=1) self-reported their child had a VUS and the other 50% (n=1) self-reported being unclear about their child's results (Figure 1).

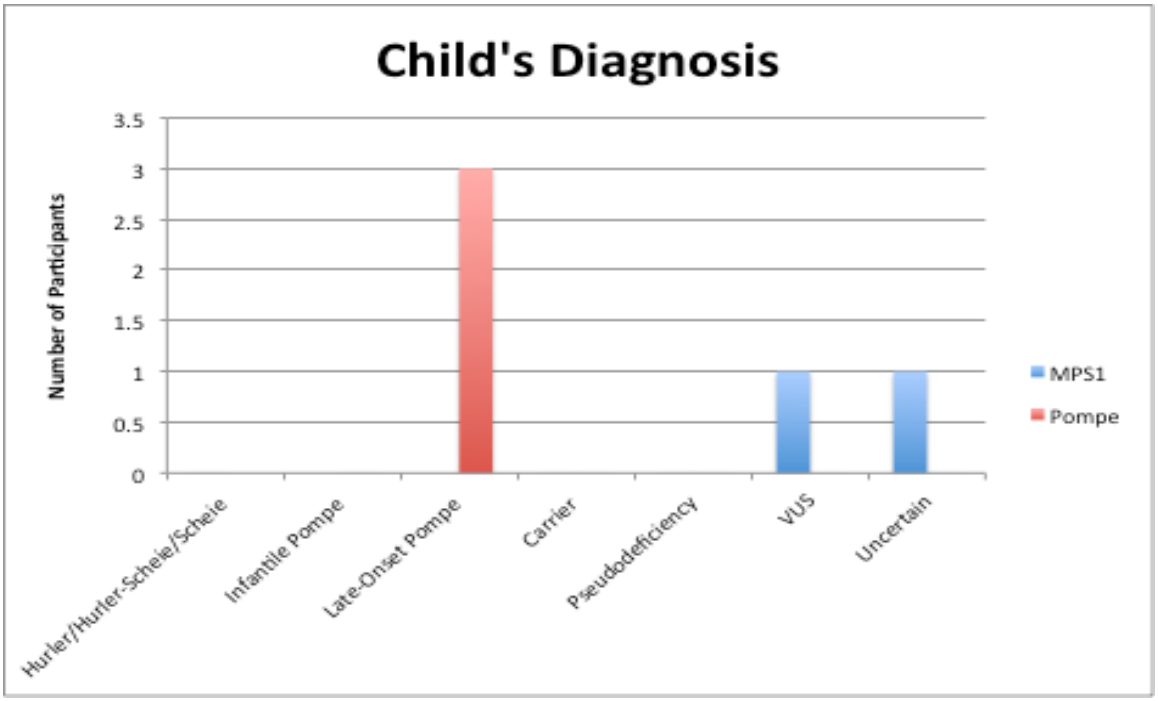


**Figure 1 Confirmed Diagnoses**

### 3.3.3.2 Perceptions and Actions Post Genetics Appointment

Likert scale questions were utilized to elicit information about the participants experience after the initial genetics appointment (Table 9, Appendix G). Participants were first asked to indicate what level they agree with the following statement, "I was relieved after the initial genetics where the screening results were discussed". Of the 5 participants, 20% (n=1) strongly disagreed, 20% (n=1) disagreed, 20% (n=1) neither agreed no disagreed, and 40% (n=2) agreed (Figure 7). Participants all agreed (100%, n=5) that waiting for the results of the urine/lab tests was stressful (Table 9, Appendix G). In response to the statement, "I changed the way I cared for my child

during this time period", 40% (n=2) of participants strongly agreed, 20% (n=1) neither agreed nor disagreed, 20% (n=1) disagreed, and 20% (n=1) strongly disagreed (Table 4).

**Table 4 Parent Perception and Actions**

| Variable | Number of participants n=5 |
|---|---|
| I was relieved after the initial genetics appointment where the screening results were discussed | |
| Strongly Agree | 0% (0) |
| Agree | 40% (2) |
| Neither agree nor disagree | 20% (1) |
| Disagree | 20% (1) |
| Strongly Disagree | 20% (1) |
| I changed the way I cared for my child during this time | |
| Strongly Agree | 40% (2) |
| Agree | 0% (0) |
| Neither agree nor disagree | 20% (1) |
| Disagree | 20% (1) |
| Strongly Disagree | 20% (1) |

### 3.3.4 Perception of Newborn Screening

The last two questions of this section aimed to capture participants' overall perception of their experience (Table 10, Appendix G). Answers varied among participants to the statement, "After my experience, I have a positive view of the newborn screening experience." Forty percent (n=2) of participants strongly disagreed, 20% (n=1) neither agreed nor disagreed and 40% (n=2) agreed (Table 5). However, when asked to what extent they agreed or disagreed with the statement, "I believe disorders similar to MPS1 and Pompe disease should be added to the newborn screen," 100% (n=5) strongly agreed (Table 10, Appendix G).

**Table 5 Parent Perception of Newborn Screening**

| Variable | Number of participants n=5 |
|---|---|
| After my experience, I have a positive view of the newborn screening experience | |
| Strongly Agree | 0% (0) |
| Agree | 40% (2) |
| Neither agree nor disagree | 20% (1) |
| Disagree | 0% (0) |
| Strongly Disagree | 40% (2) |

### 3.3.5 Stress Scale

A modified version of the Perceived Stress Scale was utilized for the survey. Participants were asked to answer, “yes”, “sometimes”, or “no” to a variety of statements in order to capture stress levels during the newborn screening process (Table 11, Appendix G) The maximum score that a participant could receive was a 22 while the minimum score was a 0. Participant scores ranged from 4 to 21. The average score amongst the participants was a 13.2 with a standard deviation of 7.56 (Table 6).

**Table 6 Stress Scale Scores**

| Participant | Total Score |
|---|---|
| #1 | 4 |
| #2 | 9 |
| #3 | 21 |
| #4 | 21 |
| #5 | 11 |
| Average ±SD | 13.2 ±7.56 |
| Range (scores) | 4-21 |

## 3.4 Discussion

Although statistical analysis could not be performed due to the limited number of participants, this study provided insight into aspects of the experience these parents underwent with newborn screening.

### 3.4.1 Demographics

The demographics of the participants in this study are similar to the study conducted by Pruniski *et al*. in 2018. In their study, all participants were mothers and identified as Caucasian. The majority of participants in both studies reported that this was not their first child. Likewise, education levels varied amongst the participants. Overall, based on the literature and patient populations at the recruitment sites, these demographics were expected. More diversity in respondents was desired due to the fact that a study by Catz *et al.* (2005), suggested that cultural orientation, education, and historical influence can impact the was individuals respond and process genetic information (Catz et al., 2005). Newborn screening is am intervention that is utilized for all populations, and because of this understanding the perspective and needs of different groups of individuals is important for holistic care.

### 3.4.2 Disclosure of Final Newborn Screening Results

#### 3.4.2.1 Details of Disclosure

The majority of the participants in this study had prior knowledge of newborn screening. This finding is not consistent with other previous studies that focused on similar topics (Davis et

al., 2006; DeLuca et al., 2011).The results of several studies have suggested that more in depth education could lessen the stress these parents experience (Kemper, Fant, & Clark, 2005; Waisbren et al., 2003). While the participants in this study had previous knowledge of newborn screening, expanding on their understanding may also lessen the emotional burden. The majority of the participants in this study as well as in the study performed by Pruniski *et al.* (2018) reported that the child's PCP was the first provider to disclose the results of the newborn screen. Other studies that focused on cystic fibrosis and sickle cell anemia also suggest that the PCP's are the main source of information for these families at the time of the disclosure (Collins et al., 2012). This finding highlights the importance of additional education for these providers. Being more informed may give more confidence to the provider when disclosing these results to parents and in turn allow them to counsel these families to the fullest extent.

#### 3.4.2.2 Perception of Newborn Screening Results Disclosure

This section of the survey aimed to elicit how the participants felt during the initial disclosure of the screening results and their perception of the provider who disclosed the results. Responses to this study were congruent with the results of the study performed by DeLuca *et al.* (2011) in that most of the participants in both studies had no knowledge of the disorder that their child was identified to be at risk for by newborn screening (DeLuca et al., 2011). LSDs are rare disorders, and therefore, it is expected that these families would not have experience. The majority of our participants also reported that in that moment they did not understand what the results meant for their child's health and that they felt like the provider who disclosed the screening results could have given them more information. Many participants turned to the Internet, which only fueled their concern. In 2006 Kemper *et al.* performed a study in which they interviewed PCP's and family medicine providers. Responses to their study suggested that PCP's are not prepared for all

aspects of newborn screening follow up (Kemper, Uren, Moseley, & Clark, 2006). Responses to the last portion of this study only reinforced their sentiments. In the final section of the survey participants were given the options to provide further comments. One participant commented that when she asked the nurse about Pompe disease, the provider responded, "It's something that involves the muscles." Another participant responded saying, "Having my PCP call me with the results but not being able to provide me with additional information is insane." PCPs may benefit from educational resources that would potentially allow them to provide parents with more accurate information to better prepare them for the future. Better quality information may also give the parents a better understanding of what the result means for their child's health, which may aid in alleviating stress.

### 3.4.3 Initial Genetics Appointment and Diagnosis

#### 3.4.3.1 Diagnoses

Similar to a pilot study performed in New York City (Wasserstein et al., 2019), none of our participants reported that their children were diagnosed with IOPD or MPS1 (MPS1-H). A study performed by Tang *et al*. (2006) in California, estimated that the birth prevalence of individuals with IOPD is lower than in other regions, but the rate of LOPD is higher (Tang et al., 2020). Results such as these reinforce that children with LOPD will continue to be identified as more infants are screened in the United States and that the frequency of Pompe disease (especially LOPD) is likely to change. Likewise, more parents will continue to experience stress related to their child's newborn screen results. Understanding factors, such as lack of information, that are stressors for these parents may allow for optimal care and guidance. Pretest counseling may be explored as a means to prepare parents. As discussed in the study by Pruniski *et al.* (Pruniski et

al., 2018) with children being diagnosed with LOPD and later onset MPS1, parents experience uncertainty about their child's future medical needs. Follow up, proper counseling, education, and resources could be beneficial for these families, as it has been shown that these can help parents adjust to uncertainty (Wang, 2020).

#### 3.4.3.2 Attitude and Actions Post Genetics Appointment

All the participants reported that the period in which they waited for the results of the confirmatory testing was incredibly stressful. While one parent reported feeling reassured by the initial genetics appointment, two (40%) of the participants reported that they did not. Although providers tell parents that confirmatory testing may be negative, parents may still feel stress and anxiety until results confirm the information given to them by the genetics team (Wang, 2020). Even when the results do confirm the provider's initial diagnosis, some parents may still not feel relief. One parent in our study reported that, "It was a very stressful time and I am still scared. My son will be 3 in April and while I believe we determined him to be a carrier with pseudo symptoms, I do not know for sure because I do not have the other parent to be tested." Together, these highlight the importance of proper counseling and provision of resources, which may aid in the parent's stress and coping.

### 3.4.4 Perception of Newborn Screening

An interesting finding from this study is that all participants (100% n=5) agreed that LSDs should be on newborn screening even though they had different reactions to the newborn screening process. This positive perspective of newborn screening for LSDs is consistent with prior research that explored perceptions of parents who have undergone newborn screening. Parents tend to look

favorably upon screening, especially if there is benefit to early treatment (Catharina Plass, van El, Pieters, & Cornel, 2009; Pruniski et al., 2018). Despite the challenges faced by these parents, they have lower stress levels and are better able to cope as compared to parents whose children were not diagnosed by newborn screening (Waisbren, Rones, Read, Marsden, & Levy, 2004). These results suggest that parents see benefit in an early diagnosis and that it may play a role in helping parents cope.

### 3.4.5 Stress Scale

All the participants in this study reported some degree of stress, however, the range in scores was relatively large spanning from 4-21. The highest score that could have been attained was a 22. This range of scores demonstrates how the needs of families can vary even in similar situations, and that proper understanding of those needs is important for their care. The parent who scored 4, reported feeling relieved after the appointment with the genetics providers, and it is possible that having a knowledgeable provider can be useful in relieving stress for these parents. One participant in this study stated, "After meeting with the providers at Children's Hospital, many of my fears and worries were relieved." Other studies note that parents search for information in this time period and are willing to find providers who can answer their questions (Salm, Yetter, & Tluczek, 2012).

Although the number of respondents was low, it is still notable that 40% (n=2) of the parents reported relatively high levels of stress during the entirety of the newborn screening process. These two individuals reported "Yes" to many of the items on the stress scale, outlining the impact this process has on many aspects of these parents' life. These parents reported feeling that they did not feel on top of things in their life and had trouble sleeping, both things that could

lead to lasting psychological impact. Studies have suggested that timely return of results and psychosocial intervention could be useful for relieving stress and anxiety (DeLuca et al., 2011; Tluczek, Koscik, Farrell, & Rock, 2005).

### 3.4.6 Study Limitations

This study had several limitations, with the most important being the low response rate. This low number of participants did not allow for any inferential statistical analysis that could provide information on statistically significant results. While the results provided information on the experiences of these parents, the inability to assess the significance of these results means that the conclusions cannot be made for all parents who have undergone this process. The limited number may also be attributed to how long the survey was available to potential participants. The window for response was a month, so more time may have been warranted. The use of mailers as a recruitment tool may have also been a barrier given the extra step required to access the survey instead of being immediately available via a link in the email. Finally, recruitment from Children's Hospital of Philadelphia (CHOP) was compromised due to COVID-19. Correspondence between the lead researcher and genetic counselors at CHOP occurred March 11$^{th}$, 2020 and on March 16$^{th}$, 2020 the situation with COVID-19 increased in severity. In that time frame, the governor of Pennsylvania issued a stay at home order. This meant that individuals were required to stay indoors, and many professionals were required to work from home. This major adjustment, made it increasingly difficult to recruit individuals for this study, and unfortunately led to loss of correspondence with CHOP. As a result, no participants were recruited from this site, contributing to the small sample size.

Another limitation to this study is the demographics of the participants. All the participants identified themselves as the mother of the child and therefore, the study was not able to capture the impact this experience had on other caregivers/parents. A goal of the study was to obtain responses from different caregivers. However, given that mothers tend to be the main gatekeeper for a family's healthcare, it is not unexpected that respondents were mothers (Case & Paxson, 2001). In addition, all the participants identified themselves as Caucasian, and thus this study lacks data on the experience of other populations. Participant diversity was another goal when designing this study, however, the patient population at UPMC Children's Hospital of Pittsburgh LSD program is predominantly Caucasian. To increase diversity, the Children's Hospital of Philadelphia was added as a recruitment site.

An additional limitation to this study was the design itself. This study was retrospective, mainly recruiting individuals who have already undergone the newborn screening process. The goal was to capture the experience of parents who had undergone and who are currently going through this experience. Data is limited on the needs of parents currently in the process and further exploring these parents' experience has the potential to expand providers' knowledge of how to best meet parents' needs.

### 3.4.7 Future Directions

This study reinforces the findings of previous research regarding parent perceptions of newborn screening (DeLuca et al., 2011; Wang, 2020), while also providing additional information specific to LSDs. The number of participants was low and therefore, a continuation of this specific project would provide more data. As more infants are screened for LSDs, future research may also focus on comparing retrospective and prospective experiences of several parents and caregivers.

Results from these studies could give insight into different aspects of the parent experience, possibly revealing areas where improvement to the process is needed. Because all the participants in this study were mothers, studies could be carried out that specifically target other family members/caregivers. This could give a more holistic understanding of the impact of the newborn screening process for LSDs on the family system.

A number of studies have been carried out to obtain recommendations from parents who have undergone newborn screening and received an abnormal result (Salm et al., 2012; Wang, 2020). One study conducted by Raymond Wang (2020) examined Pompe disease. The research collected qualitative data from parents of children who were identified to be at risk for Pompe disease via newborn screening. Parents were able to voice their concerns in the hope that providers can utilize it. Studies like this can be easily translated to other LSDs including MPS1. Collecting qualitative data will continue to be important in order to understand the unique experience of these families, especially because of the rarity of these disorders. Information from these studies could then inform the ways in which health care providers manage and counsel these parents.

Lastly, further research specific to non-genetics providers who are disclosing newborn screening results is warranted. The study by Kemper *et al.* in 2006, gave excellent insight into the perspective of the PCPs (Kemper et al., 2006). Their study consisted of 350 PCPs and family physicians. Of their respondents, the majority agreed that the PCP should be the one to disclose the results of the positive newborn screen. However, multiple respondents indicated that they did not have the knowledge to discuss the conditions of the newborn screening panel. Interviews such as these could be conducted in order to evaluate the knowledge these providers have specific to LSDs. Qualitative information such as this has the potential to give insight to the disparities of

providers. Providers can utilize this information to improve their own practice and potentially seek resources for themselves and their families.

## 3.5 Conclusion

There is a paucity of literature that describes the experience of parents who have had infants identified to be at risk for LSDs by newborn screening. This study provides insight into the experience of parents whose children received an abnormal newborn screening test for Pompe disease or MPS1, and hopefully encourages future research that furthers understanding of parents' experiences with newborn screening. Results of the study are consistent with prior research. As in previous studies, the results indicate that the newborn screening process is characterized by stress and uncertainty for parents. The ranges in stress levels highlight that while these parents are undergoing the same process, the needs of parents are not the same. While the sample size in the study was small, the reported diagnoses are similar to the findings of the New York pilot study (Wasserstein et al., 2019). No guardians of infants identified with the most severe form of either Pompe disease or MPS1 responded to this survey. As more newborns are found to have later onset forms of the conditions, pseudodeficiencies, or variants of uncertain significance, understanding the impact of receiving these results will be crucial for offering anticipatory guidance for families. While controversy regarding the addition of LSDs to the newborn screen persists, this study has shown that parent support newborn screening for LSDs. All participants strongly agreed that LSDs should be included in newborn screening. Lastly, responses from the participants indicate that there is a gap in the knowledge of these disorders amongst non-genetics providers. Because these providers might be the main source of information for these families, they need to be well informed

of these conditions in order to provide parents with appropriate medical information. As more LSDs are added to the newborn screen and more infants are screened for these conditions, it will become imperative for providers to understand the experience of parents in order to address the unique needs of this population.

## 4.0 Research Significance to Genetic Counseling and Public Health

Although the results of this study cannot be used to make generalizations about the population of parents who receive abnormal LSD result on newborn screening, they can be utilized by genetic counselors that provide care for these parents. Both management guidelines for Pompe disease and MPS1 recommend the involvement of genetic counselors at time of the diagnosis (Kishnani et al., 2016; Muenzer et al., 2009). As a health care provider involved in the care of these families, it is important that genetic counselors have an understanding of the psychological and emotional impact of receiving an abnormal newborn screening result. Given their unique psychosocial skill set, genetic counselors can use this information in order to address the psychological needs of these parents. Recognizing how parents respond to the abnormal result and its disclosure can guide how genetic counselors share the diagnosis and provide education about the condition. Finally, given the disparity in the knowledge of LSDs amongst primary care providers (Kemper et al., 2006), genetic counselors could play a role in developing educational programs for these providers.

Newborn screening is a public health program that routinely screens 4 million babies each year for a variety of conditions (Moreno, 2016). Its goal is to detect infants with congenital conditions before they are symptomatic in order to initiate treatment early and hopefully lessen the long-term burden of the condition (Pitt, 2010). The Center for Disease Control, estimates that 12,500 newborns will be diagnosed with a condition from the newborn screening panel each year, which means that 1/300 newborns are diagnosed with a core condition (National Institute of Child Health and Human Development, 2017). When analyzed from the perspective of the three core functions of public health, policy development and assurance are particularly relevant (Center for

Disease Control and Prevention, 2011). Currently as it stands, there is no standard policy regarding parental consent. It not a crucial factor in newborn screening, and approaches differ from region to region (Pelias & Markward, 2001). As screening becomes more advanced and more conditions are added to screening panels, new models for informed consent for newborn screening may be worth exploring. A study performed by Ulph *et al.* (2020), utilized focus groups to examine provider and parent perspective of informed consent for newborn screening (Ulph, Dharni, Bennett, & Lavender, 2020). The study was conducted in London where informed consent is obtained for newborn screening. The focus group consisted of parents as well as screening professionals, which included hospital screening coordinators, midwives, and quality assurance managers. Responses indicated both parents and screening professionals value informed consent, but recognize the challenges in obtaining it, including training those who obtain the DBS cards and privacy concerns. A consent process could offer anticipatory guidance to these families, which may make lessen the emotional burden should they receive an abnormal result. Potentially, a model could be proposed which the states could use to regulate the consent process. Having at minimum a model to follow may make the process more attainable for providers.

One of the main components of assurance is to, "assure a competent environmental health work force"(Center for Disease Control and Prevention, 2011), which this study aimed to gain information that providers could utilize in order to provide more comprehensive care for these parents. This study identified areas in which these parents felt there were gaps in their care, such as the provider's lack of knowledge, and lack of information given to them regarding the newborn screening result. Knowing these issues, providers can hopefully fill these gaps and create an effective standard of care.

# Appendix A University of Pittsburgh IRB Approval

**University of Pittsburgh**
***Institutional Review Board***

Human Research Protection Office
3500 Fifth Avenue, Suite 106
Pittsburgh, PA 15213
Tel (412) 383-1480
www.hrpo.pitt.edu

APPROVAL OF SUBMISSION (Exempt)

| | |
|---|---|
| Date: | January 28, 2020 |
| IRB: | STUDY19100114 |
| PI: | Ashley Lahr |
| Title: | Analysis of parent and caregiver's experience with newborn screening of lysosomal storage disorders. |
| Funding: | None |

The Institutional Review Board reviewed and approved the above referenced study. The study may begin as outlined in the University of Pittsburgh approved application and documents.

**Approval Documentation**

| | |
|---|---|
| Review type: | Initial Study |
| Approval Date: | 1/28/2020 |
| Exempt Category: | (2)(i) Tests, surveys, interviews, or observation (non-identifiable) |

| Determinations: | |
|---|---|
| Approved Documents: | • AEL email_Final .docx, Category: Recruitment Materials;<br>• AEL HRP-721 Exemption_Tests Surveys Public Behavior_Version_0.01 (1).docx, Category: IRB Protocol;<br>• AEL informational script_Final .docx, Category: Recruitment Materials;<br>• AEL mailer_Final .docx, Category: Recruitment Materials;<br>• CHOP Correspondence.pdf, Category: External Site Permission Letter;<br>• Health dpt agreement.pdf, Category: External Site Permission Letter; |

As the Principal Investigator, you are responsible for the conduct of the research and to ensure accurate documentation, protocol compliance, reporting of possibly study-related adverse events and unanticipated problems involving risk to participants or others. The HRPO Reportable Events policy, Chapter 17, is available at http://www.hrpo.pitt.edu/.

Clinical research being conducted in an UPMC facility cannot begin until fiscal approval is received from the UPMC Office of Sponsored Programs and Research Support (OSPARS).

If you have any questions, please contact the University of Pittsburgh IRB Coordinator, Amy Fuhrman.

*Please take a moment to complete our Satisfaction Survey as we appreciate your feedback.*

Pitt_510_Exempt

## Appendix B Permission to Use Stress Scale

### PERMISSION FOR USE OF THE PERCEIVED STRESS SCALE

I apologize for this automated reply. Thank you for your interest in our work.

**PERMISSION FOR USE BY STUDENTS AND NONPROFIT ORGANIZATIONS**: If you are a student, a teacher, or are otherwise using the Perceived Stress Scale (PSS) without making a profit on its use, you have my permission to use the PSS in your work. Note that this is the only approval letter you will get. I will not be sending a follow-up letter or email specifically authorizing you (by name) to use the scale.

**PERMISSION "FOR PROFIT" USE:** If you wish to use the PSS for a purpose other than teaching or not for profit research, or you plan on charging clients for use of the scale, you will need to see the next page: "Instructions for permission for profit related use of the Perceived Stress Scale".

**QUESTIONS ABOUT THE SCALE**: Information concerning the PSS can be found at https://www.cmu.edu/dietrich/psychology/stress-immunity-disease-lab/index.html **(click on scales on the front page)**. Questions about reliability, validity, norms, and other aspects of psychometric properties can be answered there. The website also contains information about administration and scoring procedures for the scales. Please do not ask for a manual. There is no manual. Read the articles on the website for the information that you need.

**TRANSLATIONS**: The website (see URL above) also includes copies of translations of the PSS into multiple languages. These translations were done *by other investigators*, not by our lab, and we take no responsibility for their psychometric properties. If you translate the scale and would like to have the translation posted on our website, please send us a copy of the scale with information regarding its validation, and references to relevant publications. If resources are available to us, we will do our best to post it so others may access it.

Good luck with your work.

Robert E. Doherty University Professor of Psychology
Department of Psychology
Baker Hall 335-D
Carnegie Mellon University
Pittsburgh, PA 15213

**Appendix C Recruitment Email for the UPMC Children's Hospital of Pittsburgh**

Hello,

My name is Ashley Lahr and I am training to be a genetic counselor at the University of Pittsburgh. I have worked with the UPMC Children's Hospital of Pittsburgh to reach you to invite you to participate in a survey. The aim of this survey study is to understand the experience of parents and caretakers who have children who were identified to be at risk for Mucopolysaccharidosis Type 1 or Pompe disease via Newborn Screening. The survey will take approximately 15-30 minutes to complete. Participation is optional, and all information collected is confidential. Risks associated with participating in the survey are minimal but may include negative feelings related to answering questions about your experience with Newborn Screening. There are no direct benefits to participating in the study. However, I look forward to using the information collected from the study to help health care providers best care for families affected by Newborn Screening.

If you are interested in participating, please click the link below.

https://pitt.co1.qualtrics.com/jfe/form/SV_8nLK1L3ulk0rH5r

Thank you very much for your consideration to participate in this research study. Should you have any questions, please contact me via email at Ael70@pitt.edu.

Sincerely,

Ashley Lahr, Genetic Counseling Intern
University of Pittsburgh

## Appendix D Recruitment Mailer for the UPMC Children's Hospital of Pittsburgh

Hello,

My name is Ashley Lahr and I am training to be a genetic counselor at the University of Pittsburgh. I have worked with the UPMC Children's Hospital of Pittsburgh to reach out to you to invite you to participate in a survey. The aim of this survey study is to understand the experience of parents and caretakers who have children who were identified to be at risk for Mucopolysaccharidosis Type 1 or Pompe disease via Newborn Screening. The survey will take approximately 15-30 minutes to complete. Participation is optional, and all information collected is confidential. Risks associated with participating in the survey are minimal but may include negative feelings related to answering questions about your experience with Newborn Screening. There are no direct benefits to participating in the study. However, I look forward to using the information collected from the study to help health care providers best care for families affected by Newborn Screening.

If you are interested in participating please type the link provided below in to your internet browser of choice to complete the survey.

https://pitt.co1.qualtrics.com/jfe/form/SV_8nLK1L3ulk0rH5r

Thank you very much for your consideration to participate in this research study. Should you have any questions please feel free to reach out to me via email at Ael70@pitt.edu.

Sincerely,

Ashley Lahr, Genetic Counseling Intern
University of Pittsburgh

## Appendix E Recruitment Email for the Children's Hospital of Philadelphia

Hello,

My name is Ashley Lahr and I am training to be a genetic counselor at the University of Pittsburgh. I have worked with the Children's Hospital of Philadelphia to reach you to invite you to participate in a survey. The aim of this survey study is to understand the experience of parents and caretakers who have children who were identified to be at risk for Mucopolysaccharidosis Type 1 or Pompe disease via Newborn Screening. The survey will take approximately 15-30 minutes to complete. Participation is optional, and all information collected is confidential. Risks associated with participating in the survey are minimal but may include negative feelings related to answering questions about your experience with Newborn Screening. There are no direct benefits to participating in the study. However, I look forward to using the information collected from the study to help health care providers best care for families affected by Newborn Screening.

If you are interested in participating, please click the link below.

https://pitt.co1.qualtrics.com/jfe/form/SV_8nLK1L3ulk0rH5r

Thank you very much for your consideration to participate in this research study. Should you have any questions, please contact me via email at Ael70@pitt.edu.

Sincerely,

Ashley Lahr, Genetic Counseling Intern
University of Pittsburgh

## Appendix F Survey

# Survey of parent and caregiver experience with newborn screening of lysosomal storage disorders

Start of Block: Default Question Block

Q1

My name is Ashley Lahr, and I am training to be a genetic counselor at the University of Pittsburgh. During my training, I had the opportunity to meet with families at various stages of the newborn screening process and am interested in learning more about the experience of parents/caregivers. If you are a parent or caregiver of at least one child who was identified to have or possibly have Mucopolysaccharidosis Type 1 (MPS1) or Pompe disease on the newborn screen, I am inviting you to take part in a research study I have developed as part of my education.

I work with UPMC Children's Hospital of Pittsburgh and Children's Hospital of Philadelphia. This is an invitation to participate in the survey for my study. Your participation is voluntary. If you choose to participate in the survey, it will take approximately 15-20 minutes to complete. You may pause the survey and return to it later if you use the same computer. At any point in the survey, you may choose to end participation and your answers will not be recorded. The goal of the study is to better understand your views, as a caregiver in the newborn screening process. We hope that health care providers are able to use the information to better understand and address the needs of families during the newborn screening process.

There are no direct benefits for participation. While foreseeable risks associated are minimal, they may include emotional responses or negative feelings brought on from answering questions about your experience with newborn screening. If you choose to participate, your responses will not be identifiable. All responses to the survey are confidential and cannot be linked to you. In the future, the data we collect may be shared with other researchers. In this case, the information shared will remain de-identified.

I, Ashley Lahr, am the principal investigator of this research study. If you have any questions or concerns regarding the study, please contact me at ael70@pitt.edu. Thank you for your time and consideration.

- ○ Yes, I would like to take the survey (1)
- ○ No, I do not want to take the survey (2)

Q5 What do you identify as your race?

- White (1)
- Black or African American (2)
- American Indian or Alaska Native (3)
- Asian (4)
- Native Hawaiian or Pacific Islander (5)
- Other: please specify (6) _____
- Prefer not to respond (7)

Q6 What is the highest education level you have?

- Some High-School or GED (1)
- High-School diploma (2)
- Associate degree (3)
- Some College (4)
- College 4 year degree (5)
- Master degree (6)
- Doctorate degree (7)
- If other please specify: (8) _____
- Prefer not to respond (9)

*Display This Question:*

*If How are you related to this child? = Mother*

*Or How are you related to this child? = Father*

Q8 Did you have any other children with the same partner prior to giving birth to this child?

- ○ Yes (1)
- ○ No (2)

*Skip To: Q9 If Did you have any other children with the same partner prior to giving birth to this child? = Yes*

*Skip To: Q10 If Did you have any other children with the same partner prior to giving birth to this child? = No*

*Display This Question:*

*If How are you related to this child? = Mother*

*Or How are you related to this child? = Father*

Q9 If you answered yes to the previous question, how many children with the same partner did you have prior to having this child? Please enter number below

_____

Q10 Before going to the genetics appointment, who was the first person to tell you about the final newborn screen results?

- ○ Primary Care Physician (PCP) (1)
- ○ Genetic Counselor (2)
- ○ Geneticist (3)
- ○ Other: Please Specify (4) _____

Q11 By what means were you first told about the final newborn screening results?

- ○ During a doctors appointment (1)
- ○ Over the phone (2)
- ○ Other: Please Specify (3) _____

Q12 Had you heard about newborn screening prior to this experience?

- ○ Yes (1)
- ○ No (2)

Q15 Including yourself and the child, how many people were at the initial genetics visit with you? This would have been the visit where you first met with a genetics provider in person including a genetic counselor and/or geneticist.

- ○ 1-2 (1)
- ○ 3-5 (2)
- ○ 6+ (3)

*Display This Question:*

*If Was your child identified to be at risk for MPS1 or Pompe Disease? = MPS1*

Q14 If you were referred for MPS1, after further testing what is your understanding of your child's diagnosis? Definitions of the different diagnoses are provided below:

Pseudodeficiency: When an individual has low enzyme activity, but does not have MPS1

Carrier: When an individual has a genetic change in one copy of their gene, but does not have MPS1

Variant of Uncertain significance: A change in a gene is found, but there is not enough information to determine if it is benign or disease causing

- ○ MPS1 (Hurler, Hurler-Scheie, Scheie) (1)
- ○ Carrier for MPS1 (2)
- ○ Pseudodeficiency (3)
- ○ Variant of Uncertain Significance (4)
- ○ Uncertain (5)

*Display This Question:*

*If Was your child identified to be at risk for MPS1 or Pompe Disease? = Pompe Disease*

Q16. If you were referred for Pompe disease, after further testing what was your understanding of your child's diagnosis? Definitions of the different diagnoses are provided below:

Pseudodeficiency: When an individual has low enzyme activity, but does not have Pompe disease

Carrier: When an individual has a genetic change in one copy of their gene, but does not have Pompe disease

Variant of Uncertain significance: A change in a gene is found, but there is not enough information to determine if it is benign or disease causing

- ○ Infantile (1)
- ○ Late-Onset (2)
- ○ Carrier (3)
- ○ Pseudodeficiency (4)
- ○ Variant of Uncertain Significance (5)
- ○ Uncertain (6)

Page Break

Q17 Below are a series of questions regarding your experience with newborn screening. These questions pertain to the experience of receiving the final results of the newborn screen for the first time. Please choose to what level you agree or disagree with the following statements.

| | Strongly disagree (1) | Disagree (2) | Neither agree nor disagree (3) | Agree (4) | Strongly agree (5) |
|---|---|---|---|---|---|
| I was unaware that my child had newborn screening (1) | ○ | ○ | ○ | ○ | ○ |
| It was difficult hearing the results of the newborn screen for the first time (2) | ○ | ○ | ○ | ○ | ○ |
| *Was your child identified to be at risk for MPS1 or Pompe Disease? = MPS1* | ○ | ○ | ○ | ○ | ○ |
| I knew what MPS1 was before this process (3) | | | | | |
| *Was your child identified to be at risk for MPS1 or Pompe Disease? = Pompe Disease* | ○ | ○ | ○ | ○ | ○ |
| I knew what Pompe disease was before this process (4) | | | | | |
| I felt the need to look up more information after first | ○ | ○ | ○ | ○ | ○ |

| | | | | | |
|---|---|---|---|---|---|
| receiving the final results of the newborn screen (5) | | | | | |
| I understood the information I was given by the health care provider about the final newborn screening results (6) | ○ | ○ | ○ | ○ | ○ |
| I understood what the results meant for my child's health (7) | ○ | ○ | ○ | ○ | ○ |
| I feel like the health care provider who first told me the results could have given me more information (8) | ○ | ○ | ○ | ○ | ○ |

Page Break

Q19 The next set of questions pertain to the period of time from the first genetics appointment to after the child's diagnosis was confirmed with lab/urine tests. Please choose to what level you agree or disagree with the following statements.

| | Strongly disagree (1) | Disagree (2) | Neither agree nor disagree (3) | Agree (4) | Strongly agree (5) |
|---|---|---|---|---|---|
| I was relieved after the initial genetics appointment where the screening results were discussed (1) | ○ | ○ | ○ | ○ | ○ |
| It was stressful waiting for the results of the lab/urine tests ordered by genetics to confirm my child's diagnosis (2) | ○ | ○ | ○ | ○ | ○ |
| I changed the way I cared for my child during this time (3) | ○ | ○ | ○ | ○ | ○ |
| I felt the need to follow up with genetics after receiving the lab/urine results (4) | ○ | ○ | ○ | ○ | ○ |
| After my experience, I have a positive view of the newborn screening experience (5) | ○ | ○ | ○ | ○ | ○ |

| | | | | | |
|---|---|---|---|---|---|
| I believe disorders similar to MPS1 and Pompe disease should be added to the newborn screen (6) | ○ | ○ | ○ | ○ | ○ |

Page Break

Q20
Questions in this section ask you about your feelings and thoughts during the newborn screening process. In each case, you will be asked to choose whether or not you experienced the feeling or thought.

Newborn screening process= the period of time from when the final results of the newborn screen were first disclosed to after the child's diagnosis was confirmed with lab/urine tests.

| | Yes (1) | Sometimes (2) | No (3) |
|---|---|---|---|
| During the newborn screening process I felt stressed (1) | ○ | ○ | ○ |
| During the newborn screening process I felt confident in my ability to handle my personal problems (2) | ○ | ○ | ○ |
| During the newborn screening process I felt things were going my way (3) | ○ | ○ | ○ |
| During the newborn screening process I could not cope with all the tasks I had to do (4) | ○ | ○ | ○ |
| During the newborn screening process I could not control irritations in my life (5) | ○ | ○ | ○ |
| During the newborn screening process I felt on top of things (6) | ○ | ○ | ○ |
| During the newborn screening process I was often angered by things outside my control (7) | ○ | ○ | ○ |
| During the newborn screening process I had trouble sleeping (8) | ○ | ○ | ○ |
| During the newborn screening process I often spoke with my child's medical team (9) | ○ | ○ | ○ |
| During the newborn screening process I thought about my child being different | ○ | ○ | ○ |

| | | | |
|---|---|---|---|
| from others (10) | | | |
| During the newborn screening process I worried about long-term impact of the condition (11) | ○ | ○ | ○ |

Page Break

Q21 Please provide any additional comments. Thank you for your time!

End of Block: Default Question Block

## Appendix G Supplemental Figures

**Table 7 Additional Demographic Information**

| Variable | Number of participants n=5 |
|---|---|
| Race | |
| White | 100% (5) |
| Black or African American | 0% (0) |
| American Indian of Alaska Native American | 0% (0) |
| Asian | 0% (0) |
| Native Hawaiian or Pacific Islander | 0% (0) |
| Other | 0% (0) |
| Prefer not to respond | 0% (0) |
| Education | |
| Some High-School or GED | 0% (0) |
| High-School Diploma | 0% (0) |
| Associate Degree | 20% (1) |
| Some College | 20% (1) |
| College 4 year degree | 20% (1) |
| Masters Degree | 0% (0) |
| Doctorate Degree | 20% (1) |
| Other | 20% (1) |

**Table 8. Perception Toward Newborn Screening Results Disclosure**

| | Strongly Disagree | Disagree | Neither agree nor disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| **I was unaware that my child had newborn screening** | 3 (60%) | 1 (20%) | 1 (20%) | 0 (0%) | 0 (0%) |
| **It was difficult hearing the results of the newborn screen for the first time** | 0 (0%) | 0 (0%) | 0 (0%) | 1 (20%) | 4 (80%) |
| **I knew what MPS 1 was before this process** | 1 (50%) | 0 (0%) | 0 (0%) | 1 (50%) | 0 (0%) |
| **I knew what Pompe disease was before this process** | 3 (100%) | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) |
| **I felt the need to look up more information after receving the final results of the newborn screen** | 0 (0%) | 0 (0%) | 0 (0%) | 1 (20%) | 4 (80%) |
| **I understood the information I was given by the health care provider about the final newborn screening results** | 0 (0%) | 1 (20%) | 1 (20%) | 3 (60%) | 0 (0%) |
| **I understood what the results meant for my child's health** | 1 (20%) | 1 (20%) | 1 (20%) | 2 (40%) | 0 (0%) |
| **I feel like the health care provider who first told me the results could have given me more information** | 0 (0%) | 0 (0%) | 1 (20%) | 2 (40%) | 2 (40%) |

**Table 9 Perception Post-Genetics Appointment**

| | Strongly Disagree | Disagree | Neither agree nor disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| **I was relieved after the initial genetics appointment where the screening results were discussed** | 1 (20%) | 1 (20%) | 1 (20%) | 2 (40%) | 0 (0%) |
| **It was stressful waiting for the results of the lab/urine tests ordered by genetics to confirm my child's diagnosis** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 5 (100%) |
| **I changed the way I cared for my child during this time** | 1 (20%) | 1 (20%) | 1 (20%) | 0 (0%) | 2 (40%) |
| **I felt the need to follow up with genetics after receiving the lab/urine results** | 0 (0%) | 1 (20%) | 1 (20%) | 0 (0%) | 3 (60%) |

**Table 10 Perception of Newborn Screening**

| | Strongly Disagree | Disagree | Neither agree nor disagree | Agree | Strongly Agree |
|---|---|---|---|---|---|
| **After my experience, I have a positive view of the newborn screening experience** | 2 (40%) | 0 (0%) | 1 (20%) | 2 (40%) | 0 (0%) |
| **I believe disorders similar to MPS1 and Pompe disease should be added to the newborn screen** | 0 (0%) | 0 (0%) | 0 (0%) | 0 (0%) | 5 (100%) |

**Table 11 Stress Scale**

| | Yes | Sometimes | No |
|---|---|---|---|
| **During the newborn screening process I felt stressed** | 4 (80%) | 0 (0%) | 1 (20%) |
| **During the newborn screening process I felt confident in my ability to handle my personal problems** | 2 (40%) | 1 (20%) | 2 (40%) |
| **During the newborns screening process I felt things were going my way** | 0 (0%) | 3 (60%) | 2 (40%) |
| **During the newborn screening experience I could not cope with all the tasks I had to do** | 2 (40%) | 1 (20%) | 2 (40%) |
| **During the newborn screening process I could not control irritations in my life** | 2 (40%) | 0 (0%) | 3 (60%) |
| **During the newborn screening process I felt on top of things** | 1 (20%) | 2 (40%) | 2 (40%) |
| **During the newborn screening process I was often angered by things outside my control** | 1 (20%) | 1 (20%) | 3 (60%) |
| **During the newborn screening process I had trouble sleeping** | 2 (40%) | 2 (40%) | 1 (20%) |
| **During the newborn screening process I often spoke with my child's medical team** | 1 (20%) | 2 (40%) | 2 (40%) |
| **During the newborn screening process I thought about my child being different from others** | 4 (80%) | 1 (20%) | 0 (0%) |
| **During the newborn screening process I worried about long-term impact of the condition** | 4 (80%) | 1 (20%) | 0 (0%) |

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