KNOWLEDGE AND ATTITUDES ABOUT NEWBORN SCREENING FOR FABRY DISEASE

by

Kavitha Aneesha Kolla

BS Genetics, University of Minnesota, 2015

Submitted to the Graduate Faculty of

the Department of Human Genetics - Genetic Counseling

Graduate School of Public Health in partial fulfillment of

the requirements for the degree of

Master of Public Health and Master of Science

University of Pittsburgh

2017

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Kavitha Aneesha Kolla

It was defended on

June 9, 2017

and approved by

Robin E. Grubs, MS, PhD, LCGC, Assistant Professor, Director of the Genetic Counseling Program, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Katie Long, MS, LCGC, Medical Science Liaison, US Medical Affairs – Rare Disease Division, Sanofi US, Adjunct Instructor, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Candace Kammerer, PhD, Associate Professor, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

Thesis Advisor: Catherine M. Walsh Vockley, MS, LCGC, Senior Genetic Counselor, Division of Medical Genetics, Children's Hospital of Pittsburgh of UPMC, Adjunct Instructor, Department of Human Genetics, Graduate School of Public Health, University of Pittsburgh

KNOWLEDGE AND ATTITUDES ABOUT NEWBORN SCREENING FOR FABRY DISEASE

Kavitha Aneesha Kolla, MS, MPH

University of Pittsburgh, 2017

ABSTRACT

Newborn screening is a public health program that identifies newborns who are at risk of having a life-threatening condition that will affect their health in infancy or childhood. Fabry disease is an X-linked lysosomal storage disorder with a variable age of onset from childhood through adulthood that was recently added to a few states' newborn screening panels. Research on patient attitudes towards newborn screening for Fabry disease has been limited and this qualitative study aimed to gain a more complete understanding of the reasoning of adults with Fabry disease regarding the appropriateness of newborn screening for Fabry disease, their knowledge of newborn screening, and their experiences with Fabry disease. Participants were recruited from Children's Hospital of Pittsburgh of UPMC's Lysosomal Storage Disorders Clinic and six adults who have Fabry disease were interviewed. These interviews were transcribed and thematic analysis revealed six themes: influences of clinical spectrum and severity of Fabry disease, support systems, family dynamics, impact of timing of diagnosis and treatment availability on attitudes towards newborn screening, knowledge and attitudes towards newborn screening for Fabry disease, and impact of earlier diagnosis. Based on their personal experiences with Fabry disease, all participants were in favor of newborn screening for Fabry disease. Participants' experiences with Fabry disease also reflected aspects of their family dynamics. The results of this qualitative study can inform genetic counseling practice for Fabry disease and future studies on NBS for Fabry disease. The opinions of stakeholders, including patients

affected by the condition, are of public health significance and the results of this study can inform public health decisions as state legislators and state newborn screening programs consider whether to include Fabry disease on their state's newborn screening panel.

TABLE OF CONTENTS

LIST OF TABLES

PREFACE

Thank you to all of the individuals who made this project possible. First of all, a special thanks to the participants who shared their stories and opinions. Secondly, thank you to Nadene Henderson for her assistance in recruiting participants and to Jennifer Baker for her help with the IRB approval process. Additionally, I am extremely thankful for the guidance, advice, and support from my thesis advisor, Catherine Walsh Vockley and committee members Dr. Robin Grubs, Dr. Candace Kammerer, and Katie Long. And thank you to my family and friends for their support throughout this project.

1.0 INTRODUCTION

Newborn screening (NBS) is a public health program that identifies newborns who are at risk of having a life-threatening condition that will affect their health in infancy or childhood[1]. For newborns diagnosed with a life-threatening condition by confirmatory testing following NBS, a treatment or management plan is immediately created. Each state decides which conditions to include on its NBS panel[1,2]. When making decisions about additions to the NBS panel, the state considers recommendations from the federal government's Advisory Committee on Heritable Disorders in Newborns and Children and the requests of parent activists and organizations[3,4].

One condition that was recently added to a few states' NBS panels is Fabry disease, an X-linked lysosomal storage disorder. Fabry disease is caused by mutations in the *GLA* gene, which result in a deficiency of the lysosomal enzyme α-galactosidase A (α-Gal A) and the accumulation of globotriaosylceramide (GL3) in the lysosomes of cells throughout the body[5,6]. It is a progressive disorder and the clinical features of Fabry disease include neuropathic pain, progressive renal disease, cardiomyopathy, gastrointestinal (GI) symptoms, heat and cold intolerance, stroke, hypohidrosis, angiokeratomas, and corneal opacity[7–12]. Both hemizygous males and heterozygous females vary in which features they manifest and in the level of disease severity[7,13,14]. Compared to most conditions on NBS panels that have onset in infancy, the age of onset for Fabry disease is later, varying between childhood and adulthood, and treatment is

typically not recommended until there is an appearance of symptoms[15–18]. However, there is ongoing debate regarding which symptoms and signs to consider in this decision making and how to identify the earliest disease manifestations for both males and females[15–18]. The treatment for Fabry disease includes enzyme replacement therapy and management of symptoms[17]. Concerns have been raised among healthcare providers and experts about the appropriateness of screening for this condition due to the lack of consensus and evidence for when to start treatment in asymptomatic individuals[19–21].

Qualitative and quantitative studies have explored opinions about NBS among parents in the general population and parents of children with conditions on NBS panels[22–26]. In the general population, there is support for NBS for early-onset conditions and conditions which have a treatment available[22]. Parents, for example, generally support NBS for MPS I and Pompe disease, two lysosomal storage disorders that have variable ages of onset, including severe early infantile presentations, and have recently been added to some states' NBS panels[23,24]. Research on patient attitudes towards NBS for Fabry disease has been limited to two studies that asked adults with Fabry disease about the timing of their diagnosis and their opinions on how a diagnosis at birth by NBS would have impacted their life and health[25,26]. In these studies, participants, in general, supported NBS for Fabry disease.

The goal of this qualitative study is to gain a more complete understanding of the perceptions of adults with Fabry disease and parents of a child with Fabry disease regarding the appropriateness of newborn screening for Fabry disease. The results of this study have the potential to provide state legislators and healthcare providers with insight into the value assessment of NBS for Fabry disease among those living with the disorder. For states that have started screening for Fabry disease or will begin screening in the near future, these results will

also provide NBS programs and healthcare providers with information on the type of resources and support parents may want when faced with a positive newborn screen for Fabry disease.

1.1 RESEARCH QUESTIONS

- What understanding do adults and parents of a child with Fabry disease have of newborn screening's purpose and process?
- How do adults who have Fabry disease and parents of a child with Fabry disease view newborn screening for Fabry disease?

1.2 SPECIFIC AIMS

Specific Aim 1: To conduct semi-structured interviews with adults with Fabry disease and parents of a child with Fabry disease.

Specific Aim 2: To analyze the interviews via thematic analysis to describe:

- What adults who have Fabry disease and parents of a child with Fabry disease understand about newborn screening's purpose and process.
- The attitudes of adults who have Fabry disease and parents of a child with Fabry disease on newborn screening for this condition.

To achieve these specific aims, adults who have Fabry disease and parents of a child who has Fabry disease were identified and recruited from the Children's Hospital of Pittsburgh of UPMC's Lysosomal Storage Disorders Program with the aid of the clinic's primary clinical

genetic counselor. Semi-structured interviews were conducted by telephone with six participants who have Fabry disease, five of whom have at least one first degree relative who is also affected. These interviews were transcribed and analyzed via thematic analysis to describe the participants' understanding of newborn screening and their attitudes towards newborn screening for Fabry disease.

2.0 LITERATURE REVIEW

2.1 FABRY DISEASE

Fabry disease is an X-linked lysosomal storage disease that affects multiple organ systems. The onset of Fabry disease ranges from childhood through adulthood and it affects both males and females. The terms "classic" and "late-onset" are used to describe Fabry disease phenotypes, but as more is learned about the disease, these two terms do not adequately capture the wide spectrum and heterogeneity of the disease[10]. The classic phenotype tends to refer to individuals who experience multiple symptoms of Fabry disease with onset in childhood or early adulthood and the late-onset phenotype tends to refer to phenotypes which involve only one organ system and have onset in adulthood[10,13,27]. Fabry disease is a panethnic condition, meaning it is present in all races and ethnicities[5]. Before newborn screening was initiated in several countries and several US states for Fabry disease, the incidence of this condition was thought to be between 1 in 60,000 and 1 in 40,000 males[28]. The numbers from various states' and countries' newborn screening studies, which are described in the newborn screening section, indicate the incidence of Fabry disease ranges between 1 in 3859 and 1 in 2875[29,30].

2.1.1 Clinical Course

2.1.1.1 Clinical Features

Fabry disease is a vascular disease that affects multiple body systems, including the cardiac, renal, gastrointestinal, and nervous systems[10,15]. The condition also includes skin and eye changes, which are pathognomonic features of Fabry disease[9,10].

Cardiac features of Fabry disease include structural and conduction abnormalities in the heart[11,31]. The structural changes include mitral and aortic valve changes and progressive cardiomyopathy[11,31]. The typical presentation of cardiomyopathy in Fabry disease is left ventricular hypertrophy[11]. Conduction abnormalities in Fabry disease increase the susceptibility to arrhythmias[31]. Both males and females can develop cardiac symptoms, but males tend to develop these symptoms 10 years earlier than females[31,32]. The median age for males to develop cardiac symptoms is 43.5 years versus 54.9 years in females[32].

Individuals with Fabry disease are also at increased risk of cerebrovascular events, such as hemorrhagic strokes and transient ischemic attacks[33]. In a natural history study with 2,446 individuals from the global Fabry Registry, approximately 6.9% of males and 4.3% of females with Fabry disease experienced a cerebrovascular event at a mean age of 39 years for males and 45.7 years for females[33]. While the proportion of individuals who have cerebrovascular events is lower than those who experience cardiac or renal complications, 50% of males and 38.3% of females who have a stroke experienced their first stroke prior to being diagnosed with Fabry disease[33].

In the nervous system, the main feature of Fabry disease is acroparasthesia[7]. Acroparasthesias refer to neuropathic pain that starts in the palms of the hands and the soles of the feet; the pain may spread proximally to the joints and to the abdomen[7]. Individuals with

acroparasthesias have varying levels of burning and tingling, with similar mean age of onset in childhood and similar phenotype in both males and females[7,34]. Other nervous system features of Fabry disease are dizziness, tinnitus, hearing loss, and white matter hyperintensity in the brain[35]. The cause of white matter hyperintensities in the brain appears to be related to cerebrovascular disease and increases with disease progression, aging, and stroke[35,36].

There are also cognitive and psychological features in Fabry disease[37,38]. Individuals with more white matter lesions unrelated to stroke or compromised cerebrovascular integrity have slightly more cognitive, learning, and memory deficits than controls [37,38]. Studies ranging in size from 17 to 25 individuals with Fabry disease from Germany and Australia suggest males have a slower speed of information processing and reduced performance on measures of executive function than controls[37,38]. Other studies have not seen the same cognitive findings[38,39]. There is also a higher prevalence of psychological distress such as anxiety, depression, and decreased social-adaptive functioning in individuals with Fabry disease[38–40]. The rate of depression in these studies ranged from 48% to 60%[37,41]. Researchers speculate that the higher frequency of depression is related to the burden of having a chronic multi-organ hereditary disease and not to the structural brain changes[37]. Research has found that depression rates are similar among individuals with varying amounts of white matter lesions[37].

The renal system is also affected by the accumulation of GL3 evidenced by progressive kidney disease[42,43]. The damage to the kidneys begins in childhood, but the symptoms of progressive kidney disease typically do not present until adulthood[42,43]. These symptoms include proteinuria, hypertension, increased serum creatinine, and reduced glomerular filtration rate[42]. Although there may be minimal symptoms present during childhood, there are significant pathological changes detectable by kidney biopsy in young males and females such as

glomerular and vascular changes and significanct GL3 accumulation[44,45]. In males, these symptoms present at a median age of 20 years and in females, at a median age of 28 years[15].

Gastrointestinal (GI) symptoms in Fabry disease include irritable bowel syndrome, unspecified functional bowel disorder, abdominal pain, diarrhea and functional bloating[12,46]. The onset of GI symptoms is in childhood, with 49.3% of children experiencing abdominal pain and 25.4% with diarrhea[12]. Across all age groups, approximately 52% of individuals with Fabry disease experience GI symptoms and the most common symptoms are abdominal pain and diarrhea[12]. While other features of Fabry disease have a similar prevalence in both genders or a higher prevalence in males, 54.2% of females reported GI symptoms compared to 48.9% of males[12]. This difference between the genders for GI symptoms is also seen in the general population[12].

In addition to the major organ involvement described above, the hallmark features of Fabry disease include eye and skin findings and changes related to the autonomic nervous system such as temperature regulation and lack of sweating[8–10]. Approximately 50% of males and females have cornea verticillata, which are whorl-like opacities in the cornea that do not affect vision[9]. Less common eye findings are tortuous vessels and cataracts[9]. The hallmark skin finding in Fabry disease are angiokeratomas, which are benign small raised dark red spots that increase in number and size with age[10]. Individuals with Fabry disease can have hypohidrosis and heat and cold intolerance[8].

2.1.1.2 Age of Onset

The age of onset of Fabry-related symptoms varies between males and females and also varies by phenotype. Data from the first 1765 individuals with Fabry disease in the Fabry Registry showed that the mean age of onset for males is 9 years and for females is 13 years[15].

Males with the classical phenotype can present with symptoms as early as 2 years[8]. For individuals with an atypical or later-onset phenotype, symptoms related to the renal, cardiac or cerebrovascular symptoms have an onset in middle age[13,16,27]. Males and females experience a diagnostic lag after the onset of symptoms[7,15]. The average age at diagnosis for a male is 23 years and for females it is 32 years[7,15].

2.1.1.3 Inheritance and Recurrence Risk

Fabry disease is inherited in a X-linked pattern[47]. Both males and females who have a pathogenic variant in the *GLA* gene exhibit features of Fabry disease[10,14]. There is a wider range of disease severity in females believed to be due in part to random X chromosome inactivation[10,11,27]. For males with Fabry disease, there is a 100% chance their daughters will inherit the *GLA* pathogenic variant and a 0% chance of their sons will inherit the *GLA* pathogenic variant. For females with Fabry disease, each of child (son or daughter) has a 50% chance of inheriting the *GLA* pathogenic variant[5].

2.1.1.4 Females with Fabry Disease

Females who carry one pathogenic variant in the *GLA* gene were previously thought to be asymptomatic carriers[7]. Various studies involving heterozygous females have shown that females are not just carriers, but they exhibit features of Fabry disease with a range of disease severity depending on random X-inactivation[7,14,48,49]. Up to 1% of heterozygous females have the same level of severity in their symptoms as males[7]. Compared to the general population, females with Fabry disease have a higher prevalence of heart palpitations (48% Fabry vs. 13%), joint pain (58% Fabry vs. 25%), fatigue (89% Fabry vs. 57%), GI symptoms (82% Fabry vs. 51%), dizziness (60% Fabry vs. 19%), and loss of libido (60% Fabry vs. 23%)[48]. Females with Fabry

disease also have neurological features, cardiac features, and renal features[34]. These features convey a significant disease burden and can impair quality of life[14]. Data from the Fabry Outcome Survey from a European registry for Fabry disease provide information on the natural history and the prevalence and onset of symptoms in females[34]. Approximately 77% had neuropathic pain with mean age of onset equal to 16 years[34]. Other symptoms (cardiac, renal, GI, angiokeratomas) were present in 40-60% of women with a mean age of onset in their 20s and 30s[34].

2.1.2 Molecular and Biochemical Basis of Fabry Disease

2.1.2.1 Molecular Genetics and Disease Mechanism

Fabry disease is a X-linked lysosomal storage disease (LSD)[47]. The lysosome is a cellular organelle which is responsible for breaking down complex macromolecules and recycling cellular debris[50]. In LSDs, the deficiency in a specific lysosomal enzyme results in the accumulation of its substrate in lysosomes[50]. The resulting accumulation of the substrate in lysosomes leads to impaired cellular function and progressive tissue and organ damage[50].

Fabry disease is caused by mutations in the *GLA* gene, which is located on chromosome Xq22.1[6,47]. The *GLA* gene makes the lysosomal enzyme α-galactosidase A (α-Gal A)[47]. In lysosomes, α-Gal A breaks down the glycolipid globotriaosylceramide (GL3)[51]. In Fabry disease, the deficiency in α-Gal A leads to the accumulation of GL3 in lysosomes in the cells of most organs[51]. Although the exact mechanism of the features of Fabry disease are still being studied, the progressive accumulation of GL3 in cells leads to some of the features, such as heart and kidney disease[52–55]. In the heart, myocytes grow larger from the accumulation of GL3 and this leads to hypertrophic cardiomyopathy[53,55].

2.1.2.2 Genotype-Phenotype Correlations

The genotype-phenotype correlations in Fabry disease are limited. More than 750 pathogenic variants have been identified in the *GLA* gene, but most of these variants are private mutations and their correlations with phenotype have not been well studied[13,56]. Low enzyme activity does not clearly predict phenotype[29]. Functional variants have been identified in the *GLA* gene that lead to low enzyme activity and no apparent disease features[29]. A few pathogenic variants are associated with later-onset phenotypes of Fabry disease in which only one organ system is affected, like the heart, the kidneys, or the cerebrovascular system[13,27,35]. One, the IVS4+919G>A allele, is associated with cardiac symptoms in adulthood and abnormalities on brain MRI that are similar to the abnormalities seen in the classical phenotype[27,35]. Having one D313Y allele may be associated with mild clinical symptoms, but there is also evidence this allele may be a benign polymorphism[13,57]. Two variants, p.Arg118Cys and D313Y, have been identified as risk factors for cerebrovascular disease[13,58,59].

2.1.3 Diagnosis

For individuals with features suspicious for Fabry disease, a family history of the disorder, or a positive newborn screen, Fabry disease is diagnosed either through enzymatic testing or through molecular genetic testing. In males, demonstration of α-Gal A deficiency in a blood plasma or leukocyte sample is a definitive method of diagnosis[10,60]. In females, a blood sample may not determine if α-Gal A is deficient due to random X inactivation[61]. Therefore, molecular genetic testing and the identification of a pathogenic variant in the *GLA* gene is required to confirm a diagnosis of Fabry disease in a female[10]. Molecular genetic testing

confirms the diagnosis in males and provides the genotype, which may help in determining anticipated disease severity[17].

Diagnostic testing can also be performed in the prenatal period when the familial mutation is known[62]. Prenatal diagnostic testing can be done through amniocentesis or CVS and the samples undergo molecular testing[62]. Since Fabry disease is highly variable in females due to random X inactivation, the use of prenatal testing to diagnose heterozygous females is controversial and is not routinely performed[62].

2.1.4 Management

The management of individuals with a pathogenic variant in the *GLA* gene requires a multidisciplinary approach with a team that often includes a geneticist, genetic counselor, nephrologist, cardiologist, and neurologist[17,18]. This multidisciplinary team is involved in treating the condition and its features, as well as in providing surveillance for other Fabry-related features that can occur[17,18]. The treatment and management of Fabry disease begins after the appearance of symptoms in males and females of any age[17]. Asymptomatic individuals with an identified pathogenic variant in the *GLA* gene should be followed closely for the development of any symptoms so treatment can begin before any potentially irreversible damage is done to the organs[17]. Research is being done to find a reliable biomarker to monitor the progression of Fabry disease during the asymptomatic period[63]. One possible biomarker that has been identified to monitor disease progression is blood concentrations of globotriaosylsphingosine (LysoGb3), which is a deacylated form of GL3[63]. The management of Fabry disease includes enzyme replacement therapy, investigational treatments, and the specific management of any individual symptoms[17,18].

2.1.4.1 Enzyme Replacement Therapy

Enzyme replacement therapy (ERT) is a medical treatment that replaces the enzyme that is deficient in the body via an intravenous infusion[64]. The goal of ERT is to substitute at least some amount of the deficient enzyme to reduce the accumulation of the enzyme's substrate and the associated symptoms[65]. ERT for Fabry disease is agalsidase beta, which is sold as Fabrazyme® by Genzyme Corporation© in the United States[66]. Outside of the United States, ERT for Fabry disease is either Fabrazyme® or agalsidase alfa, which is sold as Replagal® by Shire HGT, Inc.[66,67]. Agalsidase beta is a recombinant form of human α-Gal A that has an identical amino acid sequence to the natural form[66]. ERT is typically given intravenously every two weeks at a dose of 1mg/kg body weight[66].

At the cellular level, agalsidase beta clears microvascular endothelial deposits of GL3 from renal, cardiac, and skin cells[53]. Clinical studies demonstrated that in the long-term and at the whole-body level, agalsidase beta reduces the number of severe clinical events, like heart failure, stroke, or kidney failure[66]. The 10-year outcome study on agalsidase beta showed that 81% of adult participants receiving this ERT remained free of severe clinical events[66]. Agalsidase beta does not appear to cross the blood-brain barrier and strokes still occur in individuals taking ERT[66].

Ideally, ERT should be started when symptoms appear or when significant changes in the organs are detected[17]. In the 10-year outcome study of the original adult participants who participated in the Fabrazyme® clinical trials, there were better outcomes in those who started ERT with less disease progression, especially related to progressive kidney disease[66]. Starting ERT after the progressive kidney disease has begun may not halt the progression or reverse the damage that has already occurred[42]. Although there were more severe clinical events in older

individuals and individuals with more advanced kidney disease, ERT prolonged their life expectancy by reducing the number of severe cardiac events[66].

2.1.4.2 Oral Chaperone Therapy

Oral chaperones are molecules that assist in folding enzymes and transporting enzymes to their proper location in the cell[68]. The goal of oral chaperone therapies is to increase enzymatic activity by assisting the affected enzyme in its folding and transportation[68]. Oral chaperone therapies only work to treat the genetic condition if the affected enzyme still has catalytic competency, i.e. the affected enzyme must still be able to bind and process its substrate[6]. Migalastat by Amicus Therapeutics, Inc. is an oral chaperone therapy that is currently being studied to treat Fabry disease[6,69]. The chaperone works by binding and stabilizing α-Gal A[6]. It then facilitates transporting α-Gal A to lysosomes where the chaperone also increases the enzyme's ability to break down GL3[6]. Individuals need an amenable mutation that lead to a protein that expresses α-Gal A with catalytic competence for Migalastat to work[6,69].

2.1.4.3 Guidelines for Management of Fabry disease

General guidelines for the screening and management of Fabry disease have been published by Eng et al. and guidelines specific to the pediatric population have been published by Hopkin et al.[17,18]. At the initial evaluation, baseline assessments of the heart, kidneys, nervous system, eyes, ears, GI, skeleton for bone mineral density, and the general quality of life and psychological state are recommended[17,18]. After the comprehensive baseline assessment, each organ system should be regularly assessed[17,18]. Hopkin et al. recommend yearly evaluations, as well as regular monitoring by specialists for the heart, kidneys, and nervous system[17]. The pediatric guidelines and the American College of Medical Genetics and Genomics (ACMG)

Work Group on Diagnostic Confirmation of LSDs recommend that newborns be followed closely by a medical team experienced with Fabry disease every 6 months[17,70]. A more specific timeline for monitoring and treatment has not been defined for newborns due to a lack of evidence[17].

In general, a multidisciplinary medical team manages ERT and treats and follows symptoms of Fabry disease. The treatment of symptoms for Fabry disease may include analgesic drugs for pain relief, medications for GI motility, antiarrhythmic drugs for conduction abnormalities in the heart, and dialysis or renal transplantation for end-stage renal failure[18]. Based on current research, no medication are contraindicated in Fabry disease[17,18].

2.1.5 Psychosocial Concerns in Fabry Disease

2.1.5.1 Quality of Life

A number of studies with sample sizes ranging from 10 to 98 individuals have been done to assess the impact of Fabry disease on patient quality of life[7,14,49,71–75]. These studies have found that the features of Fabry disease affect the quality of life in multiple areas. Health-related quality of life (HRQoL) was assessed by looking at eight domains: physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health[72–74]. Males and females had decreased HRQoL across all eight domains[73,74].

The contributors to quality of life varied slightly between males and females. Both males and females mentioned how pain, fatigue, and GI symptoms affected their quality of life[49,71]. Males perceived pain and hypohidrosis as most affecting their quality of life, whereas females perceived fatigue, exercise intolerance, and poor self-perception of health as most important to

their quality of life[14,73]. Fabry disease also affected school attendance, participation in sports, employment, and attending social activities in both males and females[49,71]. The quality of life improved significantly in individuals with Fabry disease after initiating ERT and this improvement was maintained 2 years after initiation[72].

Fabry disease-related pain is a large contributor to the quality of life[7,49,71–73,76]. Fabry disease-related pain negatively impacts multiple domains of life: occupational functioning, relationship functioning, physical functioning, and emotional functioning[76]. With these domains, the pain affects individuals' capacity to complete everyday physical tasks, like holding their child or loved one[7,76]. ERT seems to improve pain, but not significantly[72].

2.1.5.2 Other Effects of a Diagnosis and Disease Features

The features of Fabry disease and being diagnosed with Fabry disease affect individuals' perceptions of themselves and their mental health[49,71,75,76]. Angiokeratomas in the genital region led to embarrassment and decreased self-esteem in males with Fabry disease[71]. There is a higher rate of depression and anxiety in individuals with Fabry disease compared to 4.7% of the general population[37,38,77]. One study reported that 46% of individuals with Fabry disease had depression, of whom 28% were considered to have severe clinical depression[41]. The increased prevalence of depression seems to be at least partially related to having a chronic multi-organ hereditary disease and there is an association between disease severity and depression in those with Fabry disease[37,41].

2.1.5.3 Females with Fabry Disease

Females with Fabry disease have the same psychosocial concerns as males because of the diagnosis and disease symptoms, but they face additional concerns because they are females[14,76].

Heterozygous females were originally called asymptomatic carriers[14]. This label has contributed to females' additional psychosocial concerns because females were dismissed as being just carriers[14,76]. Heterozygous females were referred to as asymptomatic carriers as recently as 2001 and when a female had symptoms, the symptoms were considered mild[49]. A 2001 study on the clinical manifestations and impact of the disease in 60 obligate carrier females was one of the first studies that revealed that 30% of carriers had multiple symptoms and serious manifestations of Fabry disease[49]. In addition to previously being labeled asymptomatic carriers, symptomatic females with Fabry disease experience a diagnostic lag and are sometimes diagnosed as adults after a male relative or a younger female relative is diagnosed[75,76]. Gibas et al. noted being female is also a barrier to quality healthcare[76]. Thus, females with Fabry disease, a rare disease with non-specific symptoms, are hypothesized to be at a triple disadvantage to achieving quality healthcare[76].

A qualitative study on the experiences of being a heterozygous female with Fabry disease identified other factors apart from disease features that contribute to their psychosocial concerns[75]. Receiving the diagnosis caused concerns. Individuals who were diagnosed before symptoms developed had difficulty accepting the diagnosis[75]. For those who experienced symptoms prior to diagnosis, there was relief because the diagnosis provided a name for their symptoms[75]. The diagnosis led to a major change in how the women viewed themselves and how others, including healthcare providers, viewed them and their symptoms[75]. Prior to diagnosis, females in this qualitative study and other studies described healthcare providers as dismissive of their symptoms[75,76]. After being diagnosed, females were frustrated by their healthcare providers' lack of general knowledge about Fabry disease[75,76].

2.2 NEWBORN SCREENING

Newborn screening (NBS) is a public health program that identifies newborns who have an increased risk of having a life-threatening condition that will affect their health in infancy or childhood[1]. For newborns diagnosed with a life-threatening condition by confirmatory testing following NBS, a treatment or management plan is immediately created.

NBS is not just a public health program, it is a public health system that is continuously being assessed for quality and timeliness. Changes to the system are made based on these assessments and on the public's involvement. The assessment and change of the NBS system also includes a process for the addition of conditions to NBS panels.

2.2.1 History

NBS was made possible because of Dr. Robert Guthrie's work with phenylketonuria (PKU). In 1961, Dr. Guthrie published a method of screening for PKU that involved measuring phenylalanine levels in heel-stick blood samples dried on filter paper[78]. This method made it possible to screen for PKU at the population level because of the ease of collecting the blood sample on filter paper that was stable enough to be mailed to a central testing laboratory[79].

NBS expanded from PKU to include more conditions over the next several decades as researchers and laboratorians found methods to screen for more conditions using the dried bloodspot. Some of the early additions to NBS included congenital hypothyroidism, hemoglobinopathies, biotinidase deficiency, and cystic fibrosis[80–83]. The number of conditions that NBS screened for increased dramatically in the 1990s with the implementation of tandem

mass spectrometry[84]. Tandem mass spectrometry made it possible to use a single test and a dried bloodspot to screen for multiple biochemical disorders[85].

2.2.2 Purpose

NBS screens all newborns in a cost-effective manner to identify asymptomatic newborns who are at increased risk of having a life-threatening disorder or a disorder with long-term morbidities[1,86]. For infants identified to have one of these disorders in the newborn period through confirmatory testing, treatment and management can begin before the development of life-threatening symptoms or morbidities.

NBS's purpose and the conditions in NBS have been shaped by the Wilson and Jungner Criteria for screening[19,87]. Wilson and Jungner designed criteria to assess whether public health screening is appropriate for a specific condition[87]. These ten criteria were modified to assess conditions being considered for NBS[19,88]. Wilson and Jungner's ten criteria are described in Table 1[87].

Table 1. Wilson and Jungner Criteria

1) Condition is an important health problem
2) Treatment is available for the condition
3) Facilities are available for diagnosis and treatment
4) Condition has a presymptomatic or early symptomatic stage
5) A test or exam exists to screen for the condition
6) Population finds screening test acceptable
7) There is an adequate understanding of the condition's natural history
8) There is a policy on whom to treat as patients
9) The cost of positive screens, diagnostic testing and treatment of diagnosed individuals should be cost-effective
10) Screening for the conditions should be a continuing process

Wilson and Jungner's criteria are still considered as conditions are added to NBS panels. These criteria have shaped the process by which conditions are approved for inclusion on NBS panels, including the Recommended Uniform Screening Panel, which is described in section 2.2.3.1[89] .

2.2.3 Addition of Conditions to Newborn Screening Panels

In the United States, NBS programs are operated at the state level[2]. Each state decides which conditions to include on its NBS panel[1]. Because of this, there was considerable variability in the conditions on NBS panels between states prior to 2006[2]. State legislatures consider recommendations from the federal government and requests from their constituents in composing their state's NBS panel, as well as budgets, resource availability, and technology.

2.2.3.1 Recommended Uniform Screening Panel

In 2002, the Department of Health and Human Services (HHS) wanted to make NBS programs more uniform across states[89]. To accomplish this goal, the US Secretary of the Department of HHS contracted with the American College of Medical Genetics to create the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC)[3,89]. The committee consisted of an expert panel that was tasked with informing the Secretary of HHS with evidence-based recommendations of conditions to include on NBS[3,89]. The committee's work resulted in the Recommended Uniform Screening Panel or RUSP[89]. The initial RUSP was proposed by ACHDNC to the Secretary of HHS in 2006 and the Secretary endorsed the RUSP in 2010[3]. The panel originally included 29 core conditions and 25 secondary conditions[89].

The RUSP was proposed by ACHDNC and endorsed by the Secretary of HHS to provide states with guidance on which conditions to include in their NBS programs[3]. For newly

nominated conditions to be added to the RUSP, ACHDNC uses specific criteria in their rigorous, evidence-based assessment of a condition[3]. The Committee, in part, considers the benefits and harms in screening for the condition, the efficacy of the screening test, and how medical management would change if diagnosed through NBS[2,3]. Under medical management, ACHDNC evaluates whether the condition has an established therapeutic approach, including a specific treatment[2,3]. In 2013, ACHDNC revised these criteria to also include an evaluation of whether it is feasible, in part from workforce and fiscal perspectives, with each added new condition for the NBS and healthcare systems to screen for and follow up positive screens in the short-term and in the long-term[3].

Multiple LSDs have been nominated to the ACHDNC for inclusion on the RUSP: Pompe disease, mucopolysaccharidosis type I (MPS I), Krabbe disease, Niemann-Pick disease types A/B and Fabry disease[4,16,90]. Pompe disease was approved for inclusion in March of 2015 and MPS I was approved for inclusion in February of 2016[4,16]. Fabry disease was proposed for inclusion in 2008 and the preliminary ACHDNC review recommended to not move to a full evidence review due to major gaps in data for review[16]. These included uncertainties in test sensitivity, lack of prospective NBS and treatment studies, and the relative prevalence of late-onset disease variants[16].

2.2.3.2 Other Methods of Adding Conditions to Newborn Screening Panels

Along with the recommendations from ACHDNC via the RUSP, states also consider adding conditions to their NBS panels that are proposed by parents and advocacy groups who lobby at the state level for the addition of a specific condition to their state's NBS panel[91]. X-linked adrenoleukodystrophy, a genetic disorder that primarily affects the nervous system, was added through this method to the New York and Connecticut NBS panels[92]. Through this

method, screening for Krabbe disease, another LSD, was implemented in New York in 2006[91]. In Illinois, parents successfully lobbied their legislature to mandate screening for five LSDs, including Fabry disease[91].

2.2.4 Newborn Screening Process

In the United States, NBS programs are operated by the states[2]. All states in the United States have a law that mandates or offers NBS[93]. Each state program decides the details of how to screen newborns and how to follow-up with any positive screens, but the general process is similar across all states. A blood sample is collected via heel stick on to filter paper from the newborn no later than 48 hours of life[1]. Filter papers are sent to the state's NBS laboratory or the commercial laboratory that has been contracted by the state[93].

The steps following a positive newborn screen vary by state and by condition. For some conditions, a positive screen is followed by reflexing to a more specific test that measures additional analytes or sequences DNA for common pathogenic variants[1]. This step reduces false positive rates and aids in the diagnostic process following a positive screen. Some conditions that NBS screens for are considered time-sensitive and are conditions in which treatment must begin immediately[1,94]. When there is a positive screen for one of these time-sensitive conditions, the NBS lab must contact the specialist or the primary care provider within 5 days of birth with the results[94]. The follow-up procedures for positive screens for conditions that are not time-sensitive varies slightly state by state. In general, positive NBS results are communicated by the NBS laboratory to the physician listed on the newborn's NBS bloodspot card and to the specialty clinic. The physician then relays these results to the newborn's parents. In all cases, a positive newborn screen is followed by an appointment with a specialist and confirmatory diagnostic

testing to confirm or rule out the diagnosis[1]. A treatment or management plan is created for newborns with a confirmed diagnosis.

As a public health system, NBS in the United States not only involves the process of testing dried bloodspots and following positive screens, but it also involves continuously assessing and improving the NBS system. At the national level, different programs are responsible for quality assurance, assessment, and implementing research into NBS practice[86]. The Newborn Screening Quality Assurance Program (NSQAP) at the Centers for Disease Control and Prevention helps NBS laboratories with providing high quality testing, minimizing false-positives and improving the process to ensure testing does not delay a newborn's diagnosis[86]. Another resource available to NBS laboratories, researchers, and healthcare providers is the Newborn Screening Translational Research Network (NBSTRN). One major initiative of Mayo Medical Laboratories and NBSTRN is the Region 4 Stork Collaborative Project (R4S), which developed a system to interpret analyte ratios to improve the screening predictability for metabolic disorders involving amino acids and acylcarnitines, primarily to reduce false positive screens[16]. This project has expanded to include LSDs and some of the pilot studies on NBS for LSDs are sharing their data with R4S[16,95]. The R4S project evolved to become the Collaborative Laboratory Integrated Reports (CLIR), which collects data on true positives from across the world, includes more conditions, and can be used outside of NBS[96].

2.2.5 Newborn Screening for Fabry Disease and Other Lysosomal Storage Disorders

A number of research groups, states, and countries have studied various components of NBS for Fabry disease and other LSDs: the method of screening, feasibility of NBS for Fabry disease, and the short-term and long-term implications of NBS for Fabry disease[29,30,97–105].

2.2.5.1 Newborn Screening Methods for Fabry Disease and Other Lysosomal Storage Disorders

Two main methods have been developed to screen for Fabry disease from a NBS dried bloodspot: the fluorometric method and tandem mass spectrometry[50,97,98,106–108]. Both methods measure enzymatic activity[50,97,108]. The fluorometric method uses an artificial fluorescent substrate and tandem mass spectrometry uses a substrate that is closer to the natural substrate[50,107,108]. A modified version of the fluorometric method is used in digital microfluidics, which measures enzyme activity on a microchip[50,106].

Most pilot studies and NBS programs use tandem mass spectrometry to screen for Fabry disease and other LSDs[97,100,101]. Comparisons between different research and pilot studies that used tandem mass spectrometry or digital microfluidics revealed that tandem mass spectrometry is better at differentiating between affected and unaffected individuals, resulting in fewer false positive newborn screens[106]. Multiple research groups have worked on a method to screen for multiple lysosomal enzymes in a single multiplex assay with tandem mass spectrometry[97,98]. This approach provides an internal control that minimizes the number of false positives[97]. If more than one lysosomal enzyme is low, it is a clue that there may be an error in the assay and the newborn may not have that LSD[97,99].

While tandem mass spectrometry has proven to be accurate in detecting newborns with a LSD, its ability to detect newborn females with Fabry disease has limitations. Because Fabry disease is a X-linked condition, heterozygous females have a wide range of α-Gal A activity in their blood cells due to random X inactivation[97]. Females with low α-Gal A activity in their blood cells will screen positive with this method, but it will primarily detect hemizygous males who have low or no α-Gal A activity[61,97].

2.2.5.2 In the United States

A few states in the United States have passed legislation that instituted screening for Fabry disease and other LSDs through NBS. Missouri, Illinois, and New York citizens have passed legislation and programs have begun screening for Fabry disease and other LSDs either at the population level or in pilot studies[99–101]. New Jersey, New Mexico, and Pennsylvania have legislation to screen for Fabry disease and other LSDs, but screening has not yet been implemented for Fabry disease[109,110].

Missouri was the first state to perform a full population pilot study starting in January of 2013 on four LSDs: Fabry disease, Pompe disease, Gaucher disease and MPS I[99,111]. The entire NBS process for LSDs from testing dried bloodspots to follow-up referrals to genetics centers was investigated[99]. This state also started a full population pilot study on NBS for Krabbe disease in August of 2012[111]. Unlike other NBS programs that used tandem mass spectrometry for their testing, the Missouri program uses the digital microfluidic method to screen for these four LSDs and Krabbe disease[99]. For Fabry disease, there were 89 newborns, both males and females, with positive screens[112,113]. Of these newborns, 40 were confirmed to have Fabry disease because of low enzyme levels and genetic testing[112]. Genotype data showed that one newborn has the classic form, 35 newborns have late-onset, and four newborns have variants of uncertain significance[112]. Based on these numbers, the incidence of Fabry disease in Missouri is about 1 in 2875 people[112]. Through this population pilot study, Missouri found a high prevalence of the A143T allele, seen in 26 of the 40 diagnosed newborns[112]. The Missouri NBS program thought further research was needed to clarify whether the A143T allele is a pathogenic variant or if it is a pseudodeficiency allele[112]. Lenders et al. studied this allele further and classified it as a most likely a neutral variant or a possible modifier[114]. They found that males with this genotype still have significant

residual enzyme activity, less severe symptoms, and no renal or cardiac involvement[114]. The pathogenicity of the A143T allele is still an area of ongoing debate and research[115].

Illinois began a pilot study to screen for five LSDs (Pompe disease, Fabry disease, Gaucher disease, MPS I, and Niemann Pick disease types A and B) using tandem mass spectrometry in November of 2014[100]. The pilot study transitioned to statewide screening in June of 2015[100]. By September of 2015, the state had screened 63,007 newborns for these five LSDs. Of these newborns, 40 screened positive for Fabry disease[100]. Four newborns, all males, were confirmed to have Fabry disease, 15 newborns had negative diagnostic testing, 19 newborns had pending results, one newborn's family refused further testing, and one newborn passed away before further testing[100]. Genetic testing in the four boys with Fabry disease showed two boys have late-onset variants and two boys have genotypes with unknown phenotypes[100]. An investigation of the positive newborn screens for Fabry disease at Lurie Children's Hospital in Chicago noted that many of the newborns with low α-Gal A activity have previously unreported, novel mutations in the *GLA* gene that are predicted to be associated with late-onset Fabry disease[116].

New York passed legislation in 2006 and instituted screening for Krabbe disease, another LSD[16]. For other LSDs, New York is currently conducting a prospective consented pilot study in four New York City hospitals to investigate the clinical aspects of screening newborns for LSDs[101]. Between May of 2013 and September 1, 2016, 73% of approached parents consented to have their newborn screened for Fabry disease, Pompe disease, MPS I, Gaucher disease, and Niemann-Pick disease types A and B[101]. Using dried bloodspots and tandem mass spectrometry, 49,996 newborns were screened for these LSDs[101]. For Fabry disease, 16 newborns screened positive. 15 of the 16 newborns were followed up with additional testing: 10 newborns had

later-onset genotypes, three newborns had negative genetic testing, and two newborns have results pending[101]. This pilot study has only detected later-onset genotypes for Fabry disease, which poses a challenge to the traditional purpose of NBS of identifying newborns at risk of developing symptoms in infancy or childhood[101].

2.2.5.3 Around the World

Italy, Taiwan, Austria, Japan, Hungary, and Mexico have conducted pilot studies on NBS for Fabry disease[29,30,102–105]. These studies have found that the prevalence of Fabry disease is approximately 1 in 3000 people, which is much higher than the previously quoted prevalence of 1 in 40,000 males[28–30,102]. The studies also found a high ratio of late-onset genotypes compared to classical genotypes[30,102,103]. These countries have not started screening newborns for Fabry disease. While their methods have proven effective in detecting newborns with variants in the *GLA* gene, most of these research groups have reservations about population-wide screening in newborns for multiple reasons. Their research has revealed a high prevalence of individuals with late-onset Fabry disease, a high prevalence of variants that are not well defined, and no clear guidelines on how to manage newborns diagnosed with a late-onset condition[30,102,103,117]. Italy's research group suggested screening for Fabry disease in early adulthood given the high prevalence of late-onset variants[102].

2.2.6 Issues in NBS for Fabry Disease

A number of stakeholders (NBS researchers, bioethicists, and genetics healthcare providers) have voiced their concerns about NBS for Fabry disease. Their issues and concerns with NBS for Fabry disease include whether NBS should be done for Fabry disease, how a

condition is added to NBS, issues with the screening test, concern over the availability of resources for follow-up, how asymptomatic children would be followed, and psychosocial and ethical concerns related to these issues.

These stakeholders have questioned whether NBS Fabry disease should be screened as part of NBS because of a lack of understanding of the disease's natural history and management. Additional concerns include the limited knowledge on genotype-phenotype correlations, limited natural history information on late-onset and atypical variants, and limited research on when treatment in asymptomatic individuals should begin[19–21,118,119]. Limited management guidelines exist for how to manage an asymptomatic individual with Fabry disease, which is particularly problematic for asymptomatic newborns diagnosed through NBS[19,20,118,119]. Some stakeholders are concerned with the screening test because it fails to detect 1/3 of heterozygous females with Fabry disease[19,61].

These stakeholders have additional concerns with the resources required for NBS for Fabry disease[19–21,119]. With the follow-up required for positive newborn screens, there is concern with the shortage of genetic healthcare providers and the small number of diagnostic laboratories that provide tests for LSDs[20,21]. The financial costs of additional tests, evaluations, and treatments to the family, the healthcare system, and the insurance system are also worrisome, particularly since guidelines for symptomatic individuals are being applied to manage asymptomatic newborns[20,119]. Others point out that the costs must be weighed between the management of an untreated individual with Fabry disease and the management of an asymptomatic diagnosed individual[20]. But cost-effectiveness studies on NBS for Fabry disease have not yet been completed to determine whether it is less costly to be diagnosed at birth[20].

Many of the concerns with testing, resources, and follow-up raise psychosocial concerns for families who receive a positive screen or diagnosis for Fabry disease for their newborn child. Families experience emotional distress between the time they receive a positive newborn screen and when results of diagnostic testing are available[118]. Since there are no clear genotype-phenotype correlations, natural history information on some of the later-onset and atypical variants, or consensus on when to start treatment in asymptomatic individuals with Fabry disease, families are given ambiguous test results for their newborn child, which increases parental anxiety[21]. Parent advocates of NBS for LSDs have argued that avoiding the diagnostic odyssey is a benefit of NBS[118]. While NBS would avoid the psychological harms of a diagnostic odyssey, there is concern over the psychological harms of a "diagnosis-in-waiting"[118]. With a diagnosis at birth, parents may be over-protective of the child diagnosed with Fabry disease when there are no symptoms[118].

The ambiguous test results and high prevalence of later-onset variants raises ethical concerns with NBS for Fabry disease. The data from multiple pilot studies show that most Fabry disease variants are later-onset[19]. In the clinical setting, healthcare providers do not test children for adult-onset conditions to give children the autonomy to decide when they are adults whether they want testing[19,21]. Given the high prevalence of later-onset variants in Fabry disease, NBS for Fabry disease goes against the position of not testing children for adult-onset conditions[19]. Another ethical issue with NBS for Fabry disease is that NBS is done without informed parental consent[19,119]. Parents have the option to opt-out of NBS in some states, but that means parents decide about screening for all conditions on NBS or none of them[120].

2.3 PARENTS' ATTITUDES AND OPINIONS ON NEWBORN SCREENING

Qualitative and quantitative studies have asked participants about their attitudes and opinions on NBS in general and on NBS for specific conditions. Some focus on attitudes of parents in the general population. Others have focused on parents of children with conditions being added to NBS panels and adults with these conditions and examine what they think of NBS for these conditions.

2.3.1 General Population

In the general population, parents are in support of NBS for conditions where an earlier diagnosis has clinical benefit[22,121]. Parents considered an established and effective treatment for the condition and an early-onset condition, especially one that might not be easily diagnosed, as the most important clinical benefits of NBS for the condition[121]. Many parents saw a benefit in NBS for an early-onset condition that does not have an established treatment to plan finances, care-giving needs, and reproductive decisions[121]. For later-onset conditions that had no clinical benefit from earlier diagnosis, many parents suggested waiting to screen for these conditions or to make these conditions optional[121]. Parents in the general population were more in support of NBS when an earlier diagnosis for affected newborns meant significant health improvements and were willing to tolerate the burdens of testing their unaffected newborns for these significant health improvements[22]. Parents who have a child seen by genetics healthcare providers supported a broader variety of conditions for inclusion on NBS than parents who do not have a child followed at a genetics clinic[121]. A few parents were concerned about the harms of screening

newborns for these conditions, including the harms to the diagnosed newborn and the harms to the family if NBS results in a false positive[22,121].

2.3.2 Specific Conditions

2.3.2.1 MPS

Mucopolysaccharidoses (MPS) are a group of LSDs that have variable ages of onset from infancy through adulthood[23]. MPS type I, was added to the RUSP in 2016[4]. Hayes et al. surveyed adults with a MPS disorder and parents of a child who has a MPS disorder for their opinions on NBS for MPS disorders[23]. The participants' level of support depended on the severity of the specific MPS and whether treatment was available[23]. 97% of participants were in support of NBS for MPS when an early treatment is available that has clinical benefit, 87% supported NBS for severe forms of MPS that have no treatment available, and 84% supported NBS for mild forms of MPS that have no treatment available[23]. The most common reason participants shared in support of NBS for MPS disorders is to avoid a delay in diagnosis and to avoid the distress that accompanies a delayed diagnosis[23]. As in the general population, a few participants mentioned concerns with diagnosing a newborn with MPS who otherwise looks healthy[23,121].

2.3.2.2 Duchenne/Becker Muscular Dystrophy and Spinal Muscular Atrophy

Duchene muscular dystrophy, Becker muscular dystrophy, and spinal muscular atrophy are neuromuscular disorders that have an age of onset ranging early childhood to adulthood[122]. Wood et al. surveyed parents of children who have Duchenne or Becker muscular dystrophy, parents of children who have spinal muscular atrophy, and expectant parents from a prenatal clinic about their opinions on NBS for these three conditions[122]. Without further advancements in

treatment, 95.9% of parents with an affected child and 92.6% of expectant parents supported NBS for Duchenne and Becker muscular dystrophies and spinal muscular atrophy[122].

2.3.2.3 Pompe Disease

Pompe disease is a LSD that has infantile and later-onset forms[24]. This condition was officially added to the RUSP in 2015[16]. Before it was added to the RUSP, Weinreich et al. surveyed parents of a child with Pompe disease and a group of parents from the general population about their opinions on NBS for Pompe disease[24]. 87% of the group from the general population and 88% of parents of a child with Pompe disease supported NBS for Pompe disease[24]. Although there was equal support for NBS for Pompe disease from both groups, the parents of a child with Pompe disease expected a greater benefit from a newborn being diagnosed with later-onset Pompe disease than the group from the general population[24].

2.3.2.4 Fabry Disease

The research on attitudes about NBS for Fabry disease has focused on asking adults with Fabry disease about the timing of their diagnosis and how their lives would have been impacted by a diagnosis at birth via NBS[25,26].

Bouwman et al. conducted a qualitative study on the timing of diagnosis in adults with Fabry disease[25]. Based on the results of this study, Bouwman et al. suggested the timing of diagnosis is a relevant aspect to consider when deciding about NBS for Fabry disease[25]. The researchers found some disparities in what participants were saying about the implications of an earlier diagnosis because of the differences in their experiences with Fabry disease. The participants with more severe symptoms felt misunderstood and were frequently misdiagnosed, whereas other participants felt the diagnosis led to labeling and medicalization[25]. While there

were differences in how participants viewed an earlier diagnosis, a common theme among the participants was that an earlier diagnosis would lead to timely initiation of treatment before the disease progresses[25].

Lisi et al. surveyed adults with Fabry disease and other later-onset LSDs about the timing of their diagnosis, their opinions on NBS for later-onset LSDs, and how a diagnosis at birth would have impacted them[26]. The timing of diagnosis varied considerably among the 47 Fabry participants[26]. Of the Fabry participants, 60.9% experienced a diagnostic lag of at least five years. The second largest subset of Fabry participants, 28.3%, were diagnosed before any symptoms appeared. In general, most participants supported NBS for these later-onset LSDs (Fabry disease, Gaucher disease, and Pompe disease) and recognized that a diagnosis via NBS could prevent irreversible damage. The survey also questioned participants about how a diagnosis at birth via NBS would have impacted their lives. Approximately half of the participants thought their health would be better and they would be more satisfied if diagnosed at birth. From the survey response choices provided, several participants said they would make different life decisions, including reproductive decisions. In the free-response section, a few participants elaborated on their survey responses. Some Fabry participants elaborated that being diagnosed earlier would have had a negative impact because they would have made more cautious life decisions. The free-response section also revealed that some Fabry participants felt differently about being diagnosed earlier based on the onset and severity of their symptoms. One participant who still did not have symptoms said an earlier diagnosis would not have changed his life. Another participant stated that if he had been diagnosed earlier, he would not be as handicapped and he could have worked and socialized more.

3.0 MANUSCRIPT

3.1 BACKGROUND

3.1.1 Fabry disease

Fabry disease is an X-linked lysosomal storage disease (LSD)[47,51]. It is caused by mutations in the *GLA* gene, which leads to a deficiency in the enzyme α-galactosidase A (α-Gal A) and the accumulation of its substrate globotriaosylceramide (GL3) in cells throughout the body[47,51]. The features of Fabry disease include progressive cardiomyopathy, progressive renal disease, stroke, gastrointestinal symptoms, neuropathic pain, angiokeratomas, heat and cold intolerance, hypohidrosis, and corneal opacity[7–12,15].

The spectrum and severity of features varies among individuals and the age of onset ranges from childhood through adulthood[7,13–15]. The terms "classic" and "late-onset" are used to describe Fabry disease phenotypes, but as more is learned about the disease, these two terms do not adequately capture the wide spectrum of the disease[10]. The classic phenotype tends to refer to individuals who experience multiple symptoms with onset in childhood or early adulthood and the late-onset phenotype refers to phenotypes which involve only one organ system and have onset in adulthood[10,13,27]. Genotype-phenotype correlations are limited in Fabry disease because

most pathogenic variants are private mutations that have not been well studied[13,56]. A few pathogenic variants have been found to be associated with late-onset phenotypes[13,27,35].

3.1.1.1 Treatment and management of Fabry disease

It is recommended that a multidisciplinary team manage treatment and monitoring of disease progression in affected patients[18]. Based on current guidelines, treatment begins after symptoms appear and asymptomatic individuals with Fabry disease are closely followed to monitor for the emergence of symptoms[17,18]. Research is being done to find a reliable biomarker to monitor the progression of disease during the asymptomatic period and one possible biomarker is globotriaosylsphingosine (LysoGb3)[63]. The treatment guidelines for Fabry disease do not have specific recommendations for asymptomatic patients with late-onset variants or asymptomatic newborns[17]. Treatment for Fabry disease includes management of individual symptoms, enzyme replacement therapy (ERT), and investigational treatments[6,17,18]. ERT for Fabry disease (Fabrazyme® by Genzyme Corporation© and Replagal® by Shire HGT, Inc.) reduces the number of severe clinical events, such as heart and kidney failure, and prolongs life expectancy[66,123]. Better outcomes have been reported in individuals who started ERT with less disease progression[66]. ERT does not reverse the damage that has already occurred and it does not appear to cross the blood-brain barrier[42,66]. Migalastat, an oral chaperone that stabilizes and transports α-Gal A to lysosomes, is being investigated as a possible treatment for individuals with variants of α-Gal A that are able to bind and break down GL3[6].

3.1.1.2 Psychosocial concerns in Fabry disease

Some of the features of Fabry disease, particularly pain, negatively impact multiple domains of quality of life[7,14,49,71,72,74,75]. There is a higher rate of depression and anxiety in

individuals with Fabry disease compared to the general population, which may be partially associated with having a chronic hereditary disease[37,38,41]. Symptomatic individuals with Fabry disease have described healthcare providers as being dismissive of their symptoms and the diagnosis provided a name for their symptoms, which changed how they viewed themselves and how healthcare providers viewed them[75,76]. Females with Fabry disease face additional psychosocial concerns because they were referred to as asymptomatic carriers as recently as 2001[14,49,76].

3.1.2 Newborn screening for Fabry disease

Fabry disease was recently added to a few states' newborn screening panels. Newborn screening (NBS) is a public health program that identifies newborns who are at risk of having a life-threatening condition that will affect their health in infancy or childhood[1]. For newborns diagnosed with a life-threatening condition by confirmatory testing following NBS, a treatment or management plan is immediately created. In the United States, each state decides which conditions to include on its NBS panel[1,2]. The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), a federal committee, makes recommendations to state NBS programs through the Recommended Uniform Screening Panel (RUSP)[3,89]. ACHDNC conducts an evidence-based assessment to see if a nominated condition meets specific criteria before recommending to the US Secretary of Health and Human Services that it be added to the RUSP[3]. Fabry disease was nominated for inclusion in 2008 and ACHDNC rejected the proposal without requesting an evidence review because of the prevalence of late-onset disease variants, uncertainties in test sensitivity, and the lack of prospective NBS and treatment studies[16]. Parents

and advocacy groups have lobbied at the state level for conditions to be added to the state's NBS panel, which is how Fabry disease and four other LSDs were added to Illinois's NBS panel[4,91].

Missouri, Illinois, New York, New Jersey, New Mexico, and Pennsylvania have passed legislation for Fabry disease to be added to the state's NBS panel[99–101,109,110]. Missouri and Illinois are screening all newborns for Fabry disease and New York is currently conducting a prospective consented pilot study in four New York City hospitals[99–101]. Data from these pilot studies and screening programs revealed a higher prevalence of Fabry disease and a higher ratio of late-onset variants compared to classic variants than anticipated[100,101,112,116]. Pilot studies from other countries found similar results[29,30,103–105,124]. These studies and screening programs have found that the prevalence of Fabry disease is about 1 in 3000 people, which is higher than the previously quoted prevalence of 1 in 40,000 males[28–30,112,124].

3.1.3 Concerns with newborn screening for Fabry disease

The results of these newborn screening programs' and pilot studies' as well as various stakeholders have raised multiple concerns with NBS for Fabry disease. Stakeholders have addressed the potential impact of NBS for Fabry disease on the small number of medical centers and genetics healthcare providers who treat LSDs and the financial costs of more tests, evaluations, and treatments[19–21,119]. These providers follow any newborn with a positive screen and the newborn's family members who are subsequently diagnosed[125]. There are also concerns with the screening test since it does not detect 1/3 of heterozygous females with Fabry disease[19,61]. Limited information on genotype-phenotype correlations makes it difficult to categorize an asymptomatic newborn as classic or late-onset[19–21,104,105,116,118]. There is no consensus on when to start treatment and how to follow asymptomatic individuals because of the

limited number of studies on these topics[19,20,118]. Limited information on genotype-phenotype correlations and management makes it difficult for healthcare providers to create a management plan and to counsel families with a diagnosed newborn[20,116]. The high ratio of late-onset variants raises ethical concerns with testing children for an adult-onset condition[19,21,101,124]. For newborns diagnosed at birth and their families, research on families' experiences with uncertain NBS results suggest the psychological harms of a "diagnosis-in-waiting" may outweigh the benefits of avoiding the diagnostic odyssey[118,126].

3.1.4 Parents' and patient's opinions on newborn screening

As more conditions are added to NBS panels, quantitative and qualitative studies have explored individuals' opinions on NBS. In the general population, parents are in support of NBS for conditions when an earlier diagnosis has clinical benefit[22,121]. Parents, for example, generally support NBS for MPS I and Pompe disease, two lysosomal storage disorders that have variable ages of onset, including severe early infantile forms, and have recently been added to some states' NBS panels[23,24].

Analysis of opinions and attitudes on NBS for Fabry disease are limited to one qualitative study and one quantitative study[25,26]. The qualitative study explored the timing of diagnosis in adults with Fabry disease and found that participants generally supported an earlier diagnosis for earlier treatment initiation[25]. Participants with more severe symptoms felt misunderstood and were frequently misdiagnosed prior to diagnosis while other participants felt the diagnosis led to labeling and medicalization[25]. The quantitative study surveyed adults with Fabry disease and other late-onset LSDs (Gaucher disease and Pompe disease) to gain a more complete understanding of how a diagnosis at birth through NBS would have impacted them[26]. These

participants completed a survey about the timing of their diagnosis, their opinions on NBS for late-onset LSDs, and how a diagnosis at birth would have impacted them[26]. Most participants supported NBS for late-onset LSDs[26]. From the survey answer choices provided, about half of the participants who have Fabry disease indicated an earlier diagnosis would have led to better health, greater life satisfaction and different life decisions, including reproductive and financial decisions[26]. Out of 47 participants with Fabry disease, a few participants elaborated on their survey responses in the free-response section[26]. These responses revealed how a diagnosis at birth would have impacted their lives positively ("would not be as handicapped") or negatively ("would not have pursued athletics as intensely and successfully as I did").

As conditions are added to NBS panels, it is important to understand the opinions of different stakeholders, including people who have been affected by the condition. Previous studies have explored the opinions of some NBS stakeholders, like healthcare providers, family members of patients, and the general public, but very few LSD patients have been included in NBS research thus far[22–24,121,122]. This qualitative study aimed to gain an understanding of the perceptions of adults with Fabry disease regarding the appropriateness of NBS for Fabry disease, the reasoning behind their opinions on NBS, and their knowledge of NBS. To accomplish these aims, semi-structured interviews were conducted with adults who have Fabry disease and these interviews were analyzed via thematic analysis.

3.2 METHODS

3.2.1 Participants

The target population for this study included adults (18 years or older) who have Fabry disease or adults who have a child who has Fabry disease. Participants were recruited from the Children's Hospital of Pittsburgh of UPMC's Lysosomal Storage Disorders Clinic. The primary clinical genetic counselor for the Lysosomal Storage Disorders Clinic identified potential participants from the clinic roster and sent an invitation letter to them on behalf of the study team (Appendix B). The genetic counselor provided the study team with potential participants' names and contact information before the invitation letters were sent out for the purpose of tracking responses. The invitation letter introduced the lead researcher, the purpose of the study, and the format of the interview with participants. Enclosed with the invitation letter, potential participants were provided with a response card to indicate their interest in learning more about the study and to provide their contact information if they were interested. When potential participants indicated they were interested on the returned response card, the researcher called them to speak further about the study and to obtain informed consent through the verbal consent script (Appendix C). The verbal consent script covered the purpose of the study, format of the interview, the voluntary and confidential nature of the interview, how data would be stored securely, and contact information for the study and IRB office should they have any questions or concerns. The lead researcher also called potential participants who did not send back response cards a maximum of two times to inquire about their interest in learning more about the study, and obtained informed consent from those who were interested. Once consented to participate in the study, the participant was given the option to schedule a time for an in-person or phone

interview. Before the scheduled interview, participants were sent an educational brochure on the purpose and process of newborn screening in a sealed envelope with directions that it was to be opened during the interview. The educational brochure was created for this study and its information was tailored to newborn screening for Fabry disease (Appendix E). Federal and state government websites on newborn screening were referenced for the content of the brochure. Writing of the brochure was targeted to an 8th grade reading level; however, a 9th grade reading level was achieved. This was assessed through use of a readability calculator throughout its development. Six participants with Fabry disease, two males and four females, participated in the study. Participants were not provided with any financial compensation.

An interview guide for the semi-structured interviews was created to explore participants' experiences with Fabry disease and their opinions on newborn screening for Fabry disease (Appendix D). The guide was created by the lead researcher and supplemented and edited by three genetic counselors with experience in qualitative research and genetic counseling for lysosomal storage disorders. The first part of the interview guide asked open-ended questions about participants' and their family's experiences with Fabry disease, including how and when they were diagnosed, symptoms they have experienced, and how the diagnosis has impacted them and their families. The second part of the interview guide asked open-ended questions about participants' opinions on newborn screening for Fabry disease, the type of counseling and support they would want with a diagnosis via newborn screening, and how a diagnosis at birth via newborn screening would have impacted them and their families. The study was reviewed and approved by the University of Pittsburgh IRB committee (Appendix A).

3.2.2 Data Collection

Semi-structured interviews were conducted between December 2016 and March 2017. All six participants opted to have their interviews conducted over the phone. All interviews were conducted by the same researcher and lasted between 35 minutes and 1 hour. At the beginning of each interview, participants were reminded that participating in the study was completely voluntary and all their information would be de-identified and kept confidential. With the participants' permission, all interviews were audio recorded. The researcher used the interview guide to direct the interview and asked follow-up questions based on participants' responses to learn more about their experiences with Fabry disease and to understand their views on newborn screening for Fabry disease. Between the first and second parts of the interview, the researcher asked the participants to open the educational brochure on newborn screening and the researcher went through the brochure with the participants. Recordings of the interviews were transcribed verbatim by the same researcher and transcripts were de-identified as they were transcribed.

3.2.3 Data Analysis

Transcripts were analyzed via thematic analysis using the steps described by Braun and Clarke[127]. The intent was to generate themes that describe participants' experiences with Fabry disease, their understanding of newborn screening and their attitudes on newborn screening for Fabry disease. The researcher coded transcripts in Microsoft Word using the Comments function to connect the relevant pieces of transcripts to the corresponding codes and codes and emerging themes were tracked in a codebook in Microsoft Excel. Codes were identified and analyzed using the inductive approach to analysis, with coding and further analysis being driven by the

data and not by a pre-existing question or theoretical scheme[127]. Themes were identified from the codes using the semantic approach, which identifies themes within the surface meaning of the data[127]. Throughout the analytic process, memoing was used to describe the codes and emerging themes and to capture ideas about what concepts should be explored in future data analysis. The qualitative analysis process was discussed with two researchers who are genetic counselors with experience in qualitative analysis and have experience with Fabry disease. The lead researcher met regularly to review each coded transcript, memo and the codebook with a genetic counselor experienced in qualitative analysis. Any discrepancy between the genetic counselor's and the lead researcher's perceptions of the codes and themes were resolved until consensus was reached. Through this analysis, six themes were identified.

3.3 RESULTS

Six participants who have Fabry disease were interviewed for this study. Their ages ranged from early 40s to 75 years. Four were female and two were male. Age of diagnosis ranged from 7 years to 65 years. Each participant had multiple features of Fabry disease and the manner of diagnosis varied among participants. Table 2 describes participants' Fabry disease status.

Table 2. Demographics of participants

Participant	Age at Outward Symptoms	Age at Diagnosis	Diagnosis	Gender	Disease Status
P1	None	7 years ("carrier") 50 years (affected)	Family history	Female	Renal failure, heart damage, cornea verticillata
P2	Childhood	65 years	Family history	Female	Acroparasthesias, GI symptoms, kidney issues

Table 2 Continued					
P3	Teens	Early 50s	Symptoms	Female	Fatigue, GI symptoms, acroparasthesias, hypohydrosis, cornea verticillata, cardiomyopathy
P4	Childhood	49 years	Family history	Female	Acroparasthesias, heart damage
P5	Childhood	36 years	Symptoms	Male	Hypohidrosis, heat and cold intolerance, acroparasthesias, kidney failure and kidney transplant, heart damage
P6	None	Mid 30s	By chance	Male	Proteinuria

Six themes were identified from the interviews with these participants: influences of clinical spectrum and severity of Fabry disease, support systems, family dynamics, impact of timing of diagnosis and treatment availability, knowledge and attitudes towards NBS for Fabry disease, and impact of earlier diagnosis. These themes are described below.

3.3.1 Theme #1: Influences of clinical spectrum and severity of Fabry disease

Participants and their families experienced a wide range of clinical symptoms and severity of Fabry disease. Their experiences with the disease seemed to influence their lives, their understanding of the disease, and the impact of being diagnosed.

3.3.1.1 Impact of disease features and receiving a diagnosis

Those who had experienced symptoms since childhood shared how disease features had impacted their physical and mental health. For the participants who spent years searching for a cause of their health problems, they described their diagnostic odyssey experiences. Participant 5 said:

> I've seen doctors ever since I was 7 years old for this [pain]. Some said it was like childhood pain and some said I'd grow through it.

The features, particularly pain, affected their quality of life, such as the ability to participate in school, sports, work, and everyday functioning. They also shared the impact of having unexplained symptoms on their mental health. Participant 5 described it as:

> That's hell when you've got a problem and nobody believes you.

For these individuals, being diagnosed with Fabry disease provided a name for what they were experiencing. When asked about the impact of the diagnosis, participant 2 said:

> Just the idea that, I guess I have something to put all of these symptoms that they never figured out what was going on.

It also confirmed their feelings that there was something wrong with them. Participant 3 said:

> It puts my mind at ease because I just have always thought that there's something wrong with me, you know like something major, like I had cancer or something weird going on. You just get that intuition or something and now I can, now there's something a name there and you can face it and move on.

Participant 3 was the first one diagnosed in her family and after her diagnosis, doctors said her mother most likely passed away from Fabry disease. After learning this, participant 3 said:

> My big worry is that my life will end like my mother's. I don't want to have that happen. That scares me. Because her death was painful, it was just very bad. I mean, so that part scares me now that, you know, with that diagnosis.

Other participants and a participant's child were diagnosed in adulthood prior to developing outward symptoms of Fabry disease. The individuals diagnosed after a family member's diagnosis seemed to have a difficult time accepting the diagnosis when they had no outward symptoms of the disease, which seemed to make it more challenging to understand the need for ERT. Participant 1 said:

> I was like this isn't true, you know what I mean? Like I don't have any symptoms. Why are you starting me on something that I just don't have any symptoms for and yeah it kind of felt, I don't know you get kind of paranoid when stuff like that happens. It's just a

> sci fi thing and they are trying out a drug on me to see if it's going to work because it does seem super strange.

This participant watched her father pass away from Fabry disease during her childhood and at that time she was diagnosed as a "carrier." When she was diagnosed as affected in her 50s, she said:

> When I first found out I was devastated because you know all I imagined was that my whole entire life was going to be defined by this disease, how it was going to impact my career and my family and everything I just thought, you know, I just imagined the worst.

After she learned more about the disease, participant 1 appeared to eventually accept the diagnosis. She described her feelings about knowing the diagnosis due to her family history.

> I feel fortunate that I at least knew what it was because my dad had it. But when I talk to these other people, they have no clue and they went to numerous doctors and those doctors could not find anything wrong with them.

Participant 6 was diagnosed by chance after a physical examination identified proteinuria.

> I don't know what most people, how they feel or whatever if they do have Fabry disease. Like I said, I felt fine, you know what I mean. I'm probably actually fortunate to have to get a DOT [Department of Transportation] physical, you know what I mean, to get to find out that I had it for treatment or whatever.

3.3.1.2 Understanding of disease

Participants' experiences with the disease seemed to influence some of their understandings of Fabry disease. Participant 1 has no outward symptoms.

> I'd say it's terrible, but you know, these are the things that you can do, you can adjust your life and work around these things and be happy […] This to me is something that is an inconvenience, but you know, we deal with it.

In contrast, participant 4 has had pain since childhood and in the following, she discusses her understanding of Fabry disease.

> They first start having trouble, you know, throughout the body, you know, they always cry about their hands and their feet.

Other participants seemed to have a broader understanding of the possible spectrum of Fabry disease and thought they did not know enough about Fabry disease to identify all of its features. For example, participant 3 said:

> You never know if it [symptom] is something that is connected with it [Fabry disease]. And you never know what it could be because it could really be something that is connected to it.

All participants had some organ damage at the time of diagnosis and they understood the seriousness of organ involvement in Fabry disease. However, for some participants, the seriousness of organ involvement did not seem to align with their perceptions of their overall health when they had no outward symptoms. Participant 1, who has third stage renal failure and some heart damage said:

> I go to the gym every day and I teach yoga and you know, I don't have a single issue […] I feel really healthy.

3.3.2 Theme #2: Support systems

The type of emotional and medical support and how much support participants received varied among participants. The variability seemed to depend on their families, healthcare providers, and support from other sources, like the Fabry community.

3.3.2.1 Family

Some participants described how their spouse or other family members were an important source of support. Participant 3 said, "My husband was very supportive," at the time of her diagnosis. However, there were varying amounts of support from family members. Some family members were dismissive of symptomatic participants prior to diagnosis and remained

dismissive or were indifferent to the participant after diagnosis. When asked how the diagnosis has impacted his family, participant 5 said:

> I can't say it really has 'cause they always wonder 'what if he weren't taking the medicine.' My dad's the kind of guy who believes 'you don't even know if you need be on that' you know. I said well I can't stop it, cause if I stop what if shit shuts down again.

Participants' family dynamics, support, and attitudes are described further in the "Family dynamics" theme section.

3.3.2.2 Healthcare providers

Participants described their interactions with a variety of healthcare providers through their diagnostic odysseys and after diagnosis. During the diagnostic odyssey, participants shared how some doctors did not believe their symptoms, missed symptoms, and made comments dismissing their symptoms. Participant 3 said:

> I always had things, little things, going on that, you know, they [doctors] always said oh no, you didn't test positive for this.

Participant 5 saw a specialist for pain and shared the following.

> She gave me issues about the pain meds I was on. And I said I'm constantly in pain every day. And I don't think she totally believed that. And then when they started doing the biopsies, she come and apologized for the way she acted. But still don't take the fact away that I had to experience that.

Through their journeys with their symptoms and diagnosis, participants seemed to value providers that listened to them, addressed their concerns, explained what was happening, and learned about Fabry disease to provide more appropriate care. Participant 4 seemed to appreciate the care her geneticist took to provide her with support.

> I used to go that one hospital every 2 weeks [for ERT], but then the taxi driver, the taxi company quit taking us down there so it was like 5 months I didn't have my medicine. So then [geneticist] before he left made sure I was getting it in my home, you know. So I get it in my home now every other week.

Participants seemed to form close relationships with these providers and considered them a part of their support system. When talking about the Fabry specialist group, participant 5 said:

> Them people couldn't be nicer. It's just something, I consider them family […] they're sweethearts down there. You know, they bring a cake in every time, every birthday. Yeah it's something, really caring people.

Some participants have noticed a lack of knowledge about Fabry disease among their primary care providers and some specialists. Participant 3 shared the following.

> My mom, right before she passed away, they got close enough to say it was amyloidosis. That was still in the same family, but after I was diagnosed, they said 'no it wasn't amyloidosis, it had to be Fabry.' […] They misdiagnosed her. They didn't test her, you know, for that. That isn't something, cause it's so rare.

Because of the rarity, some healthcare providers have limited knowledge of Fabry disease and this created some challenges for participants. For example, participant 3 also shared:

> I had to find a new doctor. Which was tough, because I had to find one that was willing to go through some training and really do some research and find out about my disease.

Participant 2 considered knowledge to be a part of support.

> I just sort of feel left in limbo a little bit […] it comes down to people don't know enough about it. My son just complains that every time he says something to the doctor, they say, "oh that doesn't go with Fabry's" but when you are reading on Facebook and everyone is complaining about the same thing. So you know, that's part of his problem, also part of my problem too.

Some participants have educated their doctors about Fabry disease. Participant 5 said:

> Still people don't know what Fabry is. I mean I've handed out pamphlets to my doctors, you know them little booklets. I hand them out to everybody.

3.3.2.3 Other sources of support

Most participants sought out other sources of support to supplement what they had from their families and healthcare providers. Participant 3 said:

> I have a psychologist that I see. And I was seeing that person at that time [diagnosis], which was very helpful.

Some participants had attended support groups and meetings for Fabry disease. Participants seemed to find varying levels of support from the Fabry community based on where they saw themselves on the Fabry spectrum of severity. On one end of the spectrum was participant 1, who has had no outward symptoms.

> Sometimes Genzyme will pull people together for little meetings and when I see them and I see how debilitated they are, it makes me happy that I actually started [ERT] before I had the symptoms.

In the middle of the spectrum was participant 3.

> The support group I have online is wonderful. 'cause you can just, you can, if you are having a bad day, you can just put that out there and people can say well I did this and this helped or that helped or have you guys ever had this happen to you, or what is this, I don't understand this. So that kind of stuff really helps.

At the severe end of the spectrum, participant 5 did not seem to find support groups helpful.

> There's a lot of support groups, but how can I say it? These were guys that worked all their life and then developed symptoms later, like somewhere around their retirement or in their 30s, in their 40s. see I was messed up from child, I couldn't go to work and stuff. And I had no reason why.

3.3.3 Theme #3: Family dynamics

Family dynamics describe how family members interact with each other and their relationships with each other. The family dynamics prior to diagnosis seemed to influence how the family reacted to the participant's diagnosis and how they felt about testing for themselves. For participants who had symptoms since childhood, the family dynamics seemed to be shaped by how the family dealt with the participant's unexplained symptoms. These family dynamics then appeared to affect how much support the participant had from his/her family. When symptoms were present in childhood, several participants described how some family members dismissed their symptoms. Participant 3 said:

> […] ‘cause my family always told me I was a hypochondriac growing up.

Similarly, participant 5 shared:

> They [family] kind of blew it off or were like childhood pain or just being lazy, I was faking. You know, I was called everything. You know, by my own father. […] cause when it was up to my family before I was of age, they you know, my dad would get pissed off because I had to go to Pittsburgh to get some kind of test done. So I had to hear that all the way down there and the way back.

His symptoms affected his relationship with his siblings.

> Growing up, there was a competition between me and my siblings. But I was always sick and I couldn’t cut the grass or do yardwork, so just little things like that. And it really I guess irritated them. I’m finding this out now. I didn’t know it then. But I guess it was a big problem when I was a child.

The behavior and actions of his family members seemed to isolate the participant within the family. When participant 2’s family found out her cousin had Fabry disease, she said:

> The rest of my brothers and sisters told me to get tested because I’d probably be the only one that had it.

Participant 2 indicated that her siblings never got tested.

All participants had told their families about their diagnosis and some shared how they educated their family members about Fabry disease. Through these descriptions, it appeared that participants wanted to pass on health information pertinent to their family members, explain the cause of their symptoms to family members, and get support from their families. The experiences participants shared suggested that it took families time to believe the diagnosis or in some cases, family members still do not accept it. When participant 3 discussed her diagnosis with her siblings, she did not get the reaction she was expecting.

> I really thought I would get a little bit more empathy from like my siblings and things. And nothing. It’s like they treat me like nothing is even wrong with me […] I said well I’ve been having mini strokes, that’s why I have to have this done or something. And none of them had any concern, you know, at all. So that’s been depressing, you know, that your family like doesn’t support you.

When asked how her siblings initially reacted to the diagnosis, she said:

> Well because they didn't know anything about it, they just thought it was a bunch of ho shmo. And when I said that's what my mom really had, they didn't believe it. They said no, she had this. And they didn't believe me. And then when I told them all this information about, you know, on the disease and you know, them misdiagnosing her and […] that the chances of me having that were so, I mean first off, it's a rare disease, but it's even rarer just to have that happen to you. They were like, ok, so then they were thinking oh maybe she's right. But I still have one brother, I have one brother that still does not believe that it came from my mom. And that's, that's like saying that I'm lying that I have this because that's where it came from.

Participant 3 thought her family would have reacted differently to the diagnosis if she had been diagnosed earlier and her mother would have been alive to be tested and diagnosed too.

> They [family] would understand it [disease] better. Especially knowing that my mom had it. Because everyone, you know, loved my mom. And my mom is what kept the family together. And so, that would have made a huge difference 'cause they would have really learned more about the disease for her.

Participant 5's family was dismissive of his medical problems before diagnosis and continued this behavior after his diagnosis.

> They think that if I would stop taking the medicine, that I would be fine, so. Well they're actually under the theory that when a problem arises, that's when they'll take care of it. And I keep telling them you need to be on the Fabrazyme® to hold all the problems from even occurring. And you know, they just don't listen to me.

Most participants had some family members who did not want to learn about Fabry disease and did not want to be tested. There seemed to be a difference between some of their families' attitudes towards testing and the participants' favorable opinions of NBS for Fabry disease. Participant 1 described her attitudes and her family's attitudes towards testing as the following.

> You would be really stupid if you opted out [of NBS for Fabry disease and other later onset conditions]. Given the opportunities to make sure that your child is healthy and well and having no issues and this is like a little drop of blood out of a heel, I would say you would be very very foolish to do that. But then again, I know people, like my own family, opted out of a lot of this when they found out I had it. They didn't want their children tested, they didn't want, all they had to do is produce some blood, but were

> unwilling to do that. […] They [family] don't want to know anything about it. And they never, like my cousins now all have children who have children and they don't want to know anything about it. Just like their head is in the sand.

Participant 4's family knew Fabry disease was in the family and she said:

> My brother, he knew he had it and he didn't want to go get the medicine, you know, he didn't want to worry himself. If he was going to die, he was going to die and it's what he did, he passed on just like my older brother.

Some participants wondered why their family members would not get tested when they had children who were at risk. One of participant 3's brothers has not gotten tested.

> I mean they have a girl, so you would think that they would want to […] if I were the mother, I would have gotten the daughter tested. Just to be sure. But I'm not that mother.

A common trend through most of these families seems to be a lack of communication. This included not following up with their children who decided not to get tested, families not asking how the participant was doing after diagnosis, and the diagnosis not being communicated from the family to the participant. Participant 3's daughter is still deciding about testing.

> I think that after she has kids, that then she would be willing to get tested. That I believe she doesn't want to talk to me about it. So she's old enough to make that decision for herself.

Participant 4 was adopted early in life and had limited contact with her biological family, which led to a delay in her diagnosis. After her aunt told her, participant 4 said:

> Why didn't you let us know when we were younger. Then we could have got it [ERT] started or when they first came out with it. But there was never no answer.

3.3.4 Theme #4: Impact of timing of diagnosis and treatment availability on attitudes towards NBS

The timing of when participants were diagnosed and the availability of treatments specific to Fabry disease seemed to impact their attitudes towards NBS for Fabry disease. All

participants were diagnosed with Fabry disease as adults, after ERT and oral chaperone therapy became available, and all had some organ damage at the time of diagnosis. Receiving a diagnosis led to all participants getting treatment specifically for Fabry disease. Participant 4 said:

> I think the medicine is really great. I really do. For people that have the Fabry disease, I think it's really good, 'cause it keeps me going, you know. I mean I got to have it the rest of my life, but if it keeps me going and keeps me kicking it's good.

Multiple participants shared their understanding that ERT maintains their organ status, but cannot reverse organ damage. Participant 3 said:

> The sooner you get started, the better off you are because then it can help prevent stuff going on before it happens. Don't wait until the symptoms start because then you've already had some damage to your body.

The availability of ERT seemed to have an impact on participants' answers about NBS for Fabry disease. Based on their experiences, all participants were in favor of NBS for Fabry disease because an earlier diagnosis would mean earlier ERT. Participant 5 said:

> By the time I got on it [ERT], the FDA had just approved it. So I kind of got on it right when they came out with it anyhow.

Some mentioned how they would want parents deciding about NBS to know that there is a treatment to prevent disease features. Participants had varying reactions to when ERT would begin in an asymptomatic child. Some wondered when ERT would begin if a child had no symptoms. Participant 1 said:

> I kind of want to know how long, how soon before the child would need to start replacement therapy. Like, you know, for me it obviously took 50 years for things to start. So, what's the timeline, I guess is what I'm looking for.

Other participants wanted treatment to begin right away. Participant 5 said:

> I think that would piss me off a little bit…if the doctors knew I had it and they wanted to wait until symptoms, I think that would upset me a bit. Because the treatment can hold off problems.

3.3.5 Theme #5: Knowledge and attitudes towards NBS for Fabry disease

Participants were asked what they knew about NBS before participating in this study and their opinions on NBS for Fabry disease and other late-onset conditions. Their responses to these questions and their experiences with Fabry disease provided insights into their reasons behind their opinions on NBS for Fabry disease.

3.3.5.1 Knowledge of NBS

Two participants had heard Fabry disease was being added to NBS and seemed to have a good understanding of the general purpose of NBS. They thought the purpose of NBS was for awareness and to be able to start treatment before the condition affects cognitive and physical development. Four of the participants had not heard of NBS before participating in this study. A number of the participants were not sure what conditions NBS looks for, but some guessed that it looked for genetic conditions. A couple participants thought it looked for either organ damage or malfunctions in the body and that a diagnosis via NBS would mean ERT could be started earlier.

3.3.5.2 Opinions on NBS for Fabry disease

All participants were in favor of NBS for Fabry disease before and after going over the educational brochure. Most mentioned earlier treatment and awareness of symptoms as reasons for NBS. Participant 2 described it as:

> I think it's a good idea because then you're aware and when the symptoms do appear, then you can start treatment before something happens that cannot be fixed I guess is the easiest way to say it.

Some said they would rather have an answer about whether their child has Fabry disease at birth and participant 5 said:

> I don't see why it's such a big deal, you know, why don't they just do it [NBS for Fabry disease].

Five participants thought Fabry disease met the NBS definition of urgency because of the seriousness of organ involvement. Participant 1 thought Fabry disease did not meet the NBS definition of urgency and said:

> I don't think it's urgent that the baby, like a newborn, has the procedures in infancy. But I think early.

About half said NBS for later-onset conditions "should be mandatory" and the other half said parents should think carefully about the consequences of not testing if their child has a condition.

3.3.5.3 Reasons in favor of NBS for Fabry disease

Participants described several reasons for being in favor of NBS for Fabry disease and a diagnosis at birth: awareness, improved physical functioning, psychological impact, and more family support. A number of participants said they would have been more aware of their symptoms or their child's symptoms, with a diagnosis at birth. Participant 2 said:

> I think I would have been a little bit more aware of what is going on and noted if there were any symptoms along the way.

Participant 3 said:

> [with a diagnosis via NBS] you are more aware of the body and what are symptoms of the disease. Because I had little symptoms too. I mean even when I was younger … And if I'd been diagnosed as a baby, that's possible that those are things that could have been detected a lot sooner.

Some participants shared how a diagnosis at birth would have impacted their physical functioning. Participant 4 said:

> I would have been working for longer than I was and I wouldn't have as much problems and those surgeries like I had.

Participant 5 said:

> I think if I was tested sooner, or I mean if I could have been tested as an infant, none of this damage might have occurred. I truly believe that.

Some participants also shared how a diagnosis at birth would have had a psychological impact. Participant 5 said:

> My kidneys might not have shut down, my heart would not be bad, I don't think any of that would have happened. And the psychological with that. Yeah I had to deal with that and I had doctors, parents and everybody tell me that there's nothing wrong. I knew in my heart that there was something wrong. I mean I could tell you stories you would not believe. Yeah, it's just, it's hell. […] The screen would take care of that [people believing you].

Some believed their families would have reacted differently to Fabry disease and their symptoms and the family would have been more supportive. Participant 3 thought Fabry disease's non-specific symptoms were a reason to be in favor of NBS for Fabry disease.

> They're [symptoms] hard to tell what they are. So you really need that test, 'cause there's so many little things going on with me that I, you couldn't tell that there were. And if it hadn't been for my eye pattern [identified by an ophthalmologist], I still wouldn't know what's wrong with me.

3.3.5.4 Attitudes towards NBS results

Participants' attitudes to different NBS results seemed to vary by experiences with Fabry disease, personality, and previous understanding of NBS. The two participants who had heard of NBS before this study had slightly different reactions to NBS results. Participant 2 said:

> I would rather have a negative result than any of the others. It's just like the other newborn tests that they give, you know, and once you've had that result then you don't have to worry about that anymore.

About a false positive newborn screen, participant 3 said:

> I'd be relieved. And I know that sometimes things like that happen.

The other four participants did not seem to completely trust NBS results. Their responses to NBS results varied: some wanted to have more testing in the future while others would be anxious

until more testing was done to confirm the results. About a negative newborn screen, participant 1 said:

> I would check up on that on a regular basis 'til I was absolutely positively sure.

Participant 6's response to all types of newborn screen results was:

> I wouldn't mind getting it checked out down the road just to make sure, you know, that maybe it doesn't show up real early in life and that kind of thing.

3.3.5.5 Information at the time of diagnosis or positive newborn screen

Based on their experiences, participants would recommend families talk to a specialist and genetic counselor initially to learn more about Fabry disease. Participant 6 said:

> Probably a specialist [after diagnosis through NBS], I would think you know, they know what exactly is going on. They [parents] would get more out of that I think.

Some also recommended connecting families to support groups or others with Fabry disease for the family to have another source for information. Participant 1 said:

> For young parents for when their child is diagnosed, there needs to be somebody there who has Fabrys to talk to them. So that they can say like "look I'm 60, I'm 70, I'm 50 or whatever and I'm still doing just fine" or even some of the young children I have met, they need to be there to talk to these parents and say "everything is going to be good, you just need to do these certain kinds of things" […] there needs to be somebody there who has the disease, who has gone through everything, who can help talk to them.

In contrast, participant 5 discussed the need to educate parents about the serious manifestations of Fabry disease.

> I think they [parents deciding about NBS] should actually meet somebody with Fabry that's had the transplant, or you know, with the heart or the kidneys or whatever.

3.3.6 Theme #6: Impact of earlier diagnosis

Participants described how they would raise a child diagnosed with Fabry disease. Many said the diagnosis would not affect the way they raised their child, but then described actions that

could be considered more vigilant than usual and they discussed how they would advocate for their child.

3.3.6.1 Vigilance

Many participants discussed actions that could be described as being more vigilant if their newborn child were diagnosed: closely monitor the child for any signs of Fabry disease, take the child to the doctor more often, wonder if any cough or sickness was something serious connected with Fabry disease, and re-check test results. When asked how a diagnosis before the appearance of symptoms would affect how she raised a child, participant 2 said:

> I think that she [mother] would be a little hypervigilant and looking for symptoms that might not have even occurred.

Participant 1 said:

> You're looking at a newborn and like I thought for sure I was going to kill my kid before she reached 4, you know every time she had a cough or sniffles. I thought 'oh my god, I'm going to kill her, she's going to die, I don't know what I'm doing' and then that becomes even larger when you know your child has a disease. Every cough, every sniffle, every temperature, you know, oh my god is this related to [Fabry disease].

Their descriptions of what they would do in a hypothetical situation resembled what they had experienced in real life. Participants with younger family members who had not been tested described being hypervigilant with these family members for signs of Fabry disease. One participant who was initially diagnosed as a "carrier" pursued invasive prenatal testing at a time when it was still a new procedure and had her daughter re-checked later in life to confirm the test results.

3.3.6.2 Advocate for child

Participants said they would advocate for their child by watching for symptoms, listening to their child's concerns, moving closer to a medical center, talking to doctors, and asking doctors for ERT to prevent manifestations of Fabry disease. Participants' descriptions of what they would do in a hypothetical situation seemed to represent how they would want their child's experiences with Fabry disease to be different than their experiences. Participant 1 said:

> If I lived out in the middle of nowhere/no mans land, I couldn't get any help, I would move to a center where within miles I'd be able to, yeah I'd move. You know those are options that are important to me. They've made my life easier and those are some recommendations I'd make to people.

Participant 4, who experienced a delay in receiving a diagnosis because her family did not tell her about the presence of Fabry disease in the family, said:

> I would take the baby when it goes to the doctor's for the first time and explain it to the baby doctor saying, you know, same way I have it, could you please check my daughter or him that if he has it so they could get started right away [on ERT].

Participant 5, whose family did not believe his symptoms in childhood, said:

> Well if I had a child and he had Fabry and was saying what I was saying, I think I would have took better care of him, you know. And I didn't have that. I was always pushed away.

3.3.6.3 Life decisions

Some participants mentioned how the diagnosis would have impacted their decisions on having children. Participant 1, who was initially diagnosed as a "carrier", said she would want to talk to a genetic counselor.

> I'd want to know more about, like I stopped, I was already 31 when I had [participant 1's daughter] so I was content…I didn't know anything, so I just stopped at one. If I had more information and more people who could have talked to me about my life, I might have had more children.

Participant 3 said if she had been diagnosed at birth via NBS:

I would have definitely made my decision on having children probably.

3.4 DISCUSSION

Participants in this study were asked about their experiences with Fabry disease, their knowledge of NBS, and their opinions on NBS for Fabry disease. Their responses regarding these topics provided insights into their reasoning behind their opinions about NBS for Fabry disease.

3.4.1 Theme #1: Influences of clinical spectrum and severity of Fabry disease

This study's participants seemed to have similar experiences with Fabry disease as participants in other studies on Fabry disease. Participants who had outward symptoms described how these symptoms interfered with their participation in sports and holding down jobs and this is consistent with results from other studies on quality of life and Fabry disease[49,71,73,74]. Participants in this study and other studies had varying reactions to the diagnosis based on the symptoms they had prior to diagnosis[25,26,75]. Those who had noticeable symptoms prior to diagnosis seemed relieved with the diagnosis because it provided a name and reason for what they were experiencing[25,26,75]. The participants who had no noticeable symptoms before diagnosis seemed to have a more difficult time accepting the diagnosis[25,26,75]. Participants in this study had some cryptic organ damage at diagnosis, which may explain why they came to accept

the diagnosis and need for ERT, whereas asymptomatic participants in other studies felt the diagnosis led to labeling and medicalization[25].

3.4.2 Theme #2: Support systems

Participants in this study shared their perceptions of the support they receive from their family members and from their healthcare providers. Research on motivations behind disclosing genetic test results to family members has found the main motivations include familial obligation to share health information and seeking social support[128,129]. Some participants' responses suggested these were their motivations for sharing the diagnosis with family. Multiple participants shared their frustration and sadness that some or all family members did not offer support after the participant's diagnosis; this seemed to affect the emotional and psychological health of participants' experiences with Fabry disease. These experiences are consistent with research on family support and chronic illness that have found that there are better outcomes when there is more family support[130,131].

Participants in this study seemed to define knowledge of Fabry disease among their healthcare providers as a form of support. Some participants in this study and other studies noticed a lack of knowledge about Fabry disease among their healthcare providers[75,76]. Before they were diagnosed, participants shared how doctors missed their symptoms or seemed dismissive of their symptoms[75,76]. After being diagnosed, participants in this study and other studies noticed their healthcare providers lacked knowledge about Fabry disease and some were frustrated by this lack of knowledge[75,76].

3.4.3 Theme #3: Family dynamics

This study provided new insights into the dynamics in families affected by Fabry disease. A family's beliefs about illness range from viewing illness as a part of life to deal with to viewing illness as a threat to be avoided[132]. From participants' descriptions, some families seemed to accept the diagnosis as something to deal with, while other families seemed to avoid the illness and its consequences. Avoiding the diagnosis may have also been a coping mechanism. Participants' families seemed to use disbelief, deferral, and dismissal as coping mechanisms after they learned of the diagnosis[133]. Disbelief is used as a coping mechanism when symptoms or signs of the disease are absent and a lack of signs makes it difficult to accept the information[133]. When disbelief is used as a coping mechanism, acceptance of the information usually comes with more time and information. Participant 3's siblings seemed to use disbelief as a coping mechanism after they learned about her diagnosis. Participant 3 had symptoms since childhood and she was the first person diagnosed with Fabry disease in her family. After her diagnosis, participant 3 explained to her siblings that her symptoms and their mother's death were caused by Fabry disease. It seemed like her siblings did not initially believe participant 3 about Fabry disease because participant 3 and her mother had different symptoms. Most of her siblings came to accept the diagnosis as they learned more about it. When deferral is used as a coping mechanism, individuals put off accepting the diagnosis and making decisions about it because the implications of the diagnosis are difficult to handle[133]. Participant 3's daughter may be using deferral as a coping because she has not gotten tested and participant 3 speculated her daughter is waiting to get tested until she has children. Individuals who use dismissal as a coping mechanism disregard recommendations and do not value the information provided by healthcare

providers[133]. Participant 5's family may be using dismissal as a coping mechanism since they thought ERT was not needed to treat or prevent symptoms.

Families' views of Fabry disease may be shaped by their family histories when they have seen multiple generations affected with the disease. These families have experienced loss and grief over multiple generations and they may not have connected these medical problems to a genetic cause[129,134]. The first person who gets genetic testing connects a genetic etiology to the family's medical problems and the family has an emotional transition as it processes this information and changes how the family views the medical problem[134]. As the first person diagnosed in her family, participant 3 linked the family's various medical problems to Fabry disease and it took time for her siblings to accept the diagnosis. Some families in this study were diagnosed in the transition from no treatment for Fabry disease to ERT becoming available. Participants described the painful deaths older family members had before ERT was available and without knowing more about advances in treatment, these experiences may influence how untested family members view Fabry disease[134].

Research on family communication and genetic conditions has found that relationships and tensions that existed before diagnosis affect communication about the genetic condition[129,130,135,136]. Conflicts that existed prior to diagnosis or a family member's death related to the diagnosis affected family communication about the genetic condition[135]. The results from this study are consistent with this research. In this study, families that dismissed participants' symptoms before diagnosis continued to be dismissive or in some cases, indifferent.

Participants were not explicitly asked in this study why their family members had or had not decided to get tested, but previous research on familial attitudes towards genetic testing provides relevant information. A study on siblings' perceptions of risk for hereditary

hemochromatosis (HH), a genetic condition that leads to excess iron storage and has non-specific symptoms like Fabry disease, found that siblings had low perceived susceptibility to HH because of denial, their doctor did not think they had it, lack of knowledge, or not experiencing the same health problems as the diagnosed sibling[137]. The emotional aspects of the disease, disease severity, and age of onset also influence testing decisions[134]. Relationships change based on who in the family gets tested, their results, and who does not get tested[134]. Participants in this study seemed to feel isolated in their families when family members did not get tested or if family members tested negative. A study on family communication and genetic conditions and this study noticed increased tension when participants thought family members (i.e. siblings) should get tested to provide information for younger family members (i.e. participants' nieces and nephews)[135].

There were noticeable differences in participants' views on NBS for Fabry disease and some of their family members' views on testing for Fabry disease. On one hand, participants thought NBS for Fabry disease should be mandatory or would strongly suggest to parents not to opt out of NBS for Fabry disease. On the other hand, some of their family members seemed to be against testing for themselves and for their children after learning Fabry disease is in the family. Some participants noticed the discrepancies between their views on NBS for Fabry disease and their family members' attitudes towards testing. These participants seemed perplexed by family members' decision to not get tested, particularly when, in their view, testing to only involves a blood sample.

3.4.4 Themes #4 and #5: Impact of timing of diagnosis and treatment availability on attitudes towards NBS & Knowledge and attitudes towards NBS for Fabry disease

Multiple studies have asked individuals their opinions on NBS in general and for specific conditions, but these studies did not assess participants' understandings of NBS[22–24,26,122]. In this study, participants were asked what they knew about NBS before going through the educational brochure and after the educational brochure were assessed for increases in their understanding of NBS. Most participants seemed to understand the general process after the educational brochure, but one participant still thought NBS checks a newborn's genes and organs. All participants seemed to understand that a diagnosis via NBS would lead to earlier treatment. Most participants did not seem to understand the NBS definition of need for urgent intervention to prevent complications, which was defined for them as "infants at immediate risk of developing life-threatening symptoms associated with a serious condition." Five participants said Fabry disease met the definition of urgency because of heart and kidney damage, even though these participants did not have heart or kidney damage until adulthood.

All participants in this study were in favor of NBS for Fabry disease before and after the educational brochure. Participants seemed to have similar reasons for being in favor of NBS for Fabry disease as other studies that investigated opinions towards NBS. The clinical benefit of an early diagnosis leading to earlier initiation of ERT was mentioned by participants in this study and studies on NBS in the general population and NBS for MPS disorders[22,23,121]. Participants in this study and other studies on MPS and Fabry disease mentioned the psychological benefits of earlier diagnosis and avoiding the diagnostic odyssey as reasons for being in favor of NBS[23,25]. Despite some participants' lack of trust in NBS results, indicated by their desire to have their child tested later in life, all participants in this study support NBS for Fabry disease.

Despite attempts by the interviewer to elicit comments on the potential harms of an early diagnosis well before treatment would start, participants did not comment on the potential harms that were presented in other studies[22,23,25]. Participants in other studies mentioned how an earlier diagnosis would change how the child is viewed and could lead to the child being labeled[22,23,25].

3.4.5 Theme #6: Impact of earlier diagnosis

Participants in this study were asked how a diagnosis at birth would affect how they raised their child given the concerns raised by other studies[19,21–23,25,118]. They said the diagnosis would not change how they raised their child, but their descriptions of possible actions they would engage in could be characterized as being hypervigilant. For example, taking any cough or sniffle as a possible symptom, moving to be closer to a medical center, and taking the child to the doctor more frequently. Participants in this study did not mention how these actions would impact the child and family. These responses are in contrast to the experiences of families with a child diagnosed with a genetic condition at birth or soon after[126,138–140]. Studies in this population found that it took parents time to mourn the loss of a healthy child and build a parent-child relationship[138,139]. Instead of the child being the focus in the child's early years, the disease and healthcare providers became the focus[138,140]. With a late-onset, variable condition like Fabry disease, there is more uncertainty that may make parents either hypervigilant or skeptical of the need for evaluations and follow-up[126].

3.4.6 Limitations

One limitation of this study is the size of the sample and participant demographics. All participants were older, ranging from 40s to 70s, had Fabry disease, and had some heart and/or renal damage at the time of diagnosis. These factors may have influenced their opinions on NBS for Fabry disease. There also may have been selection bias because the participants who volunteered to participate in the study were willing to speak about their experiences with Fabry disease during an hour-long interview. Within the interviews, participants were asked many questions about their experiences, knowledge of NBS, and opinions on NBS for Fabry disease. However, due to participants sharing more than anticipated about their families' experiences with Fabry disease and having one hour for each interview, there were limitations on the depth and quantity of the questions that could be asked, as well as limited time to re-contact participants following preliminary data analysis.

3.4.7 Future directions

The results of this qualitative exploratory study can inform future studies on Fabry disease and NBS. Future studies can continue to gain an understanding of the opinions on NBS for Fabry disease and family dynamics from younger adults with Fabry disease and unaffected parents of a child who has Fabry disease. Participants in this study alluded to their siblings' views on Fabry disease; future studies could ask siblings of individuals with Fabry disease about their opinions. Since some states have begun NBS for Fabry disease, future studies could focus on parents of a child diagnosed with Fabry disease via NBS to learn their opinions on NBS for Fabry disease and how the diagnosis impacts the child and the family, particularly related to

evolving family dynamics in the face of early identification of asymptomatic individuals not yet eligible for ERT. Participants' responses in this study revealed some gaps in their understanding of NBS and the current status of knowledge and guidelines for Fabry disease. Moving forward, parent advocates could be educated about these topics and why genetics healthcare providers, bioethicists and NBS researchers have concerns about NBS for Fabry disease.

3.5 CONCLUSIONS

As conditions are added to NBS panels, it is important to understand the opinions of different stakeholders, including people who have been affected by the condition. This study is the first qualitative study to explore knowledge and attitudes towards NBS for Fabry disease. Participants' responses and experiences provided insights into how their family dynamics have been influenced by Fabry disease, their knowledge of NBS, and their reasons for wanting NBS for Fabry disease. The results of this qualitative study can inform future studies on this topic and aid state NBS programs and genetics healthcare providers as they consider and prepare for NBS for Fabry disease.

4.0 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING AND PUBLIC HEALTH

The goal of this qualitative study was to gain a more complete understanding of the reasoning of adults with Fabry disease regarding the appropriateness of newborn screening (NBS) for Fabry disease and to assess their knowledge of NBS. In the process, more was learned about participants' and their families' psychosocial concerns related to Fabry disease. The results of this study can provide guidance to public health decision-makers regarding NBS for Fabry disease and future genetic counseling research and practice for Fabry disease.

4.1 RESEARCH SIGNIFICANCE TO GENETIC COUNSELING

During their interviews, participants were asked about their experiences with Fabry disease and the types of counseling and support they would want if their child was diagnosed with Fabry disease through NBS. Participants' descriptions of their experiences with Fabry disease revealed psychosocial concerns related to their families' dynamics and their families' attitudes towards clarification of their own disease status through cascade testing. These psychosocial concerns and responses about information desired at the time of a NBS diagnosis can help inform future studies on Fabry disease and guide genetic counseling for families with Fabry disease.

The information and type of support participants would want after a positive newborn screen or diagnosis were congruent with current genetic counseling practices for NBS. Participants said they would want to talk to a specialist and genetic counselor to learn more about the disease and next steps for treatment and management. Many participants said they would want to be connected to support groups to learn more about the disease. Participants' responses about support groups provided insights into what types of support groups to suggest to families of a newborn diagnosed with Fabry disease. Given the clinical spectrum of Fabry disease, some participants indicated it would be helpful to meet people with Fabry disease who are affected differently by the disease. However the participant at the severe end of the spectrum did not seem to find it helpful to meet people from the milder end of the spectrum. NBS for Fabry disease will identify families from across the clinical spectrum of Fabry disease, such as families with late-onset variants and those who may have experienced many of the disease's non-specific symptoms. Participants also expressed different preferences for support group meeting formats, in person versus online. The results of this study suggest that it is important to consider what type of support the family desires and what experiences they have had with Fabry disease before NBS.

While a few studies have researched quality of life and psychosocial concerns in individuals with Fabry disease, not many have explored families' experiences with Fabry disease[14,49,71,73–76]. The results of this qualitative study provided insights into the experiences and psychosocial concerns of families diagnosed with Fabry disease through multiple transitions: from no treatment to ERT becoming available, from heterozygous females being referred to as "carriers" to affected, and from no known cause for symptoms to the diagnosis explaining symptoms. These transitions affected how the participants and their families viewed Fabry

disease. Research on transitions and genetic conditions has found that individuals can feel isolated after a diagnosis, the amount of support from family and peers made a difference, and adjustment to the diagnosis occurs in stages[141,142]. Future studies on Fabry disease and genetic counseling can continue to explore these psychosocial concerns and family dynamics, particularly at times of transitions.

4.2 RESEARCH SIGNIFICANCE TO PUBLIC HEALTH

The addition of Fabry disease to some states' NBS panels has broadened the perspective of Fabry disease from a rare genetic condition to a more general public health concern. The goals of this study included gaining an understanding of the views of one stakeholder group about NBS for Fabry disease, adults who have Fabry disease, and assessing their knowledge of NBS. As states and their NBS programs contemplate adding Fabry disease to their state's NBS panel, the results of this study can inform three of the ten essential public health services: inform, educate, and empower people about health issues; mobilize community partnerships and action to identify and solve health problems; and develop policies and plans that support individual and community health efforts.

Related to the first essential public health service, "inform, educate, and empower people about health issues," the results of this study identified two stakeholder groups that can be educated about NBS and Fabry disease. This study elicited participants' understanding and knowledge of NBS for Fabry disease. Their responses revealed gaps in their knowledge and understanding of the purpose of NBS. Most participants thought Fabry disease met the NBS definition of urgency because of organ involvement in Fabry disease, even though NBS urgency

refers to serious medical concerns in the first few days to weeks of life and the participants in this study were not affected by organ involvement until adulthood. Participants also did not seem to understand how Fabry disease differed from other conditions screened for by NBS. They also did not seem to understand the concerns other stakeholders, like genetics healthcare providers and bioethicists, have about NBS for Fabry disease. The concerns of these stakeholders include the emotional distress following a newborn's diagnosis, the psychological harms of diagnosing a child with a late-onset condition, and over-medicalization of the diagnosed child[19–21,118]. Moving forward, adults with Fabry disease and parents with a child who has Fabry disease can be educated about the purpose of NBS and the concerns other stakeholders have about adding Fabry disease to NBS.

While sharing their experiences with Fabry disease and their opinions on NBS for Fabry disease, participants noticed a lack of knowledge about Fabry disease among some of their healthcare providers. Some of the participants were in favor of NBS for Fabry disease because healthcare providers may not otherwise recognize and diagnose someone with Fabry disease. After they were diagnosed, some participants mentioned their healthcare providers, both PCPs and specialists, lacked knowledge of Fabry disease. As Fabry disease is added to NBS panels, healthcare providers can be educated about Fabry disease and provided with up-to-date resources. This is detailed further in the public health essay in the next chapter.

For the second essential public health service, "mobilize community partnerships and action to identify and solve health problems," partnerships can be formed with healthcare providers in states considering NBS for Fabry disease to identify the education and support healthcare providers would want through the process of implementing NBS for Fabry disease. Stakeholder groups for NBS for Fabry disease, like adults with Fabry disease, parents with a

child who has Fabry disease, genetics healthcare providers, and NBS programs, can form partnerships to educate each other and identify ways to work collaboratively to solve problems related to Fabry disease and public health. As these stakeholders work together, the third essential public health service, "develop policies and plans that support individual and community health efforts," can be worked on to develop policies and plans for NBS for Fabry disease that are agreeable with these various stakeholder groups.

5.0 PUBLIC HEALTH ESSAY: FACTORS TO CONSIDER AS PENNSYLVANIA AND OTHER STATES CONTEMPLATE NEWBORN SCREENING FOR FABRY DISEASE

Pennsylvania amended the Newborn Child Testing Act in 2014 to include six lysosomal storage disorders (LSDs): Fabry disease, Pompe disease, Krabbe disease, Gaucher disease, mucopolysaccharidosis type I (MPS I), and Niemann-Pick disease types A and B, to the newborn screening (NBS) panel[110]. The state began screening for Pompe disease in February of 2016 and the other LSDs will be added to the NBS panel as Pennsylvania's Newborn Screening and Follow-up Technical Advisory Board (NBSTAB) confirms that appropriate screening tests and follow-up protocols are in place[110]. As Pennsylvania and other states consider if and when to begin NBS for Fabry disease, they can assess the experiences and challenges of states and countries that have initiated screening for LSDs. These experiences reveal the infrastructure and resource needs and stakeholders at each step of the newborn screening process for Fabry disease. The steps include the laboratory screening process including short-term follow-up of positive screens including confirmation of diagnosis, education of healthcare providers about NBS for Fabry disease, screening of at-risk family members after a newborn is diagnosed, and long-term follow-up for newborns and family members diagnosed with Fabry disease after NBS.

5.1 SHORT-TERM FOLLOW-UP ON POSITIVE SCREENS

NBS staff, and healthcare providers are involved in the short-term follow-up of newborns with abnormal NBS results[143]. Data from pilot studies and NBS programs for Fabry disease have found that current technologies and methods have a similar ratio of true positives to false positives as compared to other newborn screened conditions[29,99,102,104]. Although NBS yields a similar true positives to false positives ratio, these NBS programs and pilot studies did not anticipate the higher number of positive screens for Fabry disease that corresponds with an incidence of 1 in 3000 people versus the previous estimated incidence of Fabry disease of 1 in 40,000 males[28,30,99].

For each positive newborn screen, short-term follow-up involves multiple stakeholders, their time, and resources: NBS program staff, the newborn's PCP, a specialist for that condition, genetic counselors, pediatric nurses, dietitians in some cases, resources and personnel for confirmatory testing, and the newborn's family. As Pennsylvania and other states consider implementing NBS for Fabry disease, they will need to evaluate the capacity of the LSD specialty clinics in the state to provide short-term and long-term follow-up for the number of positively screened patients for Fabry disease. States may also determine what steps the state and LSD specialty clinics need to take to prepare as NBS for Fabry disease is implemented.

Various methods have been proposed and used to reduce the number of false positive screens for Fabry disease. One method utilizes the Region 4 Stork Collaborative Project (R4S). R4S was developed as a system to interpret analyte ratios to improve the screening predictability for metabolic disorders involving amino acids and acylcarnitines, primarily to reduce false positive screens[16]. This project has recently expanded to include LSDs and some of the pilot studies on NBS for LSDs are sharing their data with R4S[16,95]. R4S could be integrated into the

workflow of state NBS programs to interpret abnormal Fabry disease screens and reduce the number of false positives that are called out. Alternatively, Missouri's NBS program created an algorithm to reduce their number of false positives for Fabry disease and other LSDs[99]. As part of this algorithm, a newborn's dried bloodspot is re-tested after a positive screen and the average enzyme level from the two tests is assessed and compared to enzyme levels for other LSDs on NBS run on the same assay[99]. Newborns who are considered high-risk after this assessment are referred to one of the state's genetic referral centers[99].

Pennsylvania's Newborn Screening and Follow-Up Technical Advisory Board (NBSTAB) LSD Screening Workgroup has estimated the number of positive screens for LSDs each LSD referral center will see, possible methods to reduce false positives and turnaround time for confirmatory testing, and short-term and long-term follow-up procedures for newborns with Fabry disease (G. Vockley, personal communication, April 2017). Pennsylvania's plan to reduce false positives will utilize R4S and adding second-tier testing for LSDs on the NBS panel (G. Vockley, personal communication, April 2017). In second-tier testing, positive screens reflex to a more specific test, such as measuring more analytes or DNA sequencing to check for common pathogenic variants[1].

5.2 FAMILY SCREENING

The newborn's diagnosis following NBS will lead to cascade screening for Fabry disease in the family. Because the newborn may be the first person to be diagnosed with Fabry disease in the family, the subsequent screening of at-risk family members will increase demands on the state's genetics referral centers' resources and infrastructure. The newborn may be the first

person to be diagnosed with Fabry disease in the family. Data from NBS programs and research studies indicate that Fabry disease is underdiagnosed and has a higher incidence of late-onset variants than previously recognized[13,27,30,99,102]. In the Italian NBS pilot study, researchers conducted family studies on all 12 diagnosed newborns and reported that all 12 mothers were heterozygotes and that multiple families had histories of cardiac or renal disease that are now attributed to Fabry disease[102]. On average, five family members are expected to be diagnosed after the index case, the newborn, is diagnosed in the family[125].

Cascade screening in the family would begin with the newborn's parents. Given Fabry disease's X-linked inheritance pattern, Missouri's NBS follow-up procedures first screen the diagnosed newborn's mother with a clinical evaluation and molecular testing[47,113]. These follow-up procedures, however, did not specify what happens when a newborn female is diagnosed with Fabry disease, in which case either the newborn's mother or father may be affected. From the mother's test results, other at-risk family members can be tested. Any older siblings of the diagnosed newborn who were not screened at birth would also be tested. For each family member, there is bloodwork and results disclosure. Male relatives can be screened and diagnosed from testing α-Gal A levels in the blood, but female relatives must undergo molecular testing because 1/3 of heterozygous females may not have low blood α-Gal A levels[10,60,61].

As Pennsylvania and other states contemplate NBS for Fabry disease, the state's NBS program and medical genetics clinics will need to consider how to handle the number of family referrals that will come in following a newborn's diagnosis. Prior to NBS for Fabry disease, at-risk family members of a diagnosed individual would undergo a full clinical evaluation with a genetic counselor and a geneticist during their screening appointment. With the higher than expected number of newborns diagnosed in Missouri, the state's genetics referral centers are

considering how to re-work the current workflow to test the newborns' at-risk family members[113]. For example, they have considered ordering testing for at-risk family members without a genetics clinic visit or having only the genetic counselor see these family members[113]. At-risk family members diagnosed with Fabry disease will have evaluations with the genetics clinic and other specialties that deal with the organ systems affected in Fabry disease, like cardiology and nephrology. Similar to the genetics clinics, these specialists will also be impacted by the number of family members diagnosed after the newborn, particularly in rural areas where there may be limited access to specialists.

5.3 LONG-TERM FOLLOW-UP FOR INDIVIDUALS WITH CONFIRMED DIAGNOSIS

From a public health perspective, there are multiple concerns with the long-term follow-up and management of individuals diagnosed with Fabry disease through NBS. Most conditions on NBS diagnose the newborn with a condition and identify one or both parents as carriers. In these cases, long-term follow-up after NBS only involves follow-up management for the diagnosed newborn. Unlike those conditions, Fabry disease is an X-linked condition that affects hemizygous males and heterozygous females, which means a parent and other relatives will likely be diagnosed after the newborn. Long-term follow-up after a diagnosis via NBS for Fabry disease includes follow-up visits with a geneticist and genetic counselor and with other specialists as needed (cardiology, nephrology, neurology, and gastroenterology) for the newborn, the newborn's parent, and any other relatives that have been diagnosed [17]. A diagnosis through NBS will get these family members access to treatment and evaluations with these specialists,

which will reduce morbidities associated with Fabry disease and reduce the cost of treating these morbidities, like renal failure. But a concern with NBS for Fabry disease is the number of people who will be identified with late-onset variants, for which limited natural history information is known. For example, Missouri's NBS program diagnosed multiple newborns with Fabry disease who have the A143T allele[112,113]. The Fabry population in Missouri's genetics clinics has tripled in three years because of the number of diagnosed newborns and diagnosed relatives[113]. 61% of the clinics' new patients have the A143T allele and in this population, there are few symptomatic adult patients[113]. Further research on the A143T allele indicates this allele is likely a benign variant or a disease-modifying variant[114].

While workforce availability issues are significant, an additional concern regarding long-term follow-up is the question of whether the workforce and resources are being used appropriately to follow individuals who are diagnosed with Fabry disease through NBS. Many of the diagnosed newborns and their family members have late-onset variants[99,100,102]. Current guidelines provide limited information on how to monitor and manage asymptomatic newborns or asymptomatic individuals with late-onset variants[17,18]. In addition, research is still being conducted to determine if LysoGB3 is a reliable biomarker to track disease progression[20,63]. With the current guidelines and lack of a validated biomarker, a newborn with a late-onset variant would see the LSD clinic team every six months to a year to be monitored for disease progression[17,144]. Cost-benefit analyses have not been done to compare the costs of diagnosing and managing an asymptomatic newborn versus the costs of diagnosing someone after symptoms appear[20].

More evidence is needed to better assess when to start enzyme replacement therapy (ERT) for Fabry disease and the natural history of late-onset variants so that guidelines can be

updated[20]. The long-term follow-up component of the NBS system may aid in this process. According to the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), the federal committee that makes recommendations about NBS, the goals of NBS long-term follow-up include care coordination, evidence-based treatment, continuous quality improvement, and new knowledge discovery[145,146]. Long-term follow-up that is led by a NBS program will allow for uniform data collection to assess various aspects of these goals[145]. As with other conditions that were added to NBS and other population screenings, NBS for Fabry disease has identifed late-onset variants and variants of unknown significance that were previously unknown[29,99,102]. To achieve the goal of new knowledge discovery, additional data on these variants need to be collected. Federally-funded projects, like Inborn Errors of Metabolism Information System (IBEM-IS) and the Newborn Screening Translational Research Network's Longitudinal Pediatric Data Resource (LPDR), are long-term data collection programs that will lead to a better understanding of Fabry disease's natural history and how to treat it[147,148]. Participants in national and international programs are also researching how to utilize current NBS infrastructure and resources to collect this data for long-term follow-up[70,149,150].

Another concern with NBS for Fabry disease and other later-onset conditions is the continuity of access to and use of NBS results. The purpose of NBS has transformed slightly as NBS has started screening for late-onset conditions. With late-onset conditions like Fabry disease, diagnosed newborns are followed instead of being treated or managed soon after diagnosis. Although the purpose of NBS is not to identify individuals with later-onset conditions, once a newborn has been diagnosed via NBS with a later-onset condition, the NBS system or healthcare providers will need to ensure that the result will not be lost. This requirement raises the questions of whether NBS results will remain a part of the newborn's medical records into

adulthood, whether parents will remember the diagnosis when their child starts showing symptoms, and whether parents will communicate the results to their child[151]. These questions surrounding NBS for Fabry disease are especially concerning for females because PCPs and other healthcare providers may not diagnose a female with Fabry disease.

5.4 EDUCATION OF HEALTHCARE PROVIDERS

Before screening for Fabry disease is implemented as part of the NBS system, it would be advantageous for Pennsylvania and other states to communicate with healthcare providers who will be involved in both short-term and long-term follow-up of newborns with positive screens and confirmed diagnoses. Primary care providers (PCPs) are often the ones who disclose positive newborn screen results to parents and several research studies indicate a need for more education for PCPs regarding NBS and Fabry disease. This education could include information about interpretation of NBS results in the context of Fabry disease, follow-up protocols for an abnormal screen, as well as general information about Fabry disease[152–154].

A few research studies have explored PCPs' attitudes towards NBS and their knowledge of the conditions covered by NBS[152–154]. Most providers are in favor of NBS, even for later-onset conditions, and agree it is their responsibility to provide information and care to families with a positive newborn screen[152,155]. These studies reported gaps in providers' knowledge of NBS, but providers shared the type of training and resources they would find helpful[152,153,155]. Providers displayed varying levels of comfort and knowledge with conditions on NBS panels and how to disclose results[153–155]. With cystic fibrosis and sickle cell disease, two of the more common conditions on NBS panels, there was significant misunderstanding among providers regarding

what different NBS results mean and the significance of being a carrier for sickle cell disease or cystic fibrosis[155]. Given these results and the complexities of Fabry disease being an X-linked condition that affects both males and females, it will be important to educate providers on what NBS results for Fabry disease mean and caution them that NBS does not detect 1/3 of females with Fabry disease[61].

Healthcare providers' and NBS coordinators' responses in these studies indicated ways healthcare providers can be given education and training about NBS in general and for specific conditions. Some PCPs thought it would be helpful to have training on how to give bad news[153]. With the addition of Fabry disease and other later-onset conditions to NBS, training on how to disclose results for different types of NBS conditions would be helpful. PCPs valued the information sheet sent with NBS results and wanted an information sheet to give parents at the results disclosure[153]. For condition-specific information, PCPs tended to search online for information and contacted specialty centers[153]. More online resources, such as the one currently being developed by a team from the Society for Inherited Metabolic Disorders, would enable PCPs to have easy access to information about Fabry disease and other NBS conditions to prepare for the initial results disclosure and for caring for the diagnosed child[156]. One research group suggested developing existing NBS online resources further, like STAR-G by the Western States Genetic Services Collaborative and NBS Connect by Emory University[154].

5.5 CONCLUSIONS

The results from current NBS programs and pilot studies has shown that NBS for Fabry disease will increase the number of people diagnosed with Fabry disease across all age

groups[102,113]. The development of more online educational resources for healthcare providers about Fabry disease would benefit PCPs involved in the care of a diagnosed newborn and it would benefit healthcare providers involved in the care of family members diagnosed after the newborn. After they were diagnosed, some participants in this study shared that their healthcare providers were not familiar with Fabry disease, but some of their healthcare providers sought out resources and guidelines to educate themselves about the disease. The development of up-to-date resources for healthcare providers is especially important for diagnosis and treatment of at-risk females to ensure that healthcare providers understand that females can be affected and are not just carriers.

APPENDIX A: IRB APPROVAL LETTER

University of Pittsburgh
Institutional Review Board

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

Memorandum

To: Kavitha Kolla
From: IRB Office
Date: 10/19/2016
IRB#: PRO16060309
Subject: Knowledge and Attitudes About Newborn Screening for Fabry Disease

---

The University of Pittsburgh Institutional Review Board reviewed and approved the above referenced study by the expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110. Your research study was approved under:

45 CFR 46.110.(6)
45 CFR 46.110.(7)

The IRB has approved the waiver for the requirement to obtain a written informed consent.

The IRB has approved the waiver for the requirement to obtain informed consent to use protected health information to identify potential research subjects.

The risk level designation is Minimal Risk.

Approval Date: 10/19/2016
Expiration Date: 10/18/2017

The following documents were approved by the IRB:
Educational piece on newborn screening and Fabry disease

For studies being conducted in UPMC facilities, no clinical activities can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

APPENDIX B: PARTICIPANT INVITATION LETTER

Dear Mr./Mrs. _____,

I am writing on behalf of Kavitha Kolla, a genetic counseling intern at the University of Pittsburgh. Ms. Kolla is conducting a research study at the Children's Hospital of Pittsburgh to learn more about patient and family knowledge and thoughts about newborn screening for Fabry disease.

For this study, Ms. Kolla will be interviewing both parents of children who have Fabry disease and adults who have Fabry disease to learn more about their experiences with Fabry disease and to learn about their attitudes about newborn screening for Fabry disease.

I invite you to consider participating in an audio recorded one-on-one interview with Ms. Kolla. Participation is completely voluntary. Your decision to participate will not affect your medical care or your child's medical care at any UPMC facility. Your identity and responses will be kept confidential.

The interview would last about an hour, either over the phone or in person at Children's Hospital of Pittsburgh or Montefiore Hospital. Questions will focus on various aspects of newborn screening for Fabry disease. During the interview, you only have to share as much information as you feel comfortable sharing.

If you have any questions about participating in the study or would like to learn more about how to participate, please fill out the attached response card with your contact information and one of our study staff will contact you.

Sincerely,

Genetic Counselor

APPENDIX C: PARTICIPANT VERBAL CONSENT SCRIPT (TELEPHONE)

Hello, my name is Kavitha Kolla and I'm a genetic counseling intern from Children's Hospital of Pittsburgh. I'm working on a study called "Knowledge and Attitudes about Newborn Screening for Fabry Disease". The genetic counselor from the Lysosomal Storage Disorders Clinic at Children's Hospital of Pittsburgh referred you to this study by letter and you expressed interest in hearing more about it. Is now a good time for a brief introduction?

You are being asked to participate in this research study because you or your child, or both, have been diagnosed with Fabry disease. The purpose of this research study is to better understand the experiences of parents of children who have Fabry disease and adults who have Fabry disease and to learn what they think of newborn screening for Fabry disease. To accomplish this, we will be interviewing parents of children who have Fabry disease and adults who have Fabry disease.

Participants are asked to complete a telephone or in person interview with me, the main investigator in the study, which last about one hour. In person interviews can take place at either Children's Hospital of Pittsburgh or Montefiore Hospital, if you receive enzyme replacement therapy infusions at Montefiore Hospital. The interview will explore your experiences with Fabry disease, the timing of the diagnosis, and your thoughts on newborn screening for Fabry disease. Interviews will be audio recorded, typed, and evaluated. Identifying information, such as your name or your child's name, will be removed from the typed document. A member of the study team might contact you after you complete your interview for a follow-up interview to explore new topics raised by later interviewees.

All responses to the interview are confidential and responses will be stored in a secure manner. Personal password-protected computers and a locked file cabinet will be used to store records at Children's Hospital of Pittsburgh. Per University of Pittsburgh policy, all research records for this study will be stored for at least 7 years without information that can be linked to participants' identities. It is possible that in the future, other investigators interested in performing similar research will request access to data or materials from this study. If data is shared with other investigators, they will not be able to link the data to the participants' identities in any way.

Your participation may not directly benefit you, but information gathered through this study may be shared with state personnel who may consider adding newborn screening for Fabry disease to the newborn screening panel. This knowledge will help healthcare professionals provide better support and education during the newborn screening process.

There is minimal risk to participating in this study since there is no blood draw or other medical procedures. Some of the interview questions may cause some distress because they will ask about your experiences with Fabry disease and thinking about how an earlier diagnosis would have impacted you and your family. During the interview, you only have to answer questions you are comfortable answering and share as much as you want.

Your participation is voluntary and you may withdraw from this project at any time. Any answers recorded in the interview prior to withdrawal will remain a part of the study. Your decision to participate or not to participate will not affect your current or future health care at any of the University of Pittsburgh Medical Center facilities.

In unusual cases, in response to a court order, the investigators may be required to release identifiable research study information (which may include your identifiable medical information) related to your participation in this research study. If investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform the appropriate agencies, as required by Pennsylvania law. No medical procedures will be performed in this study, but if you believe that the research procedures have resulted in injury to you, contact the Principal Investigator immediately. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of UPMC. Your insurance provider may be billed for the costs of this emergency treatment, but none of those costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care. There is no plan for any direct additional financial compensation for participation in this study.

You are encouraged to ask questions and voice concerns or complaints about any aspects of this research study during the course of this study and in the future. Questions and concerns will be addressed by a qualified individual, the Principal Investigator, Kavitha Kolla at _____, or the co-investigator Catherine Walsh Vockley at _____. You may contact the Human Subjects Protection Advocate of the IRB office at the University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable.

Do you have any questions about the study or the information I just went over?

Are you interested in participating in this study?

If yes, can we arrange a time for the interview now, or do you want me to re-contact you at a specific time in the future to do that?

APPENDIX D: PARTICIPANT INTERVIEW GUIDE

Introduction to research project (review information from verbal consent that was previously obtained)

Getting to know participant
To begin, could you tell me a little bit about yourself and your family?

What have your experiences with Fabry disease been like?
Follow-up questions to consider asking for experience with Fabry disease:

Tell me about some of your earliest experiences with Fabry disease.

How were you/your child diagnosed with Fabry disease?

What symptoms or features started the path to diagnosis? Did the family medical history play a role in your/your child's diagnosis?
(if yes, family history did play a role) Were you/your child tested for Fabry based only on the family history?

How old were you when you were diagnosed with Fabry disease? or
How old was your child when he/she was diagnosed with Fabry disease?

How many doctors and specialists did you see between the time symptoms started and when you/your child was diagnosed? Who was responsible for the diagnosis being confirmed?

How much time was there between when the symptoms started and when you/your child was diagnosed with Fabry disease?

Do you think your primary care provider understood the diagnosis?
Did your specialists/specialty care team provide written materials for you and/or for your PCP to learn more about Fabry?
What other resources did you use to understand Fabry?

Impact
How has the diagnosis impacted you/your child?

How has the diagnosis impacted your family?

Have any other family members been diagnosed since you/your child were diagnosed?

Have you/your child started enzyme replacement therapy? If yes, at what age?

The treatment for Fabry disease, enzyme replacement therapy, is started after symptoms appear. How would you feel if you or your child was diagnosed with Fabry disease before symptoms appear?

Imagine that you have a child who is diagnosed with Fabry disease before symptoms appear and before treatment is needed. How might this affect the way you raise your child?

Previous knowledge about newborn screening

What have you heard about newborn screening before participating in this study?

What do you believe is the purpose of newborn screening?

Do you know when newborn screening is done?

What kinds of conditions do you think newborn screening looks for?

What do you think are some reasons why a condition would be included on newborn screening?

Based on those reasons, what is your opinion on Fabry disease being a part of newborn screening?

Educate about newborn screening. Explain how newborn screening for Fabry works.

Educational piece (separate document). Walk through educational piece together

Opinions on newborn screening and hypothetical questions

The advisory committee that reviews conditions to be added to newborn screening usually includes conditions that start in infancy and have a treatment. What is your opinion on conditions being included in newborn screening that start later, for example, in childhood or adolescence?

The original purpose of newborn screening is to identify infants at immediate risk of developing life-threatening symptoms associated with a serious condition. Do you think Fabry disease meets this definition of urgency?

Newborn screening results can come back positive (which means a higher risk for a specific condition), negative, or unclear.

Imagine that your newborn child has a positive screen for Fabry disease on newborn screening. A positive screen is followed by a diagnostic test. The diagnostic test for Fabry disease shows that your child has Fabry disease. How would you feel about your newborn child receiving a diagnosis of Fabry disease?

After a positive screen, the diagnostic test for Fabry disease shows that your child does not have Fabry disease. This is known as a false positive result. How would you feel about your newborn child receiving a positive screen followed by a negative diagnostic test?

One possible result on newborn screening is a negative result, which means the baby is not at increased risk of having Fabry disease. How would you feel about your newborn child receiving a negative screen for Fabry disease?

Another possible result on newborn screening is unclear results, which means we do not know if the baby is at increased risk or not for Fabry disease. How would you feel about unclear test results for your newborn child?

In most states, parents can opt out of newborn screening, but parents are encouraged not to opt out because of the critical health implications for their child if he or she tests positive.
Should parents be given the option to opt out of testing for Fabry and other later onset conditions on newborn screening?
What sort of information do you think parents should be given about these conditions before making their decision?
Do you think parents should know that if their child has one of these conditions and they do not pursue newborn screening for Fabry and other later onset conditions on newborn screening, it may take multiple doctors or multiple years to be diagnosed?

How would a diagnosis at birth through newborn screening have impacted you/your child? Your family?

What sort of counseling and support did you receive at the time of your/your child's diagnosis?
What sort of counseling and support should go along with a diagnosis at birth?

After a positive screen, who would you want to talk to for more information and support?
Would you want to talk to a genetic counselor? Would you want to talk to a physician/specialist? Or both?
What other forms of support or resources would you want after a positive screen?

In summary, do you think NBS should be done for Fabry? Why or why not?

APPENDIX E: EDUCATIONAL BROCHURE

What is Newborn Screening?

Newborn screening (NBS) is a system that checks all newborns in the United States for serious health conditions.

The NBS blood test looks for certain genetic and metabolic conditions.

Newborn screening also uses other tests to look for hearing loss and specific heart problems in infants.

Why is it done?

Babies with one of these conditions usually look healthy at birth. For babies identified through newborn screening, a treatment plan can be set up right away.

Resources Available for Newborn Screening and Fabry Disease

- Baby's First Test (http://www.babysfirsttest.org)
- Save Babies through Screening Foundation (http://www.savebabies.org)
- Fabry Support and Information Group (http://www.fabry.org)
- Genetics Home Reference (https://ghr.nlm.nih.gov/condition/fabry-disease)

References

NewSTEPs (https://www.newsteps.org)
STAR-G (http://www.newbornscreening.info)
Missouri Department of Health (http://health.mo.gov/living.families/genetics/newbornscreening)
Illinois Department of Health (http://www.idph.state.il.us/HealthWellness/fs/fabry.htm)
CDC (https://www.cdc.gov/newbornscreening)

Newborn Screening for Fabry Disease

Conditions on Newborn Screening Panel

Each **state's Department of Health** decides which conditions are on the Newborn Screening Panel.

The conditions on newborn screening may change as more information is learned.

An **Advisory Committee** to the Federal government advises on conditions to include on newborn screening panels.

This committee carefully studies a condition before recommending that the condition is added to newborn screening.

Some of the factors the committee considers:

- Does the condition affect babies or children?
- Does the condition have a treatment?
- Is there a good screening test and diagnostic test for the condition?

States Screening for Fabry

States currently screening for Fabry: Illinois, Missouri, and New York (offered to some groups)

States that may screen for Fabry in the near future:
Pennsylvania and New Jersey

Bloodspot Newborn Screening Process

- **When:** 24 to 48 hours after birth, while the baby is still at the hospital or birthing location.
- **How:** A few drops of the baby's blood is taken from his/her heel. The blood is collected on a special type of paper, which is sent for testing to the state's newborn screening lab or a private lab working with the state.
- **Positive screening results** are returned to parents within 5-7 days. All results are available at the time of the first well-baby visit at about 2 weeks of age.
- If a baby screens positive for one or more conditions on the newborn screening panel, the baby will need to see a **specialist**. The specialist can examine the baby and then order **diagnostic tests** for the condition(s) of concern.
- If the diagnostic test confirms the baby has the condition, a **treatment plan** will be set up.

Screening Test Vs. Diagnostic Test

Screening test: a test used to detect people who have a greater chance of having a specific condition

Diagnostic test: a test used to confirm whether or not a person has a specific condition

Possible Results of Newborn Screening

- **Negative:** the baby most likely does not have one of the conditions on the NBS panel
- **Positive:** the baby may have one or more of the conditions on the NBS panel
- *True positive:* a follow-up diagnostic test confirms the baby has that condition
- *False positive:* a follow-up diagnostic test shows the baby does not have that condition
- **Borderline:** the results from newborn screening are uncertain and more testing is needed to show if the baby has the condition or not

Current Process for Newborn Screening for Fabry Disease

- A **small sample** of the baby's blood is taken from his/her heel 24-48 hours after birth. The sample is sent to a private lab that screens for Fabry disease.
- **If the screening test is positive** for Fabry disease, the baby has a diagnostic test to confirm whether he/she has Fabry disease.
- **If the diagnostic test confirms** the baby has Fabry disease, he/she will see a doctor who specializes in this condition.
- The family will receive **genetic counseling** and information about follow-up plans and **support services**.
- Enzyme replacement therapy or other **treatment** starts when symptoms begin.

BIBLIOGRAPHY

1. Almannai, M., Marom, R. & Sutton, V. R. Newborn screening. *Curr. Opin. Pediatr.* **28,** 694–699 (2016).

2. Bailey, D. B. *et al.* Newborn Screening. *JAMA* **313,** 1511 (2015).

3. Kemper, A. R. *et al.* Decision-making process for conditions nominated to the Recommended Uniform Screening Panel: statement of the US Department of Health and Human Services Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. *Genet. Med.* **16,** 183–187 (2014).

4. Tortorelli, S. *et al.* Simultaneous Testing for 6 Lysosomal Storage Disorders and X-Adrenoleukodystrophy in Dried Blood Spots by Tandem Mass Spectrometry. *Clin. Chem.* **62,** 1248–1254 (2016).

5. Laney, D. A. *et al.* Fabry Disease Practice Guidelines: Recommendations of the National Society of Genetic Counselors. *J. Genet. Couns.* **22,** 555–564 (2013).

6. Giugliani, R. *et al.* A Phase 2 study of migalastat hydrochloride in females with Fabry disease: selection of population, safety and pharmacodynamic effects. *Mol. Genet. Metab.* **109,** 86–92 (2013).

7. Gibas, A. L., Klatt, R., Johnson, J., Clarke, J. T. R. & Katz, J. A survey of the pain experienced by males and females with Fabry disease. *Pain Res. Manag.* **11,** 185–92 (2006).

8. Hopkin, R. J. *et al.* Characterization of Fabry Disease in 352 Pediatric Patients in the Fabry Registry. *Pediatr. Res.* **64,** 550–555 (2008).

9. Pitz, S. *et al.* Ocular signs correlate well with disease severity and genotype in Fabry disease. *PLoS One* **10,** e0120814 (2015).

10. Germain, D. P. *et al.* Fabry disease. *Orphanet J. Rare Dis.* **5,** 30 (2010).

11. Weidemann, F. *et al.* Fibrosis: a key feature of Fabry disease with potential therapeutic implications. *Orphanet J. Rare Dis.* **8,** 116 (2013).

12. Hoffmann, B., Schwarz, M., Mehta, A., Keshav, S. Fabry Outcome Survey European Investigators. Gastrointestinal Symptoms in 342 Patients With Fabry Disease: Prevalence and Response to Enzyme Replacement Therapy. *Clin. Gastroenterol. Hepatol.* **5,** 1447–1453 (2007).

13. Oder, D. *et al.* Organ manifestations and long-term outcome of Fabry disease in patients with the GLA haplotype D313Y. *BMJ Open* **6,** e010422 (2016).

14. Wang, R. Y., Lelis, A., Mirocha, J. & Wilcox, W. R. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. *Genet. Med.* **9,** 34–45 (2007).

15. Eng, C. M. *et al.* Fabry disease: Baseline medical characteristics of a cohort of 1765 males and females in the Fabry Registry. *J. Inherit. Metab. Dis.* **30,** 184–192 (2007).

16. Matern, D. *et al.* Newborn screening for lysosomal storage disorders. *Semin. Perinatol.* **39,** 206–216 (2015).

17. Hopkin, R. J. *et al.* The management and treatment of children with Fabry disease: A United States-based perspective. *Mol. Genet. Metab.* **117,** 104–113 (2016).

18. Eng, C. M. *et al.* Fabry disease: guidelines for the evaluation and management of multi-organ system involvement. *Genet. Med.* **8,** 539–48 (2006).

19. Ross, L. F. Newborn screening for lysosomal storage diseases: an ethical and policy analysis. *J. Inherit. Metab. Dis.* **35,** 627–634 (2012).

20. Peake, R. W. A. *et al.* Newborn Screening for Lysosomal Storage Disorders: Quo Vadis? *Clin. Chem.* **62,** (2016).

21. Lisi, E. C. & McCandless, S. E. Newborn Screening for Lysosomal Storage Disorders: Views of Genetic Healthcare Providers. *J. Genet. Couns.* **5,** 373–384 (2016).

22. Miller, F. *et al.* Public Perceptions of the Benefits and Risks of Newborn Screening. *Pediatrics* **136,** E413–E423 (2015).

23. Hayes, I., Collins, V., Sahhar, M., Wraith, J. & Delatycki, M. Newborn screening for mucopolysaccharidoses: opinions of patients and their families. *Clin. Genet.* **71,** 446–450 (2007).

24. Weinreich, S. *et al.* Public support for neonatal screening for Pompe disease, a broad-phenotype condition. *Orphanet J. Rare Dis.* **7,** (2012).

25. Bouwman, M. *et al.* Fabry patients' experiences with the timing of diagnosis relevant for the discussion on newborn screening. *Mol. Genet. Metab.* **109,** 201–207 (2013).

26. Lisi, E. C., Gillespie, S., Laney, D. & Ali, N. Patients' perspectives on newborn screening for later-onset lysosomal storage diseases. *Mol. Genet. Metab.* **119,** 109–14 (2016).

27. Liu, H.-C. *et al.* Age at First Cardiac Symptoms in Fabry Disease: Association with a Chinese Hotspot Fabry Mutation (IVS4+919G>A), Classical Fabry Mutations, and Sex in a Taiwanese Population from the Fabry Outcome Survey (FOS). *JIMD Rep.* **22,** 107–13 (2015).

28. Meikle, P. J., Hopwood, J. J., Clague, A. E. & Carey, W. F. Prevalence of lysosomal storage disorders. *JAMA* **281,** 249–54 (1999).

29. Inoue, T. *et al.* Newborn screening for Fabry disease in Japan: prevalence and genotypes of Fabry disease in a pilot study. *J. Hum. Genet.* **58,** 548–552 (2013).

30. Mechtler, T. P. *et al.* Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. *Lancet* **379,** 335–341 (2012).

31. Kampmann, C., Perrin, A. & Beck, M. Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment. *Orphanet J. Rare Dis.* **10,** 125 (2015).

32. Kampmann, C. *et al.* Onset and progression of the Anderson–Fabry disease related cardiomyopathy. *Int. J. Cardiol.* **130,** 367–373 (2008).

33. Sims, K., Politei, J., Banikazemi, M. & Lee, P. Stroke in Fabry Disease Frequently Occurs Before Diagnosis and in the Absence of Other Clinical Events: Natural History Data From the Fabry Registry. *Stroke* **40,** 788–794 (2009).

34. Deegan, P. B. *et al.* Natural history of Fabry disease in females in the Fabry Outcome Survey. *J. Med. Genet.* **43,** 347–352 (2006).

35. Lee, H.-J. *et al.* A comparison of central nervous system involvement in patients with classical Fabry disease or the later-onset subtype with the IVS4+919G>A mutation. *BMC Neurol.* **17,** 25 (2017).

36. Rost, N. S. *et al.* Determinants of white matter hyperintensity burden in patients with Fabry disease. *Neurology* **86,** 1880–6 (2016).

37. Schermuly, I. *et al.* Neuropsychiatric symptoms and brain structural alterations in Fabry disease. *Eur. J. Neurol.* **18,** 347–353 (2011).

38. Sigmundsdottir, L. *et al.* Cognitive and psychological functioning in Fabry disease. *Arch. Clin. Neuropsychol.* **29,** 642–50 (2014).

39. Segal, P. *et al.* Psychiatric and cognitive profile in Anderson-Fabry patients: a preliminary study. *J. Inherit. Metab. Dis.* **33,** 429–436 (2010).

40. Laney, D. A. *et al.* Social-adaptive and psychological functioning of patients affected by Fabry disease. *J. Inherit. Metab. Dis.* **33,** 73–81 (2010).

41. Cole, A. L. *et al.* Depression in adults with Fabry disease: A common and under-diagnosed problem. *J. Inherit. Metab. Dis.* **30,** 943–951 (2007).

42. Najafian, B., Mauer, M., Hopkin, R. J. & Svarstad, E. Renal Complications of Fabry Disease in Children. *Pediatr. Nephrol.* **28,** (2013).

43. Schiffmann, R. *et al.* Fabry disease: progression of nephropathy, and prevalence of cardiac and cerebrovascular events before enzyme replacement therapy. *Nephrol. Dial. Transplant* **24,** 2102–11 (2009).

44. Tondel, C., Bostad, L., Hirth, A. & Svarstad, E. Renal Biopsy Findings in Children and Adolescents With Fabry Disease and Minimal Albuminuria. *Am. J. Kidney Dis.* **51,** 767–776 (2008).

45. Tondel, C. *et al.* Foot process effacement is an early marker of nephropathy in young classic Fabry patients without albuminuria. *Nephron* **129,** 16–21 (2015).

46. Pensabene, L. *et al.* Gastrointestinal Symptoms of Patients with Fabry Disease. *Gastroenterol. Res. Pract.* **2016,** 1–7 (2016).

47. Bernstein, H. S. *et al.* Fabry disease: six gene rearrangements and an exonic point mutation in the alpha-galactosidase gene. *J. Clin. Invest.* **83,** 1390–1399 (1989).

48. Bouwman, M. G. *et al.* Prevalence of symptoms in female Fabry disease patients: a case-control survey. *J. Inherit. Metab. Dis.* **35,** 891–8 (2012).

49. MacDermot, K. D., Holmes, A. & Miners, A. H. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 98 hemizygous males. *J. Med. Genet.* **38,** 750–760 (2001).

50. Yu, C., Sun, Q. & Zhou, H. Enzymatic Screening and Diagnosis of Lysosomal Storage Diseases. *N. Am. J. Med. Sci. (Boston).* **6,** 186–193 (2013).

51. Brady, R. O. *et al.* Enzymatic Defect in Fabry's Disease. *N. Engl. J. Med.* **276,** 1163–1167 (1967).

52. Askari, H. *et al.* Cellular and tissue localization of globotriaosylceramide in Fabry disease. *Virchows Arch.* **451,** 823–834 (2007).

53. Eng, C. M. *et al.* A phase 1/2 clinical trial of enzyme replacement in fabry disease: pharmacokinetic, substrate clearance, and safety studies. *Am. J. Hum. Genet.* **68,** 711–22 (2001).

54. Christensen, E. I. *et al.* Distribution of alpha-galactosidase A in normal human kidney and renal accumulation and distribution of recombinant alpha-galactosidase A in Fabry mice. *J. Am. Soc. Nephrol.* **18,** 698–706 (2007).

55. Seydelmann, N., Wanner, C., Störk, S., Ertl, G. & Weidemann, F. Fabry disease and the heart. *Best Pract. Res. Clin. Endocrinol. Metab.* **29,** 195–204 (2015).

56. Ferreira, S. *et al.* Variations in the GLA gene correlate with globotriaosylceramide and globotriaosylsphingosine analog levels in urine and plasma. *Clin. Chim. Acta* **447,** 96–104 (2015).

57. Schiffmann, R., Fuller, M., Clarke, L. A. & Aerts, J. M. F. G. Is it Fabry disease? *Genet. Med.* **18,** 1181–1185 (2016).

58. Brouns, R. *et al.* Belgian Fabry Study. *Stroke* **41,** (2010).

59. Ferreira, S. *et al.* The alpha-galactosidase A p.Arg118Cys variant does not cause a Fabry disease phenotype: Data from individual patients and family studies. *Mol. Genet. Metab.* **114,** 248–258 (2015).

60. Mayes, J. S., Scheerer, J. B., Sifers, R. N. & Donaldson, M. L. Differential assay for lysosomal alpha-galactosidases in human tissues and its application to Fabry's disease. *Clin. Chim. Acta* **112,** 247–251 (1981).

61. Linthorst, G. E., Vedder, A. C., Aerts, J. M. F. G. & Hollak, C. E. M. Screening for Fabry disease using whole blood spots fails to identify one-third of female carriers. *Clin. Chim. Acta* **353,** 201–203 (2005).

62. Desnick, R. J. Prenatal diagnosis of Fabry disease. *Prenat. Diagn.* **27,** 693–694 (2007).

63. Spada, M. *et al.* Metabolic progression to clinical phenotype in classic Fabry disease. *Ital. J. Pediatr.* **43,** 1 (2017).

64. Barton, N. W. *et al.* Replacement Therapy for Inherited Enzyme Deficiency — Macrophage-Targeted Glucocerebrosidase for Gaucher's Disease. *N. Engl. J. Med.* **324,** 1464–1470 (1991).

65. Ries, M. Enzyme replacement therapy and beyond—in memoriam Roscoe O. Brady, M.D. (1923–2016). *J. Inherit. Metab. Dis.* **40,** 343–356 (2017).

66. Germain, D. P. *et al.* Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. *J. Med. Genet.* **52,** 353–8 (2015).

67. Pisani, A. *et al.* Effects of switching from agalsidase Beta to agalsidase alfa in 10 patients with anderson-fabry disease. *JIMD Rep.* **9,** 41–8 (2013).

68. Yam, G. H.-F., Zuber, C. & Roth, J. A synthetic chaperone corrects the trafficking defect and disease phenotype in a protein misfolding disorder. *FASEB J.* **19,** 12–8 (2005).

69. Hughes, D. A. *et al.* Oral pharmacological chaperone migalastat compared with enzyme replacement therapy in Fabry disease: 18-month results from the randomised phase III ATTRACT study. *J. Med. Genet.* **54,** 288–296 (2017).

70. Wang, Y., Caggana, M., Sango-Jordan, M., Sun, M. & Druschel, C. M. Long-term follow-up of children with confirmed newborn screening disorders using record linkage. *Genet. Med.* **13,** 881–886 (2011).

71. MacDermot, K. D., Holmes, A. & Miners, A. H. Anderson-Fabry disease: clinical manifestations and impact of disease in a cohort of 60 obligate carrier females. *J. Med. Genet.* **38,** 769–775 (2001).

72. Hoffmann, B. *et al.* Effects of enzyme replacement therapy on pain and health related quality of life in patients with Fabry disease: data from FOS (Fabry Outcome Survey). *J Med Genet* **42,** 247–252 (2005).

73. Gold, K. F. *et al.* Quality of life of patients with Fabry disease. *Qual. Life Res.* **11,** 317–327 (2002).

74. Street, N. J., Yi, M. S., Bailey, L. A. & Hopkin, R. J. Comparison of health-related quality of life between heterozygous women with Fabry disease, a healthy control population, and patients with other chronic disease. *Genet. Med.* **8,** 346–353 (2006).

75. von der Lippe, C., Frich, J. C., Harris, A. & Solbrække, K. N. Experiences of Being Heterozygous for Fabry Disease: a Qualitative Study. *J. Genet. Couns.* **25,** 1085–1092 (2016).

76. Gibas, A. L., Klatt, R., Johnson, J., Clarke, J. T. R. & Katz, J. Disease Rarity, Carrier Status, and Gender: A Triple Disadvantage for Women with Fabry Disease. *J. Genet. Couns.* **17,** 528–537 (2008).

77. Ferrari, A. J. *et al.* Global variation in the prevalence and incidence of major depressive disorder: a systematic review of the epidemiological literature. *Psychol. Med.* **43,** 471–481 (2013).

78. Guthrie, R. Blood Screening for Phenylketonuria. *JAMA* **178,** 863 (1961).

79. Guthrie, R. & Susi, A. A Simple Phenylalanine Method for Detecting Phenylketonuria in Large Populations of Newborn Infants. *Pediatrics* **32**, 318-343 (1963).

80. Garrick, M. D., Dembure, P. & Guthrie, R. Sickle-Cell Anemia and Other Hemoglobinopathies. *N. Engl. J. Med.* **288,** 1265–1268 (1973).

81. Dussault, J. H., Parlow, A., Letarte, J., Guyda, H. & Laberge, C. TSH measurements from blood spots on filter paper: A confirmatory screening test for neonatal hypothyroidism. *J. Pediatr.* **89,** 550–552 (1976).

82. Gregg, R. G. *et al.* Application of DNA analysis in a population-screening program for neonatal diagnosis of cystic fibrosis (CF): comparison of screening protocols. *Am. J. Hum. Genet.* **52,** 616–26 (1993).

83. Heard, G. S., Secor McVoy, J. R. & Wolf, B. A screening method for biotinidase deficiency in newborns. *Clin. Chem.* **30,** (1984).

84. Millington, D. S., Kodo, N., Norwood, D. L. & Roe, C. R. Tandem mass spectrometry: a new method for acylcarnitine profiling with potential for neonatal screening for inborn errors of metabolism. *J. Inherit. Metab. Dis.* **13,** 321–4 (1990).

85. Zytkovicz, T. H. *et al.* Tandem Mass Spectrometric Analysis for Amino, Organic, and Fatty Acid Disorders in Newborn Dried Blood Spots. *Clin. Chem.* **47,** (2001).

86. De Jesús, V. R., Mei, J. V, Cordovado, S. K. & Cuthbert, C. D. The Newborn Screening Quality Assurance Program at the Centers for Disease Control and Prevention: Thirty-five Year Experience Assuring Newborn Screening Laboratory Quality. *Int. J. neonatal Screen.* **1,** 13–26 (2015).

87. Wilson, J. M. G., Jungner, G. & Organization, W. H. Principles and practice of screening for disease / J. M. G. Wilson, G. Jungner. *Public Health Pap.* (1968).

88. Wilcken, B. Ethical issues in newborn screening and the impact of new technologies. *Eur. J. Pediatr.* **162,** S62–S66 (2003).

89. Watson, M. S., Mann, M. Y., Lloyd-Puryear, M. A., Rinaldo, P. & Howell, R. R. Newborn Screening: Toward a Uniform Screening Panel and System—Executive Summary. *Pediatrics* **117,** (2006).

90. U.S Department of Health and Human Services, Health Resources and Services Administration, Advisory Committee on Heritable Disorders in Newborns and Children. Summary of Nominated Conditions to the Recommended Uniform Screening Panel (RUSP). (2016).

91. Ross, L. F. & Waggoner, D. J. Parents: Critical Stakeholders in Expanding Newborn Screening. *J. Pediatr.* **161,** 385–389 (2012).

92. Norton, S. Connecticut becomes second state to implement ALD screening in newborns. *New Haven Register* (2016). Available at: http://www.nhregister.com/health/20160824/connecticut-becomes-second-state-to-implement-ald-screening-in-newborns. (Accessed: 23rd April 2017)

93. Therrell, B. L. & Adams, J. Newborn screening in North America. *J. Inherit. Metab. Dis.* **30,** 447–465 (2007).

94. Freedenberg, D. *et al.* SIMD Position Statement: Identifying abnormal newborn screens requiring immediate notification of the health care provider. (2014).

95. Lysosomal Storage Disorders Collaborative. *Newborn Screening Translational Research Network* Available at: https://www.nbstrn.org/supported-projects/lysosomal-storage-disorders-collaborative. (Accessed: 8th April 2017)

96. Mayo Medical Laboratories. Advancing a New Standard of Care for Newborn Screening - Insights. (2016). Available at: https://news.mayomedicallaboratories.com/2016/12/12/advancing-a-new-standard-of-care-for-newborn-screening/. (Accessed: 15th May 2017)

97. Duffey, T. A. *et al.* A tandem mass spectrometry triplex assay for the detection of Fabry, Pompe, and mucopolysaccharidosis-I (Hurler). *Clin. Chem.* **56,** 1854–61 (2010).

98. Elliott, S. *et al.* Dataset and standard operating procedure for newborn screening of six lysosomal storage diseases: By tandem mass spectrometry. *Data Br.* **8,** 915–24 (2016).

99. Hopkins, P. V. *et al.* Lysosomal Storage Disorder Screening Implementation: Findings from the First Six Months of Full Population Pilot Testing in Missouri. *J. Pediatr.* **166,** 172–177 (2015).

100. Burton, B. K. *et al.* Newborn screening for lysosomal disorders in Illinois. *Mol. Genet. Metab.* **117,** S31–S32 (2016).

101. Wasserstein, M. *et al.* The New York pilot newborn screen for lysosomal diseases: 40 month data. *Mol. Genet. Metab.* **120,** S138 (2017).

102. Spada, M. *et al.* High incidence of later-onset fabry disease revealed by newborn screening. *Am. J. Hum. Genet.* **79,** 31–40 (2006).

103. Hwu, W.-L. *et al.* Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). *Hum. Mutat.* **30,** 1397–405 (2009).

104. Wittmann, J. *et al.* Newborn screening for lysosomal storage disorders in hungary. *JIMD Rep.* **6,** 117–25 (2012).

105. Navarrete-Martínez, J. I. *et al.* Newborn screening for six lysosomal storage disorders in a cohort of Mexican patients: Three-year findings from a screening program in a closed Mexican health system. *Mol. Genet. Metab.* (2017). doi:10.1016/j.ymgme.2017.03.001

106. Gelb, M. H. *et al.* Newborn screening for lysosomal storage diseases. *Clin. Chem.* **61,** 335–46 (2015).

107. Schielen, P., Kemper, E. & Gelb, M. Newborn Screening for Lysosomal Storage Diseases: A Concise Review of the Literature on Screening Methods, Therapeutic Possibilities and Regional Programs. *Int. J. Neonatal Screen.* **3,** 6 (2017).

108. Chamoles, N. ., Blanco, M. & Gaggioli, D. Fabry disease: enzymatic diagnosis in dried blood spots on filter paper. *Clinica Chimica Acta* **308,** 195–196 (2001).

109. Sista, R. S. *et al.* Multiplex Newborn Screening for Pompe, Fabry, Hunter, Gaucher, and Hurler Diseases Using a Digital Microfluidic Platform. *Clin. Chim. Acta.* 12–18 (2013). doi:10.1016/j.cca.2013.05.001

110. Murphy, K. Newborn Screening and Follow-Up Program; Addition of Lysosomal Storage Disorders to the Mandatory and Follow-Up Screening Panels. *PA Bulletin* (2017). Available at: http://www.pabulletin.com/secure/data/vol47/47-3/117.html.

111. Atherton, A. M. *et al.* The first two years of full population pilot newborn screening for lysosomal disorders: The Missouri experience. *Mol. Genet. Metab.* **114,** S15 (2015).

112. Atherton, A. M. *et al.* Newborn screening for Fabry disease: Is the A143T allele a pathogenic mutation or a pseudodeficiency allele? *Mol. Genet. Metab.* **114,** S14–S15 (2015).

113. Rogers, S. Missouri's Experience Implementing Lysosomal Storage Disorders Screening and Follow-up for Pompe, Gaucher, Fabry and MPS-I and Krabbe Disorders. in (2016).

114. Lenders, M. *et al.* Alpha-Galactosidase A p.A143T, a non-Fabry disease-causing variant. *Orphanet J. Rare Dis.* **11,** 54 (2016).

115. Marcellus, S. A., Holida, M. D. & Bernat, J. A. Detection of three families with GLA p.A143T mutation and low ?-galactosidase levels by newborn screening for Fabry disease. *Mol. Genet. Metab.* **120,** S91 (2017).

116. Widera, S., Corkery, J. & Charrow, J. Novel mutations for late onset Fabry disease are being identified from newborn screening in the state of Illinois. *Mol. Genet. Metab.* **120,** S140 (2017).

117. Ikawa, M., Inoue, N., Benham, A. M. & Okabe, M. Fertilization: a sperm's journey to and interaction with the oocyte. *J. Clin. Invest.* **120,** 984–94 (2010).

118. Waggoner, D. & Tan, C. Expanding Newborn Screening for Lysosomal Disorders: OpportunitiesandChallenges. *Dev. Disabil. Res. Rev.* **17,** 9–14 (2011).

119. Vockley, C. W. & Atherton, A. M. Ethical Considerations When Including Lysosomal Storage Disorders in Newborn Screening Programs. *Curr. Genet. Med. Rep.* **3,** 177–190 (2015).

120. Tarini, B. A. & Goldenberg, A. J. Ethical issues with newborn screening in the genomics era. *Annu. Rev. Genomics Hum. Genet.* **13,** 381–93 (2012).

121. Lipstein, E. *et al.* Parents' Decision-Making in Newborn Screening: Opinions, Choices, and Information Needs. *Pediatrics* **126,** 696–704 (2010).

122. Wood, M. F. *et al.* Parental attitudes toward newborn screening for Duchenne/Becker muscular dystrophy and spinal muscular atrophy. *Muscle Nerve* **49,** 822–8 (2014).

123. Eng, C. M. *et al.* Safety and Efficacy of Recombinant Human α-Galactosidase A Replacement Therapy in Fabry's Disease. *N. Engl. J. Med.* **345,** 9–16 (2001).

124. Spada, M. *et al.* High incidence of later-onset fabry disease revealed by newborn screening. *Am. J. Hum. Genet.* **79,** 31–40 (2006).

125. Laney, D. A. & Fernhoff, P. M. Diagnosis of Fabry disease via analysis of family history. *J. Genet. Couns.* **17,** 79–83 (2008).

126. Timmermans, S. & Buchbinder, M. Patients-in-Waiting. *J. Health Soc. Behav.* **51,** 408–423 (2010).

127. Braun, V. & Clarke, V. Using thematic analysis in psychology. *Qual. Res. Psychol.* **3,** 77–101 (2006).

128. Greenberg, M. & Smith, R. A. Support Seeking or Familial Obligation: An Investigation of Motives for Disclosing Genetic Test Results. *Health Commun.* **31,** 668–678 (2016).

129. Peterson, S. K. The Role of the Family in Genetic Testing: Theoretical Perspectives, Current Knowledge, and Future Directions. *Heal. Educ. Behav.* **32,** 627–639 (2005).

130. Van Oostrom, I. *et al.* Family system characteristics and psychological adjustment to cancer susceptibility genetic testing: a prospective study. *Clin. Genet.* **71,** 35–42 (2007).

131. Rosland, A.-M., Heisler, M. & Piette, J. D. The impact of family behaviors and communication patterns on chronic illness outcomes: a systematic review. *J. Behav. Med.* **35,** 221–239 (2012).

132. Årestedt, L., Benzein, E. & Persson, C. Families Living With Chronic Illness. *J. Fam. Nurs.* **21,** 206–231 (2015).

133. Lubinsky, M. S. Bearing Bad News: Dealing with the Mimics of Denial. *J. Genet. Couns.* **3,** (1994).

134. Rolland, J. S. & Williams, J. K. Toward a Biopsychosocial Model for 21st-Century Genetics. *Fam. Process* **44,** 3–24 (2005).

135. Forrest, K. *et al.* To tell or not to tell: barriers and facilitators in family communication about genetic risk. *Clin. Genet.* **64,** 317–26 (2003).

136. Gilbar, R. Communicating genetic information in the family: the familial relationship as the forgotten factor. *J. Med. Ethics* **33,** 390–3 (2007).

137. Bylund, C. L., Galvin, K. M., Dunet, D. O. & Reyes, M. Using the Extended Health Belief Model to understand siblings' perceptions of risk for hereditary hemochromatosis. *Patient Educ. Couns.* **82,** 36–41 (2011).

138. Grob, R. Is my sick child healthy? Is my healthy child sick?: Changing parental experiences of cystic fibrosis in the age of expanded newborn screening. *Soc. Sci. Med.* **67,** 1056–1064 (2008).

139. Grob, R. Parenting in the genomic age: the ‘cursed blessing’ of newborn screening. *New Genet. Soc.* **25,** 159–170 (2006).

140. Kwon, J. M. & Steiner, R. D. "I’m fine; I’m just waiting for my disease": the new and growing class of presymptomatic patients. *Neurology* **77,** 522–3 (2011).

141. Asif, I. M. *et al.* Stages of psychological impact after diagnosis with serious or potentially lethal cardiac disease in young competitive athletes: A new model. *J. Electrocardiol.* **48,** 298–310 (2015).

142. Pichini, A. *et al.* Experience with genetic counseling: the adolescent perspective. *J. Genet. Couns.* **25,** 583–595 (2016).

143. Hoff, T., Hoyt, A., Therrell, B. & Ayoob, M. Exploring barriers to long-term follow-up in newborn screening programs. *Genet. Med.* **8,** 563–570 (2006).

144. Wang, R. Y., Bodamer, O. A., Watson, M. S. & Wilcox, W. R. Lysosomal storage diseases: Diagnostic confirmation and management of presymptomatic individuals. *Genet. Med.* **13,** 457–484 (2011).

145. Hinton, C. F. *et al.* What questions should newborn screening long-term follow-up be able to answer? A statement of the US Secretary for Health and Human Services’ Advisory Committee on Heritable Disorders in Newborns and Children. *Genet. Med.* **13,** 861–865 (2011).

146. Kemper, A. R. *et al.* Long-term follow-up after diagnosis resulting from newborn screening: Statement of the US Secretary of Health and Human Services’ Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children. *Genet. Med.* **10,** 259–261 (2008).

147. Newborn Screening Translational Research Network. Longitudinal Pediatric Data Resource (LPDR). *Newborn Screening Translational Research Network* Available at: https://www.nbstrn.org/research-tools/longitudinal-pediatric-data-resource. (Accessed: 20th May 2017)

148. Berry, S. A. *et al.* Inborn Errors of Metabolism Collaborative: large-scale collection of data on long-term follow-up for newborn-screened conditions. *Genet. Med.* **18,** 1276–1281 (2016).

149. Hinton, C. F. *et al.* Developing a public health-tracking system for follow-up of newborn screening metabolic conditions: a four-state pilot project structure and initial findings. *Genet. Med.* **16,** 484–90 (2014).

150. Sahai, I., Eaton, R. B., Hale, J. E., Mulcahy, E. A. & Comeau, A. M. Long-term follow-up to ensure quality care of individuals diagnosed with newborn screening conditions: Early experience in New England. *Genet. Med.* **12,** S220–S227 (2010).

151. Ulph, F., Cullinan, T., Qureshi, N. & Kai, J. Informing Children of Their Newborn Screening Carrier Result for Sickle Cell or Cystic Fibrosis: Qualitative Study of Parents' Intentions, Views and Support Needs. *J. Genet. Couns.* **23,** 409–420 (2014).

152. Hayeems, R. Z. *et al.* Primary care role in expanded newborn screening: After the heel prick test. *Can. Fam. Physician* **59,** 861–8 (2013).

153. Finan, C., Nasr, S. Z., Rothwell, E. & Tarini, B. A. Primary Care Providers' Experiences Notifying Parents of Cystic Fibrosis Newborn Screening Results. *Clin. Pediatr. (Phila).* **54,** 67–75 (2015).

154. Bellcross, C. A., Harmond, L., Floyd-Browning, P. & Singh, R. Infrastructure and Educational Needs of Newborn Screening Short-Term Follow-Up Programs within the Southeast Regional Newborn Screening & Genetics Collaborative: A Pilot Survey. *Healthc. (Basel, Switzerland)* **3,** 964–72 (2015).

155. Stark, A., Lang, C. & Ross, L. A Pilot Study to Evaluate Knowledge and Attitudes of Illinois Pediatricians toward Newborn Screening for Sickle Cell Disease and Cystic Fibrosis. *Am. J. Perinatol.* **28,** 169–176 (2011).

156. Society for Inherited Metabolic Disorders. Available at: http://www.simd.org/. (Accessed: 23rd May 2017)