Open Access

OBM Genetics

Review

Overview of Newborn Screening of Lysosomal Storage Diseases for Pediatric Care Providers

Ashley Lahr [1,*], Nadene Henderson [1,*], Lee Williams [2], Georgianne Arnold [1,*], Damara Ortiz [1]

1. UPMC Children's Hospital of Pittsburgh, 4401 Penn Avenue, Pittsburgh, PA 15224, USA; E-Mails: ashley.lahr@chp.edu; Nadene.Henderson@chp.edu; georgianne.arnold4@chp.edu; damara.ortiz@chp.edu
2. Children's Hospital of Philadelphia, 3401 Civic Center Blvd, Philadelphia, PA 19104, USA; E-Mail: williamk33@chop.edu

* **Correspondences:** Ashley Lahr, Nadene Henderson and Georgianne Arnold; E-Mails: ashley.lahr@chp.edu; Nadene.Henderson@chp.edu; georgianne.arnold4@chp.edu

Academic Editor: Milan Macek Jr.

Special Issue: Newborn Screening and Inherited Metabolic Disorders

OBM Genetics
2023, volume 7, issue 3
doi:10.21926/obm.genet.2303194

Received: June 14, 2023
Accepted: September 17, 2023
Published: September 25, 2023

Abstract

Lysosomal storage disorders (LSD) are caused by enzymatic failure to degrade specific cellular byproducts of metabolism within the lysosome. They have a wide range of presentations involving multiple body systems and can manifest from infancy through adulthood. As treatments have become available for many of these disorders, newborn screening has been adapted for early identification and pre-symptomatic treatment. This article will review some of the LSD that are now being added to newborn screening panels, including globoid cell leukodystrophy (Krabbe), Gaucher disease, Fabry disease, Mucopolysaccharidosis Type I (Hurler; MPSI), Mucopolysaccharidosis Type II (Hunter; MPSII), Acid Sphingomyelinase deficiency (ASMD), and Pompe disease.

Keywords
Lysosomal storage disease; newborn screening; Pompe disease; mucopolysaccharidosis; Krabbe; Gaucher; acid sphingomyelinase deficiency

1. Introduction

Lysosomal storage disorders (LSD) are a category of single-gene disorders classified by accumulation of cellular byproducts in the lysosomes of the body's cells. Lysosomes are organelles that serve as the cell's recycling center-waste or excess byproducts of cellular metabolism are shuttled to the lysosomes for breakdown and repurposing. The disease state is caused by the deficiency or absence of lysosomal enzymes used to break down these byproducts. Deficiency of one or more of these enzymes leads to substrate accumulation inside the lysosome, which can lead to cellular dysfunction and cell death. Different disorders have different modes of inheritance, and many have wide spectrums of severity from severe early-onset to a milder later-onset course. The correlation between a person's genetic variants (genotype) and their physical presentation of disease (phenotype) can occasionally be predictable, however, it has also often been observed that two individuals with the same genetic changes in the same family may have different disease trajectories [1].

In the United States, several of these disorders are screened for in the newborn period with the intention that early identification of these conditions will result in better outcomes for affected individuals. In recent decades there have been multiple advancements in therapies for LSD, with some conditions even having multiple therapeutic options. Sibling control studies have provided valuable evidence for improved outcomes if treatment is initiated early. In 2010 a comparison of two siblings with Mucopolysaccharidosis type VI (Maroteaux-Lamy; MPS VI) at the age of 3.6 years showed that the sibling who had been on ERT from birth had not developed scoliosis, had minimal joint involvement, normal facial appearance, and normal cardiac valves [2]. Similarly, longitudinal studies of patients treated with ERT provided evidence that early initiation and long-term treatment resulted in better clinical outcomes [3]. This has spurred interest in enhancing newborn screening by including these disorders.

1.1 History of Newborn Screening

Newborn screening (NBS) refers to the testing that a newborn infant undergoes between the first 24-72 hours of life and its subsequent follow up, confirmatory testing, education, and support. It is a public health program and results in intervention for all newborns in the United States, where the stated goal is to initiate treatment early for life-threatening health conditions in order to decrease the morbidity [4]. NBS was made possible by the pioneering work of Robert Guthrie in the 1960s. In his work as a microbiologist, Guthrie developed a bacterial inhibition assay that was able to detect phenylalanine. This allowed for early detection of Phenylketonuria (PKU), which is integral to the management of these patients. The utility of the screen was quickly realized, and many newborn screening programs commenced. In the United States, the National Institute of Child Health and Human Development instituted the Recommended Uniform Screening Panel (RUSP) to

standardize the newborn screen across the country, however these are voluntary guidelines, and it is the responsibility of each state to determine which conditions are included on its newborn screening panel.

Numerous states have instituted pilot or screening programs for a variety of LSD including globoid cell leukodystrophy (Krabbe), Gaucher, Fabry, Mucopolysaccharidosis Type I (Hurler; MPSI), Mucopolysaccharidosis Type II (Hunter; MPSII), Acid Sphingomyelinase deficiency (ASMD), and Pompe disease (Glycogen Storage Disorder II). The addition of LSD to the newborn screen was made possible by advancement in technology and availability of treatment. Screening for various conditions, including LSD, involves the collection of a blood sample on a Guthrie or dried blood spot card. The sample is then analyzed using high performance liquid chromatography, digital microfluidic platform and/or tandem mass spectrometry [5]. As a first-tier test, enzyme activity is measured in the dried blood sample. In some states, first tier testing for Krabbe also includes a psychosine level. Second tier testing is variable by state, but may include repeat enzyme analysis, biomarkers, and/or molecular testing. Criteria for referral to a metabolic specialist based on first (and if available second) tier screening is determined by individual states.

2. Methodologies

NBS requires a method that is highly sensitive and specific. The process often operates on a multiple-tier system, with rapid and sensitive first-tier testing, often followed up with more specific second-tier testing, and ultimately diagnostic testing. For LSD NBS, first-tier testing typically includes assaying enzyme activity, which can be done rapidly on dried blood spots. Second-tier tests such as DNA sequencing or measurement of biomarkers differ between disorders and programs. Various methods have been published to measure enzyme activity; initially fluorometric assays were described, now being replaced with tandem mass spectrometry, high-performance liquid chromatography, and digital microfluidic assays [6]. Enzyme activity can appear low the presence of disease, but also due to under-saturation of the dried blood spot, environmental factors, pseudodeficiency, or carrier status. Thus, second tier testing can help to better clarify the infant's status. The definition of a pseudodeficiency variant is that a change has been identified in the DNA that results in low enzyme activity within a laboratory environment when one is using artificial substrates but does not interfere with enzyme activity in the natural environment within the cells. Where genotype-phenotype relationships are clear, DNA sequencing can help to identify mild or severe (or early vs late onset) alleles, or carrier status and help guide management decisions. Unfortunately, in some cases genotype-phenotype relationships are not well-defined or DNA sequencing reveals variants of uncertain significance. A variant of uncertain significance is defined as a genetic change that has not been observed, as of yet, in an affected individual and would need more investigation to determine its pathogenicity. The difficulty of clinical diagnosis based on molecular findings is highlighted by the results of pilot studies performed in New York. Over a course of 4-years 65,605 infants were screened for 3 LSD. Of those infants 69 screened positive, 23 were true positives (all late onset phenotype), 8 were carriers, 31 were unaffected, 6 were categorized as undetermined disease status, and one individual was lost to follow up despite molecular testing being part of the NBS results provided [7]. Studying biomarkers can also be helpful for diagnosis. These disease markers may not be amenable to rapid first-tier testing but can be useful in following-up an abnormal newborn screen. For example, glucose tetrasaccharide can be useful to differentiate

Pompe Disease from pseudodeficiency, or glucosylceramide in Gaucher disease [8]. In some cases, this testing is done by the screening program as a part of the newborn screening protocol, but in other programs this more specific testing is done by the follow-up medical provider as a part of the diagnostic process.

3. LSD Conditions on NBS

A summary of the conditions to be discussed below is included in Table 1.

Table 1 Overview of Enzymes, Biomarkers, and Available Treatments.

Disorder	Enzyme Deficiency	Secondary Tests	Approved Disease-Specific Treatments
Pompe Disease	Acid alpha-glucosidase	CPK, Urine Hex4	ERT
MPSI	Alpha-L Iduronidase	Urine/Plasma GAG	ERT ± HSCT
MPSII	iduronate 2-sulfatase	Urine/Plasma GAG	ERT
Krabbe Disease	Galactocerebrosidase	Psychosine	HSCT
Niemann-Pick A/B	Acid sphingomyelinase	Lyso-SM	ERT
Fabry Disease	alpha-galactosidase	Lyso-GL3	ERT, Protein chaperone
Gaucher Disease	beta-glucocerebrosidase	GL1, Lyso-GL1, ACE/TRAP/CHITO,	ERT, SRT

3.1 Pompe Disease

Pompe disease is an autosomal recessive condition due to a deficiency of the enzyme acid alpha-glucosidase (GAA), necessary for the breakdown of glycogen within the lysosomes. Thus, it is both a lysosomal disorder and a glycogen storage disease. The disorder is caused by pathogenic changes in the *GAA* gene. The incidence of this condition is estimated to be 1 in 40,000 live births [9]. There is a higher incidence of the disease in the African American population (1/14,000) as well as Northern Europeans of Dutch origin and Southeast Asian [10]. Like most LSD, there is a range of severity from infantile onset to milder juvenile and adult onset. The diagnoses are distinguished by age of onset, severity of symptoms, organs impacted, and rate of progression [11]. Diagnosis is made by enzyme activity analysis on the Guthrie card, with second tier or diagnostic testing that may include biomarkers and molecular testing.

Children with the severe form typically present with signs and symptoms within the first year of life. Typical findings include hypertrophic cardiomyopathy, hypotonia and weakness, leading to heart and respiratory failure without treatment. Dysostosis multiplex typical of other LSD is not a finding. Hypertrophic cardiomyopathy can be a presenting feature of earlier onset forms, alongside the progressive muscle weakness. The EKG demonstrates a short PR interval and very tall QRS complexes [11]. Later onset forms more commonly manifest as weakness and myopathy. Currently, the U.S. Food and Drug Administration (FDA) has approved treatments for all types of Pompe with biweekly infusions of alglucosidase alfa enzyme replacement therapy or, for late-onset Pompe patients over the age of 1 year, with biweekly infusions of avalglucosidase alfa-ngpt. Treatment guidelines have been published [11], but the age at which enzyme replacement therapy should be initiated in later onset cases is not yet clear. Gene therapy trials have also begun.

The NBS process can identify pseudodeficiency variants and variants of uncertain significance. Thus, in many cases there can initially be some degree of diagnostic uncertainty regarding expected age of onset or even whether the patient is ever likely to manifest symptoms. A referral to a genetic or metabolic specialist can be helpful but, in some cases, diagnostic uncertainty can persist [12].

3.2 Mucopolysaccharidosis Type I

Mucopolysaccharidosis type I (MPSI, historically Hurler Syndrome [MPSI-H]; Hurler-Scheie Syndrome [MPSI H/S]; and Scheie Syndrome [MPSI-S]) is an autosomal recessive lysosomal storage disorder with an estimated incidence of 1/100,000 live births [13]. Prevalence of MPSI has been found to be highest in the United Kingdom, Netherlands, Germany, and Australia [14].

MPSI is caused by pathogenic changes in the *IDUA* gene leading to a deficiency of the lysosomal enzyme alpha-L-iduronidase. When this enzyme is not functioning properly, glycosaminoglycans (GAGs) accumulate in the body. This accumulation of GAGs leads to a variety of health concerns associated with MPSI. The most severe form of the disorder MPSI (MPSI-H) is categorized by early onset of neurological disease typically appearing around 12-24 months of age in the form of developmental delay [13]. Early development may appear appropriate; however, skill development will usually cease, and neurological decline will commence shortly after [13]. Other hallmarks of the disease include corneal clouding, dysostosis multiplex, coarse facial features, hepatosplenomegaly, hearing loss, and recurrent upper airway infection [15]. Attenuated phenotypes (MPSI-H/S, MPSI-S) are categorized by a later age of onset and absent or mild intellectual disability.

Management guidelines were published in 2009 which recommend patients with MPSI establish care with a multidisciplinary team, initiate enzyme replacement therapy (ERT), and in severe cases undergo hematopoietic stem cell transplant (HSCT) [13]. Treatment with ERT (laronidase) and HSCT early in disease course has been shown to improve clinical outcomes in patients with MPSI (MPSI-H) [13, 16]. Therefore, in the event of a true positive a referral should be made to centers that can coordinate these treatments.

While there has been considerable support for the addition of MPSI to the newborn screen, testing has not come without challenges [17]. Due to the sensitivity of the screen, carriers, variants of uncertain significance, and pseudodeficiencies are often identified. Diagnostic uncertainty can lead to undue psychological burden on families [18]. Referral to a provider familiar with MPSI for screen positive infants can help to mitigate stress and enhance diagnostic certainty [19].

3.3 Mucopolysaccharidosis Type II

Mucopolysaccharidosis type II (MPSII or Hunter syndrome), is an X-linked lysosomal storage disorder caused by deficiency of the enzyme iduronate 2-sulfatase. Like the other MPS disorders, deficiency of this enzyme results in the buildup of GAGs in the lysosomes, which can be detected at higher levels in the blood and urine of affected patients. The disorder is caused by either de novo or inherited hemizygous pathogenic variants in the *IDS* gene in males. Rarely, females may exhibit symptoms of the disease, and a diagnosis of a female is made generally when suggestive clinical features are present with a heterozygous pathogenic variant in *IDS*. The incidence of MPSII is estimated to be between 1/100,000-170,000 live births [20].

Children with this condition typically present with signs and symptoms between 18 months and 4 years of life. There is a significant clinical overlap in symptoms between the MPS disorders. MPSII

most commonly presents with short stature and bone changes including dysostosis multiplex, as well as umbilical hernia, coarse facies, joint contractures, hepatosplenomegaly, and frequent ear and respiratory infections. Corneal clouding, seen in many MPS disorders is not seen in MPSII. In laboratory readings of plasma and urine GAGs there will be significant elevations of dermatan sulfate and heparan sulfate. Because of the significant clinical overlap between MPS disorders, suspicion of one of the conditions should prompt a full work up for any one of the MPS disorders including multigene testing when NBS is not involved. Currently, the FDA-approved treatment in the United States for this condition is weekly enzyme replacement therapy with idursulfase. Though outcomes have not been examined in the clinical trial space, hematopoietic stem cell transplant (HSCT) can be another option for treatment when the diagnosis is made early in life.

With the addition of MPSII to the RUSP in 2022, more states are implementing newborn screening for the condition. In those states already screening for potentially affected infants, false positives can be detected due to genetic changes causing pseudodeficiency of the enzyme. Those pseudodeficient infants identified had low enzyme with no detectable accumulation of GAGs and absent phenotypic findings [21].

3.4 Krabbe Disease

Krabbe disease (globoid cell leukodystrophy), is a rare autosomal recessive neurodegenerative lysosomal storage disorder caused by pathogenic changes in the *GALC* gene. The incidence of Krabbe varies widely across the world but is estimated to be 1/100,000 live births and about 1/250,000 births in the United States [22]. There are known populations with higher incidence of this condition including the Druze population of Israel [23]. The severe end of the disease spectrum is an infantile-onset form characterized by onset of spasticity, feeding difficulties, irritability, staring episodes, peripheral neuropathy, developmental delay, and regression of milestones before one year of life with neurological deterioration and death by 24 months (about 2 years) on average. Later-onset Krabbe disease (LOKD) presents any time after a year of life and has a more variable and unpredictable prognosis. Low or absent activity of the galactocerebrosidase (GALC) enzyme causing buildup of psychosine in the lysosomes underlies all forms of the disease. This accumulation of toxic psychosine in the lysosomes causes the neurologic deterioration and dysfunction characteristic of the disease.

Currently, there is no FDA-approved treatment for Krabbe disease. For potentially affected infants urgent counseling and evaluation at a metabolic center with experience in HSCT is critical to improving clinical outcomes. When a true positive is identified, it is vital that an immediate referral and potential admission is made to a center capable of arranging for rapid HSCT to stabilize or reduce the rate of neurologic deterioration. However, it is important to note that false positives on newborn screening for this condition are quite common with current screening technology and the prevalence of genetic changes that cause enzymatic pseudodeficiency. As with all uncertain or positive newborn screens, a genetics provider must be notified as soon as possible to accurately assess the risk of a true positive and coordinate counseling and initiate treatment for the family.

Adding NBS for Krabbe Disease has been controversial, largely due to concerns about the efficacy of HSCT for treatment and the high rate of diagnostic uncertainty. There is hope that adding psychosine as a second-tier test might improve the ability to differentiate affected vs unaffected infants [22].

3.5 Acid Sphingomyelinase Deficiency (ASMD)

Acid sphingomyelinase deficiency (ASMD; Niemann-Pick disease types A and B) is an autosomal recessive disorder caused by a deficiency of the lysosomal enzyme acid sphingomyelinase (AMS) due to pathogenic changes in the *SMPD1* gene. The estimated incidence of ASMD is 1/250,000 births, though it is far more common in some areas of Chile, where the carrier frequency is closer to 1/105.7 [24]. Deficiency of the enzyme leads to the accumulation of sphingomyelin and other lipids in various organs including the spleen, liver, and lungs. Diagnoses are made through enzymatic assays and molecular testing [25].

There is a wide spectrum of severity associated with this disease. Those with severe infantile onset were historically called Niemann-Pick disease type A (NPA), while the later-onset chronic patients were designated as having Niemann-Pick disease type B (NPB). Clinical signs and symptoms of NPA present in infancy and include massive hepatomegaly, developmental delay, failure to thrive, cherry-red macular spot, hypotonia and pulmonary involvement. Patient phenotypes with the later onset type (NPB) are characterized by variable age of onset and milder symptoms. Individuals typically present with hepatosplenomegaly in childhood to adulthood, with variable delayed growth and puberty, bone pain, low platelet count, osteopenia, and pulmonary dysfunction.

Clinical treatment guidelines are available which recommend a multidisciplinary team and ERT to address the different manifestations of the disease [26]. Olipudase alfa was FDA-approved for treatment of ASMD in 2022 and has been shown to be effective in reducing non-neurological symptoms of the disease. HSCT has also been recommended early in disease course to improve blood count and reduce liver and spleen volume. HSCT is not recommended for individuals already presenting with neurological disease [26, 27].

Newborn screening for ASMD has presented with similar challenges as screening for other lysosomal storage disorders. A New York pilot study consented 65,605 infants for participation in a broad panel including several other LSD [7]. Of those infants, 69 screened positive, and two of those were screen positive for ASMD. Molecular testing revealed homozygous variants. Both infants' disease status was indeterminate. Results such as these highlight the difficulty of interpreting low enzymes when variants of uncertain significance are identified [7]. The biomarker lyso-sphingomyelin (lyso-SM) may be helpful in the future to determine the clinical utility of these variants [28].

3.6 Fabry Disease

Fabry disease is a X-linked lysosomal storage disorder due to deficiency of the enzyme alpha galactosidase caused by pathogenic changes in the *GLA* gene. It has an incidence of about 1:40,000-1:117,000 births [29]. There is not a known ethnic predisposition; however, due to founder effects there are higher incidences noted in Nova Scotia, Canada, and West Virginia, USA [30]. There are two presentations of Fabry described in males, classical (<1% enzyme activity) and late-onset/non-classical (<30% enzyme activity) [31]. Deficiency of the enzyme leads to a buildup of globotriaosylceramide (GL3) in the body. This accumulation occurs in multiple body systems including renal, cardiovascular, nervous, and gastrointestinal. The disease has life-long effects. Individuals can present as early 2-2.5 years with pain crises and gastrointestinal issues at 1 year of age [30]. In adulthood, patients develop progressive renal failure as well as early strokes and other cardiovascular manifestations with an average life expectancy for untreated men reduced by about

20 years and in females 15 years [30]. Other signs and symptoms may include angiokeratomas, anhidrosis/hypohidrosis, visual disturbances, and hearing concerns. Males typically manifest the most severe problems at an earlier age; however, females can present with mild to severe symptoms comparable to their male counterparts [32]. Screening is performed by measuring enzyme activity on the Guthrie card. Molecular testing is recommended for infants identified with low enzyme [30]. Of importance, enzyme levels in females can be in the normal range thus molecular testing is especially beneficial for diagnosis.

Currently, enzyme replacement therapy (ERT) is approved by the U.S. FDA (agalsidase beta and pegunigalsidase alfa-iwxj) and Europe (agalsidase alfa, agalsidase beta, and pegunigalsidase alfa). The therapy has shown promise in stabilizing the symptoms of the disease but has less efficacy if started later in life [29]. Enzyme replacement has been shown to be effective in clearing GL3 in children, which indicates potential for better long-term outcomes [30]. Initiation guidelines have been proposed, but it is not yet known at what age intravenous enzyme replacement should begin in affected children [30]. Oral protein chaperone therapy (migalastat) is also available for affected adults with amenable *GLA* variants and residual enzyme activity. Gene therapy trials have also been initiated.

The first NBS pilot study for Fabry occurred in 2006 in Northern Italy. In this study they found that of the 12 infants that screened positive, 11 were diagnosed with the later onset form. Similar findings were noted in the New York pilot study and a study performed in Taiwan [7, 33]. Identification of presymptomatic individuals can be helpful for monitoring; however, it can also create stress for the caregivers of those patients [34]. Presentation of symptoms can be variable and hard to predict especially if molecular testing reveals variants of uncertain significance. Identification of an affected infant may unmask other affected family members who might benefit from therapy.

3.7 Gaucher Disease

Gaucher disease is inherited in an autosomal recessive manner and is due to the deficiency of beta-glucocerebrosidase, caused by pathogenic changes in the *GBA* gene. The estimated incidence of Gaucher disease is 0.39-5.80/100,000 [35], but the prevalence in the Ashkenazi Jewish population is higher with 1/450 being affected [36]. Deficiency of beta-glucocerebrosidase results in accumulation of the substrate glucocerebroside (GL1). This mainly occurs in the macrophages of the lysosomes (then called Gaucher cells) typically found in the bone marrow, spleen, liver, lungs, and lymph nodes [37]. The NBS measures GBA enzyme activity on the Guthrie card. Molecular testing of *GBA* is recommended as a second tier to confirm diagnosis [36].

Gaucher disease can be categorized into three types - 1, 2, and 3. Features common to all three types are hepatosplenomegaly, skeletal abnormalities, and cyotpenias [38]. Type 1 is the most common. Symptoms can present between infancy and late adulthood [37]. Other features may include bone crisis, interstitial lung disease, polyclonal gammopathy, cholestasis, secondary neurologic disease and increased metabolic markers. Types 2 and 3 are considered neuronopathic as they both present with progressive neurological disease. Type 2 Gaucher is typically fatal by 1-2 years of age due to rapid neurodegeneration. Type 3 can have variable neurological presentation. Symptoms in Type 3 may include impaired cognitive function, cerebellar ataxia, myoclonic epilepsy,

vitreous opacities, cardiac disease with specific genetic variants and horizontal ophthalmoplegia [36].

Current disease-specific therapies include intravenous ERT (imiglucerase, velalgucerase alfa, taliglucerase alfa) or oral substrate reduction therapy (SRT) (migulstat, eliglustat). Both types of therapies have been approved in the US for treatment of type 1 Gaucher. Both forms have been shown to improve non-neuronal symptoms of the disease including liver and spleen volumes and blood counts [38, 39]. ERT is recommended for children and adults presenting with symptoms of the disease and SRT is reserved for affected adults in the US [36]. Gene therapy trials have also been initiated.

Newborn screening for Gaucher disease like the other LSD has the potential to identify presymptomatic individuals who require annual monitoring and can be left with uncertainty about presentation [36]. This was highlighted in the results of the New York pilot study performed in 2019 in which 17 infants screened positive for Gaucher and 15/17 were diagnosed with a later-onset form [7]. Likewise, the newborn screen could identify infants with Type 2, which is currently not treatable due to the inability of therapies to cross the blood brain barrier and poor outcomes with HSCT.

4. Pediatric Care Providers' Role in Newborn Screening

Pediatricians and family physicians are often the first providers to deliver the results of the newborn screen to families [34]. It is important to note at the moment of disclosure that most parents have not heard of the conditions that their children have screened positive for [19]. Often parents are filled with anxiety, fear, and uncertainty about the results of the screen. Many families may turn to the internet to research the condition their child is screened positive for. This has the potential to exacerbate any negative emotions [34]. Providers may also have uncertainty about these rare disorders, which can add strain to this responsibility and the doctor/patient relationship.

A study in 2006 was conducted by Kemper et al in which they surveyed pediatricians and family physicians on their experiences with positive newborn screens. Participants noted that they did not feel prepared to discuss the results of the newborn screen and would prefer newborn screening sites to provide the initial work-up. However, most participants agreed that the pediatrician should be the provider to disclose the initial results [40]. Given these responses, pediatricians and family doctors may benefit from educational resources that would allow them to give accurate information to families (i.e. features of conditions and next steps after a positive screen). This has the potential to alleviate some stress the parents may be experiencing during this period.

5. The Future

Significant ethical concerns exist in NBS for LSD, particularly regarding ambiguous or indeterminate results, as well as the long-term efficacy of some treatments. Of particular concern is that for many disorders the majority of cases identified have later or adult onset [41], and for many we do not yet know at what age expensive and potentially risky treatments should be initiated. While a number of new LSD have been added to the RUSP over time, there are pressures to add others simply because a treatment exists, even before there is a full understanding of the natural history of screening and treatment outcomes. Over time it is likely that the screening process will improve in both sensitivity and specificity, and the number of ambiguous or indeterminate results will decrease. Significant research is needed to determine the natural history of screened and early-

treated LSD to develop appropriate evidence-based standards of care. The screening process will most certainly expand to more LSD disorders in time.

6. Conclusions

Newborn screening is a meaningful public health intervention that identifies many at-risk individuals in the newborn period and can have a significant impact on the course of disease for those truly affected. Currently, the most commonly screened for lysosomal storage disorders in the newborn period include Fabry disease, Gaucher disease, MPSI, MPSII, Krabbe disease, Pompe disease, and acid sphingomyelinase deficiency. Many infants identified earlier in life have been able to benefit from earlier access to interventions and therapies for genetic conditions.

However, a "positive" newborn screen prompting referral to a specialty genetics center does not always mean the child is affected by the genetic condition due to confounding variables such as pseudodeficiencies and decreased enzymatic activity in unaffected carriers. The psychological impact of an abnormal newborn screen on a family as they welcome a new baby into their home can be exceedingly difficult, especially for those families for whom results appear ambiguous. Many families with later-onset variants will experience the anxiety and frustration of regular examinations in an otherwise healthy child who may one day begin to exhibit symptoms of the disease, potentially into adulthood. Though newborn screening has provided many families with the benefits of early access to care and has decreased early morbidity and mortality for many, it is important to consider the families of infants who will be flagged on newborn screening without a clear diagnosis.

Inherent to the complex nature of results disclosure, confirmatory testing, and potentially lengthy periods of follow-up for at-risk newborn screens, communication between pediatricians and genetics providers is key to providing families with proper counseling and connection to resources. With time, better treatments and screening methods will emerge, and it is likely that more lysosomal storage disorders than those discussed above will become routinely screened for on this newborn test. It is important that pediatricians begin to have some familiarity with the diseases they may see on a flagged newborn screen and both genetics providers and primary care providers work together to ensure ongoing collaborations as the NBS grows in size and scope.

Author Contributions

Sections were divided up by author and all revisions throughout this process were managed by all authors.

Competing Interests

The authors have declared that no competing interests exist.

References

1. Alliance G, New York Mid Atlantic Consortium for Genetic and Newborn Screening Services. Understanding genetics: A New York, mid-Atlantic guide for patients and health professionals. Washington, DC: Genetic Alliance; 2009.

2. McGill JJ, Inwood AC, Coman DJ, Lipke ML, De Lore D, Swiedler SJ, et al. Enzyme replacement therapy for mucopolysaccharidosis VI from 8 weeks of age-a sibling control study. Clin Genet. 2010; 77: 492-498.
3. Wyatt K, Henley W, Anderson L, Anderson R, Nikolaou V, Stein K, et al. The effectiveness and cost-effectiveness of enzyme and substrate replacement therapies: A longitudinal cohort study of people with lysosomal storage disorders. Health Technol Assess. 2012; 16: 39.
4. Therrell BL, Padilla CD, Loeber JG, Kneisser I, Saadallah A, Borrajo GJ, et al. Current status of newborn screening worldwide: 2015. Semin Perinatol. 2015; 39: 171-187.
5. Wilcke0n B, Wiley V, Hammond J, Carpenter K. Screening newborns for inborn errors of metabolism by tandem mass spectrometry. N Engl J Med. 2003; 348: 2304-2312.
6. Schielen PC, Kemper EA, Gelb MH. Newborn screening for lysosomal storage diseases: A concise review of the literature on screening methods, therapeutic possibilities and regional programs. Int J Neonatal Screen. 2017; 3: 6.
7. Wasserstein MP, Caggana M, Bailey SM, Desnick RJ, Edelmann L, Estrella L, et al. The New York pilot newborn screening program for lysosomal storage diseases: Report of the first 65,000 infants. Genet Med. 2019; 21: 631-640.
8. Gelb MH, Scott CR, Turecek F. Newborn screening for lysosomal storage diseases. Clin Chem. 2015; 61: 335-346.
9. Haley SM, Fragala MA, Skrinar AM. Pompe disease and physical disability. Dev Med Child Neurol. 2003; 45: 618-623.
10. Dasouki M, Jawdat O, Almadhoun O, Pasnoor M, McVey AL, Abuzinadah A, et al. Pompe disease: Literature review and case series. Neurol Clin. 2014; 32: 751-776.
11. Kishnani PS, Steiner RD, Bali D, Berger K, Byrne BJ, Case LE, et al. Pompe disease diagnosis and management guideline. Genet Med. 2006; 8: 267-288.
12. Pruniski B, Lisi E, Ali N. Newborn screening for Pompe disease: Impact on families. J Inherit Metab Dis. 2018; 41: 1189-1203.
13. Muenzer J, Wraith JE, Clarke LA, International Consensus Panel on Management and Treatment of Mucopolysaccharidosis I. Mucopolysaccharidosis I: Management and treatment guidelines. Pediatrics. 2009; 123: 19-29.
14. Çelik B, Tomatsu SC, Tomatsu S, Khan SA. Epidemiology of mucopolysaccharidoses update. Diagnostics. 2021; 11: 273.
15. Matte U, Yogalingam G, Brooks D, Leistner S, Schwartz I, Lima L, et al. Identification and characterization of 13 new mutations in mucopolysaccharidosis type I patients. Mol Genet Metab. 2003; 78: 37-43.
16. Donati MA, Pasquini E, Spada M, Polo G, Burlina A. Newborn screening in mucopolysaccharidoses. Ital J Pediatr. 2018; 44: 126.
17. de Ru MH, Bouwman MG, Wijburg FA, van Zwieten MC. Experiences of parents and patients with the timing of Mucopolysaccharidosis type I (MPS I) diagnoses and its relevance to the ethical debate on newborn screening. Mol Genet Metab. 2012; 107: 501-507.
18. Parini R, Broomfield A, Cleary MA, De Meirleir L, Di Rocco M, Fathalla WM, et al. International working group identifies need for newborn screening for mucopolysaccharidosis type I but states that existing hurdles must be overcome. Acta Paediatr. 2018; 107: 2059-2065.
19. DeLuca JM, Kearney MH, Norton SA, Arnold GL. Parents' experiences of expanded newborn screening evaluations. Pediatrics. 2011; 128: 53-61.

20. Nelson J, Crowhurst J, Carey B, Greed L. Incidence of the mucopolysaccharidoses in Western Australia. Am J Med Genet A. 2003; 123: 310-313.
21. Burton BK, Hickey R, Hitchins L. Newborn screening for mucopolysaccharidosis type II in Illinois: An update. Int J Neonatal Screen. 2020; 6: 73.
22. Orsini JJ, Saavedra Matiz CA, Gelb MH, Caggana M. Newborn screening for Krabbe's disease. J Neurosci Res. 2016; 94: 1063-1075.
23. Rafi MA, Luzi P, Zlotogora J, Wenger DA. Two different mutations are responsible for Krabbe disease in the Druze and Moslem Arab populations in Israel. Hum Genet. 1996; 97: 304-308.
24. Acuña M, Martínez P, Moraga C, He X, Moraga M, Hunter B, et al. Epidemiological, clinical and biochemical characterization of the p. (Ala359Asp) SMPD1 variant causing Niemann-Pick disease type B. Eur J Hum Genet. 2016; 24: 208-213.
25. McGovern MM, Dionisi Vici C, Giugliani R, Hwu P, Lidove O, Lukacs Z, et al. Consensus recommendation for a diagnostic guideline for acid sphingomyelinase deficiency. Genet Med. 2017; 19: 967-974.
26. Geberhiwot T, Wasserstein M, Wanninayake S, Bolton SC, Dardis A, Lehman A, et al. Consensus clinical management guidelines for acid sphingomyelinase deficiency (Niemann-Pick disease types A, B and A/B). Orphanet J Rare Dis. 2023; 18: 85.
27. Shah AJ, Kapoor N, Crooks GM, Parkman R, Weinberg KI, Wilson K, et al. Successful hematopoietic stem cell transplantation for Niemann-Pick disease type B. Pediatrics. 2005; 116: 1022-1025.
28. Breilyn MS, Zhang W, Yu C, Wasserstein MP. Plasma lyso-sphingomyelin levels are positively associated with clinical severity in acid sphingomyelinase deficiency. Mol Genet Metab Rep. 2021; 28: 100780.
29. Lenders M, Brand E. Fabry disease: The current treatment landscape. Drugs. 2021; 81: 635-645.
30. Zarate YA, Hopkin RJ. Fabry's disease. Lancet. 2008; 372: 1427-1435.
31. Michaud M, Mauhin W, Belmatoug N, Garnotel R, Bedreddine N, Catros F, et al. When and how to diagnose Fabry disease in clinical pratice. Am J Med Sci. 2020; 360: 641-649.
32. Wang RY, Lelis A, Mirocha J, Wilcox WR. Heterozygous Fabry women are not just carriers, but have a significant burden of disease and impaired quality of life. Genet Med. 2007; 9: 34-45.
33. Hsu TR, Niu DM. Fabry disease: Review and experience during newborn screening. Trends Cardiovasc Med. 2018; 28: 274-281.
34. Wang RY. A newborn screening, presymptomatically identified infant with late-onset Pompe disease: Case report, parental experience, and recommendations. Int J Neonatal Screen. 2020; 6: 22.
35. Castillon G, Chang SC, Moride Y. Global incidence and prevalence of Gaucher disease: A targeted literature review. J Clin Med. 2022; 12: 85.
36. Kishnani PS, Al Hertani W, Balwani M, Göker Alpan Ö, Lau HA, Wasserstein M, et al. Screening, patient identification, evaluation, and treatment in patients with Gaucher disease: Results from a Delphi consensus. Mol Genet Metab. 2022; 135: 154-162.42.
37. Roh J, Subramanian S, Weinreb NJ, Kartha RV. Gaucher disease-more than just a rare lipid storage disease. J Mol Med. 2022; 100: 499-518.
38. Pastores GM, Barnett NL, Kolodny EH. An open-label, noncomparative study of miglustat in type I Gaucher disease: Efficacy and tolerability over 24 months of treatment. Clin Ther. 2005; 27: 1215-1227.

39. Beutler E, Kay AC, Saven A, Garver P, Thurston D, Dawson A, et al. Enzyme replacement therapy for Gaucher disease. Blood. 1991; 78: 1183-1189.
40. Kemper AR, Uren RL, Moseley KL, Clark SJ. Primary care physicians' attitudes regarding follow-up care for children with positive newborn screening results. Pediatrics. 2006; 118: 1836-1841.
41. Wasserstein MP, Orsini JJ, Goldenberg A, Caggana M, Levy PA, Breilyn M, et al. The future of newborn screening for lysosomal disorders. Neurosci Lett. 2021; 760: 136080.