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EXPANDING NEWBORN SCREENING FOR LYSOSOMAL DISORDERS: OPPORTUNITIES AND CHALLENGES

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Newborn screening (NBS), since its implementation in the 1960s, has traditionally been successful in reducing mortality and disability in children with a range of different conditions. Lysosomal storage disorders (LSD) are a heterogeneous group of inherited metabolic diseases that result from lysosomal dysfunction. Based on available treatment and suitable screening methods, the LSDs that are considered for NBS generally include Fabry, Gaucher, Krabbe, MPSI, MPSII, MPSV, Metachromatic leukodystrophy, Niemann-Pick, and Pompe. Utilizing traditional and expanded criteria for consideration of NBS leads to a set of fundamental questions that need to be explored when considering the opportunities and challenges of adding LSDs to NBS panels. © 2012 Wiley Periodicals, Inc.
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INTRODUCTION TO NEWBORN SCREENING

Newborn screening (NBS) is a state-based public health program, which utilizes different testing strategies to screen for a range of disorders including hemoglobinopathies, inborn errors of metabolism, infectious disease, endocrine disorders, and others. Since the routine institution of screening in the 1960s, NBS has been successful in reducing mortality and disability in children with a range of different conditions. The traditional NBS approach focused on screening newborns and the potential advantage for the individual child but broader measures of benefit, including family counseling, detecting carriers for disease, and screening for later onset disorders, are now considered.

The number of diseases included in NBS programs has undergone rapid expansion in part due to technological and treatment advances, political influence from public campaigning from family and parent advocacy groups, and the availability of private laboratory screening options. In the US, there is no national policy on NBS and although recently all states screen for a core panel as recommended by the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children, state governments have led the way in mandating or deciding what tests to add to the individual state panels. There is variability within states as to administrative structure, tests offered, laboratory and medical follow-up services, and medical management. This expansion has also resulted in a national discussion/debate about the ethics and legality of the growing list of conditions being considered for NBS [Kunk 1998; Ross 2006; Bailey et al., 2008] and how the evolving criteria for inclusion in newborn panels is challenging the more traditional approach to screening.

In 1968, Wilson and Jungner [1968] published a set of criteria for inclusion of diseases in screening programs. The American College of Medical Genetics (ACMG) in a report for the Health Resources and Services Administration [American Academy of Pediatrics, 2006] Advisory Committee on Heritable Disorders and Genetic Diseases of Newborns and Children, which is an advisory committee to the Secretary of the U.S. Dept. of Health and Human Services, developed a more specific set of criteria. These criteria are utilized to evaluate conditions proposed for expansion, and to recommend a core panel of diseases for standardized screening across all states [U.S. Department of Health and Human Services, 2004]. In general, the issues considered are broadly based on frequency, severity of the disease in the untreated population, availability of a reliable testing methodology, effective treatment options, and cost effectiveness.

In general, NBS programs and diseases being considered for addition to NBS programs need to consider questions regarding the natural history, epidemiology and treatments for the condition, screening and testing modalities, the burden of follow-up for the state, and potential anxiety and benefits for the individual and family. In this article, we will explore these issues as they apply to NBS for lysosomal storage disorders (LSD).

INTRODUCTION TO LYSOSOMAL STORAGE DISEASES

LSDs are a heterogeneous group of inherited metabolic diseases that result from lysosomal dysfunction. The lysosome is an intracellular organelle that contains enzymes used in the metabolism of macromolecules. Lysosomal dysfunction leads to accumulation of the substrates that cause cell destruction and eventual organ damage [Wenger et al., 2003]. The LSDs have complex and variable presentation with interfamilial variation complicating the early diagnosis of these conditions.

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The age of onset, progression of disease and severity of symptoms are not routinely and easily predicted based on biochemical or genetic factors. The natural history and extent of these disorders is still being defined and studied [Wilcox, 2004].

The diagnosis of LSDs is important for treatment and counseling issues. The diseases are inherited in an autosomal recessive or X-linked pattern which has important implications for counseling and family planning. Given the variability in age of presentation and disease complexity, symptomatic individuals may undergo extensive and prolonged evaluation prior to a diagnosis being established. This delay in diagnosis may not allow families to make informed decisions about their recurrence risk.

Treatments for the LSDs revolve around reduction of the accumulated substrate within the lysosomes and affected organs. Augmentation of enzyme activity can be achieved by hematopoietic stem cell transplantion (HSCT) or intravenous recombinant enzyme replacement therapy (ERT). Therapies under investigation include intrathecal enzyme replacement, stabilization of enzyme with small molecule chaperones, and gene therapy [Marsden and Levy, 2010]. None of the therapies are curative and are complicated by issues of tissue rejection, crossing the blood brain barrier, and expense. Nonetheless for some LSDs these therapies have been shown to have great impact on quality of life and most beneficial when they are initiated before the onset of symptoms. The need for early detection for the LSDs makes them a candidate for NBS. The LSDs that are considered for NBS include the ones for which a therapeutic option exists and generally include Fabry, Gaucher, Krabbe, MPSI (Hurler, Hurler-Scheie, Scheie syndromes), MPSII (Hunter syndrome), MPSVI (Marotteaux-Lamy), Metachromatic leukodystrophy, Niemann-Pick, and Pompe (Table 1).

EXPLORATION OF OPPORTUNITIES AND CHALLENGES OF LSD NBS

LSDs with their broad spectrum of clinical manifestations equally fit with and challenge the classic Wilson and Jungner criteria for NBS. As technology and treatment, as well as parental advocacy, evolve and accelerate, the questions of which LSDs to include on NBS panels will continue to arise. There has been limited experience with NBS for LSDs to date with reports on the outcome of screening for specific diseases including Krabbe (New York State), Pompe (Taiwan), and Fabry (Italy and Taiwan). Treatments for the LSDs have only recently become available and reliable, and combined with the lack of a clear understanding of the natural history of these disorders, performing NBS for the LSDs is challenging. Utilizing traditional and expanded criteria for consideration of NBS leads to a set of fundamental questions that need to be explored when considering the addition of LSDs to NBS panels.

Is The Condition Screened For An Important Health Problem And Is Its Natural History Well Understood?

Traditional NBS criteria have considered disease frequency as a measure of the impact on public health. Individually the LSDs are rare but collectively as a group they have a notable frequency (1 in 7,000 to 8,000) [Meikle et al., 1999]. NBS to date and in the foreseeable future will implement only individual or several LSDs making their individual population frequency more relevant to discussions of expansion at this time. In reality the true incidence of many of the specific LSDs is not known because of the disease variability with late onset and milder variants. NBS programs for other disorders such as fatty acid oxidation defects [Rhead, 2006] have revealed a more accurate estimate of disease frequency and this will likely be the case for the LSDs as well.

The majority of knowledge regarding the natural history of LSDs comes from the classical infantile or childhood forms of the disease which have a clear and devastating effect on affected individuals, making them good candidates for NBS. Many LSDs however, have adult-onset forms and mild variants for which there is limited natural history information as well as disease presentations that are as of yet unrecognized. NBS will identify all forms including the adult onset variants and counseling for late onset diseases will be hampered by the lack of long-term follow-up data. NBS pilot experience for Fabry disease in Italy and Taiwan illuminate this issue where 37,104 and 90,288 newborn males were screened respectively. In total, 85 males were identified with Fabry disease and the majority of the mutations found were suggestive of a later-onset phenotype [Spada et al., 2006; Hwu et al., 2009]. Although it is clear that early detection, genetic counseling and therapeutic intervention is beneficial for the classic Fabry phenotype, these studies bring to light the issues of screening for later-onset variants of Fabry. Potentially identifying large numbers of patients who will remain clinically asymptomatic for the majority of their lifetime may be controversial and discordant with the traditional criteria of universal NBS.

On the other hand, NBS has been a mechanism for learning more about the natural history of a condition as well as understanding the long term outcomes from treatments. This benefit which comes from the outcome of NBS has been noted by Bailey et al., 2009 "using a screening test in a NBS program for conditions that have an uncharted course and no known treatment creates a burden for states, pediatricians, and families, but unless NBS is initiated, the natural history of a condition may never be known." Achievement of this goal will require protocol changes as NBS programs although variable within states, in general are not designed and do not have the infrastructure to provide long-term follow-up. The ACMG/National Institute of Health NBS Translational Research Network was created to address such issues. Long-term follow-up of NBS is a central mission of this network, who through large collaborative efforts seeks to stimulate research, and advocate pilot screening programs, and protocol-based systematic long term follow of infants identified through NBS which will provide information on the conditions, their treatments, tests and cost-effectiveness of screening [Levy, 2010].

New York State's experience with NBS for Krabbe, which was initiated in 2006, highlight the inherent complexities of screening for a condition in which information on the natural history of the condition is at best limited [Kemper et al., 2006]. Krabbe disease can be categorized into four subtypes: early infantile, late infantile, juvenile and adult and there is limited ability to distinguish between the phenotypes other than clinical observation, and the data regarding the progression and outcomes of the later onset diseases is poorly understood. After mandated screening was legislated in New York, the Krabbe Consortium was formed, consisting of metabolic specialists, child neurologists, neuroradiologists, neurophysiologist, transplant physicians, neurodevelopmental pediatricians and members of the state NBS group. The New York Krabbe consortium developed a follow up protocol based on the limited information available. Screen

Table 1. Enzyme, Features, and Treatment Available for LSDs Which Are Considered for NBS (Wang et al, 2011)

Disease (Inheritance Pattern); OMIM ID #	Enzyme	Features	Treatment
Fabry (X-linked); 301500	α-Galactosidsase A	Classic disease presents between ages 4–8 years, atypical forms present later in life. Acroparesthesias, angiokeratomas, hypohidrosis, corneal opacities, hypertrophic cardiomyopathy, renal failure, stroke. Females have later onset and better long term prognosis.	ERT: Initiated in symptomatic males and females, no consensus on when to start treatment for asymptomatic male infants.
Gaucher (AR); 230800	β-Glucocerebrosidase	Type 1: Hepatosplenomegaly, anemia, abdominal pain, skeletal pain, no CNS involvement. Onset in childhood to adult.	ERT: reduces hepatosplenomegaly, improves pain and blood counts.
		Type 2: CNS degeneration in infancy, Similar somatic affects as Type 1.	SRT: oral therapy for patients who cannot tolerate ERT.
		Type 3: Milder course with respect to CNS involvement.	
Krabbe (AR); 245200	β-Galactocerebrosidase	Classic infantile form: irritability, increasing spasticity, blindness, deafness, neuropathy, presents in first year of life.	HSCT: prior to symptoms attenuates development of neurological symptoms.
		Late: Behavior change, slow CNS degeneration.	
MPS I (AR); 607014	α-L-Iduronidase	Age of onset, disease severity and progression variable. Severe disease includes CNS involvement (progressive cognitive deterioration); attenuated disease somatic symptoms only. Coarse facial features, corneal opacities, macrocephaly, hearing loss, hepatosplenomegaly, skeletal findings.	HSCT: varying rates of success ERT: affective for somatic symptoms, does not cross blood brain barrier so little anticipated benefit for severe CNS disease. No consensus on when to initiate therapy in asymptomatic patients.
MPS II (X-linked); 309900	Iduronate-2-sulphatase	Age of onset, disease severity and progression variable. Severe disease includes CNS involvement (progressive cognitive deterioration); attenuated disease somatic symptoms only. Coarse facial features, macrocephaly, hearing loss, hepatosplenomegaly, skeletal findings.	HSCT: varying rates of success ERT: affective for somatic symptoms, does not cross blood brain barrier so little anticipated benefit for severe CNS disease. No consensus on when to initiate therapy in asymptomatic patients.
MPS VI (AR); 253200	Arylsulfatase B	First symptoms usually noted in first several years of life. Skeletal deformities, motor dysfunction, kyphosis, heart defects, corneal opacities, hepatomegaly. Normal intelligence.	HSCT: varying rates of success ERT: some improvement in nighttime oxygen saturation, and heart function.
Pompe (AR); 232300	α-Glucosidsase	Infantile form: onset within first few months of life, failure to thrive, cardiomegaly, severe (cardio) myopathy with progressive muscle damage, respiratory failure.	ERT: must be initiated as soon as diagnosis is known and long term improvement only seen if initiated prior to respiratory failure.
		Late onset form: slowly progressive Proximal muscle weakness.	

AR, autosomal recessive; CNS, central nervous system; ERT, enzyme replacement therapy; HSCT, hematopoietic stem cell transplant; SRT, substrate reduction therapy.

positive patients are stratified into three risk categories (high, medium and low) based on enzyme activity, and treatment decisions are made based in part on follow-up studies including neurologic examinations, brain MRI, and neurodiagnostic studies (lumbar puncture, VER, BAER, nerve conduction). Neuropsychologic testing is also performed at regular intervals based on the infant's category. As of 2008, 550,000 children had been screened and four high risk, six intermediate risk and 15 low risk patients identified. Two high risk patients were referred for transplant, two were followed and were asymptomatic at 8 and 16 months and none of the other individuals had developed symptoms [Duffner et al., 2009a]. The ongoing screening program in New York is providing valuable information about a potential protocol for other programs to follow.

The burden of collecting and collating follow-up data is beyond the ability of the many state screening programs. In New York, the establishment of the Hunter James Kelly Research Institute's clinical database and registry was an answer to the call for longitudinal follow-up for Krabbe disease [Duffner et al., 2009a]. New York State's multidisciplinary standardized approach to the evaluation of these infants may serve as a model for the implementation of LSD screening in other states [Duffner et al., 2009a]. Creation of independent databases that require individual consent and partner closely with NBS programs may be a solution to achieving the goal of collecting long-term follow up data without putting a burden on the state programs.

In 2009, the SACDHNC committee chose not to recommend the addition of Krabbe to the core panel because of uncertainties related to population-based screening, the diagnosis of early-infantile Krabbe disease, the impact of a positive screen on families,

and treatment outcomes. A published report of the review for consideration of screening for Krabbe cited two major concerns: the inability to determine shortly after a positive screen which children would benefit from urgent transplantation and (2) the lack of long term follow-up data for those children who have received transplants, especially neurodevelopmental outcomes [Kemper et al., 2010]. To date, four LSDs have been nominated to the Advisory Committee on Heritable Disorders in Newborns and Children for consideration of an evidence review for addition to the Committee's Recommended Uniform Screening Panel. Fabry disease and Niemann-Pick disease were initially deemed by the Committee as not ready for evidence review [Advisory Committee on Heritable Disorders in Newborns and Children, 2010]. Krabbe and Pompe disease both had a complete evidence review but were not approved for addition to the Recommended Uniform Screening panel [Advisory Committee on Heritable Disorders in Newborns and Children 2008, 2009].

Is Treatment Available And Is Treatment At An Early Stage of More Benefit Than At A Later Stage?

The efficacy and long term outcome of the treatments need to be considered. A report by the American Academy of Pediatrics stated that a condition is a good candidate for NBS only if "the treatment for the condition is effective when initiated early, accepted among health care professionals, and available to all screened newborns [American Academy of Pediatrics, 2000.]. As of 2011, ERT is available and an accepted treatment for Gaucher, Pompe, Fabry, MPS1 (Hurler) and MPSII (Hunter) and MPS VI (Maroteaux-Lamy) [Wang et al., 2011]. ERT has been found to be effective and clinically beneficially in the treatment of these patients non-neuronopathic symptoms. HSCT is the only therapy presently available for Krabbe disease and has been mostly studied in the classic infantile form and currently would not be offered presymptomatically to individuals with juvenile or adult onset disease (Table 1).

The report of New York State's experience with NBS for Krabbe disease reveal that despite successful engraftment most transplanted infants for early-infantile Krabbe developed signs of neurological disease [Duffner et al., 2009b]. Although transplanted infants survive longer than would be expected without intervention, the clinical manifestations of Krabbe disease after transplantation are progressive [Duffner et al., 2009b].

Despite the success of ERT at treating somatic symptoms it does not treat all symptoms and recommendations on when to start therapy for pre-symptomatic individuals is not available. ERT for Gaucher is targeted at the somatic symptoms and although useful in quality of life in patients with neurological disease does not alter the course of disease progression. Fabry is a late onset disorder and ERT is recommended for symptomatic individuals but little data is available as to when to start treatment of an asymptomatic patient or if pre-symptomatic treatment alters the long term outcome. Thus while treatment is available for many LSDs, the outcomes are highly variable depending on the subtype of disease. Defining "treatment" and the implications of that become more difficult for all patients. Achieving a balance between the benefit of detecting the clearly treatable subtype and harm from finding a progressive and as of yet untreatable subtype is a challenge when considering LSDs for NBS [Hwu et al., 2010].

Although some LSDs have no or poorly efficacious treatment, early diagnosis through screening is supported by many parents of affected children even if a diagnosis would not lead to treatment that would favorably affect the prognosis [Parsons et al., 2002; Campbell and Ross 2003; Parsons and Bradley 2003; Skinner et al., 2003; Hayes et al., 2007]. Previous studies involving untreatable conditions like duchenne muscular dystrophy (DMD) and Fragile X syndrome provided little evidence to suggest that screening for these conditions causes a greater level of distress and anxiety than diagnosis by other methods. In a prospective trial of DMD NBS, no significant difference in parental anxiety or wellbeing was appreciated as a result of identifying an asymptomatic boy with DMD by NBS [Parsons et al., 2002]. In a survey of parents of children with Fragile X syndrome, the majority believed that receiving a diagnosis at birth would not have an effect on parental bonding [Skinner et al., 2003].

IS There A Suitable And Reliable Test Available?

The development of high throughput assays for testing LSDs on dried blood spots has been a challenge but several assays are available. The genetic heterogeneity of mutations in the LSDs makes mutation screening impractical. In addition, the lack of general and specific metabolic markers limits the use of biochemical screening assays. Specific assays that allow individual direct measurement of enzyme activity or the use of specific antibodies for indirect measurement have been developed but are limited by one assay per disease approach and costs. Multiplexing assays using immune quantification and tandem mass spectrometry (MS/MS) are available. Immune quantification has been developed for 11 different LSDs utilizing monoclonal or polyclonal antibodies directed at specific enzyme and measuring fluorescence as a determination of enzyme activity. This technique has been used successfully for Fabry disease in Italy and Taiwan and Pompe disease in Taiwan. Drawbacks to all of the methods include the cost of buying or developing the antibodies which are not commercially available. MS/MS has been developed for eight LSDs which require separate enzyme incubations and then quantified by MS/MS. Little data is available as to the sensitivity or specificity of these assays which limits their availability to NBS. The Centers for Disease Control and Prevention make substrates and internal standards available at no cost to facilitate interest in this screening technology [Marsden and Levy 2010; Wang et al., 2011]. Utilization of these techniques will generate more data about the reliability of these screening assays but this raises a series of questions of its own. How much data needs to be available about the performance characteristics of these technologies so that their use is not considered research? As most states perform NBS without parental consent this is an important question in introducing new tests to a state panel. The availability of a test and substrates without adequate data on performance straddles a line of test development (research) versus pilot testing (implementation) for a new test.

In addition to screening enzyme assays LSDs will need to utilize genetic testing to help in the determination of the clinical phenotype. Fabry enzyme activity level may be useful in predicting the classic severe form (<1% activity) from the milder variants (>1% activity) but enzyme activity is not as predictable for other diseases. Krabbe disease has some genotype/phenotype information predictive of specific outcomes. Homo-

zygosity for the 30-kb deletion is associated with the infantile onset and the New York screening program utilizes this to determine which infants will be referred for transplant. Unfortunately, not all patients with infantile onset have this mutation [Wenger et al., 2000] and there are not reliable predictive genotypes for the other clinical variants. Fabry genotype/phenotype data is limited as most mutations are private but it has been suggested that mutations leading to complete loss of function of the gene product (nonsense, frameshift) are associated with classic Fabry disease, and conversely, mutation resulting in amino acid substitutions (missense) may occasionally be associated with a milder phenotype [Schaefer et al., 2005]. Similarly, Gaucher disease has mutations that are suggestive of phenotypes but the most common mutation among the non-Jewish population is the L444P mutation, which can be associated with all three subtypes of Gaucher. There is some experience with using genetic testing in NBS for cystic fibrosis (CF) where a panel of mutations is tested but some of the LSD will require full gene sequencing which will be more challenging.

Are Adequate Health Services Provisions Available?

A significant challenge in expanded NBS is clinical follow-up. [James and Levy, 2006]. Treatment of LSDs require a coordinated multidisciplinary team approach to ensure that all positive screens as well as confirmed cases have access to care as well as assuring that only infants requiring therapy would be subjected to potentially life-threatening intervention [Pass et al., 2006]. In Taiwan, of the 132,538 newborns screened for Pompe, 1,093 repeat dried blood spot samples were requested and tested, and 121 newborns were recalled for additional evaluation. These additional evaluations included blood chemistry assays, physical examination looking for cardiac signs, EKG and chests radiographs, and echocardiograms if anything looked suspicious. Four newborns were confirmed to have Pompe disease [Chien et al., 2008]. The protocol utilized for Krabbe disease, reviewed above, and the Taiwanese experience highlight the burden of follow-up that will face individuals, families and health care providers. Missed, delayed or erroneous information exact an enormous toll on families. Bailey et al., [2009] points out that 'with expanded NBS, families from a wide-range of educational, socioeconomic, and cultural backgrounds will need access to comprehensive, yet comprehensible information in a range of formats on the condition that affects their child." The importance of genotype information is critical and it is not clear whether genetic testing to help clarify the clinical variation and provide recurrence risk information will be included as part of the NBS test or considered part of private follow up. In the latter case the ability of any individual to get access to genetic testing will be related to their insurance coverage. As long as newborn-screening programs are maintained and managed at the state level, variations in programs and information provided will persist. Minimizing these difference and potential inconsistencies, will be a significant challenge to the implementation of expanded NBS. Finally, there is no consensus or widely available protocols on how to follow a child who is at risk for disease but for which there is no ability to predict the severity or timing of progression of disease. The health care resources needed for these children will be significantly increased.

Another challenge will be educating the health care community about these rare diseases and the genetic literacy needed to interpret and translate the genotype/phenotype information and inheritance. Many families learn about an abnormal NBS through their child's primary care provider who may not be prepared to manage the follow-up care of children with a LSD [Kemper et al., 2006]. Providing accurate and balanced information regarding a genetic condition and its implications is challenging, and as a number of studies have indicated, primary health care providers are neither well educated in genetics nor interested enough in becoming so to effectively contribute [Greendale and Pyeritz, 2001]. Much of this education will fall on medical genetic services providers like medical geneticists and genetic counselors. However, as the number of physicians who seek training in medical genetics declines [Cooksey et al., 2006; Bernhardt et al., 2009], there are currently not enough trained geneticists and genetic counselors to meet the growing population demands for genetic services.

Are the Risks, Both Physical And Psychological, Less Than The Potential Benefits?

Concern about a parent's acute stress in the time of receiving an abnormal NBS result and in the diagnosis of an otherwise healthy newborn need to be assessed with the expansion of NBS programs. One study in CF NBS showed that parents experience high levels of emotional distress during the waiting period between notification of a positive NBS to a diagnostic test [Tluczek et al., 2005]. However, avoiding a delay in diagnosis and the accompanying distress that accompanies the "diagnostic odyssey" is often cited as a psychosocial benefit of screening that may outweigh the acute stress a family experiences with a positive newborn screen [Bailey et al., 2008]. An early diagnosis also gives families access to information about genetic inheritance and carrier status and provides parents the opportunity to make future reproductive decisions.

The diagnosis of an otherwise healthy newborn with a LSD can present several unique challenges. Instead of a prolonged diagnostic odyssey, families are instead faced with a "diagnosis-in-waiting." In this setting the family has an asymptomatic child with a diagnosis that is not readily apparent which can lead to distrust in the health care team. In addition, symptoms, if they develop, could be severe and rapidly progressive, and there may not be any treatment to offer in this pre-symptomatic state or at the time when symptoms appear. This situation may worsen the idea of a "vulnerable child syndrome" (parental overprotection of a child in the absence of symptoms) [Bailey et al., 2009]. Although one study surveying parents of individuals with mucopolysaccharidoses showed support for NBS [Hayes et al., 2007], no studies to date have examined these issues in individuals who have experienced the diagnosis of a LSD at birth by NBS. How this higher level of ambiguity regarding phenotypic variability affects parental stress and anxiety is unknown. It is difficult to project the attitudes of families with an affected child to those who are in the "diagnosis in waiting" stage of NBS. Whether the avoidance of the stress and anxiety of a diagnostic odyssey is significantly more beneficial and ameliorative than the additional stress and anxiety of a diagnosis-in-waiting cannot be speculated upon based on the current literature to date. One wonders, before embarking on the full-scale expansion of screening for LSDs, whether the examination of these unknowns would provide useful and valid input to the delivery and support of LSD NBS.

CONCLUSIONS

There have been great advances in NBS and as the number of conditions increases the benefits will become more apparent. The expansion has come with new lessons and has appropriately pushed the traditional boundaries of NBS as established by Wilson and Jungner. LSDs will continue to become more prominent on NBS panels as several states have already committed to screening and the experience from these initiatives will be a valuable resource for future decisions on NBS for LSDs. Inclusion of LSDs on NBS panels should proceed with caution as there are many challenges to overcome and future research will be needed to help define the natural history, treatment outcomes and options and need for consent. The excitement over the opportunity to help should be tempered with equal desire to avoid premature decisions that may lead to harm. ■

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