J Genet Counsel (2016) 25:373–384
DOI 10.1007/s10897-015-9879-8

ORIGINAL RESEARCH

Newborn Screening for Lysosomal Storage Disorders: Views of Genetic Healthcare Providers

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Received: 25 March 2015 / Accepted: 12 August 2015 / Published online: 29 August 2015

Abstract Lysosomal storage diseases (LSDs), lysosomal enzyme deficiencies causing multi-system organ damage, have come to the forefront in newborn screening (NBS) initiatives due to new screening technologies and emerging treatments. We developed a qualitative discussion tool to explore opinions of genetic healthcare providers (HCPs) regarding population-based NBS for MPS types 1 and 2, Pompe, Gaucher, Fabry, and Krabbe diseases. Thirty-eight telephone interviews conducted by a single researcher were analyzed and coded for thematic trends. Six major themes emerged: 1) treatment availability and efficacy is crucial; 2) early age of disease onset is important; 3) ambiguity regarding prognosis is undesirable; 4) parents' ability to make reproductive decisions is seen by some as a benefit of NBS; 5) paucity of resources for follow-up exists; and 6) the decision-making process for adding conditions to mandated NBS is concerning to HCPs. Among the LSDs discussed, Pompe was considered most appropriate, and Krabbe least appropriate, for NBS. MPS1 and MPS2 were overall considered favorably for screening, but MPS1 ranked higher, due to a perception of better efficacy of therapeutic options. Fabry and Gaucher diseases were viewed less favorably due to later age of onset. The themes identified in this study must be addressed by decision-makers in expanding NBS for LSDs and may be applied to many diseases being considered for NBS in the future.

Keywords Newborn screening · Lysosomal storage diseases · Qualitative research · Healthcare providers' opinions

Abbreviations

NBS	Newborn screening
HCP	Healthcare providers
HSCT	Hematopoetic stem cell transplant

Introduction

Lysosomal storage diseases (LSDs) are a heterogeneous group of enzyme deficiencies causing multi-organ system damage, with a combined incidence of ~1 in 7000 to 9000 (Fletcher 2006). Symptoms and age of onset vary and are primarily determined by the type of substance that accumulates and the amount of residual enzyme activity present. Recent advances in therapies (including enzyme replacement therapy [ERT], substrate reduction therapy [SRT], and hematopoietic stem cell transplant [HSCT]), enhanced advocacy efforts, and more effective assays for screening have moved LSDs to the forefront in NBS initiatives. Both ERT and HSCT are most beneficial when initiated at a pre-, or minimally, symptomatic stage (Civallero et al. 2006; Hayes et al. 2007; Matern et al. 2013; Miekle et al. 2006). Unfortunately, newborn screening for LSDs has several drawbacks, including identification of late-onset forms of a disease in which symptoms will not manifest until adulthood, potentially leading to medicalization

Electronic supplementary material The online version of this article (doi:10.1007/s10897-015-9879-8) contains supplementary material, which is available to authorized users.

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of the child and increased caregiver stress (Kwon and Steiner 2012; Ross 2012). Additionally, those LSDs having no treatment, or treatment that cannot correct neurocognitive decline, may fall outside the traditional parameters of mandated NBS programs.

Several studies have been conducted documenting the opinions of patients and their caregivers on NBS for their/their child's LSD. A postal study in Australia and a qualitative study in the United States examined the diagnostic experiences of parents of children with Mucopolysaccharidosis type 1 (MPS1) and patients with MPS1 themselves with the goal of advising the medical community about NBS initiatives for this condition. Themes identified included diagnostic delays causing significant frustration, loss of knowledge for reproductive planning, and delayed initiation of treatment. The authors conclude that NBS would be beneficial in earlier diagnosis and treatment but both studies only touched on the potential drawbacks of receiving a diagnosis of MPS1 as a newborn (de Ru et al. 2012; Hayes et al. 2007). Ross and Waggoner discuss many of the possible negative ramifications of NBS for LSDs in their commentary in 2012, arguing that informed consent should be given by parents of newborns for expanded conditions that do not outright meet the Wilson and Jungner criteria. They also contend that advocacy groups have lobbied for LSD NBS without consulting with those who would be responsible for its implementation, i.e. the Department of Public Health and pediatric providers caring for these patients (Ross and Waggoner 2012).

Typically the providers responsible for the care of patients with LSDs, diagnosed clinically or by newborn screening, are biochemical geneticists and genetic counselors. They, along with other healthcare providers, have been studied in regard to necessity of informed consent and reporting of incidental findings in newborn screening (Bombard et al. 2010; Duffner et al. 2009). Additionally, a group in the Netherlands performed a study similar to our present study to determining perceptions of newborn screening in HCPs for Pompe disease only. However, they did not interview genetics providers specifically, rather pediatricians, other subspecialists, and patient organization staff members. This study demonstrated that treating earlier and decreasing a diagnostic odyssey were perceived as benefits of NBS for Pompe disease. Furthermore, diagnosing late-onset cases could be potentially harmful because of ambiguity and creating dilemmas for reproductive decision making (van El et al. 2014).

There have been no efforts, however, to determine the experience and opinions of U.S. providers or genetics providers in regard to newborn screening for multiple LSDs, including MPS1/2, Fabry, Gaucher, and Krabbe diseases, despite NBS being performed for these conditions in Missouri, Illinois, and in multiple states in the near future. We developed a qualitative study to ascertain the opinions and experiences of genetic healthcare providers working with patients with inborn errors of metabolism and/or lysosomal storage diseases in order to elicit the opinions of experts in the field regarding population-based testing for LSDs, including testing for later-onset and less treatable diseases.

Methods

Participants

Participants included genetic healthcare providers (HCPs): medical geneticists who are board-certified in biochemistry or general genetics, genetic counselors who work in metabolic or LSD clinics, and directors of biochemical genetics laboratories. Providers were excluded if they did not have experience with metabolic/LSD patients. Participants were recruited by an email advertisement sent to the Metab-L listserv (an online listserv for healthcare providers caring for patients with metabolic disease), the Society for Inborn Errors of Metabolism (SIMD) members, and Ohio genetic counselors' distribution list. Individuals who were interested in participation replied to the author by email to arrange for a telephone interview. Participants were provided with a $25 gift card upon interview completion.

A semi-structured interview guide was created to explore opinions of the HCPs regarding population-based testing for MPS types 1 and 2, Pompe, Gaucher, Fabry, and Krabbe diseases (see Supplemental Table 1). Demographic questions were initially asked, centering on type of practitioner, experience with metabolic disease and scope of practice, as well as experience with newborn screening for LSDs. The study questions, mostly open-ended but with some Likert-scale oriented, asked the participants' opinions on diseases currently on the NBS panel in their state, opinions of LSDs being included on the NBS, importance of age of onset and treatability, concerns about potential harms of early diagnosis of late-onset conditions, and acceptable risks of treatments. When ranking favorability of diseases being on the NBS on a Likert scale (1 meaning strongly agree), other archetypal diseases were included for comparison, including phenylketonuria (PKU), Huntington disease, and Fragile X syndrome. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study via verbal consent described above. The study was reviewed and approved by the UHCMC IRB committee.

Data Collection

Semi-structured telephone interviews were conducted between March, 2013 and July, 2013 by a single researcher. A

consent statement was read aloud by the researcher prior to the start of the interview that emphasized the voluntary nature of the study and that the interview would be made anonymous upon transcription. All of the interviews were tape-recorded with permission and transcribed verbatim by the researcher. Any identifiable information was made anonymous during the transcription. The participants were asked questions exploring their views on conditions currently on the NBS and then their views of LSDs. Follow-up questions were asked to gather more detailed information about their perceptions and experiences. The authors met regularly throughout data collection and reflected on the trends which were emerging to ensure that they collected variability in data. Data collection was ceased once saturation was reached (when no new ideas or issues were identified in subsequent interviews).

Data Analysis

Data analysis was informed by grounded theory which utilizes an iterative approach to data collection, analysis, and development of emerging themes. The key features of grounded theory include deductive and inductive reasoning to study data from verbatim transcripts which provide the study participants' "emic" perspectives. Codes are developed to describe the data which are then used to create explanatory theories and themes (Hennink et al. 2011). Verbatim transcripts in the present study were transferred ATLAS.ti 6.0, a software program used for qualitative research analysis. Based on reading and reflecting on current literature and the data from our study, deductive and inductive codes were developed and six themes emerged from the open-ended questions and are discussed in detail below. (See Supplemental Table 2 for representative quotes for each theme). Questions using a Likert-scale (questions 2, 4, 5, and 8) were analyzed using descriptive statistics, however inferential statistical analyses were not performed due to the small sample size for this largely qualitative study. For questions 4 and 5, the number of participants who selected each option (i.e. strongly agree, agree, neutral, disagree, strongly disagree) was determined. For questions 2 and 8, overall mean approval of individual diseases was calculated, and the mean approval score for each disease in each group was calculated independently for Question 8. Additionally, the mean approval score for each disease was calculated for the HCPs who had experience with NBS for LSDs and for those who did not.

Results

Forty interviews were conducted, and 38 interviews were transcribed and analyzed (2 were excluded because the participant did not meet inclusion criteria). After 40 interviews, saturation was reached in the opinion of the researchers, thus recruitment was discontinued. Characteristics of the participants are summarized in Table 1. Participants lived in 18 states and one Canadian Province. One provider was from India (training in the U.S. temporarily).

Mean approval scores were calculated for each HCP group independently, showing some differences between groups (Fig. 1). Physician biochemical geneticists were least in favor of NBS for all six LSDs discussed compared with the other groups, and genetic counselors tended to be most in favor overall. The most striking differences of opinion related to Krabbe disease, where physicians tended to disagree (higher score) with adding the condition to NBS panels, whereas GCs tended to agree (average score 4 vs. 2.2, respectively). As shown in Fig. 1, the average response from genetic counselors tended toward agreeing that NBS should be considered, whereas biochemical geneticists surveyed tended to disagree that screening is indicated for 4 of the 6 LSDs, only agreeing for Pompe and MPS1 diseases.

Participants in this study agreed on some topics, including the value of early detection and avoidance of a "diagnostic odyssey" as benefits of NBS for LSDs. Providers identified a concern about whether adequate resources, such as provider time and number of providers, would be available for follow-up. One area of discordance among providers was the consideration of reproductive benefit as an appropriate reason for NBS. Additionally, the opinions of NBS for specific diseases discussed in the study varied considerably between providers.

Figure 2 shows average approval ratings from all providers combined for a variety of conditions, ranked from most support for screening on the left to least support on the right. The dotted line parallel to the X-axis defines the cut-off between tending to agree (numbers below 2.5) and tending to disagree (numbers above 2.5) that NBS is appropriate for the given condition. The archetypal conditions included show either high support for conditions historically approved on the NBS or little support (higher numbers) for adult onset conditions like Huntington disease or breast/ovarian cancer variants.

During the interview, HCPs were asked to rank five potential harms of diagnosing a late-onset condition on the NBS on a Likert scale, with 1 being "very harmful" (Fig. 3). Potential harms included: increased parental anxiety, loss of autonomy of the child, "medicalization" of the child, unnecessary healthcare costs to society due to this medicalization, and risk of detrimental effect on insurability and employability. All five potential problems have been raised in the American College of Medical Genetics Policy statement on genetic testing in children (2013) and by individual bioethicists (Acharya and Schindler 2013; Grosfeld et al. 1997; Ross and Acharya 2009; Ross et al. 2013). HCPs had generally similar views on these issues. Most felt that all five were true potential harms (Fig. 3), but barriers to insurability/employability and "medicalization" of the child (requiring multiple medical appointments for surveillance or treatment) were most concerning. The least

Table 1 Study Participant Demographics

	Biochemical geneticist *N*=13 (34 %)	General geneticist *N*=6 (16 %)	Genetic counselor, RN *N*=13, 1 (37 %)	Biochemical lab director *N*=4 (11 %)
Experience				
<1 year	15 %	0	14 %	0
1–5 years	0	14 %	43 %	25 %
6–10 years	23 %	71$	29 %	0
>10 years	63 %	14 %	14 %	87 %
# Pts seen per month				
1 to 10	0	14 %	21 %	0
11 to 30	15 %	0	29 %	0
31 to 50	31 %	72 %	35 %	0
Over 50	54 %	14 %	8 %	0
NA			8 %	100 %
NBS for LSDs performed in your State?				
Yes	2	2	1	0
No	11	4	13	4

concerning potential problem for HCPs was the cost to society of unnecessary medical care- "cost of medicalization on society". The most marked variability of opinion relate to the potential loss of the child's autonomy by NBS, and the potential for "cost of medicalization to society". Almost as many disagreed that these were true concerns as agreed.

The number of HCPs who had experience with NBS for LSDs is too small for a meaningful comparison (*N*=5). However, we did note that the views of those who had NBS for LSDs in their state had overall similar views to those in other states. Those with experience were slightly more in favor of NBS for PD (1.4 vs. 1.76 approval score) and slightly less in favor of NBS for Krabbe disease (3.4 vs. 3.1 approval score). One provider was very much in favor of NBS for all LSDs discussed in the study, while another was unenthusiastic about the mandate that had occurred in his/her state, particularly for Krabbe disease. This HCP felt that the cost of ambiguous findings was too high to find a very few patients in which we may or may not be able to prevent disease.

Major Themes

1. Available, efficacious treatment is important.

As a whole, HCPs generally favored NBS for diseases having an available treatment with proven efficacy. Diseases with available ERT were most positively considered, particularly if hematopoietic stem cell transplant (HSCT) has also been shown to be effective. Ability to prevent, or at least slow, central nervous system deterioration appears to be particularly important. Alternatively, diseases without treatment or with equivocal efficacy are not highly favorable for NBS*: "I have some ambivalence where we don't clearly make an impact."*

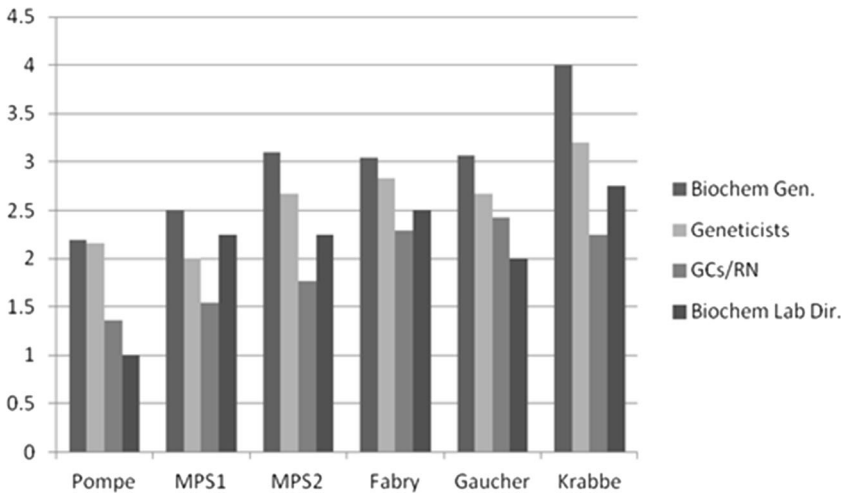

Fig. 1 Average response of genetics providers by type of healthcare provider to the question, "are you/would you be in favor of the following conditions being targeted on the NBS". 1 = strongly agree with NBS, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree

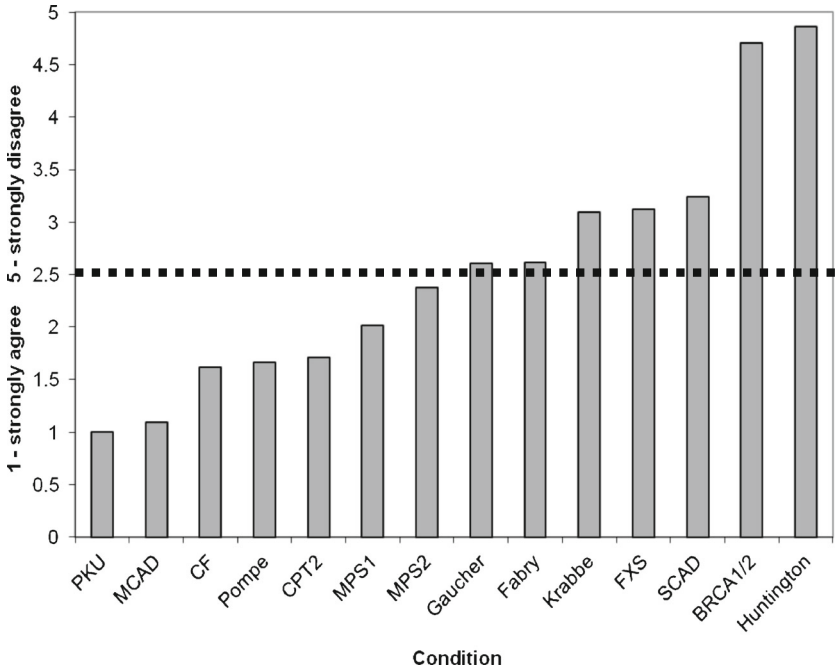

Fig. 2 Ranking of approval for NBS for multiple genetic conditions for all providers. 1 = strongly agree with NBS, 2 = agree, 3 = neutral, 4 = disagree, 5 = strongly disagree

When asked to rate factors that support including a disease on NBS panels, 71 % of providers ranked availability of treatment very important or important. Eighty-eight percent of HCPs felt that the risk associated with HSCT is at least sometimes acceptable, depending on when it is used, however some providers were less enthusiastic about HSCT: *"The side effects from HSCT are high, the outcomes for Krabbe (and that's the only thing I can base it on) are not compelling, and the expense is very high."*

Pompe disease and MPSI had the most favorable scores when participants were asked to rate the priority for diseases for NBS on a Likert scale (Fig. 2). *"Clearly there is a treatment that is effective for infantile Pompe disease, and clearly the literature supports the fact that the timing of the onset of treatment affects outcome. Many of these babies aren't diagnosed immediately so I think that it really meets all the [Wilson and Jungner] criteria."* Krabbe disease had the lowest priority mean score of 3.14 (range 1–5) (Fig. 1). *"I gave Krabbe a [lower priority] because there is a treatment; but there isn't an effective treatment. The pilot data in New York [suggests that] the outcomes have been very poor with regard to patient survival."*

One potential complication in interpreting these data were revealed when HCPs were asked to define what they consider to be "treatment", revealing discrepancies in how different individuals define treatable conditions. Early intervention is a key example of this, with one provider stating, *"I use a broad range of treatment; so [occupational therapy], [physical therapy], [speech therapy], all of those kind of things we [use] for autism patients…I lump in as treatment."* Another

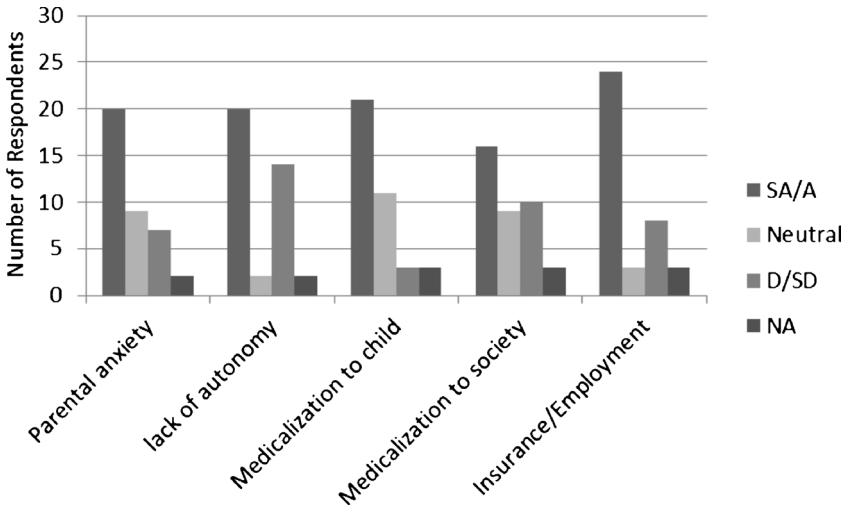

Fig. 3 Responses to the question, "do you feel that the following are harmful in NBS for later-onset LSDs?" Categories were combined to show general agreement (*SA* strongly agree that this is harmful, *A* agree that this is harmful), neutrality, and general disagreement (*D* disagree that this is harmful, *SD* strongly disagree) with the assertion of the question

provider disagrees, saying, *"My definition of treatable is definitely anything that would cure or significantly decrease the signs or symptoms of a disease. I would have to say I don't consider early interventions to be truly treatments in this scenario."*

2. Younger age of onset is favorable for conditions on the NBS.

Generally, infantile Pompe disease and MPSI, which have onset in infancy in the severe forms, were considered more favorably than Fabry and Gaucher type I diseases, which typically manifest in childhood or adulthood. Pompe disease and MPSI received the highest priority quantitative mean score of 1.72 and 2.04, respectively, on the question regarding favorability for screening. Although ERT is available for all four diseases, Fabry and Gaucher diseases received lower priority mean scores of 2.68 and 2.67, respectively, because of the lack of perceived need for early treatment. "*The problem is that they are time bombs. Most of the Gaucher [disease patients] that you pick up are going to be adult-onset so now you've doomed this child to becoming a chronically ill child in the family's view. And so that, and Fabry [disease], are time bombs."* Others note that, because both MPSI and Pompe disease also can have an attenuated, later-onset forms, screening in the newborn period can be complicated. One respondent, discussing late-onset Pompe, described this dilemma: *"I think that's really tough- it doesn't fit the criteria. It's not really the purpose of NBS to be identifying later-onset conditions. I think having that hanging over your head during your formative years could be… difficult."*

3. Lack of ambiguity in results and prognosis is important.

Although unclear results are not a new phenomenon in NBS, participants were concerned about increased parental anxiety and stigmatization of patients with ambiguous results or an unclear prognosis. Providers were most concerned about ambiguity surrounding onset of symptoms in Krabbe disease, based on the experience of NY State, and for late-onset conditions. Reflecting current concerns about variants of unknown significance in DNA sequencing, one stated, *"I think screening for Krabbe is difficult. It's hard to interpret the results. We are finding a lot of carriers, and [we are putting] a lot of people into limbo. They have a mutation that has never been reported, and we don't know what it means."*

4. Reproductive Benefit

The issue of being able to use information obtained from a NBS for reproductive decision making for family members (although not directly discussed in the semi-structured interview questions), was mentioned spontaneously by several healthcare providers, becoming the most debatable issue among HCPs in our study. Many HCPs feel that a disease "*doesn't necessarily have to be treatable immediately or at all because some people may want that information for reproductive planning."* However, others "*don't think the role of NBS is to identify carriers or try to provide recurrence risk information."*

Many HCPs were in favor of reproductive benefit: *"something else that's not in the classic criteria that I think is important: genetic counseling before the birth of a second child.*" Other health care providers were not in favor of reproductive benefit alone being a justification for NBS: *"NBS is not done for reproductive decision making for parents. If we are moving into a model where we are collecting information in order to benefit not only that human being but the family and society as a whole, it's just a whole different model."*

5. Paucity of resources for follow-up

Some HCPs are worried about a lack of available resources for following up of abnormal NBS results for LSDs, while others are unconcerned. When asked about concern regarding paucity of resources, a provider in a Southeastern state replied, "*Because we have few metabolic physicians…the burden is more on the family. Some have to drive 5 h to come to an appointment, so resources are a problem"* while a provider in a large Midwestern city stated, *"I am not at all concerned about that (access to care)."* Although the Discretionary Advisory Committee on Heritable diseases in Newborns and Children (DACHDNC) developed a Recommended Universal Screening Panel (RUSP) for all states using a standardized evaluation tool, the availability of resources continues to be a variable issue among states. Additionally, the cost of the treatments, tens of thousands of dollars per infusion for some patients, is an issue for a minority of HCPs. One participant stated that treatment *"should be available to any patient regardless of insurance coverage and should be affordable."*

6. Decision-making Process

Providers, as a whole, expressed general dissatisfaction with current mechanisms for determining which conditions will be added to NBS panels. Due in part to disparity among states and concern about how diseases were added to the NBS panel in different states, the DACHDNC was chartered to help make uniform recommendations about testing using systematic evidence review. Some HCPs, however, do not think this goes far enough. "*What happens in medicine is that decisions are made impulsively. People adopt things before they are proven, sometimes with really harmful effects."* Some HCPS feel that pilot studies are a better option than legislatively mandated clinical screening: "*Not many people have discussed pilot studies but I think that it's a really good idea*

instead of the advisory committee saying yes or no." In our study, many HCPs expressed concerns about patient advocacy groups (who may have a specific agenda), and politicians (who may feel the need to respond more to political concerns than medical and public health concerns) determining which diseases should be included on the NBS without evidence-based research. One HCP stated: *"I have a problem with [current approaches that are] political and…done without forethought. We [end up] screening everybody to treat a few. The cost to society is going to be enormous…and I think that that money would be better spent on preventable things."*

Discussion

Practice Implications for Genetic Counselors

This study reveals the complexity of opinions around NBS for a variety of conditions and demonstrates the need for ongoing discussion of these topics. The issues faced by genetic counselors and other HCPs, including diagnosing later onset conditions, facing ambiguous results, and less than ideal treatment efficacy are not novel for dicussions of NBS for LSDs. Many metabolic conditions such as carnitine palmitoyl transferase 2 (CPT2) deficiency and very long chain acyl-CoA dehydrogenase deficiency (VLCADD), currently tested for on NBS, can have later-onset phenotypes similar to Fabry, Gaucher, and late onset Pompe diseases. Conditions such as short chain acyl-CoA dehydrogenase deficiency (SCADD) have debatable symptomatology (van Maldegem et al. 2010). Finally, many of these conditions have inadequate treatment to prevent all symptoms. For example, the presence of intellectual disability, ataxia, and premature ovarian failure has been demonstrated in adults diagnosed with classical galactosemia as newborns and restricted from lactose/galactose throughout life (Schweitzer-Krantz 2003).

Moreover, genetic counselors have faced many of the issues found in our study with the advent of multi-gene panel testing and whole exome sequencing (WES). Variants of uncertain significance (VOUSs) have become the rule rather than the exception in these tests, causing uncertainty in making recommendations for clinical follow up and treatment. VOUSs are particularly relevant in counseling for LSDs, as treatment timing is important for preventing disease sequelae but is costly, time-consuming, and burdensome to some families. Interestingly, patients seem to be less concerned about the need for treatment efficacy than some HCPs; a survey of parents and prospective parents in the general population of the Netherlands demonstrated strong support for NBS for less treatable (88 %) and untreatable childhood-onset disorders (73 %) (Plass et al. 2010). Weinreich et al. (2012) found that among both parents of children with Pompe disease and the general public in the Netherlands, an overwhelming majority (88 and 87 %, respectively) were in favor of NBS for PD and most felt that the possibility of false positive results and diagnosing late onset PD was acceptable (Weinreich et al. 2012). Although genetic counselors and other HCPs may be concerned about NBS for LSDs and other conditions not clearly outlined by Wilson and Jungner, parents and the general public appear to be less so.

Pompe Disease

Pompe disease was perceived in this study to be most favorable in terms of treatment efficacy, age of onset, and lack of ambiguity of confirmatory test results, with a mean approval score of 1.72 (1 = strongly agree), similar to two conditions already on the uniform screening panel, cystic fibrosis (CF) and carnitine palmitoyl transferase type II (CPT2). Typically, severe infantile Pompe disease manifests at or soon after birth with severe hypotonia, left ventricular hypertrophy and elevated creatine kinase levels. Treatment with enzyme replacement therapy (alglucosidase alfa) has been shown to prolong survival in infantile Pompe disease by up to 95 % and significantly reduce the need for mechanical ventilation and symptomatic cardiomyopathy (Kishnani et al. 2009). Later initiation of treatment appears to be less efficacious, suggesting benefit for early diagnosis by NBS (Kishnani et al. 2007). Thus, Pompe disease demonstrates many of the traditional characteristics of conditions traditionally deemed appropriate for NBS.

However, several issues complicate genetic counseling and clinical management following a positive NBS for Pompe disease. Based on data from Taiwan and U.S. States currently performing NBS for PD, more infants diagnosed with PD will have late onset Pompe disease (LOPD) than infantile onset, raising concerns about stigmatization and questions about timing of treatment. Additionally, these pilot programs have demonstrated a higher incidence of pseudodeficiency alleles in these populations that originally anticipated which create further ambiguity in clinical management for genetic counselors and other care providers (Hopkins et al. 2015; Yang et al. 2013).

Krabbe Diseease

Krabbe disease was considered least appropriate for NBS among the LSDs discussed, with a mean approval score of 3.14. It is interesting to note, though not further explored in this study, that the level of agreement regarding appropriateness for NBS for Krabbe disease was similar to scores for short-chain acyl-coA dehydrogenase (SCAD) deficiency, which is currently on most NBS panels, and fragile X syndrome, which is not currently recommended for NBS. Krabbe, in the classical form, begins in infancy, but data on treatment efficacy are variable. Kemper et al. (2010) (Kemper

et al. 2010) reviewed the available literature on hematopoetic stem cell transplant (HSCT, including bone marrow and cord blood transplants). They concluded that HSCT may provide net benefits in decreasing mortality and some morbidity, while the procedure itself causes mortality and morbidity, but long-term outcome data are not available. New York State began NBS for Krabbe disease in 2006, which Duffner et al. describe in their review (2009) (Duffner et al. 2009). Prior to screening, the ambiguity of test results was underappreciated. The authors conclude: "After 24 months of screening for Krabbe disease, there are many more questions than answers. It remains unknown whether infants considered at low risk will ever develop signs and symptoms of Krabbe disease, and it is not known whether any or all of the high-risk and moderate-risk children will develop disease at some point in their lives" (Duffner et al. 2009). Other studies have shown that ambiguity can be more stressful than either a positive or negative test result (Broadstock et al. 2000; O'Neill et al. 2009). Additionally, parents do not always understand a false-positive result, much less a result that is unclear (Tluczek et al. 1992). Providing anticipatory guidance for ambiguous results is one of the biggest challenges for genetic counselors in these cases, particularly when such a devastating condition may (or may not) be lurking around the corner. Thus, Krabbe does not obviously meet traditional criteria for NBS, although additional data could lead to increased support in the future.

Fabry and Gaucher Diseases

HCP's opinions regarding NBS for both Gaucher and Fabry diseases were similar, trending toward disagreement that they are appropriate for NBS, with mean approval scores of 2.67 and 2.68, respectively. Both have available treatments. A recent study of enzyme replacement therapy for Fabry disease described stabilization of left ventricular posterior wall thickness and renal function in patients treated earlier in life and with less advanced disease compared with older or more advanced patients (Germain et al. 2015). Reviews of treatment options for Gaucher (Beck 2010) showed improvement in spleen size, reduced hematological and bone manifestations, and increased energy levels in treated patients (Beck 2010; Pisani et al. 2012). Both conditions have onset after the newborn period, though, which led many respondents to disagree with their appropriateness for NBS. Timing of treatment initiation is a controversial issue in these conditions. Comments also suggest concern that treatment started too early burdens the patient and family as well as the healthcare system. Conversely, organ damage can become irreversible if not treated early enough (Warnock et al. 2012). The ability to diagnose affected family members is considered by some respondents as a benefit of NBS for Fabry disease (an X-linked condition) in the current study; one earlier study suggested that, on average, five other family members are found to be affected with Fabry disease, after the proband is identified in the family (Laney and Fernhoff 2008). This is another non-traditional argument for NBS that, like reproductive benefit, relies on benefit for individuals other than the infant being tested.

One potential genetic counseling dilemma that has arisen out of mandated NBS for LSDs in Missouri is the very high incidence of patients with the A143T mutation in *GLA*. Of the 40 positive screens for Fabry disease in the first 18 months of screening, 26 carry the A143T mutation (65 %) (Atherton et al. 2015). This, combined with other studies examining the phenotype of patients with A143T, raises questions about the pathogenicity of this variant (Desnick et al. 2015). Again, this is not a new dilemma in the genetic counseling arena and is now commonplace with WES. Further studies should be conducted on phenotypic significance of the A143T variant, however as NBS for LSDs and other new conditions begins in earnest, questionable variants will undoubtedly continue to arise. Professional organizations representing genetics HCPs should remain involved in decision-making policies about these complicated counseling dilemmas.

MPSI and MPSII

MPSI and MPSII were both viewed positively by HCPs for NBS (mean approval scores 2.04 and 2.44 respectively). However, MPSI was more favored than MPSII. Both conditions, in the most severe forms, have early age of onset and treatment strategies are fairly well established, leaving less ambiguity (Giugliani et al. 2010; Muenzer et al. 2009). Multiple studies have shown improved physical and neurocognitive outcomes of HSCT in Hurler syndrome when performed early. However HSCT in MPSII has been less well-studied, but has shown less evidence of neurocognitive improvement (Aldenhoven et al. 2008; Boelens et al. 2010; Guffon et al. 2009; Peters et al. 1996, 1998; Wraith et al. 2008). Thus, the paucity of evidence for neurological treatment efficacy in Hunter syndrome likely contributed to its lower approval score. As stated by one respondent, *"we don't know about stem cell transplant, if it's really effective or not, so we have mixed messages there."* Most HCPs stated that ERT in Hunter syndrome is effective enough to support inclusion in the newborn screen, but a significant minority felt less convinced, given the absence of improvement in neurocognitive decline. As clinical trials for new ERTs that potentially cross the blood brain barrier through intrathecal delivery (J. Muenzer et al. 2015) or a molecular "Trojan Horse" approach (Boado et al. 2013) emerge, approval of NBS for the neurocognitive forms of MPSI and MPSII may increase.

Diagnosing Later Onset LSDs

Unfortunately, the issue of later-onset forms of LSDs being diagnosed in the newborn period cannot easily be rectified.

None of the proposed dried blood spot testing methods for LSDs, including flourometric assay, MS/MS, and immune-quantification techniques, can distinguish between the infantile or later-onset forms of the disorders (Civallero et al. 2006; Matern et al. 2013; Mechtler et al. 2012; Miekle et al. 2006). Discriminating early and late-onset forms of LSDs by genotype-phenotype correlation may be possible for these disorders but is imperfect in Gaucher disease type 1, limited in Pompe, Krabbe and MPSII, and is not available for Fabry disease because of significant allelic heterogeneity (Hoefsloot et al. 1990; Terlato and Cox 2003). The more ambiguity in age of symptom onset, the less ideal a condition is viewed for NBS in our study. Although Weinreich et al. found that most parents of children with PD and those in the general public are not concerned about detecting later onset disease in the newborn period, further research should be conducted in this area (Weinreich et al. 2012).

NBS for Reproductive Benefit

Reproductive benefit, defined as the benefit of learning reproductive risk information for family planning, has been a considered as a secondary goal for several diseases on the newborn screen including sickle-cell disease and cystic fibrosis (Bombard et al. 2010; Massie et al. 2011; Ross 2012). Whether the information is actually used by families for reproductive planning in these populations remains unclear (Massie et al. 2011; McClaren et al. 2013). Reproductive benefit has been proposed as a primary goal of NBS for diseases with less evidence of treatment efficacy, such as with Duchenne muscular dystrophy and Fragile X syndrome (Abrams et al. 2012; Cyrus et al. 2012; Ross and Acharya 2008). However, as demonstrated in the recent study by van El et al. (2014), having knowledge of Pompe disease could also create an additional burden when making reproductive decisions (van El et al. 2014). Using NBS for this purpose remains controversial, particularly with the current model of screening with assumed consent (Ross and Acharya 2008). The ability to provide recurrence risk information and the possibility of prenatal diagnostic testing is certainly an important tool for the genetic counseling community, but the possible ramifications of having "toxic knowledge" for patients should be considered.

Lack of Resources for Follow-Up

Regarding the issue of resources for follow up, there is an obvious discrepancy based on where in the United States a baby is born. The third criteria developed by Wilson and Junger in 1968 states: "Facilities for diagnosis and treatment should be available." When the DACHDNC was chartered in 2003, great disparity was found among states regarding which diseases were mandated on NBS panels. Some states screened for over 30 conditions, while others mandated only 4 conditions. The committee recognized that some of this discrepancy results from availability of resources, including personnel, equipment, and service capacity (Fletcher 2006). The current study mirrored that finding, with some participants being concerned about resources while others were not, which was at least partially attributable to geographical location. Nationwide, there is a well-known dearth of HCPs with genetics expertise, including (but not limited to) genetic counselors. Genetic counselors are increasingly being asked to provide their services to patients with uncertain diagnoses for panel testing and WES, and positive NBS results with uncertain significance will certainly add to this workload.

Concern About Decision-Making Policy

Lastly, many HCPs have trepidation about how diseases are often haphazardly added to state newborn screening panels. These participants are not the first to express this concern: healthcare providers and bioethicists across the country are now considering the impact of patient advocacy groups, and their supporters, on NBS legislation. The recent experience of a high-profile patient support group successfully advocating for the addition of Krabbe disease to the New York State NBS panel and another pushing through several LSDs in Illinois without the input of those responsible for its implementation has made providers concerned about conflicts of interest, particularly with its controversial outcome data (Ross 2012). In this study, one respondent was adamant: "*I just don't appreciate, in general, one advocacy group in particular trying to shove this down the throats of states for a disorder in which the data wasn't very good to begin with. Now we have the data, and it's not good, and yet they keep pushing it*." Clearly, the concern here is not questioning that parents are critical or thoughtful stakeholders in the process. Rather, the essential question is how can we ensure an unbiased and rational approach to selection of conditions for NBS?

Research Recommendations

The discrepancy in opinion regarding newborn screening for LSDS among biochemical genetics clinicians versus genetic counselors was not expected. This may not be a surprising finding, however, based on an earlier study evaluating HCP's perceptions of the obligation to inform parents of carrier status found by NBS for sickle cell disease (Duffner et al. 2009) which showed that genetics providers (both geneticists and genetic counselors) tended to be less approving of disclosure than other healthcare providers, which the authors attributed to their knowledge and experience of ethical and policy issues with genetic testing. This may reflect hesitation of the biochemical geneticists in the present study with regard to NBS for LSDs, but it does not explain why genetic counselors are more approving than the biochemical geneticists. One

explanation for this discrepency would be that genetic counselors may tend to place a higher value on the "reproductive benefit" to the family from NBS for a condition that is less amenable to treatment, whereas the physicians tend to have a more traditional view of the criteria for screening. Comparing HCPs with experience working with NBS for LSDs with those that did not have experience, the mean approval scores were similar, again, consistent with a higher value assigned to the potential reproductive benefit. This discrepancy warrants further investigation, especially if it does, in fact, reflect a divergence of opinion in the field regarding reproductive benefit as a criterion for NBS.

Study Limitations

This paper was performed as a largely qualitative study to determine the perceptions of genetic healthcare providers and should be transferable to genetic healthcare providers in general but is not generalizable to all healthcare providers. The study population does include individuals from several fields in medical genetics and are from varied geographical areas, thus providing variability in data collection. However, genetic counselors from Ohio were overrepresented, as the Ohio Genetic Counselor Listserv was used for participant recruitment. It is possible that ascertainment bias may have occurred due to our recruitment strategies. After 40 interviews, the study reached saturation, thus a larger sample size should not have affected results. However, it is possible that the individuals who felt most strongly about NBS for LSDs (both positively and negatively) contacted us to participate, however this is difficult to mitigate in any population in which recruitment involves advertisement. The first author who performed all interviews, is herself a genetic counselor working with patients with LSDs, thus she may have been influenced by her experiences which may have impacted her interpretation of the data. Participants could have been inhibited in sharing their opinions in some way knowing the background of the interviewer. Additionally, there is inherent subjectivity when researchers embark in qualitative research, thus the authors practiced reflexivity and attempted to reduce bias wherever possible. Finally, the interviewers were performed almost 2 years prior to the date of submission of this manuscript, and discussions of NBS for LSDs have increased during this time period. It is possible that the providers interviewed have more experience with NBS for LSDs and/or changed their opinions about this controversial issue in the interim.

Conclusions

Healthcare providers working in the field of metabolic genetics have the most experience with NBS for inborn errors of metabolism and treating patients with LSDs, yet they have varying opinions on the inclusion of these diseases on NBS panels. In general, HCPs' opinions regarding criteria for screening are consistent with those elucidated by Wilson and Jungner 50 years ago: diseases included on the NBS should have effective treatment, younger age of onset, straightforward test results, and the natural history and prognosis should be well established. Of the LSDs discussed, Pompe disease is most favored for inclusion by HCPs. Generally in keeping with traditional criteria, MPSI and MPSII receive higher priority from HCPs, while Fabry and Gaucher diseases are less generally favored for NBS. Krabbe disease is least favored for NBS.

HCPs disagree about whether reproductive benefit is an acceptable reason for NBS, whether we have enough resources in place for follow up and treatment for abnormal newborn screens for LSDs, who should decide what diseases are included on mandated NBS, and even how to define "effective" treatment. There appears to be a general sense of dissatisfaction with the current approach to evaluating conditions to be added to NBS panels and a clear desire for more evidence based approaches. There is much to learn before implementing NBS for additional conditions, including: information about penetrance and expression of the specific variants identified by screening, relative value to parents of the benefits of early detection (especially for reproductive planning), and relative burden of false positive tests and variants of unknown significance.

Finally, HCPs appear to value the information gained from carefully designed pilot studies of new approaches and new conditions for NBS. We anticipate that the results from this study will help inform decision-makers on NBS for LSDs, and should provide support for designing and funding pilot studies, continued engagement of key stakeholders through mechanisms like the DACHCNC, and development of even more evidence-based criteria for adding conditions to the recommended NBS panel. Additionally, the themes that emerged have broader implications for other diseases that arise for possible inclusion on the NBS in the future.

Acknowledgments The authors would like to thank Aaron Goldenberg, Ph.D. and the Center for Genetics Research Ethics And Law (CGREAL) at Case Western Reserve University for their advice on study design, use of the ATLAS.ti 6.0 software, and critical reading of the manuscript. We also acknowledge Shire and Pfizer for unrestricted funding that made this study possible.

Conflict of interest Emily C. Lisi and Shawn E. McCandless declare that they have no conflict of interest.

Human Studies and Informed Consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

Animal Studies No animal studies were carried out by the authors for this article.

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