Newborn Screening for Pompe Disease

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abstract Started in 1963 by Robert Guthrie, newborn screening (NBS) is considered to be one of the great public health achievements. Its original goal was to screen newborns for conditions that could benefit from presymptomatic treatment, thereby reducing associated morbidity and mortality. With advances in technology, the number of disorders included in NBS programs increased. Pompe disease is a good candidate for NBS. Because decisions regarding which diseases should be included in NBS panels are made regionally and locally, programs and efforts for NBS for Pompe disease have been inconsistent both in the United States and globally. In this article, published in the "Newborn Screening, Diagnosis, and Treatment for Pompe Disease" guidance supplement, the Pompe Disease Newborn Screening Working Group, an international group of experts in both NBS and Pompe disease, review the methods used for NBS for Pompe disease and summarize results of current and ongoing NBS programs in the United States and other countries. Challenges and potential drawbacks associated with NBS also are discussed.

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NEWBORN SCREENING

Newborn screening (NBS) is an important public health initiative that was established as a means of early detection and identification of serious conditions in newborns for which there is effective therapy.[1,2] Considered by many as one of the great public health achievements in history, advocates of NBS recently celebrated its 50th anniversary.[3] It was started in 1963 when Robert Guthrie developed an intriguing yet simple method to use blood dried on filter cards, the "Guthrie card," to screen newborn infants for elevated phenylalanine levels by using a bacterial inhibition test, the "Guthrie test."[4,5]

NBS originally was intended as a means to screen newborns for conditions for which presymptomatic treatment would be beneficial and minimize developmental disability and mortality. With the availability of better screening methods that can accurately identify disorders and with therapies available for the identified disorders, advocates of NBS are citing other benefits of NBS and the need for expanding and standardizing screening initiatives. As new technologies have emerged, the scope of NBS has expanded. Additional disorders were added over time, although it was not until the advent of tandem mass spectrometry (MS/MS) when there was a "quantum leap" in disorders included in NBS programs.[6]

The NBS decision process to identify disorders to include in screening programs is based on work by Wilson and Jungner, who outlined criteria for population-based screening.[7] These criteria have been broadly adapted for NBS, and most of the current screening conditions do not actually fulfill all of the Wilson and Jungner criteria. In this context, target disorders should pose a significant public health problem and be identifiable through a suitable, reliable, and relatively inexpensive NBS test. Effective treatments that can prevent long-term morbidity should be available and the cost of screening and treatment justifiable when compared with the cost of care for untreated patients. In addition, diagnostic and management guidelines should be agreed on and the natural history of individual disorders should be known.[1,8] Not surprisingly, decision processes around the world for inclusion of disorders vary widely.[9] The United States has taken a highly organized approach that is based on available evidence to decide on what conditions to include in their screening program. Some European countries and those in other geographic areas have been extremely cautious and restrictive in their approaches to expansion of NBS programs.[10,11]

In the United States, conditions can be nominated for inclusion in the Recommended Uniform Screening Panel (RUSP), which is the list of diseases recommended for NBS, via the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC; previously the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children); (http://www.hrsa.gov/advisorycommittees/mchbadvisory/heritabledisorders/index.html). If this committee determines that the evidence supports NBS for the condition, it advises the Secretary of Health and Human Services to add the condition to the RUSP. Should the Secretary agree with the committee, the decision to screen for a condition still remains with the individual states.

NBS AND POMPE DISEASE

Diagnosis of Pompe disease can be difficult because of its rarity, variable nature and onset of symptoms, and overlap of signs and symptoms with other disorders. This may lead to misdiagnosis as well as delays in diagnosis and initiation of effective treatment. Pompe disease is associated with significant morbidity and mortality. The introduction of reliable and accurate means for screening in presymptomatic newborns can lead to improved clinical outcomes for affected infants compared with those identified by clinical signs and symptoms.

With specific treatment available (that is, enzyme replacement therapy [ERT] with alglucosidase alfa), interest in NBS for Pompe disease has increased.[8,12,13] In March 2015, the US Secretary of Health and Human Services approved the recommendation made by the ACHDNC in May 2013 to add Pompe disease to the RUSP. Generally, patients affected with conditions that are recommended for the NBS panel are likely to benefit from early diagnosis and treatment.[14]

METHODS FOR NBS FOR POMPE DISEASE

Technical advances have contributed significantly to the feasibility of NBS for Pompe disease, such as the availability of better, more accurate, and easier means of diagnosis (eg, dried blood spots [DBSs]) for measuring enzymatic activity for Pompe disease. With DBS testing, only small amounts of blood are needed and enzymes remain stable. These advances have helped Pompe disease to be integrated into standard NBS programs.[15] Methods for NBS for Pompe disease should fulfill the following minimum characteristics: acceptable performance characteristics (high specificity and sensitivity), applicability in DBSs, high throughput and multiplex capabilities, acceptable cost, and reliable supply of reagents. Multiplex assays that can measure the activity of several enzymes are cost-effective in NBS.[16,17]

Different methods have been reported during the past years.

TABLE 1 Analytical Methods Used for NBS for Pompe Disease

Characteristics	Screening Methods		
	MS/MS	Fluorometry	Microfluidics
High specificity (>98%) and sensitivity (99.9%)	Yes	Yes	Yes
Doable on DBS	Yes	Yes	Yes
High throughput	Yes	Yes	Yes
Multiplex	Yes	No	Yes
NBS program(s)	New York State Illinois Kentucky Mississippi Pennsylvania Washington State (pilot)	Taiwan Hamburg (pilot)	Missouri

These assays are based on the analysis of enzyme activities by using artificial substrates in DBS, either by fluorometry, MS/MS,[17] or microfluidics combined with fluorometry.[18,19] Other methods are based on analysis of accumulating substrate,[20–22] immune quantification,[23] and/or immune capture activity of the enzyme of interest.[24] Characteristics of each of the analytical methods used for NBS are summarized below and can be compared in Table 1. There are no published data currently available that allow reliable and meaningful comparisons of the costs and logistical requirements associated with implementing each of the screening assays. However, the costs of the assays, space requirements, and feasibility should be carefully considered by individual laboratories in the decision-making process regarding which methods to use for NBS.[17]

The summaries and discussions of the methods used for NBS are based on the collective experience and expertise of the members of the Pompe Disease Newborn Screening Working Group.

These guidelines and recommendations do not necessarily reflect the policy of the American Academy of Pediatrics, and publication herein does not imply endorsement.

Fluorometry (Enzyme Activity)

Chamoles et al[21,25–28] invented and championed the use of a fluorometric method for the analysis of enzyme activities in DBS for Pompe disease[21] as well as for mucopolysaccharidosis (MPS) type I,[26] Gaucher disease and Niemann-Pick disease,[27] and Fabry disease.[28] Typically, a 3-mm DBS per sample is punched into separate wells of a 96-well plate with the first and last wells reserved for blank filter card punches. Blood is extracted from DBSs by using an extraction buffer and then incubated with an enzyme-specific 4-methylumbelliferone (4-MU) substrate for at least 6 to 10 hours. The measured fluorescence after the release of fluorescent 4-MU is proportional to the enzyme activity in DBS. 4-MU substrates are currently available for Pompe disease and a number of other lysosomal storage disorders (LSDs) (see Glycosynth, SigmaAldrich, Moscerdam Substrates, Toronto Research Chemicals). One important disadvantage of the fluorometric method is the lack of multiplex capabilities precluding the simultaneous analysis of a second enzyme for quality purposes (eg, integrity and quality of DBS) (Table 1). Taiwan has been using a fluorometric enzyme assay for NBS for Pompe disease since 2007.[29,30] The reported false-positive rate of 1.04% and a positive predictive value of 0.65%, however, do not compare favorably to other screening techniques[31] (Table 2).

MS/MS (Enzyme Activity)

Gelb et al[38] and Li et al[39] designed artificial substrates and internal standards for analysis of several lysosomal enzyme activities using MS/MS. In brief, DBSs are incubated with disease-specific substrates and internal standards at 37°C for several hours before a series of extraction steps and analysis by using MS/MS.[40] The analytical protocols have been optimized to improve throughput and sensitivity.[32,39,41] Substrates and internal standards are currently available for Pompe, Fabry, Gaucher, Niemann-Pick, and Krabbe diseases as well as MPS types I, II, and IVA.[38,41–44] The Newborn Screening and Molecular Biology Branch at the Centers for Disease Control and Prevention has been providing analyte-specific reagents for 6 of these assays to NBS laboratories free of charge through a program sponsored by Sanofi Genzyme. This service was discontinued at the end of 2016, and Perkin Elmer will be the only provider of these substrates and internal standards.

Microfluidics and Fluorometry (Enzyme Activity)

In the digital microfluidic platform for NBS for Pompe disease and several other LSDs, enzyme activity is measured by using a fluorometric enzyme assay based on the same principle that has been described previously.[18,19] Sample and substrate are moved as droplets through electrodes by using electric currents.

TABLE 2 Results of NBS Programs for Pompe Disease

Newborn Screening Program or Initiative	Total No. Samples	Screening Method(s)	Positive	Abnormal Screening Results (First- or Second-Tier Testing)				Total Cases Pompe Disease		Positive Predictive Value	Prevalence
				Pseudodeficiency	Carrier	Other	Total False Positive	Classic IOPD	LOPD		
Global											
Taiwan[29]	473 738	Fluorometric enzyme assay	250: 31 (first tier), 219 of 2210 (second tier)	10	0	0	222 (1:2133)	9	19	0.11	1/16 919
Austria[32]	34 736	ESI-MS/MS	5	0	0	0	1 (1:34 736)	0	4	0.8	1/8684
Italy[33]	3403	Fluorometric enzyme assay	12 (first test), 3 (recall)	0	0	0	12 (1:283)	0	0	0.0	N/A
Hungary[34]	40 024	MS/MS	64 of 163 (second tier)	0	25	0	154 (1:262)	7	2	0.06	1/4400
Japan[35]	530[a]	Modified fluorometric assay	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
United States											
Illinois[b] (pilot study)	166 463	MS/MS	110	12	12	10	99 (1:1681)	2	9	0.1	1/15 133
Missouri[c]	269 500	Digital microfluidics	137	23	29	61	113 (1:2384)	4	20	0.18	1/11 229
Washington[36,37] (pilot studies)	154 544	MS/MS	24	7	4	3	14 (1:11 038)	0	5	0.21	1/31 000
New York[d]	390 000	MS/MS	75	14	0	30	44 (1:8863)	1	1 non-classic IOPD; 29 potential LOPD[e]	0.03	1/165 000

Classic IOPD includes patients with onset of symptoms ≤12 mo of age with cardiomyopathy. LOPD includes patients with onset of symptoms >12 mo of age and patients with onset of symptoms ≤12 mo of age without cardiomyopathy (non-classic infantile-onset patients). ESI-MS/MS, electrospray ionization tandem mass spectrometry. N/A, not applicable.

[a] Comprised 496 healthy Japanese controls, 29 Japanese patients, and 5 obligate carriers.

[b] Barbara Burton, MD, Illinois State NBS program, unpublished data (see Acknowledgments).

[c] Patrick V. Hopkins, BS, Tracy Klug, BS, Sharmini Rogers, MPH, Julie Raburn-Miller, MSW, and Jami Kiesling, BSN, Missouri NBS program, unpublished data (see Acknowledgments).

[d] Michele Caggana, ScD, Joseph Orsini, PhD, Colleen Stevens, PhD, and Erin Hughes, MS, New York State NBS program, unpublished data (see Acknowledgments).

[e] Of the 29 potential cases of LOPD, 15 were classified as "probable" LOPD and 13 as "possible." Results were not available for 1 patient at the time of publication.

The microfluidics technique has been developed recently and requires a kit assay, which is currently under regulatory review with the US Food and Drug Administration for use in the United States. It does compare favorably, however, to the other more established techniques (Table 1).

MOLECULAR SEQUENCING

Molecular sequencing of the acid α-glucosidase (*GAA*) gene is important for confirmatory (second-tier) testing after a positive newborn screen for Pompe disease. Because screening laboratories generally do not have sequencing capabilities, second-tier screening is not part of most NBS programs. A number of NBS programs, however, do have second-tier screening that includes full gene sequencing.

PSEUDODEFICIENCY IN POMPE DISEASE AND ITS EFFECT IN NBS

Pseudodeficiency is caused by variants in the *GAA* gene that result in low measured GAA activity in enzyme assays. However, pseudodeficiency is not associated with clinical features or a diagnosis of Pompe disease. Whether the presence of a pseudodeficiency variant may influence the effect of another variant is not fully understood at this time. The prevalence of pseudodeficiency varies regionally, with a high frequency seen in Asian populations.[45,46] Screening laboratories need to be aware of the possibility of pseudodeficiency, which could increase false-positive screen results. Confirmation of a diagnosis of Pompe disease with secondary testing and clinical examination is essential. Gene sequencing is important for identification of pseudodeficiency allele(s).

SUMMARY OF RESULTS OF NBS PROGRAMS FOR POMPE DISEASE

The effectiveness of NBS in LSDs to improve outcomes was first demonstrated in Pompe disease. The authors of a study from Taiwan demonstrate beneficial long-term outcomes after diagnosis of classic infantile-onset Pompe disease (IOPD) through NBS and timely treatment with ERT.[47] However, the authors also demonstrate limitations of early ERT because of the occurrence of pelvic muscle weakness in patients >2 years of age and a high incidence of ptosis and speech disorders.[47]

The results of NBS programs for Pompe disease, some still ongoing, are summarized below and in Table 2.

Global NBS Initiatives

Taiwan

Results of NBS have been summarized for 473 738 newborn samples screened for Pompe disease.[29] Samples were collected at age 48 to 72 hours for the first DBS. In Taiwan, a fluorescence assay is used to screen GAA activity. Two assays were performed at screening (first-tier testing): GAA activity measured at pH 3.8 in the presence of acarbose and neutral α-glucosidase (NAG) activity measured at pH 7.0 without acarbose. A cutoff ratio for NAG/GAA ≥100 was indicative of a positive screen and led to confirmatory testing. A third assay, in which the total GAA activity measured at pH 3.8 without acarbose, was performed as a second-tier test for samples that had inconclusive first-tier screening results (NAG/GAA ratio ≥30 to <100). Positive screen results for second-tier testing led to referral for confirmatory testing. NBS in Taiwan resulted in identification of 9 cases of classic IOPD and 19 cases of late-onset Pompe disease (LOPD), including patients with non-classic IOPD.

Austria

Electrospray ionization MS/MS was used to screen specimens from DBSs collected from 34 736 newborns for a pilot study by using a multiplex screening assay (Pompe disease, Gaucher disease, Fabry disease, and Niemann-Pick disease types A and B).[32] Molecular testing was done when there was a suspected enzyme deficiency. The cutoff for GAA enzyme activity was 2.0 μmol/hr/L. The first-line screening identified 25 samples with low GAA activity. The samples were retested in duplicate by using the same DBS. Five were positive by biochemical analysis for Pompe disease. Variant analysis confirmed Pompe disease in 4 samples; 1 was false-positive.

Italy

A pilot NBS program for 4 LSDs (Pompe disease, Gaucher disease, Fabry disease, and MPS type I) was conducted involving 3403 newborn infants in Italy.[33] A fluorometric assay was used to measure enzyme activity on DBSs. The established cutoff value for GAA was ≤25% normal median activity (24.5 nmol/hr/mL). Retested samples with blood spot activity less than the cutoff value were recalled and tested with conventional leukocyte or lymphocyte assays. Low GAA levels initially were detected in 12 samples. A second DBS was obtained for these and GAA activity was found to be low in 3 of the 12 samples. Follow-up testing on whole blood revealed normal activity in the 3 patients. No cases of Pompe disease were identified among the 3403 newborn infants.

Hungary

MS/MS was used to screen 40 024 NBS samples for 4 LSDs: Fabry disease, Gaucher disease, Niemann-Pick disease, and Pompe disease.[34] If the first screening result was less than the set cutoff values for the respective disease, then the samples were subsequently analyzed twice.

If the means of the results of the 3 assays were less than the respective cutoffs, then samples were used for confirmatory molecular testing. The cutoff value for GAA enzyme activity was 3.00 μmol/hr/L. Abnormal low activity for GAA was found in 163 (0.41%) samples during the initial testing and 64 samples after retesting. The 64 samples were considered highly suspicious of being affected and were therefore sent for molecular genetic testing. Of these, 9 were confirmed for Pompe disease, 25 were carriers, and 3 were classified as uncertain because variant analysis was inconclusive; 27 were normal.

Japan

To assess the feasibility of NBS in Japan, GAA activity was assayed in DBS samples obtained from 496 healthy Japanese controls, 29 Japanese patients with a confirmed diagnosis of Pompe disease (2 classic IOPD, 14 juveniles, and 13 adults), and 5 obligate carriers.[35] A modified fluorometric assay was used to determine GAA activity. Three assays were performed for screening: total GAA activity measured at pH 3.8, GAA activity measured at pH 3.8 in the presence of acarbose, and total NAG at pH 7.0 without acarbose and the NAG/GAA ratios calculated. DNA sequencing was done in the DBS samples. A cutoff for GAA activity of 8% (1.7 pmol/punch per hour) of the normal average identified all 29 patients with Pompe disease (100%), 5 healthy homozygotes with pseudodeficiency alleles (33%), 1 obligate carrier (20%), and no healthy controls. The overall false-positive rate was 0.3%.

NBS Programs in the United States

A number of states in the United States have opted to expand NBS to include LSDs because of lobbying efforts of different advocacy groups. Some conditions, most notably Krabbe disease, underwent an evidence review by ACHDNC but were recommended for inclusion in the RUSP in 2008, although New York State started NBS for Krabbe disease in 2006.[48]

Washington

Screening of 111 544 anonymized DBS samples was done at the University of Washington by using MS/MS for a multiplex screen for Pompe disease, Fabry disease, and MPS type I.[36] The cutoff for GAA activity for Pompe disease was ≤2.6 μmol/hr/L (≤15% of the mean). At first-tier testing for Pompe disease, GAA activity of 17 samples was ≤2.6 μmol/hr/L. Variant analysis revealed that 4 samples were consistent with possible Pompe disease, 4 samples were carriers, 3 were from carriers who also had a pseudodeficiency allele, and 6 were pseudodeficiencies. In a recent pilot study done at the Washington state NBS laboratory, a new 6-plex (Fabry, Gaucher, Krabbe, MPS type I, Niemann-Pick types A and B, and Pompe diseases) flow-injection MS/MS assay was used for the screening of ∼43 000 (range: 42 391–44 485) newborn DBSs. Of the 44 074 samples screened for Pompe disease, 2 were found to have GAA enzyme activity less than the established cutoff of <1.24 μmol/hr/L (10% of the daily mean of 12.41 μmol/hr/L). One was found to be affected by Pompe disease and the other was shown to have nonpathogenic variants common in the Asian population. The number of screen-positive samples for Pompe disease thus was 4.5 per 100 000 newborns.[37]

Missouri

The state of Missouri requires screening for LSDs (Pompe disease, Fabry disease, Gaucher disease, MPS type I, and Krabbe disease). A full-population NBS pilot study using multiplex fluorometric enzymatic assay (digital microfluidics) was started in January 2013 and went fully "live" on August 3, 2015.[13] The Missouri NBS program was the first full-population screening study with follow-up care for 4 LSDs (Pompe disease, Fabry disease, Gaucher disease, and MPS type I) and the first NBS program to use a digital microfluidic method for screening in the world. Results were analyzed and published after the first 6 months, during which 43 701 nonblinded DBS samples from newborns were screened to validate the effectiveness of the digital microfluidics method and the cutoffs used for disease detection and to evaluate the overall NBS program. The GAA activity cutoff, 8.0 μmol/hr/L, was set conservatively at the start. Positive DBS results led to referral for confirmation of diagnosis in 18 patients. Of these 18 patients, 3 patients were confirmed to have IOPD (2 classic IOPD and 1 non-classic IOPD), 3 with LOPD, and 2 with a condition of unknown significance or onset.[13] Additional information from the Missouri program is now available, although it has not been published. As of June 15, 2016, the researchers with the Missouri NBS program screened ∼269 500 newborns. There were 137 positive screen results for Pompe disease. Of these, 24 were confirmed for Pompe disease (6 with IOPD [4 classic IOPD and 2 non-classic IOPD] and 18 with LOPD); 8 were conditions of unknown significance or onset; 23 were pseudodeficiencies; 29 were carriers; 42 had confirmatory enzyme levels that were within the normal range, therefore no DNA testing was conducted; 1 was lost to follow-up; and 10 are pending (P.V. Hopkins, BS, T. Klug, BS, S. Rogers, MPH, J. Raburn-Miller, MSW, J. Kiesling, BSN, unpublished data [see Acknowledgments]).

Illinois

A pilot screening program for 5 LSDs was initiated in selected hospitals in Illinois in November 2014 and became statewide in June 2015. An ultrahigh pressure liquid chromatography–MS/MS method is

being used. Among the first 166 463 infants screened, a total of 11 cases of Pompe disease were identified, yielding an incidence of 1 in 15 133. There were 2 cases of IOPD, both of which started on ERT, and 9 cases of LOPD, 7 of which were homozygous for the common splice site variant. A total of 110 infants required definitive testing because of an initial positive screen. Of these, 65 were normal, 12 were carriers of Pompe disease, 12 had pseudodeficiency, 2 were unresolved because of death or family relocation, and 8 were pending at the time of data analysis (B. Burton, MD, unpublished data [see Acknowledgments]).

New York

The New York State NBS Program currently uses multiplex MS/MS assays to screen for x-linked adrenoleukodystrophy (X-ALD) as well as Pompe disease and Krabbe disease. Of ~390 000 samples screened in New York, 75 were referred for confirmatory diagnostic testing when a cutoff for GAA activity of ≤15% of the daily mean was used. One classic and 1 non-classic case of IOPD were identified. Twenty-nine of the 75 samples were identified as potential cases of LOPD (GAA activities 5.6%–14.3%). Fifteen of the 28 were classified as "probable" LOPD and 13 as "possible" LOPD. Among infants not referred for confirmatory diagnostic testing, 14 infants were found to have pseudodeficiency alleles only. GAA activity in these patients ranged from 9.4% to 14.7%. Fifteen infants with low GAA activity values (11.5%–15.0%) were found to have normal allelic variants only. All but one of the 15 infants had been in the NICU or had delayed specimen collections (M. Caggana, ScD, J. Orsini, PhD, C. Stevens, PhD, and E. Hughes, MS, unpublished data [see Acknowledgments]).

CHALLENGES, DRAWBACKS, AND NEGATIVE ASPECTS ASSOCIATED WITH NBS

There are a number of challenges, drawbacks, and negative aspects associated with NBS for Pompe disease that need to be considered and addressed. The occurrence of pseudodeficiency can complicate NBS in Pompe disease, particularly in Asian populations, in whom it has a high frequency.[16,49] At this time, the frequency of pseudodeficiency in other populations is not known because in some NBS pilot programs, follow-up genetic testing is not done. However, our knowledge on the occurrence of pseudodeficiency will likely unfold as more NBS programs are started in other states and countries and the number of infants screened for Pompe disease increases, allowing us to gather this much-needed, important information.

Although classic IOPD is always rapidly progressive, it does not fully meet the definition of being acute and therefore does not meet the Society for Inherited Metabolic Disorders criteria to be considered a critical condition.[50] All members of the Pompe Disease Newborn Screening Working Group do agree and strongly recommend that results of NBS should be provided in a timely manner so a diagnosis can be confirmed and treatment started as early as possible for patients with classic IOPD because any delay in diagnosis can significantly change the treatment outcome.

When positive screening results are obtained, parents may not always agree to confirmatory testing. Diagnosis of LOPD when phenotype prediction is challenging may be a drawback. Many times, when a later-onset form of Pompe disease that is currently asymptomatic and with an unpredictable age of onset is identified, patients are lost to follow-up. Emotional stress associated with positive results has to be considered, even when initial positive results subsequently are identified as false. Rapid and available means of confirmatory testing are needed. Effective education, communication, and follow-up with parents throughout the process are crucial.

Because predictions of phenotype and/or age of symptom onset can be challenging, additional diagnostic tests (eg, biomarker, genetic modifier) need to be developed to reliably estimate individual disease burden and onset. Timing of treatment initiation can be critical to prevent morbidity and mortality as demonstrated by the outcome data reported from the Taiwan NBS program.[47]

The challenges associated with NBS for Pompe disease underscore the need for coordination of care and collaboration among the health care team and specialties involved regarding diagnosis, treatment, follow-up, reimbursement, and associated ethical issues.[8,15] Standardization of NBS can be difficult because of potential associated costs, an overall lack of trained specialists who are familiar with NBS and the diseases being screened and a lack of facilities to effectively implement NBS, and increased difficulty in screening and a need for appropriate resources as NBS programs expand.[8] Because there is considerable variability in both phenotypes and genotypes between different patient populations, clinicians need to rely on and learn from the collective experience reported by other clinicians treating patients with Pompe disease. The majority of NBS programs depend on referring physicians to report data on molecular testing back to the individual programs. Regional and disease registry programs, which often are repositories for data of enrolled patients with rare diseases, such as the Pompe Registry, also are sources of important clinical

information for clinicians. The Pompe Registry, sponsored by Sanofi Genzyme, is an observational program. Enrollment in the Pompe Registry is voluntary and patients are required to provide informed consent prior to enrollment. Site-specific Registry data are available to enrolling clinicians. By enrolling patients, physicians are afforded the opportunity to request aggregate patient data from the Registry. However, NBS programs are unable to access and evaluate patient genotype data from the Pompe Registry. Requests for such data sharing are not permitted because this type of data is outside the scope of the patient consents. Details about the Pompe Registry and instructions on how to enroll patients can be found at https://www.registrynxt.com.

Despite the challenges and potential drawbacks one may cite that are associated with NBS, the lives of the children that have already been saved and improved through existing NBS programs and the many that can and will be saved with standardization and expansion of NBS programs far outweigh any negative aspects. For diseases such as Pompe disease that have early-onset forms and for which the earliest diagnosis and initiation of treatment can make a difference between survival and positive outcomes and death and severe disability, few can dispute the importance of NBS for these disorders.[8]

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ABBREVIATIONS

4-MU: 4-methylumbelliferone
ACHDNC: Advisory Committee on Heritable Disorders in Newborns and Children
DBS: dried blood spot
ERT: enzyme replacement therapy
GAA: acid α-glucosidase
IOPD: infantile-onset Pompe disease
LOPD: late-onset Pompe disease
LSD: lysosomal storage disorder
MPS: mucopolysaccharidosis
MS/MS: tandem mass spectrometry
N/A: not applicable
NAG: neutral α-glucosidase
NBS: newborn screening
RUSP: Recommended Uniform Screening Panel
X-ALD: x-linked adrenoleukodystrophy

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