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NEWBORN SCREENING FOR LYSOSOMAL STORAGE DISEASES: CURRENT LANDSCAPE AND STATE-WIDE PERSPECTIVES IN THE US

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ABSTRACT

Background -

Lysosomal storage disorders (LSDs) are a group of inherited metabolic disorders caused by abnormal accumulation of waste products in the lysosomes. Newborn screening (NBS) programs were introduced in the early 1960s to enable early detection of certain inherited diseases. In the United States, such programs have evolved to include various diseases on each state's individually administered screening panel. LSDs are among the most recent to be introduced as a part of expanded panels. This study summarizes the current LSD landscape in the US and quantitatively analyzes the various underlying factors for including LSDs on NBS panels.

Methodology

We conducted a nationwide survey of state NBS programs in which a telephonic survey was administered to the individuals in the National Newborn Screening and Genetics Resource Center (NSGRC) database. The survey assessed the importance of different factors in the decision to add a new disease to the state's NBS panel.

Results

The survey shows there are several factors influencing a state's decision to include a LSD in its newborn screening panel. Out of these, the need for supporting infrastructure, constituent pressure and route of approval were important factors, commonly observed across all the states, to include LSDs on NBS.

Conclusions

The survey results help understand the current landscape of NBS for LSDs. We conclude that there is a need to design potential educational initiatives that will support a uniform national screening process for LSDs.

INTRODUCTION

Lysosomal storage disorders (LSDs) are a group of approximately 50 inherited metabolic disorders, caused by a deficiency of enzymes. LSDs are characterized by storage of different substrates in various tissues and organs, causing a variety of pathologies and clinical manifestations. Over the last two decades, significant progress has been made in developing treatment for many of the LSDs including enzyme replacement therapy, substrate reduction therapy (SRT), pharmacological chaperones, and hematopoietic stem cell transplantation, among others. [1-3]

Newborn screening takes place before the newborn leaves the hospital. NBS identifies conditions that can affect long-term health or survival. Such diseases may be rare, but early detection, diagnosis, and intervention can prevent morbidity and mortality to enable the newborn to reach their greatest potential. Newborn screening was first introduced in the early 1960s through the work of Dr. Robert Guthrie, who developed a screening test that could identify those newborns at risk of phenylketonuria (PKU) before it was clinically symptomatic.[4-6] While the test was not perfect, PKU screening was considered a success and spurred interest in improved screening to guide early treatment for other metabolic diseases. As NBS programs matured, many national and international agencies began defining standards to guide the selection of diseases that would be suitable for newborn screening. In 1968, the World Health Organization (WHO) published a report called "Principles and Practice of Screening for Disease," outlining 10 main principles to guide screening including the capability for early detection and availability of treatment.[7,8] These principles are commonly known as the Wilson-Jungner principles, still upheld today as the "gold standard of screening assessment."[9]

Since the WHO report, screening programs have become more organized and advances in technology have allowed

many different disease screenings to be combined into one test. While both US federal and state governments oversee newborn screening, the federal government's role is limited to the creation and oversight of supporting organizations and laws, such as the Secretary's Advisory Committee on Heritable Disorders in Newborn and Children (SACHDNC), the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) and the US Food and Drug Administration (FDA). The SACHDNC was established as an official advisory body to the Secretary of the Department of Health and Human Services to explore the ethical, social, clinical and political implications of newborn screening while the CLIA-88 ensures that laboratory tests abide to established standards and the FDA approves the screening tests. In contrast, the responsibility to shape an individual state's screening program, such as the number of diseases screened, criteria for inclusion, change in testing protocols, allocation of funds and establishment of infrastructure, falls under state jurisdictions. [9] Therefore, the lack of a federal mandate creates a disparity among state screening practices.

Because of the disparity in newborn screening adoption policies and a varying panel of diseases screened in each state, the Maternal and Child Health Bureau of the federal Health Resources and Services Administration (HRSA) commissioned the American College of Medical Genetics (ACMG) to recommend a uniform panel of conditions in 2004. In 2006, the ACMG recommended 29 core conditions for a uniform panel.[9] In addition to the core panel, the ACMG report also created a list of secondary targets or conditions. These included 25 conditions that fell short of the inclusion requirements to be added on the primary core panel, but can be identified in the screening process through multiplexed screenings.[9] The Recommended Uniform Screening Panel (RUSP) proposed by the ACMG consisted of a total of 56 conditions with 31 core conditions and 25 secondary conditions.[9] The RUSP has since been endorsed by advocacy groups, professional organizations, and the SACHDNC.[9] The committee has recently codified the RUSP with 34 core conditions and 26 secondary conditions since 2015. Guidelines for adding conditions to the RUSP include incidence, benefits to the child, treatment availability, cost, and feasibility, evidence-based review of the conditions and feasibility of implementation of screening at the state level. The decision regarding screening ultimately lies with the state health departments. [10]

The states consider the recommendations from the SACHDNC, while allocating funds to these screening programs, in addition to following the National Committee for Clinical Laboratory Standards (NCCLS), and guidance from the HRSA-funded Council of Regional Networks for Genetic Services (CORN). [9,11-12] The decision to add a condition to the newborn screening panel is typically under the control of the state health officials, a state board of health, or a genetics or newborn screening advisory committee through independent processes.[11]

The state public health department screening programs operate through various partnerships or contractual relationships between public and private entities.[11] These partnerships usually follow the guidance from CORN, including the selection and evaluation of additional conditions to the screening panel, quality assurance, funding, diagnosis, management, treatment and counseling guidelines, program evaluation and management of screening information database. [9,11-12] In January 2013, the Advisory Committee adopted a revised decision-making matrix to consider conditions that could be nominated to the newborn screening panel. This revised matrix considers the capability of State NBS programs to implement screening based on their feasibility and readiness. The key features of readiness and feasibility include resources for screening, financial resources and laboratory resources. [13]

Currently, seven of more than 50 known LSDs are candidates for newborn screening in the US, including: Gaucher, Pompe, Fabry, Niemann-Pick Type A and B, Mucopolysaccharidosis I & II and Krabbe disease. Pompe disease and mucopolysaccharidosis type I (MPS I) have been recently reviewed and recommended for inclusion into NBS. Fabry disease has been reviewed but not recommended for inclusion into the NBS and Krabbe, Niemann Pick, and Gaucher diseases have not been reviewed at all. [14] Every state screens for a panel of diseases it deems fit to include on its screening panel. This decision is based on disease-specific criteria, state capabilities such as financial, technical and human resources, and national body recommendations. There are three routes of approval to add a disease to a state's NBS panel: a) legislation b) executive order and c) state health department. Hence, there seems to be an increasing interest in the patient advocacy community to include these groups of disorders in the recommended NBS panel.

Currently, LSD screening varies among different states in the United States. In this study, we try to understand and analyze the current LSD screening landscape, and some of the important factors that were considered while incorporating LSDs on the NBS panel.

For purposes of this study, we defined a state as "active" if they:

- Currently screen for at least one LSD
- Have amended legislation to include LSDs on their NBS panel, but do not currently screen for LSDs
- Are considering the addition of LSD screening to their NBS panel

All other states are classified as "inactive." We have identified a group of nine 'active states' and 36 "inactive states" in reference to LSD NBS. Some of the key factors taken into account in amending a state's NBS panel include the prevalence of the disease, differences in approval processes, the presence of an approved screening test, cost to the state, and the availability of treatment. The year 2013 marked the 50th anniversary of newborn screening in the US. Comparing key differences between 'active states' and 'inactive' states in LSD NBS may give us a better understanding of:

1. The current landscape of NBS for LSDs
2. The influence of the process by which states add diseases to their NBS panels
3. Key factors that influence the addition of screening tests to NBS panels.

METHODS

A nationwide survey of newborn screening programs was carried out from January 2013 to April 2013, covering all 50 states in the US. A telephonic survey was administered to individuals that have been identified by the National Newborn Screening and Genetics Resource Center (NSGRC) database and work typically as the supervisor of a newborn screening program or state laboratory. Direct telephone calls to the state department of health were also made in cases where the contact persons in the NSGRC were not available. The survey questionnaire was created with input from the US Centers for Disease Control and Prevention.

The survey asked respondents to rate, on a scale of one through five, the importance of a given factor for adding a new disease to the NBS panel. In addition, they were asked about the features of the existing program (including the number of diseases screened, the infrastructure of laboratory screening services) and the process of adding a new disease to the state recommended screening panel. Responses from the telephone interviews were transcribed into a database for analysis.

Fischer's exact test (with a 2 X 2 contingency table) was used to determine the significance values in this study. The two groups being studied were classified as being "Supportive of NBS" and "Not Supportive of NBS"; the outcomes being binary for all the variables tested.

RESULTS

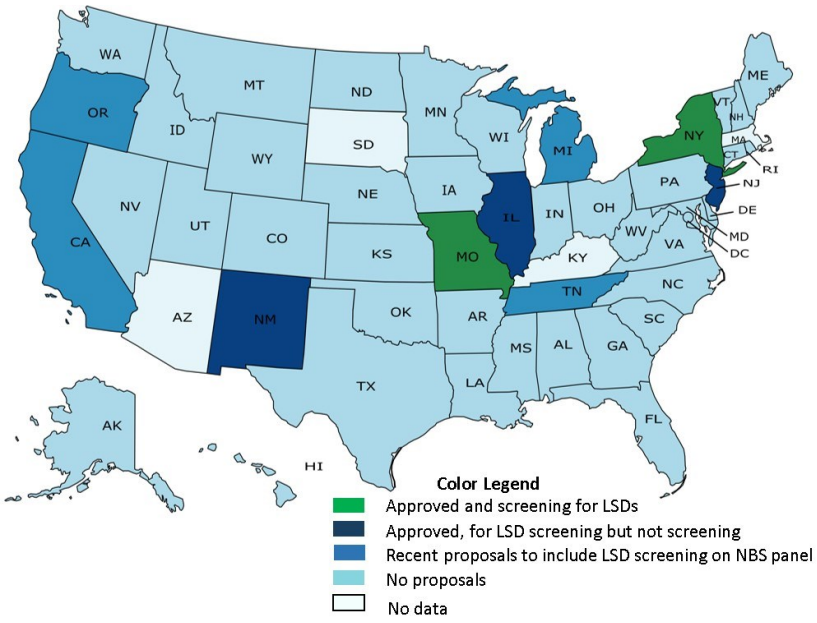
Out of the 50 states surveyed, 45 states responded. Of these, two states had amended their recommended newborn screening panel to include LSDs and are currently screening for these diseases. An additional three states had amended their recommended newborn screening panel to include LSDs, but were not screening. Four other states are currently considering the addition of LSDs to their newborn screening panels (**Figure 1**). We classified these nine respondents as "active" states. The remaining 36 states were classified as "inactive". After the study was completed, Pennsylvania passed a law adding LSDs to their newborn screening panel.

Some of the state-wide criteria for adding a new disease to the newborn screening panel are:

1. Prevalence of disease
2. Availability of treatment
3. Approved screening method
4. Supporting infrastructure
5. Cost to state

Across all respondent states, the number of diseases screened ranged from 29-80 with a median of 50. However, the number of diseases screened varied between the active and inactive groups. The range of diseases screened by active states (n=9) was 47-80 with a median of 54 diseases. The range of diseases screened by inactive states (n=36) was 29-58 with a median of 47.5 diseases ($p < 0.01$). The administrative process of adding a new disease to a state newborn screening panel differs significantly ($p < 0.01$) between active and inactive states (Table 4). Of the nine active states interviewed, six (66.7%) indicated that legislative action is required to add a new disease to their state newborn screening panel. In contrast, among the 36 inactive states, only 10 (27.8%) indicated that legislative action is required to add a new disease to their panel.

Figure 1. Current Landscape of Newborn Screening for Lysosomal Storage Disorders.



Two states (green) are screening for LSDs after having them approved for the NBS panel. Three states (navy blue) have approved some LSDs for the NBS panel but do not currently screen. Four states (blue) have recent proposals to include LSD screening on the NBS panel. 36 states (gray blue) did not have any proposals for adding LSDs to their NBS panel at the time of the study. We could not gather NBS data for four states (light blue).

Table 1. - Current landscape of statewide newborn screening programs in the United States.

Criteria For Nation-Wide Analysis	States
States requiring legislation to add disease to NBS panel	California, Connecticut, Illinois, Michigan, Nebraska, Nevada, New Hampshire, New Jersey, New Mexico, North Carolina, Oklahoma, Oregon, Texas, Virginia, Washington, West Virginia
States that take constituent pressure into consideration	Alabama, Michigan, Mississippi, Nebraska, Nevada, New Mexico, Oklahoma, Oregon, South Carolina, Texas, Tennessee, Utah, Virginia, New Hampshire
States screening ≥ 50 diseases	Alaska, California, Connecticut, Delaware, Hawaii, Indiana, Iowa, Michigan, Minnesota, Mississippi, Missouri, Nevada, New Mexico, New Jersey, New York, North Dakota, Oregon, Oklahoma, Pennsylvania, South Carolina, Tennessee, Utah, Wisconsin, West Virginia
States screening diseases beyond the SACHDNC recommended panel	California, Connecticut, Illinois, Maine, Maryland, Mississippi, Nebraska, New Hampshire, New York, North Dakota, Pennsylvania, Tennessee
States which have expressed interest in LSD proceedings	California, Illinois, Iowa, Kansas, Mexico, Michigan, Missouri, Minnesota, New Jersey, New Wisconsin, New York, Oregon, South Carolina, Tennessee, Washington, Pennsylvania

Table 2 summarizes states with existing legislation for approving LSD screening and Table 3 lists states that were considering adding LSDs to their NBS panels.

Table 2 .States with Legislation to include Lysosomal Storage Disorders on their Newborn Screening Panel.

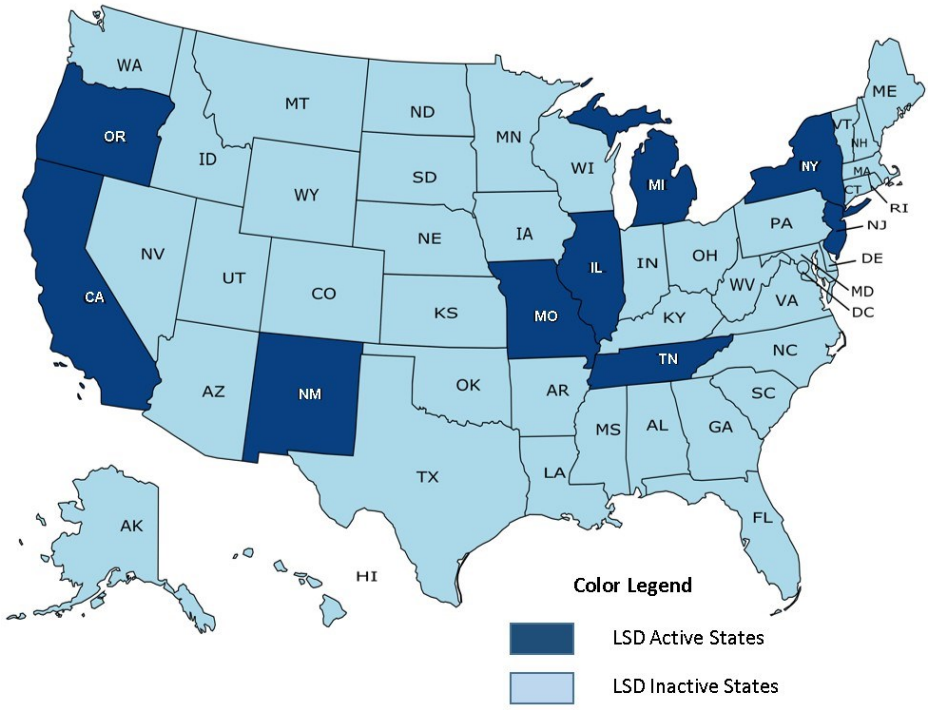
State	Comments
Illinois	• First state to pass NBS legislation for multiple lysosomal storage disorders. • Liam Hammond Memorial Act passed on November 5, 2007 • Act provided for screening of Fabry, Pompe, Krabbe, Gaucher and Niemann-Pick. Follow-up bill in 2011 added MPS I, MPS II and SCID to the panel.
Missouri	• Brady Alan Cunningham Newborn Screening Act passed in 2009. • Screening began in January 2013. • Currently screening for five Lysosomal Storage Disorders including Fabry, Pompe, Krabbe, Gaucher and Niemann-Pick.
New Jersey	• Emma's Law passed in January 2009 • Allows for screening of Fabry, Pompe, Krabbe, Gaucher and Niemann-Pick disease. • Follow up bill in 2013 added Hunter's Syndrome to the panel. • Currently waiting for budget approval to procure resources as of 2013.
New Mexico	• Bill HB 201 passed on March 9, 2010 • Allows for screening of Fabry, Pompe, Krabbe, Gaucher and Niemann-Pick disease.
New York	• First state to screen for a Lysosomal Storage Disorder (Krabbe disease) since 2006. • Raised national interest in newborn screeening for Lysosomal Storage Disorders. • Currently performing pilot studies for Krabbe, Fabry, Pompe and Niemann-Pick A/B, Gaucher, MPS 1 diseases at four hospitals.
Pennsylvania	• After the study was completed, passed Hannah's Law (Bill 1654) on October 15, 2014 • Allows for screening of Fabry, Pompe, Gaucher, Niemann-Pick and Hurler disease

Table 3. States considering including Lysosomal Storage Disorders to their Newborn Screening Panel.

State	Comments
California	• Focus on two diseases – Krabbe disease and Hurler Syndrome.
Michigan	• Added Pompe, MPS 1 disease in 2015 and interested in addition of other LSDs with approved therapies to the newborn screening panel.
Oregon	• SB 284 introduced in March 2013. • Proposes addition of Fabry, Pompe, Krabbe, Gaucher and Niemann-Pick disease.
Tennessee	• "Dylan May Newborn Screening Act" introduced in February 2013. • Proposes addition of Fabry, Pompe, Krabbe, Gaucher, Niemann-Pick diseases and Hurler syndrome.

"Active" and "inactive" states (**Figure 2**) were then compared based on the factors previously mentioned as discussed with the respondents.

Figure 2. LSD Active and LSD Inactive States.



States that have passed a legislation to screen for LSDs as a part of the NBS panel or have expressed interest in passing such a legislation have been called 'LSD Active' states and are shown in dark blue, while the remaining states are called 'LSD Inactive' for the purpose of this study.

Table 4. Comparing LSD Active and Inactive States

Characteristics of State Newborn Screening Program	LSD Inactive (n=36)		LSD Active (n=9)		*P* value
Number of diseases screened	Median	Range	Median	Range	
	47.5	29 - 58	54	47 - 80	0.0066
Location of screening services	In-state	Not in-state	In-state	Not in-state	
	20	16	6	3	0.4157
Route of approval	Legislative	Not legislative	Legislative	Not legislative	
	10	26	8	1	0.0037
Key Factors for Addition of New Disease	**LSD Inactive (n=34)**		**LSD Active (n=9)**		***P* value**
	Median	**Mean**	**Median**	**Mean**	
Prevalence of disease*	4.0	3.45	3.0	3.56	0.4288
Availability of treatment	5.0	4.68	5.0	4.89	0.1134
Approved screening method	5.0	4.65	5.0	4.56	0.4225
Supporting infrastructure	4.0	4.18	5.0	4.89	0.0003
Cost to state*	4.0	3.73	4.0	3.78	0.4418
Constituent pressure	3.0	2.82	3.0	3.00	0.3560
*LSD Inactive n=33					

Location of screening laboratory services was not found to be a differentiating factor between active and inactive states. Across both active and inactive states, 19 (42.2%) respondents indicated that they outsource at least one of their newborn screening tests to out-of-state contract laboratories. Of the active states (n=9), six (66.7%) had all newborn screening services in-state and three (33.3%) outsourced at least one disease to out-of-state laboratories. Of the inactive states (n=36), 20 (55.5%) had all newborn screening services conducted in-state and 16 (44.5%) contracted with an out-of-state entity for at least one disease (Table 4).

Lastly, we looked for differences between how LSD active and inactive states rated six factors that are considered during the decision of adding a new disease. While other differences exist between LSD active and inactive states, (Table 4), we found that active states gave more importance to supporting infrastructure (rating = 4.89, $p < 0.01$) than the inactive states (rating = 4.18).

DISCUSSION:

Supporting infrastructure is an important factor in adding a disease to the screening panel

Prevalence of disease, treatment availability, approved effective screening method, cost to state and constituent pressure were not found to be significantly different between LSD active and inactive states while considering addition of a disease to the state's NBS panel. The presence of supporting infrastructure among others was a factor that was statistically different between LSD active and inactive states. The need for a strong supporting infrastructure features heavily into the review process while adding a disease for a LSD active state. This might imply that LSD active states are more aware of the organization and resources required to screen for additional diseases. Nevertheless, rating the existence of infrastructure as very important does not entail its actual existence in the state.

Our survey suggests that active states screened for an increased number of diseases in comparison to the inactive states (median=54 vs. 47.5). An increased percentage of active states (66.7% vs. 27.8%) require legislation in order to add a disease to their NBS panel. States that screen for more diseases may be early adopters for diseases not recommended by the (Discretionary Advisory Committee on Heritable Disorders in Newborns and Children (DACHDNC) or the former SACHDNC). Therefore, active states may be more agreeable to add LSDs to their NBS panel. However, the legislative route can bypass stringent disease inclusion review, which suggests it may be easier to add a disease not recommended by the SACHDNC (or DACHDNC) onto an active state's NBS panel.

STAKEHOLDERS CAN PLAY A CENTRAL ROLE IN THE DISEASE SCREENING INCLUSION PROCESS

Clinicians and Researchers:

Clinicians and academic researchers are important stakeholders as they can present relevant data to the state and policymakers involved in the NBS screening decision-making process. Pilot studies performed by academic labs and clinics can provide valuable data on the prevalence of the disease and benefits of early screening and treatment. They will also prove to be important disease management tools in the future.

Advocacy Organizations:

Our studies indicate that citizens and patient advocacy organizations collectively need to take a larger initiative to support inclusion of more LSDs on the NBS panel. For example, Pompe disease patient advocacy organizations have been focused on getting SACHDNC approval and families affected by Krabbe disease have been primary drivers for NBS at a state level but both have limited resources to support these efforts. Therefore, higher interaction between LSD patient advocacy organizations and their individual members located in states across the country can help exert a stronger influence on legislators and policymakers. The success of this approach is however dependent upon understanding an individual states' political atmosphere.

Role of Constituents and Their States:

According to our study, the significance of constituent pressure was not much different between active and inactive states. Constituent pressure commonly misaligns with state capabilities. Common challenges include procuring equipment and availability of funds and that impacts the follow-up regimen as well. Each state has a significant responsibility to provide the appropriate resources to implement any legislation.

For example, both Illinois and New Mexico have NBS legislations in place for multiple LSDs as a result of constituent pressure but they were not screening due to lack of financial resources. They allow screening of the newborns on a chargeable basis if not covered under the state-funded entitlement programs.

Role of Industry:

Currently available screening tests for LSDs have low specificity which affects the overall cost effectiveness. Moreover, there is lack of a standardized method to diagnose a LSD positive newborn.

To address these challenges, there is a need for studies to demonstrate the benefits of NBS. With appropriate funding, clinicians and researchers can provide such data for the SACHDNC to consider. The Pharmaceutical and Biotechnology industry can provide educational grants to clinicians and academic researchers or to patient advocacy organizations for collaborative approaches to these projects. Data obtained from these studies will help us determine the clinical benefits of early treatment intervention, as well as the educational health benefits of diagnosing later onset forms of LSDs at birth.

The Pharmaceutical and Biotechnology industry also can provide education and awareness about LSDs to the general public which would increase parents' knowledge of these diseases. This in turn would result in increased parental consent, thereby helping data collection and research studies. The industry can encourage grassroots advocacy efforts by working with healthcare organizations to identify active and/or interested families in amenable states who want to support NBS. Disease-approval logistics and the priorities of each state government also feature heavily into the realities of these kinds of initiatives. Therefore, it is important to understand the political atmosphere of each target state.

Advanced education should be provided to clinicians and state officials via seminars and workshops specific to LSDs. Public awareness can be increased via social media, print media, public events, fund-raisers and patient advocacy organizations.

All stakeholders need to come together to advocate a uniform national screening process for LSDs. While it has been shown that early identification of LSD patients can improve outcomes[15] and despite existence of effective treatments, there is no national effort to screen for LSDs. It became clear that there is a need to understand the current landscape of NBS of LSDs. Advancing newborn screening policy to keep pace with the availability of new treatments and the promise of additional therapeutic innovations, will result in improved patient outcomes and better long-term public health.

ETHICAL CONCERNS ARE BEING RECENTLY ADDRESSED

Transparency and trust are the most significant ethical issues currently affecting newborn screening programs. States used to vary significantly in their practices for storage and use of 'residual' dried blood spots leftover after newborn screening was completed,[16] Residual dried blood spot storage was usually done without parental consent, due to the lack of need for parental consent for newborn screening itself. This lack of transparency led to concern by some parents and deterioration in trust of the overall system leading to families filing a lawsuit in a few states. Parents need to be educated on the importance of sample storage and its use for research as that may lead to development of new diagnostic methods and treatments thereby allowing optimal outcomes for these children.

Newborn Screening Saves Lives Reauthorization Act of 2014 eliminates the discrepancies among states by defining guidelines in how they handle and store the residual blood spots and in how they inform the parents about the procedure followed. These guidelines allow privacy protection by de-identifying the samples and review of research protocols by institutional human subjects review boards (IRBs). Section 12 of the Reauthorization Act requires that all federally funded research using newborn samples be considered human subjects research and it removes the option for IRBs to allow waivers of informed consent when dried blood spots are used in research. In response to this new law, questions have been raised about distinction between research and programmatic activities and quality assurance/control of these samples.[10]

Various stakeholders are working towards a guidance advising states so that newborn screening activities can be maintained and parents can be educated about the potential uses and storage of their childrens' samples. These stakeholders include representatives from the Secretary's Advisory Committee on Human Research Protections, the National Institutes of Health, the Advisory Committee on Heritable Disorders in Newborns and Children, the Office for Human Research Protections, the Food and Drug Administration, the Association of Public Health Laboratories, individual state health departments, biobanks, advocacy groups, and parents. Many states are considering options to develop systems to inform parents and obtain consent for these purposes.[10]

CONCLUSIONS

Our study has uncovered several elements influencing a state's decision to include a LSD on its newborn screening panel that include disease prevalence, treatment availability, an approved screening method for the disease, supporting infrastructure and cost incurred by the state.

Among these, a need for supporting infrastructure, constituent pressure and route of approval were some of the required factors, commonly observed across all the states. Stakeholders such as clinicians and researchers, advocacy groups, state constituents and the industry can work collectively and play an important role to include a LSD screening test on the NBS panel for a particular state.

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Competing Interests

"The authors declare that they have no competing interests"

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