Expanding the Reach of SCID Testing:

A Report on the Severe Combined Immunodeficiency Newborn Screening Implementation Experience

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APHL ASSOCIATION OF PUBLIC HEALTH LABORATORIES®

NewSTEPs

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SCID Cooperative Agreement Subawardees:

- Alabama Department of Health Bureau of Clinical Laboratories
- Arizona Department of Health
- Immune Deficiency Foundation
- Kansas Department of Health and Environmental Laboratories
- Kentucky Department for Public Health
- Maryland Department of Health
- North Carolina State Laboratory of Public Health
- North Dakota Department of Health
- Puerto Rico Newborn Screening Program, University of Puerto Rico
- Tennessee Department of Health Division of Laboratory Services
- Utah Department of Health

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Additional SCID Newborn Screening Stakeholders

- Baby's First Test, Genetic Alliance
- Centers for Disease Control and Prevention
- Jeffrey Modell Foundation
- March of Dimes
- Newborn Screening Translational Research Network, American College of Medical Genetics and Genomics

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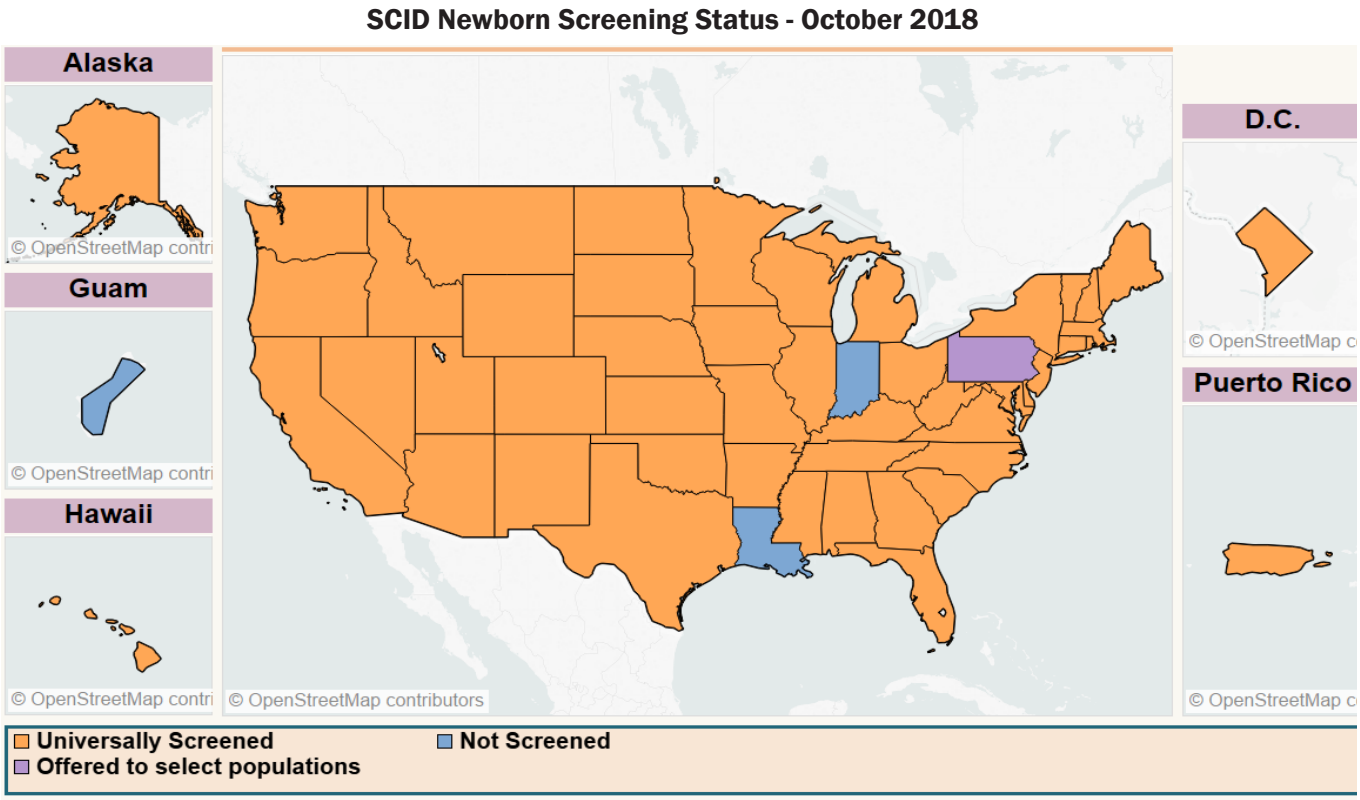
Table of Contents

EXECUTIVE SUMMARY

The Association of Public Health Laboratories (APHL) received funding via a cooperative agreement from the Health Resources and Services Administration (HRSA) to provide technical assistance, educational and financial support to state newborn screening (NBS) programs. The goal of this project was to increase the number of states offering population-wide newborn screening for Severe Combined Immunodeficiency (SCID). The addition of SCID to the Recommended Uniform Screening Panel (RUSP) posed challenges and opportunities unique to each subawardee. Adding SCID to the RUSP requires the application of a molecular assay to every newborn screening specimen for the most efficient screening and the inclusion of a new field of clinical experts and algorithms to newborn screening.

The introduction of new NBS technology coupled with limitations in funding, laboratory space and technical expertise proved to be challenging. Some programs experienced slow and cumbersome legislative processes, while others noted the lag time between approval for SCID newborn screening and the initiation of testing. While SCID implementation involved continuous changes to each program, it also revealed areas for growth and collaboration. In fact, convening multidisciplinary teams enabled programs to support each other by sharing protocols, advice and expertise.

This report provides a comprehensive overview of APHL SCID implementation activities resulting from the HRSA Cooperative Agreement, lessons learned and some notes on the future of SCID screening. This report may also serve as a guidance tool for NBS programs to reference when they are adding new disorders to their state panels. It explores the stages and complexities involved in successful implementation, including authorization, equipment acquisition, training, assay validation, pilot studies, short-term follow-up, clinical engagement and education. As national NBS programs continue to implement expanded screening panels, the need to sustain such community-based national newborn screening technical assistance remains clear.[1]



BACKGROUND

SCID is a primary immune deficiency characterized by the lack of a functioning immune system, affecting approximately one in 58,000 births in the United States. Screening also identifies one in 20,000 newborns who have non-SCID T-cell lymphopenia (TCL). Newborns with SCID (and TCL) appear healthy in the neonatal period, but are extremely vulnerable to infection. Exposure to common infections and live vaccines is life threatening unless immediate treatment, usually stem cell transplantation, is provided in infancy. SCID is treatable if detected early in life by the NBS system.[2]

NATIONAL SCID PILOT STUDY

Jennifer Puck, MD is a professor of immunology and pediatrics at the University of California San Francisco and a member of the SCID Newborn Screening Working Group of the Immune Deficiency Foundation and the Jeffrey Modell Foundation. In September 2007, Dr. Puck nominated SCID for inclusion on the RUSP on behalf of the Working Group.[3] The RUSP is a list of disorders that are recommended by the Secretary of the US Health and Human Services (HHS) for states to screen population-wide as part of their newborn screening programs.[4] SCID was the first condition to undergo evidence review by the Secretary's Advisory Committee on Heritable Disorders of Newborns and Children (ACHDNC). Following this nomination, an evidence review workgroup performed and presented a series of detailed analyses projecting the likely outcomes of SCID population-based NBS. The evidence review workgroup presented their findings to ACHDNC in February 2009, at which time the committee voted against recommending the addition of SCID to the RUSP, noting "specific gaps in evidence that should be addressed before SCID could be added to the RUSP: (1) prospective identification of at least one confirmed case of SCID through a population-based newborn screening program, (2) demonstrated willingness and capacity of additional states to implement newborn screening for SCID, (3) reproducibility of the screening test and continuance of a false positive rate of less than 0.1 percent, and (4) creation of a laboratory proficiency testing program through the Centers for Disease Control and Prevention's (CDC) National Quality Assurance Program." In January 2010, the nomination of SCID to the RUSP was again brought to ACHDNC.[3,5]

In January 2008, the Wisconsin Newborn Screening Program began the first statewide SCID newborn screening pilot project with funding support from the Jeffrey Modell Foundation and the Children's Hospital of Wisconsin. The pilot project continued for an additional five years through funding support from the US Centers for Disease Control and Prevention (CDC). CDC also provided the same funding support for a SCID pilot study conducted in Massachusetts that started in 2009. In January 2010, additional data obtained from these NBS programs—including information about infants identified with related immunodeficiency disorders through NBS that required medical intervention and the feasibility of SCID newborn screening—were presented to ACHDNC. Following review of this evidence, ACHDNC agreed to recommend to the Secretary that SCID be added to the RUSP with the understanding that the National Institutes of Health (NIH) Eunice Kennedy Shriver National Institute of Child Health and Development (NICHD) would fund "surveillance activities to determine health outcomes of affected newborns with any T-cell lymphocyte deficiency receiving treatment as a result of prospective NBS".[5] In addition, the evidence review group shared their findings with CDC's Newborn Screening Quality Assurance Program (NSQAP) to support the production of proficiency testing materials accessible to all NBS laboratories to aid in quality control and quality assurance measures. These early-adopting programs also produced educational materials for families and health care providers.[5]

In May 2010, the Secretary accepted the recommendation to add SCID as a core condition to the RUSP. By the end of 2010, the Massachusetts, Wisconsin, New York and California newborn screening programs were offering universal screening for SCID,[6,7,8,9] accounting for roughly 22% of total US births.[10] This was the first disorder to be reviewed and recommended for nationwide screening and inclusion on the RUSP, and the first utilizing molecular technology as a screening test.[5]

In October 2010, NICHD's National SCID Pilot Study began as recommended by ACHDNC with the primary goal of providing comprehensive SCID screening to as many newborns as possible. Deliverables of the pilot included "establishment of T-cell receptor excision circle (TREC) assay into routine, high-volume newborn screening protocols, creation of laboratory and clinical follow-up algorithms, mechanisms for reporting, and protocols for treatment."[5] The pilot was conducted in New York, California, Louisiana (screened through the Wisconsin NBS program) and Puerto Rico (screened through the New England NBS program) and a total of 654,053 babies were screened. Pilot findings and nationwide screening statuses were reported to ACHDNC in May 2011.[5]

In addition to these deliverables, there were many lessons learned. Amy Brower, PhD, project manager at the Newborn Screening Translational Research Network (NBSTRN)—a resource funded by a contract to the American College of Medical Genetics and Genomics (ACMG) from NICHD—shed light on the unique challenges and successes. Through her experiences supporting NBS programs in this pilot study, Dr. Brower noted that, as the first molecular NBS test, one of the biggest hurdles was purchasing new equipment and training professionals on this screening methodology.[11]

Additionally, the combined NIH and CDC pilot studies allowed public health professionals and clinicians to learn more about SCID. Through expansion of population screening, researchers were able to have a stronger understanding of the genetics. Through the initial cases detected, it was discovered that SCID was no longer considered a condition that affected primarily white males, but affected females and other ethnicities as well.[11]

Dr. Brower and others expressed concerns about adding a condition to the RUSP without comprehensive understanding of clinical readiness and treatments. For example, even though SCID was detectable through NBS, in the early years much was unknown about the benefits and risks of treatment (bone marrow transplants, gene therapy, etc.). This was a whole new realm for immunologists, who were not previously involved in the NBS system.[11]

APHL COOPERATIVE AGREEMENT

In May 2010, HHS Secretary Kathleen Sebelius accepted the ACHDNC recommendation to add SCID to the RUSP.[12] At that time, challenges faced by state NBS programs in implementing SCID screening included:

(1) integration of new screening technology within the newborn screening laboratory,

(2) laboratory staffing to conduct new tests,

(3) clinical follow-up capacity and resources,

(4) funding for personnel, equipment, education, and

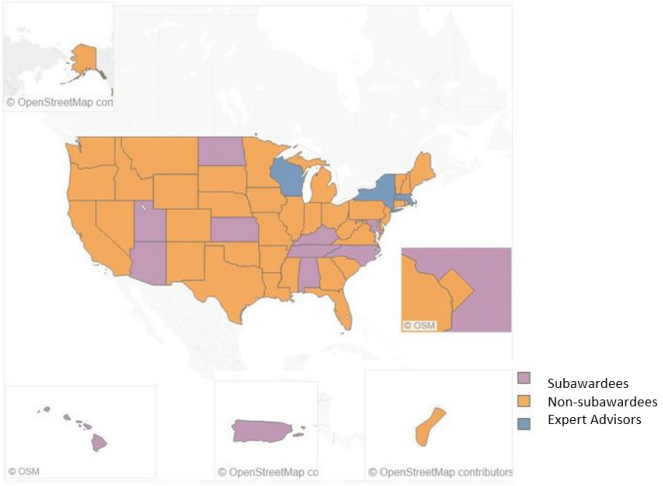
(5) legislative or statutory approval.

In 2014, APHL was awarded funding from HRSA under Cooperative Agreement #UG5MC27837 to provide technical assistance, education and financial support to state NBS programs in order to move all programs toward full SCID implementation. Specifically, APHL pursued progressive activities during 2014-2017 to support widespread adoption of early and accurate laboratory detection of SCID in newborns. The following goals guided the activities of the now complete project:

> *Goal 1: Assess needs, develop partnerships, and provide resources to increase the number of programs that fully implemented for Severe Combined Immunodeficiency (SCID) screening.*
>
> *Goal 2: Assemble, Develop, and disseminate education and training materials for laboratory scientists, NBS Follow-up staff, families, and public health and health care professionals on SCID screening and treatment.*

During this three-year effort, APHL supported 11 NBS programs with awards of up to $300,000. APHL's initiative provided financial support to state NBS programs that had not achieved full SCID NBS implementation, with

the goal of universal NBS in the US. During the course of this project, APHL strengthened the network of NBS professionals to support each other as they embarked on SCID NBS implementation by developing mentorships, collaborations and expert advisory groups. Efforts were guided by the needs of each awardee with objectives directed toward all stages of the implementation process (legislative/regulatory approval, laboratory methodologies and equipment, short-term follow-up, clinical diagnosis and treatment and education). Throughout each phase, APHL provided technical assistance and support to NBS laboratory and follow-up personnel, state public health decision makers, clinical care providers, and family advocacy groups. For many programs, this resulted in statewide mandates that newborns receive SCID screening and all laboratory, follow-up, and educational components be in place for full implementation.



SCID Newborn Screening Cooperative Agreement

Newborn Screening Program	APHL SCID Subawardee	Year Implemented
Alabama	Yes	2018
Alaska	No	2016
Arizona	Yes	2017
Arkansas	No	2015
California	No	2010
Colorado	No	2012
Connecticut	No	2012
Delaware	No	2012
District of Columbia	No	2014
Florida	No	2012
Georgia	No	2016
Guam	No	
Hawaii	Yes	2015
Idaho	No	2016
Illinois	No	2014
Indiana	No	
Iowa	No	2014
Kansas	Yes	2017
Kentucky	Yes	2016
Louisiana	No	
Maine	No	2014
Maryland	Yes	2016
Massachusetts	No	2009
Michigan	No	2011
Minnesota	No	2013
Mississippi	No	2012
Missouri	No	2017
Montana	No	2015

Newborn Screening Program	APHL SCID Subawardee	Year Implemented
Nebraska	No	2014
Nevada	No	2018
New Hampshire	No	2015
New Jersey	No	2014
New Mexico	No	2014
New York	No	2010
North Carolina	Yes	2017
North Dakota	Yes	2016
Ohio	No	2013
Oklahoma	No	2015
Oregon	No	2014
Pennsylvania	No	2013
Puerto Rico	Yes	2015
Rhode Island	No	2014
South Carolina	No	2015
South Dakota	No	2015
Tennessee	Yes	2016
Texas	No	2012
Utah	Yes	2013
Vermont	No	2016
Virginia	No	2015
Washington	No	2014
West Virginia	No	2014
Wisconsin	No	2008
Wyoming	No	2012

CHALLENGES

State Approvals to Implement SCID

In May 2010, the HHS Secretary adopted the recommendation to add SCID to the RUSP. Some NBS programs follow the RUSP when adding new disorders to state panels, some consider the RUSP as one factor in decision making and others take a more active and state-centered role in decision making. Information about adding disorders to state panels, including whether or not national recommendations are followed, can be found in the state profiles section of the NewSTEPs data repository. Programs may also rely on technical, clinical and community advisory groups to evaluate the addition of new NBS tests for particular disorders. These deliberations may be public, with the opportunity for input from health care providers, medical experts, parents, advocates, legislators and public health programs. More information about decision making processes and considerations can be found on APHL's website.[13] Barriers for SCID NBS policy (obtaining legislative mandates to screen, when necessary, and securing fee increases) are similar to challenges faced when other disorders are added to the RUSP.

Newborn Screening Fee Increases

Eight of the 11 subawardees under the SCID Cooperative Agreement did not require legislative approval before universally implementing SCID NBS, but adoption of SCID NBS to these state panels was significantly influenced by available funding. In addition to the financial assistance provided through this cooperative agreement, nine

of these NBS programs required a fee increase prior to moving forward with a sustainable implementation process. The fee increase requirement is frequently accompanied by the need for approval from legislative representatives or internal leadership.[14]

State	Fee Increase Required?
Alabama	No
Arizona	Yes
Hawaii	Yes
Kansas	No Fee
Kentucky	Yes
Maryland	Yes
North Carolina	Yes
North Dakota	Yes
Puerto Rico	Yes
Tennessee	Yes
Utah	Yes

Expectations for State Approvals

The process of navigating legislative sessions proved time consuming for the three states which were required to seek legislative approval in order to move forward with implementation and/or to adopt a fee increase. Preparation for and attendance at open legislative sessions took a significant amount of staff time and effort. It was often noted that even once bills were passed, it could take a significant amount of time to hire staff, acquire equipment and prepare the laboratory for SCID newborn screening.[14]

The legislative approval can also come with specific expectations for NBS programs. For example, once legislative approval was granted in Arizona, the program was given 90 days to implement statewide screening. Due to this limited timeframe, Arizona had to seek assistance from another NBS program that had capacity and was willing to receive and screen for Arizona's samples until Arizona's in-house process was ready. Arizona's NBS staff were able to screen their samples in-house within 60 days of receiving legislative approval.[15]

Partnerships with Advocacy Organizations

Partnerships with advocacy organizations, such as the Immune Deficiency Foundation (IDF) and the Jeffrey Modell Foundation (JMF), proved to be invaluable throughout these approval-seeking legislative processes. IDF's Public Policy Unit worked individually with NBS programs to advocate for legislative and regulatory changes. During in-person meetings with state legislative representatives, IDF offered customizable tools, such as state-specific fact sheets that included fiscal impact information, which gave state programs and governmental decision makers a better understanding of the cost/benefit analysis of SCID NBS. Lynn Albizo, IDF's senior director of public policy, noted that, "Each state had unique challenges. Different approaches worked in different states with different administration."[16]

In addition to financial support, JMF provided informative tools for NBS programs to share with legislators. For example, the JMF Analysis and Decision Tool (https://link.springer.com/article/10.1007/s12026-014-8485-4)[17] provided a working algorithm or "decision-tree" validated by peer-reviewed scientific literature that allowed NBS programs to assess the economic impact of implementing SCID NBS. Representatives from these organizations appreciated the power of having patient advocates and their families share their stories.[16,18] Local chapters of the American Academy of Pediatrics and the March of Dimes, as well as SCID Angels for Life, a family based organization, were also significant supporters of this process.[14]

Introduction of New Instrumentation

Screening for SCID was unprecedented as it introduced the first molecular first-tier NBS test. This molecular screening method required that many NBS programs acquire new instrumentation. In fact, nine of the SCID

Cooperative Agreement subawardees had to seek new instrumentation to support this method. [14]

Acquiring new instrumentation poses challenges for NBS programs including 1) funding to support purchases, 2) adequate laboratory space for the equipment, and 3) trained staff to handle equipment. Eight subawardees required modifications to laboratory space prior to implementing SCID NBS. Two of the 11 subawardees did not perform screening in-house. Space modifications included installing drywall and new plumbing for sinks, relocating existing processes and adjusting electrical systems. These modifications were crucial to ensuring a unidirectional workflow, therefore reducing risk of contamination.[14]

Alabama's experiences in modifying their existing laboratory space highlighted many adjustments that NBS programs must consider. The Alabama NBS program restructured two rooms for the purpose of SCID testing to accommodate a sound molecular workflow. This process required relocating their designated space for test review and reporting, as well as relocating their specimen preparation space for tandem mass spectrometry (MS/MS) testing. A service technician was hired to assist with moving all existing equipment to the appropriate location. Relocation of these processes created a tighter space for MS/MS preparation, testing, maintenance and reporting. Through participation in a customer preference test, the Alabama NBS program was able to troubleshoot issues, which were accompanied by many delays.[19]

When addressing barriers to SCID NBS equipment, Anne Comeau, PhD, deputy director, New England Newborn Screening Program, remarked, "Many programs did not have a laboratory layout that was conducive to the unidirectional workflow that is required for quality molecular testing. Some renovated workspaces, some used specialized hoods creatively, some worked within other areas of their public health departments. They understood the need to prevent contamination."[20]

State	Modification to Lab Space
Alabama	Yes
Arizona	Yes
Hawaii	Not Applicable (sends to Oregon)
Kansas	Yes
Kentucky	Yes
Maryland	No
North Carolina	Yes
North Dakota	Not Applicable (sends to Iowa)
Puerto Rico	Yes
Tennessee	Yes
Utah	Yes

Laboratory and Clinical Competencies

SCID Expert Advisors

Many SCID subawardees required assistance with:

- training NBS program personnel on molecular screening technology
- establishing appropriate clinical referral networks for follow-up and treatment
- developing educational materials, awareness materials and/or campaigns for families, patient advocacy and support groups.

APHL partnered with external laboratory, clinical, education and policy advisors to provide consultation, site visits and training. These expert advisors from New England, New York and Wisconsin contributed to training on-site and off-site, provided evidence-based insight to algorithm developments and shared data. The advisors also gave

multiple presentations at regional and national conferences and workshops. Interviews with advisors showcased specific contributions that are noted below.

The New England NBS program supported the initial development of proficiency samples with CDC and the Wisconsin NBS program. Upon request, the New England and Wisconsin NBS programs provided protocols, offered trainings and distributed calibrators to other states. Additionally, this program offered to run large sets of specimens in parallel with other NBS programs to verify data consistency.[20]

The New York State NBS program also distributed protocols, assays and panels of specimens—including positive SCID specimens—to other programs when possible. Additionally, all three programs shared a significant amount of data to support the development of a CLSI guideline document on SCID. The program conducted the national pilot study and supported the preparation and facilitation of national NBSTRN calls.[21]

The Wisconsin NBS program shared protocols and sample reports, hosted in-house trainings and offered site visits to NBS programs who sought assistance. They provided technical assistance and offered to help states no matter their state size, workforce or schedule. Programs across the US, as well as Brazil, Sweden, Germany and Qatar, visited Wisconsin seeking SCID NBS assistance. Mei Baker, MD, FACMG, co-director of the NBS Laboratory at the Wisconsin State Laboratory of Hygiene, stressed the need for communication among SCID stakeholders. She encouraged programs to consider the whole NBS system when onboarding SCID, including results interpretation, differences in neonatal intensive care unit (NICU) patients and influence of transfusions.[22]

Centers for Disease Control and Prevention

In addition to the aforementioned expert advisors, the US Centers for Disease Control and Prevention (CDC) played a critical role in supporting NBS programs toward implementation of universal SCID NBS.

CDC held its first SCID workshop in 2010 with 12 trainees from various state laboratories. It included presentations on preliminary data, protocols and algorithms. After the initial workshop, CDC changed the format to individually tailored sessions with no more than two NBS programs (four people) in order to have a good trainer-trainee ratio and to meet programmatic needs. Since 2010, CDC has conducted two to four trainings per year which spanned three or four days each. They typically included a lecture session for background on clinical, molecular and technical information related to SCID testing, hands-on bench training, and discussion on analysis of test results. CDC scientists also taught participants how to prepare quality control (QC) materials; in short, the goal was to provide trainees the necessary knowledge to train their staff on SCID testing and interpretation upon returning to their respective laboratories. There are programs that have come back for a second round of training due to personnel changes in their lab or lack of QC materials. "It takes more than funding or advice to get the state lab to implementation," Dr. Lee stated. "Some labs pick up fast and others need more guidance through the process. You need to customize the approach for each lab for best results."[23]

> "SCID testing required a new test platform, molecular PCR techniques. Most state newborn screening labs were not equipped, at that time, in terms of either technical expertise or the instrumentation. However, if you compare to the first introduction of mass spectroscopy to newborn screening, the adaptation of the real-time PCR platform (for SCID) was actually quite a bit faster. Having gained that experience, states are even faster in bringing on another condition, Spinal Muscular Atrophy (SMA) that has recently been added to RUSP, because labs are now more confident in taking on a new molecular technique." [23]
>
> *Francis Lee, MSc, PhD, SCID expert*
> *NBS and Molecular Biology Branch*
> *CDC*

Local Assay Validation

The objective of the SCID screening tests was to measure TRECs, which are produced during the development of normal T-cells. Low TREC levels aid the identification of patients with SCID and other serious medical conditions associated with low T-cell numbers. To validate the TREC assay, state NBS programs had the option of utilizing a vendor kit based on single-point polymerase chain reaction (PCR), or a laboratory developed test (LDT) utilizing real-time PCR. There

were various benefits to both methods. The vendor kit provides ready quality assurance and quality control support, while the LDT offered screening flexibility, particularly the potential of adding new conditions (such as Spinal Muscular Atrophy (SMA)).[23]

The majority of the APHL SCID subawardees opted for a laboratory developed assay. Advantages of using an in-house laboratory assay included cost-effectiveness and faster implementation. Michele Caggana, ScD, FACMG, of the New York NBS program noted that the LDT was easier to develop because, "the laboratories had a better understanding of how it works and more control over what is being done."[21]

Several subawardees adapted another type of LDT: an automated in situ dried blood spot real time PCR TREC assay developed by CDC. In this method, instead of a separate deoxyribonucleic acid (DNA) extraction step, the dried blood spot remained in the well during the PCR stage. This approach simplifies and shortens the assay run, but is limited to real-time PCR instruments with the 96-well format. Wisconsin and Massachusetts, the early adopters of SCID implementation, participated in CDC's pilot for the development of proficiency testing materials. Many states credited Wisconsin, Massachusetts and CDC for providing troubleshooting assistance and samples during their assay validation processes.[5]

The programs that elected to use a US Food and Drug Administration (FDA)-approved kit did so through PerkinElmer's EnLite™ Neonatal TREC Kit, which received approval in January 2015. The EnLite™ Kit was an in vitro diagnostic device designed to detect TREC and beta-actin DNA in newborn dried blood spot filter paper cards.[24]

The Utah NBS Program validated both the EnLite™ kit and a LDT during the course of the funding period.[25] Validating both methods allowed the program to compare methods, screen for SCID faster with lower costs per test and generate flexibility to implement TREC in combination with prospective SMA screening.

All three testing platforms have been successfully implemented in NBS. Therefore, states can select the platform best suited for individual needs and laboratory conditions.

State	Assay
Alabama	PerkinElmer EnLite™
Arizona	PerkinElmer EnLite™
Hawaii	Laboratory Developed Test (LDT)
Kansas	LDT
Kentucky	LDT
Maryland	LDT
North Carolina	LDT
North Dakota	LDT
Puerto Rico	LDT
Tennessee	PerkinElmer EnLite™
Utah	Initiated screening with PerkinElmer EnLite™, transitioned to LDT in July 2018

Local Pilot Studies

Conducting pilot studies provided an opportunity for NBS programs to examine feasibility of testing as well as to examine modifications of screening algorithms. Optimizing testing conditions helped determine appropriate cutoffs and reduce the number of false positive results.[26] Four out of 11 funded APHL subawardees conducted pilot studies prior to SCID NBS population implementation (two of the 11 subawardees did not perform screening in-house). The timeframe for pilot studies took between 10 to 15 months for the subawardees.[14]

One challenge identified in conducting pilot studies was not obtaining enough samples to perform repeat testing. Requesting true positive specimens from other states earlier in the process was a lesson learned. Another challenge was having enough staff available who were fully dedicated to implementation. At the same time that programs were working to implement SCID, some were managing a change in technology for cystic fibrosis (CF) screening. Some programs with limited staff had to put SCID implementation on hold to prioritize navigating through revision of CF testing and reporting procedures.[14]

North Carolina's pilot study identified several lessons learned. At one point, the program experienced high screen-positive numbers because one hospital was collecting all specimens with heparinized capillary tubes. Once this issue was addressed, the program's screen-positive numbers dropped significantly and was comparable to other states. As a result of their pilot study findings, the program also developed a protocol for handling transfused infants with borderline TREC results and communication with immunologists.[27]

During Puerto Rico's pilot study, approximately 60,000 newborns were screened. There was one screen-positive case for SCID. The patient was successfully treated with a bone marrow transplant.[28] Kentucky also identified one screen-positive case out of over 36,000 samples during their eight-month pilot study.[29]

Local Implementation

Status of SCID Newborn Screening

As of October 2018, 96% of all newborns born in the US are screened for SCID in 48 states, as well as Washington DC and Puerto Rico. The remaining two state NBS programs continue to work toward full implementation.[10]

All of the 11 funded APHL subawardees have successfully implemented SCID screening in their program. Individual programs have since reported positive screens for classic SCID, syndromes with low T-cell numbers, secondary T-cell lymphopenia, preterm birth alone and idiopathic T-cell lymphopenia (variant SCID).[14]

Implementation

Implementation was not without its challenges. One major implementation barrier was the fiscal constraints on laboratory equipment and infrastructure necessary to conduct molecular testing. Inadequate lab space required some states, as in the case of Connecticut, to be creative with available resources. Although not a subawardee, the Connecticut NBS program converted a storage closet to a sample preparation area to contain all pre-PCR steps and equipment.[30]

Programs also faced staffing shortages and lack of trained staff in molecular techniques. To address these needs, programs attended customized trainings at CDC, visited laboratories of early adopting states and participated in the APHL and CDC NBS Molecular Training Workshop held annually.[14]

Implementation of a new screening test is a continual process that requires flexibility and creativity in order to update testing procedures and meet programs' needs.

SCID National In-Person Meetings

In July 2015, APHL hosted a national SCID In-Person Meeting in Bethesda, MD for subawardees and other states who supported the implementation of new disorders added to the RUSP. Partners and stakeholders who had significant experience with implementing SCID NBS were also in attendance. This meeting, attended by representatives from 40 states, the District of Columbia and Puerto Rico, addressed current challenges faced by state NBS programs in implementing SCID screening. Topics included integration of new technology, laboratory staffing to conduct screens, clinical follow-up capacity and resources, funding for personnel, equipment, education and legislative or statutory approval. Through this open forum, NBS programs had the opportunity to discuss challenges, share experiences and identify strategies for moving all toward full SCID implementation.[31]

In August 2017, APHL held a second national meeting in Washington, DC which focused on engaging the NBS community and clinicians to strengthen clinical referral networks within each state and region. Several issues were addressed during this meeting including inconsistent interpretation of molecular testing results for follow-up across NBS programs, variations in defining short and long-term follow-up, and the need for the harmonization of diagnostic terminology (e.g. variant versus idiopathic; classic versus typical).[32]

Ongoing Technical Assistance Resources to Support Implementation

Public Health Surveillance Case Definitions: NewSTEPs has engaged clinical experts in developing public health surveillance case definitions to support consistent classifications for diagnoses across NBS programs.[33]

Quarterly National Webinars: NewSTEPs, in collaboration with the American College of Medical Genetics and Genomics' (ACMG) Newborn Screening Translation Research Network (NBSTRN), hosts national SCID webinars to serve as a resource to the NBS community as more states implement screening. The webinars continue to address legislative challenges, laboratory methodologies and techniques, follow-up and education efforts relating to SCID. This platform highlights state implementation experiences and often provides clinical vignettes to participants. In this effort, states can learn how to engage with clinical immunologists.[34]

Currently, NewSTEPs has been working with NBSTRN to consider common data elements that can bridge the gap between short and long- term follow up, and to understand the varying databases that already exist.

Short-Term Follow-Up and Tracking

Although it varies by state, several programs noted that if there is an abnormal, equivocal or presumptive positive result the follow-up protocol is as follows:

- the NBS program makes an initial call to the immunologist and/ or genetic center for assistance
- Short-term follow-up (STFU) notifies the primary care physician (PCP) with a recommendation for immediate consultation with a pediatric specialist.[14]
- Communication with the PCP often occurs in conjunction with distribution of PCP and parent letters, brochures, ACT sheets from the American College of Medical Genetics and Genomics (ACMG) and/or additional education materials and referrals.[35]
- STFU is involved until confirmatory diagnosis is obtained. Here is an example of SCID follow-up protocol from the Hawaii Newborn Screening Program.[36]

It is important to note that while the preliminary STFU protocol might have been established after validation, that original protocol has most likely been, and will likely continue to be, modified several times as more data is collected. Because the treatment for SCID is immune reconstitution through stem cell transplant, gene therapy or enzyme replacement, immunologists were introduced to the NBS system. This required additional workflows and communication strategies. For example, during the Kentucky SCID NBS pilot, immunologists were notified of presumptive-positive results while University NBS Coordinators were not in the initial communication chain and were unaware of the referral until later in the process. In the current process, the University NBS Coordinators are notified at the same time as the immunologists and are able to initiate contact to advise the neonatal intensive care unit (NICU) or PCP of the next step of evaluation.[29]

In programs participating in the APHL SCID Cooperative Agreement, experts and immunologists guided and supported development of all follow-up protocols. In fact, although involvement differed by program, all NBS programs that established SCID follow-up protocol as a part of grant funding noted the involvement of immunologists as part of this process. Some immunology groups established protocols for handling abnormal screening results into and through diagnosis and intervention.[14] Others, as in the case of the North Carolina NBS program, involved immunologists around the state (as well as personnel from the public health division) in an in-person meeting before screening started and a follow-up conference call to discuss follow-up protocols and patient evaluation after screening several thousand specimens.[27] The Hawaii NBS program

noted the need to build strong partnerships with treatment centers as well. To ensure babies born in Hawaii had access to life-saving treatment options, a partnership between Kapi'olani Medical Center for Women and Children, the University of California at Los Angeles Mattel's Children's Hospital and the Hawaii Department of Health was created.[37] Dr. Anne Comeau of the Massachusetts NBS program noted that it was the first time that immunologists realized they needed at least one person from each institution working with SCID (e.g. immunologist, transplantation specialist, sometimes infectious disease specialist).[20]

The time frame for development of SCID STFU protocols varied by program, taking between one month and one year. The programs that did not yet have a STFU protocol implemented in place at the time of funding noted that a protocol would be established based on national recommendations, what other states have implemented and on the recommendations of clinicians and laboratory experts.[14]

Establishment of a SCID follow-up protocol was not without challenges, including lack of staffing, competency of follow-up team and high rate of false positives. It was also noted that SCID is unique in that it may require a case management nurse to handle.[14] Programs including the California NBS program, although not a subawardee, have established testing and follow-up algorithms that have proved to be time-saving and cost-effective.

Education

Nine of the 11 programs participating in the APHL SCID Cooperative Agreement had targeted education plans for health care providers. Examples of effective education included webinars, brochures translated in multiple languages, factsheets, newsletters, YouTube videos, presentations, conference exhibits, SCID Awareness Weeks and incorporation of SCID education into already existing continuing education unit (CEU) approved training.[14] The Tennessee NBS program continues to send letters to all providers with a link to an introductory video about SCID that was a collaborative effort between laboratory, follow-up and pediatric immunologists.[39] Puerto Rico published an informative supplement with articles about SCID in a local newspaper, met with health care providers, and participated in conferences for health care providers to implement education about SCID.[28] Most programs also utilized state websites as a modality for distribution of educational materials, and some distributed materials by harnessing partner organizations' networks.[14]

The Arizona NBS program performed targeted outreach to Arizona Native American tribes which included a conference for tribal leaders and medical directors, as well as a training on the San Carlos reservation for clinicians serving Navajo and Apache members. A partnership with the Arizona Advisory Council on Tribal Health Care was influential in ensuring engagement with tribal leaders, including health care providers. The program also developed a survey from their regional trainings which included questions related to preferred methods for dissemination of information so that additional information and resources could be made available.[15]

While strategies to measure the impact of educational outreach targeted to health care providers were difficult to realize, some programs tracked distribution of materials, while others offered pre- and post-tests to establish learning levels and note change in knowledge. The North Carolina NBS program was in the process of developing a data reporting form at the time of the APHL SCID Cooperative Agreement to record outreach activities. The form included outcome measures such as name of outreach activity, name of participating audience, number of attendees, target population, date of activity, location of activity, number of counties impacted by the event/activity, number of educational materials distributed and name of staff that distributed materials.[27]

Eight of the 11 funded programs offered targeted education plans for parents at the time of the APHL SCID Cooperative Agreement. Parent education included parent pamphlets, brochures, factsheets, conferences, videos and social media. Websites again were an effective channel for material distribution, as well as familial involvement in development of educational materials and in testifying in front of legislative committees.[14] The North Dakota NBS program had a specific link on their website for parents to post and share their NBS story, as well as the opportunity to view stories of other affected families.[40]

APHL and IDF developed a video for distribution to US state health departments for families whose newborns tested positive. Multiple programs noted the video and other IDF resources as a method for parental SCID education. Part of the mission of IDF is to educate about primary immunodeficiencies and provide information, support and resources for affected families. IDF has a comprehensive website, a YouTube channel and brochures for a range of audiences provided at no cost. Materials are distributed electronically, by mail and can be accessed on flash drives as well. The flash drives were sent to laboratories in every state and included PDFs of educational materials, which were developed through guidance of a Medical Advisory Committee. PDFs of these materials are included in the appendix of this report.[41]

Five programs also offered education targeted at the general public. General public education included brochures, newspaper articles and social media. Programs were restricted from advocating the addition of SCID to their NBS panels, so some harnessed support from advocacy groups such as March of Dimes and Raising Special Kids. Program websites were also a great tool to raise awareness, as well as parent picnics and baby fairs.[14] The North Dakota NBS Program had indoor and outdoor billboards to educate the general public about the importance of NBS. Additionally, the program created a video that was also used as an advertisement pop-up for social media messaging.[40]

It is evident that education played an instrumental role in SCID NBS implementation. As the Arizona NBS program noted, "This grant had a direct impact on our ability to promote SCID using outreach strategies. Collaborating with internal and external partners as well as inviting parents in early were key to our success."[15]

APHL partner organizations are important SCID educational sources for general public and internal laboratory education. JMF has a public awareness program for primary immunodeficiency diseases, including SCID. The campaign includes four PSAs that primarily focus on public awareness and physician education. The message "When I grow up, I want to be..." is posted across the US on billboards, bus shelters, taxis, airports and more. Additionally, JMF has a social media campaign that reaches millions of people.[42] CDC is also developing an educational module for SCID targeting lab directors and follow-up personnel. It will touch on areas outside of laboratory training.[22] Baby's First Test of the Genetic Alliance also has condition-specific information about SCID, SCID follow-up testing and support for SCID geared toward expectant and new parents, health professionals, industry representatives and the general public.[43]

LESSONS LEARNED

The addition of SCID to the RUSP introduced a new paradigm in NBS, which posed barriers and challenges unique to each program, but offered opportunities for growth and collaboration.

The subsequent implementation of NBS for SCID has served as a model for translating new discoveries into public health practice in a way that benefits clinical care for children born with genetic conditions. Early adopter states training other states proved a mutually beneficial approach in the long run. In addition, the ground-breaking discovery at the NIH of a way to detect the absence of an early marker of a functioning immune system led to state-based pilots of NBS for SCID; an evidence review and recommendation to screen by ACHDNC; development of QC materials by CDC; an expanded NBS SCID pilot in states with high birth numbers which was coordinated by NIH/NICHD's Newborn Screening Translational Research Network (NBSTRN); and a coordinated implementation program by the APHL SCID Cooperative Agreement.

> "SCID implementation was facilitated by inclusion of not only laboratory but follow-up and experts in immunology. The expert advice offered through participation in the grant made this the simplest implementation of a test ever conducted at this laboratory… Any new test additions will be approached from the same standpoint as SCID, meaning bringing in follow-up, lab and experts to iron out specifics regarding the disorder prior to implementation."[39]
>
> *–Tennessee NBS Program*

Collaboration and development of multidisciplinary teams were also important for providing true positive specimens in the validation and implementation phases.[14] Kansas noted that having previous proficiency

material was beneficial, and in the future, the request for proficiency material from CDC will be made earlier in the process.[44] Dr. Anne Comeau said, "SCID implementation is one of the best examples of NBS programs supporting each other; people shared wildly different protocols and advice. There was a lot of communication."[20]

However, not every program had the same ease of implementation. Some programs mentioned discomfort with new platforms and lack of funding, laboratory space and technical expertise. More laboratory space was needed to account for new equipment and the need for additional dedicated and trained personnel. Space was also needed to reduce contamination issues.[14] Maryland noted the need for upper management support and fiscal commitment, adequate staff coverage and ample time to complete data analysis to establish cutoffs.[45]

Other lessons learned were in regard to legislative processes. Several programs learned that it was beneficial to begin the process of adding disorders to an individual panel early on, in some instances allowing nearly two years prior to enactment. Furthermore, passing a law did not necessarily mean it went into effect right away. It remains important to stay flexible as each state is unique in law and processes. Legislative timelines and the murky distinction between advocacy and awareness education were challenging for several programs to navigate. Furthermore, the implementation of a new test has shown to be a continuous process of changes that align with individual programmatic needs. There are no "one size fits all" solutions.[14]

LOOKING TO THE FUTURE

There is much to look forward to in the future for SCID NBS, especially since all states in the US have initiated screening and have added new technologies for diagnosis or multiplexing with SMA. Dr. Francis Lee of the CDC says the immediate future of SCID screening will be multiplexing with SMA because it is easily achievable. As far as the laboratory is concerned, it is cost efficient to do so, adding about 10 cents to the consumables. He adds, however, that it will take time before sequencing is added to NBS. Currently, genetic analysis is used by clinicians when they want to understand the etiology of SCID and TCL, and to direct therapy. From 2015 to 2018, CDC has funded the New York State NBS program in a project to establish protocols and capacity in next generation sequencing for SCID genotypes. CDC is currently sponsoring five additional state NBS laboratories to expand sequencing capability in NBS.[23]

Dr. Michele Caggana of the New York NBS program agrees about multiplexing. She says that most programs thinking about implementing SMA are going to multiplex with SCID. The ultimate goal is to have SMA TRECs and kappa-deleting recombination excision circles (KRECs) in the same tube, so all tests are done for only the cost of the probe and primer. Although there is still a need to do follow-up downstream, the actual laboratory piece in multiplexing is relatively simple.[21] Dr. Mei Baker of the Wisconsin NBS Program agrees. She says SMA and SCID multiplexing is a no-brainer.[22]

Both Drs. Baker and Caggana also touched on the fact that some programs, including in New York and European countries, are looking at the kappa receptor rearrangements for B cell deficiencies.[21,22] The KREC assay will detect X-linked agammaglobulinemia, which has an estimated frequency of 1:379,000 in the US. However, it will not cover all primary B cell deficiencies; it would not detect conditions due to class switch recombination defect (e.g., hyper-IgM syndrome).[21]

Dr. Michele Caggana also hopes that DNA sequencing will be validated soon. Although B cell deficiencies do not pose the same urgency as SCID and have additional insurance complications, Dr. Caggana says that they would really like to do the genetic test because there is no charge and they receive information on potential phenotype, or subsequent information on treatment options available to the family.[21]

Dr. Anne Comeau of the New England NBS program says that multiplexing, like any assay, should fit the program's needs. A program should not do something just because they can, she says. "Our New England program must provide high quality services for a variety of states. This means that the SCID assay we offer to e.g., Vermont newborn screening must be the same quality as the one that we provide to Massachusetts.

Thus, we perform the same SCID assay for all states. We've had good experience with research projects that multiplex KREC or SMN1, but to put such assays into clinical production is not feasible at this time. We have just implemented SMA screening. If we were to multiplex TREC and SMN1 to possibly make an assay cheaper in MA, we would be providing one SCID assay for Massachusetts and a different assay for the other states, which we will not do because it is just not good practice." Dr. Comeau adds that it remains to be seen whether or not multiplexing is less expensive, depending on rates of false positives when multiplexed.[20]

SCID is a devastating genetic condition and is uniformly fatal in the first years of life unless the immune system can be restored. NBS saves the lives of newborns with SCID by alerting the family and healthcare providers of a suspected immune dysfunction before the onset of overwhelming infections. The development of a novel screening test led to recommended nationwide screening for SCID in 2010. Since then, more than 500 newborns have been diagnosed with SCID and have received life-saving treatment. With NBS, the incidence of SCID doubled; infants with SCID are being identified and treated before death from infection and failure to thrive. Groundbreaking discoveries about SCID have been realized because of this unbiased population-based screening, and providers have welcomed the rapidly advancing knowledge base and the treatment choices NBS provides.

The APHL SCID Implementation Experience Report details how SCID NBS has markedly improved since its addition to the RUSP in 2010. Understanding health outcomes of newborns diagnosed with SCID and TCL through NBS will inform future efforts to improve SCID NBS, STFU, and education. In addition, with the steady and rapid expansion of genomic sequencing, the prospective possibilities of SCID NBS are shifting the paradigm of screening practices.

ACRONYMS

ACHDNC	Advisory Committee on Heritable Disorders in Newborns and Children
ACMG	American College of Medical Genetics and Genomics
APHL	Association of Public Health Laboratories
CDC	US Centers for Disease Control and Prevention
CEU	Continuing Education Unit
CF	Cystic Fibrosis
CLSI	Clinical & Laboratory Standards Institute
DNA	Deoxyribonucleic Acid
FDA	US Food and Drug Administration
HHS	Health and Human Services
HRSA	Health Resources and Services Administration
IDF	Immune Deficiency Foundation
JMF	Jeffrey Modell Foundation
KREC	Kappa-deleting Recombination Excision Circles
LDT	Laboratory Developed Test
MS/MS	Tandem Mass Spectrometry
NBS	Newborn Screening
NBSTRN	Newborn Screening Translational Research Network
NICHD	National Institute of Child Health and Human Development
NICU	Neonatal Intensive Care Unit
NIH	National Institutes of Health
NSQAP	Newborn Screening Quality Assurance Program
NSTRI	Newborn Screening Translational Research Initiative
PCP	Primary Care Physician
PCR	Polymerase Chain Reaction
QC	Quality Control
RUSP	Recommended Uniform Screening Panel
SCID	Severe Combined Immunodeficiency
SMA	Spinal Muscular Atrophy
STFU	Short Term Follow-Up
TCL	T-cell Lymphopenia
TREC	T-cell Receptor Excision Circles

APPENDIX

Immune Deficiency Foundation

- Arizona SCID Factsheet: https://www.newsteps.org/sites/default/files/idf_arizonascidfactsheet.pdf
- Live Rotavirus Vaccines Brochure for Providers: https://www.newsteps.org/sites/default/files/idf_liverotavirusvaccines2017.pdf
- Materials for Parents Following Newborn Screening: https://www.newsteps.org/sites/default/files/idf_materialsforparentsfollowingnbs.pdf
- Materials Packet Cover Level: https://www.newsteps.org/sites/default/files/idf_materialspacketcoverletter.pdf
- Presentation for Parents Following Diagnosis: https://www.newsteps.org/sites/default/files/idf_presentationforparentsfollowingdiagnosis.pdf
- Resources for SCID Flyer: https://www.newsteps.org/sites/default/files/idf_resourceforscidflyer.pdf
- SCID Flyer Abnormal Screen (English): https://www.newsteps.org/sites/default/files/idf_scidflyerabnormalscreenenglish.pdf
- SCID Flyer Abnormal Screen (Spanish): https://www.newsteps.org/sites/default/files/idf_scidflyerabnormalscreenspanish.pdf
- SCID Parents Guide: https://www.newsteps.org/sites/default/files/idf_scidparentsguideenglish.pdf
- Understanding Low T Cell Results Guide: https://www.newsteps.org/sites/default/files/idf_understandinglowtcellresultsguide.pdf

Cost-Effectiveness/ Cost-Benefit Analysis of Newborn Screening for Severe Combined Immune Deficiency in Washington State: https://www.jpeds.com/article/S0022-3476(16)00031-7/abstract

Jeffrey Modell Foundation Sample Education Material: https://www.newsteps.org/file/1425

March of Dimes SCID Factsheet: https://www.newsteps.org/sites/default/files/mod_scidfactsheet.pdf

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Association of Public Health Laboratories

The Association of Public Health Laboratories (APHL) works to strengthen laboratory systems serving the public's health in the US and globally. APHL's member laboratories protect the public's health by monitoring and detecting infectious and foodborne diseases, environmental contaminants, terrorist agents, genetic disorders in newborns and other diverse health threats.

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