Spinal Muscular Atrophy

New Disorder Resources and Tools

JUNE 2021

NewSTEPs

A Program of the Association of Public Health Laboratories™

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ABOUT NewSTEPs

The Newborn Screening Technical assistance and Evaluation Program (NewSTEPs) is a program of the Association of Public Health Laboratories (APHL). It is a national newborn screening program designed to provide data, technical assistance and training to newborn screening programs across the country and to assist states with quality improvement initiatives. NewSTEPs is a comprehensive resource center for state newborn screening programs and stakeholders.

HOW TO USE THIS RESOURCE

This resource was developed by the NewSTEPs New Disorders Workgroup as a tool to aid state newborn screening (NBS) programs in communication and education of key stakeholders during the implementation of new disorders. NBS programs are continually being asked to consider the expansion of disorders to their state panel. The process of adding new disorders is complex and can be lengthy. The intended audience for this tool is state newborn screening programs who can distribute it amongst key stakeholders such as specialists, advocacy groups, or legislators and governmental agencies seeking information and NBS disorder implementation.

NewSTEPs VISION

Dynamic newborn screening systems have access to and utilize accurate, relevant information to achieve and maintain excellence through continuous quality improvement.

NewSTEPs MISSION

To achieve the highest quality for newborn screening systems by providing relevant, accurate tools and resources and to facilitate collaboration between state programs and other newborn screening partners.

WHAT IS NEWBORN SCREENING?

Newborn screening (NBS)—recognized as the largest and most successful disease prevention system in the US—is the practice of testing every newborn for certain harmful or potentially fatal conditions that are not otherwise apparent at birth. Newborn screening takes place before the newborn leaves the hospital and identifies serious, life-threatening conditions before symptoms begin. Although such conditions are usually rare, they can affect a newborn's normal physical and mental development. Early detection is crucial to prevent death or a lifetime of severe disabilities.[1]

Key Points of Newborn Screening

- **NBS is comprised of three different parts:** dried blood spot, hearing and critical congenital heart disease[2] (see **Appendix**) This resource is focused on dried blood spot newborn screening, as the method used for Spinal Muscular Atrophy screening.
- **NBS programs are essential public health programs that perform laboratory screening, conduct follow-up on abnormal newborn screening results and refer infants to clinical care.**
    - Successful programs require knowledge and coordination from multiple stakeholders who play a critical role in the screening process.
    - Newborn screening laboratories test large numbers of dried blood spot specimens each day and many of the disorders screened for are considered time-critical in that intervention should take place by the newborn's fifth day of life or sooner to prevent injury or death to the infant.
- **NBS programs are state-based.**
    - Variations between newborn screening programs exist from state-to-state, including the number of disorders screened and the number of specimens that are collected from each newborn.
    - While states determine which disorders to screen, federal guidance is provided by the Health and Human Services (HHS) Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and includes the Recommended Uniform Screening Panel (RUSP).[3]
    - A state-by-state list of disorders[4] updated in real time is provided by The Newborn Screening Technical assistance and Evaluation Program (NewSTEPs).[5]
    - Occasionally, states may add certain disorders through legislative routes motivated by parents, disease foundation advocates and/or specialists and clinicians. These disorders can be unique to certain states' screening panels and not necessarily be screened nationwide.
- **NBS programs are opt-out programs.** In most states parents can refuse newborn screening in writing based on their beliefs, otherwise newborn screening is automatically conducted. This process is typically referred to as "Dissent" as opposed to "Consent."
- **NBS programs are designed to detect treatable conditions of the newborn.** Disorders on the newborn screening panel typically have to meet certain criteria for screening (such as affect newborns and not be clinically obvious), have an available screening modality or technologies (from dried blood spots) with acceptable sensitivity and specificity (not too many false positive or false negative results), and have effective treatments available.

1 APHL. Newborn Screening & Genetics Program, https://www.aphl.org/programs/newborn_screening/Pages/program.aspx. Accessed 12 May 2021.

2 NewSTEPs. Newborn Screening. https://www.newsteps.org/sites/default/files/nbsmod3screenstabletop_educationalresource_july2017_ss.pdf

3 US Health Resources & Services Administration (HRSA). Advisory Committee on Heritable Disorders in Newborns and Children. Recommended Uniform Screening Panel. 6 Feb 2020. Available from: https://www.hrsa.gov/advisory-committees/heritable-disorders/rusp/index.html

4 APHL. Screened Conditions Report. Available from: www.newsteps.org/data-resources/reports/screened-conditions-report. Accessed 11 May 2021.

5 NewSTEPs website, https://www.newsteps.org/

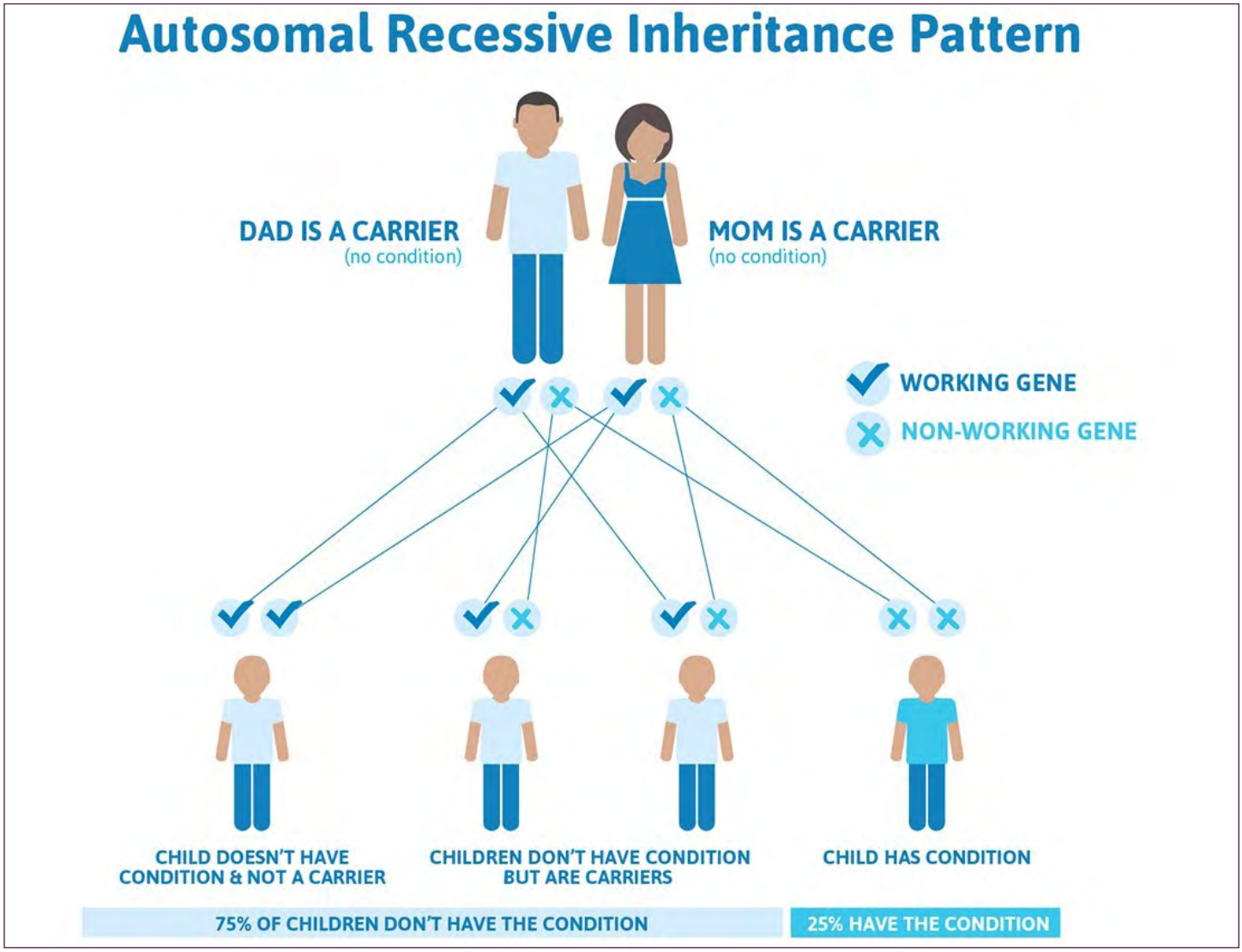
WHAT IS SMA AND WHY WAS IT CONSIDERED FOR NBS?

Spinal Muscular Atrophy (SMA) is a progressive muscular dystrophy caused by mutations in the Survival Motor Neuron (SMN1) gene. The SMN1 gene encodes for an essential protein called Survival Motor Neuron (SMN). The SMN protein is essential for motor neuron function. A deficiency of the SMN protein results in progressive muscle atrophy and weakness.[1]

Genetics of SMA

SMA is inherited when each parent passes down a non-working SMN1 gene to their offspring. Only individuals with two non-working SMN1 genes—one from the mother and one from the father—will have SMA (**Figure 1**). There are different genetic changes or mutations that result in a non-working copy of the SMN1 gene. The most common type of mutation in SMA is a deletion of the SMN1 gene. Approximately 95% of patients with SMA have a deletion in both copies of the SMN1 gene. This is called a homozygous deletion. Currently, newborn screening of SMA relies on the detection of the SMN1 deletions and therefore only identifies these 95% of patients. Other types of genetic mutations in SMN1 will not be identified via newborn screening, resulting in false negative screens for approximately 5% of patients with SMA.

Figure 1. Autosomal Recessive Inheritance Pattern[2]



1 HRSA. Spinal muscular atrophy. Available from: https://newbornscreening.hrsa.gov/conditions/spinal-muscular-atrophy. Accessed 22 June 2021.

2 Autosomal Recessive. Patient Library. Available from: www.geneticsupport.org/genetics-101/inheritance-patterns/autosomal-recessive Accessed 12 Feb 2019.

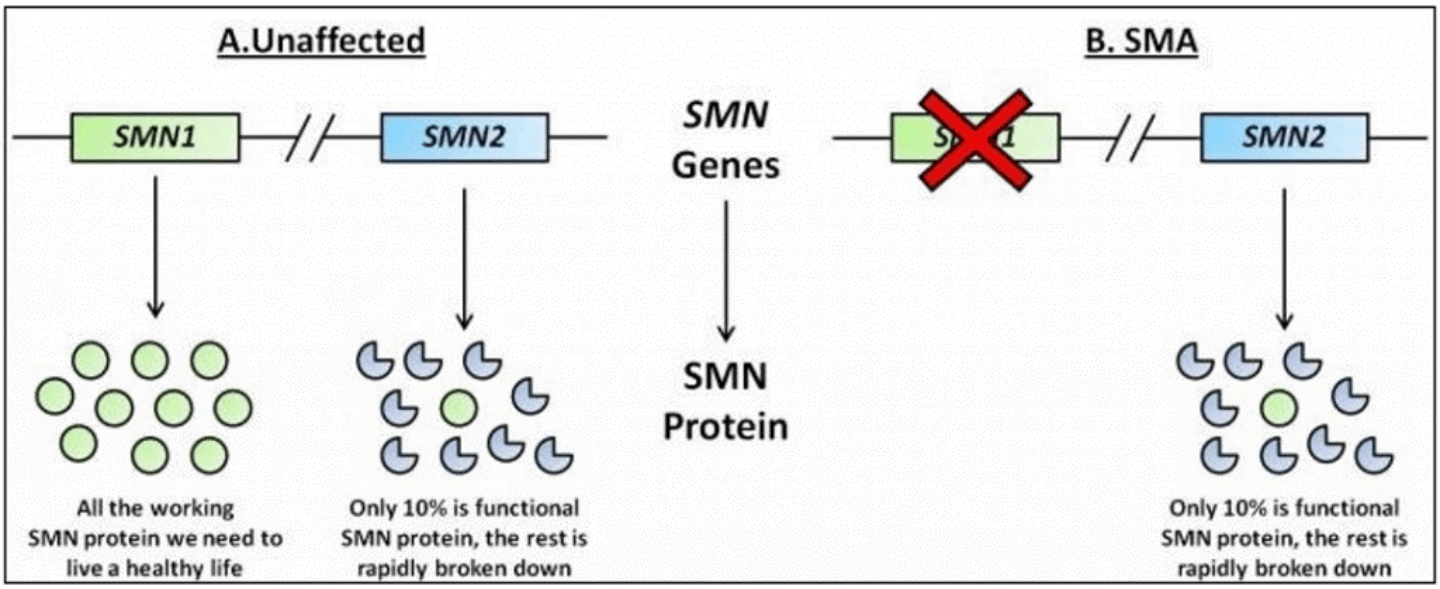
Severity of SMA

There is a wide spectrum of SMA symptoms. Historically, the type of SMA was classified based on age of onset and highest level of motor development achieved. There are five types described (type 0, I, II, III and IV) with type 0 being the most severe and lethal with symptoms appearing right at birth. SMA type I is the most common form, accounting for 60% of cases. Patients with SMA type I develop significant hypotonia (muscle weakness) of the limbs and truncal muscles by six months of age with progression of the muscle weakness resulting in breathing problems, respiratory infections, difficulty feeding and eventually death by age two. However, "with treatment, individuals may gain more physical milestones than they would have otherwise. As NBS for SMA becomes more common, infants can receive treatment even before symptoms begin. Because of these factors, doctors believe that we may soon stop describing SMA as specific "types," and instead focus on the highest motor milestone achieved: non-sitter, sitter and walker. As these categories suggest, even with treatment and screening, there will still be a wide range of severity associated with SMA."[1]

The Role of the SMN2 Gene

The onset and severity of symptoms relies on the function of a nearly identical gene to SMN1 known as SMN2. SMN2 is considered a back-up gene to SMN1. Most often, a small portion of SMN2 is spliced out or removed during the process of transcription of the SMN2 gene to RNA. This results in the majority of SMN protein made by SMN2 to be non-functioning. In SMA patients, they are missing their SMN1 gene and thus rely solely on their SMN2 genes to produce their only functioning SMN protein (**Figure 2**). The number of SMN2 genes can vary from person to person. Typically, if an SMA patient has only a few copies of SMN2, they will make little functioning SMN protein and show early and severe symptoms of SMA. Likewise, typically when an SMA patient has more copies of SMN2, they will make more SMN protein typically resulting in later onset and less severe symptoms of SMA. Thus, the number of copies of SMN2 that each child has impacts the severity and type of SMA.

Figure 2. Production of SMN Protein in Unaffected and SMA Populations[2]



1 CureSMA. Types of SMA. Available from: www.curesma.org/types-of-sma Accessed 17 Feb 2021.

2 Stichting Team Jayme. About SMA. Available from: https://teamjayme.nl/over/sma. Accessed 11 May 2021.

Treatments for SMA

As of January 2021, three recent advances in treatment including both medication and gene therapy have drastically improved the outcome of patients with SMA, especially patients with SMA type I or II. In 2016, the US Food and Drug Administration (FDA) approved Spinraza® (nusinersen) as a drug treatment option for patients diagnosed early in the disease course, notably less than two years of age. While Spinraza® improves patients' ability to meet motor milestones, it does not reverse muscle damage that has already occurred.

In 2019, FDA approved a gene therapy option called ZOLGENSMA® (onasemnogene abeparvovec-xioi) for patients diagnosed with SMA less than two years of age. In 2020, FDA approved a third new treatment option called Evrysdi®(risdiplam). Evrysdi® is a medication that is approved for all types of SMA and patients are able to take the medication by mouth.[1]

With three new treatments available, patients with SMA receiving treatments early in life often meet their motor milestones including sitting and walking. The new treatment options prevent respiratory involvement allowing children with SMA to live for many years. Therefore, timely diagnosis and early treatment are essential for changing the course of affected patients. NBS is leading the way in achieving this goal.

The US Secretary of Health and Human Services added SMA to the RUSP in 2018 following an evidence review and recommendation of the federal ACHDNC.[2]

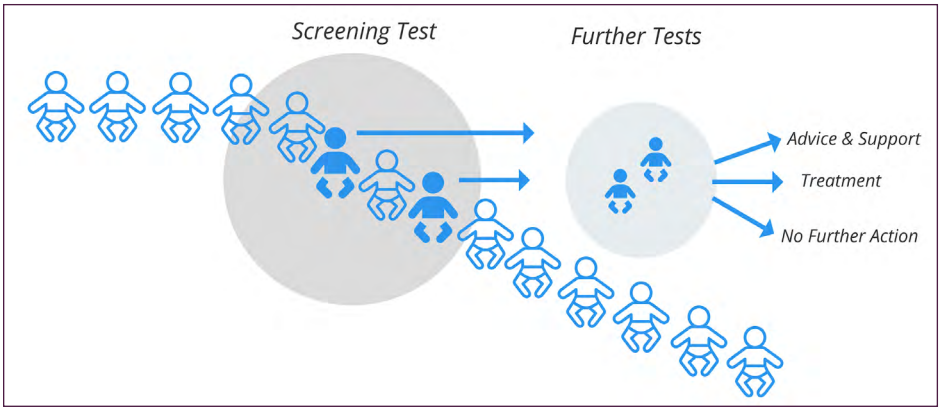
With availability of new treatment options, newborn screening for SMA could prevent about 50 infants from needing a ventilator and about 30 deaths due to SMA Type I in the United States every year.

THE NEWBORN SCREENING PROCESS

Screening vs Diagnostic Tests

NBS allows for population-based screening of all newborns to be performed in a timely and affordable manner. Currently, most states screen for close to 40 disorders in which timely diagnosis and management improves overall outcome. NBS programs establish cut-offs in an attempt to identify all newborns with a specific disorder without burdening the system with a high rate of false-positive screens (**Figure 3**). Newborns identified to be at risk for a disorder through newborn screening will require additional diagnostic testing to confirm the screen and make the diagnosis (**Table 1**).[3]

Figure 3. Newborn Screening Process



1 SMA News Today. Evrysdi (Risdiplam). Available from: https://smanewstoday.com/evrysdi-risdiplam Accessed 16 Apr 2021.

2 HRSA. Newborn Screening for Spinal Muscular Atrophy: A Summary of the Evidence and Advisory Committee Decision. Available from: www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/previous-nominations/sma-consumer-summary.pdf Accessed 13 Mar 2018.

3 APHL. Overview of Cutoff Determinations and Risk Assessment Methods Used in Dried Blood Spot Newborn Screening- Role of Cutoffs and Other Methods of Data Analysis. www.aphl.org/programs/newborn_screening/Documents/Overview%20on%20Cutoff%20Determinations%20and%20RIsk%20Assessment%20Methods_final.pdf . Accessed 11 May 2021.

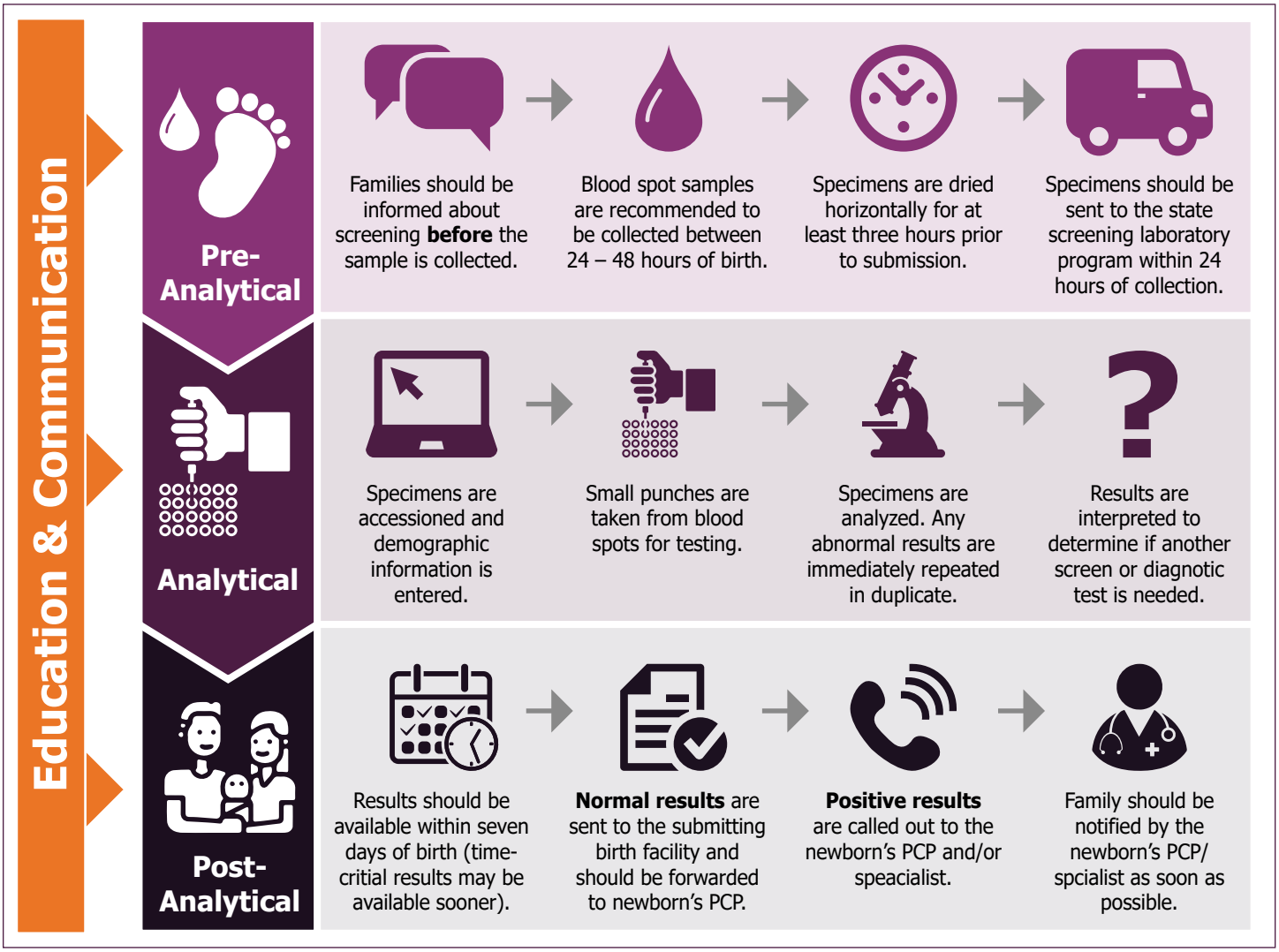
Table 1. Screen vs. Diagnostic Test

	Screen	Diagnostic Test
Population (offered the test)	Those **without clear signs or symptoms** of disease where early detection is essential.	Those **with symptoms**. Those undergoing further work-up **after a positive screen**.
Results	Result is an **estimate of level of risk**. Determines whether a diagnostic test is warranted.	Result provides a **definitive diagnosis**.
Test Metrics	Cutoffs set towards high **sensitivity**. Acceptance of **false positive results**.	Cutoffs set towards high **specificity**. Greater **precision and accuracy**.

Components of the NBS Process

Newborn dried blood spot screening is a process that has three phases: pre-analytical, analytical and post-analytical (**Figure 4**).

Figure 4. Phases of the NBS Blot Spot Process



State-specific Algorithms

NBS programs are state-run public health programs and, therefore, work in the confines of their own state governments. Each state will determine its own testing algorithm and follow-up process, often with input and guidance from stakeholders, specialists and other state and national partners. This algorithm may include the number of days of the week the specimens will be processed and analyzed, as well as which days of the week the results will be reported. Some states require a second screen to be conducted on all newborns, while other states may only require additional screening on their premature and/or ill newborn population.

Types of Results

A breakdown of the types of newborn screening results is found in **Table 2**. For SMA, all positive NBS results are "presumptive positives" due to the high accuracy of the results.

Table 2. Type of Possible NBS Results

Result Interpretation	Result Meaning
Normal/Negative/ Within Normal Limits	• The child is at low-risk for having the condition. • All values were within the expected range for unaffected newborns.
Unsatisfactory/Invalid	• The specimen was deemed invalid for accurate screening. • Results cannot be accurately interpreted. • Repeat NBS is needed.
Borderline/Inconclusive	• The child is at low- to medium-risk for having the condition. • A repeat screen is usually requested and often (but not always) resolves the result.
Abnormal/Positive/ Out-of-Range	• The child is at moderate- to high-risk for having the condition. • Clinical evaluation and specialty referral are advised.
Presumptive Positive	• High probability that the infant is affected. • Clinical evaluation is needed.

Performance Metrics

NBS results are intended to identify infants at risk for the screened disorder. Screening is not diagnostic; it will identify some infants with out-of-range results who do not have the disorder, and, on rare occasions, may not detect truly-affected infants. The performance of the screens, which need to be continually monitored, is measured through the following indicators:

True Positives

Infants identified through screening who are confirmed to be affected with the disorder.

False Positives

Infants identified through screening who are confirmed to not be affected with the disorder. This category typically includes unaffected carriers of the disorder who sometimes get picked up on the screening test and need to obtain further diagnostic testing to rule out the presence of the disorder.

False Negatives

Infants affected with a disorder that are not identified through newborn screening. Most screens are designed to minimize false negatives (maximizing sensitivity).

True Negatives

Infants with in-range newborn screening results who are not affected with the disorder.

Sensitivity

The ability of correctly identifying those with the disease (True Positive Rate).

Specificity

The ability of correctly identifying those without the disease (True Negative Rate).

It is rare for a screening test to ever have 100% sensitivity or specificity.

For SMA, NBS has a high positive predictive value with very low rate of false positives. However, based on the technology used and the genetics of SMA, it is estimated that approximately 5% of SMA patients will be missed by NBS (false-negatives).

Predictive Value Positive (PPV)

The proportion of true positives among all positive screens.

Negative Predictive Value (NPV)

The proportion of true negatives among all negative screens.

Accuracy

Proportion of patients correctly identified (True positives and True Negatives/All tests).

Prevalence/Incidence/Detection Rate

The number of true positives per number of births. This is typically figured on an annual basis; however, disorders that are very rare may need to be calculated over an average of five years, depending on the state's birth rate.

Figure 5. **NBS Outcomes**

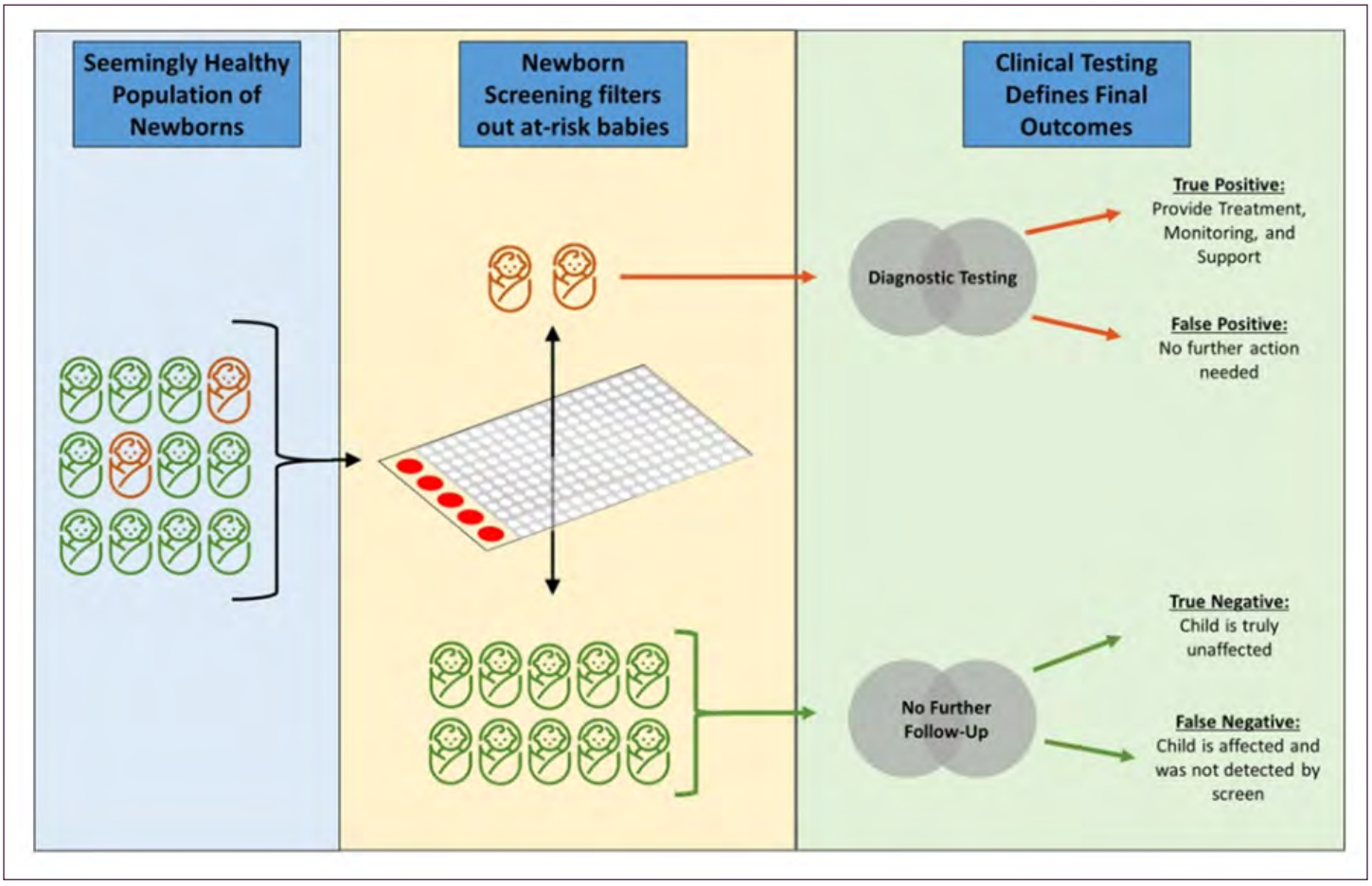


Figure 6. **NBS Test Results** [1]

	Disorder	No Disorder
Positive Test Result	True Positive (TP)	False Positive (FP)
Negative Test Result	False Negative (FN)	True Negative (TN)

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)
PPV = TP/(TP+FP)
NPV = TN/(FN+TN)

1 Carvajal, Diana & Rowe, Peter. (2010). Sensitivity, specificity, predictive values, and likelihood ratios. Pediatrics in review / American Academy of Pediatrics. 31. 511-3. 10.1542/pir.31-12-511.

Stakeholders

There are many stakeholders in the newborn screening process. These stakeholders may include:

- Families
- Advocacy groups
- Birthing providers (e.g., doctors, nurses, midwives)
- Hospitals and birthing centers
- Couriers for timely transport of specimens
- Primary care providers
- Clinical specialists
- Genetic counselors
- NBS laboratory
- NBS follow-up
- Policy makers
- Researchers

Fiscal Constraints

The key factors to NBS are readiness and feasibility of the screen to the screening program.[1] Almost all state programs charge a nominal fee for the screen with some states receive additional funding to support screening through state funding. The addition of a new disorder to the newborn screening panel can be costly. Therefore, funding can be a major hurdle in the overall implementation process. For SMA, the screening can be "multiplexed" with a disorder currently screened for by NBS programs: Severe Combined Immunodeficiency (SCID). This ability to add SMA to the pre-existing method used for SCID screening can help reduce laboratory start-up costs of a new test and staffing needs. State programs are often asked to show cost effectiveness of NBS when implementing a new disorder. These cost analyses are not always readily available and can be difficult to perform, and vary state to state. Lastly, many of the treatments for rare diseases are costly.

NBS COST CONSIDERATIONS

- Adding additional laboratory and/or follow-up staff. Creating new positions within state government can be difficult during poor state revenue, hiring freezes and other fiscal scenarios.
- Laboratory equipment needed to screen.
- Physical capacity of laboratory, how much additional lab space is required.
- Testing materials and reagents needed to screen.
- Startup costs for development and validation. Sometimes the NBS fee cannot be increased until after the program has gone live with testing and reporting.
- Creating and distributing education materials.
- Revisions to or added information technology (IT) components.
- Medical specialist contracts.

Timeline Hurdles

- Obtaining appropriate approval for the disorder's official addition to State panels, including fee increases and revision of rules/regulations as needed.
- Working through all of the above possible considerations.
- Completing pilot testing and finalizing screening cutoffs and decision algorithms.
- Education of stakeholders regarding SMA, the plan for screening, and available treatment options within the state.

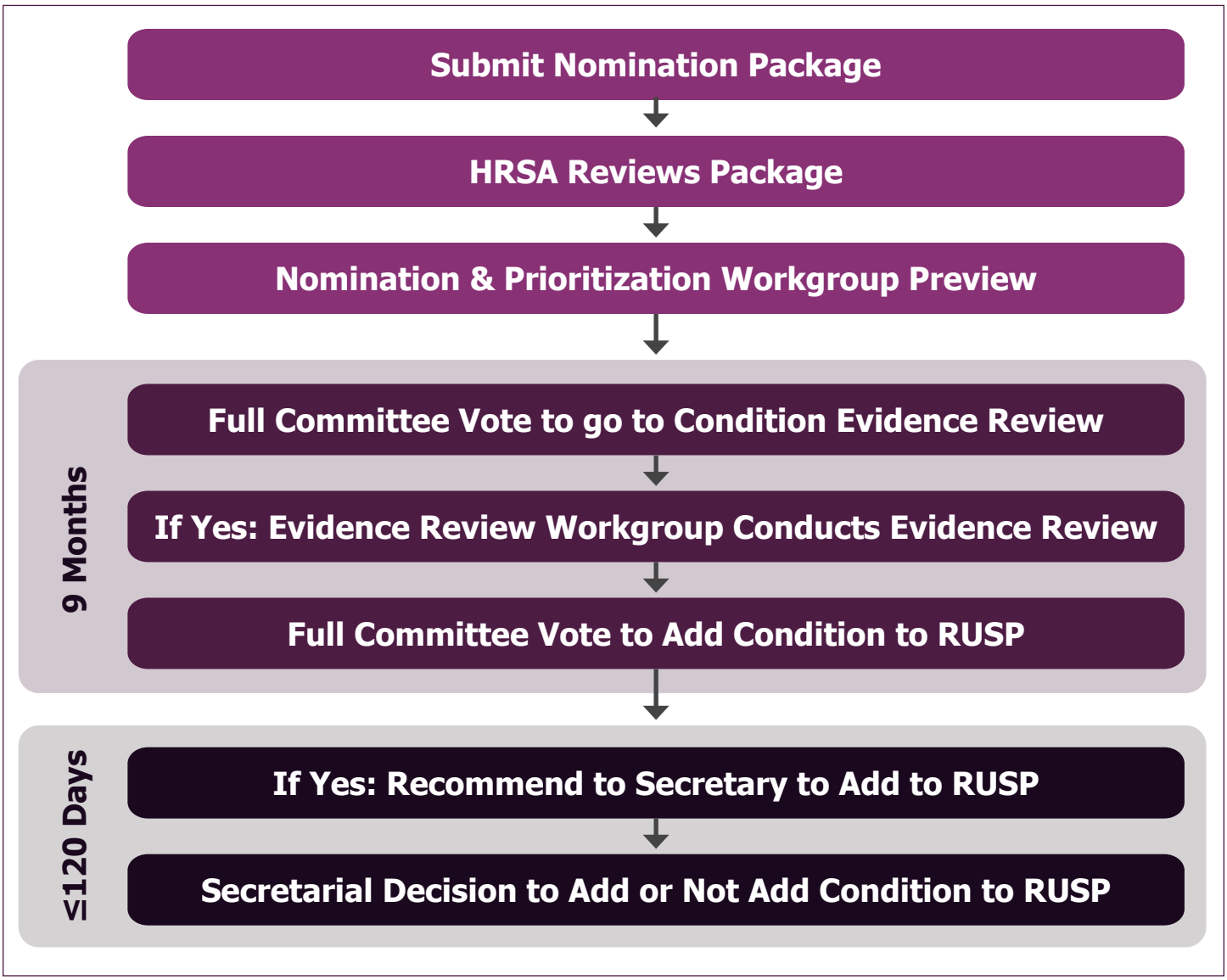
1 APHL. NewSTEPs 2019 Annual Report. Available from: https://www.newsteps.org/sites/default/files/resources/download/nbs-newsteps-2019-annual-report.pdf

GETTING READY TO SCREEN FOR A NEW DISORDER

Before a state can implement statewide screening of a new disorder, many things need to happen. In many states, there is a well-established process to get approval to add a condition to the state newborn screening panel.

In some states, the addition of new disorders is achieved through legislative action, relying on the effort of advocates and legislators. In other states, the process includes changes to rules and regulations that govern the newborn screening program through actions by the state board of health or the newborn screening advisory committee. Some states rely on national guidance through ACHDNC, utilizing their process of adding disorders to the RUSP. The RUSP lists disorders that have passed scientific evidence review and are recommended for universal screening in the US. The RUSP was based on a report authored by the American College of Medical Genetics and Genomics (ACMG) and endorsed by the US Secretary of Health in 2010. The RUSP was created in response to a recommendation from the American Academy of Pediatricians Newborn Screening Task Force to create uniformity in screening throughout NBS in the US as well as a process for government, professionals, and consumers to nominate a disorder to be considered by all state NBS programs. Although the RUSP provides recommendations and not requirements, most states look to the RUSP when determining whether to screen for a disorder.

Figure 8. **How Disorders Become Added to the RUSP**



Approval to Screen

If legislation has mandated that a state begin screening for a new disorder, the processes and time frame for activities required by the legislation will dictate the course of events to add the disorder.

If a state is considering adding a disorder to its newborn screening panel, the NBS program may need to gain approval and authority to screen for the disorder. Each state newborn screening system follows its own processes, but here is an example of the possible steps that will need to be taken.

Most state NBS programs conduct implementation pilots to build the state capacity to screen for the disorder and to validate testing methodology, evaluate follow-up processes, and ensure all NBS system components are operating as designed. NBS implementation pilots may require separate or additional approvals.

STEPS FOR APPROVAL/ AUTHORITY TO SCREEN

- Obtain approval to screen for the disorder from the NBS Advisory Committee (beginning with an initial presentation/meeting through to final approval).
- Obtain approval to screen for the disorder from approval by Board of Health, Commissioner/other leaders for funding (from initial NBS Advisory Committee letter of recommendation to final approval).
- Develop a budget to show costs for developing the newborn screening program's capacity to screen, and then for costs of statewide screening—including laboratory testing, follow-up, information technology, etc.
- Obtain approval by NBS Advisory Committee for funding, including funds necessary to build the newborn screening program's infrastructure and capacity to screen, prior to adding the disorder to the screening panel.
- Obtain approval by the State Budget Authority for funding, including funds necessary to build the newborn screening program's infrastructure and capacity to screen, prior to adding the disorder to the screening panel.
- Approval for fee increase, if required.

Laboratory Readiness to Screen for SMA

The factors influencing laboratory readiness are broad reaching and can vary from state to state, and from one disorder to another. The key things NBS labs need to consider well in advance of routine screening for SMA are:

Readiness Steps for NBS Laboratory Screening

- **Identify which screening method to use**; some disorders have up to four laboratory methods available to use for screening.
- **Have needed equipment for testing.** Contract for purchasing or renting the testing equipment may take up to a year to ratify and become available for the laboratory.
- **Have space needed for testing equipment.** Some test equipment requires major retrofitting, ventilation and electrical changes, has a large footprint and/or needs multiple platforms depending on the birthrate of the state.
- **Ensure testing method performance validations and verifications to meet regulatory requirements** for the NBS laboratory.
- **Ensure testing cutoffs and decision schemes meet specificity/sensitivity and other performance targets** to meet the goals of the NBS program. Second tier testing may need to be added also.
- **Define true and false positives** for measurement of the screen's performance metrics once full population testing begins.
- **Obtain adequate lab staffing for full population screening.** May require approval for additional staff to be hired and/or require time for some current staff cross-training.
- **SMA testing workflow integrated** with all NBS lab workflow.
- **Communication algorithm established** with short term follow-up program (phone, IT, messaging).

With implementation of NBS for SMA, in the coming years we will have a better understanding of the true prevalence, including identification of more mild cases.

Testing Methodology

- What are pros/cons of possible testing methods?
- What equipment is needed?
- Purchasing versus reagent rental?
- Is more/different facility space needed?
- Is additional power/construction needed?
- Will the program utilize a tiered testing algorithm?
- Will the program contract out for additional tiered testing?
- How does the proposed algorithm affect timeliness metrics?

Validation of testing strategy

- Prospective (current specimens) versus retrospective (stored specimens)?
- Identified, de-identified, or anonymized specimens?
- If identified, how will results be confirmed? Who will call out abnormal results?
- What is the availability of positive specimens, Quality Assurance (QA), reference, proficiency testing materials?

Lab and Follow-Up Staff Needs

- Are new hires needed? At what level?
- Is training needed for existing and new staff?
- Include educational needs on new disorders, new testing methodology, clinical expectations, etc.
- Will additional staff be needed on weekends?
- Will new specialist contracts be needed?

After Screening Starts: Heterogeneity of Conditions/Spectrum of Findings

- Will family members be detected?
- What else is being detected?
- What is the distribution/prevalence of mild versus severe patients and is that different than what was expected?
- How is the screen performing?

Follow-Up Readiness

Follow-up is an essential component to the NBS process and therefore vital for successful implementation of a new disorder. NBS follow-up can include communication of positive or out-of-range results to primary care providers and families, coordination of confirmatory testing, and connecting identified babies to appropriate specialists and/or treatment centers. For SMA, follow-up staff will need to work closely with local neuromuscular specialists and treatment centers to determine a plan of communication including information to be shared to Primary Care Providers (PCPs) and families. Some NBS programs might consider a script or outline when implementing a new disorder. Also, follow-up staff can work with the specialists to identify timeliness metrics of initial results, confirmatory testing and referral to specialists for initial evaluation. Follow-up often can identify delays in the process, barriers to confirmatory testing and access to care issues including delays in management and treatment.

Long-term follow-up is also a beneficial component of newborn screening as health departments may track key indicators for an extended time once an infant is confirmed to have a disorder. These activities can include care coordination, assuring access to both care and treatment, mode of treatment and periodic assessment of outcomes in patients. This additional data can be valuable when accessing the success of implementation. The data collected will inform the NBS program and can be beneficial for continuing quality improvement.

Key components of follow-up readiness for SMA screening include:

- Integration of SMA follow-up workflow with all follow-up workflows.
- Identification and communication with medical specialists and/or treatment centers for infants with positive SMA newborn screen.
- Development of action plan templates for PCP and parents, including any confirmatory testing needed.
- Development of a communication plan for follow-up coordinator and family/PCP.
- Development of a procedure for referral from short term follow-up program to neuromuscular specialist.
- Informing some third-party payors of SMA pilot and ensuring understanding of the need for coverage for treatments/therapies.

For SMA, there remain unanswered questions regarding the long-term effectiveness of new treatments and the outcome of the patients that receive these treatments at an early age. Data collection will be essential to fully answer these questions.

Information Technology (IT) Readiness

NBS programs process tens of thousands of specimens a year requiring robust information management systems, inclusive of laboratory information management system (LIMS) and case information management system (CIMS) used for follow-up. These systems may be developed by the state program or purchased from a vendor. Each time a disorder is added or changes are made to the NBS program, these systems must be modified for the analyte cut-offs, analyte reporting logic, new reports, assay quality control definitions, follow-up logic, parent letters and result reports, and diagnostic criteria and case definitions. Some programs include long-term follow-up in their systems. Fields need to be query able for continued evaluation of implementation and quality improvement efforts. NBS reports are securely distributed to birthing facilities, midwives, primary care physicians and/or other medical providers through a web-based portal, electronic messaging or paper copies by fax or mail. It is important to have stakeholder input when revising these reports so that the results are easy to understand and appropriate guidance is provided when there is a positive result or need for a repeat specimen. Any changes to a NBS program's systems takes time (i.e., specification gathering, extensive testing, user acceptance), expertise, stakeholder involvement and funding.

Key components of IT readiness include:

- **Integration of disorder into LIMS Testing & Reporting** (i.e., web portals, state health information exchange (HIE) and other reporting entities).
- **Integration of disorder into CIMS Reporting System** (i.e., web portals, state HIE and other reporting entities)
- **Integration of disorder into Electronic Orders and Results Protocol.** Determine vocabulary and message standards, and coordinate changes with each partner.

Notify submitters of report changes, such as:

- How will the NBS report change?
- What are reference ranges? Possible results?
- What are the relevant vocabulary standards (e.g. Logical Observation Identifiers Names and Codes (LOINCs))?

Establishing Relationships with Specialists

It is important for state NBS programs to establish partnerships and strong relationships with specialists. Relationships start during consideration and implementation of a new disorder. It is beneficial for state programs to form a task force/subcommittee with all the specialists across the state. The work groups should include laboratory, follow-up, specialists and parent advocates. As the process evolves, these task forces/subcommittees can begin discussing contracts, continuous quality improvement during and following implementation, development of educational materials, technical assistance and content expertise.

SMA is among the first muscular dystrophies added to newborn screening and therefore neuromuscular specialists are often new to the process. New partnerships may need to be fostered.

IDENTIFYING & MEETING WITH SPECIALISTS

- Are "new to newborn screening" sub-specialists involved?
- What clinical coverage does the state have for evaluation and treatment?
- Will testing need to occur on weekends for this condition?
- Who should be notified of screen-positive results? How urgently?
- After which tier should specialists be notified?
- What is appointment availability for positive NBS in their clinic?
- What barriers might there be to follow-up testing?
- Who can treat which individuals? On which insurances?
- What are monitoring protocols?
- What are associated risks?

EDUCATIONAL TOOLS FOR SMA

Education of providers, hospitals/birthing facilities and families is a key component of successful implementation. Since providers are often the first to discuss positive NBS results with families, educational tools and resources should be provided to them to facilitate this initial communication and ensure that accurate information is shared with the family. State programs can work with their specialists, disease specific support groups and families to develop educational material. It is important to review existing educational material of the specific disorder, since the current tools developed for clinically diagnosed patients may not be suitable for patients identified by NBS. Educational materials are often shared between state programs or materials are developed for national use through Expecting Health or CureSMA.

When a state is in the process of implementing a new disorder, it is beneficial to work with the communications group of the health department to develop a press release announcing the new disorder and benefits of screening. NBS programs may even consider working with stakeholders to develop a news story highlighting the implementation.

EDUCATIONAL READINESS TASKS

- Develop educational and support materials for PCPs, hospitals and families
- Translate educational materials for families into appropriate languages
- Develop script for PCPs to use with families
- Establish a communication plan between NBS program, specialists and PCP

With SMA, older educational materials sometimes show patients that are significantly impacted by SMA and may not reflect patients that were identified shortly after birth and treated early.

NEWBORN SCREENING PERFORMANCE METRICS & CONTINUOUS QUALITY IMPROVEMENT

When implementing a new disorder, it is helpful for NBS programs and key stakeholders to define goals including metrics to measure successes and shortcomings. These metrics can define timeliness of screening, reporting, referral and initiation of treatments. Following implementation, evaluation and continuous quality improvement efforts should be outlined. Frequent communication by NBS laboratory and program staff with the birthing facility, the newborn's primary care provider and clinical specialists will be beneficial in collecting these metrics and determining if further improvement or adjustments need to be considered.

An example of timeliness performance measure metrics for SMA NBS is given in **Table 3**. These metrics may be variable depending on the state performing the screening and recommendations by local neuromuscular specialists and stakeholders.

Following implementation of NBS for SMA, it is important that the stakeholders continue to meet regularly to review metrics and evaluate both the successes and shortcomings of NBS. Continuous quality improvement is an essential component to a newborn screening program.

Table 3. Timeliness Performance Measures*

Timeliness Performance Measure	Timeliness Metric Goals
Birth to specimen collection	24-48 hours
Specimen collection to receipt by lab	24-48 hours
Time from specimen receipt to reporting out of results	5-7 days
Birth to referred to specialist	8 days
Birth to seen by specialist	10 days
Birth to diagnostic blood collection	11 days
Birth to diagnosis	16 days
Birth to therapeutic planning and, as needed, intervention(s)	16 days

* The timeliness metric goals provided in this table are recommendations created by experts and do not represent national recommended benchmarks.

PILOT STUDIES vs. FULL STATEWIDE IMPLEMENTATION

Most state NBS programs conduct implementation pilots to build the state's capacity to screen for the disorder, validate testing methodology, evaluate follow-up processes, and ensure all newborn screening system components are operating as designed. Pilots may last a year or more in order to properly screen a representative sample of newborns, particularly if the disorder is very new to NBS nationally.

Some states use a "consented" pilot, meaning that consent will be obtained from the parents of some or all of the newborns screened through the pilot screening process. This is most common when NBS programs want to use blood spot specimens from newborns known to have SMA so they may validate their testing methodology to obtain a certain result. Some states will use an "opt in" process—parents have to agree to the screening for SMA—until the disorder is added to the state newborn screening panel and SMA screening is implemented statewide. States often need to include their health department's Institutional Review Board (IRB) for approval of the pilot process.

During an implementation pilot, normal (negative) newborn screening results are not usually reported on the laboratory report. If the NBS for SMA should return a positive (out-of-range) result, the laboratory will notify the follow-up program staff, who will notify the newborn's primary care provider after consultation with the NBS program's clinical specialist so that affected babies can benefit from the pilot.

Other state NBS programs that have already implemented a new disorder may be willing to share their implementation process and experiences with states that are planning their own implementation.

Prior to testing specimens during a pilot, the newborn screening program and the clinical specialists should determine a plan of action for reporting identified cases of SMA so that these babies and their families can benefit from the pilot.

CONCLUSION

The intent of this SMA resource has been to provide an overview of information regarding the many aspects that are involved in the addition of a new disorder to a state NBS panel. Please direct any questions regarding implementation or technical assistance needs to NewSTEPs at newsteps@aphl.org.

Learn more about SMA on HRSA's website: newbornscreening.hrsa.gov/conditions/spinal-muscular-atrophy.

ACKNOWLEDGMENTS

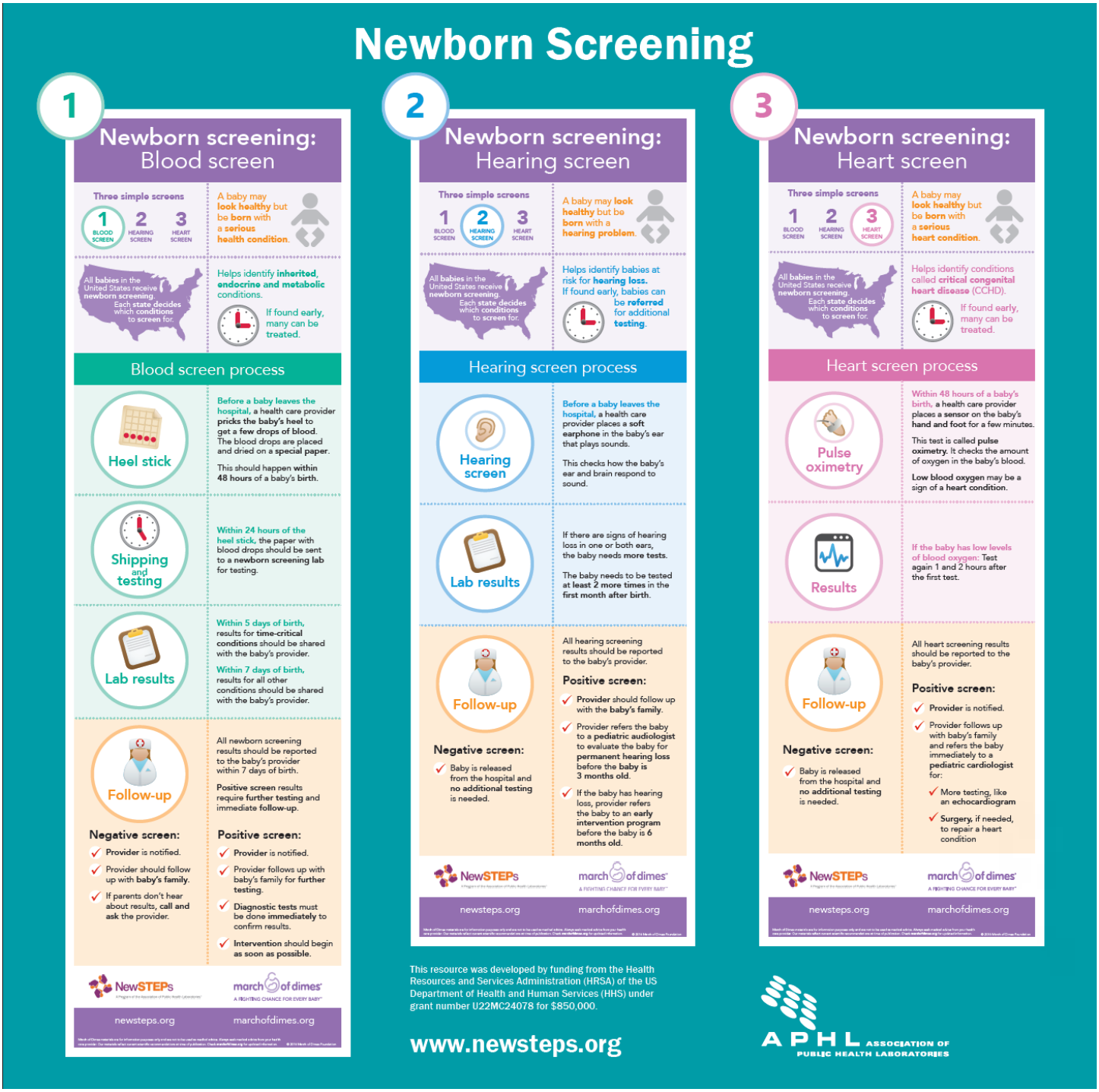
This publication is supported by the Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services (HHS) as part of an award totaling $1,500,000 with 0% financed with non-governmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS or the US Government. For more information, please visit HRSA.gov.

APHL gratefully acknowledges the contributions of:

- Patrick Hopkins
- Yvonne Kellar-Guenther, PhD
- Erica Wright, MS, CGC
- Amy Gaviglio, MS, LCGC
- NewSTEPs New Disorder Workgroup
- Sari Edelman, MPH
- Kshea Hale, MPH
- Sikha Singh, MHS, PMP
- Careema Yusuf, MPH

APPENDIX

NBS is comprised of three different parts: dried blood spot, hearing and critical congenital heart disease.



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Newborn Screening Technical Assistance and Evaluation Project

The Newborn Screening Technical assistance and Evaluation Project (NewSTEPs) is a national newborn screening project designed to provide data, technical assistance, quality improvement resources and training to newborn screening programs. NewSTEPs functions with the goal of improving outcomes for newborns by facilitating newborn screening initiatives and programmatic outcomes, thus improving the overall quality of the newborn screening system.

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