Metachromatic Leukodystrophy

Newborn Screening Implementation Resources and Tools

AUGUST 2026

NewSTEPs

A Program of the Association of Public Health Laboratories™

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INTRODUCTION

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 (NBS) program designed to provide data, technical assistance and training to NBS programs across the United States and to assist states (for the purposes of this report we will refer to states and territories as "states") with quality improvement initiatives. NewSTEPs is a comprehensive resource center for state NBS programs and partners.

How to Use This Resource

The NewSTEPs New Disorders Workgroup developed this tool to aid state and territorial NBS programs in communication and education of key partners during the implementation of new diseases. NBS programs routinely consider the expansion of their state and territorial panels, a process that can be lengthy and complex. The intended audiences for this tool are state and territorial NBS programs who can distribute it amongst key partners such as specialists, advocacy groups, or legislators and governmental agencies seeking information on NBS disease implementation.

APHL NEWBORN SCREENING

Vision

All babies have a healthier start through newborn screening.

Mission

Driving newborn screening systems to excellence by shaping policy, promoting data-driven improvements, and pursuing innovations in public health laboratory practices.

WHAT IS NEWBORN SCREENING?

Newborn screening (NBS)—recognized as the largest and most successful disease prevention system in the United States—is the practice of screening every newborn for certain harmful or potentially fatal diseases that are not otherwise apparent at birth. NBS takes place before the newborn leaves the birth facility and identifies serious, life-threatening diseases before symptoms begin. Although such diseases are usually relatively rare, together they affect over 13,000 newborns each year in the US. Early detection is crucial to prevent death or a lifetime of severe health problems.[1]

Key points of NBS:

- **NBS is comprised of three different parts:** dried blood spot (DBS) screening, hearing screening and critical congenital heart disease screening[2] (see **Appendix**). This resource is focused on DBS as the method used for metachromatic leukodystrophy (MLD) screening.
- **NBS programs are essential public health programs that perform laboratory screening, conduct follow-up on actionable results and refer newborns to clinical care for diagnosis and treatment as necessary.**
    - Successful programs require knowledge and coordination from multiple partners who play critical roles in the screening process.
    - NBS programs test large numbers of dried blood spot specimens each day, and many of the diseases screened for are considered time-critical. Time-critical diseases are those that pose a significant health risk to newborns within days of birth.[3]
- **NBS programs are state- or territory-based.**
    - Variations between NBS programs exist from state-to-state (for the purposes of this report we will refer to states and territories as "states"), including the number of diseases screened and the number of routine specimens collected from each newborn.
    - While states determine which diseases to screen, federal guidance was formerly, until 2025, provided by the US Department of Health and Human Services' (HHS) Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and includes the Recommended Uniform Screening Panel (RUSP).[4] MLD was nominated to the RUSP and approved for initiation of evidence review in August 2024 (HRSA, 2024).[5] Information is publicly available from the ACHDNC from August 2024 about the status of the MLD RUSP nomination. Results from the completed evidence review are available through Pediatrics[6] and the EveryLife Foundation.[7]
    - Given the lapse in the ACHDNC as of April 2025, a Federal Register Notice was released to add MLD to the RUSP.[8] The HHS Secretary approved the addition of MLD to the RUSP on December 16, 2025.[9]

1 APHL. Newborn Screening & Genetics Program. Available from: www.aphl.org/programs/newborn_screening/Pages/program.aspx

2 NewSTEPs. Newborn Screening Educational Resource. July 2017. www.newsteps.org/sites/default/files/nbsmod3screenstabletop_educationalresource_july2017_ss.pdf

3 NewSTEPs. Time Critical Conditions. Accessed August 15, 2022: www.newsteps.org/sites/default/files/case-definitions/qi_source_document_time_critical_disorders_0.pdf

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

5 Phornphutkul, et al. (2024). Nomination and Prioritization Workgroup Report on: Metachromatic Leukodystrophy .

6 Lam, et al. (2025). Evidence Regarding Metachromatic Leukodystrophy Newborn Screening.

7 EveryLife Foundation. MLD Evidence Review Recording

8 National Archives, Federal Register. Notice With Request for Comment: Consideration of Adding Metachromatic Leukodystrophy to the Recommended Uniform Screening Panel

9 HHS. Secretary Kennedy Adds Duchenne Muscular Dystrophy, Metachromatic Leukodystrophy to Newborn Screenings | HHS.gov

- A state-by-state list of diseases,[10] updated in real time, is maintained by the Newborn Screening Technical assistance and Evaluation Program (NewSTEPs)[11] of the Association of Public Health Laboratories (APHL).[12]
- Occasionally, states may add diseases through legislative routes motivated by parents, disease advocates and/or specialists, researchers and clinicians. These diseases can be unique to certain states' screening panels and may not necessarily be screened nationally.

- **NBS programs are opt-out programs.** In most states, parents can refuse NBS in writing based on their beliefs; otherwise, it is automatically conducted. This process is typically referred to as "opt-out" as opposed to "consent."
- **NBS programs are designed to detect treatable diseases of the newborn.** Diseases on the NBS panel typically must meet certain criteria for screening, such as:
  - Can affect newborns
  - May not be clinically obvious
  - Have an available screening modality (e.g., analysis of dried blood spots) with acceptable sensitivity and specificity (not too many false-positive or false-negative results)
  - Have effective pre-symptomatic treatments available.

WHAT IS EARLY-ONSET MLD AND WHY WAS IT CONSIDERED FOR NBS?

Metachromatic leukodystrophy (MLD) is a rare autosomal-recessive lysosomal disease. MLD is caused by biallelic variants in the *ARSA* gene (ARSA; MIM *607574) that encode the enzyme arylsulfatase A (ARSA). Deficiency of ARSA enzyme activity leads to the accumulation of sulfatides in the nervous system and throughout the body.[13,14] MLD is a neurodegenerative disease in which excess sulfatides in microglia lead to progressive demyelination in the central and peripheral nervous system. Clinically, this manifests as rapid motor and cognitive decline and premature death, particularly in its early-onset forms. As such, early-onset MLD is the target of NBS and was added to the RUSP in December 2025.

Table 1: Types and Characteristics of MLD Presentations

Phenotype	Subtype	Symptom onset	Percentage of cases
Early-onset	Late infantile (LI)	≤ 30 months	20-40%
	Early Juvenile (EJ)	30 months and 7 years	
Late-onset	Late Juvenile (LJ)	7 years and 16 years	10-20%
	Adult onset	≥ 17 years	

Disease progression in untreated patients with the severe early-onset forms of MLD is highly predictable, with fast deterioration in motor and cognitive function occurring within months after patients enter the rapidly progressive phase of the disease.[15,16] MLD is pan-ethnic, with an estimated global birth prevalence of approximately 1 per 100,000 live births across all subtypes (range 1 per 40,000 to 160,000). Higher prevalences have been reported among Arab

10 APHL. Screened Conditions Report. Available from: www.newsteps.org/data-resources/reports/screened-conditions-report
11 NewSTEPs website: www.newsteps.org
12 APHL website: www.aphl.org
13 Gomez-Ospina et al. (2006 [Updated 2024]). Arylsulfatase A Deficiency.
14 Asbreuk et al. (2025). Metachromatic Leukodystrophy: New Therapy Advancements and Emerging Research Directions.
15 Kehrer et al. (2011). The natural course of gross motor deterioration in metachromatic leukodystrophy.
16 Kehrer et al. (2021). Association of Age at Onset and First Symptoms With Disease Progression in Patients With Metachromatic Leukodystrophy

groups in Israel (1 per 8,000), members of the Navajo Nation in Arizona and Utah (1 per 2,500), and the Native American population of Alaska.[17,18,19,20,21,22,23,24,25,26,27]

Evidence from clinical trials have shown that optimal efficacy is achieved if patients with early-onset MLD are treated pre-symptomatically, with either *ex vivo* gene therapy for early-onset MLD and allogenic hematopoietic stem cell transplantation (HSCT) for late-onset MLD.[28,29,30,31,32] Gene therapy for the treatment of severe early-onset MLD was approved in the European Union (EU), the United Kingdom (UK), and the US in 2020, 2021 and 2024, respectively. International consensus guidelines advise that pre-symptomatic early-onset MLD patients receive gene therapy treatment within the first year of life, further underscoring the importance of newborn screening.[33,34]

Given these advancements, MLD, especially early-onset MLD, is considered a condition suitable for NBS because of its severity if left untreated and the criticality of pre-symptomatic treatment administration. The initial signs and symptoms of MLD can be subtle and non-specific and can go unrecognized or misdiagnosed for months or years.[35,36] The absence of MLD NBS for the early-onset forms has raised ethical concerns, as early identification and access to life-saving treatment have historically been limited to newborns with a known family history, allowing intervention primarily in subsequently affected siblings.[37]

In 2025, Norway became the first country to implement national NBS for MLD.[38] The New York State Department of Health has conducted a consented pilot NBS for MLD since 2021 through the National Institutes of Health (NIH) funded ScreenPlus program. In the second half of 2025, New York expanded this work by launching a statewide NBS pilot for MLD under the NIH IDIQ contract. In addition, Pennsylvania and Illinois began screening for MLD in 2026.

17 Bonkowsky et al. (2021). Association of Diagnosis of Leukodystrophy With Race and Ethnicity Among Pediatric and Adolescent Patients

18 Söderholm et al. (2020). Elevated Leukodystrophy Incidence Predicted From Genomics Databases.

19 Heim et al. (1997). Leukodystrophy incidence in Germany.

20 Poorthuis et al. (1999). The frequency of lysosomal storage diseases in The Netherlands.

21 Pinto et al. (2004). Prevalence of lysosomal storage diseases in Portugal.

22 Holve et al. (2001). Metachromatic leukodystrophy in the Navajo: fallout of the American-Indian wars of the nineteenth century.

23 Pastor-Soler et al. (1995). Metachromatic leukodystrophy among southern Alaskan Eskimos: molecular and genetic studies.

24 Lugowska et al. (2011). Population carrier rates of pathogenic ARSA gene mutations: is metachromatic leukodystrophy underdiagnosed?

25 Hult et al. (2014). Epidemiology of lysosomal storage diseases in Sweden.

26 Stellitano et al. (2016). Leukodystrophies and genetic leukoencephalopathies in childhood: a national epidemiological study

27 Chang et al. (2024). A systematic review on the birth prevalence of metachromatic leukodystrophy.

28 Boucher et al. (2015). Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report

29 Groeschel et al. (2016). Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Juvenile Metachromatic Leukodystrophy Compared With Nontransplanted Control Patients | Child Development | JAMA Neurology | JAMA Network

30 Beschle et al. (2020). Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy

31 Fumagalli et al. (2022) Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access

32 Fumagalli et al. (2025). Long-Term Effects of Atidarsagene Autotemcel for Metachromatic Leukodystrophy

33 Adang et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

34 Laugwitz et al. (2024). Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy

35 Harrington et al. (2019). Insights into the natural history of metachromatic leukodystrophy from interviews with caregivers

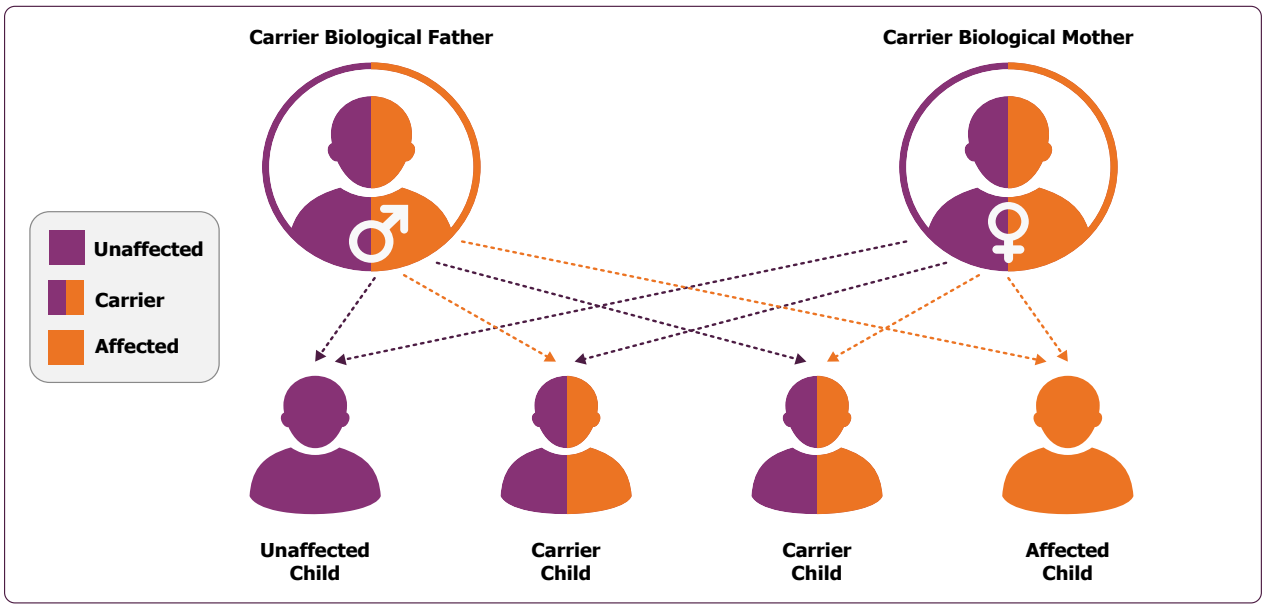
36 Eichler et al. (2022). Understanding caregiver descriptions of initial signs and symptoms to improve diagnosis of metachromatic leukodystrophy

37 Horgan et al. (2023). A retrospective cohort study of Libmeldy (atidarsagene autotemcel) for MLD: What we have accomplished and what opportunities lie ahead

38 Health Systems and Policy Monitor Network (2024). Norward expands its newborn screening programme to 30 rare serious congenital disorders

Figure 1. Autosomal Recessive Inheritance Pattern

Diagram modified from NxGen MDx. Accessed January 3, 2022 from: nxgenmdx.com/genetic-screening/



Genetics and Inheritance of MLD

MLD is caused by biallelic pathogenic variants in the arylsulfatase A (*ARSA*) gene, located on chromosome 22, that result in deficiency of the encoded lysosomal enzyme ARSA.[39] It is classified into four subtypes based on the age of symptom onset (**Table 1**).[40]

The early-onset MLD phenotype includes the late infantile (LI) and early juvenile (EJ) subtypes, and the late-onset MLD phenotype includes the late juvenile (LJ) and adult subtypes. Most MLD patients have an early-onset phenotype, and it is this phenotype that is on the RUSP.

In addition to age of symptom onset in the patient, MLD phenotypes can often be characterized based on their *ARSA* genotype and the level of residual ARSA enzyme activity in leukocytes, especially if an assay with increased sensitivity is employed.[41,42] Of the more than 1,400 known *ARSA* gene variants, almost 400 have been classified as pathogenic.[43,44] Pathogenic variants of *ARSA* can be functionally divided into two broad groups differing in predicted severity: null (0) or "severe" variants associated with little or no enzyme activity, and R variants encoding for ARSA with higher levels of residual enzyme activity.[45,46,47,48]

39 Gomez-Ospina et al. (2006 [Updated 2024]). Arylsulfatase A Deficiency.
40 Eichler et al. (2022). Understanding caregiver descriptions of initial signs and symptoms to improve diagnosis of metachromatic leukodystrophy
41 Kehrer, et al, (2011). The natural course of gross motor deterioration in metachromatic leukodystrophy
42 Santhanakumaran, et al. (2022). Predicting clinical phenotypes of metachromatic leukodystrophy based on the arylsulfatase A activity and the ARSA genotype? - Chances and challenges
43 Cesani, et al. (2016). Mutation Update of ARSA and PSAP Genes Causing Metachromatic Leukodystrophy
44 ClinVar, 2024: https://www.ncbi.nlm.nih.gov/clinvar/?term=%22ARSA%22%5BGENE%5D&redir=gene (last assessed September 5, 2025)
45 Gomez-Ospina et al. (2006 [Updated 2024]). Arylsulfatase A Deficiency.
46 Cesani, et al. (2016). Mutation Update of ARSA and PSAP Genes Causing Metachromatic Leukodystrophy
47 Santhanakumaran, et al. (2022). Predicting clinical phenotypes of metachromatic leukodystrophy based on the arylsulfatase A activity and the ARSA genotype? - Chances and challenges
48 Trinidad, et al. (2023). Predicting disease severity in metachromatic leukodystrophy using protein activity and a patient phenotype matrix

Diagnosis and Clinical Manifestations of MLD

International consensus publications provide structured guidance on how to confirm a diagnosis of MLD and predict subtype after newborn screening, while also informing appropriate monitoring strategies and clinical care.[49,50,51] These guidelines incorporate both international and US-based expertise and include an overview of clinical management of all MLD subtypes (including uncertain subtype) as well as potential differential diagnoses (e.g., multiple sulfatase deficiency and prosaposin B deficiency).[52] The international MLD Initiative (MLDi) disease registry also offers valuable clinical resources on the disease.[53]

Diagnostic Confirmation Following Positive NBS Screen

In newborns who screen positive for MLD, the following tests are performed to clinically confirm the diagnosis:

- ARSA enzyme activity in leukocytes
- Urine sulfatide concentration
- *ARSA* genotyping of the baby (if not completed by the NBS program) and their biological parents.

ARSA genotype supplemented with residual ARSA enzyme activity levels enable prediction of the age of onset of clinical disease and disease progression in most screen-positive newborns, including those with early-onset MLD subtypes.[54,55]

Natural History

The natural history of MLD is well understood and has been described in various studies.[56,57] Gomez-Ospina (2024) has further gathered and consolidated this information,[58] summarized in **Table 2**.

49 Adang et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

50 Laugwitz, et al. (2024). Newborn screening in metachromatic leukodystrophy – European consensus-based recommendations on clinical management

51 Laugwitz, et al. (2024). Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy

52 Adang, et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

53 Schoenmakers, et al. (2022). Modified Delphi procedure-based expert consensus on endpoints for an international disease registry for Metachromatic Leukodystrophy: The European Metachromatic Leukodystrophy initiative (MLDi)

54 Santhanakumaran, et al. (2022). Predicting clinical phenotypes of metachromatic leukodystrophy based on the arylsulfatase A activity and the ARSA genotype? - Chances and challenges

55 Trinidad M, et al. (2023). Predicting disease severity in metachromatic leukodystrophy using protein activity and a patient phenotype matrix

56 Kehrer, et al. (2011). The natural course of gross motor deterioration in metachromatic leukodystrophy

57 Kehrer, et al. (2014). Language and cognition in children with metachromatic leukodystrophy: onset and natural course in a nationwide cohort

58 Also citing Eichler et al 2022; Kehrer et al 2021; Kehrer et al 2011; Fumagalli et al 2021; Gieselmann & Ingeborg 2019; and Mahmood et al 2010.

Table 2: MLD Disease Progression

MLD Type	Initial Findings	Disease Progression	Later Signs / Final Stage
Late infantile (early-onset)	• Decline or plateau in gross motor skills, often new toe walking, foot drop, or decreased stability (ataxia) • Decline or plateau of language skills (loss of complexity of language, dysarthria) • Peripheral neuropathy with slow nerve conduction velocities (NCVs) and decreased reflexes • Esotropia or strabismus	• Regression of cognitive, language, and motor skills • Pain in extremities • Feeding difficulties necessitating gastrostomy tube • Hyperreflexia • Increasing spasticity of limbs	• Appendicular hypertonicity • Axial hypotonia • Seizures • Hearing/vision impairment • Loss of independent movement and communication • Death typically within 5-10 years of symptom onset, but can vary
Early juvenile (early-onset)	Similar to LI	• Similar to LI • Rate of early motor deterioration signals rapid disease progression and poor prognosis	• Similar to LI • Premature death, can vary
Late juvenile (late-onset)	• Behavioral disorders • Declining school performance • Regression of language skills • Gait problems • Tremor	Rate of early motor deterioration signals rapid disease progression and poor prognosis	• Similar to LI • Premature death in early adulthood, can vary
Adult MLD (late-onset)	Neuropsychiatric • Declining school/job performance • Substance use • Emotional lability • Anxiety, depression • Psychosis	• Chronic decline with worsening neuropsychiatric symptoms • May span two to three decades • Motor decline often a later finding • Loss of self-care skills	• Similar to LI • Premature death in adulthood, can vary, but often after decades of declining function

Imaging or other clinical findings observed in MLD include:

- White matter hyperintensities on T2-weighted brain magnetic resonance imaging (MRI)
- Accumulation of sulfatides in the gallbladder, which can be symptomatic[59,60]

Surveillance

In the subset of newborns for whom subtype cannot be determined, surveillance includes:

- Brain magnetic resonance imaging (MRI) to track myelination
- Assessment of motor function via gross motor function measurement (GMFM)
- Nerve conduction studies
- Gallbladder imaging

59 Rappard van DF, et al. (2016). Gallbladder and the risk of polyps and carcinoma in metachromatic leukodystrophy

60 Mutua et al, (2025) Characterization of gallbladder disease in metachromatic leukodystrophy across the lifespan - PubMed

Further monitoring and management recommendations are available for all MLD subtypes, including detailed monitoring recommendations for individuals with late or uncertain disease onset.[61,62]

Treatments for MLD

Treatment for MLD consists of targeted therapy and multidisciplinary supportive care, accompanied by family support services and screening of asymptomatic siblings.[63]

Targeted Therapy

As of March 2024, atidarsagene autotemscel (Lenmeldy®), abbreviated as arsa-cel, has been approved by the US Food and Drug Administration (FDA) for the treatment of patients with:

- Presymptomatic LI MLD
- Presymptomatic EJ MLD
- Early-symptomatic EJ MLD who still have the ability to walk without support and have not experienced cognitive decline

Arsa-cel was previously approved in the United Kingdom, European Union, Iceland, Liechtenstein, Norway and Switzerland under the trade name Libmeldy®. Arsa-cel is an *ex vivo* gene therapy that involves harvesting autologous hematopoietic CD34+ stem cells, genetically modifying them in the laboratory with a lentiviral vector containing functional human *ARSA* gene, then reinfusing the treated cells into the patient after myeloablative busulfan conditioning. The best gross motor and cognitive outcomes for arsa-cel are observed in patients who are treated before MLD symptoms occur.[64,65] Expert consensus guidelines strongly recommend arsa-cel as the standard of care for treatment of patients with the MLD subtypes specified above.

For patients with slower-progressing, later-onset MLD, allogeneic hematopoietic stem cell transplantation (HSCT) is an available treatment option.[66,67,68,69,70,71,72,73,74,75,76] Long-term studies have shown that patients with LJ and Adult MLD also benefit most from HSCT if transplanted during presymptomatic or early symptomatic periods. Treated patients exhibit improved survival and stabilization of cognitive and motor functions compared to those who have not received HSCT. Long-term outcomes of HSCT in later-onset MLD have been discussed in some studies.[77,78,]

61 Adang, et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

62 Laugwitz et al. (2024b). Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy

63 Fumagalli et al. (2022). Lentiviral haematopoietic stem-cell gene therapy for early-onset metachromatic leukodystrophy: long-term results from a non-randomised, open-label, phase 1/2 trial and expanded access

64 Lenmeldy USPI: Lenmeldy. Package insert. Orchard Therapeutics; 2024 https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/lenmeldy. Accessed 1st September 2025.

65 Laugwitz, et al. (2024). Newborn screening in metachromatic leukodystrophy – European consensus-based recommendations on clinical management

66 Adang, et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

67 Bredius, et al. (2007). Early marrow transplantation in a pre-symptomatic neonate with late infantile metachromatic leukodystrophy does not halt disease progression

68 Martin, et al. (2013). Neurodevelopmental outcomes of umbilical cord blood transplantation in metachromatic leukodystrophy

69 Bley, et al. (2013). Hematopoietic stem cell transplantation (HSCT) in nine patients with juvenile MLD. Neuropediatrics

70 Boucher, et al. (2015). Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report

71 Rappard van DF, et al. (2016). Gallbladder and the risk of polyps and carcinoma in metachromatic leukodystrophy

72 Groeschel et al. (2016). Long-term Outcome of Allogeneic Hematopoietic Stem Cell Transplantation in Patients With Juvenile Metachromatic Leukodystrophy Compared With Nontransplanted Control Patients | Child Development

73 Tan, et al. (2019). Hematopoietic Stem Cell Transplantation in Inborn Errors of Metabolism

74 Beschle, et al. (2020). Early clinical course after hematopoietic stem cell transplantation in children with juvenile metachromatic leukodystrophy

75 Armstrong, et al. (2023). A systematic review of clinical effectiveness and safety for historical and current treatment options for metachromatic leukodystrophy in children, including atidarsagene autotemcel

76 Schoenmakers, et al. (2025). Modified Delphi procedure-based expert consensus on endpoints for an international disease registry for Metachromatic Leukodystrophy: The European Metachromatic Leukodystrophy initiative (MLDi

77 Boucher, et al. (2015). Long-term outcomes after allogeneic hematopoietic stem cell transplantation for metachromatic leukodystrophy: the largest single-institution cohort report

78 Berepoot, et al. (2025). ARSA Variants Associated With Cognitive Decline and Long-Term Preservation of Motor Function in Metachromatic Leukodystrophy

Supportive Care

For MLD patients who are not eligible for preventive therapies or are otherwise symptomatic, supportive care includes:

- Developmental/educational services
- Minimizing neuromuscular complications via orthopedic care, physical medicine/rehabilitation, and physical/occupational therapy
- Managing gastrointestinal and feeding problems, nutrition, speech therapy; monitoring for gallbladder involvement
- Controlling neurological manifestations, such as seizures
- Addressing vision and hearing impairments
- Establish respiratory plans to decrease risk of pneumonia
- Assisting and educating families and caregivers
- Coordinating multi-specialty care

Expert guidelines for the care of symptomatic leukodystrophy patients have been published.[79,80,81] General considerations for the care of MLD patients have further been summarized.[82,83]

79 Bonkowsky, et al. (2021). Association of Diagnosis of Leukodystrophy With Race and Ethnicity Among Pediatric and Adolescent Patients

80 Keller, et al. (2021). Practical Approaches and Knowledge Gaps in the Care for Children With Leukodystrophies

81 Adang, et al. (2017). Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies

82 Adang, et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

83 Gomez-Ospina et al. (2006 [Updated 2024]). Arylsulfatase A Deficiency.

THE NEWBORN SCREENING PROCESS

Screening vs. Diagnostic Tests

Newborn screening allows for population-based screening of all newborns in a timely and affordable manner. Currently, all states screen for numerous diseases in which timely diagnosis and management improves overall outcome. NBS programs establish analytical cutoffs and result decision algorithms to try to identify all newborns with a specific disease without burdening the system with a high rate of false-positive results (**Figure 2**). Newborns identified to be at risk for a disease through NBS will require additional diagnostic testing to confirm the screening and to make the diagnosis (**Table 3**).[84]

Figure 2. Newborn Screening Process

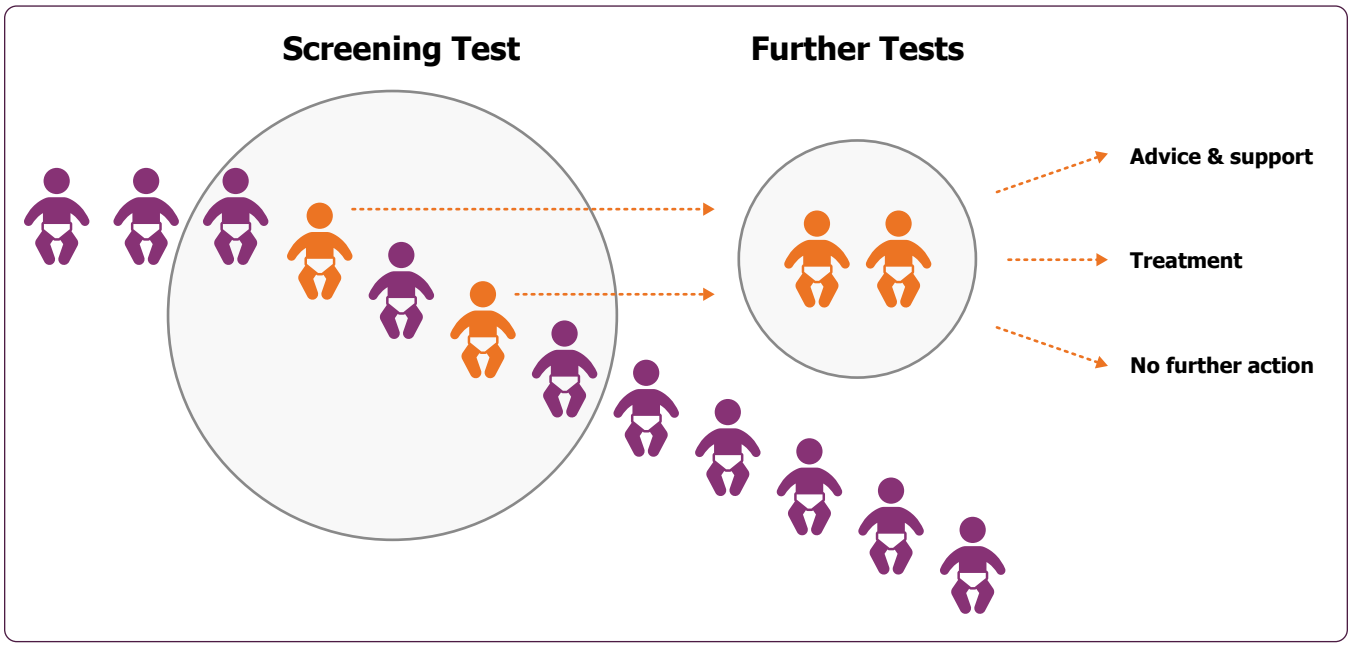


Table 3. Screen vs. Diagnostic Test

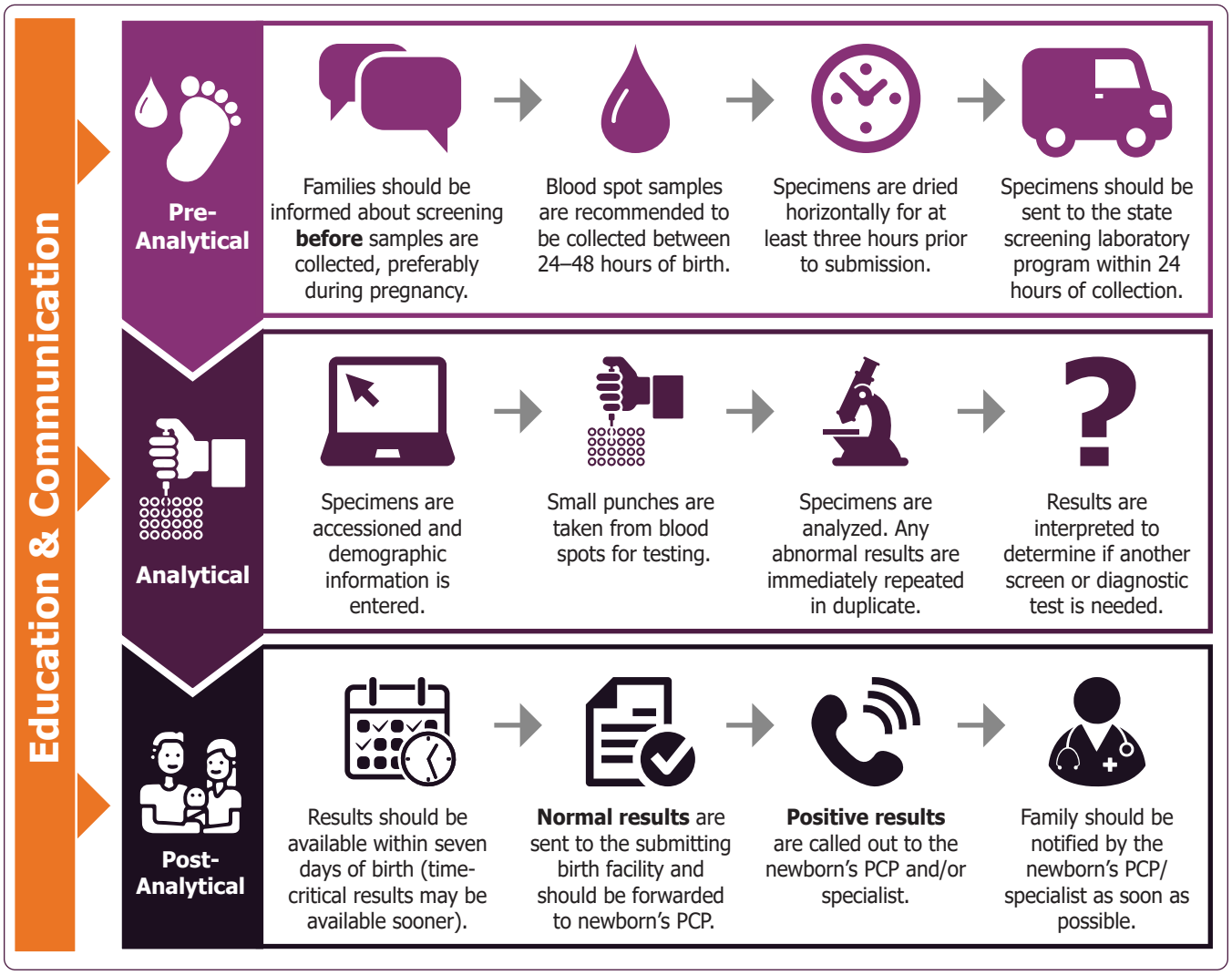
	Screen	Diagnostic Test
Population (offered the test)	Those **without clear signs or symptoms** of disease where early detection is essential.	Those **with symptoms**. Those undergoing further work-up **after a positive screen.**
Results	Result is an **estimate of level of risk**. Determines whether a 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**.

84 APHL (March 2019). Overview of Cutoff Determinations and Risk Assessment Methods Used in Dried Blood Spot Newborn Screening- Role of Cutoffs and Other Methods of Data Analysis.

Components of the NBS Process

Newborn DBS screening is a process that has three phases: pre-analytical, analytical and post-analytical (**Figure 3**).

Figure 3. Phases of the NBS Blood Spot Process



State-specific Algorithms

NBS programs are state-run public health programs and, therefore, work within the confines of their own state governments. Each state will determine its own testing algorithm and follow-up processes, often with input and guidance from community members, 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 for 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 NBS results is found in **Table 4**.

Table 4. Types of Possible NBS Results

Result Interpretation	Result Meaning
Normal/Negative/ In-range	• The child is at low risk for having the disease. • 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 disease. • 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 disease. • Clinical evaluation and specialty referral are advised.

Performance Metrics and Continuous Quality Improvement

NBS is intended to flag that may be at risk for the screened disease. Screening is not diagnostic; it will flag some newborns who do not have the disease with a false-positive result, and, on rare occasions, may be unable to detect truly affected newborns, thus presenting a false negative result.

When implementing a new disease, it is helpful for NBS programs and key partners to define goals, including metrics to measure successes and shortcomings. These metrics can define timeliness of screening, reporting, referral, confirmatory results and initiation of treatments. Following implementation, evaluation and continuous quality improvement efforts should be outlined. The performance of NBS, which needs to be continually monitored, is measured through the following indicators:

True Positives

Newborns identified through screening that are confirmed to be affected with the disease.

False Positives

Newborns identified through screening that are confirmed to not be affected with the disease. This category typically includes unaffected carriers and some completely unaffected individuals who may be flagged on the screening test but prove to be negative upon further diagnostic testing.

False Negatives

Newborns affected with a disease that are not identified through NBS. Most screens are designed to minimize false negatives, maximizing sensitivity.

True Negatives

Newborns with in-range NBS results who are not affected with the disease.

Sensitivity

The test's ability to correctly identify those with the disease (True Positive Rate).

Specificity

The test's ability to correctly identify those without the disease (True Negative Rate).

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

Positive Predictive Value (PPV)

The proportion of true positives among all positive screens.

Negative Predictive Value (NPV)

The proportion of true negatives among all negative screens.

Accuracy

The proportion of patients correctly identified (true positives plus true negatives divided by all screens).

Birth Prevalence/Incidence/Detection Rate

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

Timeliness

Federal recommendations[85] include time from:

- Birth to specimen collection: **< 48 hours**
- Specimen collection to receipt by NBS program: **24 hours**
- Birth to notification and reporting of screen-positive results (time critical conditions): **Five days**
- Birth to notification and reporting of all other results: **Seven days**

Programs should also consider ensuring timely diagnosis and administration of intervention or treatment to ensure the best possible health outcomes for affected newborns. Disease-specific guidelines around time to diagnosis and intervention may be available.

DBS collected as part of routine NBS can be used for the MLD NBS algorithm. To achieve a minimal positive rate, a multi-tier strategy has been recommended. When adopted into pre-existing nationwide NBS programs, MLD NBS requires no additional sampling or consent. When conducted in its entirety, the MLD NBS algorithm enables identification of patients with MLD, timely intervention and improved outcomes. While MLD is not considered a time-critical NBS disease, recent expert consensus guidelines emphasize the importance of early diagnosis and treatment and highlight the critical role of NBS in this paradigm.[86,87]

85 HRSA (2017) NBS Timeliness Goals.

86 Adang, et al. (2024). Consensus guidelines for the monitoring and management of metachromatic leukodystrophy in the United States

87 Laugwitz et al. (2024b). Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy

Figure 4. NBS Test Results [88]

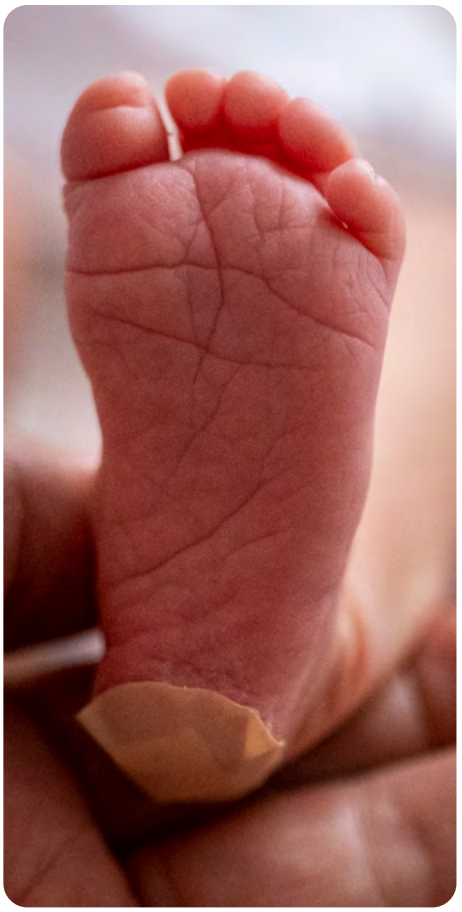
	Disorder	No Disorder
Positive Test Result	**True Positive (TP)**	**False Positive (FP)**
Negative Test Result	**False Negative (FN)**	**True Negative (TN)**

Sensitivity	Specificity	PPV	NPV
$\frac{TP}{(TP+FN)}$	$\frac{TN}{(TN+FP)}$	$\frac{TP}{(TP+FP)}$	$\frac{TN}{(TN+FN)}$

Collaborators

There are many collaborators in the NBS process; they 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 (PCPs)
- Clinical specialists
- Genetic counselors
- NBS laboratory and follow-up
- Policy makers
- Researchers



88 Adapted from: Carvajal & Rowe (2010), Sensitivity, specificity, predictive values, and likelihood ratios.

Fiscal Constraints

The key factors to NBS are readiness to screen and feasibility of adding the screen to the screening program.[89] Almost all state programs charge a fee for the screen, and some states receive additional support for screening through state funding. The addition of a new disease to the NBS panel can be costly; therefore, funding can be a major hurdle in the overall implementation process.

State programs are often asked to demonstrate the cost effectiveness of NBS when implementing screening for a new disease. For MLD, however, several publications have addressed the cost effectiveness of NBS.

A cost-effectiveness study to evaluate adding a three-tier NBS algorithm for MLD to the UK's NBS program calculated the total annual cost of screening 704,328 newborns to be £122,625 (£0.17 per newborn).[90] In this analysis, based on a decision-tree framework for each MLD subtype using long-term outcomes derived from an established survival and Markov economic model, NBS remained cost-effective under a wide range of factors, including fluctuations in MLD incidence, discount rates, screening test costs and response to treatment. Model results showed that without NBS only ~2.6 of the seven expected annual MLD cases would be identified early enough to receive arsa-cel. With NBS all cases would be expected to be identified in time for pre-symptomatic treatment. The study supports MLD NBS as a cost-effective use of National Health Services resources and recommends inclusion in the UK NBS program.[91]

Limited information from two congress abstracts indicated similar results for cost-effectiveness in the US.[92,93] A model based on the 2021 annual birth cohort in California (420,608 newborns) showed that screening for MLD in California would result in a positive net economic benefit of greater than $70 million and the avoidance of 5.09 premature deaths.[94] Similarly, a cost-benefit analysis demonstrated that MLD NBS is a cost-effective use of resources in the US, due to the positive long-term health outcomes associated with pre-symptomatic treatment of MLD patients.[95]

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. Can the new disease be multiplexed with current equipment?**
- **Physical capacity of laboratory. How much additional lab space is required?**
- **Testing materials and reagents needed to screen. FDA Kit versus laboratory-developed test (LDT)?**
- **Start-up 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.**

89 APHL (2023). NewSTEPs 2022 Annual Report.

90 Bean et al. (2024b). Exploring the Cost-Effectiveness of Newborn Screening for Metachromatic Leukodystrophy (MLD) in the UK

91 Bean et al. (2024b). Exploring the Cost-Effectiveness of Newborn Screening for Metachromatic Leukodystrophy (MLD) in the UK

92 Bean et al. (2024a). Cost-effectiveness framework by tandem mass spectrometry (TMS) for newborn screening of metachromatic leukodystrophy (MLD) in the United States (US)

93 Bean et al. (2025). Exploring the net monetary benefit of implementing newborn screening for metachromatic leukodystrophy in California. Molecular Genetics and Metabolism, 144(2), Article 108651

94 Bean et al. (2025). Exploring the net monetary benefit of implementing newborn screening for metachromatic leukodystrophy in California. Molecular Genetics and Metabolism, 144(2), Article 108651

95 Bean et al. (2024a). Cost-effectiveness framework by tandem mass spectrometry (TMS) for newborn screening of metachromatic leukodystrophy (MLD) in the United States (US)

Lastly, many of the treatments for rare diseases, including MLD, are costly, and there also may not be a specialized treatment center close to the family's home or even within the state.

Timeline Hurdles

- Obtaining appropriate approval for the disease's official addition to state panels, including fee increases and revision of rules/regulations as needed.
- Working through all the possible considerations (see **NBS Cost Considerations** box).
- Completing pilot testing (if necessary) and finalizing screening cutoffs and decision algorithms.
- Educating partners regarding MLD, the plan for screening and available treatment options within the state.

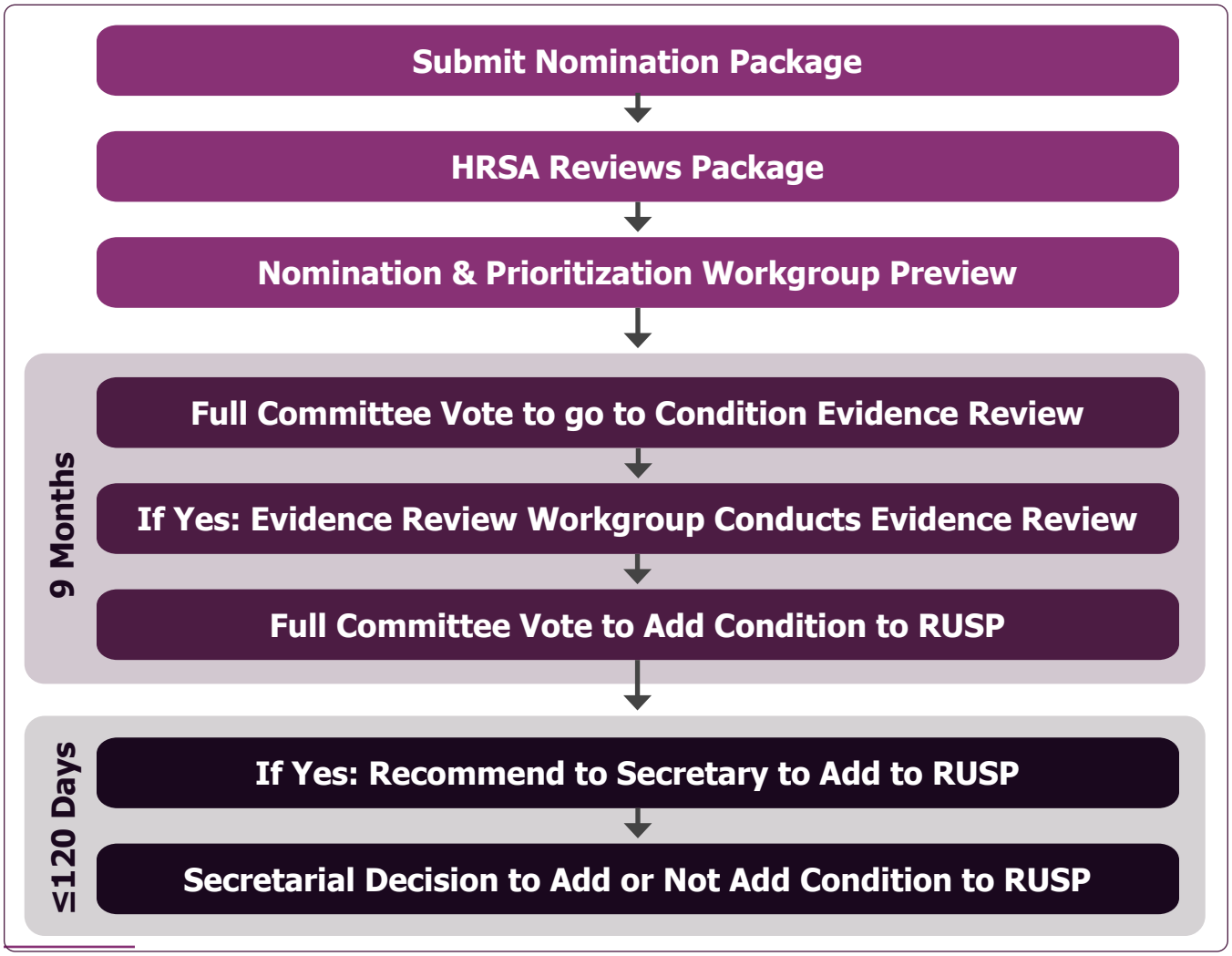
GETTING READY TO SCREEN FOR A NEW DISEASE

Before a program can implement statewide screening for a new disease, many things need to happen. In many states, there is a well-established process to get approval to add a disease to the state NBS panel.

In some states, the addition of new diseases is achieved through legislative action, relying on the efforts of advocates and legislators. In other states, the process includes changes to rules and regulations that govern the NBS program through actions by the state board of health or the NBS advisory committee. Some states relied on national guidance through the former ACHDNC, while still utilizing their own process of adding diseases to their state panels. The RUSP is a list of diseases 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 and Human Services in 2010.[96]

The RUSP was created in response to a recommendation from the American Academy of Pediatrics (AAP) Newborn Screening Task Force to create uniformity in NBS throughout the US as well as a process for government, professionals and consumers to nominate a disease to be considered by all state NBS programs. Although the RUSP provides recommendations and not requirements, many states look to it when determining whether to screen for a disease.

Figure 5. How Diseases are Added to the RUSP[97]



96 Watson M, Lloyd-Puryear M, Mann M et al. (2006). Main Report. Genet Med 8, 12–252. doi:10.1097/01.gim.0000223467.60151.02

97 This was the previous process under the ACHDNC. The process for MLD was stopped at the Full Committee Vote stage and then added directly by the Secretary.

Approval to Screen

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

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

Most state NBS programs conduct implementation pilots to build and/or assess the state capacity to screen for the disease 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.

Support for Disease Implementation

Understanding that successful disease implementation requires numerous resources, states may seek assistance from organizations like the US Centers for Disease Control and Prevention (CDC), HRSA and APHL when working towards implementation of diseases. CDC, HRSA and APHL provide financial resources through grants as well as technical assistance and testing materials that can aid in successful implementation.

In addition to services provided by national organizations, states may also seek guidance and assistance from their peers and subject matter experts. For example, APHL offers subject matter expert support for specific projects related to screening implementation, laboratory and follow-up practices, educational activities, continuity of operations planning (COOP), information technology (IT) systems, workforce development, program administration, policy support and quality improvement activities.

STEPS FOR APPROVAL / AUTHORITY TO SCREEN

- **Obtain approval to screen for the disease from the NBS Advisory Committee.**
- **Obtain approval to screen for the disease from the Board of Health, commissioner or other leaders.**
- **Develop a budget to show costs for developing the NBS program's capacity to screen, and then for costs of statewide screening—including laboratory testing, follow-up, IT, etc.**
- **Obtain approval by NBS Advisory Committee for funding, including funds necessary to build the NBS program's infrastructure and capacity to screen.**
- **Obtain approval by the State Budget Authority for funding, including funds necessary to build the NBS program's infrastructure and capacity to screen.**
- **Approval for fee increase, if required.**

Laboratory Readiness to Screen for MLD

The factors influencing laboratory readiness to screen are broad reaching and can vary from state to state and one disease to another. NewSTEPs offers resources for laboratories as they prepare for new testing, including a Readiness Scale and a Readiness Checklist.

NBS laboratories need to consider the following well in advance of routine screening for MLD:

Readiness Steps for NBS Laboratory Screening

- **Identify which screening method to use**, including necessary higher-tier testing.
- **Have needed equipment for testing.** Contract for purchasing or renting the testing equipment may take up to a year to become available to the laboratory.
- **Have space needed for testing equipment.** Some test equipment requires major retrofitting, ventilation and electrical changes, have a large footprint and/or need 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- or third-tier testing may need to be added as well.
- **Define true and false positives** for measurement of the screen's performance metrics once full population screening begins.
- **Obtain adequate staffing for full population screening.** May require approval for additional staff to be hired and/or require time for some current staff cross-training.
- **Integrate MLD testing workflow** with all other NBS workflows.
- **Establish communication algorithm** with short-term follow-up program (phone, IT, messaging, ACTion (ACT) sheets/algorithm).

Considerations for 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 tiered testing?
- How does the proposed algorithm affect timeliness metrics?

Considerations for Testing Validation

- Prospective (current specimens) versus retrospective (stored specimens)?
- Identified, de-identified or anonymized specimens?
- If identified, how will the results be confirmed? Who will call out out-of-range results?
- What are the availabilities of positive specimens and quality assurance (QA), reference and proficiency testing materials?

Considerations for Program Staff Needs

- Are new hires needed? At what level?
- Is training and education needed for existing and new staff? Including testing and clinical considerations?
- Will additional staff be needed on weekends?
- Will new specialist contracts be needed?

After Screening Starts: Heterogeneity of Disease/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 from what was expected?
- How is the screen performing?

Laboratory Methodology Examples

A multi-tier screening algorithm is available, which is suitable for high-throughput MLD NBS, and is highly sensitive and specific for MLD (**Figure 6**). It has been validated and applied in prospective MLD NBS pilot studies and nationwide MLD screening settings to detect patients with early-onset MLD for timely treatment.[98,99] MLD NBS protocols have been published.[100]

All tiers utilize the initial NBS dried blood spot (DBS). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) is utilized in the first- and second-tier:[101,102] Sulfatides C16:0 and C16:1-OH are quantified in the first-tier, and this analysis can be multiplexed with other LSD analyses, as well as for X-ALD.[103] If sulfatides are elevated, ARSA enzyme activity is measured as a second-tier test. Measurement of sulfatides in the first-tier avoids the detection of ARSA enzyme pseudodeficiency. To expedite diagnosis and phenotypic prediction, the *ARSA* gene may be sequenced as a third-tier test. Because there are two biochemically related diseases to MLD—multiple sulfatase deficiency and prosaposin B—additional genes (*SUMF1* and *PSAP* respectively) may also be sequenced to aid in differentiating a diagnosis.[104]

Internal standards, necessary reagents and quality control materials are available commercially. Laboratory-developed tests (LDTs) are required for MLD NBS because currently no FDA test kits are commercially available as of March 1, 2026.

Samples are screened for MLD using the percentage of the daily median of C16-1 OH Sulfatide (primary analyte marker) and C16:0 Sulfatide (secondary analyte marker) cutoffs.

The biggest advantage to this assay is that it can be multiplexed with other diseases, such as guanidonoacetate methyl-transferase deficiency (GAMT) and X-linked adrenoleukodustrophy (X-ALD).

Note: Multiplexing GAMT with MLD and X-ALD requires an MS/MS instrument capable of polarity switching between positive and negative mode.

98 Laugwitz et al. (2024a). Newborn Screening in Metachromatic Leukodystrophy

99 Laugwitz et al. (2024b). Newborn Screening and Presymptomatic Treatment of Metachromatic Leukodystrophy

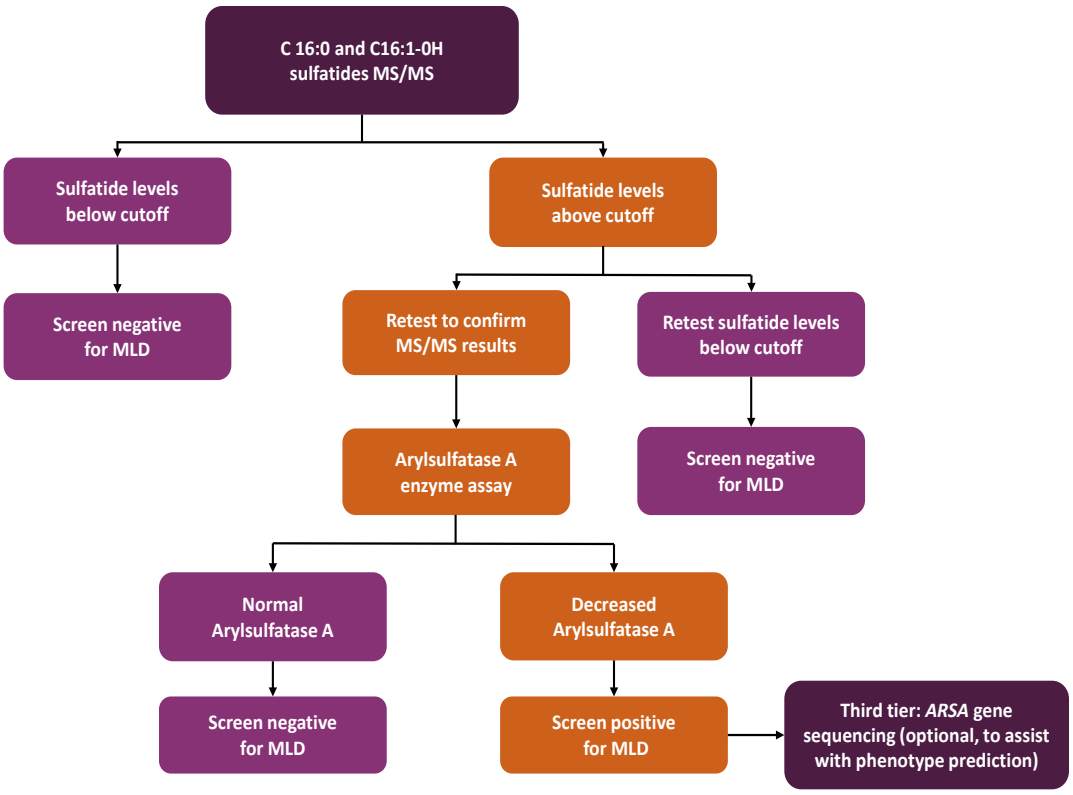
100 Shaff et al. (2025). Newborn screening for metachromatic leukodystrophy: Preparation of reagents and methodology for measurement of sulfatides and arylsulfatase A enzymatic activity in dried blood spots

101 Hong et al. (2020a). Leukocyte and Dried Blood Spot Arylsulfatase A Assay by Tandem Mass Spectrometry

102 Hong et al 2021. Toward newborn screening of metachromatic leukodystrophy: results from analysis of over 27,000 newborn dried blood spots

103 Hong et al. (2020b). A highly multiplexed biochemical assay for analytes in dried blood spots: application to newborn screening and diagnosis of lysosomal storage disorders and other inborn errors of metabolism

104 Gomez-Ospina (2006). Arylsulfatase A Deficiency



Prepare the Extraction Working Solution (EWS) as described.

1. Punch 3.2 mm samples from the controls and patient samples into a 96-well U-bottom microplate.
2. Add 100 µL of EWS into each well that contains a sample, including the blank control wells.
3. Cover the microplate(s) with an adhesive plate cover. Place the microplate(s) on the shaking incubator to shake at room temperature at 400 RPM for one hour.
4. Remove the microplate(s) from the incubator and centrifuge the plate at 3000 RPM for five minutes.
5. Transfer 70 µL* of each well into the corresponding wells of a new U-bottom microplate.
6. Cover the microplate with a microplate seal and run the MS/MS method.

** Volume of final extract may vary from laboratory to laboratory depending on instrument sensitivity and other factors.*

Follow-Up Readiness

Follow-up is essential to the NBS process and is therefore vital for successful implementation of a new disease. NBS follow-up can include communication of screen-positive results to PCPs and families, coordination of confirmatory testing, and connecting identified newborns to appropriate specialists and/or treatment centers. For MLD, follow-up staff will need to work closely with local genetics/metabolic specialists and qualified treatment centers (QTCs), which may be in a different state, to determine a plan of communication and logistics, including information and resources to be shared with PCPs and families.

Table 5. Qualified Treatment Centers in the US (as of May 2026)

Name	Address	Referral Contact Information for Leukodystrophy/Rare Disease Inquiries	URL
M Health Fairview Masonic Children's Hospital (UMN)	2450 Riverside Ave, Minneapolis, MN 55454	Emerging Therapy Solutions (ETS) Email: medicalservices@emergingtherapies.com Telephone: 877-445-4822; 612-672-4009	https://www.mhealthfairview.org/department/Rare-Diseases
Children's Hospital of Philadelphia (CHOP)	3401 Civic Center Blvd., Philadelphia, PA 19104	Leukodystrophy Center Email: LCE@chop.edu Telephone: 215-590-1719; 215-590-3025	https://www.chop.edu/centers-programs/leukodystrophy-center/your-childs-appointment#:~:text=To%20schedule%20an%20appointment%20with,child%20may%20need%20to%20see.
Texas Children's Hospital (TCH)	6621 Fannin Street, Houston, TX 77030	Online referral form via the "Refer a Patient – Cell Therapy and Bone Marrow Transplant" portal Email: providerconnect@texaschildrens.org Telephone: 1-800-226-2379	https://www.texaschildrens.org/departments/cell-therapy-and-bone-marrow-transplant/conditions-treatments-and-related-information
Children's Healthcare of Atlanta (CHOA)	1405 Clifton Road NE, Atlanta, GA 30322	Email: scdcurativetherapies@choa.org (request referral to Curative Therapies program) Telephone: 404-785-1358	https://www.choa.org/medical-services/cancer-and-blood-disorders/curative-therapies
UCSF Medical Center (Benioff Children's Hospital SF)	1855 Folsom Street, San Francisco, CA 94103	Telephone: 877-822-4453	https://www.ucsfbenioffchildrens.org/clinics/blood-and-marrow-transplant-bmt-clinic

Name	Address	Referral Contact Information for Leukodystrophy/Rare Disease Inquiries	URL
Primary Children's Hospital (PCH), Salt Lake City, UT	100 Mario Capecci Dr Salt Lake City, UT 84113	Telephone: 801-213-3599	https://intermountainhealthcare.org/childrens-health/brain-and-spine/leukodystrophy-program
Ann and robert H Lurie Children's Hospital (LCH), Chicago, IL	225 E Chicago Ave Chicago, IL 60611	Email: genetherapy@luriechildrens.org Telephone: 1-800-543-7362	https://www.luriechildrens.org/en/specialties-conditions/gene-and-cellular-medicine-program/

ACT sheets and follow-up algorithms are available to assist all NBS programs in the provision of actionable screening results and follow-up action recommendations.

Follow-up staff should understand potential geographical, financial or cultural barriers that may arise and hamper timely follow-up, diagnosis and treatment. Additionally, it is important to recognize that families receiving news of a positive NBS result may need added support in accepting the potential of a very serious disease in their seemingly healthy newborn.

Some NBS programs might consider a script or outline for initial notifications when implementing a new disease. Follow-up staff can also work with specialists to identify timeliness metrics for initial results, confirmatory testing and referral to specialists for initial evaluation. Follow-up can often identify delays in the process, barriers to confirmatory testing, and access to care issues including gaps in management and treatment.

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

KEY COMPONENTS OF READINESS

Key components of follow-up readiness for MLD include:

- **Integration of MLD follow-up workflow with other follow-up workflows.**
- **Identification and communication with medical specialists and/or treatment centers for newborns with actionable MLD NBS results.**
- **Development of action plan templates and fact sheets for PCPs and families, including any confirmatory testing needed.**
- **Development of a communication plan for follow-up coordinator and family/PCP.**
- **Development of a procedure for referral from NBS program to genetics or metabolic specialist.**
- **Communication to third-party payers of MLD screening and understanding of the need for coverage for treatments/therapies.**
- **Development of clinical data elements to be collected to determine diagnostic outcome (true positive vs. false positive) and severity of disease.**

Information Technology Readiness

NBS programs process tens of thousands of specimens a year and require robust information management systems, inclusive of laboratory information management systems (LIMS) and case management systems (CMS) used for follow-up. These systems may be developed by the state program or purchased from a vendor. Each time a disease is added or changes are made to the NBS program, these systems must be modified for the analyte cutoffs, 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 able to query for continued evaluation of implementation and quality improvement efforts. NBS reports must be 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 partner 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 a need for a repeat specimen.

Any changes to a NBS program's systems takes time (i.e., specification gathering, extensive testing, user acceptance), expertise, NBS partner involvement and funding.

Key components of IT readiness include:

- **Integration of disease into LIMS Testing & Reporting** (i.e., web portals, state health information exchange (HIE) and other reporting entities).
- **Integration of disease into CMS Reporting System** (i.e., web portals, state HIE and other reporting entities).
- **Integration of disease 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 the consideration and implementation of a new disease. 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.

IDENTIFYING & MEETING WITH SPECIALISTS

- **Are "new to NBS" 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 MLD

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 materials. It is important to review existing educational materials for the specific disease, 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, though organizations such as Expecting Health and others develop materials for national use.

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

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

Updated educational resources for MLD can be found here:

- HRSA NBS Clearinghouse
- ACMG ACT Sheets
- MLDVoices
- MLD Foundation
- MLD IMPACT
- United Leukodystrophy Foundation
- NewSTEPs

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.**

PILOT STUDIES vs. FULL IMPLEMENTATION

Most state NBS programs conduct implementation pilots to build the state's capacity to screen for the disease, validate testing methodology, evaluate follow-up processes and ensure all NBS 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 disease is very new to NBS nationally.

Some states use a consented pilot, meaning that consent will be obtained from the parents of those newborns participating in the pilot screening process. A consented pilot may be conducted on a subset of newborns in the state or on all newborns born in the state. This is most common when NBS programs want to use DBS specimens from newborns known to have MLD so they may validate their testing methodology to obtain a certain result.

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

Some states will use an "opt-in" process—parents have to agree to the screening—until the disease is added to the state NBS panel and MLD 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) NBS results are not usually reported on the laboratory report. If the NBS for MLD should return a positive result, the laboratory will notify the follow-up program staff, who will notify the newborn's PCP after consultation with the NBS program's clinical specialist so that affected newborns can benefit from the pilot.

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

CONCLUSION

This resource provides an overview of the many aspects involved in the addition of a new disease to a state NBS panel, with specific focus on screening for MLD. Please direct any questions regarding implementation or technical assistance needs to NewSTEPs at newsteps@aphl.org.

Learn more about MLD on HRSA's website: Newborn Screening Programs | MCHB

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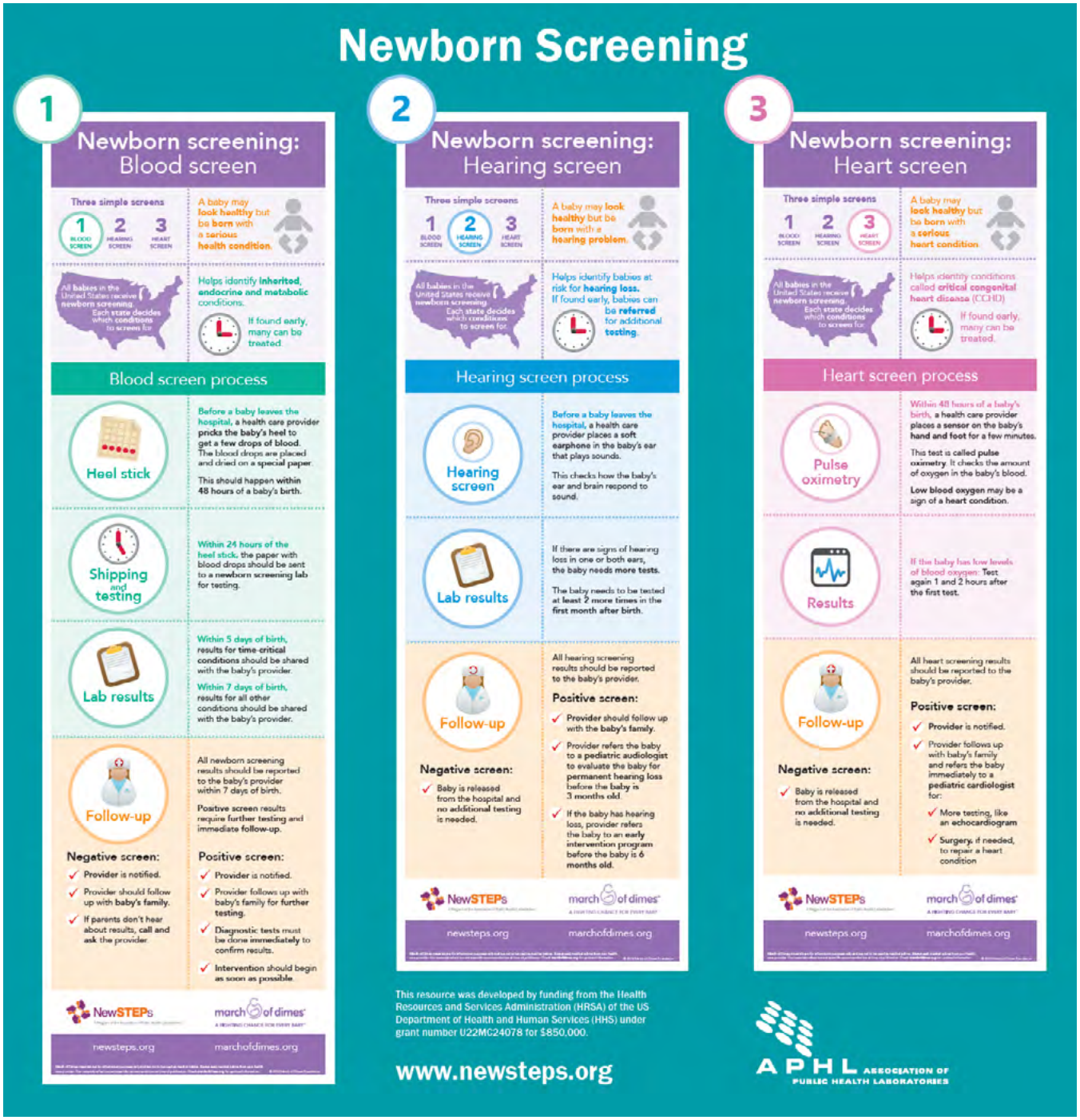
APPENDIX: THREE PARTS OF NBS

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



NewSTEPs Newborn Screening Educational Reference

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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