Newborn Screening Pilot Study Overview

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Background

Prior to 2006, newborn screening (NBS) programs across the country varied a great deal in terms of which conditions were screened for and the methods that laboratories used for testing. To address the variability and concerns about a lack of adequate evidence to support screening tests, the federal **Advisory Committee on Heritable Disorders in Newborns and Children** (ACHDNC) emphasized an evidence-based approach to support the **Recommended Uniform Screening Panel** (RUSP). The emphasis on evidence-based decision-making has helped reduce state-to-state variability in the conditions targeted and testing approaches used.[1]

Gathering evidence that supports adding a new condition to NBS programs usually requires conducting one or more "pilot studies." Pilot studies are defined as "systematic investigations or public health activities designed to evaluate the efficacy and safety of incorporating a new test or condition into state NBS programs on a population-based level." Pilot studies are designed to test the sensitivity and specificity of the assay developed to screen for a particular condition. **Their goal is to prospectively identify one or more babies born with the condition from the time the pilot starts, with minimal (or no) false-positive screens or missed cases.**

Conducting pilot studies is a significant challenge for the field, due to the significant investment of effort, time, and financial resources required. Pilot studies for individual conditions can range from 3 to 10 years, depending on the study design, the overall size of the screened population, the frequency of the condition of interest in the subject population, and the validity of the test being piloted.

Despite these challenges, these studies are important to demonstrate the feasibility and positive public health impact of adding a new condition to one or more NBS programs. "For pilot studies, public health programs may be responsible for scaling a validated screening method and coordinating follow-up for any identified infants; these tasks may raise both foreseeable and unanticipated issues, but generally fall within the scope of work performed by programs. However, pilot studies also require educating and recruiting participants, which is not typical for public health personnel. External collaborators are vital to conduct these activities."[2]

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[1] Report and Recommendations of the Pilot Studies Workgroup to the ACHDNC, May 2016.
[2] Lessons learned from coordination between research, public health and newborn screening programs. Presented at Newborn Screening: Current Landscape and Future Directions: Meeting hosted by the National Academies of Sciences, Engineering, and Medicine, 2024. See meeting report, below.

Traditionally, the U.S. Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), the Health Resources and Services Administration (HRSA), and the Agency for Healthcare Research and Quality (AHRQ) have supported research efforts related to newborn screening, including various forms of support for and population-wide pilot studies (Brosco, 2024).[3] The current administration's priorities for supporting NBS-related research are unclear, especially following the sudden dissolution of the ACHDNC in April 2025.

State-Based Pilot Programs

Several state NBS programs conduct research to develop screening tests for conditions on or under consideration for their state screening panel. These special programs implement assays as part of population-based pilot studies. In some other states, newborn screening laws do not permit the state laboratory to conduct pilot screening studies (e.g., Pennsylvania). Three state-based pilot testing programs are:

- **New England Newborn Screening Program:** The Massachusetts Department of Public Health may authorize and direct research studies of new tests or pilot studies in the newborn screening program. Research studies on new tests are conducted when the Department of Public Health expects they could benefit both the individual and public health. Tests screen for a number of disorders in addition to routine testing. The newborn's parent(s) must consent to be screened for the additional conditions included in the pilot. Results of tests being piloted are reported with routine screening results.

  The pilot studies attempt to address the following questions for each test being piloted:
  - What is the extent of benefit from newborn screening for these disorders?
    - Does it save lives?
    - Does it prevent serious life-compromising outcomes?
    - Do the treatments work as expected?)
  - How often do these disorders occur in Massachusetts?
  - How good are the laboratory tests used to screen for these disorders?

- **ScreenPlus** (New York): ScreenPlus is the largest pilot screening study of its kind in the U.S., conducted at eight participating hospitals in New York City. Parents may consent to have their child's blood tested for additional disorders being studied under this program. In 2025, tests for 12 disorders are part of the ScreenPlus pilot program. A grant from the National Institute of Child Health and Human Development (NICHHD) of the National Institutes of Health (NIH) has supported some of the costs related to the ScreenPlus program.

- **Early Check** (North Carolina): A research study that offers additional free screening for serious conditions in newborn babies, using the same blood sample collected for routine screening. Early Check began in 2018 by screening for a panel of rare genetic

[3] National Academies of Sciences, Engineering and Medicine. 2025. Newborn Screening in the United States: A Vision for Sustaining and Advancing Excellence. Washington, DC: The National Academies Press. https://doi.org/10.17226/29102.

conditions. In 2023, the study was expanded to offer genomic screening for over 200 conditions. Initially, Early Check was supported by the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH). Now it is supported through a public-private partnership.

Conditions screened for as part of the Early Check program are split into three groups. All babies enrolled in Early Check are screened for Group 1 conditions. Parents can choose to have their babies screened for Groups 2 and 3.

- Group 1: Rare conditions that are treatable, meaning that early treatment can prevent the most serious symptoms.
- Group 2: Rare conditions that have potential treatments, meaning treatments may not be able to prevent the most serious symptoms, or treatments are still being studied.
- Group 3: Risk for Type 1 diabetes, a common, treatable childhood disease.

Single-Disease Pilot Studies

The 2016 ACHDNC Pilot Studies Workgroup report includes case studies of the role of pilot studies in three conditions reviewed by the ACHDNC: **Mucopolysaccaridosis Type I (MPS I)** (page 22), **Severe Combined Immunodeficiency (SCID)** (page 23), and **Krabbe disease** (page 24). These case studies underscore the role of population-based pilot studies in generating evidence to support nominations for newborn screening tests.

Spinal Muscular Atrophy (SMA): In 2008, the ACHDNC concluded that the nomination of SMA was premature, and recommended implementation of prospective pilot studies. Data from two prospective population-based pilot studies conducted in New York and Taiwan provided important evidence supporting a second nomination in 2017, and the addition of SMA to the RUSP in 2018. The National Taiwan University Hospital began screening for SMA in November 2014. Of the 120,627 babies screened by September 2016, 15 had a positive first-tier screen, with second-tier screening tests leading to the detection of 7 newborns with confirmed SMA diagnoses within 4-11 days of age. Six of the 7 babies were asymptomatic at the time of diagnosis. A second pilot study in New York state was conducted in partnership with Columbia University with funding from Biogen. The study began in January 2016, prior to the approval of nusinersen in December 2016. In the first year of the pilot study, screening results detected 59 carriers and 1 confirmed presymptomatic case of SMA Type I at 7 days of age. The infant was enrolled in an open-label trial of nusinersen for presymptomatic infants at 15 days of age. As of the 12-month clinical assessment (the last reported in the NBS evidence report), the baby appeared normal and had achieved all development milestones.

Guanidinoacetate Methyltransferase (GAMT) Deficiency: Another example is the set of pilot screening studies conducted for GAMT deficiency, as described in the final evidence review report issued as a basis for GAMT deficiency being added to the RUSP in 2023. Individual population-based screening studies were conducted in two states, one Canadian province, and in Victoria, Australia, each using slightly different laboratory assays or cutoffs, as described in

the final report issued by the Evidence-Based Review Group for the ACHDNC. In Utah, 321,305 newborns were screened between 2015-2021, with three babies referred for diagnostic testing and one case of GAMT deficiency identified. This case, detected in 2020, was pivotal. GAMT was first nominated for inclusion on the RUSP in 2016, and again in 2017, but no cases had yet been identified by any of the pilot studies under way, and neither nomination advanced to the next step. The Utah case enabled a follow-up nomination in 2021, leading to the approval in 2023.[4] Before that approval was achieved, another pilot study in New York began screening in 2018, with 759,246 infants screened from 2018 to 2022. Twenty-four infants were referred for diagnostic evaluation, resulting in the identification of one new case. Screening in British Columbia (B.C.) began on a pilot basis in 2012 and expanded to routine screening in 2015. Between 2012 and 2022, 428,140 newborns were screened, among whom 1,228 had a positive first-tier screen and 28 had a positive second-tier screen. Three infants were referred for follow-up genetic testing, all of whom were carriers. No new cases of GAMT deficiency were identified in B.C. during this 10-year period. Screening for GAMT deficiency began in Victoria, Australia, in 2002. Approximately 1.4 million newborns were screened between 2002-2022, with one "likely" case of GAMT deficiency identified.

Sequencing-Based Pilot Studies

Innovative technologies are increasingly being developed and used to detect diseases and spot disease risk factors, some of which could potentially be applied to newborn screening. Genomic sequencing has garnered attention from researchers, ethicists, and economists as a future alternative or adjunct to traditional newborn screening methods. In 2025, a consensus study report issued by the National Academies of Sciences concluded, "At this stage, genomic sequencing is not yet ready for implementation at scale in public health programs outside of a consented research study context. More research is needed to address the scientific, technical, ethical, and practical challenges before genomic sequencing could be considered for implementation in the United States."[5]

While not a near-term replacement for current public-health-based screening newborns, pilot studies of next-generation sequencing (NGS) and rapid whole genome sequencing (rWGS) in newborn screening are underway in the U.S. and other countries. These studies may be conducted within a specific healthcare system, by a network of research hospitals, or at a state or country level. Examples of sequencing-based pilot studies include:

- **BabySeq Study:** This study began with researchers at Brigham and Women's Hospital and Boston Children's Hospital, and has expanded to sites in New York City and Birmingham, Ala. Enrolled families' newborns are randomized to receive genomic sequencing or be in a control group with routine screening and care. Infants who receive

[4] "US Secretary of Health Recommends Universal Newborn Screening for GAMT Deficiency," January 16, 2023, Association for Creatine Deficiencies,
[5] National Academies of Sciences, Engineering, and Medicine. 2025. Newborn Screening in the United States: A Vision for Sustaining and Advancing Excellence. Washington, DC: The National Academies Press, page 172.. https://doi.org/10.17226/29102.

genome sequencing will have their DNA analyzed for thousands of health risks that could affect their medical care in childhood.

- **beginNGS study:** Rady Children's Institute for Genomic Medicine leads this pilot study across a network of birthing hospitals across the U.S. and abroad. Parents of babies born in partner hospitals can elect to have blood-spot tests screened for approximately 400 genetic diseases with known intervention options.
- **GUARDIAN study:** Conducted at NewYork-Presbyterian Hospitals, this is a free, optional study parents can opt into for screening of 450 additional genetic conditions using the same bloodspot test collected for routine newborn screening.
- **BEACONS (Building Evidence and Collaboration for GenOmics in Nationwide Newborn Screening):** Announced in October 2025, "BEACONS is the first NIH-funded national research partnership with state newborn screening programs, offering families the option of genomic screening for childhood conditions where early detection can lead to treatment, proactive management, or closer monitoring." Study leaders aim to enroll up to 30,000 newborns across up to 10 states over three years.
- **The Sunshine Genetics Act:** Effective July 1, 2025, this five-year genetic sequencing pilot program will enable families of babies born in Florida to opt in to have the newborn's full genetic code sequenced at no cost. The study will be conducted by the Sunshine Genetics Consortium, linking researchers, clinicians, and biotech innovators across Florida. It is the first statewide genomic screening pilot in the U.S.
- **Generation Study (United Kingdom):** A publicly funded study conducted in partnership with the National Health Service (NHS) with a goal to sequence the genomes of 100,000 newborn babies for changes in genes linked to more than 200 rare conditions that appear within the first few years of life, can be improved if caught early, and can be treated through the NHS. This study aims to understand how genomic and health data can be used to help clinicians diagnose, treat, and prevent illnesses in the future.