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REVIEW

# Newborn screening: past, present, and future

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ABSTRACT

Newborn screening (NBS) is one of the most successful public health programs in the United States, with thousands of lives saved or improved each year through the early identification and treatment of conditions. The mandatory nature of state NBS programs demands a high standard and rigorous scientific evidence for selecting conditions that should be included. Despite the development of new treatments for rare disorders and numerous pilot studies using genomic NBS, recent changes at the federal level have made the addition of new conditions recommended for NBS challenging.



## Introduction

Newborn screening (NBS) is a screening system based in the public health system that is used to identify infants with treatable conditions before symptom onset. In the United States, NBS measures analytes from infants' dried blood spot cards obtained within the first 24 to 48 hours of life. To detect infants at risk for hearing loss and critical congenital heart disease, point-of-care testing is done in hospitals. With few exceptions, the conditions screened for have an onset of symptoms in infancy or early childhood. Early detection and treatment have been shown to prevent disability and death. It is estimated that 3.6 million newborns are screened[1] and at least 12,000 infant lives are saved or improved annually in the United States.[2]

New advances in technology have often been the driving force behind the expansion of NBS. In the early 1990s, tandem mass spectrometry expanded the ability to screen for more inborn errors of metabolism.[3] This new technology was adopted in some states but not others to increase the number of conditions screened. This further led to large interstate discrepancies.[1,4] In 2002, a federal expert task force, funded by the Health Resources and Services Administration contracting with the American College of Medical Genetics and Genomics (ACMG), was formed to rectify these discrepancies. The task force recommended a core panel of 29 conditions that should be screened for in all states and a secondary panel of 29 conditions detected in screening for the core conditions.[5] In 2003, the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) was established by the Maternal and Child Health Bureau of the Health Resources and Services Administration to give recommendations to the US Secretary of the Department of Health and Human Services (DHHS) regarding adding new conditions to a Recommended Uniform Screening Panel (RUSP). At their first meeting, the ACHDNC approved the conditions from the ACMG report, becoming the original RUSP.[5] To add new

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conditions, 9-month evidence-based reviews were conducted and presented to the ACHDNC, with members voting on whether there was sufficient net benefit to children of early detection and treatment and preparedness of the public health system to screen for the condition.[6] There are currently 40 core conditions on the RUSP and 26 secondary conditions. The ACHDNC was abolished by the Secretary of DHHS in 2025.[7] Since its dissolution, the Secretary approved adding metachromatic leukodystrophy and Duchenne muscular dystrophy to the panel in 2025 based on completed scientific evidence reviews and support by advocacy groups.[8] At the time of this writing, there was neither a federal system in place to fund evidence-based reviews for new conditions nor an advisory committee to review this evidence. To bridge this gap, the ACMG has organized an independent group of clinical and laboratory NBS experts, bioethicists, and patient advocates—the Newborn Screening Collaborative—to review collected data regarding new conditions and assess the benefits vs harms of inclusion in NBS. Although not replacing the RUSP, it is hoped that this information will be helpful to states and other NBS stakeholders and narrow the ever-widening gap between states and conditions screened.[1,9] However, this is not a permanent solution. A federal system is needed to ensure that all infants in the country are screened for all conditions meeting the criteria, avoiding what has been termed death by ZIP code because of the patchwork system currently in place.

## State Panels

The DHHS recommends that conditions on the RUSP be adopted by state NBS programs, but this is not mandatory.[1,10] Conditions that are not on the RUSP may be added by states to their NBS panels. At the time of this writing, 15 states have passed RUSP alignment legislation that requires state NBS programs to begin screening for conditions on the RUSP within a specified period and provide resources to implement screening.[11] Cuts in public health funding over the past several years have challenged states to keep up with the addition of new conditions to their state NBS panels. It is estimated that it takes up to 10 years for all US states to begin screening for a new condition after it is added to the RUSP.[1,4] This would translate to delays in the diagnosis of these conditions by several years in the states with slow screening uptake.

## Mandated NBS

Most states mandate NBS because of the potential for death or disability if conditions are undetected.[12,13] Some states allow refusal because of philosophical or religious reasons.[13] Mandated screening has been justified because state programs have the responsibility to protect citizens, such as newborns who are unable to protect themselves. This is the concept of "parens patriae," a legal doctrine that gives states the right to assume responsibility of the parents if it benefits the child and society.[14] Risks associated with collecting a few drops of blood from an infant and the potential of false positive results have been deemed minimal compared with the benefits of detecting the condition early, saving lives, or preventing disability.[15] If parents refuse to have their infant undergo NBS, the possibility of not detecting a child with one or more of the screened conditions is estimated to be approximately 1 in 600.[16] To continue this mandate, rigorous scientific evidence demonstrating the benefit of early identification and treatment, the accuracy of testing, and that the benefits of screening outweigh the risks is required.

## Genomic NBS

It is estimated that there are 10,000 rare diseases[17]; approximately 80% are genetic,[18] and many of them affect children.[19] Approximately 1 in 10 individuals has a rare disease.[20] Developing treatments for rare disorders is an area of active research with many clinical trials and new Food and Drug Administration–approved therapies. Presymptomatic therapy often results in the best outcome for the individual. Although some conditions can be added to NBS using existing screening technologies, such as tandem mass spectrometry, many other conditions cannot be added. For example, monogenic cancer predisposition disorders with childhood onset, for which surveillance to detect early signs of cancer can be lifesaving, cannot be screened for with current NBS methods. If the underlying genetic cause of a condition is known, screening may be possible through molecular genetic methods.[21]

Although the cost (up to a thousand dollars per sample)[22] currently prohibits the use of genome sequencing in public health NBS, costs are decreasing. There are more than 35 genomic NBS (gNBS) projects completed, active, or planned around the world.[23] The International Consortium on Newborn Sequencing organizes leaders of these projects for monthly virtual meetings and annual in-person meetings.[24] The gene-disease pairs analyzed in the subjects participating in these projects vary greatly, ranging from roughly 100 to more than 4000.[23] A study that compared conditions on panels between several early studies found that there were only 55 genes that were the same in 6 gNBS research projects and that 14 of 27 projects had unique gene-disorder pairs not shared by any of the other studies.[25]

The recently initiated US multistate Building Evidence and Collaboration for GenOmics in Nationwide Newborn Screening project, now named BRIDGES-NBS, is investigating the feasibility of offering gNBS as part of the already existing state NBS programs. States participating in the study will return results for 777 conditions.[26]

## Challenges of gNBS

Adding hundreds of new conditions by using gNBS to a RUSP while adhering to stringent evidence-based reviews one condition at a time will be logistically impossible. Evidence-based guidelines for the management and care of patients with rare diseases are not available for many conditions included in gNBS. Without orthogonal confirmatory testing or a family history of the condition, confirmation will not be possible. The penetrance of many conditions in gNBS projects is unknown. It will be difficult to provide families with information regarding the likelihood that their presymptomatic infant will develop a condition. Identifying infants with pathogenic variants in genes who will never manifest symptoms and could be harmed by unnecessary treatments must be weighed against early identification and appropriate treatment that may save lives. The readiness of NBS systems, which are underfunded in many states, for incorporating genomics into screening with a large expansion of disorders screened must be considered before implementing gNBS in public health. Issues of workforce, access to (often expensive) treatments, public distrust in the public health system, and a lack of evidence of clinical utility will be challenging to overcome.

Providing access to follow-up care will be challenging in gNBS. Primary care providers will need to have accurate information about the disorder detected through screening, possible symptoms to look for in their patients, confirmatory testing, appropriate specialist referrals, and explaining results to parents. A postdiagnostic odyssey may result if there is no centralized access to appropriate experts.[15]

There is a lack of data in the United States on long-term outcomes of patients with RUSP conditions detected through NBS because of the lack of funding for data collection, a transient population, the number of patients with rare conditions, multiple NBS systems, problems with system interoperability (public health records, multiple care providers, health care systems and electronic health records), privacy concerns, and a lack of unique identifiers for infants.[15] Adding hundreds of new conditions to NBS will require long-term outcome data to determine the benefits and harms of early identification of these conditions. Data sharing between research and pilot projects will be critical to reach the goals of gNBS.

## Future Scenarios

In the opinion of this author, gNBS will not replace standard analyte NBS in the near future until more information is available about variant interpretation, but it may expand NBS to detect more conditions. The cost of genome sequencing is currently prohibitive but, as noted above, is decreasing. Public health gNBS may initially be limited to a small number of gene-disorder pairs with evidence of clinical utility from early detection. With improvements in our ability to interpret genetic variants in a population with multiple ethnicities, the development of new treatments for monogenic disorders, and evidence gathered about the net benefit to children of early detection and treatment, more gene-disorder pairs will be added.

A return to greater inequality between states, if some offer gNBS and others do not, and the potential for widening social disparities, if gNBS is offered in the private sector with access only to those who can afford it, are additional factors that must be considered as gNBS moves forward.[15]

Some genetic disorders do not require surveillance or treatment until a child is older. An example of this is familial adenomatous polyposis. Given this concept, the use of genomic screening of children at different ages outside of the newborn period is being studied.[27] This would be done as part of preventive pediatric health care and not in public health NBS.

Pilot studies and data sharing will be critical to achieving the goals of gNBS and ultimately saving or improving more lives through the use of genomics. To justify the mandate of NBS and not jeopardize this successful public health program, we must proceed with caution.

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## Conflict of Interest

The author declares no conflicts of interest.

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