Genetics in Medicine (2025) ■, 101433

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Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

ACMG STATEMENT

The importance of residual newborn screening dried blood spots, 2025 revision: A position statement of the American College of Medical Genetics and Genomics (ACMG)

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ARTICLE INFO

Article history:
Received 1 April 2025
Accepted 4 April 2025
Available online xxxx

Keywords:
Newborn screening
Public health
Residual dried blood spots

Introduction

Newborn screening (NBS) is a population-based screening program designed to identify congenital conditions in newborns before the onset of symptoms, preventing complications that can lead to permanent disability or death. All 50 US states, the District of Columbia, and most US territories have statutory requirements for NBS. Given its comprehensive application, NBS results in the early detection of these disorders, allowing for prompt intervention for infants regardless of geographic, ethnic, or socioeconomic differences.[1,2] About 3.6 million newborns are screened in the United States annually,[3] and more than 12,000 lives are saved or improved each year through NBS in the United

The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on 18 March 2025.
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doi: https://doi.org/10.1016/j.gim.2025.101433
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States.[4] NBS is widely considered to be one of the great successes of public health in the last 50 years.

Currently, NBS includes 3 different screening methods: a hearing test to screen for congenital hearing loss, pulse oximetry to identify some forms of critical congenital heart disease, and a blood sample, which is obtained via a heel prick and placed on filter paper between 24 and 48 hours of age. This filter paper containing the blood spot specimen is dried and a portion is used to screen for conditions specified by states and in most states those conditions closely match the Recommended Uniform Screening Panel.[5] The remaining dried blood spot (DBS) material, referred to as residual DBS (RDBS), may be stored and used for purposes beyond the initial screening.

This statement focuses on the use, storage, and value of RDBS.

Uses of RDBS

Although the direct application of NBS benefits the individual, RDBS are used in addition to screening, for test development and improvement, laboratory quality control (which benefits individual patients and their families), research, and public health. Repositories of RDBS established by states are unique in that they represent a population not subject to selection bias.

Test development

As new conditions are added to NBS panels, laboratory screening tests must be developed to screen for these disorders. Before implementation, NBS programs must validate the accuracy, sensitivity, and specificity of a new screening assay typically using archived DBS samples. RDBS samples are often the only source available for these preliminary efforts, serving a critical role in quality control and improvement.[6] Without access to RDBS, it would be difficult or even impossible to ensure that new screening tests are appropriately validated, which often occurs through pilot programs before use.

Test improvement and quality assurance

Similar to development of a new test, modifications and improvements to existing tests must also be validated. Existing tests must be evaluated on a regular basis to ensure that they are continuing to perform as intended and test quality is maintained over time. RDBS are the primary source of specimens used for such testing.

In addition, if an individual is later diagnosed with a panel condition that was not originally detected by NBS, the RDBS from the affected individual can be reanalyzed. This information can then be utilized to adjust cutoff values to improve test accuracy and validation.[7]

Benefits of follow-up testing to individuals and families

In addition to research and public health implementation, RDBS samples can benefit individuals. For example, cytomegalovirus is a common congenital infection that can cause significant complications to newborns; however, the presence of infection is often not detected at birth. When a case is identified beyond the newborn period, the individual's RDBS can be tested to determine if the infection was present at birth. Because identification requires analyzing samples obtained during the first weeks of life, RDBS is often the only specimen available to confirm the diagnosis.[8]

RDBS samples have also been used in the diagnosis of older siblings when new conditions are added to panels to elucidate the genetic cause of death for children that become unexpectedly ill or for preconception management. For example, when a newborn is diagnosed with a genetic condition after NBS, this information can lead to identification of a previously undiagnosed condition in an older sibling born before that condition was added to the screening panel.[9] RDBS have proven valuable in postmortem diagnosis of children who have died suddenly and unexpectedly with no relevant family history.[10] In cases in which the older sibling is deceased, testing of the RDBS can provide information to the family, as well as enable them to better understand the risks to potential future pregnancies.

Disease incidence and prevalence

RDBS also can be used as a source of DNA for genetic testing to determine the incidence or prevalence of specific disorders in the population.[11,12] Because of the unbiased, population-wide nature of NBS in the United States, RDBS repositories are often the only source of specimens that can be used to accurately assess disease incidence and prevalence.

In addition to genetic conditions, RDBS are used to test for exposure to infectious agents[13] or environmental exposures. This helps determine a more accurate prevalence of these conditions and identify potential needs for improved public health screening and monitoring. These processes, most often performed on deidentified RDBS, are critical for improving public health. In some cases, targeted studies using identified RDBS may also be informative.

Storage and retention policies for RDBS

Although there are similarities among the screening programs operated in the United States, state and territory statutes, rules, regulations, protocols, and financing strategies vary significantly. Consequently, there is a lack of uniformity in NBS practices across the country, including storage and retention practices. However, in response to increased scrutiny regarding storage and use of RDBS for any purpose, state programs and the Association of Public Health Laboratories have worked to strengthen their policies.[14] NBS programs securely retain the unused portions of RDBS specimens for periods ranging from one month to indefinitely at temperatures ranging from room temperature to −80 °C.[15] In addition, NBS programs use a variety of

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methods to ensure specimens are handled properly to protect personal information. Although RDBS samples are generally stored without consent, long-term storage is typically done in a deidentified manner. In those cases, programs maintain a link to be able to retrieve a specific specimen when necessary. Reasons to retrieve a specific sample include the need to honor a request to destroy the sample for additional testing or for a parental request via established consent processes. Parents may wish to enroll their child in research studies. Programs can release specimens to parents for future clinical testing, diagnosis of an older sibling, or for their current child who becomes ill or dies. Storage of specimens may allow state NBS programs to recreate the test process, if necessary.

Because most NBS is conducted under a public health mandate that does not require explicit parental consent for screening, NBS programs must be responsible stewards of these specimens, and a variety of state statutes and policies affect retention and/or use of RDBS.[16] Protecting RDBS as a public health resource requires assuring the public that the samples will be managed safely and ethically, while acknowledging privacy concerns. In response, some states have enacted statutes, some have acted subject to court orders, some continue to permit sample retention and use, and others are considering new legislative and policy proposals.[17]

Policy considerations: Public health benefits, privacy, and patient protections

Recent litigation has challenged state NBS program policies for retaining samples.[18] Primary concerns are the use of the information by law enforcement and commercial entities or for research without parental consent.[19] Plaintiffs claim these uses violate their fundamental constitutional rights to make decisions about the care of their children and amount to unconstitutional searches and seizures in violation of the Fourth Amendment.

No federal law governs ownership of biological specimens collected for any purpose. The Health Insurance Portability and Accountability Act (HIPAA) privacy rule covers protected individually identifiable health information and thus may apply to information revealed by the RDBS but not the residual specimens per se. HIPAA has a significant exception for disclosures to public health authorities as authorized by law[20] and contains additional limited exceptions for disclosures to law enforcement or in legal proceedings. Disclosures to law enforcement require a court order, warrant, subpoena or summons issued by a judicial officer, grand jury subpoena, or legally authorized administrative demand that is limited in scope.[21] Disclosures in judicial or administrative proceedings require either express authorization by a court or administrative tribunal[22] or, if made in response to a subpoena without such authorization, require satisfactory assurance that reasonable efforts have been made to ensure that the individual who is the subject of the health information has been given notice of the request.[23]

For the use of identifiable protected health information in research, HIPAA requires patient authorization, unless the use comes within a specific exception such as approval by a privacy board/institutional review board.[24] HIPAA permits use of information that has been deidentified to appropriate standards without authorization, so long as there are protections against reidentification.[25] HIPAA also permits use of information in a limited data set that has been constructed to remove specified identifiers and that is subject to a data use agreement.[26] These provisions represent a balance between protecting patient privacy and allowing public health research.

In all cases, establishment of policies related to storage, retention, and use of RDBS requires careful consideration of the unique resource these specimens provide. For example, the Institute of Medicine's framework to guide policymakers and healthcare professionals in improving the quality of healthcare through the United States consists of 6 aims: safe, effective, patient-centered, timely, efficient, and equitable.[27] When considering RDBS policies, these aims should be considered collectively to improve public health without creating unintentional harm. Legal challenges and uninformed legislation can threaten this invaluable resource. Ultimately, it is critical to establish appropriate, informed policies to balance the goal of improving public health while recognizing the preferences of families.

Summary

Accordingly, it is the ACMG's position that

- NBS RDBS are a valuable national resource that significantly contribute to the health of all children and families.
- RDBS are necessary for test development, quality control, and quality assurance. Federal and state policies should allow for storage, retention, and use of RDBS for these purposes and other key goals of their programs.
- RDBS should be stored with rigorous control and respect for privacy and confidentiality to protect the public.
- Federal and state policies should allow for the appropriate clinical and research uses of deidentified RDBS relevant to child health and include consent requirements for uses in which RDBS will be or could be reidentified.
- States should strengthen policies and laws regarding use of RDBS by law enforcement.
- As states continually revise policies affecting retention of RDBS, careful consideration must be given to the irreplaceable value to child health provided by these specimens.

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Conflict of Interest

Michele Caggana runs the newborn screening program for New York State; the program conducts many tests on dried blood spots. The program conducted a pilot study for congenital cytomegalovirus while this document was being written. One reference refers to guanidinoacetate methyltransferase deficiency and the laboratory screens for this condition. All other authors declare no conflicts of interest.

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19. See, eg, Opinion and Order, Kanuszewski v. *Michigan Department of Health and Human Services*, No;1:18-cv-10472-TLL-PTM:3 (Mich ED. September 13, 2022) (appeal filed Aug. 16, 2023).
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