Newborn Screening

History, Current Status, and Future Directions

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KEYWORDS

• Inborn errors of metabolism • Newborn screening • Tandem mass spectroscopy

KEY POINTS

- Newborn screening aims to achieve presymptomatic diagnosis of treatable disorders to allow for early initiation of medical care to prevent or reduce significant morbidity and mortality related to the screened disorders.
- Many of the conditions tested in the newborn screening are inborn errors of metabolism; however, a wide variety of other nonmetabolic disorders may be included.
- In the United States, the Advisory Committee on Heritable Disorders in Newborn and Children (ACHDNC) provides recommendations regarding conditions to be included in newborn screening program panels; however, the final decision of which disorders to be added to the newborn screening is typically made by each individual state.
- Newborn screening tests are not designed to be diagnostic. Therefore, further diagnostic tests are needed to confirm or exclude the suspected diagnosis.
- Further advancement in technology is expected to allow continuous expansion of newborn screening with reduction in cost, shorter turnaround time, and more accurate results.

INTRODUCTION

Newborn screening aims to achieve early presymptomatic diagnosis of treatable disorders for which timely intervention is critical to improve the outcome. Many of the conditions included in the newborn screening panels are inborn errors of metabolism; however, screening for endocrine, hematologic, immunologic, and cardiovascular diseases, and hearing loss is also included in many panels. Newborn screening includes point-of-care tests (eg, hearing test) and blood analysis of samples collected on filter

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paper spots between 24 and 48 hours of age. Tests in newborn screening are not designed to be diagnostic. Therefore, abnormal newborn screen results should prompt the initiation of further diagnostic testing, neonate evaluation, and consideration of treatment initiation while waiting for the diagnostic test results.[1–3] This article focuses on newborn screening for inborn errors of metabolism. The goals and history of newborn screening are discussed. Then how disorders are selected for inclusion in newborn screening and how to optimize its results are explained. Logistics, factors affecting newborn screening results, and confirmation process are then presented. Finally, future directions of newborn screening are discussed.

GOALS OF NEWBORN SCREENING

Newborn screening aims to achieve presymptomatic and rapid diagnosis of treatable disorders for which timely intervention is critical to improve the outcome. These conditions are typically not evident at birth and if not diagnosed and treated could result in disability or death. Therefore, the goal of newborn screening is the prevention or reduction of significant morbidity and mortality related to various disorders. Newborn screening programs have enabled early diagnosis and initiation of medical care for the screened diseases, which has modified the outcome for many disorders that were previously associated with high morbidity (eg, inborn errors of metabolism, cystic fibrosis, and primary immunodeficiencies) or with significant neurodevelopmental disabilities (eg, phenylketonuria and congenital hypothyroidism). Improving the outcome for affected children is productive for society and the individual child.[2–4]

Because early diagnosis by newborn screening facilitates early intervention, the outcome of newborn screening programs has been favorable. Several studies of long-term follow-up of individuals ascertained by newborn screening indicated significant improvement in morbidity and mortality for all diseases that have been studied including fatty acid oxidations defects, urea cycle disorders, severe combined immunodeficiency, cystic fibrosis, and sickle cell disease.[5–9]

HISTORY OF NEWBORN SCREENING

The establishment of newborn screening was based on early work in the management of phenylketonuria. The importance of early diagnosis for phenylketonuria emerged when it was observed that individuals with phenylketonuria had improvement in their clinical status when given formulas modified to restrict phenylalanine intake, and such restriction can typically prevent intellectual disability associated with phenylketonuria if started early in life.[10,11] In 1963 Guthrie and Susi[12] reported a simple method for detecting phenylketonuria in large populations of newborns. Not different from today's sampling method, the blood for this test was collected from newborns on filter paper. The analysis method, which is known as bacterial inhibition assay, depended on placing a small punch from the filter paper on an ager plate containing a heavy inoculum of *Bacillus subtilis* bacteria and β_2-thienylalanine, which is an inhibitor of bacterial growth that is counteracted by any significant excess of phenylalanine in the blood sample. Elevated phenylalanine in phenylketonuria reverses the effect of the inhibitor, and the extent of bacteria growth surrounding the filter paper disk is correlated with phenylalanine level in the blood spot.[12] In the same year, Massachusetts began universal mandatory screening for phenylketonuria, and rapidly, other states started establishing newborn screening programs.

Screening tests for other inborn errors of metabolism were subsequently developed. The bacterial inhibition assay was used to detect other inborn errors of metabolism, such as galactosemia, maple syrup urine disease, and homocystinuria,