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Mini-Review

Newborn Screening through the Ages: Evolution, Expansion, and Emerging Frontiers

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Abstract: Newborn screening (NBS) is one of the most impactful population-based public health programs, exemplifying the power of early detection and timely intervention in preventive medicine. Its primary goal is to identify metabolic and genetic disorders that are often asymptomatic at birth but can lead to serious morbidity or mortality if left untreated. NBS began in the 1960s, when Robert Guthrie introduced dried blood spot (DBS) collection and a bacterial inhibition assay to detect phenylketonuria (PKU). Following the success of PKU screening and treatment, NBS gradually expanded to include other conditions such as congenital hypothyroidism, galactosemia, maple syrup urine disease, congenital adrenal hyperplasia, and hemoglobinopathies—though each was added individually. The introduction of tandem mass spectrometry (MS/MS) in the 1990s transformed NBS by enabling simultaneous detection of multiple disorders from a single DBS sample. Advances in microfluidics and molecular techniques further enhance the capabilities of NBS. However, rapid expansion led to significant variability in NBS programs. To address this, the Recommended Uniform Screening Panel (RUSP) was established in 2006 and currently includes 38 core conditions and 26 secondary conditions. Emerging genomic technologies—such as targeted DNA panels, whole exome sequencing, and whole genome sequencing—are further expanding the scope of NBS, though challenges related to cost, ethics, and interpretation of uncertain findings persist. Artificial intelligence (AI) and machine learning offer new opportunities to enhance diagnostic accuracy and follow-up. Expanding NBS globally will require affordable, scalable technologies and ongoing collaboration across disciplines.

Keywords: newborn screening; dried blood spot (DBS); Recommended Uniform Screening Panel (RUSP); tandem mass spectrometry (MS/MS)

Newborn screening (NBS) is one of the most far-reaching and transformative population-based public health programs. It illustrates the power of early detection and timely intervention as fundamental strategies in preventive medicine. By identifying a range of metabolic and genetic disorders many of which are asymptomatic at birth but potentially devastating if untreated, NBS has been successful in reducing morbidity, preventing disability and decreasing healthcare expenditures. Today, it is the largest public health screening program in the United States and is practiced globally, with over 40 million newborns screened each year.

The historical foundation of newborn screening (NBS) traces back to early 20th-century breakthroughs in genetics and biochemistry. In 1902, Dr. Archibald Garrod introduced the concept of "inborn errors of metabolism" after observing that alkaptonuria followed a Mendelian recessive inheritance pattern [1]. Shortly thereafter, in 1908, Dr. Von Rues described galactosemia in an infant with failure to thrive and hepatosplenomegaly. In 1934, Dr. Asbjørn Følling, identified phenylketonuria (PKU) after detecting abnormal urinary metabolites, initially

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described as “ketone bodies” and later identified as phenylpyruvic acid, in two siblings with intellectual disability [2]. Ferric chloride test which was used to detect “ketone bodies”, gained widespread use for the detection of PKU. The field saw a transformative change when Dr. Horst Bickel, in collaboration with Dr. Louis Woolf, developed a low-phenylalanine diet that dramatically improved neurodevelopmental outcomes in patients with PKU [3]. This dietary intervention dramatically improved outcomes for individuals with PKU and laid the foundation for modern therapeutic strategies to manage metabolic disorders.

Systematic newborn screening began in the early 1960s, when Robert Guthrie and Ada Susi introduced a simple yet revolutionary method for collecting blood on filter paper via heel prick to create dried blood spots (DBS), ideally obtained between 24 and 48 h after birth. They used bacterial inhibition assay for the detection of PKU from the blood collected on a filter paper [4]. This approach allowed for mass screening of newborns, leading to widespread adoption of newborn screening (NBS) across the United States and eventually the globe. Recognizing the immense benefits of early diagnosis and treatment, NBS programs rapidly expanded beyond PKU, incorporating a growing number of disorders. By the 1970s, congenital hypothyroidism was incorporated into many NBS programs, followed in the 1980s by classic galactosemia and maple syrup urine disease, as Guthrie and colleagues developed additional bacterial inhibition assays. The 1990s brought further expansion of NBS by the inclusion of hemoglobinopathies and congenital adrenal hyperplasia, each addition reflecting a growing consensus that early detection could drastically alter disease outcomes [5].

For decades, the expansion of NBS was based on the principle of “one test, one disorder” model, with each condition requiring a separate assay. Although this approach was effective, it limited the number of conditions that could be screened. The introduction of tandem mass spectrometry (MS/MS) in1990s to early 2000s revolutionized NBS. This technology fundamentally reshaped the landscape of newborn screening by enabling simultaneous detection of multiple conditions from a single DBS sample by a single test. This shifted the paradigm from discrete, disease-specific testing to multiplexed biochemical profiling [6]. This approach rapidly expanded the NBS to include a broad array of inborn errors of metabolism, such as amino acid disorders, organic acidemias, and fatty acid oxidation defects. Like tandem mass spectrometry (MS/MS), microfluidics entered newborn screening (NBS) as a multiplexed technology capable of detecting multiple metabolic and genetic disorders from a single dried blood spot. Though, MS/MS is a gold standard technology, microfluidic platforms offer advantages in portability, automation, and cost, making them a promising tool for expanding access to NBS, especially in resource-limited settings. These techniques have not only improved efficiency and accuracy but also redefined the possibilities of population-based screening in preventive medicine.

The inclusion of conditions in newborn screening (NBS) programs has traditionally followed the Wilson and Jungner principles of screening and public health, first established in 1968 [7]. These principles emphasize the importance of selecting conditions with significant health impact, well-understood natural history, availability of effective treatments, and the existence of reliable, acceptable, and cost-effective screening methods. These principles also stress the need for the availability of diagnostic and treatment services and the existence of clear policies to ensure continuity of care. For decades, these principles served as the ethical and practical guide for NBS policy. However, as technological capabilities advanced and the scope of screening expanded—particularly with the advent of high-throughput methods such as tandem mass spectrometry, microfluidics and molecular testing —broader considerations began influencing decision-making. Ethical, legal, and social implications, as well as practical variability in implementation capacity across states, contributed to a significant variability in how conditions were added to newborn screening panels across different NBS programs. By the 1990s and 2000s, this divergence became evident—while some states screened for only a few conditions, others expanded their panels to include over 50 conditions, often without consistent scientific standards.

Recognizing the need for greater uniformity and scientific rigor, the federal Health Resources and Services Administration (HRSA), in 2002, commissioned the American College of Medical Genetics (ACMG) to establish evidence-based guidelines for inclusion of conditions in NBS. In 2006, based on a structured scoring process that assessed disease severity, treatability, and feasibility of detection, the Recommended Uniform Screening Panel (RUSP) was published [8]. The RUSP included 29 core conditions and 25 secondary conditions—disorders that may be detected incidentally during screening for the core conditions. Since its inception, the RUSP has grown in response to scientific discovery, therapeutic innovation, and advocacy. As of today, the panel includes 38 core conditions, notably including point-of-care screening for critical congenital heart disease and hearing loss—conditions that depart from traditional biochemical screening but share the same imperative of early detection and intervention (Table 1). The number of secondary conditions has also grown to 26 [9]. While the RUSP provides national guidance, it does not carry federal enforcement, leaving states with discretion in implementation. As a result, several NBS programs have gone beyond the RUSP, incorporating conditions such as Niemann-Pick disease types A/B, Gaucher disease, Fabry disease, Duchenne muscular dystrophy (DMD), Glycogen Storage Disease Type II, and Wilson disease.

Table 1. Recommended Uniform Screening Panel (RUSP).

Category	Core Conditions	Secondary Conditions
Amino Acid Disorders	• Argininosuccinic aciduria • Citrullinemia, type I • Classic phenylketonuria • Homocystinuria • Maple syrup urine disease • Tyrosinemia, type I	• Argininemia • Benign hyperphenylalaninemia • Biopterin defect in cofactor biosynthesis • Biopterin defect in cofactor regeneration • Citrullinemia, type II • Hypermethioninemia • Tyrosinemia, type II • Tyrosinemia, type III
Organic Acid Disorders	• 3-Hydroxy-3-methyglutaric aciduria • 3-Methylcrotonyl-CoA carboxylase deficiency • ß-Ketothiolase deficiency • Glutaric acidemia type I • Holocarboxylase synthase deficiency • Isovaleric acidemia • Methylmalonic acidemia (cobalamin disorders) • Methylmalonic acidemia (methylmalonyl-CoA mutase) • Propionic acidemia	• 2-Methyl-3-hydroxybutyric aciduria • 2-Methylbutyrylglycinuria • 3-Methylglutaconic aciduria • Isobutyrylglycinuria • Malonic acidemia • Methylmalonic acidemia with homocystinuria
Fatty Acid Oxidation Disorders	• Carnitine uptake defect/carnitine transport defect • Long-chain L-3 hydroxyacyl-CoA dehydrogenase deficiency • Medium-chain acyl-CoA dehydrogenase deficiency • Trifunctional protein deficiency • Very long-chain acyl-CoA dehydrogenase deficiency	• 2,4 Dienoyl-CoA reductase deficiency • Carnitine acylcarnitine translocase deficiency • Carnitine palmitoyltransferase type I deficiency • Carnitine palmitoyltransferase type II deficiency • Glutaric acidemia type II • Medium/short-chain L-3-hydroxyacyl-CoA dehydrogenase deficiency • Medium-chain ketoacyl-CoA thiolase deficiency • Short-chain acyl-CoA dehydrogenase deficiency
Other Metabolic Disorders	• Biotinidase deficiency • Classic galactosemia • Glycogen Storage Disease Type II (Pompe) • Guanidinoacetate Methyltransferase Deficiency • Infantile Krabbe Disease • Mucopolysaccharidosis Type I • Mucopolysaccharidosis Type II • X-linked Adrenoleukodystrophy	• Galactoepimerase deficiency • Galactokinase deficiency
Endocrine Disorders	• Congenital adrenal hyperplasia • Primary congenital hypothyroidism	
Hemoglobin Disorders	• S, βeta-thalassemia • S,C disease • S,S disease (Sickle cell anemia)	• Various other hemoglobinopathies
Other Disorders	• Critical congenital heart disease • Cystic fibrosis • Hearing loss • Severe combined Immunodeficiencies • Spinal Muscular Atrophy due to homozygous deletion of exon 7 in SMN1	• T-cell related lymphocyte deficiencies

In the future, newborn screening (NBS) will undoubtedly continue to expand in response to advancements in analytical technologies, genomics, and precision medicine. DNA-based testing, whether targeting individual genes or panels, is increasingly being incorporated as first-tier or second-tier testing. Genetic testing is now routinely applied in screening for several disorders, including cystic fibrosis, spinal muscular atrophy (SMA), and severe combined immunodeficiency (SCID). Looking forward, whole exome sequencing (WES) and whole genome sequencing (WGS) have been proposed as next-generation tools to further enhance the scope and precision of NBS [10,11]. However, these approaches face challenges, including high costs, the ethical and clinical complexities of identifying carrier status, and the frequent detection of variants of uncertain significance (VUS). As our ability to interpret genomic data improves and costs decrease, the role of genetic testing in newborn screening will certainly expand. Additionally, artificial intelligence (AI) and machine learning algorithms hold the potential to enhance the specificity and sensitivity of screening, streamline laboratory workflows, and optimize follow-up of screen positive conditions.

While NBS is nearly universal in high-income countries, many low- and middle-income nations still face significant barriers to its implementation [12]. The emergence of cost-effective platforms, such as portable mass spectrometry and microfluidics could make global expansion more feasible. As the field continues to evolve, the potential of NBS will require not only innovation in technology but also sustained interdisciplinary collaboration among clinicians, scientists, policymakers, and global health leaders to extend the promise of early detection and intervention to every newborn, everywhere.

Conflicts of Interest

The authors declare no conflict of interest.

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