VIEWPOINT

Genomic Newborn Screening—A Long Road From Pilot to Public Policy

François Boemer, PharmD, PhD; Laurent Servais, MD, PhD

Genomic newborn screening (gNBS)—the use of genomic sequencing technologies in publicly administered, population-level neonatal screening programs—represents a substantial advancement in neonatal health assessment, heralding a new era of early disease detection and prevention. Until now, population-based detection of treatable disorders in newborns has been largely limited to metabolic and endocrine diseases, with the recent exception of spinal muscular atrophy. This limitation has stemmed primarily from technical constraints, as traditional screening methods rely on detecting excess metabolite in a newborn's blood. gNBS, however, offers the possibility of substantially expanding newborn screening to include a broader range of treatable genetic conditions that would otherwise go undetected.

Recently, 27 initiatives have emerged across various countries to evaluate the feasibility of gNBS.[1] While these initiatives vary in scope, with some implementing newborn sequencing at the population level and others applying it in specific settings, their initial findings demonstrate both feasibility and the potential to revolutionize neonatal care. However, they also underscore the challenges of implementation.[2,3] The International Consortium on Newborn Sequencing (ICoNS) seeks to consolidate insights from these diverse pilot projects. Despite collective enthusiasm within the ICoNS community, the deployment of gNBS raises numerous questions.[4]

Economic Considerations

In many countries with publicly funded health care systems, conventional NBS was introduced as a public health initiative to reduce the medical costs associated with rare diseases by screening the entire population. This approach is based on the economic principle that screening all newborns and managing presymptomatic cases is more cost-effective than treating symptomatic individuals. The economic benefits have been established.[5] However, given the rarity of these conditions, very large populations and multiyear follow-ups are necessary to accurately assess cost-effectiveness.

Because gNBS costs exceed $300 per screening, most pilot programs are limited to around 10 000 newborns and last only 1 to 3 years. Consequently, no pilot study is currently large enough to generate meaningful data for a comprehensive health economic assessment. Decisions to nationally fund large-scale gNBS programs would therefore require substantial recurring expenditures and several years of data collection, similar to efforts such as the National Institutes of Health All of Us Research Program,[6] to justify the investment.

Clinical and Societal Implications

A major challenge lies in the variable penetrance, expressivity, and pleiotropy of genetic variants, which must now be considered at the level of each specific variant. This granular approach acknowledges that different variants within the same gene can carry widely varying probabilities of causing disease (penetrance), differing symptom severity (expressivity), or distinct phenotypic traits (pleiotropy).

Boemer et al[3] recently highlighted this challenge by reporting a case involving a neonate carrying a heterozygous variant in the *MYH7* gene, associated with dominantly inherited cardiomyopathy. During confirmatory workup, familial investigation revealed that the father had signs of previously undiagnosed cardiac hypertrophy. The natural history of *MYH7*-related cardiomyopathies shows variable ages of onset and phenotypic heterogeneity, even within the same family.[7] Except in cases involving de novo mutations, dominant phenotypes are typically well documented within affected families.

This raises the question: Should NBS identify conditions with mild or late-onset manifestations? While traditional NBS programs focus on early childhood intervention, there is growing recognition that early detection of later-onset disorders may also offer substantial benefits.

This issue ties back to the cost-effectiveness and societal impact of NBS. gNBS faces the challenge of balancing prevention with the risk of overdiagnosis. A key concern is that it could overburden health care systems by requiring lifelong preventive consultations for neonates diagnosed with a condition that may not manifest until much later in life.

Data Protection

The implementation of gNBS raises serious privacy concerns, including risks of genetic discrimination, unauthorized access, and unintended discoveries of familial relationships. Misuse of sequencing data by insurers, employers, or law enforcement could harm individuals and erode public trust.

Long-term data storage offers potential clinical benefits but also increases the risk of misuse, making strong data protection policies essential. These should include clear access guidelines, secure storage or destruction options, and parental choice regarding data retention. Future research must explore practical solutions that balance privacy with responsible integration of data into health care systems.

Psychosocial Impact

The psychosocial impact of gNBS is complex and multifaceted, yet empirical data remain limited. Studies such as the BabySeq project have shown no sustained negative effects on parental mental health or parent-child bonding.[8] However, initial anxiety and uncertainty can occur.

Parental distress, which is often triggered by a misinterpretation of results—especially false positives or ambiguous findings—can lead parents to perceive their child as more vulnerable. This may result in overprotection or altered expectations. While most parents adjust over time, the emotional burden of uncertainty can strain

family dynamics. This underscores the need for clear communication, prompt confirmatory testing, and expert support. Long-term effects on children, such as anxiety, identity issues, or stigmatization, remain underresearched. These potential outcomes highlight the need for careful counseling and long-term follow-up.

Population Health Considerations

At the individual level, gNBS has demonstrated significant benefits.[2,3] However, its population-level effectiveness remains unproven. A similar debate surrounds carrier screening, which enables couples to assess their risk of passing on recessive or X-linked conditions. While it benefits individuals, widespread adoption could necessitate in vitro fecundation or prenatal testing for up to 4% of individuals,[9] a demand that most health care systems are currently ill-equipped to meet.[10]

The integration of gNBS introduces a new public health model: applying individualized genomic data at a population level. While some trials have made strides in recruiting diverse populations,[2] many studies lack adequate representation. There is an ongoing need for large, diverse study samples to ensure gNBS is equitable, interpretable across ancestries, and generalizable.

Unlike conventional NBS, which relies on uniform biochemical markers and defined thresholds, gNBS generates highly personalized results based on genetic variant, disease expressivity, family history, and ancestry. This evolution challenges the foundational cost-benefit models that have traditionally guided publicly funded screening. Policy-makers must now grapple with managing individualized risk profiles across populations while maintaining equity, cost-effectiveness, and clarity in public health messaging. In essence, gNBS shifts the paradigm from a standardized, population-wide approach to a hybrid model, blending personalized genomic insights with broad public health goals. This shift carries major implications for resource allocation, long-term follow-up infrastructure, and ethical governance.

ARTICLE INFORMATION

Author Affiliations: Biochemical Genetics Laboratory, Department of Human Genetics, CHU Liege, University of Liege, Liege, Belgium (Boemer); Division of Child Neurology, Reference Center for Neuromuscular Diseases, Department of Pediatrics, CHU Liege, University of Liege, Liege, Belgium (Servais); MDUK Neuromuscular Center, Department of Pediatrics, University of Oxford, Oxford, United Kingdom (Servais).

Corresponding Author: François Boemer, PharmD, PhD, Biochemical Genetics Laboratory, Department of Human Genetics, CHU Sart-Tilman, University of Liege, B35, Liege 4000, Belgium (f.boemer@chuliege.be).

Published Online: October 6, 2025. doi:10.1001/jamapediatrics.2025.3639

Conflict of Interest Disclosures: Dr Servais reported receiving personal fees from Illumina; receiving grants from LaCAR MDX Technologies, Sanofi, Orchard Therapeutics, Takeda, Roche, and Novartis; and serving as an external administrator for the Thameus Project outside the submitted work. No other disclosures were reported.

Additional Contributions: We thank Fardowsi Kazi (Oxford University) for language editing assistance. No financial compensation was provided for this contribution.

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