Mini Review

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Newborn screening for rare diseases: expanding the paradigm in the genomic era

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Abstract

Background: Newborn screening (NBS) has long been a cornerstone of public health, initially designed to detect a few congenital disorders such as phenylketonuria and congenital hypothyroidism. This early intervention prevents irreversible health consequences. With the advent of genomic technologies, NBS programs are expanding to include a broader range of rare diseases (RDs), offering new opportunities and challenges in clinical implementation, ethics, and health system readiness.

Content: This mini-review traces the evolution of NBS from biochemical assays to next-generation sequencing (NGS) and whole-exome sequencing (WES). It highlights complexities in integrating RDs into NBS panels, including condition selection, test validation, confirmatory pipelines, and the need for robust follow-up. Ethical tensions between public health goals – focused on population benefit – and the personalized medicine paradigm are discussed, along with the importance of international harmonization to ensure equitable access.

Summary: Expanding NBS to include RDs can transform early diagnosis, reduce diagnostic delays, and enable timely interventions that improve outcomes. Successful genomic NBS (gNBS) integration requires clear, evidence-based inclusion criteria, validated diagnostics, and sustainable follow-up systems.

Outlook: Rapidly evolving genomic tools will reshape NBS, demanding agile policies, secure data infrastructures, and careful attention to consent, privacy, and equity. International collaboration and stakeholder engagement will be essential to ensure these technologies are implemented ethically and effectively, balancing public health priorities with individualized care.

Keywords: newborn screening (NBS); genomic NBS; rare diseases; public health; personalized medicine

Introduction

Rare diseases (RDs), defined in the European Union as conditions affecting fewer than one in 2,000 individuals, collectively impact more than 30 million people across Europe. Although individually uncommon, their cumulative burden is significant, owing to their often early onset, chronicity, and severity. Over 70 % of rare diseases manifest in childhood, and more than 80 % are believed to have a genetic basis [1]. Despite advances in diagnostics and biomedical research, patients with RDs frequently encounter a prolonged and fragmented diagnostic pathway, often referred to as a “diagnostic odyssey,” which typically spans over 6 years and involves consultations with numerous specialists [2, 3]. This delay can lead to irreversible health deterioration and missed windows for effective intervention. As highlighted by Groft et al., global efforts to improve the identification and management of rare diseases have gained momentum, yet significant disparities remain in awareness, infrastructure, and access to care [4]. The development of a comprehensive national RD ecosystem has been proposed to address such systemic gaps, emphasizing early diagnosis, data integration, patient-centered policy, and the inclusion of rare diseases within broader public health planning frameworks. These national and international initiatives underscore the need for coordinated, equity-driven strategies to improve outcomes for individuals living with rare diseases [5, 6].

Newborn screening (NBS) offers a powerful tool to interrupt this cycle by enabling presymptomatic diagnosis and early treatment [7]. Initiated in the 1960s with Robert Guthrie’s test for phenylketonuria (PKU), NBS has evolved from a single-test, single-disease approach to an integrated system encompassing dozens of conditions [8–10]. However, the inclusion of rare diseases into NBS panels raises new

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questions, such as how should conditions be selected; what are the implications of uncertain or variable phenotypes; uncertain borders between clinically relevant abnormalities and benign biochemical or genetic abnormalities in most conditions; can emerging genomic technologies be integrated responsibly; and how to maintain current levels of trust into the NBS programs.

This review examines these questions by analyzing the current landscape of NBS for RDs, assessing ethical and operational challenges, and exploring the future trajectory of genomic NBS (gNBS).

Current landscape of NBS for rare diseases

The implementation of NBS programs varies significantly across countries, reflecting differences in health system priorities, funding, technical capacity, and policy frameworks [7, 9, 10]. While some conditions like PKU and congenital hypothyroidism are almost universally screened in Europe, others – such as biotinidase deficiency or medium-chain acyl-CoA dehydrogenase deficiency (MCADD) – are only included in a subset of countries [10]. Furthermore, not all the inherited disorders that would warrant early detection to prevent severe consequences are currently widely adopted in the NBS programs [11]. According to a 2021 survey by Loeber et al., only a minority of countries screen for more than 20 conditions routinely [10]. Furthermore, significant inequalities in NBS programs still exist, and several European countries screen only for a few conditions or even have no NBS program in place [7, 12].

The development of tandem mass spectrometry (MS/MS) has enabled the simultaneous detection of multiple inborn errors of metabolism from a single dried blood spot [9, 13]. This expanded NBS model can identify over 40 metabolites, supporting the detection of aminoacidopathies, organic acidurias, and fatty acid oxidation disorders [14]. The uptake of NBS remains exceptionally high (>99 %) across most European countries, reflecting its critical role in public health [10]. However, the evolving composition of NBS panels highlights a persistent tension between traditional (i.e. Wilson and Jungner) screening criteria and the rapid advancements in diagnostic capabilities. The inclusion of rare diseases such as spinal muscular atrophy (SMA) and severe combined immunodeficiency (SCID) illustrates the expanding potential of NBS in identifying conditions that can significantly benefit from early intervention [7]. As the scope of NBS continues to grow, the integration of novel diagnostic tools, particularly genomic technologies, presents new challenges. The application of next-generation sequencing (NGS) and tandem mass spectrometry (MS/MS) to NBS is advancing the ability to detect a broader range of metabolic and genetic disorders, yet the pace at which new conditions are added remains slow [9, 15].

The integration of these new technologies, while promising, raises concerns about the clinical implications of overdiagnosis, false positives, and the strain on healthcare resources. As the number of conditions screened for increases, so does the complexity of managing false positives and ensuring timely, appropriate follow-up [7, 15]. These concerns underscore the need for clear, evidence-based inclusion criteria that balance the benefits of early diagnosis with the potential harms of unnecessary interventions. Furthermore, robust follow-up systems are essential to ensure that positive results lead to timely confirmation and intervention, avoiding the risk of unnecessary treatments or misdiagnoses [15].

Currently, NBS programs enable detection of a very small proportion of all the pediatric-onset rare diseases, even if we consider only treatable diseases. According to estimates, childhood-onset RDs, constitute approximately 75 % of the estimated over 8,000 RDs globally (actionable diseases, with treatments or management strategies available, encompass between 500 and 1,000 gene-disease pairs; around 500 of RDs are considered treatable) [1–4]. On the other hand, only around 50 RDs are currently included in the best of the established NBS programs, highlighting a significant gap in early detection and intervention opportunities [9–11].

Challenges in selecting conditions for NBS panels

Traditionally, inclusion in NBS panels has relied on the Wilson and Jungner criteria established by the World Health Organization in 1968 [16]. These principles emphasize the importance of disease severity, availability of treatment, early symptomatic stages, and cost-effectiveness of screening. While these remain foundational, they were conceived in an era with limited therapeutic options and rudimentary diagnostics [17]. Applying them rigidly to rare diseases may exclude many conditions that, while individually uncommon, are severe, treatable, and detectable in the neonatal period.

In the context of rare diseases and the advent of genomic technologies, several of the classical Wilson and Jungner screening criteria warrant reinterpretation or cautious reapplication [18, 19]. As Andermann and colleagues [19] argue, while the core principles of screening remain valid, new challenges have emerged that were not

foreseen in the original 1968 framework. For example, the criterion that a condition should have a "recognizable latent or early symptomatic stage" becomes problematic when applied to disorders that present with sudden, irreversible symptoms in the neonatal period – such as severe combined immunodeficiency (SCID) or certain inborn errors of metabolism. In such cases, the absence of a latent stage paradoxically strengthens the rationale for presymptomatic screening, as clinical recognition may come too late for effective intervention.

Similarly, the requirement that screening should be "cost-effective in relation to possible expenditure on medical care as a whole" is particularly difficult to operationalize for ultra-rare diseases. By their very nature, these conditions lack robust prevalence and outcome data, making conventional cost-effectiveness modeling imprecise or even misleading. Moreover, available treatments – though expensive – may dramatically alter the prognosis, raising ethical questions about how value is defined in public health contexts. As genomics expands the scope of screenable conditions, a more nuanced and flexible interpretation of these criteria is needed – one that balances evidence-based rigor with the ethical imperatives of early diagnosis and equitable access to care [19].

To address the limitations of classical screening criteria – especially for rare and ultra-rare diseases – expert bodies have developed structured, evidence-based frameworks for evaluating candidate conditions. The U.S. Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC), established in 2003 under the Newborn Screening Saves Lives Act and tasked with advising on additions to the Recommended Uniform Screening Panel (RUSP), exemplified this approach [20]. The RUSP was established to propose a tiered approach to evaluating conditions for inclusion [21]. The ACHDNC applied a systematic, multi-criteria decision-making model that integrated disease severity, availability of timely and effective interventions, implementation feasibility, stakeholder input, clinical and economic evidence, and ethical considerations. However, in April 2025, the committee was abruptly terminated – leaving the United States without its only federal advisory body guiding RUSP updates – a decision that has been widely criticized as creating "a dangerous vacuum" in the NBS infrastructure [22]. In contrast, many European countries continue to use similar multi-factorial frameworks through national expert panels to evaluate NBS expansions. The sudden absence of a centralized, transparent advisory process in the U.S. underscores the urgent need for robust, ethically grounded governance to navigate the complex expansion of NBS in the genomic era.

However, the process remains uneven globally [7]. In Europe, NBS panels vary widely despite shared regulatory frameworks and comparable economic contexts [10]. This inconsistency reflects differences in political will, advocacy pressure, and institutional inertia. As a result, a child born in one country may have access to life-saving NBS and early diagnosis, while another in a neighboring state may not [7, 8, 12].

The urgency to develop harmonized, transparent, and evidence-based processes for condition selection is further amplified by the acceleration of genomic technologies, which can detect hundreds of conditions in a single assay [10, 15]. Without clear frameworks, the risk of premature or inequitable implementation grows.

Public health vs. rare disease paradigms

NBS initially started as in the context of the public health paradigm, while more recent are tendencies to shift towards the rare disease (personalized medicine) paradigm. Each paradigm brings different priorities, values, and methodologies (see Table 1).

The public health paradigm is population-focused. It prioritizes equity, cost-effectiveness, and the responsible use of public resources. NBS programs in this model are designed to maximize overall benefit while minimizing harm and unnecessary intervention [8, 9, 15]. It adheres closely to established principles like those of Wilson and Jungner, emphasizing standardization, program metrics, and scalability. NBS is seen not as a diagnostic process, but as a means of risk stratification leading to further evaluation [17].

In contrast, the rare disease paradigm emphasizes individual benefit. Advocates for this model argue that even conditions with very low prevalence should be included in NBS panels if early diagnosis can significantly alter outcomes. This approach draws from the principles of personalized medicine, emphasizing tailored follow-up, genomic diagnostics, and cascade testing in families. It is driven by ethical imperatives to avoid preventable suffering and irreversible damage, even when population-level cost-effectiveness is not demonstrable [1–4, 23].

These paradigms are not inherently in conflict, but their priorities can lead to tension. Public health authorities may resist including ultra-rare conditions with marginal or uncertain evidence, while rare disease advocates may push for rapid expansion based on emerging treatments [16, 17, 23]. Resolving this tension requires

Table 1: Comparison of the Public Health and Rare Disease Paradigms applied to the newborn screening.

Dimension	Public health paradigm	Rare disease/Personalized medicine paradigm
Primary objective	Maximize population health outcomes; reduce overall morbidity and mortality	Optimize individual outcomes through early and accurate diagnosis
Screening justification	Based on classical criteria (Wilson & Jungner): Importance, treatability, cost-effectiveness	Based on ethical urgency, treatability, and individual benefit – even with low prevalence or limited cost data
Scope of conditions	High-prevalence, well-characterized, cost-effective disorders (e.g., PKU, CH, MCADD)	Rare or ultra-rare genetic conditions, often newly actionable (e.g., SCID, SMA, LSDs; genomic pilots)
Testing approach	Biochemical methods (e.g., MS/MS, immunoassays); standardized protocols	Genomic technologies (e.g., WES/WGS); tailored follow-up and cascade testing in families
Decision-making criteria	Emphasis on population-level benefit, feasibility, and cost-effectiveness	Emphasis on clinical urgency, ethical imperatives, and possibility of significant individual health impact
Ethical framework	Consequentialist (maximize benefit, minimize harm); cautious expansion	Principlist (beneficence, autonomy, justice); tolerant of uncertainty if outcome is serious and preventable
Consent model	Implicit or opt-out consent under public health authority	Increasingly favors explicit informed consent due to data sensitivity and scope of testing
Equity focus	Equal access to standardized national services	Equitable inclusion of underserved rare disease patients despite low prevalence
Data use & governance	Public health surveillance systems; key performance indicators; centralized QA/QC	Decentralized or hybrid governance; data-sharing infrastructures for research and personalized care
Limitations	May exclude low-prevalence but treatable conditions; rigid criteria	May overextend resources; risk of overdiagnosis or uncertain findings (e.g., VUS)
Governance models	National public health bodies (e.g., RUSP, WHO recommendations)	Multi-stakeholder advisory models, often involving patient groups and genetic experts
Conceptual foundations	Wilson and Jungner [16], WHO principles, Andermann et al. [19]	Precision public health (Baynam et al. 2017), ESHG guidance, rare disease advocacy frameworks

PKU, phenylketonuria; CH, congenital hypothyroidism; SCID, severe combined immunodeficiency; SMA, spinal muscular atrophy; LSDs, lysosomal storage disorders; MS/MS, tandem mass spectrometry; WES, whole exome sequencing; WGS, whole genome sequencing; QA/QC, quality assurance/quality control; VUS, variant of unknown significance; RUSP, recommended uniform screening panel; WHO, World Health Organization; ESHG, European Society of Human Genetics.

governance models that allow for deliberation across these perspectives.

One proposed solution is the implementation of a precision public health framework, which seeks to integrate genomic innovation with public health infrastructure, balancing individualized benefit with population-level impact. This model emphasizes equitable access to diagnostic advances, robust data integration, interdisciplinary care, and international collaboration – all grounded in ethical and sustainable policy development [23, 24].

Pilot programs that integrate gNBS – such as those underway in the UK, Belgium – offer a testing ground for reconciling these paradigms [25, 26]. Transparent evaluation, stakeholder engagement, and attention to distributive justice are critical. Ultimately, NBS must evolve into a hybrid model, balancing public good with personalized benefit.

Emerging role of genomics in NBS

Next-generation sequencing (NGS) technologies, including whole-exome and whole-genome sequencing (WES/WGS), are rapidly transforming the landscape of NBS [15, 25–28]. These tools offer the potential to identify hundreds of monogenic disorders in a single assay, often before clinical symptoms emerge. In pilot initiatives across Europe and North America, gNBS is being explored as a complement – or in some cases, a replacement – for traditional biochemical methods [25–28]. A notable example is the system developed by Kingsmore et al., which used rapid whole-genome sequencing to screen for over 380 severe genetic conditions, demonstrating high sensitivity and specificity within a consented, clinically integrated model [29]. Betzler et al. analyzed seven published gene-disease lists from gNBS studies and observed substantial variation in total gene count (median 480, range 237–889) and disease group composition; an intersection was identified for only 53 genes, 83 % of them were related to the inherited metabolic diseases [30]. In the NBSeq project, Adhikari et al. demonstrated the potential of exome sequencing as a complementary tool for NBS, showing high specificity in identifying inborn errors of metabolism [31]. Furthermore, in a nationally representative survey, approximately 74 % of parents expressed interest in newborn whole-genome sequencing through public health programs [32].

gNBS introduces several advantages: it can detect conditions not amenable to biochemical markers, clarify diagnoses with variable phenotypic expression, and enable cascade testing in families. Moreover, it holds promise for personalized treatment approaches, pharmacogenomics, and gene-targeted therapies [15, 33]. Notably, early data from pilot studies indicate that gNBS may improve diagnostic yield while reducing time to diagnosis for complex conditions. In addition, costs have reduced dramatically over the last several years and continue to do so [15, 34].

However, these advances are accompanied by significant challenges. Technical considerations include variant interpretation, test sensitivity and specificity, and limitations in detecting non-exonic or structural variants [15]. Clinical challenges include the potential for uncertain or incidental findings, variable penetrance, and unclear prognoses. Ethical concerns revolve around consent, privacy, and the psychosocial impact of early genetic information. In addition, ethical frameworks for genetic testing in minors emphasize deferring testing for late-onset conditions unless early intervention is possible [15].

Currently, most gNBS programs adopt a targeted gene panel approach, focusing on actionable conditions with high penetrance and early onset [15]. This strategy limits ethical and clinical uncertainty while preserving the benefits of early genomic insight. Informed consent – ideally offered during pregnancy – remains a cornerstone of these programs, ensuring that parents understand both the benefits and limitations of genomic data [15].

Ultimately, the successful integration of genomics into NBS will depend on establishing clear inclusion criteria, robust confirmatory testing pipelines, multidisciplinary support for families, and policies for data storage and reanalysis. Lessons from existing NBS systems – such as the need for equitable access, longitudinal follow-up, and public trust – must guide the design of gNBS [9, 15].

Future directions

The future of NBS for rare diseases lies in a gradual but deliberate transition from reactive diagnostics to proactive, data-driven prevention [9]. As biomedical research continues to uncover disease mechanisms and therapeutic targets, NBS programs must evolve to match this progress.

One key direction is the development of internationally agreed-upon standards for the inclusion of conditions in NBS panels. A collaborative approach among health authorities, professional societies, and patient advocacy groups is essential to reduce inequalities in access and ensure quality assurance. Platforms such as the European Reference Networks (ERNs) and international consortia could serve as vehicles for such alignment [8].

Another important trend is the convergence of multi-omics data – integrating genomics, metabolomics, transcriptomics, and proteomics – to enhance diagnostic precision and predictive power [9]. The availability of digital health infrastructure, artificial intelligence, and biobanks will further support real-time decision-making, enabling individualized follow-up and dynamic care pathways.

At the same time, social and ethical frameworks must keep pace. Policymakers will need to clarify data governance, consent policies, and criteria for reporting variants of uncertain significance. Special attention should be paid to ensuring informed parental participation and protecting the child's future autonomy [35]. According to ASHG/ACMG guidelines, genetic testing in children should be initiated only when it offers clear medical benefit, with psychosocial implications factored into decision-making [36, 37]. In addition, the AAP and ACMG emphasize that genetic testing of minors should prioritize the child's best interests, limiting testing to conditions with actionable childhood interventions and discouraging nonclinical or direct-to-consumer screening models in pediatric populations [38].

Long-term outcome registries, ideally linked to NBS data, will be indispensable for evaluating program impact, guiding clinical guidelines, and informing cost-benefit analyses. Investment in such infrastructure should be seen as a public health priority [8, 9].

Ultimately, the goal is moving towards a more anticipatory model of medicine – where diagnosis, prevention, and intervention begin at birth or even before, transforming the life course of individuals with rare diseases.

Conclusions

NBS is considered one of the most successful public health interventions, and its extension to additional treatable RDs, that need to be detected at birth, represents both an ethical imperative and a technological opportunity. While the inclusion of rare and ultra-rare conditions challenges traditional frameworks, it also holds the potential to dramatically improve lives through earlier diagnosis and treatment.

The ongoing transition from classical biochemical NBS to genomics-enabled platforms requires utmost careful implementation. This evolution must be based on evidence, maintaining high ethical standards, must be aligned with health system capacities, and have transparent governance.

In the emerging future, NBS will be increasingly bridging preventive public health and personalized medicine paradigms. Ensuring equitable access, minimizing

harm, maintaining high levels of trust, and supporting families throughout the diagnostic and care pathway will be essential to realize its full promise. Ultimately, the goal is not only to detect disease early but to affirm each child's right to a healthy start in life.

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