Genome Sequencing for Newborn Screening—An Effective Approach for Tackling Rare Diseases

Shan Jiang, PhD; Haiyin Wang, PhD; Yuanyuan Gu, PhD

Newborn screening is a crucial global public health initiative, with a primary aim to identify congenital disorders that could lead to significant morbidity and mortality if left untreated. However, the scope of traditional newborn screening methods is limited, detecting only a finite number of conditions. With the advent of next-generation genome sequencing technologies, gene panel sequencing as a first-tier newborn screening test is a promising strategy, potentially enabling comprehensive and accurate diagnosis of a broad spectrum of genetic conditions at birth.

In the pivotal study by Chen et al,1 the largest prospective study to assess the potential benefits of a genomic test as a first-tier screening approach on a population scale to our knowledge, has marked a significant leap forward in this domain in China. The research investigated the effectiveness of gene panel sequencing as a first-tier newborn screening test at a large-population scale. Recruiting nearly 30 000 newborns, the study concurrently performed traditional biochemical newborn screening and targeted gene panel sequencing for 128 conditions. The findings were enlightening: 59 cases undetected by traditional biochemical newborn screening were identified by genome sequencing, translating to 1 in every 500 newborns who could benefit from this technology. The study demonstrated that genomic newborn screening supplemented traditional biochemical newborn screening by improving detection capability and screening more patients, thus providing evidence-based suggestions that genomic screening could be considered as a crucial method for first-tier screening. This study represents a significant step toward the possibility of integrating genomic medicine into routine health care in China, setting the stage for future research in this field.

Screening for Rare Diseases by Genome Sequencing

The introduction of genome sequencing into newborn screening has the potential to dramatically improve health outcomes for newborns with genetic conditions, most of which constitute rare diseases. Rare diseases are often overlooked in traditional newborn screening due to their low prevalence. However, their cumulative impact on public health is significant. It is estimated that there are between 6000 and 8000 known rare diseases, affecting an estimated 300 to 350 million people worldwide.2 This means that while any 1 rare disease may affect fewer than 1 in 2000 people, together, rare diseases affect a significant proportion of the population. For example, cystic fibrosis, a genetic disorder that primarily affects the lungs and digestive system, is considered a rare disease. Yet, it affects about 70 000 individuals worldwide and requires intensive medical care throughout a person's life, placing a substantial burden on health care systems.2

Moreover, many rare diseases are chronic and debilitating, leading to decreased quality of life and premature death. They often require long-term specialized treatments that are both expensive and challenging to access. For example, novel therapies such as gene therapies, enzyme replacement therapies, and other targeted treatments often have extremely high prices. Zolgensma (Novartis Gene Therapies), a gene therapy for spinal muscular atrophy, is priced at over $2 million per treatment, making it one of the most expensive therapies in the world. These high costs can pose significant barriers to access, particularly for individuals in low-income households or in countries with less developed health care systems. Often, these treatments are not universally covered by insurance providers, leaving families to grapple with out-of-pocket expenses that can lead to financial...
distress. The challenges in affordability and accessibility further underscores the importance of early awareness and interventions targeting rare diseases through genome sequencing.

**Challenges of Applying Genome Sequencing for Newborn Screening**

Incorporating genome sequencing into newborn screening as a standard health care service introduces a unique set of challenges. First, there is still much we do not know about the numerous genetic variants and how they manifest in different individuals, which could lead to ambiguous or misleading results. Even for those pathogenic variants we have sufficient knowledge about, the interpretation of genomic data is complex and requires considerable expertise. Second, genome sequencing can lead to false-positive and false-negative results, which can cause unnecessary anxiety, lead to additional testing, or miss important diagnoses. Third, there are significant ethical and legal considerations related to the handling and storage of genomic data, particularly for newborns who cannot provide informed consent. Issues related to privacy, data security, and potential discrimination based on genetic information need to be addressed. Fourth, the integration of genome sequencing into routine newborn screening would require substantial infrastructure and resources, including trained personnel to perform the tests, interpret the results, and provide genetic counseling. Fifth, standardization of sequencing methods, data interpretation, and reporting is a significant challenge. Quality control across different laboratories and platforms must be ensured. Sixth, there is a need for effective systems for long-term follow-up and care for individuals diagnosed with genetic conditions through newborn screening. Seventh, the psychosocial impact of genomic information on families, particularly information about risk for conditions that may not manifest until later in life, is not well understood and requires further study. Last, ensuring equitable access to genome sequencing in newborn screening is a significant challenge. There are concerns that the benefits of genome sequencing could be primarily accessible to those in higher-income brackets or in certain geographical locations, exacerbating existing health disparities.

**Cost-Effectiveness of Genomic Newborn Screening**

Establishing the cost-effectiveness of a health technology, known as the fourth hurdle, is critical to ensuring the financial sustainability of publicly funded health care insurance systems. Yet, demonstrating the value for money of newborn screening through genome sequencing is a formidable challenge. While genome sequencing has become increasingly accessible, it remains a high-cost procedure, especially when scaled to population-level applications. Its cost-effectiveness remains unclear, and proving this is essential before wide-scale implementation can be considered. At present, no health care systems formally recognize genome screening for reimbursement. This necessitates further research into the cost-effectiveness of genome sequencing for newborn screening across different countries, particularly in those with limited resources, such as China.4

However, substantial challenges arise when investigating the cost-effectiveness of genome sequencing. The multitude of hereditary conditions that could be revealed through genome sequencing, coupled with the downstream consequences and corresponding interventions, make it extremely difficult to develop an economic model that comprehensively captures the impact of genome sequencing. The debate over whether to incorporate both patient and physician preferences in the economic model, given that physicians often serve as gatekeepers for patients, adds another layer of complexity.5 One pragmatic approach might be to initially focus on the cost-effectiveness of secondary genomic findings.6 These findings could serve as an add-on economic module for the cost-effectiveness analysis of any genetic/genomic sequencing programs, providing a stepping stone toward understanding the broader economic implications of genome sequencing.
Toward Precision Public Health

Precision public health, an evolving field, is dedicated to delivering the “right intervention to the right population at the right time”7 to safeguard population health, such as using genomic newborn screening results for early interventions. The study by Chen et al1 illuminates the invaluable potential of genome sequencing in newborn screening, marking a significant stride toward the realization of precision public health in China. Nevertheless, it also underscores the complexities and considerations that require careful navigation before this technology can be seamlessly integrated into routine health care services. As we delve deeper into the realm of genomic medicine, it is paramount that we critically assess both the scientific and economic implications, thus ensuring that its benefits are fully optimized for all.

ARTICLE INFORMATION
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Corresponding Author: Shan Jiang, PhD, Macquarie University Centre for the Health Economy, Macquarie Business School and Australian Institute of Health Innovation, Macquarie University, Sydney, New South Wales, Australia (mingshan1018@gmail.com).

Author Affiliations: Shanghai Health Development Research Centre, Shanghai, China (Jiang, Wang); Macquarie University Centre for the Health Economy, Macquarie Business School and Australian Institute of Health Innovation, Macquarie University, Sydney, New South Wales, Australia (Jiang, Gu).

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