Enhancing Neonatal Intensive Care With Rapid Genome Sequencing
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Early diagnosis through genome sequencing can significantly transform clinical care for critically ill neonates. Traditional testing methods often fall short in accurately diagnosing genetic conditions due to overlapping symptoms in this age group. Genome sequencing, on the other hand, has proven more effective and has been used in various contexts for identifying hereditary conditions. The recent study by Marom et al. highlights the practicality and benefits of rapid trio genome sequencing (rtGS) in neonatal intensive care units (NICUs) in Israel. This study, involving medical genetics institutes and NICUs across the country, managed a rapid report turnaround of just 7 days, covering 130 neonates with suspected genetic disorders.

The study’s findings are quite significant. The rtGS technology identified various genetic conditions, including 12 chromosomal disorders, 52 monogenic disorders, and a range of variants of unknown significance (VUSs). Notably, these findings led to changes in medical management for 22% of the neonates (24 of 107). Results led to immediate precision medicine for 6 diagnosed infants and palliative care for 2 other infants. This demonstrates the effectiveness of rtGS in a public health care setting, suggesting its potential for wider adoption in routine neonatal care.

The Value of Genome Sequencing in Neonatal Intensive Care

The introduction of rtGS in neonatal intensive care represents a significant advancement, particularly in searching for pathogenic and pharmacogenomic variants. This technology empowers health care practitioners to apply precision medicine strategies, tailored to the genetic profiles of individual patients. Early identification of genetic disorders through rtGS enables timely and targeted interventions, markedly improving patient outcomes. The capability to diagnose and intervene at an early stage is a significant leap forward in neonatal intensive care, emphasizing the crucial role of rtGS in modern health care practices.

Moreover, the study demonstrated the value of rtGS in revealing secondary findings (SFs) and VUSs. SFs not only provide insights into potential health risks for the neonates undergoing genome sequencing, but also yield benefits for their immediate and extended family members, such as siblings, parents, and grandparents. On the basis of informed consent, these family members can examine their own carrier status of the SFs through cascade testing, thereby evaluating the potential health risks for themselves. Importantly, the identification of actionable SFs has the potential to prevent severe health outcomes later in life. In addition, the study also shed light on VUSs, interpreting them through pathogenicity prediction models. Managing VUSs remains a complex task, necessitating a delicate balance between the uncertainties in these findings and respect for patient autonomy. The interpretation of VUSs, as demonstrated in this study, consistently contributes to the broader genetic knowledge base, thereby enriching future diagnostic methodologies that potentially evolve from our current understanding of today’s VUSs.

Challenges in Implementation

Despite its clinical value, the primary obstacle to the application of genome sequencing in neonatal care is economic rather than technical. The cost-effectiveness of implementing genome sequencing in neonatal intensive care remains a complex and challenging issue.
First, many diseases potentially identifiable in neonates are rare and often lack comprehensive medical strategies for management. This limitation hinders the development of a complete economic model for sequencing, as the downstream implications of numerous health conditions remain uncertain.

Second, economic evaluations must consider the vast array of disorders detectable by this technology, necessitating the use of complex and large-scale models that encompass a wide range of conditions. Accurately accounting for the full spectrum of costs and outcomes of these conditions, including those arising from both the upstream and downstream events, such as future medical events, is extremely challenging.

Third, while the detection of SFs may improve the cost-effectiveness of genome sequencing for the neonates through cascade testing, it is worth noting that the disclosure of SFs should be on an informed consent basis. Accurately evaluating the impact of SFs on the cost-effectiveness of genome sequencing depends on our ability to ascertain and integrate the preferences of parents (the guardians of the neonates) and physicians (the gatekeepers of SFs) toward the disclosure of neonatal patients’ SFs into economic models. Without measuring and incorporating these preference parameters, it becomes challenging to precisely determine the extent to which the inclusion of SFs improves the cost-effectiveness of genome sequencing. Similarly, the detection of VUSs complicates the assessment of cost-effectiveness. Presently, the implications of VUSs are not fully understood, potentially causing stress for families and lowering their quality of life such that cost-effectiveness is reduced. However, as genetic knowledge advances, these VUSs may become actionable genomic findings, thereby improving the cost-effectiveness through the reanalysis of genetic data.

Additional challenges include the spillover effects on the lives and productivity of parents and caregivers of neonates, which are difficult to quantify but essential for comprehending the overall value of the technology. Furthermore, it is worth noting that the extreme heterogeneity among neonatal patients requires the utilization of dynamic simulation models to capture individual-specific pathways and accurately assess the benefits and costs of genome sequencing.

**Clinical Utility of Early Precision Medicine**

The emergence of precision medicine, made possible through rapid genome sequencing, marks a pivotal development in neonatal intensive care. This approach enables the timely detection and treatment of genetic disorders, potentially reshaping the life trajectory of neonatal patients. By offering tailored treatments at an early stage, genome sequencing not only enhances the quality of care but also holds the promise of improving long-term health outcomes, as evidenced by empirical studies. This advancement highlights the increasingly critical role of genome sequencing in the dynamic landscape of neonatal health care.
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REFERENCES