RAPID EXOME/GENOME SEQUENCING: IS IT A COST-EFECTIVE & VALUABLE TOOL FOR NICU?

Tuan Tran, MD, PhD., Unit of Genetic & Genomic Medicine, Family Hospital, Da Nang

In the article by Crawford et al., about “Diagnosing newborns with suspected mitochondrial disorders”, the early exome sequencing (eES), particularly "trio" eES, is cost-effective and often cost-minimizing compared to Typical Care (TC). Is this finding valid and robust?

Exome sequencing (ES) is the simultaneous sequencing of all ~20,000 genes in the human genome, and is increasingly a first line diagnostic test for children with multiple congenital anomalies, complex neurodevelopmental phenotypes, and other likely monogenic disorders. Numerous studies have demonstrated that ES provides a definitive molecular diagnosis in 30–50% of children with these phenotypes. However, ES is not yet in broad use in pediatric and neonatal intensive care units. Obstacles to the widespread use of ES in the ICU setting include the impression that the turnaround time (TAT) is too long to be useful in the critical care setting; complex test logistics, requiring pretest genetic counseling and samples from both parents; high test costs with poor reimbursement, and just emerging data on how ES can be used in the clinical management of these children.

The validity of this conclusion is supported by several factors, though it is subject to the inherent limitations of economic modeling.

1. Analysis of Validity: Why the Finding Holds

The study’s validity stems from its alignment with the "diagnostic odyssey" phenomenon. Mitochondrial disorders (MtD) are notoriously difficult to diagnose because they mimic other conditions.

- **Cost-Minimization through Speed:** The model correctly identifies that the primary "cost" in a neonatal intensive care unit (NICU) is time. By using eES as a first-line tool, the hospital avoids a "shotgun" approach of metabolic screens, muscle biopsies, and serial imaging.
- **The "Trio" Advantage:** The study finds trio sequencing (testing the infant and both parents) to be superior. This is valid because it allows for immediate filtering of benign variants inherited from healthy parents, significantly increasing the diagnostic yield and reducing the time spent in the NICU.
- **Sensitivity Analysis:** The authors performed Probabilistic Sensitivity Analysis (PSA), which showed that even when varying costs and probabilities, trio eES remained the most likely cost-effective strategy at a standard willingness-to-pay threshold.

2. Potential Caveats to Validity

While the conclusion is internally valid (the model works given the inputs), real-world validity depends on:

- **Turnaround Time (TAT):** For eES to be "early," results must return within days. If a hospital's lab takes 4–6 weeks, the cost-minimizing benefits of reduced NICU stay disappear.
- **Expertise Availability:** The model assumes that a diagnosis leads to a change in management (e.g., stopping futile treatments or starting specific supplements). Without a medical geneticist to interpret and act on results, the "value" of the diagnosis is diminished.

3. Supporting Evidence and References

The findings of Crawford et al. are corroborated by several larger-scale studies and clinical trials that demonstrate the clinical and economic utility of rapid genomic sequencing in the NICU.

- **Evidence of Clinical Utility:** A landmark study (the **NSIGHT1** trial) showed that rapid genomic sequencing resulted in a change in management for 57% of infants diagnosed, supporting the "value" used in Crawford's model.

  Reference: Freed, A. S., et al.(2020) The Impact of Rapid Exome Sequencing on Medical Management of Critically Ill Children. *The Journal of Pediatrics*, *226*, 202. https://doi.org/10.1016/j.jpeds.2020.06.020

- **Confirmation of Cost-Effectiveness:** Research from the **Project Baby Bear** initiative in California demonstrated that rapid whole-genome sequencing (WGS) saved approximately $2.5 million in healthcare costs across 178 infants by reducing NICU days and avoiding unnecessary surgeries.

  Reference: Dimmock D, et al. Project Baby Bear: Rapid precision care incorporating rWGS in 5 California children's hospitals demonstrates improved clinical outcomes and reduced costs of care. Am J Hum Genet. 2021 Jul 1;108(7):1231-1238. doi: 10.1016/j.ajhg.2021.05.008. Epub 2021 Jun 4. PMID: 34089648; PMCID: PMC8322922. https://pubmed.ncbi.nlm.nih.gov/34089648/

- **Yield Comparison (Trio vs. Singleton):** Meta-analyses confirm that trio sequencing increases diagnostic yield by roughly 10-15% over singleton sequencing by identifying *de novo* mutations more accurately.

  Reference: Clark, M. M., et al. (2019). Diagnosis of genetic diseases in seriously ill children by rapid whole-genome sequencing and automated phenotyping and interpretation. *Science*

Translational Medicine, *11*(489), eaat6177. https://pmc.ncbi.nlm.nih.gov/articles/PMC9512059/

- **Specific to Mitochondrial Disease:** The complexity of the mitochondrial genome and nuclear-encoded mitochondrial proteins makes exome sequencing a "gold standard" compared to older biochemical methods.

  Reference: Schlieben, L. D., & Prokisch, H. (2020). The Dimensions of Primary Mitochondrial Disorders. *Frontiers in Cell and Developmental Biology*, *8*, 600079. https://doi.org/10.3389/fcell.2020.600079

4. Conclusion

The finding is **valid**. The shift toward "genome-first" or "exome-first" diagnostics in the NICU is currently being adopted by major medical centers (such as Rady Children's and CHOP) specifically because it replicates the cost-savings and diagnostic efficiency modeled in this article.

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