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Is Rapid Exome Sequencing Standard of Care in the Neonatal and Pediatric Intensive Care Units?

In this volume of *The Journal*, Freed et al report the results of a 3-year trial of the clinical utility of rapid exome sequencing in critically ill children in the neonatal, pediatric, and cardiac intensive care units of a tertiary children's hospital.[1] The authors conclude that rapid exome sequencing should be considered standard of care for some such children. For readers who are not—yet—aficionados of rapid genomic medicine, let me provide some context for this provocative statement.

See related article, p 202

It is now possible to decode the human genome to clinical standards and make a diagnosis of a genetic disease in 19 hours using rapid whole-genome sequencing.[2] Here, genetic disease refers to single-locus disorders, not complex disorders: It includes both ~7000 Mendelian diseases and ~10 000 diseases associated with structural or chromosomal variants. As the name implies, rapid whole-genome sequencing involves decoding about 90% of a critically ill child's 6.4 billion nucleotide diploid nuclear genome and mitochondrial genome and using the child's clinical presentation to search that DNA sequence for the etiology underlying their presentation. This involves both ruling-in and ruling-out specific genetic differential diagnoses, as well as evaluating all known single-locus diseases. The rapid exome sequencing, used by Freed et al, is used interchangeably with rapid whole-genome sequencing but instead involves decoding only the ~60 million diploid nucleotides that are the ~180 000 exons of genes. Rapid exome sequencing identifies ~85% of the variants that cause genetic disease and costs ~75% that of rapid whole-genome sequencing.[2,3] Rapid genomic medicine (or rapid precision medicine) describes the nascent clinical discipline in which rapid whole-genome sequencing or rapid exome sequencing is used as a first-tier test during an intensive care unit stay, and inpatient management is guided by rapid genome sequence results. The turnaround time for such tests to merit the designation "rapid" is evolving. The mean turnaround time in the cohort described by Freed et al was 9 days. Speed is critically important: 12% of the patients reported by Freed et al died before return of results. However, optimal benefit from rapid whole-genome sequencing or rapid exome sequencing requires minimization of time from onset of symptoms to initiation of effective treatment, rather than just testing.[4]

Freed et al report that 43% of children receiving rapid exome sequencing were diagnosed with a genetic disease. This is consistent with other studies of rapid exome sequencing and rapid whole-genome sequencing (weighted average of 37% across 18 studies). Indeed, we have historically underdiagnosed genetic diseases greatly in infants and children in intensive care units. The current estimate is that the incidence of genetic diseases in infants in regional intensive care units is ~15%.[5] Furthermore, the presentations of children who benefit from rapid exome sequencing and rapid whole-genome sequencing are much broader than suspected. Freed et al found that one-half of cases had congenital anomalies with or without congenital heart defects, respiratory failure, or heart failure. Thus, rapid genomic medicine is poised to impact all pediatric subspecialties, not just medical genetics.

Freed et al report that 52% of children tested by rapid exome sequencing had a consequent change in management. This is somewhat greater than other studies (weighted average of 28% across 17 studies). One reason for this is that Freed et al included the clinical utility of negative results. A hitherto under-recognized value of rapid exome sequencing and rapid whole-genome sequencing is ability

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to rule out the presence of known pathogenic variants (mutations) in specific genetic differential diagnoses. We are on the cusp of an exciting era in which we can start to tell parents that their child has a "healthy" genome!

So, should rapid exome sequencing and rapid whole-genome sequencing indeed be considered the new standard of care for critically ill children in regional ICUs? The measured answer is yes, but with 3 qualifications: First, the indications for testing—currently presentations for which the etiology is unknown—require further refinement. Second, as Freed et al suggest, the focus should shift from testing to equipping ICU teams to routinely practice rapid genomic medicine. Third, the bizarre reality is that payors generally only reimburse outpatient genomic tests. Until neonatologists and intensivists pressure payors, rapid genomic medicine will continue to be restricted to innovator institutions. ■

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