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Rapid Whole Genome Sequencing and Fulfilling the Promise of Precision Pediatric Critical Care

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In this issue of *Pediatric Critical Care Medicine*, Sanford et al (1) demonstrate the use of whole genome sequencing (WGS) in the PICU on a clinically relevant time scale. Their work shows that in a retrospective cohort of 49 pediatric intensive care patients from 4 months to 17 years old, a genetic diagnosis was identified in 45% of children using rapid WGS. Notably, over 70% of cases were nominated for sequencing by their intensivist demonstrating their ability to identify children with a high likelihood of harboring disease-related mutations independent of consultant recommendations. Identified variants spanned a wide scope of pathologies including epilepsy, encephalopathy, cardiomyopathy, ventricular dysrhythmia, autoimmune, immunologic, and inflammatory disorders. In the neonatal population, WGS has achieved a diagnostic rate of 30–50% with measurable time and cost savings in approximately 50% of cases (2–5). The literature in older children is more limited; however, this work corroborates the findings in a retrospective cohort of 24 critically ill children in the pediatric and cardiac ICU with a mean age of 16 months where

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molecular diagnoses were made in 42% of children, although with a higher fraction of syndromic diagnoses (6).

Although many diseases commonly encountered in the PICU are influenced by genetic factors, including cardiac arrest (7), status epilepticus (8), acute lung injury (9), sepsis and shock (10), historically the precise loci conveying individual risk have been elusive. Under the “common disease, common variant” hypothesis, many early genome-wide association study efforts sought to link common “polymorphisms” with critical illness. Despite some successes, these findings have limited clinical utility, identifying alleles that confer only incremental risk for disease (11).

At the other end of the spectrum are low frequency (minor allele frequency [MAF] 1–5%) and rare (MAF < 1%) genetic variants hypothesized to explain a portion of the missing heritability not accounted for by polymorphisms. They are also posited to convey larger effects with greater impact on the extreme phenotypes (11). Yet, prior to the development of rapid, reliable and parallel next generation sequencing (NGS) alongside the informatic resources for interpretation, technical barriers and time to result limited evaluation of rare variants in ICU settings.

The promise of WGS to enable precision intensive care is only in its earliest stages. Although technically sound, WGS is at risk of false negatives and positives in interpretation. At the end of the informatic pipeline, false negatives occur as a result of atypical or pleiotropic illness presentations. Additionally, WGS does not obviate the need for functional verification of novel mutations. Individual patient results continue to be limited by the challenges frequently encountered in the study of rare diseases using NGS. False positives can occur due to erroneous classification of individual variants as pathogenic or likely pathogenic on the basis of a handful of cases. As a result of the burgeoning nature of precision medicine, currently, our diagnostic capacity far outstrips our prognostic ability. Additionally, the current emphasis on precision medicine places clinicians at risk of overemphasizing a single mutation and neglecting care environment, illness course, and genetic background. Although NGS technologies offer the capacity to interrogate gene-gene interactions, multigenic inheritance, and cases of epistasis and resilience (where the effect of a single disease variant can be mitigated by another), current clinical practice largely interprets individual variants in isolation. Therefore, clinicians should be careful not to make decisions based on a genetic diagnosis without appraisal of the complete clinical context.

Still, WGS’ promises are apparent. Compared with whole exome sequencing, WGS reads both protein-coding exons and regulatory regions, and avoids the time-consuming process of exon-targeted polymerase chain reaction library synthesis. It is also less prone to error in guanine-cytosine-rich regions and has been shown to be as reliable as gold standard Sanger sequencing in well-covered regions. WGS also has the capacity to detect copy number and intronic variants which have significant impact on disease (12). This allows for simultaneous evaluation of genetically heterogeneous monogenic disorders and atypical presentations. WGS can also extending beyond a priori differential diagnoses and be dynamically interrogated as clinical course, and genetic knowledge evolves.

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The strength of the work by Sanford et al (1) is in their operationalization of a “targeted phenotype-driven analysis,” that surmounts historical limitations of time to diagnosis and diagnostic relevance. The bioinformatics workflow for variant identification and analysis leverages the global efforts to sequence over 141,456 individuals to identify rare variants (13) as well as peer-reviewed literature evaluating the functional impact of mutations in the Human Phenotype Ontology and On Mendelian Inheritance in Man (14, 15). The protocol thereby allows for the generation of patient-specific candidate gene lists that can be evaluated for phenotypic similarity to the patient, limiting results to those genes reported in human disease and consistent with patterns of inheritance.

As a result, the group achieved a median turnaround time of 10 days (mean, 13.6 d; range, 1–56 d) with six of 17 (35%) of positive tests being available within 1 week (Supplemental Table 3 in [1]). Mestek-Boukhibar et al (6) reported similar results, with a median time to diagnosis of 8.5 days. As 43% of PICU deaths occur after the first week (16), these independent reports reproducibly show that turnaround time is no longer a practical barrier in the intensive care setting. Further, authors were able to show that WGS diagnosis impacted medical management of 14 children, one-third of all those tested. In four cases, genome-informed management decisions regarding anti-arrhythmic agent, administration of IV immunoglobulin, and pursuit of comfort measures were made during ICU stay. This is consistent with previous reports.

Moving forward, further research will be required to define ICU populations in whom WGS is indicated and expanding the roles of pharmacogenomics and complex genotype beyond Mendelian disease and its effect on critical illness (17). Still, Sanford et al (1) show that rapid WGS can be employed in the PICU to the direct clinical benefit of our patients and families today, ushering in a new era of precision critical care.

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