Clinical Implementation of Whole Genome Sequencing a Valuable Step Toward Personalized Care

Joseph E. Kerschner, MD

Three years have passed since a team of physicians and researchers at the Medical College of Wisconsin (MCW) and Children's Hospital of Wisconsin first used next generation sequencing to diagnose Nic Volker, a young boy battling an unknown and unresponsive intestinal disease. Based on the findings and emerging research that supported a link between his mutated XIAP gene and GI disease, the team proceeded with a cord blood transplant to resolve his debilitating symptoms.

The success of the treatment was transformative for Nic, and it had a similar, long-term impact on the Human and Molecular Genetics Center at MCW and on our appreciation for the importance of the clinical implementation of genome sequencing. This spring, MCW, in partnership with Children's Hospital of Wisconsin and Froedtert Hospital, became the first in the world to offer complete whole genome sequencing in an end-to-end clinical program.

This is not a pilot program; we are practicing this form of personalized medicine today with a focus on cases in which conventional medicine has failed to yield a diagnosis or elucidate the cause of disease symptoms. The genomic medicine clinic has sequenced 23 pediatric patients and 2 adult patients to date and obtained a definitive diagnosis in 27% of the cases. As more genomes are sequenced and we discover the significance of currently unknown genetic variants, the value of the field to identify causative agents of disease will multiply.

While MCW leverages the expertise of its faculty, software technology, and bioinformatics to pioneer clinical implementation, we recognize that the decreasing cost and the increasing speed of sequencing and analysis will result in many, if not most, hospitals and diagnostic laboratories implementing whole genome sequencing in the future. Practicing physicians will need competencies in using data from genome sequencing. For example, they will need to understand how to use the data, how to engage in meaningful conversations with their patients about the decisions they will face, and what to do with the new wealth and volume of information.

It is in the spirit of sharing knowledge with other practitioners that MCW's clinical genomics team, led by Howard Jacob, PhD, the Warren P. Knowles Professor in Human and Molecular Genetics and Director of the Human and Molecular Genetics Center, published a commentary July 17 in Science Translational Medicine on their experience converting a research sequencing lab into a fully functioning clinical program.[1] In "Genomics in Clinical Practice: Lessons from the Frontlines," the authors describe the practical, technological, economical, and ethical barriers to deploying clinical genomics with the hope that it may serve as a guide to peers considering the launch of similar programs.

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As physicians, we tend to think of cases in terms of "what can we do?" for a particular patient. Is the information we obtain from examination, family history, or testing clinically actionable? At MCW, our philosophy as it pertains to genomic sequencing is that a diagnosis is indispensable, even if better clinical outcomes cannot be realized.

In their commentary, Dr Jacob and his associates recount the case of a child experiencing liver failure. The team, however, discovered 2 mutations in a gene with known associations to incurable neurological deterioration, and neurological symptoms were beginning to manifest. The results were not clinically actionable with

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Dr Kerschner is dean of the medical school and executive vice president of the Medical College of Wisconsin.

respect to treatment, but the parents were able to make the best choice for their child's quality of life by declining a liver transplant, which also made the donor organ available for another patient.

Whole genome sequencing presents new ethical questions that have generated much debate, though little clear consensus. Determining what data is returned to the patient, their family, or their physician is among the most disputed subjects, particularly in light of guidelines published by the American College of Medical Genetics (ACMG) recommending that mutations discovered through clinical exome and genome sequencing on any of 57 genes associated with 55 specific diseases be reported to the ordering physician. ACMG recommends incidental findings — those unconnected with the original purpose for ordering the sequencing — be reported regardless of patient preferences.[2]

It is our belief and our practice that prior to ordering sequencing, the physician and the patient should determine whether secondary results will be returned and how the information will be managed.

In addition to considering what information the patient wants to receive, there are ethical ramifications surrounding who else is permitted to access the information. Disease heredity makes genomic results significant to a patient's biological family members, and they may or may not want to know the information. Protecting privacy is paramount, since a person's genome is more unique and personally identifying than a fingerprint.

The increasing clinical utility of genomic information, however, demands that we resolve to face these challenges. How does a sequencing clinic deliver 6.4 billion new data points to a doctor who averages less than 8 minutes of contact time per visit, and how is that information managed? Who pays for sequencing and under what conditions?

These questions require answers, but the medical value of the genome makes the effort fully worthwhile. As a quantitative family history, genome sequencing is a tool capable of improving the practice of medicine. It holds the power to help patients who have exhausted standard options for care. With further discovery and refinement, we envision its eventual efficacy in identifying disease risk and developing preventive medicine plans based on genetic risk to the benefit of patients everywhere.

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