On the Ethics of Clinical Whole Genome Sequencing of Children

In 2009, scientists here at the Medical College of Wisconsin (MCW) demonstrated the ability to apply whole exome sequencing (WES) to diagnose a pediatric patient with a rare digestive disease. WES enables the evaluation of the known protein coding DNA sequence of an individual. For the MCW patient, WES provided confirmation of an immune disorder,* thereby warranting treatment with a cord blood transplant: a treatment that saved his life but would not have been undertaken without that confirmation.1

This groundbreaking story was prominently featured in a series of Pulitzer Prize–winning stories in the Milwaukee Journal Sentinel, scholarly publications, and a segment of the PBS television program Nova. As predicted by Francis Collins,2 success of WES in cases like this has spurred interest in further application of this diagnostic tool. MCW has now expanded its program to include whole genome sequencing (WGS) and has since received requests from around the world to perform WGS. Additionally, in partnership with Children’s Hospital of Wisconsin, a pilot program of clinical WGS has recently been completed. As with most new technologies, WGS has sparked controversy concerning whether its clinical application should move forward or if this technology should be confined to the research domain until specific clinical policies are established. Here, we articulate reasons to continue moving forward with clinical WGS.

Until recently, the consensus approach to genetic testing and screening in general has reflected cautious limitations on the use of genetic testing on children. In particular, predictive genetic testing was seen as justified only when clear clinical indications called for genetic information. Previous Policy Statements by American Academy of Pediatrics (AAP)3 and American Society of Human Genetics/American College of Medical Genetics and Genomics (ACMG)4 recommended predictive genetic testing only where effective treatments, preventive interventions, or the ability to slow onset of a condition existed. The most recent Policy Statement and accompanying Technical Report, released jointly by AAP and ACMG,5,6 reflects a significant evolution in how these standards are understood. Although the Technical Report excludes WGS as beyond the scope of the report, the reason for this is that this currently constitutes genetic research: a characterization challenged by our own pilot clinical program and certain to be increasingly challenged with successful application of sequencing techniques in cases like that described at the beginning of this article.

*Causal variant was validated in a third-party clinical laboratory.
Previous Policy Statements by both AAP and ACMG were clear in their expectation that clinical indicators were to be understood solely in the context of the (prospective tested) child’s best interests narrowly defined, a definition made more clear through other Policy Statements (like that of genetic testing of adoptees) that refer to these more general pediatric testing guidelines.7 These guidelines point to the need for clear clinical indications that relate to the child’s health, welfare, or condition directly. Due in large part to lack of evidence supporting the actualization of potential harms, along with broader appreciation of psychosocial benefits that testing can provide, the latest statement contains an implied expansion of “clinical indication” to include consideration of parental interests and their potential effect on the child. Although the Technical Report accompanying the Policy Statement suggests this implied expansion to be limited (eg, cases described as “disabling” parental anxiety,6 p. 238) and fairly weak (stating at another point that “If the medical benefits of a test are uncertain, will not be realized until a later time, or do not clearly outweigh the medical risks, the justification for testing is less compelling”6 p. 235), it nonetheless represents an important evolution, by opening the door for parental interests to be incorporated into the assessment of appropriate testing and allowing discussion to shift to where the bar for parental interests should be set. We believe this is precisely where debate should be focused because we believe previous approaches to genetic testing in children gave inadequate consideration to parental interests, as we describe here. Because confounding cases of debilitating or life-threatening diseases understandably pressure clinicians to apply new, and available, medical technologies, we must recognize the myriad legitimate factors motivating the translation of WGS to the clinical setting. As a member of the advisory committee overseeing the clinical WGS pilot program discussed earlier, 1 author (TM) has seen the effect of pleas from families for access to this new, and available, diagnostic technology. As we have discussed elsewhere,8 such pleas are often discounted in health care policy as emotion-based and therefore less worthy of recognition as legitimate motives to go forward with intervention (although often readily accepted as reasons to refrain). However, there are legitimate reasons to recognize the motivational force of emotions felt by parents when confronted by the uncertainties that accompany a confounding debilitating disease suffered by their children, and the cycle of testing and re-testing inflicted on the children for whom diagnosis, and therefore settled treatment approach, has eluded attending physicians.

Nonetheless, there are concerns that should be recognized in the translation of WGS to clinical application. Chief among these are moral concerns about justice, disparities in access to both testing and intervention, and the differing risks and benefits that may result given different socioeconomic status or racial background. Indeed, the report accompanying the joint AAP/ACMG Policy Statement suggests less actual harm from testing than anticipated but also notes that the little evidence assembled disproportionately reflects white individuals of higher socioeconomic status. This itself is likely a reflection of disparities in access to new health care technologies. Far more effort is needed, then, to ensure that the significant potential benefits of WGS are fairly distributed and that risks are assessed through consideration of disparate circumstances and resources.

Within our own pilot program, we have responded to these concerns by forming an advisory committee to review each case for potential issues or concerns for using WGS, as well as potential benefit from its use. The limited number of cases for which WGS was then used serve as a starting point for policy to evolve through careful oversight and discussion of the potential benefits and risks of WGS, as well as what precedent might be established by each case. Our committee consisted of representatives from clinical medicine, genomics, ethics, hospital administration, and genetic counseling.

The MCW pilot clinical program was initiated as a means of providing a potential diagnosis in situations where this has previously eluded clinicians through testing via other mechanisms, and more targeted genetic testing has proven unsuccessful in providing additional answers. Without the use of WGS, these families are often without other options. In short, we believe that the potential clinical benefits of WGS, combined with the value placed on individual autonomy by our political society, should place the burden of argument on those who would stop use of this technology from moving forward.

REFERENCES
2. Collins FS. Genome-sequencing anniversary. Faces of the genome. Science. 2011;331 (6017):546


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