Published in final edited form as:

J Pediatr. 2011 December ; 159(6): 879–80.e1. doi:10.1016/j.jpeds.2011.07.035.

Ethical considerations associated with clinical use of next-generation sequencing in children

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Next-generation sequencing (NGS) technologies have dramatically dropped the cost of whole genome or exome (the 2% of the genome represented by coding regions) sequencing. The numbers are mind-boggling: It took \$3 billion to sequence the first human genome. Today, it costs less than \$10,000. Soon, many predict, it will cost \$1,000.¹ Targeted sequencing of particular panels of genes is even less expensive and has already made it possible to cost-effectively find mutations in any of hundreds of diseases in symptomatic children.^{2,3} These techniques may portend a new era in pediatric diagnosis.^{4,5,6}

A case report by Worthey et al illustrates how this might work.⁴ A child presented at 15 months of age with poor weight gain and a perianal abscess. His condition spiraled downward. He developed severe diarrhea, failure to thrive, persistent abscesses, and recurrent infections, and a presumptive diagnosis of Crohn's disease was made. Standard treatments were unsuccessful. At 30 months of age, he weighed 8.1 kg. His doctors decided to use next-generation sequencing of his entire exome "to facilitate a clinical diagnosis." They sought institutional review board (IRB) approval for this innovative diagnostic use of NGS. The IRB determined that this was "compassionate use," rather than research, because the primary purpose was for the clinical management of the patient, not to develop generalizable knowledge. Testing produced a mind-boggling amount of data: They discovered 16,124 nucleotide variants in the child's exome. Of these, 136 were felt potentially to be capable of causing a recessive illness, of which only one – in the X-linked inhibitor of apoptosis (*XIAP*) gene – was novel. It changed a highly conserved amino acid and was not found in the general population. The mother was a carrier of this mutation. Functional studies and literature evidence confirmed that the mutation was, in fact, pathogenic in this child.

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This successful use of whole exome sequencing raises both hopes and concerns. One question concerns the categorization of such testing for regulatory purposes. Is it research? The answer depends, in part, on the purposes for which it is being used. It may be used only with the goal of making a clinical diagnosis, or it may be used to investigate associations between newly discovered mutations and clinical disease. A commentary that accompanied the case report by Worthey et al noted, “To reach a diagnosis, we were compelled to use genomic technology that, at the time, was not a clinically validated test. This case stimulated many discussions within our group and institution on the boundary between research and clinical care. Many of the same issues were raised again during review of the manuscript.”⁷ Such testing also raises other regulatory issues. Research laboratories are not required to meet CLIA standards. But if results are to be reported to families, exome sequencing will need to be done to the quality standards demanded of clinical laboratories.³

One of the most difficult issues is that doctors must hypothesize about the connection between newly discovered genetic variants and the presenting condition in order to interpret the discovered genetic variants. For novel variants and genes not previously incriminated in human disease, these will necessarily be speculative. It is hard to know what, exactly, parents should be told about the results of testing or what clinical decisions should be made.

Worthey et al at the Medical College of Wisconsin decided to offer parents such information if the parents wanted it, even in cases where the information concerned carrier status or adult-onset disease. “We schedule at minimum annual follow-up in our genetics clinic for all families in which whole-genome sequencing has been performed and discuss further options for information disclosure at these meetings, in addition to providing options to the child when they reach the age of majority.”⁴ This approach is at odds with the current recommendations of the American Academy of Pediatrics which counsels that, “Unless there is anticipated benefit to the child, pediatricians should decline requests from parents or guardians to obtain predispositional genetic testing until the child has the capacity to make the choice.”⁸ The American Society of Human Genetics takes a similar stance, “Providers caring for children may discourage actions that may be adverse to the interests or the well-being of the child.”⁹

At Children’s Mercy Hospitals and Clinics, we have begun to offer NGS-based tests for routine diagnosis of autosomal and X-linked recessive conditions in children who have symptoms suggestive of a syndrome, but in whom conventional evaluation has not yielded a definitive diagnosis. We have struggled with questions about how to deal with the vast amounts of information that will be generated by such testing. Some of the questions – and our initial answers – are discussed below.

How should we educate doctors about the capabilities of the new tests and interpretation of results?

We are developing a continuing medical education program for doctors, genetic counselors, physician assistants, and nurse clinicians on our staff. As part of this program, healthcare decision makers will be offered the opportunity to undergo NGS-based carrier testing themselves. They will then be given their results in the setting of genetic counseling. We

will evaluate the results of both the testing and the educational program on doctors' knowledge about genetics, their attitudes and beliefs, and their emotional responses to the information.

Which children should be eligible for such testing?

Our initial plan is to offer the exome testing to children who either have symptoms and signs that suggest a Mendelian disorder but for whom the known disease gene(s) does not contain mutations, or to patients with a novel syndrome that has either an inheritance pattern that appears Mendelian or a presentation that is similar to, but distinct from, a known Mendelian disorder. We are also starting to evaluate the routine use of an NGS test for 592 recessive diseases as an alternative to conventional serial additive genetic testing.^{2,3}

How will we deal with novel variants of uncertain significance?

There are extensive guidelines about how to weigh the likely pathogenicity of novel variants in known disease genes and which types to report to patients. The new situation encountered in genome and exome testing is that of the identification of a likely pathogenic variant in a plausible gene that has not previously been connected with that disease or phenotype. As suggested, one solution is to perform additional studies to obtain functional evidence of causality before reaching conclusions^{4, 7}.

How will we deal with two sorts of “incidental findings” - carrier status for recessive conditions that are not relevant to the symptoms that generated the referral; or findings associated with adult-onset conditions?

Initially, we will not communicate either carrier status or findings unrelated to the clinical diagnosis. As the project goes on, we may offer such information to parents as part of a research study, with informed consent and careful evaluation of the consequences.

In summary, the availability of this new technology offers exciting possibilities to improve the care of children and families with genetic conditions. The benefits will only outweigh the harms, however, if we pay careful attention to the ethical nuances. Richard Sharp from the Department of Bioethics and Geonomic Medicine Institute of the Cleveland Clinic recently discussed the complexities of such testing, noting, “Given the number of mutational sites and disease associations examined, it will not be possible to counsel patients about the full range of findings that might result ... Nor will it be possible to counsel patients in advance about the potential clinical implications of identifying any one of several thousand findings that may be revealed.”¹⁰ Although Sharp's concerns are important, we should remember that, in many cases, we are only left with, at most, a few dozen relevant mutations, not thousands. Time – and further research – will tell whether patients and parents can be counseled in ways that are both effective and efficient.

As with all new technologies, anticipating the ultimate usefulness and the problems that will arise is difficult. The history of technologic innovation – looking at clocks, cars, robotic surgery, or the internet - is filled with stories of mistaken predictions about the usefulness or

the riskiness of an innovation.¹¹¹²¹³ Technological innovation always builds upon scientific development, requires political and moral vision, and catalyzes social changes that reshape the environment. Together, these forces determine the usefulness or harmfulness of each innovation. Conversations involving key stakeholders, such as parents and advocacy groups, clinicians, geneticists, ethicists, policy makers, and medical educators, will be important in shaping the future applications of new genetic technologies.

References

1. Mardis ER. Anticipating the \$1000 genome. *Genome Biol.* 2006; 7:112. [PubMed: 17224040]
2. Bell CJ, Dinwiddie DL, Miller NA, et al. Carrier testing for severe childhood recessive diseases by next-generation sequencing. *SciTransl Med.* 2011; 3:65ra4.
3. Kingsmore SF, Saunders CJ. Deep sequencing of patient genomes for disease diagnosis: When will it become routine? *SciTransl Med.* 2011; 3:87ps23.
4. Worthey EA, Mayer AN, Syverson GD, et al. Making a definitive diagnosis: successful clinical application of whole exome sequencing in a child with intractable inflammatory bowel disease. *Genet Med.* 2011 Mar; 13(3):255–62. [PubMed: 21173700]
5. Lupski JR, Reid JG, Gonzaga-Jauregui C, et al. Whole-genome sequencing in a patient with Charcot-Marie-Tooth neuropathy. *N Engl J Med.* 2010; 362:1181–1191. [PubMed: 20220177]
6. Choi M, Scholl UI, Ji W, et al. Genetic diagnosis by whole exome capture and massively parallel DNA sequencing. *Proc Natl Acad Sci U S A.* 2009; 106:19096–101. [PubMed: 19861545]
7. Mayer AN, Dimmock DP, Arca MJ, et al. A timely arrival for genomic medicine. *Gen Med.* 2011; 13:195–6.
8. American Academy of Pediatrics Committee on Bioethics. Ethical Issues with Genetic Testing in Pediatrics. *Pediatrics.* 2001; 107:1451–55. [PubMed: 11389275]
9. American Society of Human Genetics Policy Statement. Points to Consider: Ethical, Legal, and Psychosocial Implications of Genetic Testing in Children and Adolescents. *Am J Hum Gen.* 1995; 57:1233–41.
10. Sharp R. Downsizing genomic medicine: approaching the ethical complexity of whole-genome sequencing by starting small. *Genet Med.* 2011; 13:191–4. [PubMed: 21311340]
11. Cardwell, D. *Wheels, clocks and rockets: a history of technology.* W. W. Norton; New York: 2001.
12. Chiu, I. *The evolution from horse to automobile: a comparative international study.* Cambria Press; 2008.
13. Barry M. Documenting the genie's escape: robotic surgery. *Med Care.* 2011; 49:340–2. [PubMed: 21407029]