MAYO CLINIC

ORIGINAL ARTICLE

Whole-Exome Sequencing of 10 Scientists: Evaluation of the Process and Outcomes

Noralane M. Lindor, MD; Kimberly A. Schahl, MS, CGC; Kiley J. Johnson, MS, CGC; Katherine S. Hunt, MS, CGC; Kara A. Mensink, MS, CGC; Eric D. Wieben, PhD; Eric Klee, PhD; John L. Black, MD; W. Edward Highsmith Jr, PhD; Stephen N. Thibodeau, PhD; Matthew J. Ferber, PhD; Umut Aypar, PhD; Yuan Ji, PhD; Rondell P. Graham, MBBS; Alexander S. Fiksdal, MA; Vivek Sarangi, MS; Kelly E. Ormond, MS, CGC; Douglas L. Riegert-Johnson, MD; Tammy M. McAllister, MA; Gianrico Farrugia, MD; and Jennifer B. McCormick, PhD

Abstract

Objective: To understand motivations, educational needs, and concerns of individuals contemplating whole-exome sequencing (WES) and determine what amount of genetic information might be obtained by sequencing a generally healthy cohort so as to more effectively counsel future patients.

Patients and Methods: From 2012 to 2014, 40 medically educated, generally healthy scientists at Mayo Clinic were invited to have WES conducted on a research basis; 26 agreed to be in a drawing from which 10 participants were selected. The study involved pre- and posttest genetic counseling and completion of 4 surveys related to the experience and outcomes. Whole-exome sequencing was conducted on DNA from blood from each person.

Results: Most variants (76,305 per person; range, 74,505-77,387) were known benign allelic variants, variants in genes of unknown function, or variants of uncertain significance in genes of known function. The results of suspected pathogenic/pathogenic variants in Mendelian disorders and pharmacogenomic variants were disclosed. The mean number of suspected pathogenic/pathogenic variants was 2.2 per person (range, 1-4). Four pharmacogenomic genes were included for reporting; variants were found in 9 of 10 participants.

Conclusion: This study provides data that may be useful in establishing reality-based patient expectations, outlines specific points to cover during counseling, and increases confidence in the feasibility of providing adequate preparation and counseling for WES in generally healthy individuals.

 ■ Mayo Clin Proc. 2015;90(10):1327-1337

The advent of massively parallel sequencing technologies ("next-generation sequencing") has promoted whole-exome sequencing (WES) from the realm of futurist fantasy to clinical reality. Multiple laboratories now offer clinical WES for guiding cancer care, for resolving diagnostic dilemmas, or in the name of preventive health care. As our institution embraced the potential of WES for individualizing medicine, we recognized gaps in basic knowledge related to its clinical implementation. The literature falls short of providing a clear representation of how many interpretable variants one should counsel a patient to anticipate, which seems relevant to obtain meaningful informed consent for clinical testing. In addition, little empirical data exist on best practices and patient preferences regarding genetic counseling preparatory to WES. To attach data to these issues, we studied the exomes of 10 medically educated scientists under an institutional review board (IRB)–approved protocol. Because of their training, they may have a fuller comprehension of the limitations of WES testing and there might be less chance of doing harm as a result of our study. If WES were to be offered to patients, it seemed reasonable to see if Mayo Clinic scientists would voluntarily have this done on themselves. The outcomes of this study could be used to better prepare the

For editorial comment, see page 1311; for a related article, see page 1323

From the Department of Health Sciences Research (N.M.L.), Center for Individualized Medicine (N.M.L., K.S.H.), and Division of Hematology and Medical Oncology (K.S.H.), Mayo Clinic, Scottsdale, AZ;

Affiliations continued at the end of this article.

TABLE 1. Talking Points for Participant/Genetic Counselor Session 1

Contracting

- Explore/understand participants' motivations for this research project and what they hope to gain.
- Review of the overall process of this study, and review the original consent form as needed.

Family history

- Obtain comprehensive family history (pedigree inclusive of first-, second-, and third-degree relatives) from each patient.
- Assess family history for potential risks, and appropriate counseling will be provided according to the history.
- Inform participant of particular parts of the family history in which WES may be informative (things that appear to be due to single gene inheritance) and what parts of the family history are unlikely to provide information through WES (likely multifactorial or unknown etiology disorders).

General discussion on WES

- Give overview of basic genetic concepts (genes, chromosomes, etc). Be explicit in stating the amount of DNA sharing between first-, second-, third-degree relatives.
- Discuss all modes of inheritance with a disease example in mind/used:
  - Dominant (new mutation vs inherited).
  - Recessive (carrier vs affected).
  - X-linked (carrier vs affected).
  - Y-linked (male only).
  - Multifactorial (genes and environment).
  - Mitochondrial (not covered by this test).
- Educate re: WES
  - Describe the technology.
  - Note that approximately 90%-95% of the exome will be captured by this test. Perhaps 85% of DNA mutations currently known to cause disease will be assessed by WES.
    - How much of your particular exome was captured in your particular sample results will be told to you.
  - Note there are certain types of genetic variants/diseases that are not detectable by this type of sequencing:
    - Copy number variants, insertions, and deletions.
    - Trinucleotide repeat diseases.
    - Mitochondrial encoded diseases (noting most mitochondrial is nuclear encoded).
    - Epigenetic diseases.
    - X-linked recessive disorder with skewed X chromosome inactivation.
    - Intronic or promoter variants.
    - Common single-nucleotide polymorphisms with associations with disease (filtered out).
  - Information that if a gene alteration is found, then that does not mean that a known diagnosis, prognosis, or a treatment will be available if condition associated with the gene is known.
- Benefits noted:
  - There is *no guarantee* that you or your family will benefit from this test. In some people, no particularly interesting or useful or recognizable gene mutation may be found. This could be reassuring.
  - In some individuals or families, the genetic cause of disease may be identified through WES.
  - If a known genetic variation is identified for a particular disease, testing for other family members may be available.
  - In some instances, finding the genetic cause of disease may help in determining management for the condition, if it is available. There is *no guarantee* that this will occur.
- Limitations noted:
  - May identify nothing useful to you.
  - Will identify many DNA variants that we currently cannot interpret.
  - May identify things that we cannot treat.
  - May identify risks for other family members.
  - May miss looking at important regions of the genome because of the technology (listed above in test description).
  - Without studying other family members, there may be limitations to the interpretation of some variants.
  - Patented genes may need to be retested at an outside laboratory, incurring expense for you.

Continued on next page

Mayo Clin Proc. ■ October 2015;90(10):1327-1337 ■ http://dx.doi.org/10.1016/j.mayocp.2015.05.021
www.mayoclinicproceedings.org