Whole-Genome Sequencing in Healthy People

Noralane M. Lindor, MD; Stephen N. Thibodeau, PhD; and Wylie Burke, MD, PhD

CME Activity

Target Audience: The target audience for *Mayo Clinic Proceedings* is primarily internal medicine physicians and other clinicians who wish to advance their current knowledge of clinical medicine and who wish to stay abreast of advances in medical research.

Statement of Need: General internists and primary care physicians must maintain an extensive knowledge base on a wide variety of topics covering all body systems as well as common and uncommon disorders. *Mayo Clinic Proceedings* aims to leverage the expertise of its authors to help physicians understand best practices in diagnosis and management of conditions encountered in the clinical setting.

Accreditation: Mayo Clinic College of Medicine and Science is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Credit Statement: Mayo Clinic College of Medicine and Science designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit(s).*™ Physicians should claim only the credit commensurate with the extent of their participation in the activity.

MOC Credit Statement: Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 1 MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

Learning Objectives: On completion of this article, you should be able to (1) identify the currently accepted clinical applications of genomic testing as well as the challenges to interpretation of the data, that is, variants of uncertain clinical significance; (2) describe how whole-genome sequencing conducted in individuals with no current diagnostic issues compares and contrasts—both scientifically and ethically—with diagnostic testing; and (3) list several arguments both for and against whole-genome sequencing in healthy individuals and recognize that there are insufficient data to yet decide whether there is net benefit.

Disclosures: As a provider accredited by ACCME, Mayo Clinic College of Medicine and Science (Mayo School of Continuous Professional Development) must ensure balance, independence, objectivity, and scientific rigor in its educational activities. Course Director(s), Planning Committee members, Faculty, and all others who are in a position to control the content of this educational activity are required to disclose all relevant financial relationships with any commercial interest related to the subject matter of the educational activity. Safeguards against commercial bias have been put in place. Faculty also will disclose any off-label and/or investigational use of pharmaceuticals or instruments discussed in their presentation. Disclosure of this information will be published in course materials so that those participants in the activity may formulate their own judgments regarding the presentation.

In their editorial and administrative roles, William L. Lanier, Jr, MD, Terry L. Jopke, Kimberly D. Sankey, and Nicki M. Smith, MPA, have control of the content of this program but have no relevant financial relationship(s) with industry.

The authors report no competing interests.

Method of Participation: In order to claim credit, participants must complete the following:

1. Read the activity.
2. Complete the online CME Test and Evaluation. Participants must achieve a score of 80% on the CME Test. One retake is allowed.

Visit www.mayoclinicproceedings.org, select CME, and then select CME articles to locate this article online to access the online process. On successful completion of the online test and evaluation, you can instantly download and print your certificate of credit.

Estimated Time: The estimated time to complete each article is approximately 1 hour.

Hardware/Software: PC or MAC with Internet access.

Date of Release: 1/1/2017

Expiration Date: 12/31/2018 (Credit can no longer be offered after it has passed the expiration date.)

Privacy Policy: http://www.mayoclinic.org/global/privacy.html

Questions? Contact dletcsupport@mayo.edu.

For editorial comment, see page 4

From the Department of Health Sciences Research, Mayo Clinic, Scottsdale, AZ, and Center for Individualized Medicine, Mayo Clinic, Rochester, MN (N.M.L.); Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN (S.N.T.); and Department of Bioethics and Humanities and Department of Medicine (Medical Genetics), Fred Hutchinson Cancer Research Center, University of Washington, Seattle, WA (W.B.).

Abstract

Recent technological advances have radically changed genetic testing from an expensive and burdensome undertaking to a rapid and less costly option for many purposes. The utility of "next-generation" sequencing has been found to establish the diagnosis for hundreds of genetic disorders, to assess pharmacogenomic variants, and to identify treatable targets within malignant neoplasms. The ready availability of genomic information has led to the question of whether there would be clinical benefit of sequencing the genome of individuals who are not seeking a diagnosis, that is, genomic screening in generally healthy people, to provide anticipatory insights for their health care. Little research has been conducted in this area. We examine the considerable unresolved scientific and ethical issues encountered when considering whole-genome sequencing of healthy people.

 ■ Mayo Clin Proc. 2017;92(1):159-172

Precision medicine is a term recently made mainstream by President Barack Obama's 2015 State of the Union address,[1] in which he announced a major new initiative by that name that proposes moving from a "one-size-fits-all" approach to more individualized health care. The Precision Medicine Initiative will develop a voluntary national research cohort of 1 million or more volunteers to propel our understanding of health and disease. The long-term goal of this project will be to collect multiple types

of data, including comprehensive assessment of genotypes, to deepen current understanding of how our genetic differences result in observable differences in health and disease, so that health care providers can provide recommendations based on more precise estimates of personal risks. An initiative of this scale is now feasible because of recent major technological advances in genetic sequencing and bioinformatics.

Precision medicine is not synonymous with whole-genome sequencing (WGS), but rather seeks application of genomic technologies as a key strategy in tailoring care to maximize benefit and minimize harm to individuals. At some point, sufficient experience will be accrued to know how to "right-size" genomic testing to achieve this lofty goal for the population as a whole. Gaining experience from pan-genomic testing in the near term, in the form of WGS, may identify that subset of genomic analysis that is most rational and cost-effective for individualized care, but empirical data are needed to establish these boundaries. As evident from a description of the challenges to follow, WGS as a health-promoting strategy is a new journey in progress. This article will focus narrowly on WGS in healthy individuals as 1 potential branch of this journey.

THE HUMAN GENOME PROJECT

The Human Genome Project (HGP), the world's largest collaborative biological project, was launched in 1990 and was officially completed in 2003. The National Institutes of Health–funded sequencing of just a single human genome cost US$3 billion and involved 20 institutions in the United States, United Kingdom, Japan, France, Germany, and China.[2] Simultaneously, Celera Genomics Corporation, a private company lead by Dr Craig Venter, began human genome sequencing in 1998 and completed their project at the same time at one-tenth the cost of the public project.[3] In 2000, President Bill Clinton and UK Prime Minister Tony Blair jointly announced the completion of a rough draft of the human genome: "Today we are learning the language in which God created life" and expressed hopes that we "accept the responsibility to make these advances work for all our people in all our countries for the common good of all humankind."[4,5] Both Dr Francis Collins, Director of the HGP, and Dr Venter were on stage for the announcement of this monumental task, illustrating visually the public and private contributions that have pushed the frontiers on genomics.

The cost of sequencing those first human genomes using variations of the 1970s technology of Sanger sequencing (sometimes called first-generation sequencing) was not merely staggering but prohibitive for any large-scale use. Given the limitations and competition for health care dollars, introduction of new technologies must always consider costs vs value-added. Fortunately, an answer to the extraordinary costs of early genome sequencing was in the wings via a new technology—next-generation sequencing (also known as next-gen or massively parallel sequencing). *Next-gen sequencing* refers to several innovations involving DNA template preparation, sequencing of hundreds of millions to billions of individual DNA templates (hence, "massively parallel"), image capture, followed by sequence alignments and assembly and variant detection (Figure 1).[6] By 2013, the cost of WGS was estimated by the Human Research Genome Institute to be about US$5000 per genome.[7] Compared to the original HGP, the director of the Clinical Genome Service at Stanford University (USA) illustrated the plummeting of costs as the equivalent of a US$400,000 Ferrari now selling for 40 cents.[8] Today, WGS is available for as little as US$999 per genome (https://www.veritasgenetics.com/), which would be 8 cents on that US$400,000 car. Thus, issues of cost have been addressed in dramatic fashion but demonstrations of value-added for health care remain unproven.

Still in its infancy, the ability to sequence the entire genome has opened a new world in the quest to understand human disease and normal variability in the population. Although next-gen sequencing is becoming readily available and quite routine, we have barely scratched the surface of our understanding of the human genome. Most of the genome remains a mystery, and the ability to interpret the effect and importance of most genetic variants remains extremely limited.

Mayo Clin Proc. ■ January 2017;92(1):159-172 ■ http://dx.doi.org/10.1016/j.mayocp.2016.10.019
www.mayoclinicproceedings.org