MAYO CLINIC

SPECIAL ARTICLE

Reconciling Opportunistic and Population Screening in Clinical Genomics

Kyle B. Brothers, MD, PhD; Jason L. Vassy, MD, MPH, SM; and Robert C. Green, MD, MPH

Abstract

Opportunistic genomic screening is becoming increasingly common as laboratories adopt recommendations to report secondary genomic findings. In parallel, interest in using genome sequencing as a population screening test has grown rapidly. We consider here 3 potential applications of genome sequencing for preventive medicine: (1) provider-ordered predispositional testing in healthy adults, (2) indication-based testing with opportunistic screening of secondary results, and (3) population screening in the public health context. We conclude that despite superficial similarities, there are important and fundamental differences in the way medical risks and benefits can be addressed in these 3 contexts. Recommendations to report secondary genomic findings should not be interpreted as an endorsement of population genomic screening. Ongoing work is developing the evidence that will be needed to fully justify current and future initiatives in population genomic screening. Ongoing work is developing the evidence that will be needed to fully justify current and future initiatives in population genomic screening.

 ■ Mayo Clin Proc. 2019;94(1):103-109

Interest in using genome sequencing in health care is growing rapidly. Genome sequencing technologies, including whole-exome sequencing and whole-genome sequencing, are increasingly being used in clinical settings to diagnose patients with rare and undiagnosed conditions[1] and to personalize cancer treatment.[2,3] Because sequencing may yield incidental findings of medical importance, formal recommendations were issued in 2013 by the American College of Genetics and Genomics (ACMG) that patients who have undergone sequencing for one clinical indication should be offered secondary results for other actionable conditions.[4,5] These recommendations were reinforced in an update that revised the gene list, but upheld all the central principles of these recommendations.[6] Most clinical laboratories performing genome sequencing in the United States now report returning secondary findings based on these ACMG recommendations, performing opportunistic screening for actionable risk variants that may inform disease prevention.

-At the same time, a number of companies, practitioners, and academic medical centers have begun to offer sequencing to healthy individuals or to research participants with the logic that screening for at least the ACMG list of actionable conditions may be beneficial.[7,8] This trend has been driven by an emphasis on medical care that is *proactive* rather than *reactive*, by the exuberant approach of companies seeking to expand the market for genetic testing, and by emerging evidence that some mutations in the general population can be associated with later development of related phenotypes.[9] Nonetheless, genome sequencing has not been widely adopted as a screening test, and population screening of healthy individuals with sequencing remains controversial.[10-14] Population screening with sequencing is neither recommended nor proscribed by the ACMG,[15] and it is not among the preventive screening measures recommended by bodies such as the US Preventive Services Task Force.[16]

These conflicting perspectives have understandably created confusion. If experts

For editorial comment, see page 7

From the Department of Pediatrics, University of Louisville School of Medicine, Louisville, KY (K.B.B.); Section of General Internal Medicine, VA Boston Healthcare System (J.L.V.), Division of General Medicine and Primary Care, Department of Medicine, Brigham and Women's Hospital (J.L.V.), and Division of Genetics, Department of Medicine, Brigham and Women's Hospital (J.L.V., R.C.G.), Boston, MA; Harvard Medical School, Boston, MA (J.L.V., R.C.G.); and Broad Institute of MIT and Harvard, Cambridge, MA (R.C.G.).

recommend offering patients secondary results related to conditions for which they have low prior probability when they undergo sequencing for another purpose (opportunistic screening), then why should not healthy individuals be offered genome sequencing as part of preventive health care (population screening)?

The most important explanation for this distinction is the fundamental difference in the way medical risks and benefits are addressed in opportunistic vs population screening. To clarify this difference, we will examine 3 potential applications of genomic technologies to preventive medicine: (1) provider-ordered predispositional testing in healthy adults, (2) indication-based testing with opportunistic screening of secondary results, and (3) population screening in the public health context. Because these 3 applications share a superficial similarity, the use of genomic testing to guide preventive health care, it is not surprising that many have interpreted the ACMG recommendations on secondary findings as an endorsement of genome-guided screening in all these contexts. We suggest, however, that these 3 applications of genomic technologies are not as similar as they first appear. Each takes place in a particular setting where context-specific strategies are used to mitigate risk and maximize benefit.

MITIGATING RISK AND MAXIMIZING BENEFIT

Like other medical interventions, clinical tests—whether diagnostic or preventive—involve some risk of harm. The most conspicuous harms from clinical tests are false-positive results, which may lead to actions or procedures that may cause unintended morbidity and mortality. The risk for false-positive results is particularly high in genomic testing. The extremely large number of sites interrogated with exome or genome sequencing increases the statistical likelihood that 1 or more analytic false-positive results will be generated.[17]

But even if all variant calls are confirmed by an orthogonal technology as some have recommended, genomic variants may be interpreted inaccurately or they may be interpreted accurately but the disease condition may never manifest. Rare or novel genomic variants occur commonly in human genomes,[18] and may initially be classified as pathogenic only to later be proven benign.[19-21] Newer large-scale population-based sequencing data are demonstrating that the penetrance of many common pathogenic variants is lower than initially estimated.[22] In practice, then, many pathogenic variants will be returned to individuals who will never develop the medical condition.

False-negative results are also relatively common in genomic tests and raise important concerns. Many genes contributing to risk for specific conditions have not yet been identified, and the pathogenicity of many variants within genes that are clearly associated with disease is often uncertain. In addition, current analytical pipelines can miss pathogenic variants because of structural variation or changes in regulatory regions.[23]

These potential blind spots contribute to a well-known challenge in clinical genetics: false reassurance. There is a dramatic difference between telling a patient they are not at risk for a condition and telling them no genetic factors that increase their risk were identified, but the distinction between these messages may be muddled by providers or misunderstood by patients.[24,25] As a result, patients can be left believing that they are not at increased risk for a condition, or even that they are entirely free of risk for that condition. This false reassurance may cause patients to forego other types of screening that would normally be recommended, including mammograms and colonoscopies.[24] If this happens, they might have been better off having never had a genomic screen.

These factors remind us that genomic tests are far less deterministic than is generally believed and therefore not *exceptional*, but that they reflect the common clinical and public health challenge of balancing medical harms with medical benefits.[26] Fortunately, experience in other domains of screening has led to the development of effective practices that can be used to maximize benefits and minimize risks when performing genomic testing.

Mayo Clin Proc. ■ January 2019;94(1):103-109 ■ https://doi.org/10.1016/j.mayocp.2018.08.028
www.mayoclinicproceedings.org

In the previous era where genetic testing was scarce and expensive, the most important of these strategies has been the careful selection of which patients would undergo testing on the basis of signs, symptoms, and family history. When clinical tests are used in patients with relevant signs and symptoms (indication-based testing), there is an increased likelihood that positive findings are accurate. In other words, when the prior probability of a positive result is high, the rate of false-positive results is correspondingly low.[27] But in the modern era where genetic testing is becoming inexpensive and abundant, and will increasingly be used for screening, new strategies will be needed. For example, detection of risk variants may need to be followed up by iterative attention to focused physical examination or diagnostic testing (so-called deep phenotyping), or to family history, because we now know that unanticipated findings often prompt unexpected detection of both.[28,29]

A second strategy to help mitigate risk relies on the context where testing takes place. Indication-driven genomic testing and provider-ordered preventive testing both take place in clinical contexts. This setting is typified by the opportunity for a shared decision-making process between patients and providers. Before testing, this type of decision-making process allows patients and providers to carefully consider how testing would address, or fail to address, the needs and circumstances of the patient. Once results are returned, shared decision making allows providers and the individuals receiving genomic results to make a considered and well-informed response to these findings accounting for the possibility of false positives. This one-on-one relationship provides a number of other benefits that potentially increase the value and decrease the risks of genomic sequencing. For example, providers have the opportunity to carefully explain the technical limitations of genomic sequencing so that false reassurance is minimized, as well as an opportunity to discuss the implications of results for family members who might carry the same variants.

Population screening, on the other hand, typically takes place in a public health context. Rather than using a shared decision-making process to select patients for testing, public health screening is generally conceptualized as applicable to everyone, often without the direct involvement of a personal health care provider. In this respect, the decision to screen is driven primarily by a protocol rather than shared decision making. In newborn screening, for example, testing is guided by state- and hospital-level protocols that direct health care facilities to screen virtually all newborns. Because this approach does not use individualized decision making to maximize benefits, the focus is on (1) ensuring that screening efforts are supported by substantial evidence for benefit within the screened population and (2) providing a coordinated infrastructure, including standard operating procedures and public health workers, to maximize the chances that the actions clinicians, patients, and families take in response to test results will bring net benefit. The infrastructure created in each state to support newborn screening programs is a good example of the substantial work that is required to ensure that population screening efforts provide more benefit than harm.

Indication-Driven Clinical Testing and Opportunistic Screening

In current clinical practice, genomic sequencing technologies are used far more frequently to answer specific clinical questions than they are to screen healthy individuals for conditions they have not yet developed. Sequencing may be performed, for example, to identify the molecular cause of an undiagnosed disease.[1] When sequencing is used to address a specific clinical indication, the provider and the patient must also decide whether to search for any secondary findings, that is, those results not directly related to the primary motivation for testing, for opportunistic screening. This is not a straightforward decision. Although the clinical indication that provided the motivation for testing will increase the likelihood that genomic variants related to this condition are true positives, these patients are similar to unselected populations

when it comes to their prior probability for having unrelated conditions.

Current ACMG recommendations on this question reflect medical practice in other areas of medicine in that clinicians should select appropriate patients for testing and should choose the most focused and validated testing technology that will address the clinical question. The ACMG recommendations suggest that once laboratory data are generated, the default practice should be to also analyze at least a minimal list of genes where discovery of a known mutation could provide patients and providers with information that would change clinical management.[4,26]

As in other diagnostic settings, there may be compelling reasons to respect a patient's preference not to receive secondary findings. The physician and patient could decide, for example, to decline the disclosure of secondary findings data because the patient's medical condition would prevent secondary findings from being useful (such as when a patient is critically ill). Alternatively, the patient's psychological state or past experiences may have resulted in a preference not to learn certain types of probabilistic risk information.

PROVIDER-ORDERED PREVENTIVE TESTING IN HEALTHY ADULTS

The question of whether to *analyze for and disclose* secondary results is fundamentally different from the question of whether to *initiate* genomic testing exclusively for the purposes of prevention. When a clinician and patient (or parents) are considering genomic testing to address a specific indication, such as identifying a diagnosis for a child with intellectual disability, the anticipated value from addressing this clinical question fulfills the imperative to minimize harm by only ordering those tests that provide potential benefits that outweigh the risks. Once that decision is made, the question of whether to also analyze for secondary findings generates a different decision structure. Whole-exome and whole-genome sequencing create large amounts of raw sequence data, and computer algorithms must then be used to call variants discoverable in this raw data. Because the decision to generate the raw data needed to call variants for secondary findings has already been made, the decision is reframed as one about how to responsibly analyze that data.

In comparison, when apparently healthy individuals want to pursue genomic screening to improve their health, there is no primary clinical question or indication that provides a clear probability of benefit. Although the risks and benefits associated with specific preventive genomic results may be relatively well defined, the overall balance of risks and benefits associated with preventive genomic testing is not yet well understood. Given current evidence, then, it is not clear that selecting genomic screening to address the health care needs of a healthy individual would meet a prudent standard for minimizing harms and maximizing benefits.

What if an apparently healthy adult individual and her provider, engaging in a shared decision-making process, decide that predispositional genome sequencing is an appropriate test to address her health goals? In this context, providers should engage with their patients in a process to consider which preventive tests and interventions are most likely to provide the health benefits they are seeking while minimizing potential harms. For persons especially focused on genomic screening, providers should provide appropriate counseling on the possible risks and benefits.[15] And in rare cases, when the individual's circumstances indicate a foreseeable risk of harm, the provider should be willing to decline the request for sequencing (or recommend against it if the patient will be pursuing consumer-directed genetic testing service).

Given the current state of evidence, translational research studies provide a useful opportunity for interested institutions and providers to explore the potential for genomic screening to improve preventive care in healthy persons.[30] Offering screening in a hybrid clinical/research setting, such as the MedSeq Project,[14] provides the opportunity to engage patients in an appropriate informed consent process. Perhaps most importantly, this approach, in conjunction with transinstitutional efforts like the National Institutes of Health–funded Clinical Sequencing and Exploratory Research

Mayo Clin Proc. ■ January 2019;94(1):103-109 ■ https://doi.org/10.1016/j.mayocp.2018.08.028
www.mayoclinicproceedings.org

consortium,[31] will provide the opportunity to develop the evidence base to establish whether this technology really does carry utility as a screening test.

POPULATION SCREENING IN THE PUBLIC HEALTH CONTEXT

In contrast with the clinical context, shared decision making does not play as prominent a role in the public health context in decisions to pursue testing. In the public health context, decisions to screen are made at the population level, and are based on a careful consideration of the risks and benefits of the screening test across the population, ideally on the strength of substantial empirical evidence. Local efforts are focused on maximizing access and uptake rather than a careful consideration of individual risks and benefits.

Population screening does not always result in net benefit. In a well-known example, hundreds of Japanese children underwent unnecessary surgery when a national program designed to screen infants' urine to identify neuroblastoma cases resulted in substantial overdiagnosis of this condition.[32] Even though clinical experience supported the assumption that screening would provide benefit, and an appropriate infrastructure was developed to bolster this effort, the leaders of this effort ultimately concluded that their experience "underscores the importance of rigorous evaluation of potential benefit and harm before a screening program is adopted as public policy."[32]

At the moment, we simply do not know whether the benefits of genomic screening in the general population will outweigh its potential harms. Before we can prudently recommend genomic screening in the public health context, it will be necessary to not only develop a sophisticated infrastructure capable of evaluating and applying high standards of evidence across a broad range of genomic variants, addressing frequent false positives, and ensuring safe and appropriate responses to findings, but also to demonstrate that such an infrastructure is adequate to mitigate harm. Until that evidence exists, professional and regulatory bodies such as the ACMG and the Food and Drug Administration should continue to encourage restraint in the application of genomic screens in the public health setting, and funding agencies should continue to support research that rigorously evaluates the risks and benefits of this new technology across multiple clinical and public health contexts.

Although a detailed discussion of consumer-directed genetic testing is beyond the scope of this article, it is worth mentioning that many of the factors that raise concerns about pursuing population genomic screening in the public health setting could also be raised in discussing consumer-directed genetic testing. Some of these companies offer access to a genetic counselor, and increasingly health care providers report being asked to provide help with interpreting these results.[33,34] By its nature, however, consumer-directed genetic testing is not typically offered as a part of either a shared decision-making process with a health care provider or in the context of a public health infrastructure designed to maximize benefits and minimize harms. These factors raise significant concerns that consumer-directed genetic testing may create risks that could otherwise have been mitigated had genomic sequencing been pursued in a clinical, or even a public health, context. However, the policy considerations for consumer-directed genetic testing are quite different from the 3 potential applications of genomic technologies to preventive medicine discussed in this article. In particular, decisions about the implementation of genomic sequencing in clinical and public health contexts fall within the scope of judgments that health care providers, health care systems, payers, and professional organizations need make about their own values and priorities.

CONCLUSION

There can be little question that preventing an illness would be preferable to reacting to an illness once it has developed. This is a powerful narrative that has driven considerable work in recent years to reorient health care to be more proactive, and genomics is rightly playing an important role in this movement. However, not all proactive efforts are equal. Some preventive applications of genetic testing will reveal predispositions that can be used to take action and forestall

devastating health effects. Others could lead patients and providers on a wild goose chase, possibly resulting in more iatrogenic harm or cost than preventive benefit. Among the thousands of results that can be generated using genome sequencing, we do not yet know which results fall into which category.

As investigators continue to study the downstream implications of clinical genome sequencing,[9] the present uncertainty about the benefits and harms of genomic testing will diminish, and it will become possible for providers, patients, and policymakers to make better-informed decisions about the way these tests should be applied to preventive health care. For the present, however, it remains critical to remember the important differences between clinical and public health contexts and the parallel distinction between opportunistic screening on someone who has already been tested for a medical indication and population screening on an individual who has no clinical indication for testing.

Abbreviations and Acronyms: **ACMG** = American College of Medical Genetics and Genomics

Grant Support: This work was supported by grant UM1 HG007301 (K.B.B.), grant U01 HG006500 (J.L.V. and R.C.G.), and grant U01 HG007307 from the Clinical Sequencing Exploratory Research (CSER) Consortium (http://cser-consortium.org), and by Career Development Award IK2-CX001262 (J.L.V.) from the US Department of Veterans Affairs Clinical Sciences Research and Development Service. CSER is funded by the National Institutes of Health's National Human Genome Research Institute and National Cancer Institute. The contents do not necessarily represent the views of the National Institutes of Health or Veterans Affairs.

Potential Competing Interests: Dr Green receives compensation for advising AIA, Applied Therapeutics, Helix, Ohana, OptraHealth, Prudential and Veritas; and is cofounder and advisor to Genome Medical, Inc, a technology and services company providing genetics expertise to patients, providers, employers and care systems. The other authors report no competing interests.

Correspondence: Address to Kyle B. Brothers, MD, PhD, Kosair Charities Pediatric Clinical Research Unit, Department of Pediatrics, 231 East Chestnut St, N-97, Louisville, KY 40202 (kyle.brothers@louisville.edu).

REFERENCES

1. Biesecker LG, Green RC. Diagnostic clinical genome and exome sequencing. *N Engl J Med*. 2014;370(25):2418-2425.
2. Offit K. Decade in review–genomics: a decade of discovery in cancer genomics. *Nat Rev Clin Oncol*. 2014;11(11):632-634.
3. Weng L, Zhang L, Peng Y, Huang RS. Pharmacogenetics and pharmacogenomics: a bridge to individualized cancer therapy. *Pharmacogenomics*. 2013;14(3):315-324.
4. Green RC, Berg JS, Grody WW, et al. American College of Medical Genetics and Genomics. ACMG recommendations for reporting of incidental findings in clinical exome and genome sequencing. *Genet Med*. 2013;15(7):565-574.
5. ACMG Board of Directors. ACMG policy statement: updated recommendations regarding analysis and reporting of secondary findings in clinical genome-scale sequencing. *Genet Med*. 2015;17(1):68-69.
6. Kalia SS, Adelman K, Bale SJ, et al. Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics. *Genet Med*. 2017;19(2):249-255.
7. Scripps Center for Executive Health—Genetic testing. Vol 2015. San Diego, CA: Scripps Health; 2015.
8. Linderman MD, Nielsen DE, Green RC. Personal genome sequencing in ostensibly healthy individuals and the PeopleSeq Consortium. *J Pers Med*. 2016;6(2). https://doi.org/10.3390/jpm6020014. pii: E14.
9. Natarajan P, Gold NB, Bick AG, et al. Aggregate penetrance of genomic variants for actionable disorders in European and African Americans. *Sci Transl Med*. 2016;8(364):364ra151.
10. Adams MC, Evans JP, Henderson GE, Berg JS. The promise and peril of genomic screening in the general population. *Genet Med*. 2016;18(6):593-599.
11. Foulkes WD, Knoppers BM, Turnbull C. Population genetic testing for cancer susceptibility: founder mutations to genomes. *Nat Rev Clin Oncol*. 2016;13(1):41-54.
12. Adams MC, Berg JS, Pearlman MD, Vora NL. Look before you leap: genomic screening in obstetrics and gynecology. *Obstet Gynecol*. 2015;125(6):1299-1305.
13. Rothstein MA. Currents in contemporary bioethics: the case against precipitous, population-wide, whole-genome sequencing. *J Law Med Ethics*. 2012;40(3):682-689.
14. Vassy JL, Christensen KD, Schonman EF, et al; MedSeq Project. The impact of whole-genome sequencing on the primary care and outcomes of healthy adult patients: a pilot randomized trial [published online ahead of print June 27, 2017]. *Ann Intern Med*. https://doi.org/10.7326/M17-0188.
15. ACMG Board of Directors. Points to consider in the clinical application of genomic sequencing. *Genet Med*. 2012;14(8):759-761.
16. Home - U.S. Preventive Services Task Force. Vol 2016. Rockville, MD: USPSTF Program Office; 2014.
17. Kohane IS, Masys DR, Altman RB. The incidentalome: a threat to genomic medicine. *JAMA*. 2006;296(2):212-215. Erratum in JAMA. 2006;296(12):1466.
18. Nelson MR, Wegmann D, Ehm MG, et al. An abundance of rare functional variants in 202 drug target genes sequenced in 14,002 people. *Science*. 2012;337(6090):100-104.
19. Berg JS, Adams M, Nassar N, et al. An informatics approach to analyzing the incidentalome. *Genet Med*. 2013;15(1):36-44.
20. Manrai AK, Funke BH, Rehm HL, et al. Genetic misdiagnoses and the potential for health disparities. *N Engl J Med*. 2016;375(7):655-665.
21. Van Driest SL, Wells QS, Stallings S, et al. Association of arrhythmia-related genetic variants with phenotypes documented in electronic medical records. *JAMA*. 2016;315(1):47-57.
22. Cassa CA, Tong MY, Jordan DM. Large numbers of genetic variants considered to be pathogenic are common in asymptomatic individuals. *Hum Mutat*. 2013;34(9):1216-1220.
23. Goldfeder RL, Wall DP, Khoury MJ, Ioannidis JPA, Ashley EA. Human genome sequencing at the population scale: a primer on high-throughput DNA sequencing and analysis. *Am J Epidemiol*. 2017;186(8):1000-1009.

24. Butterfield RM, Evans JP, Rini C, et al. Returning negative results to individuals in a genomic screening program: lessons learned [published online ahead of print June 6, 2018]. *Genet Med*. https://doi.org/10.1038/s41436-018-0061-1.
25. Arora NS, Davis JK, Kirby C, et al; MedSeq Project. Communication challenges for nongeneticist physicians relaying clinical genomic results. *Per Med*. 2016;14(5):423-431.
26. Green RC, Lupski JR, Biesecker LG. Reporting genomic sequencing results to ordering clinicians: incidental, but not exceptional. *JAMA*. 2013;310(4):365-366.
27. Scherokman B. Selecting and interpreting diagnostic tests. *Perm J*. 1997;1(2). http://www.thepermanentejournal.org/files/Fall1997/tests.pdf/. Accessed September 24, 2018.
28. Hart MR, Biesecker BB, Blout CL, et al. Secondary findings from clinical genomic sequencing: prevalence, patient perspectives, family history assessment and healthcare costs from a multisite study. [published online ahead of print October 5, 2018] *Genet Med*. https://doi.org/10.1038/s41436-018-0308-x.
29. Lebo MS, Yu TW, Fayer S, et al. Genomic sequencing reveals previously unrecognized phenotypes in a high proportion of those with unanticipated monogenic disease risk. Presented at: American Society of Human Genetics, San Diego, California, October 17, 2018.
30. Khoury MJ, Feero WG, Chambers DA, et al. A collaborative translational research framework for evaluating and implementing the appropriate use of human genome sequencing to improve health [published online ahead of print August 2, 2018]. *PLoS Med*. https://doi.org/10.1371/journal.pmed.1002631.
31. Green RC, Goddard KAB, Jarvik GP, et al. Clinical Sequencing Exploratory Research Consortium: accelerating evidence-based practice of genomic medicine. *Am J Hum Genet*. 2016;99(1):246.
32. Tsubono Y, Hisamichi S. A halt to neuroblastoma screening in Japan. *N Engl J Med*. 2004;350(19):2010-2011.
33. McGrath SP, Coleman J, Najjar L, Fruhling A, Bastola DR. Comprehension and data-sharing behavior of direct-to-consumer genetic test customers. *Public Health Genomics*. 2016;19(2):116-124.
34. Krieger JL, Murray F, Roberts JS, Green RC. The impact of personal genomics on risk perceptions and medical decision-making. *Nat Biotechnol*. 2016;34(9):912-918.