Downsizing genomic medicine: Approaching the ethical complexity of whole-genome sequencing by starting small

Richard R. Sharp, PhD

Abstract: As we look to a time when whole-genome sequencing is integrated into patient care, it is possible to anticipate a number of ethical challenges that will need to be addressed. The most intractable of these concern informed consent and the responsible management of very large amounts of genetic information. Given the range of possible findings, it remains unclear to what extent it will be possible to obtain meaningful patient consent to genomic testing. Equally unclear is how clinicians will disseminate the enormous volume of genetic information produced by whole-genome sequencing. Toward developing practical strategies for managing these ethical challenges, we propose a research agenda that approaches multiplexed forms of clinical genetic testing as natural laboratories in which to develop best practices for managing the ethical complexities of genomic medicine. ***Genet Med*** **2011:13(3): 191–194.**

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It is unlikely that the promise of genomic medicine will be realized in one-swift stroke wherein whole-genome sequencing (WGS) becomes widely available to physicians and quickly supplants existing forms of molecular diagnosis and genetic risk assessment. Instead, as with major medical innovations in the past, several interim technologies will likely emerge at various points along the path to genomic medicine. These interim technologies may not examine an individual's entire genomic sequence but will span large enough segments to lay claim to being "genomic" in scope.[1]

Clinical applications of array-based genotyping have emerged as the first of these initial genomic technologies.[2,3] With advances in oligonucleotide microarrays and chip-scanning instrumentation, it is now technically possible and economically feasible to use array-based genotyping methods to examine thousands of single-nucleotide polymorphisms in large numbers of patients.[4,5] This possibility has resulted in the launch of several commercial products that use array-based genotyping to examine a wide range of genetic traits and disease associations.[6] Although critics worry that personal genomic testing may not be ready for widespread use,[7] these services herald our first steps toward a medical future in which enormous amounts of genetic data are available to patients and their physicians.[8,9]

As capacity for producing genetic data continues to expand, it is tempting to focus on the "holy grail" of genomic medicine, the ability to generate WGS data on individual patients quickly and inexpensively.[10,11] Celebrations of sequencing milestones reinforce the importance of expanding capacity, often implying that it is merely technological limitations and economic costs that prevent us from realizing the promises of personalized healthcare and genomic medicine. To realize that vision, it seems we simply need more capacity, more genetic research, and more clinicians trained in genetics—more, more, more…

In contrast, I wish to suggest a different vision of the path to genomic medicine, a vision that focuses not on expanding capacity or lowering the cost of producing WGS data but on the ethical integration of genomic technologies into patient care. At the center of this vision is the study of ethical issues associated with our initial forays into clinical genomics, including multiplexed forms of genetic testing and clinical uses of array-based genotyping. These less comprehensive forms of genomic analysis, which examine a far smaller number of genetic loci and mutational sites, provide natural laboratories in which to consider how best to manage large volumes of genetic data in patient-care settings and counsel individuals about the wide range of inherited risk factors that may be revealed through genomic analysis.

Although the field of genomics has been driven largely by technological innovation, we are rapidly approaching a time when neither capacity nor genotyping costs are limiting factors in the emergence of genomic medicine.[12] To the extent that highly multiplexed forms of genetic risk assessment present many of the same ethical challenges that will need to be managed successfully if WGS is to achieve its full potential as a tool in patient care, these interim technologies provide a critical opportunity to begin negotiating the ethical complexities of genomic medicine. For the foreseeable future, I suggest that focusing on the clinical integration of these less comprehensive forms of genomic analysis will take us farther along the path to personalized healthcare and genomic medicine than premature efforts to integrate next-generation sequencing technologies into patient care before having established the knowledge base and clinical infrastructure required to support clinical genomic testing.

INFORMED CONSENT CHALLENGES

To illustrate the value of studying multiplexed forms of genetic testing as a context in which to develop strategies for managing the ethical complexities of genomic medicine, consider the challenge of obtaining patient consent to genomic testing. Existing standards of care for clinical genetic testing of adults include prospective patient counseling about the risks and benefits of the associated genetic test.[13] This counseling stresses the voluntary nature of genetic testing and encourages individ-

From the Department of Bioethics and Genomic Medicine Institute, Lerner College of Medicine, Cleveland Clinic; and Center for Genetic Research Ethics & Law, Case Western Reserve University, Cleveland, Ohio.

Richard R. Sharp, PhD, Department of Bioethics, Cleveland Clinic, 9500 Euclid Ave, JJ-60, Cleveland, OH 44195. E-mail: sharpr3@ccf.org.

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uals to consider how they might respond to potential test results.[14] Patients are encouraged to consider not only the medical implications of genetic risk assessment but also the potential social implications of test results, including emotional distress, threats to future insurability, and issues associated with the sharing of test results with others in their family. In addition, pretest counseling often includes a discussion of the test's analytic and clinical validity, including the assay's sensitivity, specificity, and positive predictive value in the relevant context.[15]

With the noteworthy exception of newborn screening programs, genetic risk assessment generally is discouraged for individuals who are not at increased risk based on family history or clinical presentation. In contrast to this conventional approach to genetic risk assessment, WGS evaluates very large numbers of genetic risk factors concurrently, including risks for very rare conditions that may be of limited interest to the proband. 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 from WGS, as would be expected for other forms of clinical genetic testing. 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 by WGS.[16] These inherent limitations in pretest counseling for genomic analysis will require significant departures from professional standards of care and highlight the extent to which expectations of patient consent will need to be reexamined in the context of WGS.

In contrast to WGS, it may be possible to present multiplexed forms of genetic testing to patients with a level of specificity that more closely approximates current standards of pretest counseling. For example, although array-based genotyping methods can evaluate thousands of genetic features, some multiplexed arrays focus narrowly on only those genes or chromosomal features associated with a particular clinical presentation (e.g., developmental delay) or disease type (e.g., autism-spectrum disorders).[17–19] Although it may not be possible to counsel patients about technical features of each individual assay included on such an array, the medical rationale for recommending testing and the potential clinical implications of various test results can be reviewed in detail with patients before seeking informed consent to genetic testing.[20]

Among multiplexed genotyping arrays, there can be multiple approaches. Perhaps the most conservative approach is to evaluate only well-characterized mutations that are known to be strongly associated with Mendelian diseases.[21] Many of these mutations are well established and have clear implications for diagnosis and patient care. This possibility suggests numerous applications of multiplexed genotyping in molecular diagnosis and genetic risk assessment.[22] One example is testing to examine disease etiology in individuals with complex clinical presentations such as mental retardation, autism, or seizure disorders. Other applications include predictive testing for adult-onset disorders such as cancer predisposition syndromes, prenatal testing for mutations responsible for severe genetic disorders, and screening for autosomal recessive or X-linked mutations in individuals who may have an undiagnosed reproductive risk for genetic disorders.

Although multiplexed forms of genetic testing will require significant departures from existing standards of pretest counseling and informed consent,[23] those departures will be less extensive than in clinical applications of WGS, where the range of potential results is exponentially greater. These considerations suggest that developing best practices for pretest counseling about multiplexed forms of genetic risk assessment can help clinicians prepare for WGS, which will raise many of the same ethical challenges but to a far greater degree. Clinical applications of multiplexed genetic testing present an opportunity to assess the extent to which it is possible to obtain meaningful patient consent to large-scale genomic analysis, a possibility that has been called into question in the past.[24] Studying how patients understand the benefits and risks of multiplexed testing, and interpret results from these new forms of genetic risk assessment, can also help clinicians introduce discussions of WGS in the future. In addition, studying patients' experiences of genomic testing can increase the likelihood that evolving standards of pretest counseling in clinical genetics are consistent with widely held patient values and moral beliefs.[25]

If WGS is to be integrated successfully into patient care, it is essential to establish that pretest counseling can place patients in a position to make informed choices about genomic risk assessment. Studies that evaluate pretest counseling for multiplexed forms of genetic testing are a critical first step in establishing that it is possible to obtain genuinely informed consent to clinical genomic testing.

DISCLOSING RESULTS AND PREPARING FOR LIFELONG FOLLOW-UP

Multiplexed forms of genetic testing also provide a context in which to examine the ethical complexities of several data-management challenges that will result from clinical applications of WGS. Unlike current models of genetic risk assessment, the volume of data produced through WGS will greatly exceed an individual clinician's capacity to present all relevant clinical findings that are discovered. This limitation conflicts with existing professional expectations regarding the return of diagnostic results from clinical genetic testing, where it is expected that a genetic specialist will review the full range of diagnostic findings directly with the patient tested. To avoid overwhelming patients with very large amounts of genetic information, and potentially diminishing their comprehension of major findings, clinical judgments will have to be made about the specific results to prioritize in presenting diagnostic results from WGS.

In addition to generating large amounts of information that may be directly relevant to patient care, WGS will reveal other types of genetic information that may be of potential interest to the patient tested.[26] Some of this information may not be relevant to the patient at the time the test is performed but may gain importance later, as the patient reaches a later stage in life or as more is learned about the biological implications of genetic features identified by WGS. Given our limited knowledge of human genetic variation, it may be the case that data from WGS is interpreted differently several years from now, as our knowledge improves and more clinical studies incorporate WGS. These changes in our capacity to interpret the clinical significance of findings from WGS may be sufficient to motivate some clinicians to contact their patients later to inform them of new developments. It is uncommon for genetic specialists to recontact patients after their initial diagnostic evaluation, however, and it seems that many are reluctant to do so, unless there are significant implications for the patient.[27,28]

Some of these reservations likely reflect long-standing ambiguities about the scope of a genetic professional's "duty to notify" patients about new results that may impact their health. For example, if research findings demonstrate that a variant of unknown significance is indeed deleterious, to what extent do geneticists have a moral or legal obligation to review the tests

that they have ordered in the past and recontact those patients whose results may be affected? In the context of single-gene tests, this issue occurs infrequently and can be addressed on a case-by-case basis.[29] This practical challenge will be far more complex in the context of WGS, however, where thousands of variants of unknown significance will be revealed for each patient tested.[30] The predictability of this outcome suggests a need to examine whether counseling services, clinical staff, and financial resources are available for the longer term management of WGS data. Compounding this problem is a lack of reimbursement and informatics support for these types of patient-care activities that involve the reinterpretation of prior genetic results.

A related problem is that reasonable people may disagree about the overall utility and importance of many results from WGS. An older individual's carrier status for a deleterious mutation would be one such example where the value of returning diagnostic results may be unclear. Some clinicians may feel it important to convey this information to the patient, so other family members who may be at risk can avail themselves of relevant medical services; other clinicians may disagree and choose to focus more narrowly on diagnostic results of more immediate relevance to patient management.[31,32] To the extent that judgments of clinical utility are context dependent, particularly those involving genetic results,[33] a range of opinions may exist about the value of reporting diagnostic findings of less immediate clinical significance. As larger volumes of personal genetic information are produced, it will be important to examine the criteria that patients and clinicians use to assess the value of results from genomic testing.[34]

In combination with the limited familiarity that many physicians have with clinical genetic testing,[35,36] these considerations highlight some of the many data-management challenges that will be associated with clinical applications of WGS. Similar to WGS, multiplexed forms of genetic risk assessment present many of these same challenges. Multiplexed tests can reveal previously unknown genetic risk factors and findings that are not immediately actionable. Some of these findings will require additional evaluation, which may increase healthcare costs and patient burden.[37,38] These possibilities will occur less frequently in multiplexed forms of genetic testing, however, as the number of mutational sites examined will be far fewer in comparison with WGS. This suggests that translational studies that seek to evaluate different approaches for managing data produced by multiplexed forms of genetic testing may provide a reasonable starting point for engaging the more general ethical issues associated with managing large amounts of genetic data in patient-care settings.

BUNDLING GENETIC TESTS INSTEAD OF BUNGLING GENOMIC TESTS

As WGS will require significant departures from existing standards of care in clinical genetics, it is critical that this new form of testing be introduced with care.[39] The genomic testing options that have the strongest ethical foundation today are those that involve the least substantial departures from prevailing practices. These include highly multiplexed forms of genetic analysis that examine large segments of the human genome. These multiplexed tests draw on decades of knowledge in clinical genetics and avoid some of the most difficult ethical issues that will face clinical applications of WGS. Studying the impact of these early forays into clinical genomics and developing best practices for their use can help clinicians prepare for a time in which there is stronger evidence in support of the use of WGS in patient care.[40] Thus, although counterintuitive, we suggest that the most direct path toward genomic medicine involves being more strategic in developing smaller scale forms of multiplexed genetic testing that offer real-world settings in which to study ethical and practical challenges that will be associated with the use of WGS in patient care.

As we look to a time when WGS is integrated into patient care, it is possible to anticipate a number of ethical challenges.[41,42] The most intractable of these concern informed consent and the responsible management of very large amounts of genetic information. Given the vast range of possible findings, it remains unclear to what extent it will be possible to obtain meaningful consent to genomic testing and manage the enormous volume of risk information produced by genomic analysis. Equally unclear are the clinical settings in which genomic evaluation may be useful, as either a diagnostic aid or screening tool. Until these fundamental issues are resolved, we suggest that it would be irresponsible to pursue clinical applications of WGS.

Over the next several decades, applications of WGS in research will continue to yield important insights into human health and disease.[43–50] Until the ethical issues above are addressed, however, physicians should be hesitant to use WGS for genetic risk assessment. Responsibly integrating WGS into patient care will require us to examine both current limitations in our knowledge and potential alternatives to genomic evaluation, which include not only multiplexed forms of genetic testing but also screening strategies that use family history and phenotypic biomarkers in combination with targeted forms of genetic evaluation. Unfortunately, the low cost of WGS will likely encourage its early adoption. The difficulty is that although the costs of sequencing have declined significantly, the costs of medical interpretation have remained constant. As a result, early adopters of WGS should expect that the $1000 genome may create a million dollar headache. That headache may be avoidable if clinicians choose to move away from the traditional "single-gene" paradigm for genetic risk assessment in smaller steps, beginning first with translational studies of multiplexed genetic testing.

Future research should focus on responsibly integrating genomic tools into patient care. Of special importance are studies that seek to promote informed patient decision making and develop effective ways of presenting large amounts of genetic information. These studies should seek to clarify key factors in the uptake of genomic medicine, including whether it is possible to automate some of the clinical interpretation of WGS data; which methods of communication enhance patients' understanding of multiple inherited risks; what legal duties and professional obligations may result from producing WGS data; and whether knowledge of genetic risk factors results in improved health outcomes. Studies that compare outcomes of WGS with alternative screening strategies are also critical in assessing its clinical utility. Although far less glamorous than a research agenda centered on developing new technologies and reducing the costs of WGS, until we address these basic questions about the responsible integration of genomic data into patient care, dreams of personalized healthcare will remain elusive.

CONCLUSION

Although it is clear that WGS will be a part of patient care in the future, it will be decades before there is sufficient evidence of its clinical utility to support widespread use in patient-care

settings. Until that evidence base exists, developing best practices for managing smaller scale forms of genomic analysis, particularly strategies for addressing the many ethical complexities associated with multiplexed genetic testing, can help clinicians prepare to manage the volume of data that will be produced by clinical applications of WGS. This is not to suggest that WGS should be discouraged in the context of clinical research, where sequence data will continue to provide insights into human disease. For the foreseeable future, however, ethical considerations favor more circumscribed forms of clinical genomic testing that examine smaller numbers of well-characterized loci and mutations known to be associated with disease. Although we will soon have the capacity to use WGS in patient care, we do not yet have the practical knowledge or experience to do so responsibly.

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REFERENCES

1. IOM (Institute of Medicine). Innovations in service delivery in the age of genomics: workshop summary. Public workshop at the Roundtable on Translating Genomic-Based Research. Washington, DC: IOM, 2008.
2. Allison DB, Cui X, Page GP, Sabripour M. Microarray data analysis: from disarray to consolidation and consensus. *Nat Rev Genet* 2006;7:55–65.
3. Chan EY. Advances in sequencing technology. *Mutat Res* 2005;573:13–40.
4. Grant SF, Hakonarson H. Microarray technology and applications in the arena of genome-wide association. *Clin Chem* 2008;54:1116–1124.
5. Hong KW, Oh B. Overview of personalized medicine in the disease genomic era. *BMB Rep* 2010;43:643–648.
6. Helgason A, Stefansson K. The past, present, and future of direct-to-consumer genetic tests. *Dialogues Clin Neurosci* 2010;12:61–68.
7. Hunter DJ, Khoury MJ, Drazen JM. Letting the genome out of the bottle—will we get our wish? *N Engl J Med* 2008;358:105–107.
8. Feero WG, Guttmacher AE, Collins FS. Genomic medicine—an updated primer. *N Engl J Med* 2010;362:2001–2011.
9. Guttmacher AE, McGuire AL, Ponder B, Stefansson K. Personalized genomic information: preparing for the future of genetic medicine. *Nat Rev Genet* 2010;11:161–165.
10. Hobert O. The impact of whole genome sequencing on model system genetics: get ready for the ride. *Genetics* 2010;184:317–319.
11. Zhao J, Grant SF. Advances in whole genome sequencing technology. *Curr Pharm Biotechnol* 2011;12:293–305.
12. Metzker ML. Sequencing technologies—the next generation. *Nat Rev Genet* 2010;11:31–46.
13. Burke W, Emery J. Genetics education for primary-care providers. *Nat Rev Genet* 2002;3:561–566.
14. Uhlmann WR, Schuette JL, Yashar BM. A guide to genetic counseling. New York: Wiley-Blackwell, 2009.
15. Kraft P, Wacholder S, Cornelis MC, et al. Beyond odds ratios—communicating disease risk based on genetic profiles. *Nat Rev Genet* 2009;10:264–269.
16. Ormond KE, Wheeler MT, Hudgins L, et al. Challenges in the clinical application of whole-genome sequencing. *Lancet* 2010;375:1749–1751.
17. Moeschler JB, Shevell M, American Academy of Pediatrics Committee on Genetics. Clinical genetic evaluation of the child with mental retardation or developmental delays. *Pediatrics* 2006;117:2304–2316.
18. Jordan BR, Tsai DF. Whole-genome association studies for multigenic diseases: ethical dilemmas arising from commercialization—the case of genetic testing for autism. *J Med Ethics* 2010;36:440–444.
19. Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86:749–764.
20. Shaffer LG, American College of Medical Genetics Professional Practice and Guidelines Committee. American College of Medical Genetics guideline on the cytogenetic evaluation of the individual with developmental delay or mental retardation. *Genet Med* 2005;7:650–654.
21. Kreiner T, Buck KT. Moving toward whole-genome analysis: a technology perspective. *Am J Health Syst Pharm* 2005;62:296–305.
22. Khoury MJ, McCabe LL, McCabe ER. Population screening in the age of genomic medicine. *N Engl J Med* 2003;348:50–58.
23. Speicher MR, Geigl JB, Tomlinson IP. Effect of genome-wide association studies, direct-to-consumer genetic testing, and high-speed sequencing technologies on predictive genetic counselling for cancer risk. *Lancet Oncol* 2010;11:890–898.
24. Elias S, Annas GJ. Generic consent for genetic screening. *N Engl J Med* 1994;330:1611–1613.
25. Foster MW, Sharp RR. Ethical issues in medical-sequencing research: implications of genotype-phenotype studies for individuals and populations. *Hum Mol Genet* 2006;15:R45–R49.
26. McGuire AL, Lupski JR. Personal genome research: what should the participant be told? *Trends Genet* 2010;26:199–201.
27. Fitzpatrick J, Hahn C, Costa T, Huggins M. The duty to recontact: attitudes of genetics service providers. *Am J Hum Genet* 1997;61:A57.
28. Ormond KE, Smith ME, Cirino AL, Chisholm RL, Wolf W. "Duty" to recontact participants in a population based genetic database: the NUgene experience. *Genet Med* 2004;6:261.
29. Offit K, Groeger E, Turner S, Wadsworth EA, Weiser MA. The "duty to warn" a patient's family members about hereditary disease risks. *JAMA* 2004;292:1469–1473.
30. Beaudet AL. Ethical issues raised by common copy number variants and single nucleotide polymorphisms of certain and uncertain significance in general medical practice. *Genome Med* 2010;2:42.
31. Liao SM. Is there a duty to share genetic information? *J Med Ethics* 2009;35:306–309.
32. Stol YH, Menko FH, Westerman MJ, Janssens RM. Informing family members about a hereditary predisposition to cancer: attitudes and practices among clinical geneticists. *J Med Ethics* 2010;36:391–395.
33. Beskow LM, Burke W. Offering individual genetic research results: context matters. *Sci Transl Med* 2010;2:38cm20.
34. Foster MW, Mulvihill JJ, Sharp RR. Evaluating the utility of personal genomic information. *Genet Med* 2009;11:570–574.
35. Baars MJ, Scherpbier AJ, Schuwirth LW, et al. Deficient knowledge of genetics relevant for daily practice among medical students nearing graduation. *Genet Med* 2005;7:295–301.
36. Harvey EK, Fogel CE, Peyrot M, Christensen KD, Terry SF, McInerney JD. Providers' knowledge of genetics: a survey of 5915 individuals and families with genetic conditions. *Genet Med* 2007;9:259–267.
37. McGuire AL, Burke W. An unwelcome side effect of direct-to-consumer personal genome testing: raiding the medical commons. *JAMA* 2008;300:2669–2671.
38. Giovanni MA, Fickie MR, Lehmann LS, et al. Health-care referrals from direct-to-consumer genetic testing. *Genet Test Mol Biomarkers* 2010;14:817–819.
39. American Medical Association, Council on Ethical and Judicial Affairs. Multiplex genetic testing. *Hastings Cent Rep* 1998;28:15–21.
40. Khoury MJ, Gwinn M, Yoon PW, Dowling N, Moore CA, Bradley L. The continuum of translation research in genomic medicine: how can we accelerate the appropriate integration of human genome discoveries into health care and disease prevention? *Genet Med* 2007;9:665–674.
41. Robertson JA. The $1000 genome: ethical and legal issues in whole genome sequencing of individuals. *Am J Bioeth* 2003;3:35–42.
42. Samani NJ, Tomaszewski M, Schunkert H. The personal genome—the future of personalised medicine? *Lancet* 2010;375:1497–1498.
43. Ashley EA, Butte AJ, Wheeler MT, et al. Clinical assessment incorporating a personal genome. *Lancet* 2010;375:1525–1535.
44. Bilguvar K, Ozturk AK, Louvi A, et al. Whole-exome sequencing identifies recessive WDR62 mutations in severe brain malformations. *Nature* 2010;467:207–210.
45. 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.
46. Rios J, Stein E, Shendure J, Hobbs HH, Cohen JC. Identification by whole-genome resequencing of gene defect responsible for severe hypercholesterolemia. *Hum Mol Genet* 2010;19:4313–4318.
47. Roach JC, Glusman G, Smit AF, et al. Analysis of genetic inheritance in a family quartet by whole-genome sequencing. *Science* 2010;328:636–639.
48. Ho PA, Alonzo TA, Kopecky KJ, et al. Molecular alterations of the IDH1 gene in AML: a Children's Oncology Group and Southwest Oncology Group study. *Leukemia* 2010;24:909–913.
49. Via M, Gignoux C, Burchard EG. The 1000 Genomes Project: new opportunities for research and social challenges. *Genome Med* 2010;2:3.
50. Morozova O, Marra MA. Applications of next-generation sequencing technologies in functional genomics. *Genomics* 2008;92:255–264.

