Whole-Genome Sequencing: The New Standard of Care?

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Rapid advances in DNA sequencing technology have made whole-genome sequencing (WGS) both technically and economically feasible. WGS has been used with great effect in specific settings to clarify molecular diagnosis and even to guide therapy (1, 2). But are we ready for the routine use of WGS in the care of healthy individuals?

The Problem of Overselling

Much promise has been ascribed to the concept of personalized medicine, which, at least in some iterations, includes routine use of WGS (3). It is essential for the scientific and medical communities to be realistic about the clinical potential of WGS to prevent losing public support for these important endeavors. One need only look to the optimistic predictions made at the time of completion of the first draft of the human genome 10 years ago, claiming that a medical revolution of personalized and DNA-based medicine was imminent. That revolution has largely not yet come to be, and the popular press has begun to promote a view that genetics has failed to live up to its promises (4).

The vast majority of genomic data is, at this time, not medically actionable. Nearly all of the most highly significant genetic associations resulting from genome-wide association studies for common diseases confer odds ratios too small to be useful in clinical medicine (5). This in no way negates the extraordinary biological insights and additional research that continues to flow from these studies but should caution those who make predictions about the use of such information in clinical settings. Moreover, how multiple risk variants combine in additive, multiplicative, or compensatory ways to inform clinical risk is largely unknown. In addition, data from studies of disease concordance in monozygotic twins suggest that for many common diseases, such as cancer, a negative test result from WGS data would not appreciably reduce an individual’s risk relative to the baseline population risk and would therefore not enable meaningful medical intervention (6). The challenge is to identify and validate genotypes via WGS that are robustly associated with disease phenotype and with effect sizes, sensitivity, and specificity that enable counseling about risk beyond what is predicted by traditional clinical factors.

A particular concern is that some of those making claims about the application of WGS may not be considered objective or dispassionate because of their commercial or even academic interests. Despite the public hype about the clinical utility of genomic testing, the small-print legal disclaimers of some of the organizations offering direct-to-consumer genomic testing state that the information is not intended for the “diagnosis, cure, treatment, mitigation, or prevention of any disease or other medical condition or impairment or the status of your health” (7). Genomic testing is claimed to allow one to “personalize your health,” and yet the terms of service of some tests indicate that the results do not “[recommend] any specific treatment plan, product or course of action” (8). Such contradictory claims only serve to obfuscate the public’s understanding of the utility of genomic testing.

In Need of Translation

A major obstacle to large-scale uptake of WGS is the paucity of individuals skilled to interpret and translate genome sequence data. The bottleneck in bioinformatics analysis and the cost associated with the interpretation of genomic data represent major obstacles. Even the physical storage of these vast data sets poses new challenges (9). Once the sequence data have been analyzed, annotated, and interpreted, we are faced with the profound shortage of translators of these data into meaningful clinical interactions. This includes both genetic counselors and physicians or nurses with sufficient training in genetics. The National Society of Genetic Counselors lists 2307 members in its directory or one genetic counselor for every 135,000 individuals in the United States (10). The small number of individuals who could perform this crucial function will be overwhelmed by the amount of data generated by routine WGS. Each genome is expected to contain ~150,000 novel single-nucleotide variants not currently in the public database dbSNP (11), including 250 to 300 disruptive variants in genes, 50 to 100 variants in human disease genes, and ~20 completely inactivated genes (12, 13). It is estimated that the informed-consent process alone for such testing will take several hours of direct patient contact to review the information relative to likelihood of illness, its implications, and approaches to managing disease for each gene

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White-genome sequencing may dramatically alter medicine, but there are obstacles to broad implementation.

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10. Data Sequencing Costs, National Human Genome Research Institute; www.genome.gov/sequencingcosts/.
11. Volunteers from the general public working together with researchers to advance personal genomics, www.personalgenomes.org/.

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under discussion, as well as the potential risks and benefits of knowing versus not knowing specific genomic information (14). We simply do not have sufficient numbers of trained individuals to meaningfully translate these results. The exponential advances in sequencing technology have exposed major obstacles to personalized medicine on any large scale.

Incidental-omics

The chance discovery of variants of potential clinical importance underscores the complex nature of the informed-consent process that will be required for routine WGS. We favor a model in which a patient would specifically consent to learning of categories of variants in specific genes with different clinical implications. One category would be clinically important, medically actionable variants in genes conferring specific risks. Examples would include BRCA1 and BRCA2 mutations associated with breast and ovarian cancer, APC mutations associated with familial adenomatous polyposis, or pharmacogenomic variants of high predictive value such as the HLA-B*5701 allele (which predisposes to abacavir hypersensitivity). Many patients undergoing WGS may choose to learn of such results because evidence-based interventions are potentially available to reduce risk [i.e., prophylactic mastectomy in the case of BRCA1 and/or BRCA2 mutations (15), colonic surveillance in the case of APC mutations, or avoidance of abacavir in the case of HLA-B*5701 (16)].

A second, more problematic class of variants would be those that are clinically important but not necessarily associated with a medical intervention, such as mutations in the Huntington disease gene or in PRNP, which has been associated with prion disease. Although learning of these variants may have profound personal importance and lead to changes in lifestyle, such results may have unwanted psychosocial or economic implications. Specific and informed consent is necessary to undergo appropriate counseling for this class of variants. For patients who choose not to learn of such variants, a “binning” approach could be used in which clinically important but nonactionable variants would be censored from WGS results (17).

Incorporation into Clinical Medicine

Clinical reasoning is fundamentally Bayesian. How the results of a test alter risk is crucially linked to the pretest likelihood that the patient might have the condition of interest. For example, in a patient with clinically diagnosed iron overload, homozygosity for the C282Y mutation in the HFE gene is highly predictive of the diagnosis of hereditary hemochromatosis (HH) (18). However, in an unscreened population, the C282Y mutation confers only a very low risk of developing clinical disease (19). This speaks to the penetrance of a given genetic variant, as well as the importance of interpreting the variant within a clinical context. Performing WGS routinely in healthy individuals separates the test from the clinical question. This can lead to overinterpretation or false-positives (diagnosing a condition when it is not truly present). An example would be erroneously diagnosing HH based on a mutation in the HFE gene in a low-risk individual. Routine WGS could also lead to false-negatives, i.e., missing potentially important findings because absence of a clinical question did not focus the analysis to look deeply enough. Examples of the latter would be failing to identify or correctly interpret functional nongenic variants or complex chromosomal insertions, deletions, or rearrangements.

Last, with few exceptions, there is a lack of data to suggest that genetic testing actually leads to improved health outcomes, a separate issue from the predictive ability of a genetic test. The examples described above of prophylactic mastectomy to reduce the risk of breast cancer in BRCA1 mutation carriers and avoidance of abacavir in carriers of the HLA-B*5701 allele are notable exceptions (15, 16). Once a specific genotype has been robustly shown to be predictive of a specific condition, the question of whether knowledge of this risk will enable intervention to improve health remains unanswered. Although early reports of clinical use of WGS have been encouraging (2), new clinical trials and regulatory methodologies may be required to rigorously and efficiently assess whether genomic testing will lead to improved health outcomes. This will be essential before we can legitimately advocate for WGS on a larger scale and will likely be required by payers for reimbursement of such testing.

Minding the Gaps

How will we move forward to overcome the obstacles? WGS has already proved to be an outstanding research tool, and developing publicly accessible databases of phenotype-genotype information will facilitate our growing knowledge of how to apply this information. Guidelines from professional organizations and medical groups will be helpful in guiding appropriate use of this technology. In this regard, the recent guidelines published by the UK National Health Services are a welcome contribution (20).

We must train more translators. Clinical training programs must reorganize themselves to train health-care professionals to use genomic testing. We currently face not a technological gap but a delivery gap both to the patient and to our communities (see the figure). Steps to overcome these gaps are urgently needed to fulfill the promises and hopes for the genetic revolution.

References and Notes

7. 23andme, Terms of Service; https://www.23andme.com/about/tos/.
20. C. Wright et al., Next Steps in the Sequence: The Implications of Whole Genome Sequencing for Health in the UK (PHG Foundation, Cambridge, 2011).

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