Special Communication

The Promise and Challenges of Next-Generation Genome Sequencing for Clinical Care

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With increased speed and decreased costs, next-generation gene sequencing has the potential to improve medical care by making possible widespread evaluation of patients' genomes in clinical settings. The entire genome of an individual can now be sequenced in less than 1 week at a cost of $5000 to $10 000; the cost will continue to decline. Analyses based on next-generation sequencing include whole-genome sequencing and whole-exome sequencing; DNA sequences that encode proteins are collectively known as the exome. In some instances, whole genome and whole-exome sequencing have already helped to accurately diagnose diseases with atypical manifestations, that are difficult to diagnose using clinical or laboratory criteria alone, or that otherwise require extensive or costly evaluation. For some patients with malignant neoplasms, next-generating sequencing can improve tumor classification, diagnosis, and management. Many challenges remain, however, such as the storage and interpretation of vast amounts of sequence data, training physicians and other health care professionals whose knowledge of genetics may be insufficient, effective genetic counseling and communication of results to patients, and establishing standards for the appropriate use of the technology. Rigorous studies are needed to assess the utility of whole-genome and whole-exome sequencing in large groups of patients, including comparative studies with other approaches to screening and diagnosis, and the evaluation of clinical end points and health care costs. The successes to date have been in single cases or in very small groups of patients. At present, although whole-genome or whole-exome sequencing show great promise, they should be incorporated into patient care only in limited clinical situations.

JAMA Intern Med. 2014;174(2):275-280. doi:10.1001/jamainternmed.2013.12048
Published online November 11, 2013.

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In 1990, the United States embarked on the ambitious goal of sequencing the entire human genome of approximately 3 billion base pairs.[1] The sequencing and analysis took more than 10 years to complete and cost $2.7 billion; it has been extraordinarily valuable for studying the genetic causes of disease and for clinical applications. Recently, "next-generation sequencing" technologies have been developed, enabling rapid sequencing at substantially reduced costs. The entire genome of an individual can now be sequenced in less than 1 week for $5000 to $10 000.[2] In the near future, the cost is expected to decline to less than $1000. Soon, genome sequencing may be an affordable clinical tool.

Next-generation sequencing technologies have promise in certain clinical situations, but there are substantial challenges for appropriate, successful, and widespread implementation. In this review, we address the clinical applications of next-generation sequencing, concerns about implementation, and the impact of accessible genomic data on clinical care.

Whole-Genome and Whole-Exome Sequencing

The decreased cost and increased speed of sequencing has made it possible to use large-scale genomic analysis as a clinical tool. Analyses based on next-generation sequencing include whole-genome sequencing and whole-exome sequencing. In whole-genome sequencing, genomic DNA is isolated from a patient, and the entire sequence determined. The steps involved for physicians and patients are summarized in the **Box**. A bioinformatics computer program compares the patient's sequence to a reference sequence, notes differences, and searches databases to determine the differences that could be clinically relevant.[6] In a typical person, whole-genome sequencing will reveal 3 to 4 million variants.[5] Even after variants that do not seem to be clinically relevant have been filtered out, hundreds of disease-related variants could remain.[3]

More than 85% of known disease-causing mutations occur in exons (DNA sequences that encode proteins).[4] Whole-exome sequencing examines the sequences of the exons, which are collectively known as the "exome." Generally, about 20 000 variants are identified in the exome sequence of an individual.[4] As with whole-genome sequencing, bioinformatics programs sift through the sequence data to determine which variants may be clinically meaningful. Whole-exome sequencing is less costly than whole-genome sequencing, and the exome represents a highly enriched subset of the genome in which to search for disease-causing variants, making the identification of clinically meaningful results more efficient. However, whole-exome sequencing often misses large chromo-

Box. Physicians, Patients, and the Whole-Genome and/or Whole-Exome Sequencing Process[a]

1. Physicians and other health care providers determine that the patient's symptoms and outcomes of previous care suggest that whole-genome or whole-exome sequencing may be useful for diagnosis and optimizing management.
2. Whole-genome or whole-exome sequencing options are discussed with the patient and/or guardian. The discussion includes genetic counseling that covers topics such as basic genetics, implications of results, privacy, and desire to receive incidental findings.
3. With consent, a clinical laboratory performs whole-genome or whole-exome sequencing, generating the raw sequence data.
4. A bioinformatics computer program compares the genome or exome sequence with a reference sequence and identifies variants; 3 to 4 million variants will be detected in a genome sequence, about 20 000 variants will be detected in an exome sequence.[b]
5. Bioinformatics programs further analyze variants to determine which are clinically important (likely to have an impact on the patient's health); 100 to 1000 may be classified as clinically important.[c]
6. Health professional team interprets results, researching variants classified as clinically important to determine if any may cause a relevant disease, and which incidental findings, if any, should be reported to the patient and/or guardian.
7. Physician, genetic counselor or other health care providers explain the results to patient and/or guardian, noting which variant(s) may cause the disease under consideration and discussing incidental findings, depending on the patient's or guardian's wishes.
8. A care plan for the disease is developed, informed by the identified genetic variant(s).
9. Physician and other health care providers, in consultation with the patient and/or guardian, initiate follow-up diagnostic or management strategies for diseases or disease risk incidentally found as a result of sequencing.

[a] The total time for steps 1 to 9 is dependent on the clinical situation; it can be less than 1 month, but is more likely to be 3 to 6 months. Generation of raw sequence data (step 3) takes days, but clinical interpretation of identified variants (step 6) can be time consuming. Confirmatory testing is often required.

[b] See Raffan and Semple[3] and Bamshad et al.[4]

[c] See Biesecker.[5]

somal structural variants, which whole-genome sequencing has the potential to detect.[7]

So far, whole-genome and whole-exome sequencing have shown the most clinical utility in facilitating an accurate diagnosis in individuals with disorders that present with atypical manifestations, are difficult to confirm using clinical or laboratory criteria alone, or otherwise require extensive or costly evaluation.[3-5,7,8] Such disorders are usually genetically heterogeneous, meaning that multiple genetic variants may be causal, and often, not all of the causal variants are known. The disorders also tend to have variable phenotypic presentations that make diagnosis difficult. Examples of such disorders are intellectual disability, congenital malformation, and mitochondrial dysfunction. For a disorder with a suspected genetic cause, targeted testing of single candidate genes is usually most efficient in identifying the genetic variation. But the identification of candidate genes often is not possible when the presentation is atypical, mild, or variable. Targeted genetic testing also may be very expensive and inefficient if dozens of candidates are sequenced individually. In these situations, whole-genome and whole-exome sequencing have been used to search for variations that may cause disease.

Diagnosing Disease With Whole-Genome and Whole-Exome Sequencing

Although whole-genome and whole-exome sequencing are not yet widely implemented, their utility in facilitating diagnosis and guiding therapy has been demonstrated in some instances.[9-16] A well-known example of the clinical application of whole-exome sequencing is the determination of the underlying cause of disease in a boy with symptoms of life-threatening inflammatory bowel disease, even after comprehensive clinical evaluation and targeted genetic analysis.[9] Whole-exome sequencing identified a mutation frequently associated with hemophagocytic lymphohistiocytosis. An allogeneic hematopoietic progenitor cell transplant was performed; within weeks the boy was able to eat and drink. At the time the case report was published, his symptoms had not recurred. In another instance, a pair of fraternal twins with dopa (3,4-dihydroxyphenylalanine)–responsive dystonia that was no longer well controlled with levodopa treatment underwent whole-genome sequencing after targeted genetic analysis did not detect any mutations in the primary candidate genes.[10] A mutation in a gene encoding a cofactor for the synthesis of both dopamine and serotonin was identified, leading to the recommendation that the serotonin precursor 5-hydroxytryptophan be added to the twins' therapeutic regimen.[10] At the time the case was published, both twins had shown marked improvement.

Other studies have demonstrated that systematic application of whole-genome and whole-exome sequencing has been more accurate, faster, and less expensive than conventional diagnostic procedures. Whole-genome sequencing in a neonatal intensive care unit shortened the time to diagnosis of rare, monogenic diseases to about 50 hours compared with about 19 days using a targeted gene panel.[11] In an examination of patients with unexplained intellectual disability, all of whom had undergone extensive clinical and genetic evaluation, whole-exome sequencing identified new mutations in more than half and facilitated a conclusive diagnosis in 13%.[12] These examples are noteworthy because whole-genome and whole-exome sequencing improved patient management by revealing treatment options not previously considered and by ruling out therapies that would not have been successful.

Evaluating Cancers With Next-Generation Sequencing

In many instances, genomic analysis of tumors has transformed cancer diagnosis and treatment. For example, panel-based assays that detect dozens of variations in gene expression are used to profile breast tumors and to predict prognosis and response to chemotherapy.[17,18] Next-generation sequencing has enabled tests that rapidly analyze tumor DNA to detect hundreds of variants that may drive cell growth, and to provide clues about treatment options.[19-21]

Next-generation sequencing technologies also have enabled the rapid sequencing of the tumor genome to identify variants that will more precisely classify the tumor and allow the selection of tailored therapies. For example, in a patient whose clinical presentation was consistent with acute promyelocytic leukemia but whose cytogenetic results suggested a different subtype for which bone marrow transplantation is recommended, whole-genome sequencing was performed on DNA extracted from the leukemic bone marrow.[22] A novel chromosomal translocation was discovered that led to a change in therapy; the patient was treated with retinoic acid and was no longer considered a candidate for bone marrow transplantation. In another study, a next-generation sequencing-based test revealed therapeutic options for more than three-quarters of patients with non–small-cell lung cancer.[21] Recently, whole-genome sequencing of circulating DNA from patients with cancer accurately detected chromosomal abnormalities associated with their tumors, suggesting that the approach may be a viable option for the noninvasive detection of cancer.[23]

Data Storage and Interpretation

Although next-generation sequencing technologies could potentially improve patient care, serious challenges must be addressed. One challenge is how to manage the vast amount of data in a whole-genome sequence. The storage space required for a raw sequence data file from only 1 whole-genome exceeds the capacity of most home computers.[24] Storage of that amount of data within current-generation electronic medical records is not feasible at this time.[25] Decreased costs and improvements in ancillary storage mechanisms are likely, but systems must also be developed to allow electronic medical records to seamlessly access sequence data.[25-27]

Aside from data storage, data interpretation presents a substantial hurdle. The millions of variants in a whole-genome sequence necessitate the use of bioinformatics programs that identify clinically meaningful variants.[28] The **Table** summarizes the sequence alignment and filtering steps performed by bioinformatics programs. The process often takes 1 to 2 weeks to complete; in a typical genome sequence, hundreds of possibly meaningful variants will be identified.[5]

Data interpretation also can be hindered by incomplete information on genotype-phenotype associations. Many variants are uncharacterized, and it is not clear how they affect health. Reanalysis is an additional challenge; bioinformatics algorithms are frequently updated to incorporate new research associating variants with disease.[29] Thus, an individual's genetic sequence may need to be reanalyzed periodically to detect variants that may not have been initially classified as clinically important. It remains uncertain who should be responsible for initiating reanalysis, how often it should be performed, how it should be paid for, and whether and how updated results will be incorporated into electronic medical records. A laboratory-based solution is currently being tested in one health system. Using an electronic application, the testing laboratory alerts health professionals when new clinically meaningful information becomes available about variants that have previously been identified in their patients. Although the application is currently independent of the electronic medical record, work is under way to integrate it.[30]

Table. Identification of Genetic Variants by Bioinformatics Programs[a]

Step	Description
Sequence alignment and comparison	Alignment of raw sequence to reference sequence; comparison to identify variants (nucleotides or chromosomal regions that differ from the reference sequence).
Identification of clinically important variants	Filters are applied to variants to determine which may be clinically important; filters include the known association of each variant with disease, evolutionary conservation of the sequence, the change to the resulting protein, the patient's phenotype, and possible patterns of inheritance.

[a] See Bick and Dimmock[7] and Fernández-Suárez and Galperin.[28]

Genetic Counseling and Communication of Results

After physicians and other health professionals have determined that whole-genome or whole-exome sequencing is appropriate for the clinical situation, the patient or patient's guardian(s) must be engaged in counseling to learn about the procedure and give consent. The amount of time needed for adequate genetic counseling *prior* to sequencing has been estimated at 6 to 8 hours.[7] In addition to a discussion of basic genetics, inheritance patterns, types of variation, privacy concerns, rights under the Genetic Information Nondiscrimination Act,[31] and the consent process, an important topic is the patient's desire to receive incidental or secondary findings (ie, variants that are not related to the phenotype under investigation but that may have an impact on the patient's health). The time required for effective genetic counseling is substantial, and it is uncertain whether health professionals have the time to conduct this type of counseling. Because there is a shortage of medical geneticists and genetic counselors in the United States,[32,33] a team-based approach in which several health professionals with knowledge of the patient's case are able to provide counseling is most likely to meet the need. However, since not all of the team members will be genetics professionals, specialized training in counseling may be necessary.

After whole-genome or whole-exome sequencing is completed, the time challenges are still daunting. The variants determined to be potential causes of the disease under consideration, as well as incidental findings, require evaluation. A physician could be faced with the analysis of hundreds of variants, requiring many hours of background research to determine whether any play a role in the health of the patient. Then, the results must be communicated to the patient, a task that, depending on the patient's desire to receive incidental findings, could require several more hours. In addition, confirmatory testing and other diagnostic procedures will almost certainly be needed.

It is also uncertain which genetic variants should be considered "clinically significant." Most often, the term is used to signify variants that may lead to a change in care.[34] It is uncertain whether variants that lead to a diagnosis of a disease that is not treatable should be considered meaningful. The American College of Medical Genetics and Genomics recently released a list of gene variations that, when found incidentally, meet the criteria for informing patients; these include conditions with well-known etiologies that are caused by known or strongly suspected genetic variants and that have established medical interventions.[35] For

example, a variant in the gene *APC*, which substantially increases the risk of colorectal cancer and for which early screening protocols and interventions are established, meets such criteria.[35] There are conflicting opinions about how to ensure that patients are treated for potentially pathogenic variations discovered during sequencing, and also about how to respect the patient's right to choose whether or not to be informed about such results.[36,37]

Workforce and Training

As whole-genome and whole-exome sequencing become tools to inform diagnostic and therapeutic decisions, a knowledgeable workforce of physicians and other health professionals is essential. Given the limited number of genetics professionals, physicians in other specialties will likely need to develop the requisite specialized expertise. Physicians will need an expanded level of baseline genetics knowledge; at present, however, physicians often lack such knowledge.[38-43]

Genetics training in medical school and residency programs, and for practicing physicians, should be revamped to address the gaps that already exist and that are likely to increase as sequencing technologies become more routine.[38,43-46] Recommendations for medical school curricula that emphasize genetics interpretive and communication skills have been made, and development of genomics certification programs for nongeneticist physicians have been proposed.[8,46] Integrated electronic applications that effectively incorporate genomics resources are needed. For example, physicians would benefit from electronic medical record systems that include built-in decision support for clinical situations in which genetic information is relevant. The interpretation of genomic data is increasingly reliant on bioinformatics computer programs; thus, education on the fundamentals of bioinformatics and clinical data handling is also important.

Standards and Best Practices

The many questions about appropriate clinical use of next-generation sequencing technologies have prompted calls for the establishment of standards and best practices.[4,8] The Centers for Disease Control and Prevention's Evaluating Genomic Applications in Practice and Prevention Working Group has recommended approaches that it believes will improve the development of evidence-based guidelines for whole-genome sequencing.[47] It recommends that guidelines-development processes include attention to frameworks for categorizing results, evidence thresholds for returning results to patients and taking clinical action, patient preferences, and broad stakeholder engagement.

The American College of Medical Genetics and Genomics recently adopted a policy recognizing that genomic sequencing approaches can be of great value in the clinical evaluation of individuals with suspected germ-line genetic disorders.[48] The policy suggests clinical situations in which whole-genome or whole-exome sequencing may be most valuable in a diagnostic assessment. These include cases in which (1) the phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available; (2) a patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making whole-genome or whole-exome analysis of multiple genes simultaneously a more practical approach; or (3) a patient presents with a likely genetic disorder but specific genetic tests available for that phenotype have failed to provide a diagnosis.[46]

Future Directions and Research Needs

In some instances, next-generation sequencing-based technologies can end the diagnostic odyssey for patients with disorders that are resistant to standard diagnostic procedures. For some patients with malignant neoplasms, they can improve tumor classification, diagnosis, and management. In several cases, insurers have paid for whole-genome or whole-exome sequencing, perhaps an acknowledgment that sequencing can be less costly and more effective in determining a diagnosis than analysis of individual genes or other diagnostic procedures.[7,49] Without insurance coverage, some patients who might benefit from next-generation sequencing-based tests will be unable to afford the tests. An increasing number of clinical laboratories and private companies are performing whole-genome or whole-exome sequencing. As sequencing costs continue to decline, whole-genome sequencing could become more efficient than targeted single-gene or panel-based testing in a wider range of clinical situations. Although whole-genome sequencing for screening asymptomatic individuals is not currently recommended,[48] some have suggested that it may become more efficient and accurate than current newborn screening technologies.[50,51]

It is important to caution that considerable research is needed before whole-genome or whole-exome sequencing should be routinely incorporated into patient care. The successes to date have been in single cases or in very small groups; rigorous studies are needed to assess the utility of whole-genome and whole-exome sequencing in larger groups of patients, including comparative studies with other approaches to screening and diagnosis, clinical end points, and evaluations of health care costs. These data are especially important for insurance companies and other payers as they consider whether to cover the costs of the lengthy genetic counseling sessions that are essential before and after genome sequencing.

Effective integration of whole-genome and whole-exome sequencing into clinical practice is dependent on changes to the current model of genetic services delivery, which is largely specialty-centered with limited opportunities for genetic counseling and collaboration between specialties and diverse health professionals. Thus, studies should determine how to seamlessly deliver meaningful sequencing results to physicians and other health professionals using bioinformatics resources and electronic medical records. Enhanced models of genetic counseling that can accommodate the vast amount of information that must be conveyed to patients undergoing sequencing should be tested in demonstration projects. Physicians and other health professionals should be paid for the time they spend interpreting results, researching the role of identified variants, and fully explaining the variants to patients. The educational deficit about

genetics is substantial; developing a health care workforce with contemporary knowledge in genetics is as least as important at the other needs. In sum, although whole-genome or whole-exome sequencing show great promise, at present they should be rigorously evaluated and incorporated into patient care only in limited clinical situations.

ARTICLE INFORMATION

Accepted for Publication: August 16, 2013.

Published Online: November 11, 2013. doi:10.1001/jamainternmed.2013.12048.

Author Contributions: All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Johansen Taber, Dickinson.
Acquisition of data: Johansen Taber.
Analysis and interpretation of data: Johansen Taber, Wilson.
Drafting of the manuscript: Johansen Taber.
Critical revision of the manuscript for important intellectual content: All authors.
Administrative, technical, or material support: Johansen Taber, Wilson.
Study supervision: Dickinson.

Conflict of Interest Disclosures: Dr Johansen Taber is a member of the board of directors of the National Coalition for Health Professional Education in Genetics, a nonprofit organization that receives grants from various sources, including the federal government, nonprofit organizations, and unrestricted educational grants from for-profit entities such as Myriad Genetics. She has received reimbursement for travel to academic meetings from the Institute of Medicine, Partners Healthcare, the Centers for Disease Control and Prevention, and the Mayo Clinic. No other disclosures are reported

Additional Contributions: We thank the members of the Council on Science and Public Health, American Medical Association, for their review of an earlier version of this manuscript.

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