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## Genomic Sequencing: Assessing The Health Care System, Policy, And Big-Data Implications

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### Abstract

New genomic sequencing technologies enable the high-speed analysis of multiple genes simultaneously, including all of those in a person's genome. Sequencing is a prominent example of a “big data” technology because of the massive amount of information it produces and its complexity, diversity, and timeliness. Our objective in this article is to provide a policy primer on sequencing and illustrate how it can affect health care system and policy issues. Toward this end, we developed an easily applied classification of sequencing based on inputs, methods, and outputs. We used it to examine the implications of sequencing for three health care system and policy issues: making care more patient-centered, developing coverage and reimbursement policies, and assessing economic value. We conclude that sequencing has great promise but that policy challenges include how to optimize patient engagement as well as privacy, develop coverage policies that distinguish research from clinical uses and account for bioinformatics costs, and determine the economic value of sequencing through complex economic models that take into account multiple findings and downstream costs.

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Recent years have seen the growth of personalized medicine, which is the tailoring of interventions to individuals based on their genetic makeup. However, the advent of new genomic sequencing technologies, which enable the high-speed analysis of multiple genes

simultaneously, is dramatically changing how genetic testing can be used in clinical care. To determine how sequencing—defined below—can be used most appropriately, researchers, providers, payers, policy makers, and patients will need to understand its fundamental principles.

Our objective in this article is to provide a policy primer on sequencing and illustrate how it may affect health care system and policy issues. We thus developed an easily applied classification of sequencing based on inputs, methods, and outputs. We used this classification to examine the implications of sequencing for three health care system and policy issues: making care more patient centered, developing coverage and reimbursement policies, and assessing economic value. Our sequencing classification could also be used to inform analyses of other issues related to ethics, clinical guidelines, and technology adoption.

Other articles have defined *sequencing*.<sup>1,2</sup> However, to our knowledge, there has not previously been a primer on the uses of sequencing that would assist decision makers working on health care system issues in grasping its complexities.

## Genomic Sequencing Explained

We begin with brief definitions of key concepts and terms (for more information, see the National Institutes of Health's Genetics Home Reference).<sup>3</sup> The purpose of genetic testing in general is to look for changes in the genetic code, called *variants* or *mutations*, that may indicate health conditions. Until recently, most genetic testing was performed on a limited number of known genes. An example of such testing is the analysis of the BRCA1 and BRCA2 genes for determining a person's risk for breast and ovarian cancer.<sup>4–7</sup>

Genome sequencing deciphers the order of DNA bases—the building blocks of the DNA double helix—in an entire genome. Sequencing methods were first developed in the 1970s. However, new technologies have recently been developed that enable the rapid sequencing of large amounts of DNA at lower costs than was previously possible.

These new technologies, often called next-generation, massively parallel, or high-speed sequencing, are distinguished by their ability to rapidly examine many genes simultaneously, using a single test. The technologies have opened the door for sequencing to be used in clinical care instead of only for research purposes, and possibly for sequencing to ultimately replace many current tests on specific genes. Sequencing encompasses an evolving range of methods and approaches that can be used in a variety of ways. Thus, it is helpful to think of sequencing as a continuum. On that continuum, *targeted sequencing* involves sequencing one or more specific genes, often as a panel of multiple genes. *Whole exome sequencing* involves the determination of the DNA sequence of the protein-encoding regions—collectively known as the exome—which constitute about 1 percent of the genome. And *whole genome sequencing* involves the determination of the sequence of most of the DNA content constituting the entire genome, which has about 22,000 genes. Whole exome sequencing has the potential to identify clinically relevant variations in genes at a lower cost than whole genome sequencing.

There is no one definition of *sequencing* that is applicable across all uses. Instead, any definition needs to consider the context within which the technology is used. Thus, we developed a classification of the uses of sequencing, which we present below. We also compare sequencing to methods of genetic testing that target specific, known variants in single genes, called *single mutation testing*.

The advent of sequencing has greatly reduced the time and costs associated with examining human genetic variations across the entire genome. It has also substantially increased the amount of data to be stored and the complexity of both interpreting the information and using it effectively to improve health care.<sup>8–11</sup>

Sequencing technologies are now being used in research settings and are rapidly moving into clinical care.<sup>12,13</sup> For example, there have been several recent case-study reports of how sequencing has provided more accurate diagnoses and more appropriate treatment for patients with cancer, compared to single mutation testing.<sup>14–16</sup> Trials are now examining the use of whole genome sequencing to identify appropriate treatments and future risks for both healthy populations and populations with specific conditions.<sup>17,18</sup>

## Why It is Important to Understand Sequencing

The complexity of sequencing far exceeds that of most other testing in health care, and decision makers will have to determine when and how to use sequencing. Thus, it is important to clarify its various uses. Sequencing has very different implications for the health care system depending on its use, as the two uses of sequencing described below make clear.

The first use is sequencing of malignant tumors, using established panels of a limited number of specific genes that have known roles in cancer and that therefore could guide immediate treatment decisions. For example, in patients with lung cancer, sequencing is often used to identify mutations in a targeted panel of genes that affect the likelihood of response to specific chemotherapy drugs.

The second use is whole genome sequencing in a population that has no known risk factors in an attempt to find any variants that may predict a future risk of disease, even though many of the variants found may not have any known clinical significance and the knowledge of them may have a negative impact on patients and their families. For example, whole genome sequencing can be performed on a healthy newborn baby to look for variants that may predict diseases with an onset in early childhood—such as familial hypercholesterolemia (a medical condition resulting in high low-density lipoprotein cholesterol beginning at birth that can cause heart attacks at an early age) and long QT syndrome (a medical condition resulting from an abnormality in the electrical system of the heart that can cause a variety of symptoms, including fainting and cardiac arrest). However, many of the variants found may not yet have any known clinical significance and could lead to anxiety or unnecessary future testing.

## Sequencing and ‘Big Data’

The proliferation of genomics data through the advent of sequencing technologies is a key driver of the increasing availability of “big data.” Forces behind the movement toward the use of both genomics and big data include increased amounts of genomic and other types of data, improved analytic tools, the increasingly rapid development of information technology (IT), and the need to personalize health care.<sup>19</sup>

In addition, many of the medical discoveries of the future will depend on the ability to process and analyze large genomic data sets, which continue to expand as the cost of sequencing decreases.<sup>20</sup> Health care systems are hoping to reap the benefits of big data by combining patients' genomic data with clinical, behavioral, and environmental data to facilitate the use of more-tailored treatments and to examine patterns of associations across patients.

Genomics is big indeed: The storage space required for a raw sequence data file from just one person's whole genome is approximately a hundred gigabytes, and the sequencing instruments now available around the world can collectively sequence fifteen quadrillion nucleotides per year.<sup>21</sup> To put this into perspective, the amount of data in each genome is equivalent to the information in over 100,000 photos. Big data is characterized not only by the amount of data involved, but also by the complexity, diversity, and timeliness<sup>22</sup> of what is being sequenced.

### A Classification of Sequencing Characteristics

There are many possible ways to characterize sequencing. For ease of understanding, we classified sequencing based on three categories: inputs, methods, and outputs (Exhibit 1).

#### Sequencing Input

**Which Patients are Sequenced**—An important distinction arises between disease-specific genomic medicine and general genomic medicine (Exhibit 1). In the first case, patients who have a specific disease or are considered likely to have or develop a disease because of symptoms or risk factors such as family history can be sequenced to search for variants in genes known to be associated with that disease. The results can help clinicians prescribe therapies that are known to target certain genetic variants or reduce the person's risk of developing the disease or condition. In the second case, patients who are generally healthy and do not have a strong family history of a genetic syndrome or do not know their family history (for example, people who were adopted) can be sequenced to assess future or currently undetected health risks (such as for familial hypercholesterolemia and long QT syndrome).

Until now, disease-specific genomic medicine has been the norm. However, advances in technology mean that sequencing could soon be used to screen the general population for a wide range of future risks.

**Why Patients are Sequenced**—As is the case with single mutation testing, sequencing for patients can be used for a range of purposes (Exhibit 1) and at different times, each of

which may have different implications for the health care system. For example, sequencing used to diagnose an existing condition will have very different implications than sequencing used on healthy newborns in terms of the impact on family members, health care costs and savings, and patient outcomes.

**What is sequenced**—A key distinction is whether sequencing is performed on germline (or inherited) DNA or on disease-state material (such as a tumor) that may have acquired new genetic aberrations that were not present at the patient's birth and are not hereditary (Exhibit 1). Germline DNA testing can detect inherited variants that are known to be associated with a specific trait, susceptibility, or disease. For example, germline DNA testing for a BRCA1 and BRCA2 gene mutation can identify people with an inherited risk of breast and other cancers.<sup>7</sup>

Conversely, genetic testing performed on disease specimens such as malignant tumors or infected body fluids to look for somatic mutations may provide diagnostic, prognostic, or therapeutically relevant information for the treatment of that disease state. For example, patients with lung cancer whose tumors harbor certain EGFR gene mutations are much more likely to respond to treatment with drugs such as erlotinib (Tarceva) that target the EGFR signaling pathway than to other treatments that do not target this pathway.<sup>23</sup> Such information, however, is not as relevant for family members as information derived from germline DNA testing.

## Sequencing Methods

**Technology Used**—The type of sequencing platform used (including the machine, chemistry, and software), the interpretation and reporting standards applied, and the amount of storage space needed<sup>24</sup> can affect the accuracy, reproducibility, and outcomes of sequencing. For example, a recent study found that accuracy varied greatly between sequencing platforms made by two leading companies.<sup>25,26</sup>

Such issues are not new, and they are also relevant to single mutation testing. However, they are vastly more complex in sequencing because of the amount of data involved.<sup>27</sup> The potential exists for wider variation and less transparency in how sequencing tests are run and interpreted as a result of the sophisticated algorithms used.<sup>28</sup>

**Extent of sequencing**—The ability of genomic sequencing to provide results for multiple variants in a single gene in a single disease (for example, multiple BRCA1 variants), multiple variants in multiple genes in a single disease (for example, Lynch syndrome—an inherited condition that increases the risk of colon cancer and other types of cancer) and multiple diseases at the same time (such as breast cancer and Lynch syndrome) is a characteristic that distinguishes sequencing from single mutation testing (for example, testing for a specific mutation in a specific gene and disease).

As described above, the extent of data from sequencing exists along a continuum (Exhibit 1). The use of gene panels based on sequencing technologies is moving rapidly into clinical care, and several companies are offering gene panels, including Ambry Genetics<sup>29</sup> and Invitae.<sup>30</sup>

## Sequencing Output

**Findings Examined and Reported**—If an entire genome is sequenced, almost everyone tested will have multiple findings—each with independent metrics of validity, utility, and possible interventions and outcomes. These results are likely to include incidental findings that are not related to the reason for testing. This, too, distinguishes sequencing from single mutation testing, in which incidental findings are less common. For example, a person being sequenced to determine susceptibility for breast cancer may be discovered to have Huntington's disease, which has no cure.

Furthermore, some findings from sequencing may be masked by the laboratory or reported to the provider but not to the patient, because they have unknown clinical implications and thus providing the results is considered potentially harmful. There has been much controversy about how to address incidental findings and what findings should be reported, including debates about whether experts should determine which incidental findings will be reported to all patients or whether patients should decide what specific results they want to know.<sup>31–34</sup>

**Clinical Relevance of Findings**—The goal of sequencing is to identify genetic variants that have known impacts on health and disease. However, sequencing results have variable clinical relevance to patients' and providers' decision making and to patients' outcomes.

As noted above, a critical challenge of sequencing is that it often provides many more incidental findings or findings of unknown significance and fewer variants of clinical significance, compared to single mutation testing. Each finding may be categorized as either clinically actionable, not directly actionable now, of unknown or no clinical significance, or useful only in research (Exhibit 1). Some findings may be harmful because they provide information about future conditions that cannot be treated or because they lead to unnecessary testing and interventions.<sup>1,35</sup>

Another important challenge of sequencing stems from its position at the interface between clinical research and clinical practice. The majority of findings from sequencing remain of unknown or unvalidated clinical significance. Thus, a large proportion of the big data obtained from sequencing remains in the research realm. Further translational and clinical research is required to determine whether specific sequencing variants are associated with the diagnosis or risk of a disease, its prognosis, or the likelihood of response to a particular therapy and thus improved outcomes.

## Assessing the Implications of Sequencing

Our three-part classification of sequencing described above provides a framework for assessing the possible implications of sequencing for patient-centered care, reimbursement, and economic value.

### Patient-Centered Care

There is a growing focus on patient engagement, shared decision making, and the incorporation of patients' preferences into clinical and policy decisions. The use of

sequencing will further push the delivery of health care from a disease-centered model toward a patient-centered model because it will provide more details about how a patient's genome relates to his or her specific disease or development of future disease.<sup>36</sup> The potential for personalizing health care from the perspectives of disease prevention, disease management, and therapeutics is increasing as a result of the increased availability of genomics information and big data.<sup>37</sup>

However, sequencing and big data raise privacy and security questions about how data will be stored and reevaluated over time that should consider patients' concerns: Where will the raw data be stored, who will maintain them, and who will decide when they should be reevaluated as new findings emerge?

There will be uses of sequencing in which patients' preferences are less relevant. For example, a laboratory might one day routinely use sequencing as a more efficient method of testing than single mutation tests. In that case, the choice to use sequencing might be invisible to the patient and clinician.

In general, patients' preferences will be more relevant when sequencing is used to predict future risks in a currently healthy population; when the results have implications for family members, which introduces issues about whether and how family members will be informed, what interventions will be offered to them, and what outcomes are likely; and when findings that may be returned to patients include some of unknown usefulness or others that may reveal a risk of negative outcomes, such as a fatal and untreatable condition. For example, sequencing that reveals a future risk of Alzheimer's disease will require a high level of sensitivity to patients' preferences and the need to engage patients in decision making.

### **Coverage and Reimbursement Policies**

Payers' policies play a key role in the adoption of new technologies, because ultimately such technologies have to be covered and reimbursed if they are to be widely adopted. For some uses of sequencing, payers adapt existing approaches to making coverage and reimbursement decisions. In contrast, other uses may require new approaches because existing coverage policies are insufficient.

Big data derives its utility from being used for both research and clinical applications. Payers typically cover only interventions that are for clinical use, not those that are for research. But in some cases, the distinction between clinical and research uses is blurred. One example is determining a person's eligibility to participate in a clinical trial in conjunction with his or her standard treatment. Such a situation is not uncommon in oncology, where a multigene panel may include both genes of unvalidated clinical significance (which may be used to determine eligibility for a clinical trial of investigational therapy) and those whose significance has been clinically validated (which may be used for treatment decisions).

In general, it will be challenging to create coverage policies for sequencing when its use diverges from standard clinical practice—as in the case of screening a general population for

future risk or using sequencing to justify off-label treatments. In particular, tumor sequencing can prompt off-label therapy when it identifies a mutation known to be targeted by a drug approved for a different cancer that harbors the same mutation. This could lead providers to prescribe the drug although the same mutation may not be equally responsive to it across cancer types: For example, BRAF<sup>V600E</sup> inhibitors have markedly lower activity in colorectal cancer than in melanoma, although the diseases have the same mutation.<sup>38,39</sup>

Another issue is determining who should pay for the bioinformatics infrastructure and the computational tools that are needed to interpret sequencing results. This infrastructure includes data storage and the periodic reevaluation of incidental findings that may attain clinical relevance over time. Current reimbursement and coding systems are not structured to reimburse bioinformatics as a care service or to pay for the infrastructure needed to collect and use sequencing data.

### The Economic Value of Sequencing

The adoption of sequencing technologies will ultimately depend on the value that they provide not only to individuals but also to the health care system. For example, complex economic analyses will be needed to determine the value of both sequencing that is used in the general population to detect future risk and sequencing that produces findings used to support interventions that diverge from standard clinical practices. Additionally, placing a value on sequencing whose results affect family members will require complex models that take into account the economic impact on multiple relatives as well as the patient.

The use of big data in general will also require complex analyses because of the great variability in the technologies used and the ways data are interpreted. Furthermore, economic evaluations of sequencing will need to consider the large amount of computer power required for the storage of sequencing results and other big data.

To our knowledge, there have not been any cost-effectiveness analyses or other economic analyses of sequencing. It is difficult to predict which uses will be more cost-effective than current methods of testing for genetic conditions. Nonetheless, we can provide some predictions based on similar analyses of new technologies.

In general, we expect that sequencing may not be more cost-effective than existing methods of genetic testing in two situations. The first is when there are already cost-effective methods of genetic testing, so that the additional costs of sequencing are not offset by additional benefits. The second is when sequencing is used to screen a general population for future risk if there is a lack of cost-effective interventions for the conditions identified—interventions whose results would offset the significant cost of the sequencing.

However, sequencing could be cost-effective when it detects conditions that can be treated using a cost-effective approach, or when it provides more information than single mutation testing would. For example, BRCA1 and BRCA2 testing currently costs \$3,000–\$4,000 using the test marketed by Myriad. However, it may become possible to obtain results not only for these two genes but also for many other relevant genes using a single whole genome sequencing test at the same or lower cost.



## Conclusion

We developed an easily applied classification of sequencing and illustrated how it is linked to analyses of health care system and policy issues. It is critical to begin examining the implications of sequencing for the health care system. The key question is not, “Should we do sequencing?”—the technology is here today and will be used—but rather, “Where and when is sequencing most useful, and how should we evaluate those decisions?” Whether sequencing can realize its potential to improve patient outcomes will depend on how patients and providers value the information that it provides, whether it will be covered by payers and recommended in guidelines, and whether its economic value to the health care system outweighs its costs.

Our approach can be used to define and organize analyses of the implications of sequencing for the health care system. However, we recognize that our sequencing classification represents only one approach to characterizing sequencing. The categories inherently overlap, and we focused on key factors that we felt were more relevant to the health care system and policy audience than a highly technical classification would be.

Sequencing holds great promise, but policy challenges remain—including how to optimize patient engagement as well as privacy, unravel the complexities of developing coverage policies that distinguish research from clinical uses and account for bioinformatics costs, and develop more complex economic models that take into account multiple findings and downstream costs. Health care policy makers will have to determine the most appropriate uses of this powerful, wide-reaching, and rapidly evolving new technology.

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## Exhibit 1

### A Classification Of Sequencing Characteristics

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#### Sequencing Input

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Which patients are sequenced

- People with risk factors or symptoms (disease-specific genomic medicine)
- People in the general population with no known risk factors (general genomic medicine)

Why patients are sequenced

- Diagnosis
- Treatment decisions and monitoring
- Detection of future risk
- Reproductive planning (preconception and prenatal screening)
- Newborn screening

What is sequenced

- Genetic information of a person present at birth (inherited or germline)
  - Genetic information of a disease-state material in a person (for example, tumor or infection) that emerges during the person's life (somatic or acquired)
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#### Sequencing Methods

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Technology used

- Platform used (machine, chemistry, and software), interpretation, and reporting standards
- Accuracy and reproducibility of results

Extent of sequencing

- Single mutation testing
  - Testing of panels of multiple genes or regions
  - Whole exome sequencing
  - Whole genome sequencing
- 

#### Sequencing Output

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Findings examined and reported

- Disease specific
- Incidental or secondary
- Of unknown significance

Clinical relevance of findings

- Variants with known clinical validity and utility (where an intervention exists that is associated with improved patient outcomes)
- Variants that may not currently be directly actionable
- Variants with unknown or no clinical significance
- Findings used for research purposes only