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Perspective

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First FDA Authorization for Next-Generation Sequencer

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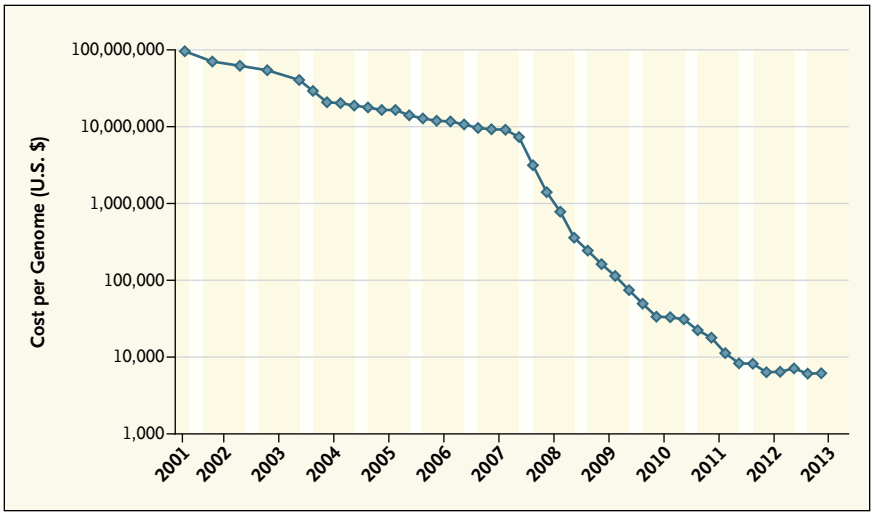
This year marks 60 years since James Watson and Francis Crick described the structure of DNA and 10 years since the complete sequencing of the human genome. Fittingly, today the Food and Drug Administration (FDA) has granted marketing authorization for the first high-throughput (next-generation) genomic sequencer, Illumina's MiSeqDx, which will allow the development and use of innumerable new genome-based tests. When a global team of researchers sequenced that first human genome, it took more than a decade and cost hundreds of millions of dollars. Today, because of federal and private investment, sequencing technologies have advanced dramatically, and a human genome can be sequenced in about 24 hours for what is now less than $5,000 (see graph). This is a rare example of technology development in which faster, cheaper, and better have coincided: as costs have plummeted and capacity has increased, the accuracy of sequencing has substantially improved. With the FDA's announcement, a platform that took nearly a decade to develop from an initial research project funded by the National Institutes of Health will be brought into use for clinical care. Clinicians can selectively look for an almost unlimited number of genetic changes that may be of medical significance. Access to these data opens the door for the transformation of research, clinical care, and patient engagement.

To see how this technology could be used, consider cancer. Comprehensive analysis of the genome sequence of individual cancers has helped uncover the specific mutations that contribute to the malignant phenotype, identify new targets for therapy, and increase the opportunities for choosing the optimal treatment for each patient. For instance, lung adenocarcinoma can now be divided into subtypes with unique genomic fingerprints associated with different outcomes and different responses to particular therapies. More broadly, recent work from the Cancer Genome Atlas demonstrates that the tissue of origin of a particular cancer may be much less relevant to prognosis and response to therapy than the array of causative mutations.[1] As a result, patients diagnosed with a cancer for which there are few therapeutic options may increasingly benefit from drug therapies originally aimed



Cost per Genome.
Adapted from the National Human Genome Research Institute.

at other cancers that share common driver mutations. The new technology allows us go from our current approach of targeted searches for specific mutations in individual cancers to widespread use of approaches that survey the entire genome.

A major area of opportunity that has yet to be fully exploited is pharmacogenomics — the use of genomic information to identify the right drug at the right dose for each patient. More than 120 FDA-approved drugs have pharmacogenomics information in their labeling, providing important details about differences in response to the drug and, in some cases, recommending genetic testing before prescribing.[2]

But the full potential of pharmacogenomics is largely unrealized, because of the logistic challenges in obtaining suitable genomic information in a timely enough fashion to guide prescribing. Placing genomic information in the electronic medical record would facilitate this kind of personalized medicine. If the patient's entire genome were part of his or her medical record, then the complexities of acquiring a DNA sample, shipping it, and performing laboratory work would be replaced by a quick electronic query.

Although this scenario holds great promise, the utility of genomic information for drug prescribing must be documented with rigorous evidence. For example, three recently published clinical trials raise questions about the clinical utility of using pharmacogenetic information in the initial dosing of vitamin K anatagonists.[3]

The FDA based its decision to grant marketing authorization for the Illumina instrument platform and reagents on their demonstrated accuracy across numerous genomic segments, spanning 19 human chromosomes. Precision and reproducibility across instruments, users, days, and reagent lots were also demonstrated.

The marketing authorization of a sequencing platform for clinical use will probably expand the incorporation of genetic information into health care. But even the most promising technologies cannot fully realize their potential if the relevant policy, legal, and regulatory issues are not adequately addressed. Already, key policy advances have helped smooth the way and address many of the public's concerns about the potential misuse of genetic information.[4] For example, the Health Insurance Portability and Accountability Act of 1996 (HIPAA) and the Genetic Information Nondiscrimination Act (GINA) prohibit health insurers from considering genetic information as a preexisting condition, as material to underwriting, or as the basis for denying coverage. GINA also protects against use of genetic information by employers. These protections do not, however, extend to the disease manifestations of genetic risks. Although genomic information showing a predisposition to cancer would be protected under GINA, other clinical signs or symptoms indicative of cancer are not protected. Provisions of the Affordable Care Act set to go into effect in 2014 go a step further and will preclude consideration of all preexisting conditions, whether genomic or not, in establishing insurance premiums. Current federal laws, however, do not restrict the use of genomic information in life insurance, long-term care insurance, or disability insurance.

The legal landscape for the use of genomics in personalized medicine grew brighter in June of this year when the Supreme Court ruled (in *Association for Molecular Pathology v. Myriad Genetics*) that isolated naturally occurring DNA cannot be patented. This decision was a breakthrough for

access to individual genetic tests but also, even more important, for the integration of genome sequencing into clinical care. Before the *Myriad* decision, there were substantial concerns that in order to offer whole genome sequencing, clinical laboratories would have to pay royalties to a long list of gene patent holders. The decision has opened the creative doors to an as yet unimaginable set of products that may benefit the public health.

The FDA has also been active in addressing other regulatory issues surrounding personalized medicine.[5] Along with authorizing the Illumina technology for marketing, the FDA recognized the need for reference materials and methods that would permit performance assessment. As a result, the FDA collaborated with the National Institute for Standards and Technology (NIST) to develop reference materials consisting of whole human genome DNA, together with the best possible sequence interpretation of such genomes. The first human genome reference materials are expected to be available for public use in the next 12 months.

This marketing authorization of a non–disease-specific platform will allow any lab to test any sequence for any purpose. Thus, putting in place an appropriate risk-based regulatory framework is now critical to ensure the validation and quality of tests (called laboratory-developed tests, or LDTs) developed in-house by clinical laboratories.

The marketing authorization for the first next-generation genome sequencer represents a significant step forward in the ability to generate genomic information that will ultimately improve patient care. Yet it is only one step. There are many challenges ahead before personalized medicine can be considered truly embedded in health care. We need to continue to uncover variants within the genome that can be used to predict disease onset, affect progression, and modulate drug response. New genomic findings need to be validated before they can be integrated into medical decision making. Doctors and other health care professionals will need support in interpreting genomic data and their meaning for individual patients. Patients will want to be able to talk about their genetic information with their doctor. With the right information and support, patients will be able to participate alongside their doctors in making more informed decisions. Reimbursement issues need to be resolved to assure that patients have access to the best tests and that manufacturers have incentives to develop them.

The arrival of next-generation sequencing at this regulatory landmark is only the beginning. We need to work together to ensure that research progresses, that regulatory policies are developed, that patients' rights and needs are addressed, and that clinical use of genomic information is based on rigorous evidence.

There are many challenges ahead before personalized medicine can be considered truly embedded in health care. These range from uncovering and validating key variants to supporting clinicians in interpreting genomic data to resolving reimbursement issues.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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