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Perspective

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The Path to Personalized Medicine

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Major investments in basic science have created an opportunity for significant progress in clinical medicine. Researchers have discovered hundreds of genes that harbor variations contributing to human illness, identified genetic variability in patients' responses to dozens of treatments, and begun to target the molecular causes of some diseases. In addition, scientists are developing and using diagnostic tests based on genetics or other molecular mechanisms to better predict patients' responses to targeted therapy.

The challenge is to deliver the benefits of this work to patients. As the leaders of the National Institutes of Health (NIH) and the Food and Drug Administration (FDA), we have a shared vision of personalized medicine and the scientific and regulatory structure needed to support its growth. Together, we have been focusing on the best ways to develop new therapies and optimize prescribing by steering patients to the right drug at the right dose at the right time.

We recognize that myriad obstacles must be overcome to achieve these goals. These include scientific challenges, such as determining which genetic markers have the most clinical significance, limiting the off-target effects of gene-based therapies, and conducting clinical studies to identify genetic variants that are correlated with a drug response. There are also policy challenges, such as finding a level of regulation for genetic tests that both protects patients and encourages innovation. To make progress, the NIH and the FDA will invest in advancing translational and regulatory science, better define regulatory pathways for coordinated approval of codeveloped diagnostics and therapeutics, develop risk-based approaches for appropriate review of diagnostics to more accurately assess their validity and clinical utility, and make information about tests readily available.

Moving from concept to clinical use requires basic, translational, and regulatory science. On the basic-science front, studies are identifying many genetic variations underlying the risks of both rare and common diseases. These newly discovered genes, proteins, and pathways can represent powerful new drug targets, but currently there is insufficient evidence of a downstream market to entice the private sector to explore most of them. To fill that void, the NIH and the FDA will develop a more integrated pathway that connects all the steps between the identification of a potential therapeutic target by academic researchers and the approval of a therapy for clinical use. This pathway will include NIH-supported centers where researchers can screen thousands of chemicals to find potential drug candidates, as well as public–private partnerships to help move candidate compounds into commercial development.

The NIH will implement this strategy through such efforts as the Therapeutics for Rare and Neglected Diseases (TRND) program. With an open environment, permitting the involvement of all the world's top experts on a given disease, the TRND program will enable certain promising compounds to be taken through the preclinical development phase — a time-consuming, high-risk phase that pharmaceutical firms call "the valley of death." Besides accelerating the development of drugs to treat rare and neglected diseases, the TRND program may also help to identify molecularly distinct subtypes of some common diseases, which may lead to new therapeutic possibilities, either through the development of targeted drugs or the salvaging of abandoned or failed drugs by identifying subgroups of patients likely to benefit from them.

Another important step will be expanding efforts to develop tissue banks containing specimens along with information linking them to clinical outcomes. Such a resource will allow for a much broader assessment of the clinical importance of genetic variation across a range of conditions. For example, the NIH is now supporting genome analysis in participants in the Framingham Heart Study, obtaining biologic specimens from babies enrolled in the National Children's Study, and performing detailed genetic analysis of 20 types of tumors to improve our understanding of their molecular basis.

As for translational science, the NIH is harnessing the talents and strengths of its Clinical and Translational Sciences Award program, which currently funds 46 centers and has awardees in 26 states, and its Mark O. Hatfield Clinical Research Center (the country's largest research hospital, in Bethesda, MD) to translate basic research findings into clinical applications. Just as the NIH served as an initial home for human gene therapy, the Hatfield Center can provide specialized diagnostic services for rare and neglected diseases, offer a state-of-the-art manufacturing facility for novel therapies, and pioneer clinical trials of other innovative biologic therapies, such as those using human embryonic stem cells or induced pluripotent stem cells.

As genetics researchers generate enormous amounts of new information, the FDA is developing the regulatory science standards and evidence needed to use genetic information in drug and device development and clinical decision making. The agency's Critical Path Initiative aims to develop better evaluation tools, such as biomarkers and new assays. Under the Voluntary Genomic Data Submission program, companies can discuss genetic information with the FDA in a forum separate from the product-review process. These discussions give the agency and companies a better understanding of the scientific issues involved in applying pharmacogenomic information to drug development and offer an opportunity for early, informal feedback that may assist companies in reaching important strategic decisions. The goal is to help companies integrate genomics into their clinical-development plans.

Today, about 10% of labels for FDA-approved drugs contain pharmacogenomic information — a substantial increase since the 1990s but hardly the limit of the possibilities for this aspect of personalized medicine.[1] There has been an explosion in the number of validated markers but relatively little independent analysis of the validity of the tests used to identify them in biologic specimens.

The success of personalized medicine depends on having accurate diagnostic tests that identify patients who can benefit from targeted therapies. For example, clinicians now commonly use diagnostics to determine which breast tumors overexpress the human epidermal growth factor receptor type 2 (HER2), which is associated with a worse prognosis but also predicts a better response to the medication trastuzumab. A test for HER2 was approved along with the drug (as a "companion diagnostic") so that clinicians can better target patients' treatment (see table).

Increasingly, however, the use of therapeutic innovations for a specific patient is contingent on or guided by the results from a diagnostic test that has not been independently reviewed for accuracy and reliability by the FDA. For example, in 2006, the FDA granted approval to rituximab (Rituxan) for use as part of first-line treatment in patients with certain cancers. Since then, a laboratory has marketed a test with the claim that it can identify the

Examples of FDA-Approved Drugs and Companion Diagnostics in Clinical Practice.*

Approved Drug	Mechanism	Approved Companion Diagnostic
Herceptin (trastuzumab)	Targets HER2 to treat metastatic breast cancer	HER2 immunohistochemistry tests, HER2 gene-amplification tests
Erbitux (cetuximab)	Targets EGFR to treat metastatic colorectal cancer	EGFR immunohistochemistry test
Gleevec (imatinib)	Targets the cell-surface tyrosine kinase receptor c-kit in gastrointestinal stromal tumors	c-kit immunohistochemistry test

* EGFR denotes epidermal growth factor receptor, and HER2 human epidermal growth factor receptor type 2.

approximately 20% of patients who are more likely to have a response to the drug. The FDA has not reviewed the scientific justification for this claim, but health care providers may use the test results to guide therapy. This undermines the approval process that has been established to protect patients, fails to ensure that physicians have accurate information on which to make treatment decisions, and decreases the chances that physicians will adopt a new therapeutic–diagnostic approach. The FDA is coordinating and clarifying the process that manufacturers must follow regarding their claims, including defining the times when a companion diagnostic must be approved or cleared before or concurrently with approval of the therapy. The agency will ensure that claims that a test will improve the care of patients are based on solid evidence, and developers will get straightforward, consistent advice about the standards for review and the best way to demonstrate that the combination works as intended.

Genetic tests are not perfect, in part because most gene mutations do not perfectly predict outcomes. Clinicians will need to understand the specificity and sensitivity of new diagnostics. The agency's goal is an efficient review process that produces diagnostic–therapeutic approaches that clinicians can rely on and allows companies that invest in establishing the validity and usefulness of tests to make specific, FDA-backed claims about benefits.

Patients should be confident that diagnostic tests reliably give correct results — especially when test results are used in making major medical decisions. The FDA has long taken a risk-based approach to the oversight of diagnostic tests, historically focusing on test kits that are broadly marketed to laboratories or the public (e.g., pregnancy tests or blood glucose tests); such kits are sold only if the FDA has determined that they accurately provide clinically significant information. But recently, many laboratories have begun performing and broadly marketing laboratory-developed tests, including complicated genetic tests. The results of these tests can be quite challenging to interpret. Because clinicians may order a genetic test only once, getting the results right the first time is crucial.

There are reports of problems with laboratory tests that have not had FDA oversight: women were erroneously told they were negative for a mutation conferring a very high risk of breast cancer; an ovarian cancer test, marketed before the completion of an NIH-funded study,[2] gave false readings that reportedly led to the unnecessary removal of women's ovaries; and flawed, mishandled data underlying a test for Down's syndrome were discovered only days before the test was to go on the market. Through a process that includes opportunities for public input, the FDA will work to ensure the quality of key diagnostic tests, helping to protect patients and giving clinicians confidence that personalized medicine will lead to real health improvements.

In addition, the NIH will address the fact that there is no single public source of comprehensive information about the more than 2000 genetic tests that are available through clinical laboratories. On the recommendation of a federal advisory committee,[3,4] the NIH — with advice from the FDA, other Department of Health and Human Services agencies, and diverse stakeholders — is creating a voluntary genetic testing registry to address key information gaps.[5] Readily available information about these tests, including whether they were cleared or approved by the FDA, will help clinicians and consumers make informed decisions about using the tests to optimize health care. The registry will also support scientific discoveries by facilitating the sharing of data about genetic variants.

In February, the NIH and the FDA announced a new collaboration on regulatory and translational science to accelerate the translation of research into medical products and therapies; this effort includes a joint funding opportunity for regulatory science. Working with academic experts, companies, doctors, patients, and the public, we intend to help make personalized medicine a reality. A recent example of this collaboration is an effort to identify new investigational agents to which certain tumors, identified by their genetic signatures, are responsive.

Real progress will come when clinically beneficial new products and approaches are incorporated into clinical practice. As the field advances, we expect to see more efficient clinical trials based on a more thorough understanding of the genetic basis of disease. We also anticipate that some previously failed medications will be recognized as safe and effective and will be approved for subgroups of patients with specific genetic markers.

When the federal government created the national highway system, it did not tell people where to drive — it built the roads and set the standards for safety. Those investments supported a revolution in transportation, commerce, and personal mobility. We are now building a national highway system for personalized medicine, with substantial investments in infrastructure and standards. We look forward to doctors' and patients' navigating these roads to better outcomes and better health.

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

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The ACA's New Weapons against Health Care Fraud

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Marshaling expanded financial resources, aggressive new legal authority, and rare bipartisan solidarity, the Obama administration is accelerating federal efforts to fight health care fraud, waste, and abuse that cost taxpayers and private insurers billions of dollars every year. Although the new forms of authority are granted by the Affordable Care Act (ACA), which Republicans unanimously opposed, most GOP legislators strongly support — and some even sponsored measures to enable[1] — the more rigorous crackdown on illegal activities that plague Medicare, Medicaid, and private insurers. Under past policies, Congress and the executive branch "way, way, way" underspent on fighting health care fraud, according to Kerry Weems, who was acting administrator of the Centers for Medicare and Medicaid Services (CMS) from 2007 to 2009.[2]

Since 1990, the Government Accountability Office (GAO) has designated Medicare as a high-risk federal program because its vast size and complexity make it vulnerable to fraud, waste, and abuse. In 2009, government-wide "improper payments" totaled $98 billion — more than half of it paid by Medicare and Medicaid. It is uncertain how much of the activity that resulted in these payments was actual fraud, but Lewis Morris, chief counsel of the Office of Inspector General (OIG), Department of Health and Human Services (DHHS), told the Senate Finance Committee last year, "Although we cannot measure the full extent of health care fraud in Medicare and Med-