Democrats and Republicans in Washington apparently agree on one thing: the need to initiate a vigorous effort to develop genetic tests and targeted, genomic medicines that reach small populations within specific disease groups. President Barack Obama highlighted the emerging effort when he announced a “Precision Medicine” initiative as part of his 2015 State of the Union speech. A proposed $215 million budget increase spread across three agencies backed up the rhetoric. That new funding would be part of the fiscal 2016 budget, which begins on October 1, 2015—but only if Congress approves the money.

At about the same time, the House Energy and Commerce Committee released a draft of legislation that is a compilation of bills arising from the committee’s series of “21st Century Cures” hearings in 2014. Committee Chairman Fred Upton (R-Michigan) and Rep. Diana DeGette (D-Colorado) are the prime movers behind the bill, which they acknowledge is “far from perfect” in draft form. The bill has a number of sections that to some extent parallel the President’s research focus, but many of its provisions go way beyond research—to Medicare payment policy, for example. Nonetheless, the draft bill, which will be revised on its way to what the committee hopes will be congressional passage by the end of 2015, is supported by both Democrats and Republicans, at least at this early stage.

There are already “targeted” treatments such as imatinib mesylate (Gleevec, Novartis), available for the past decade, which is highly effective against a form of blood cancer known as chronic myeloid leukemia. Imatinib precisely targets the cancer cells. Most of the genetic diagnostic tests used to determine whether a patient will benefit from a drug such as imatinib have been developed by the company selling that drug. But the tests often lack specificity, in part because they are unable to drill down deep enough into a patient’s genome—because the patient’s genetic code cannot yet be read due to insufficient technology, and because the testing technology that does exist is immature.

President Obama has long been interested in pushing genetic diagnostic testing into a new era. In 2007, as a senator from Illinois, he introduced the Genomics and Personalized Medicine Act of 2007. Among other things, that bill would have established a national biobanking distributed database for the collection and integration of genomic data and associated environmental and clinical health information, made information available on the safety and efficacy of genetic tests, and commissioned a study of improvements to federal oversight and regulation of such tests. That bill went nowhere. The President has essentially resuscitated the legislation’s main provisions.

Genomics has been an area of research at the National Institutes of Health (NIH) for years. “The concept of precision medicine—prevention and treatment strategies that take individual variability into account—is not new,” says NIH Director Francis Collins, PhD. “Blood typing, for instance, has been used to guide blood transfusions for more than a century. But the prospect of applying this concept broadly has been dramatically improved by the recent development of large-scale biologic databases such as the human genome sequence; powerful methods for characterizing patients such as proteomics, metabolomics, genomics, diverse cellular assays, and even mobile health technology; and computational tools for analyzing large sets of data.”

The White House termed its initiative “a bold new research effort to revolutionize how we improve health and treat disease.” The idea is to come up with a new model of patient-powered research that promises to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies so they can select the treatments that work best for each particular patient. The backbone of the plan is building and analyzing large patient data sets culled from a one-million-patient database that the NIH will develop. The effort will focus mostly on cancer therapies.

The President’s proposed budget includes $130 million for the NIH in that regard. Another $70 million would go to the National Cancer Institute (NCI) to scale up efforts to identify genomic drivers in cancer. The Food and Drug Administration (FDA) would receive $10 million for additional staff to help advance the development of high-quality, curated databases, in particular a new approach for evaluating next-generation sequencing technologies. The Office of the National Coordinator, which orchestrates electronic health-data policy within the administration, would get $5 million to support the development of interoperability standards and requirements that address privacy and enable secure exchange of data across systems. This entire program apparently hinges on the establishment of public–private partnerships devoted to existing research cohorts (patient groups).

The House draft bill has a rationale similar to the Obama initiative. It is born out of the fact, according to the committee, that among the 10,000 known diseases, 7,000 of which are considered rare, there are treatments for only 500. The information on the draft bill released by the committee quotes Dr. Collins as saying that it now takes “around 14 years and $2 billion or more” to develop a new drug and “more than 95% of [such] drugs fail during development.” So a number of the provisions

---

Mr. Barlas, a freelance writer based in Washington, D.C., covers topics inside the Beltway.
in the draft are data-oriented, as with the President's plan, and it emphasizes coordinating and improving all the components in the “discovery, development, and delivery process” so that cycle is a constantly revolving generator of innovative new treatments and cures.

To that end, data-focused provisions aim to upgrade both the FDA and NIH systems, in the case of the FDA building on the Patient-Focused Drug Development program. The provision would also allow the FDA to use private–public partnerships to qualify other types of biomarkers.

What the Skeptics Say

Some view the promise of genetic diagnostics and treatments as overly inflated. Michael Millenson, President of Health Quality Advisors LLC and the Mervin Shalowitz, MD, Visiting Scholar at Northwestern University’s Kellogg School of Management, is one of them. “Genomics is incredibly cool,” Millenson explains. “Newsweek writes about it; Oprah talks about it. We Americans believe in magic bullets for everything. What is more alluring than predicting my future? I can hardly wait. Unfortunately, the excitement over the potential for the eventual future can overwhelm reasonable expectations for how quickly that future will arrive. You have to be careful to distinguish between great sound bites and great science.”

After President Obama’s announcement, Millenson wrote a column in Forbes magazine citing an analysis by Biomarker Base of three tests meant to show whether a specific type of breast cancer will reoccur. The analysis found that these competing tests share just 12 of the 125 biological targets they employ, and no one gene is used by all three. More importantly, results of the three tests—Genomic Health’s Oncotype DX, Agenda’s MammaPrint, and NanoString Technologies’ Prosigna—often disagree.

Neil Barth, MD, Chief Medical Officer at Agendia Inc., responds that Millenson doesn’t understand that the three tests address different clinical questions. “His comments suggest a significant lack of understanding of the bases upon which these tests were developed,” Dr. Barth states. For example, Oncotype’s test identifies patients who would benefit from chemotherapy starting with patients who must be treated with endocrine therapy for five years. In contrast, Agenda’s test starts with untreated patients and identifies those who can safely forego chemotherapy. “This fundamental difference is then further amplified by differences in how the genes were selected and the testing platforms that are used to perform the test,” Dr. Barth continues. “The tests are 180 degrees different. To say they give different results, no kidding.”

The tests are almost the same, however, when it comes to price. Dr. Barth says both MammaPrint and Oncotype DX cost a nudge over $4,000 per test.

Some genetic testing companies have run afoul of the FDA. A company called 23andMe Saliva had been selling a Collection Kit and Personal Genome Service (PGS) without marketing clearance or approval from the FDA, which considered it to be a medical device subject to the agency’s approval. The company had advertised the test as providing “health reports on 254 diseases and conditions,” including categories such as “carrier status,” “health risks,” and “drug response,” and specifically as a “first step in prevention” that enables users to “take steps toward mitigating serious diseases” such as diabetes, coronary heart disease, and breast cancer. The FDA was worried about the negative impact on people who used the test and received false positives or false negatives.

In November 2013, the FDA sent the company a warning letter stating in part: “For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist.” Today, the banner at the top of the company’s home page states: “Updated February 19, 2015: 23andMe provides ancestry-related genetic reports and uninterpreted raw genetic data only. We intend to add some health-related genetic reports in the future once we have a comprehensive product offering. At this time, we do not know which health reports might be available or when they might be available.”

Public–private drug-discovery collaboration ostensibly fostered by a federal agency has also been subject to inflated expectations. Remember the Reagan-Udall Foundation? President Obama, in his January announcement, said: “Through collaborative public and private efforts, the Precision Medicine initiative will leverage advances in genomics, emerging methods for managing and analyzing large data sets while protecting privacy, and health information technology to accelerate biomedical discoveries.” The Reagan-Udall Foundation was created by Congress in 2007 “to bring all parties to the table” in advancing regulatory science and research at the FDA.

The foundation limped along for its first few years with no staff and limited funding, and it hasn’t progressed much since. Between 2009 and 2013, according to the foundation’s website, it received a grand total of $8.4 million. Early critics worried that drug companies would use contributions to further their own narrow agendas, but given the size of those contributions (or lack thereof), that was probably an empty worry.

Some prominent members of the foundation’s board of directors were contacted by email and queried about the foundation’s apparent lack of momentum. A spokesman for the American Society of Clinical Oncology (ASCO) said that Richard Schilsky, MD, FASCO, ASCO’s Chief Medical Officer and one of the foundation board members, would not comment. Allan Coulkell, Senior Director of Drugs and Medical Devices at the Pew Charitable Trusts, another member of the board, did not respond to email questions.

The NIH Is Out Front

Maybe the NIH will be more successful harnessing the private sector than the Reagan-Udall Foundation has been. President Obama’s charge to the NIH is to assemble over time a longitudinal “cohort” of one million or more Americans who have volunteered to participate in research. Participants will be asked to consent to extensive characterization of biological specimens such as cell populations, proteins, metabolites, RNA, and DNA—including whole-genome sequencing, when costs permit—and behavioral data, all linked to their electronic health records. With appropriate protection of patient confidentiality, qualified researchers from many organizations will have access to the cohort’s data. These data will also enable observational
Precision Medicine Initiative Aims for a New Generation of Diagnostics and Treatments

Studies of drugs and devices and potentially prompt more rigorous interventional studies that address specific questions. Some of these cohort studies already exist, both at the NIH and in the databases of large health insurers, whether private or governmental, such as the Department of Veterans Affairs (VA). Some insurers have already signaled their interest in participation, including Kaiser Permanente, the Mayo Clinic, the Marshfield Clinic in Wisconsin, Geisinger Health System, and the VA, NIH Director Dr. Collins told Reuters in a March interview.

But health systems use different software, and getting them to talk to one another, and to the NIH, will be a not-insignificant problem, as it has been in developing regional electronic health networks. “The software has to be transparent, and the data must be ‘exquisite,’” Dr. Collins said. “That’s not easy.” By “exquisite” he means the data must be detailed and include genetic, clinical, environmental, and lifestyle components.

Dr. Collins has been trying to establish a large, human medical data cohort for at least a decade, ever since he successfully led an international team to sequence the first human genome as director of the National Human Genome Research Institute. Dr. Collins told Reuters that his 2004 proposal fell flat, but dramatic decreases in the cost of genomic sequencing and the adoption of electronic medical records are making it feasible.

The NIH effort to establish the “Precision Medicine” database—or whatever it comes to be called—will be led by NIH Deputy Director Kathy Hudson, PhD, and Yale geneticist Richard Lifton, MD, PhD. They will select a panel that will spend several months considering various proposals, and by September or October, Dr. Collins expects to have “a good sense of how we want to start this off.”

The FDA’s Requirements for Genetic Tests

Like the NIH, which conducted a workshop in February, the FDA also moved quickly to gather thoughts on how it should shape its involvement in the Precision Medicine initiative. It held a workshop, entitled “Optimizing FDA’s Regulatory Oversight of Next Generation Sequencing Diagnostic Tests,” on February 20, 2015.7 The purpose of the workshop was to discuss and receive feedback on the FDA’s regulatory approach to diagnostic tests for human genetics or genomics using next-generation sequencing (NGS) technology, which, when combined with in vitro diagnostic devices, generates large amounts of data. These tests pose certain challenges during review of premarket submissions. At the same time, this large amount of data provides opportunities for novel approaches to ensure the analytical and clinical validity of NGS tests.

The FDA will have to approve these tests, and the agency has admitted that its current regulations are not, for the most part, adequate or clear as to what data NGS sponsors need to supply. These NGS tests are fundamentally different from the tests sold by Agendia and its competitors. Those tests look at a patient’s cancer RNA and measure how the genes are “expressed” in order to estimate the chances that the disease will recur. NGS tests are presently more focused on DNA and the “structural” changes that are present in a patient’s normal cells (germline) that may place them at risk for developing a disease. NGS is faster and perhaps more accurate than prior methods at testing the DNA of many genes at one time. The capability of the NGS platform to accurately explore RNA expression and the product of RNA, proteins, is still under evaluation. There are very few FDA-approved NGS tests so far and only with DNA. The FDA approved the first NGS devices at the end of 2013:

1. The Illumina MiSeqDx Cystic Fibrosis 139-Variant Assay, which checks specific points in the patient’s clinical and functional translation (CFTR) gene sequence to detect known variants in the gene
2. The Illumina MiSeqDx Cystic Fibrosis Clinical Sequencing Assay, which sequences a large portion of the CFTR gene to detect any difference in that gene compared to a reference CFTR gene

At the same time, the FDA approved the Illumina MiSeqDx instrument platform and the Illumina Universal Kit reagents. Jennifer Viera, a spokeswoman for Illumina, says no company spokesperson is available to discuss its cystic fibrosis test. She could not provide any information on the cost of the test or how widely it is being used.

“NGS is changing the way we look at genomics,” says Alberto Gutierrez, PhD, director of the Office of In Vitro Diagnostics and Radiological Health in FDA’s Center for Devices and Radiological Health. “Before NGS, sequencing genes associated with a particular disease was a long and costly process. Today, we have the capability to read and interpret large segments of DNA very quickly in a single test, and this information-rich technology is becoming more accessible for use by physicians in the care of their patients.”

Today’s NGS tests are at the very advanced end of a category called laboratory developed tests (LDTs), which also include the less advanced Agendia and competitor breast cancer tests. These tests may raise fewer issues than NGS; there has been some question as to whether the FDA needs to approve them or not. The FDA did approve MammaPrint and the other tests. But they fall into a newer part of the LDT category, where the tests are often used in laboratories that are independent of the health care delivery entity. Additionally, LDTs are frequently manufactured with components and instruments that are not legally marketed for clinical use and rely more heavily on complex, high-tech instrumentation and software to generate results and clinical interpretations. Today, many new LDT manufacturers are large corporations that nationally market a limited number of complex, high-risk devices, in contrast to 1976 when hospital or public health laboratories used a wide range of devices that were generally either well-characterized and similar to standard devices; used to diagnose rare diseases; or designed specifically to meet the needs of their local patients. Together, these changes have resulted in a significant shift in the types of LDTs developed, the business model for developing them, and the potential risks they pose to patients.

Since 1988, when the Clinical Laboratory Improvement Amendments Act was passed, the FDA has exercised “enforcement discretion” toward LDTs. Because of the changes in the industry mentioned above, the agency is ditching that policy. The first step in that direction was issuance of draft guidance called “FDA Notification and Medical Device Reporting for Laboratory Developed Tests (LDTs)” on October 3, 2014.8 It continued on page 352
describes a risk-based framework for addressing the regulatory oversight of LDTs, including the FDA’s priorities for enforcing premarket and post-market requirements for LDTs as well as the process by which the FDA intends to phase in requirements for LDTs over time.

Any number of industry groups, including the American Medical Association, have assailed the FDA’s draft guidance. Wrote the AMA: “As drafted, it will negatively impact the ability of physicians to provide standard-of-care testing services and limit the use of any future publicly funded NIH research that is clinically validated by physicians to guide patient care.”

Industry opposition to upgraded FDA regulation of genetic tests is only one example of the barriers the NIH, NCI, FDA, and other federal agencies will face as they try to catapult medical genetics into its next era.

REFERENCES