UNLOCKING THE CODE OF HEALTH

Bridging the Gap
Between Precision Medicine
and FDA Regulation

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Precision medicine—tailoring treatments to the biochemistry of individual patients—has the potential to cure countless diseases. Molecular biomarkers are the foundation of this approach. Many doctors—notably, oncologists—routinely prescribe drugs in ways that best fit each patient's biomarker profile. The Food and Drug Administration (FDA), however, has been slow to incorporate biomarkers into the regulatory procedures for drug approval and, as a result, has significantly slowed the development of safe and effective treatments for many diseases.

Realizing the full potential that biomarkers offer to revolutionize modern medicine will require substantive and clear regulatory standards, now lacking, for incorporating biomarkers into the drug-approval process, as well as a more transparent, predictable, and timely FDA process for reviewing biomarker submissions.

1. The Importance of Biomarkers for Drug Development and Approval

Biochemists rely on an understanding of the molecular biomarkers that propel diseases to design targeted drugs to block or control them. Doctors then prescribe the drugs to specific subgroups of patients who have the biomarkers in question (estrogen-receptor-positive breast cancer, for instance). Other biomarkers can be used to track whether a disease is advancing or retreating at every stage of its development, thus providing early indications of how well a drug is performing. Changes in biomarker status (such as lowering blood sugar in a diabetic patient) that can provide rapid, reliable evidence of efficacy also have the potential to greatly accelerate the FDA's drug-approval process.

Modern diagnostic tools have revealed that what used to be viewed as a single disease is quite often caused by biomarkers that vary significantly across patients; different groups of patients therefore respond differently to the same drug. Researchers are assembling large databases and using powerful computers to link arrays of different biomarker profiles to the same clinically defined diseases. These findings can then lead to the design of multiple different drugs to address them.

Biomarker science also sets the stage for developing drugs that can be used to take control of disease-causing molecular pathways before clinical symptoms develop. The potential benefits are enormous. For example, according to one estimate, a drug that would delay the onset of Alzheimer's by five years would save about $367 billion in direct health costs by 2050 while likely extending the life span of millions of patients.

The Costs of Inaction

The FDA's reluctance or inability to move faster on this front has serious economic and commercial implications. The U.S. is not the only nation with the scientific and industrial infrastructure capable of exploiting the full potential of biomarker science. The European Union recently launched the second phase of its Innovative Medicines Initiative (IMI2), in which biomarker development is one of four key priorities. IMI2 began in 2014 and is intended to run for ten years with a budget of €3.276 billion, focusing on a broad range of illness, including cardiovascular disease, cancer, psychiatric disorders, and autoimmune diseases. While the debate goes on in America over a new regulatory framework, other countries are already moving rapidly to translate biomarker science into new protocols for approving drugs and diagnostics.

But the much harsher consequence of delayed reform is the cost to patients. Absent a full integration of the best available biomarker science in the drug-approval process, many drugs that could save many lives simply won't get approved at all. Integrating clinical trial research into clinical care, as Britain now proposes to do, would accelerate patient access to new lifesaving therapies even more and ensure that the U.S. remains an attractive place for biotechnology investment.

Precision medicine is the future of medicine. But it is also the antithesis of the FDA's long-standing one-size-fits-all drug-approval process. Top officials at the FDA have publicly acknowledged this for over a decade, but the agency has been very slow to develop consistent and transparent standards for using biomarkers in drug trials. The absence of such standards has sharply reduced industry incentives to make the large investments needed to develop new targeted drugs or seek formal approval of new uses for existing drugs. Meanwhile, countries such as the U.K. are preparing to completely revamp their drug-approval protocols to develop and use biomarker science during the drug-approval process and approve associated precision-medicine treatment protocols. By offering companies a faster, more certain, path to market, our global competitors hope to shift pharmaceutical R&D dollars and jobs out of the U.S. and onto their own shores.

Incorporating the most recent advances in biomarker science into the drug-approval framework will significantly accelerate the development of new therapeutic options and their delivery to patients suffering from serious, currently untreatable, disorders. It will also lower the overall cost of developing new treatments and significantly lower health care costs by allowing us to detect, treat, or prevent the development of chronic ailments much more effectively than is currently possible.

2. The FDA's History of Crowd-Science Medicine

For more than a decade, the FDA has been saying the right things about biomarkers but has been very slow to act. In 2004, the FDA's *Critical Path Initiative* report identified biomarker development as a top priority. Dr. Janet Woodcock, currently head of the FDA's Center for Drug Evaluation and Research, noted that "biomarkers are the foundation of evidence-based medicine—who should be treated, how, and with what..... Outcomes happen to people, not populations." And in a May 2013 speech addressing the advent of targeted therapies and personalized medicine, Dr. Woodcock declared: "We are going to have to change the way drugs are developed. Period," adding that the agency must "turn the clinical trial paradigm on its head."

But the traditional paradigm is still standing. Under that regime, which emerged in the 1960s, a new drug is approved only if its efficacy has been established by "substantial evidence" grounded in "adequate and well-controlled" clinical trials. Its safety must also be established, though there is no express statutory standard for what kind of evidence is required. In practice, both standards are generally understood to apply only "under the conditions of use prescribed, recommended, or suggested in the labeling thereof." No drug gets approved without a label, and the label is where the FDA, in effect, approves future users.

That approval can't be well-informed, however, without an understanding of the relevant details of the patient-side chemistry. Variations in that chemistry can have strong effects on both efficacy and safety. For most of the last 50 years, however, the FDA has required that a new drug's efficacy be demonstrated by prescribing it in a standard way to a group of patients large enough to provide a statistically robust, one-dimensional correlation with a desired change in a clinical condition. Randomized, double-blind, placebo-controlled trials, dating back to the 1930s and 1940s, are still often called the "gold standard" for modern drug testing.

But those protocols lead to what can, at best, be called crowd-science medicine—though, anchored as they are in empirical correlations, they are almost all crowd and very little science. They assume broad areas of biochemical uniformity among patients, where we now know that there is significant variation. They steer medicine relentlessly toward one-size-fits-all drugs for hypothetical one-size patients.

Tested in large groups of patients selected indiscriminately, many drugs that could help subsets of patients will fail to win approval because the FDA can't tolerate the uncertainty that its own policies sustain. By focusing exclusively on clinical symptoms and effects, which often take a long time to surface, these trials are often very slow to reach any conclusion at all.

The FDA's "Accelerated Approval" rule, developed in the late 1980s and codified by Congress in 1997, already provides the regulatory framework in which the FDA can, in principle—though very rarely in current practice—allow molecular biomarkers to be used to speed the evaluation process. The rule hinges on the use of "surrogate" endpoints that the FDA deems to be "reasonably likely" to predict clinical outcomes. The acceptance of surrogate endpoints allows the agency to make a first call about the drug's efficacy without waiting for clinical effects to surface and persist for some (often arbitrary) period of time. The manufacturer must still complete studies that last long enough to confirm the drug's clinical effects but does so after the drug has been conditionally approved. The drug may be withdrawn from the market if things don't pan out. But here, too, the FDA has declined to issue clear qualification criteria for surrogate endpoints, relying instead on an ad hoc—and, therefore, unpredictable—case-by-case analysis.

3. A Bystander in the Biomarker Revolution

These policies have left the FDA as a bystander to much of the ongoing revolution in molecular medicine. Molecular biomarker science is now being used at every other stage of the drug-development process and in many areas of medical practice. Ironically, much of the expertise about biomarkers can be found in the federal government itself—specifically, at the NIH, which long ago expressed its eagerness to help the FDA incorporate biomarkers into its approval process.

The NIH, professional medical associations, and others are fast acquiring the scientific tools and resources to track the molecular mechanics of diseases from the bottom up. In so doing, they are steadily improving medicine's ability to make an accurate prognosis of how an untreated disease is likely to progress inside an individual patient. The same body of science can lead to precise, objective criteria that define the molecular-level tasks that we want drugs to perform, as well as tests that can provide early indications of when a drug causes significant changes in a disease's progress. The tools that make it possible to acquire the molecular data needed to develop this body of science continue to improve rapidly. As they come to be more widely used, their costs will continue to drop. The same is true for the power and cost of the computers and software needed to assemble and analyze the massive amounts of complex data that such tools generate.

Vast amounts of such data are already being collected and analyzed by drug companies, medical specialists, and research centers. The costs are being covered by drug companies, philanthropists, private and public health-insurance programs, and taxpayers who fund the NIH and other research institutions. Collectively, the costs undoubtedly dwarf the FDA's budget; these programs also generate far more complex data than the FDA has the in-house expertise and computational tools to handle.

The Institute of Medicine (IOM)—the independent, nonprofit health arm of the National Academy of Sciences—specializes in developing substantive evidentiary standards for applied research. In 2010, the IOM released a workshop report that recommended that "the FDA adopt a consistent scientific framework for biomarker evaluation in order to achieve a rigorous and transparent process."

But clear substantive standards for the collection and analysis of data for biomarker validation at the FDA (the biomarker "qualification" process in the FDA's regulatory jargon) remain conspicuous by their absence. Drug companies and doctors already have strong incentives to develop biomarker science. But the most powerful economic incentive for standardizing, pooling, and analyzing biomarker data is the prospect that the results can be used to frame clinical trials in ways that make it more likely that a drug will perform well and, in some circumstances, substantially shorten the time required for FDA approval.

4. The Path to Reform

In part, the FDA has been marginalized in this area because of its regulatory role. Many of the major players involved in the pooling and analysis of molecular data don't directly interact with the agency, which faces sharp limits on how

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Making Medical Sense of Tens of Thousands of Markers

How much data is involved in precision medicine? Consider this: molecular profiles of a cancerous tumor can reveal tens of thousands of markers pointing to genetic differences that distinguish it from healthy tissue. A small number of those differences typically recur in patients and are probably involved in launching or propelling the cancer. But most recur rarely or never. Some play an ancillary role in propelling tumor growth, while many others are mere "passenger mutations" that have no significant effect.

Analytical engines map out cancer pathways by comparing large databases of tumor profiles paired with those of healthy cells. These engines are able to deal with complex "hierarchical" pathways, identifying the relatively small number of genomic variations that play dominant roles—as hubs linked to other, less important, variations—and excluding the many variations that play no role at all. An analysis of this kind, for example, led to what has been the standard categorization of breast cancers into four subtypes. A more recent analysis revealed at least ten subtypes that respond well to different therapeutic regimens.

Cancers are exceptionally complex, but multiple molecular pathways also appear to be involved in many other disorders. At the molecular level, each independent pathway effectively defines a different disorder that often requires a different drug. When more than one pathway is active in the same patient, effective treatments will often require multidrug therapies that target all of them simultaneously.

Every new, precisely targeted, drug serves partly as a diagnostic instrument: its selective efficacy helps medicine further disassemble the targeted disease into a cluster of biochemically distinct diseases, driving the search for more drugs to fill the gaps. New drugs can also help expose molecular features shared by diseases that look quite different at the clinical level. Quite often, it turns out that a drug's target is involved in propelling several diseases, and the same drug can then be used to treat all of them.

When a drug provides only partial or temporary improvement in the patient's condition, it may launch further investigation that reveals that the disease advances along several molecular pathways—or is nimble enough to change on the fly in ways that ensure that no single drug can perform well on its own. Effective treatments will then depend on assembling complex cocktail therapies guided by biomarker profiles that may vary significantly by patient and at different stages of the disease.

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much contact it may have with drug companies and other experts outside the context of specific product applications. These constraints have limited the FDA's ability to keep pace with new advances. The NIH, by contrast, has a history of close collaboration with clinicians, medical research centers, professional medical societies, doctors, and patients, and NIH-funded research is often the starting point for uncovering and using newly discovered biomarkers.

To get things moving, Congress should create a framework for expert panels, convened under the auspices of the NIH and the IOM, to develop substantive standards for the use of biomarkers in the drug-approval process. Separate expert panels should be convened to develop standards that address the statistical tools needed to analyze biomarker data.

The FDA would be a partner in this process throughout, but the panels would be directed to frame standards that reflect the consensus views of the scientific community—and the standard-setting process should be dynamic and flexible enough to incorporate innovative approaches going forward. That said, the FDA would retain final authority in the drug-approval process to strike the right balance in assessing what is known, and with how much confidence, about the relevant biomarkers and surrogate endpoints used in clinical trials, a drug's safety and efficacy as established in those trials, the seriousness of the disease, and the availability of other therapies.

The objective of the reform effort should be to anchor the FDA-approval process in the best available molecular biology, speed up regulatory decision making, and ensure that the FDA's review of biomarker submissions is based on a transparent, predictable, and efficient approach.

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Huber is the author of *The Cure in the Code: How 20th Century Law Is Undermining 21st Century Medicine* (Basic Books, 2013.) He wrote *The Bottomless Well*, coauthored with Mark Mills, which Bill Gates said "is the only book I've ever seen that really explains energy, its history and what it will be like going forward." Huber's previous book, *Hard Green: Saving the Environment from the Environmentalists* (Basic Books, 2000), which was called "the richest contribution ever made to the greening of the political mind" by William F. Buckley, Jr., set out a new conservative manifesto on the environment which advocates a return to conservation and environmental policy based on sound science and market economics. In 1997 he authored two books, *Law and Disorder in Cyberspace: Abolish the FCC and Let Common Law Rule the Telecosm*, an examination of telecommunications policy (Oxford University Press) and (with the University of Pennsylvania's Kenneth Foster) *Judging Science, Scientific Knowledge and the Federal Courts* (MIT Press). Previous books include *Orwell's Revenge: The 1984 Palimpsest* (Free Press, 1994), *Galileo's Revenge: Junk Science in the Courtroom* (Perseus Book Group, 1991); and *Liability: The Legal Revolution and its Consequences* (Basic Books, 1988).

Huber has also published articles in scholarly journals such as the Harvard Law Review and Yale Law Journal, as well as in many other publications, including *Science*, *Wall Street Journal*, *Reason*, *Regulation*, and *National Review*. He has appeared on numerous television and radio programs, including *Face the Nation* and *The NewsHour with Jim Lehrer*.

Before joining the Manhattan Institute, Huber served as an assistant and later associate professor at MIT. He clerked on the D.C. Circuit Court of Appeals for Ruth Bader Ginsburg, and then on the U.S. Supreme Court for Sandra Day O'Connor. Huber also is a partner at the Washington, D.C. law firm of Kellogg, Huber, Hansen and Todd. Huber earned his law degree from Harvard University and a doctorate in mechanical engineering from MIT.

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He is also a member of the Manhattan Institute's Project FDA, a committee of physician-scientists, economists, medical ethicists, and policy experts. Their purpose is to show how twenty-first-century technologies can help better inform FDA regulations and accelerate the drug-development and drug-approval process while maintaining drug safety. In 2012, Howard served on the Health Care Policy Advisory Group for the presidential campaign of former Massachusetts governor Mitt Romney. He has also testified twice before Congress. In 2013 and 2014, he served on an expert panel as a judge for Celgene's Innovation Impact Awards.

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Unlocking the Code of Health
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Peter W. Huber & Paul Howard

INTRODUCTION

For over a decade, the FDA has been saying the right things about biomarkers but has been very slow to transform its words into effective action. In 2004, the FDA's *Critical Path Initiative* report identified biomarker development as a top priority. Dr. Janet Woodcock, currently head of the FDA's Center for Drug Evaluation and Research, noted that "biomarkers are the foundation of evidence based medicine—who should be treated, how and with what. …. Outcomes happen to people, not populations."[1]

In a 2011 presentation,[2] Dr. Woodcock described biomarkers as "crucial to efficient medical product development" but noted that, because of scientific, economic, and regulatory impediments, "biomarker development has lagged significantly behind therapeutic development." In a 2013 speech addressing the advent of targeted therapies and personalized medicine, Dr. Woodcock declared: "We are going to have to change the way drugs are developed. Period." The FDA must "turn the clinical trial paradigm on its head."[3] FDA commissioner Margaret Hamburg voiced similar thoughts in a speech given in April 2014.[4]

The clinical trial paradigm to which Dr. Woodcock referred emerged in the 1960s following the enactment of the 1962 amendments to the federal drug law. A new drug is approved only if its efficacy has been established by "substantial evidence" grounded in "adequate and well-controlled" clinical trials. Its safety must also be established, though there is no express statutory standard for what kind of evidence is

required. In practice, both standards are generally understood to apply only insofar as the drug is used "under the conditions of use prescribed, recommended, or suggested in the labeling thereof." No drug gets approved without a label, and the label is where the FDA, in effect, approves future users of the drug. That can't be done well without an understanding of the relevant details of the patient-side chemistry.

For instance, some breast-cancer cells express estrogen receptors and are thus treated with estrogen inhibitors, while others are estrogen receptor negative and are sometimes treated with estrogen itself. Variations in the P450 gene that codes for the system of cytochrome P450 drug-metabolizing enzymes (responsible for metabolizing 50 percent of all commonly prescribed drugs, including blood thinners and painkillers) can dramatically alter the effect of prescription medicines, rendering otherwise powerful drugs useless, or safe drugs deadly.[5] Pharmacology is not a science of one hand clapping.

Nonetheless, for most of the last 50 years, the FDA has required that a new drug's efficacy be demonstrated by prescribing it in a standard way to a crowd large enough to provide a statistically robust, one-dimensional correlation with a desired change in a clinical condition. The trial protocols themselves date to 1938, when the U.S. Public Health Service tested a pertussis vaccine in Norfolk, Virginia, in what is thought to have been the first randomized, double-blind trial of any pharmaceutical product. Eight years later, British researchers conducted what may have been the first double-blind placebo-controlled trial of a curative drug, streptomycin. The FDA followed their lead, and these were the protocols that emerged as what is still often called the "gold standard" for modern drug testing.

Those protocols, however, lead to what can, at best, be called crowd-science medicine—though anchored, as they are, in empirical correlations, they are almost all crowd and very little science. They assume broad areas of biochemical uniformity among patients, in whom we now know that there is significant variation. They steer medicine relentlessly toward one-size-fits-all drugs for hypothetical one-size patients.

Tested in large groups of patients selected indiscriminately, many drugs that could help subsets of patients will fail to get approved because no one has yet worked out the details of how the patient-side chemistry affects their performance. The drugs therefore perform unevenly, and the FDA can't tolerate the uncertainty that its own policies sustain. And by focusing exclusively on clinical symptoms and effects, which often take a long time to surface, these trials are often very slow to reach any conclusion at all.

As discussed throughout this paper, molecular biomarker science is now being developed and used at every other stage of the drug-development process, and in many areas of medical practice. The relevant molecular science and practice of molecular medicine have already moved far ahead of the FDA. Without changes in policy, the gap will continue to widen.

Vast amounts of data are being collected by drug companies, medical specialists, and research centers and are being analyzed using increasingly sophisticated, computationally intensive analytical tools.[6] The costs are being covered by drug companies, philanthropists, private and public health-insurance programs, and taxpayers who fund the National Institutes of Health (NIH) and other research institutions. Collectively, such costs undoubtedly dwarf the FDA's budget and these programs generate far more complex data than the FDA has the in-house expertise and computational tools to handle.

The NIH, professional medical associations, and others are fast acquiring the expertise, scientific tools, and resources to track the molecular mechanics of diseases, from the molecular bottom on up. By doing so, they will steadily improve medicine's ability to make an accurate, personal prognosis of how the untreated disease is likely to progress inside the individual patient. The same body of science can lead to precise, objective molecular criteria that define medically useful molecular-scale tasks that we want drugs to perform, and molecular tests that can provide early indications of when a drug causes medically significant changes in a disease's progress. The tools that make it possible to acquire the molecular data needed to develop this body of science

continue to improve rapidly, and as they come to be more widely used, their costs will continue to drop, too. The same goes for the power and cost of the computers and software needed to assemble and analyze the massive amounts of very complex data that such tools generate.

Along with the federal agencies that sponsor much of the basic research on biomarkers, the mission of the Institute of Medicine (IOM)—the independent, nonprofit health arm of the National Academy of Sciences—is "to help those in government and the private sector make informed health decisions by providing evidence upon which they can rely."[7] The IOM specializes in developing substantive evidentiary standards for applied research. In 2010, the IOM released a report, "Evaluation of Biomarkers and Surrogate Endpoints in Chronic Disease,"[8] which recommended that "the FDA adopt a consistent scientific framework for biomarker evaluation in order to achieve a rigorous and transparent process." A more recent IOM workshop report addresses "how genomic information is gathered, assessed, and evaluated for use in medical practice."[9]

But clear FDA standards for the collection and analysis of data that must be met for the data and analyses to be accepted for use in the approval of new drugs and diagnostic devices remain conspicuously absent. Drug companies and doctors already have strong incentives to develop biomarker science directly relevant to the development of new drugs and prescription of existing drugs. But the most powerful economic incentive for pooling and analyzing biomarker data is the prospect that the results can be used to frame clinical trials in ways that make it more likely that the drug will perform well and (in some circumstances) allow the drug's performance to be evaluated on the basis of its subclinical effects, thus substantially shortening the trials required by the FDA for marketing approval.

To accelerate the development of much-needed new therapies and diagnostic devices, the FDA should focus on systematically harnessing the expertise and resources of the many qualified, well-funded researchers and doctors actively involved in collecting molecular

biological data and analyzing how molecular factors link to medically significant clinical effects. The objective should be to anchor the FDA drug-approval process in the best available molecular biology; accelerate regulatory decision making; and ensure that the FDA's review of biomarker submissions is based on a transparent, predictable, and efficient process that uses the best currently available tools for analyzing large amounts of complex biological data and reflects the most current, consensus scientific views on the validity of biomarkers and surrogate endpoints.

The U.S. is not the only nation with the scientific and industrial infrastructure capable of exploiting the full potential of biomarker science to revolutionize the development of precision drugs and diagnostics. The European Union recently launched the second phase of its Innovative Medicines Initiative (IMI2), with biomarker development one of four key priorities. IMI2, which began in 2014, is intended to run for ten years with a budget of €3.276 billion, focusing on a broad range of diseases and drugs, including antimicrobials, cardiovascular disease, oncology, psychiatric diseases, and autoimmune diseases (see **Box 1**, page 4).[10] While we continue to think about how to create a regulatory framework that allows innovative companies and researchers to rapidly translate biomarker science into marketable drugs and diagnostics, other countries are already doing so.

PART I: MOLECULAR MEDICINE

In the last three decades, advances in structure-based drug design, monoclonal antibodies, and, most recently, cell therapies and gene-editing technologies, have given biochemists the tools to design precision drugs that modulate specific molecular targets. Selecting the right targets hinges, however, on working out the connections between what we can control down there and the clinically defined condition that we wish to control up here.

Sometimes, that is fairly easy; but much of the time, it is not. The molecular processes that propel diseases are often complex, and many common disorders won't be cured by one-size-fits-all drugs because, down at the molecular level, each one is a cluster

BOX 1. EUROPE'S INNOVATIVE MEDICINES INITIATIVE 2

IMI2 will leverage the availability of the complete sequence of the human genome and the growing body of "-omic" data sets and epigenetic markers in health and disease, the availability of, for instance, patients' electronic medical records, next generation genetics for target identification and sophisticated bioinformatics to:

- Identify new or alternative therapeutic concepts (targets) for treatment and prevention of disease and generate the research tools (e.g., chemical probes and recombinant antibodies) required to further characterise the biology of novel genes/proteins and validate new therapeutic concepts pre-clinical and clinically.
- Identify and validate biological markers, tools and assays (biochemical, imaging and functional) to support disease reclassification and patient stratification approaches, monitor disease progression, provide proof of pharmacological response, predict and monitor the efficacy and safety of drugs and vaccines as well as biomarkers that may serve as surrogate markers in clinical trials.
- Better understand the types of biomarkers, outcomes and composite endpoints that regulators and HTAs could accept and what level of validation is needed for their utilization in order to direct discovery efforts. Initiating formal consultation procedures as appropriate.
- Enhance understanding of the immunological mechanisms and host–pathogen and host–vaccine interactions to enable improvements in the design of both preventive and therapeutic vaccines.
- Improve the profiling of immune responses to infection and to vaccination in different age groups, identifying novel correlates of protection against infectious diseases and possibly other non-infectious conditions
- Better understand the molecular determinants of inter-individual variability to drug and vaccine efficacy and safety, thus reducing the underlying biological variability of trial patient populations to enable reliable measures of treatment effect.
- Understand the molecular mechanisms underlying drug toxicity in humans to drive mechanism-based drug and vaccine safety assessment and early prediction of clinical and non-clinical drug and vaccine response to improve the predictability of translating preclinical findings to the clinical setting.
- Develop non-invasive measures (such as imaging technology) of drug exposures at the organ level to deliver a better understanding of the PK/PD relationship of a drug or vaccine and therefore more accurately predict the therapeutic index of a drug (that is, the difference between the level of drug required to provide a beneficial effect and an unwanted effect).
- Develop a platform of pre-clinical assays utilising normal and disease tissue, stem cell technology, genetic manipulation and cloning to create more predictive in vitro, ex vivo and in vivo models of the relationship between drug exposure, pharmacological response, interindividual variability with respect to efficacy and safety to improve translation from preclinical testing to the clinic
- Develop systems models and strategies combining technology, biology (omics) and computational methods, with information retrieved from historical compounds tested in preclinical models or in patients for evaluation/prediction of drug safety and efficacy.

European Fed'n of Pharmaceutical Indus. & Ass'ns, et al., The Right Prevention and Treatment for the Right Patient at the Right Time: IMI2 Stragegic Research Agenda (2013), *available at* http://www.efpia.eu/uploads/Modules/MCMedias/1373296554546/IMI2%20Strategic_Research_Agenda_v%208%20July%202013.pdf.

of distinct disorders. Some diseases also change on the fly. All cancers and most viruses (most notably, HIV) mutate rapidly, quickly finding ways to dodge single-drug assaults on their chemistry. How a drug performs can also depend on how it's metabolized or on how it interacts with the patient's immune system or other molecular bystanders to cause unwanted side effects. Two distinct bodies of science are involved here: first, pure biology that describes the often complex and dynamic molecular etiology of a disease; second, an understanding of how a specific drug interacts with both its intended molecular tar-

get and bystander molecules that it may encounter elsewhere in the bodies of patients.

The pure biological science plays a central role in developing the targeted drug and testing it in the laboratory, and provides the threshold criteria for selecting patients whom the targeted drug may be able to help. The development of the biological science can also lead to tests that track whether a disease is advancing, or retreating, at every stage of its development. Molecular and cellular scale effects in a patient can usually be observed well before those effects morph into clinical symptoms; prognostic molecular tests can thus provide early indications of how well a drug is performing and greatly accelerate the drug-approval process. Drug companies routinely use such tests to provide early evaluations of drugs under development and identify the most promising candidates.[11]

Tools that allow medicine to track the progress of a disease down at the molecular level can also set the stage for approving drugs that slow its progress—or halt it completely—before clinical symptoms materialize. Used to treat degenerative diseases that develop slowly, such drugs would be extremely valuable even if they fail to provide complete cures. According to one estimate, for example, a drug that delays the onset of Alzheimer's by five years would save about $367 billion in direct health care costs by 2050, while extending the healthy life spans of many patients.[12]

Both during and after drug-approval clinical trials, the systematic study of drug-patient interactions can continue to refine and expand our understanding of the underlying biology. Every new, precisely targeted drug serves, in part, as a diagnostic instrument: its selective efficacy helps medicine further disassemble the targeted disease into a cluster of biochemically distinct diseases, driving the search for more drugs to fill in the gaps. New drugs can also help expose molecular features shared by diseases that look quite different at the clinical level. Quite often, it turns out that a drug's target is involved in propelling several different diseases—with the same drug capable of treating all of them.

When a drug provides only partial or temporary improvement in the patient's condition, it may launch further investigation, revealing that the disease advances along several molecular pathways or is nimble enough to change on the fly in ways that ensure that no single drug can perform well on its own. Effective treatments will then depend on assembling complex cocktail therapies, guided by biomarker profiles that may vary significantly from patient to patient and at different stages of the disease.

Toward Precision Medicine

In 2011, a task force convened by the National Research Council (NRC) released *Toward Precision Medicine,* a report written at the request of the NIH to address the need for "a 'New Taxonomy' of human diseases based on molecular biology." We do indeed need one, the report concludes, and to facilitate its development, the report recommends the creation of a broadly accessible "Knowledge Network" that will aggregate data spanning all molecular, clinical, and environmental factors that can affect our health.[13] Working out the molecular etiology of complex diseases will require an analysis of "biological and other relevant clinical data derived from large and ethnically diverse populations" in a dynamic, learn-as-you-go collaboration among biochemists, clinical specialists, patients, and others. Data from the network will help researchers "propose hypotheses about the importance of various [factors and connections] that contribute to disease origin, severity, or progression, or that support the sub-classification of particular diseases into those with different molecular mechanisms, prognoses, and/or treatments, and these ideas then could be tested in an attempt to establish their validity, reproducibility, and robustness."[14] The underlying data and taxonomy of diseases themselves must be "continuously" updated, tested, and refined.

The NRC report also outlines the important roles that the network could play in developing new drugs and finding new uses for existing drugs, and it recommends that doctors be allowed to consult the network to find out how other patients have fared when drugs are prescribed outside the FDA-approved boundaries.

As the report makes clear, the objective is "precision medicine." A molecular taxonomy of disease is what leads medicine to precisely targeted drugs and precise prescription protocols.

Many researchers and health care providers in the private sector had started assembling smaller knowledge networks of their own before the NRC report was published, and they continue to do so. In 2013, the director of the Genetic Variation Program at the NIH's National Human Genome Institute estimated that there were about 2,000 separate databases addressing genetic links to various diseases.[15] Google recently announced the launch of its "Base-Line Project," which will collect anonymous genetic and other data to create what Google intends to be the largest, most comprehensive database linking molecular biomarkers to diseases and health. Google will then use its computing power and considerable expertise in pattern recognition to identify relevant biomarkers and map out those links. A top priority is to detect the onset of diseases much earlier.[16] When the project is up and running, use of the data will end up being monitored by institutional review boards run by the medical schools at Duke and Stanford Universities.[17]

Google will face serious competition. Illumina, which supplies 70 percent of the world's gene-sequencing machines, recently announced plans to provide services that mine genomic databases. "One of the biggest challenges now is increasing the clinical knowledge of what the genome means," says the company's CEO. "We want to be at the apex of that effort."[18]

Knowledge networks are also being assembled from the bottom up. 23andMe, which provides consumer genetic-sequencing services and health risk assessments based on genomic data, allows other providers and software services to develop applications that interact with the data entrusted to 23andMe by its customers. Its interests, *Wired* reported, include "integrating genetic data with electronic health records for studies at major research centers and … building consumer-health applications focused on diet, nutrition, and sleep."[19] For individuals, 23andMe's platform will, in the words of the firm's director of

engineering, serve as "an operating system for your genome, a way that you can authorize what happens with your genome online."[20]

The FDA shut down 23andMe's personalized health risk reports in 2013, invoking its authority to license medical devices "intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease."[21] In the U.S., 23andMe is now limited to offering sequencing services and ancestry analysis to consumers, although the FDA recently softened its stance somewhat and approved a single 23andMe test for Bloom Syndrome, a rare, inherited genetic disease.

As part of its approval, the FDA has also said that it will reclassify a set of genetic tests called "carrier screening," used to notify parents if their offspring may inherit certain genetic diseases, if one or both of the parents are carriers for a gene known to cause the disorder. The agency says that these tests will require pre-market notification, but not pre-market review—which, at least, is one step in the right direction.

It is much less clear how the FDA intends to treat whole genome scans that utilize sophisticated algorithms to attempt to predict a person's future risk of developing a disease or condition, 23andMe's core business model. This approach is the future precision medicine, as we discuss elsewhere, and its regulatory status remains murky (at least in regards to direct-to-consumer tests). For the moment, U.S.-based subscribers have turned to third-party websites to analyze the raw genomic data. [22] Abroad (in the U.K., for instance), 23andMe still offers its portfolio of reports.

PatientsLikeMe.com, Curious, Inc. (currently in beta testing), and similar websites provide platforms for patients to share information directly. Social media are simultaneously undermining conventional randomized and blinded clinical trials by allowing patients involved in the same trials to identify one another, and then determine whether they're receiving the drug or a placebo by comparing self-assessed improvements in health or side effects.[23]

Bioinformatics

As many of the operators of these early knowledge networks recognize, the large amounts of data being collected are of little value without reliable analytical tools that can work out what the torrents of information mean and how they can be put to good use. But collecting and pooling large amounts of data is the necessary first step—and the analytical tools are fast emerging. What is needed now is a framework for ongoing testing and validation of the data-collection protocols and analytical tools.

That modern statistical tools and computers can extract medically useful information from very large, complex databases has already been convincingly demonstrated; new analytical tools, meanwhile, continue to be developed and are tested when doctors rely on them for guidance in treating patients.

Controlling HIV, for example, requires complex multi-drug cocktails because the virus mutates so quickly. Monitoring and adjusting on the fly remain essential, but the process can now be guided by analytical engines fueled by huge collections of patient records, including data on HIV genotypes, treatment histories, and responses, along with patient age, gender, race, and route of infection entry. Powered by IBM technology, the largest such engine—Europe's EuResist network—uses data from tens of thousands of patients and hundreds of thousands of treatment regimens associated with more than a million records of viral genetic sequences, viral loads, and white-blood cell counts. As described by its manager, the network is "continuously updated with new data in order to improve the accuracy of the prediction system."[24] The data are analyzed by three statistical learning engines that interact to predict responses to possible treatments.[25] When presented with 25 case histories not already in its database, EuResist beat nine of ten international experts in predicting how well the treatments had performed. The study was dubbed "Engine Versus Experts."[26]

In early 2013, IBM announced the arrival of a new engine—Interactive Care Insights for Oncology, powered by Watson—that aims to do for oncology what EuResist does for HIV. Developed in partnership with WellPoint and Memorial Sloan Kettering and powered by the supercomputer that won the engine-versus-experts challenge on *Jeopardy,* the engine was initially drawing on "600,000 pieces of medical evidence, two million pages of text from 42 medical journals and clinical trials in the area of oncology research. Watson has the power to sift through 1.5 million patient records representing decades of cancer treatment history, such as medical records and patient outcomes … Watson continues to learn while on the job, much like a medical resident, while working with the WellPoint nurses who originally conducted its training."[27]

In 2014, 12 research institutes formed the New York Genome Center to pool genomic data and analyze its clinical implications. In March 2014, the center announced that it would be using a custom-made prototype of Watson to advise oncologists on treating patients with glioblastoma, an aggressive form of brain cancer.[28] As described by the center's deputy director of informatics, following the identification of potentially relevant mutations in a patient's tumor, Watson will "do the literature search, the drug database search, and find all the relationships between those specific mutations and drugs that are available or may be in clinical trials that they can find, or even drugs that are related to the pathways that those mutations are associated with."[29] If the recommended treatment regimen is adopted, the patient's response will be tracked and results will be added to Watson's database. The program will be extended to other cancers if Watson performs well.

What we see emerging here is "rapid learning health care," a term coined in 2007 by an IOM convened group of health care experts. In brief, the workshop participants proposed a process for continuously improving drug science using data collected by doctors in the course of treating their patients, with a particular focus on groups of patients not usually included in drug-approval clinical trials. By 2008, as discussed in a recently published paper[30] authored by two experts in the field, several major cancer centers had established networks for pooling and analyzing data collected by doctors in their regions. These

systems are being used to identify new biomarkers, analyze multidrug therapies, conduct comparative effectiveness studies, recruit patients for clinical trials, and guide treatments. Several commercial vendors now offer precision oncology services.

The powerful analytical tools and protocols now available, or under development, can use data networks to recommend treatments that would "avoid unnecessary replication of either positive or negative experiments … [and] maximize the amount of information obtained from every encounter"[31] and thus allow every treatment to become "a probe that simultaneously treats the patient and provides an opportunity to validate and refine the models on which the treatment decisions are based."[32]

Analytical engines like these take statistical analysis far beyond the one-dimensional correlations traditionally relied on by the FDA in the drug-approval process. Current whole-tumor molecular profiles of a cancer patient can reveal tens of thousands of markers. A small number of genomic markers typically recur quite frequently in other patients and are probably involved in launching or propelling the cancer. But most recur rarely or never. Some play an ancillary role in propelling tumor growth while many others are mere "passenger mutations" that play no medically significant role.[33]

Analytical engines map out cancer pathways by comparing large databases of tumor profiles paired with those of healthy cells. These engines are able to deal with complex "hierarchical" pathways, identifying the relatively few genomic variations that play dominant roles as hubs linked to other, less important variations (and excluding the many variations that play no role at all). An analysis of this kind, for example, led to what has been the standard categorization of breast cancers in four subtypes defined by three receptors and the triple-negative alternative.[34] A more recent analysis revealed at least ten subtypes that correlate well with therapeutic responses.[35]

Cancers are exceptionally complex, but multiple molecular pathways also appear to be involved in many other disorders. At the molecular level, each independent pathway effectively defines a different disorder that often requires a different drug. When more than one pathway is active in the same patient, effective treatments often require multi-drug therapies that target all simultaneously.

When, by contrast, a disorder involves a single, well-understood molecular pathway, a drug's likely clinical impact can be assessed by monitoring the drug's ability to disrupt it. Chronic myelongenous leukemia, for example, was the first cancer to be clearly linked to a genetic abnormality—created when one chromosome trades its own short arm for the long arm of another to form the "Philadelphia chromosome." The gene in question codes for one of many kinase enzymes, which, among other functions, help regulate cell division. The flawed version launches a frenzy of white blood-cell production that kills the patient. In the trials launched in 2000 to test Gleevec, a drug designed to target that enzyme, doctors tracked the drug's performance by following blood counts (hematologic response) and the number of cells bearing the Philadelphia chromosome (cytogenetic response).[36] Gleevec was submitted for accelerated approval 32 months after the first patient was enrolled in the trial, about twice as fast as the average for cancer drugs undergoing traditional trials at that time.[37]

Data obtained from a single cancer patient will rarely suffice to create a new map of molecular pathways that are active in the patient but are now routinely used to determine which known pathways are active and to prescribe available drugs accordingly. And, as discussed later, data from a single patient do sometimes reveal new molecular variations that, with further study in other patients, lead to the discovery of new pathways that can affect a disease's progression.

Advances in systems biology and informatics analysis of large databases are now leading toward whole-body models that can guide future research and predict therapeutic efficacy and safety in individual patients *before* treatment begins (see **Box 2**, page 9).[38]

As Dr. Janet Woodcock put it in 2004, drug science at its best will be a " 'progressive reduction of uncertainty' about effects—or 'increasing level of

BOX 2. SYSTEMS PHARMACOLOGY

Systems approaches have long been used in pharmacology to understand drug action at the organ and organismal levels. The application of computational and experimental systems biology approaches to pharmacology allows us to expand the definition of systems pharmacology to include network analyses at multiple scales of biological organization and to explain both therapeutic and adverse effects of drugs. Systems pharmacology analyses rely on experimental "omics" technologies that are capable of measuring changes in large numbers of variables, often at a genome-wide level, to build networks for analyzing drug action. A major use of omics technologies is to relate the genomic status of an individual to the therapeutic efficacy of a drug of interest. Combining pathway and network analyses, pharmacokinetic and pharmacodynamic models, and a knowledge of polymorphisms in the genome will enable the development of predictive models of therapeutic efficacy.

Network analyses based on publicly available databases such as the U.S. Food and Drug Administration's Adverse Event Reporting System allow us to develop an initial understanding of the context within which molecular-level drug-target interactions can lead to distal effectors in a process that results in adverse phenotypes at the organ and organismal levels. The current state of systems pharmacology allows us to formulate a set of questions that could drive future research in the field. The long-term goal of such research is to develop polypharmacology for complex diseases and predict therapeutic efficacy and adverse event risk for individuals prior to commencement of therapy.

Shan Zhao & Ravi Iyengar, *Systems pharmacology: network analysis to identify multiscale mechanisms of drug action*, 52 Ann. Rev. Pharmacology & Toxicology 505 (2012).

confidence' about outcomes" that comes with "continuous" development of "multidimensional" databases and "composite" measurements of outcomes replacing "the current single dimension, binary model of clinical effect."[39]

Used in conjunction with good analytical tools, public and private knowledge networks are already delivering on that prediction, and by doing so are superseding the FDA-approved label and guiding off-label prescription of existing drugs and formulation of complex multi-drug therapies. The information being gathered often points to molecular pathways that are not currently addressed by any drug.

Yet in the absence of standards addressing when these databases and analytical tools will be accepted for use by the FDA, drug and device manufacturers cannot easily use the same information to win FDA approval of label amendments addressing new uses for existing drugs—nor can they use the information to frame clinical trials of new drugs developed in response to newly identified molecular pathways. Moreover, many players involved in pooling and analyzing biomarker data do not directly interact with the FDA, and the FDA faces limits on how much it may interact with drug companies outside the context of a specific product application. These constraints sharply limit the FDA's ability to keep pace with advances in the tools used to collect and analyze biomarker data.

Biomarkers at the National Institutes of Health

The NIH, by contrast, has a solid history of working closely with clinicians, medical research centers, professional medical societies, doctors, and patients. Indeed, NIH-funded research is often the starting point for the development of new therapeutic approaches. The NIH and its partners also have, or can acquire, the expertise and digital resources needed to extract reliable patterns from the complex torrents of molecular data that propel the advance of molecular medical science.

The NIH, industry, and patient advocacy groups have recognized that significant therapeutic advances for complex diseases will require pooling and mining large amounts of data, using them to map out biological pathways involved and how they may vary

across different groups of patients, and identifying pharmacodynamic biomarkers that can be used to track a disease's progress and provide an early read on a drug's efficacy. As demonstrated by the Accelerating Medicines Partnership (AMP), discussed later, the NIH is also able to mobilize financial resources of big drug companies to supplement government funding of biomarker research: the roughly $230 million to be spent over five years in the first round of the AMP project will be split roughly evenly between the NIH and drug companies. Patient advocacy groups will contribute $1 million and will help set research priorities.[40]

Collaborations of this kind occur under the auspices of the Foundation for the NIH (FNIH), a not-for-profit entity established by Congress in 1990 to raise private funds and create public-private partnerships that "combine the expertise and resources of NIH with those of industry, the public, and philanthropic communities … leveraging support and convening high level partnerships, for the greatest impact on the most urgent medical challenges we face today."[41] Launched in 2006, the FNIH's Biomarkers Consortium includes representatives of the NIH, the FDA, industry, and other stakeholders. Its mission is "to discover, develop, and qualify biological markers (biomarkers) to support new drug development, preventive medicine, and medical diagnostics" and "combine the forces of the public and private sectors to accelerate the development of biomarker-based technologies, medicines, and therapies for the prevention, early detection, diagnosis, and treatment of disease."[42]

A broad range of other NIH programs are also focused on the development of biomarker science in general and include, among other objectives, the development of biomarkers directly related to the development, approval, and medical use of targeted drugs.

Until quite recently, the genetic factors that influence susceptibility to common diseases were thought to be linked to common genetic variations. More recently, it has become clear that seemingly common disorders quite often reflect large numbers of rare, distinct flaws that cause the same clinical symptoms.[43] They

may be different flaws in the same protein, or flaws in two or more different proteins that must work together to maintain health. Hundreds of different proteins that control the interfaces between nerve cells, for example, can apparently play a role in choreographing Alzheimer's, Parkinson's, epilepsy, and more than 130 other brain disorders. Identifying all such variations requires data drawn from very large numbers of people representing a diverse array of people suffering from the disease. The NIH has launched a number of initiatives that no single drug or diagnostic company could hope to match, in order to assemble the large quantities of raw data that can play an important role in the development of new drugs and diagnostic devices.

In 2002, the NIH helped launch the multinational HapMap[44] project to develop "a tool that allows researchers to find genes and genetic variations that affect health and disease." The NIH also describes it as "a powerful resource for studying the genetic factors contributing to … the effectiveness of and adverse responses to drugs and vaccines"[45] and for use in the "development of tests to predict which drugs or vaccines would be most effective in individuals with particular genotypes for genes affecting drug metabolism."[46]

In 2008,[47] the NIH launched the 1000 Genomes Project,[48] which coordinates research in the U.S., the U.K., China, and Germany to compile a publicly accessible database "of almost all variants, including SNPs [single nucleotide polymorphisms] and structural variants, and their haplotype contexts."[49] The objective is "to create the most detailed and medically useful picture to date of human genetic variation … [that can] help explain individual differences in susceptibility to disease, response to drugs or reaction to environmental factors."[50]

The ClinGen project, launched in 2013, pools data supplied by a consortium of genetic researchers from around the world and analyzes the data to identify genetic variants that may play a medically significant role.[51] In 2013, the NIH announced[52] a first round of grants to three research groups whose mission will be "to develop authoritative information on the millions

of genomic variants relevant to human disease and the hundreds that are expected to be useful for clinical practice," with an initial focus on variants strongly associated with certain forms of cancer, cardiovascular disease, and metabolic disorders. Working closely with the National Center for Biotechnology Information, the investigators help "design and implement a framework for evaluating which variants play a role in disease and those that are relevant to patient care."[53] The NIH makes these findings publicly available through the ClinVar database, which a recent report describes as "the first comprehensive genetic database designed explicitly for use in a clinical setting."[54]

Noting that there were already thousands of separate databases addressing specific genes and diseases—and that different groups were using different protocols for assessing the clinical relevance of genomic variants—the NIH made it an early priority to forge a consensus "on what evidence is needed to decide whether the effects of a variant are medically relevant."[55] A rating system ranks the quality of the data. The database includes a consensus evaluation, by a panel of experts drawn from different institutions, as to whether each variant should be viewed as disease-related or benign, or whether the issue remains unsettled.[56]

More recently, the NIH has begun to launch projects that point to ways in which FDA clinical trial protocols could be modified to facilitate development and validation of biomarker science during the trials themselves.

In 2013, the National Cancer Institute (NCI) announced its Exceptional Responders Initiative. Four major research institutions are analyzing tissue samples, collected during clinical trials of drugs that failed to win FDA approval, to identify biomarkers that distinguished the minority of patients who did respond well from the majority who did not.[57] The analysis of roughly a decade of prior trials in the first year of the study identified about 100 exceptional responders.[58] In June 2014, the NCI was reportedly going to start soliciting additional reports of such patients from researchers and doctors nationwide.[59] When the biomarkers that distinguish the exceptional responders align with what the drug was designed to target, these findings could well lead to the resurrection of drugs that might have helped many patients over the last decade.

In another 2013 initiative, a group with representatives from the NCI, the FNIH, the FDA, five pharmaceutical companies, and other research institutions and patient advocacy groups announced the Lung-MAP project[60] and the Lung Cancer Master Protocol. Patients suffering from squamous-cell lung cancer are screened for variations in more than 200 cancer-related genes and undergo comprehensive genomic profiling before treatment begins. The results are used to assign patients to one of five subtrials of drugs designed to target different cancer-cell targets. The idea is to demonstrate that, when more than one targeted drug is available to treat the same disorder, structuring a master trial that tests them all simultaneously can save patients from multiple tests and trial-and-error treatments with different drugs; accelerate and increase the likelihood of approval of candidate drugs; and lower costs across the board.

Still more recently, the NCI announced plans to create standards for data collection and analysis, as well as a network to oversee and coordinate cancer-drug trials to ensure that trials are anchored in "molecularly characterized tumors." The National Clinical Trials Network will initially focus on exceptional responders; whether biomarkers can predict responses to targeted therapies in patients with advanced cancers; and treatment options for several types of lung cancer, among them, the possible advantage of "developing drugs for small subsets of molecularly characterized tumors."[61] The longer-term objective is to "spawn a new era of treatment trials that will carefully select the tumors that may respond best to investigational therapy."[62]

In February 2014, the NIH announced the Accelerating Medicines Partnership (AMP), a five-year plan to collaborate, under the auspices of the FNIH and with the FDA, ten big drug companies and eight non-profit organizations focusing on specific diseases, to unravel the molecular pathways that lead to Alzheimer's, Type 2 diabetes, rheumatoid arthritis, and lupus—and to investigate new methods to track a disease's progress that could provide early reads on

how a drug is affecting it.[63] The objective is to "ensure we expedite translation of scientific knowledge into next generation therapies."[64]

At the press conference announcing the launch of the program, Dr. Francis Collins, NIH director, remarked that all Alzheimer's clinical trials would be "decorated with the complete suite of biomarkers that you would like to have included in order to assess whether that therapeutic intervention is working." A Pfizer representative emphasized that the Alzheimer's project will attempt to develop a better understanding of the molecular pathways and networks that propel the disease. It will also include searches for pharmacodynamic biomarkers that can provide reliable, objective, and quantitative indications of whether a patient's condition is improving or deteriorating— and that can be used, as well, to develop drugs that intervene much earlier, intercepting diseases before they become irreversible and untreatable. "It will be critical to have FDA colleagues involved here to get their guidance, [on] how those biomarkers also can be regulatory endpoints," he added.[65]

The NIH has been soliciting the FDA's input on the development of biomarker science for over a decade, but there are few indications that the FDA has been equally receptive or interested in soliciting input from the NIH in deciding when biomarker science is solid enough to be used by the FDA. This is unfortunate. Collaborative effort and funding can almost certainly accelerate development of reliable biomarker science. Moreover, the main incentive for drug-company participation is a framework that promises to use knowledge generated by such projects to improve and expedite drug approval. As noted earlier, Europe's collaborative Innovative Medicines Initiative is a decade-long project spending about $400 million annually,[66] a significant part of it on similar initiatives.

The FDA should, as discussed later, be collaborating much more closely with the NIH and the IOM to accelerate development of biomarker science reliable enough for use in approving diagnostic devices and drugs. That collaboration should also set the stage for establishing consensus standards for collection and analysis of biomarker data by the many highly qualified private researchers and health care providers with much to contribute to the advancement of biomarker science and its translation into safe, effective new therapies.

PART II: BIOMARKERS AT THE FDA

As noted, top FDA officials recognized long ago that molecular biomarkers are an essential part of modern pharmacology, but they have also acknowledged that biomarkers' development has not kept pace with advances in drug development. More recently, they seem to have conceded that slowly-evolving FDA policies and standards have been part of the problem. Others have reached the same conclusion (see **Box 3**, page 13).[67]

The rate at which the FDA approves "in vitro diagnostic" (IVD) devices used to test for the presence of biomarkers in patients provides one indicator of underlying regulatory trends. The FDA won't allow a molecular biomarker to be used in the drug-approval process without a showing that a reliable diagnostic device is available to determine when it is present in a patient. According to a 2013 report conducted by a private research company, the rate at which the FDA approved IVDs in general dropped sharply around 2006, and remained relatively stable until 2012. During the same period, the rate of approval for biomarker IVDs dropped steadily, while the length of time required for approval increased.[68] There are recent signs of modest improvement: review periods grew somewhat shorter in 2012 and 2013, and approvals rose in 2013.[69]

A more direct measure is how many biomarkers the FDA accepts for use in the drug-approval process. The FDA's obligation to respond promptly to new drug applications does not extend to new biomarker submissions. In January 2014,[70] the FDA's Office of Translational Sciences reported that it had received 43 data packages for biomarker qualification. Twenty-eight were in the "advice and consultation phase," three were "in review," and only three had been approved, one in 2008, one in 2010, and one in 2012. The agency has accepted significantly more

BOX 3. THE GAP BETWEEN REGULATION AND PRECISION MEDICINE

The regulatory environment for drugs and diagnostics is likely to have a significant impact on the evolution of personalized medicine. A majority of the experts believe that the regulatory environment has not kept pace with the rapid advances in the field of personalized medicine. For example, on the therapeutics side, the U.S. FDA last published guidance for approving drug–diagnostic combinations that relies on prospective trials in 2005. However, the world of "one drug–one diagnostic" in personalized medicine may already be passé. The challenge for pharma has been that given the number of emerging biomarkers in the field and the various correlations, it is complex and expensive for the industry to conduct prospective trials in all these settings without knowing the parameters of regulatory compliance.

On the diagnostics side, while there is a set process for obtaining approval via the PMA (premarket authorization) or the 510(k) approval process in the U.S., there is also significant use of laboratory developed tests (LDTs) that do not require FDA approval but are governed under oversight mechanisms such as CLIA (clinical laboratory improvement amendments). Knowing where the line is poses a challenge for diagnostics companies to capture value, since they could spend millions on clinically validating a diagnostic that can be easily replicated as an LDT by a competing service provider. If, however, the FDA mandates that newer technologies such as next generation sequencing need FDA approval for use in clinical diagnostics, it could severely hinder the pace of innovation and adoption of advanced testing.

Overall, the majority of the experts see regulations changing slowly, with some seeing meaningful change in four or five years. While there is general agreement that the system needs to change, there is significant debate about the right path forward. On the diagnostics side, one school of thought is to create an easier path for regulations for newer technologies, and then stricter enforcement of the approved diagnostics. The opposing camp believes that such a model will stifle innovation and put the U.S. at a disadvantage vis-à-vis the EU, where the regulatory stance is lighter.

SAMARTH KULKARNI ET AL., MCKINSEY & COMPANY, PHARMACEUTICAL AND MEDICAL PRODUCTS PRACTICE, PERSONALIZED MEDICINE: THE PATH FORWARD (2013), *available at* http://www.mckinsey.com/client_service/pharmaceuticals_and_medical_products/people/~/media/mckinsey/dotcom/client_service/pharma%20and%20medical%20products/pmp%20new/pdfs/mckinsey%20on%20personalized%20medicine%20march%202013.ashx.

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biomarkers for use in connection with individual drug approvals,[71] but they nevertheless represent only a tiny fraction of the many hundreds of potentially important biomarkers, spanning a wide range of different diseases, that researchers have identified.

In 2007, the Cancer Biomarkers Collaborative (CBC), a coalition of cancer experts drawn from the American Association for Cancer Research, the FDA, and the NCI, started investigating the "growing imperative to modernize the drug development process by incorporating new techniques that can predict the safety and effectiveness of new drugs faster, with more certainty, and at lower cost."[72] The CBC published a summary of its conclusions in 2010 (see **Box 4**, page 14). By that point, "remarkable effort" by biomedical researchers had led to the discovery of "a plethora of novel biomarkers," but "most of them are stalled in a research setting, unable to be exploited for widespread clinical use."[73] The incorporation of this key component of "cutting-edge" science and "evidence-based" pharmacology into the regulatory decision making had "lagged behind." Despite "broad interest, considerable public and private research spending, and the drive toward personalized medicine, surprisingly few biomarkers have been successfully translated into fully validated diagnostic tools. Indeed, fewer than two dozen cancer biomarkers have been approved by the FDA."[74]

A recurrent criticism of the FDA's biomarker-qualification process is that it is highly unpredictable

BOX 4. ADVANCING CANCER BIOMARKERS

Recent discoveries in cancer biology have greatly increased our understanding of cancer at the molecular and cellular level, but translating this knowledge into safe and effective therapies for cancer patients has proved to be challenging. There is a growing imperative to modernize the drug development process by incorporating new techniques that can predict the safety and effectiveness of new drugs faster, with more certainty, and at lower cost. Biomarkers are central to accelerating the identification and adoption of new therapies, but currently, many barriers impede their use in drug development and clinical practice. In 2007, the AACR-FDA-NCI Cancer Biomarkers Collaborative stepped into the national effort to bring together disparate stakeholders to clearly delineate these barriers, to develop recommendations for integrating biomarkers into the cancer drug development enterprise, and to set in motion the necessary action plans and collaborations to see the promise of biomarkers come to fruition, efficiently delivering quality cancer care to patients. (p.3299)

Over the last several years, remarkable effort by the biomedical research community has gone into discovering and developing biomarkers for the diagnosis and treatment of cancer. Although this research has paid off in a plethora of novel biomarkers, most of them are stalled in a research setting, unable to be exploited for widespread clinical use. To date, it has been difficult for individual research laboratories to determine which biomarkers have the greatest potential for use in a clinical setting and to develop them, independently or concomitant with companion drug development, to standards that regulatory agencies would find acceptable. (p.3300)

Every dimension of biomarker translation—from discovery to clinical practice—is riddled with the problems of heterogeneity and an absence of universal standards. Each stakeholder may use a different language and methods of operating, restricting the potential for collaboration, utilization of others' samples, and building on previous work.…The CBC recommends action in four areas in need of standardization and harmonization: terminology, data standards, biospecimen annotation, and informed consent. (p.3305)

The NCI meta-thesaurus system provides a model for semantic mappings between representations. The work of these programs should be used as starting points for a larger-scale standardization initiative to develop a set of common data standards in which the community of researchers has influence and input. The development of standards will require the participation and acceptance of the biomedical research and regulatory communities, particularly at the interface between communities where different vocabularies, ontologies, data elements, and data collection instruments currently exist. As the field is continually and rapidly changing, the end product must be flexible enough to address evolving technical, analytic, and protocol requirements. A process for reviewing and amending the standards must also be developed. (p.3305)

Whereas there is a growing literature base on adaptive designs, and the FDA and other groups have growing experience with the use of enrichment studies, to date there has been no consensus generated on which approaches might work best or specifically enunciating good practices for this process. Best practices in the use of adaptive clinical trial designs as they apply to both drugs and diagnostic devices used in the codevelopment process should be defined. (p.3310)

Samir N. Khleif et al., *AACR-FDA-NCI Cancer Biomarkers Collaborative Consensus Report: Advancing the Use of Biomarkers in Cancer Drug Development* 16 Clinical Cancer Research 3299 (2010), *available at* http://clincancerres.aacrjournals.org/content/16/13/3299.full.

and lacks transparency. In its conclusion, the CBC paper pointed specifically to the need for standards to guide the development of biomarker science. "Every dimension of biomarker translation—from discovery to clinical practice—is riddled with the problems of heterogeneity and an absence of universal standards."[75] There has been "no comprehensive effort to develop the necessary standards," and the

lack of widely accepted standards makes collaboration among researchers almost impossible. The report also noted that many of these problems had been addressed within the data-sharing and analysis networks already developed by health care providers and the NCI. These programs, the report continues, "should be used as starting points for a larger-scale standardization initiative to develop a set of common data standards in which the community of researchers has influence and input."[76]

Since then, as discussed later, the FDA has issued various "procedural" guidances outlining factors that it will consider when evaluating biomarkers, and provided some examples, but the guidances make no attempt to provide generally applicable evidentiary standards, and they fail to address most of the issues raised regarding the collection and analysis of biomarker data.

Adaptive Trials

The biomarker-approval process—or lack thereof—can profoundly affect how clinical trials are structured, how long they last, and on their final outcome. This is most evident in oncology because cancer cells replicate rapidly and mutate wildly as they do. The CBC paper noted that "traditional population-based models of clinical trials used for drug approval are designed to guard against bias of selection, which may form the antithesis of personalized medicine, and accordingly, these trials expose large numbers of patients to drugs from which they may not benefit."[77] Many cancer drug candidates, the CBC concluded, "fail in early clinical development because outdated trial designs are used for their clinical testing and evaluation."

This problem is not restricted to cancer drugs. In the last decade, genomic research has revealed that human biochemistry is much more variable than once believed. Systematic studies of "drug target genes," conducted under the auspices of the NIH's *1000 Genomes Project*, have found that most people carry hundreds of rare variants that would probably disrupt a protein's structure in ways likely to affect how the protein would respond to targeted drugs. No practical, affordable process can identify all such

variations before a clinical trial of a new drug begins, still less evaluate their possible effects on the drug's performance. The drug's safety and efficacy may also be affected by factors—how the drug is metabolized, for example—not directly associated with the disease. Some of these factors can be investigated in laboratory tests before human trials begin, but others will surface only when doctors begin prescribing a new drug to patients. If we don't continue refining biomarker science during and after clinical trials, we will fail to approve—or end up rescinding the approval of—many drugs that many patients need.

As the Cancer Biomarkers Collaborative report (Box 4) observes, "adaptive" clinical trial protocols that allow for changes in trial structure based on biomarkers and interim results can address the problem while streamlining and enhancing trials "without losing scientific rigor." A September 2012 report, issued by the President's Council of Advisors on Science and Technology (PCAST), recommends the adoption of adaptive trial designs that use modern statistical tools to explore multiple causal factors simultaneously and extract more information from smaller trials. As the report notes, patients involved in adaptive trials often receive, on average, better treatments.[78] Dr. Raymond Woosley, former head of the Critical Path Institute—a nonprofit group established in consultation with the FDA and launched in 2005[79] to promote collaboration with drug companies and academic researchers—says that "randomized controlled trials are out of date, and it's time to use the tools of the future."[80]

The NCI's Exceptional Responders Initiative, outlined earlier, illustrates the key elements of an adaptive trial process in retrospective analyses of trials of cancer drugs that failed to win FDA approval because too few patients responded well.[81] In one such trial, a kidney-cancer drug had failed to help over 90 percent of the bladder-cancer patients to whom it had been prescribed. But the condition of one 73-year-old patient improved dramatically. The researchers ran a whole-tumor gene scan and linked the drug's efficacy to a rare genetic mutation that made that patient's cancer more sensitive to the molecular pathway that the drug modulates.[82] Similar mutations were found

in about 8 percent of other bladder-cancer patients, and the presence of the mutation correlated with the cancer's sensitivity to the drug.[83] This study, the researchers note, demonstrates "the feasibility of using whole-genome sequencing in the clinical setting to identify previously occult biomarkers of drug sensitivity that can aid in the identification of patients most likely to respond to targeted anticancer drugs."[84]

The NRC's *Toward Precision Medicine* report includes a similar illustration. In 2003 and 2004, the FDA granted accelerated approval to two lung-cancer drugs, on the strength of their dramatic effects in about one in ten non-small-cell lung-cancer patients. Over the next two years, the drugs were prescribed to many patients whom they did not help. Several follow-up clinical trials seemed to indicate that the drugs didn't work, after all—probably, we now know, "because the actual responders represented too small a proportion of the patients." Researchers then identified the genetic mutation associated with a cell proliferation receptor (EGFR) that these two drugs inhibit. "This led to the design of much more effective clinical trials, as well as reduced treatment costs and increased treatment effectiveness."[85]

With rare exceptions, however, the FDA has been very slow to welcome the use of adaptive protocols and modern statistical tools that allow investigators to refine biomarker science during drug-approval trials. The pharmaceutical industry formed a working group to promote adaptive trials in 2005.[86] As of 2010, as noted in the CBC paper, there had still "been no consensus generated on which approaches might work best or specifically enunciating good practices for this process. Best practices in the use of adaptive clinical trial designs as they apply to both drugs and diagnostic devices used in the codevelopment process should be defined."[87]

Two months earlier, the FDA had finally issued a draft guidance for adaptive drug trials. The agency has since taken a few small, hesitant steps that point to the possibility of more fundamental shifts in clinical trial protocols. A December 2012 draft guidance includes a brief discussion of adaptive "enrichment strategies for clinical trials."[88] By and large, however,

the FDA still treats patient selection as a problem that the drug company must solve either before the clinical trial begins or, to a limited extent, in its early phases, which currently involve very small numbers of patients.[89] The 2012 PCAST report noted that FDA trial protocols "have only a very limited ability to explore multiple factors"— including "individual patient responses to a drug, the effects of simultaneous multiple treatment interventions, and the diversity of biomarkers and disease subtypes."[90]

Accelerated Approval

As the NIH and its partners recognized in launching the Accelerating Medicines project, unraveling the molecular pathways that underlie diseases can, and should, accelerate the process of evaluating a new drug's efficacy. The accelerated-approval rule already provides the regulatory framework in which the FDA will, in principle though very rarely in current practice, allow molecular biomarkers to be used for that purpose.

Developed in the late 1980s and finalized in 1992, the rule's immediate objective was to allow faster approval of drugs that could suppress HIV, a retrovirus that typically takes about five to ten years to produce serious clinical symptoms. Congress codified and broadened the rule in 1997, and addressed it again in 2012. But the FDA has largely restricted application of the rule to HIV/AIDS and cancer drugs. In those two areas, the PCAST report concluded, the rule has "allowed for the development of pioneering and lifesaving … drugs over the past two decades," and the report recommended that the FDA make "full use" of accelerated approval "for all drugs…addressing an unmet medical need for a serious or life threatening illness."[91]

The acceleration in the accelerated-approval rule hinges on the use of "surrogate" endpoints that the FDA deems to be "reasonably likely" to predict clinical outcomes. The acceptance of surrogate endpoints allows the agency to make a first call about the drug's efficacy without waiting for clinical effects to surface and persist for some (often arbitrary) period of time. The manufacturer must still complete studies that

last long enough to confirm the drug's clinical effects but does so after the drug has been conditionally approved.[92] The drug may be withdrawn from the market if things don't pan out.

In addition to expediting delivery of new drugs to patients, accelerated approval can sharply lower the cost of clinical trials, which account for a substantial fraction of the overall cost of drug development. According to one 2011 estimate, a more systematic, predictable framework for applying the accelerated-approval rule to drugs developed to treat rare diseases would triple the number of drugs developed and diseases treated for the same investment.[93] As a practical matter, accelerated approval may be the only pathway that will draw substantial amounts of private capital into the pursuit of drugs that intervene early in the development of diseases that progress very slowly.

A 2006 *New England Journal of Medicine* article attributed the complete absence of drugs that would prevent, rather than just alleviate, late-stage symptoms of diseases such as Alzheimer's or osteoarthritis to a drug-approval process that "makes it hard, if not impossible" to move the drug through Washington before its patent life runs out.[94] "[D]espite considerable advances in our understanding of such diseases, there is no validated and tested path to successful FDA approval of a drug to prevent these conditions. This lack of a clear plan for drug approval adds high regulatory risk to the already high scientific risk of failure."[95] The authors of a 2011 paper on the application of the accelerated-approval rule to rare diseases reach the same conclusion: drug developers have encountered significant difficulties because of the "lack of clear qualification criteria for surrogate endpoints" and the FDA's insistence on ad hoc and, therefore, unpredictable case-by-case analysis (see **Box 5**, page 18).[96] "Clear criteria are … essential to biotechnology companies and investors since only a high degree of certainty regarding the feasibility of a surrogate endpoint-driven pivotal study will increase the incentive to initiate development programs in many rare diseases."[97]

Enacted in 2012, the clear intent of the FDA Safety and Innovation Act (FDASIA) was to significantly broaden the use of biomarkers and surrogate endpoints in the drug-approval process. The congressional findings set out at the beginning of the act note that "during the 2 decades of application of the accelerated approval mechanism, advances in medical sciences including genomics, molecular biology, and bioinformatics, have provided unprecedented understanding of the underlying biological mechanism and pathogenesis of disease" and state that FDASIA's objective is to encourage the FDA to take full advantage of "these remarkable scientific and medical advances."[98]

To that end, FDASIA directs the FDA to "establish a program to encourage the development of surrogate and clinical endpoints, including biomarkers, and other scientific methods and tools that can assist the Secretary in determining whether the evidence submitted in an application is reasonably likely to predict clinical benefit for serious or life-threatening conditions for which significant unmet medical needs exist."[99] The PCAST report echoed FDASIA in calling for broader use of accelerated approval based on "adequate statutory authority and clear interpretation of that authority for early approval of drugs based on indicators, such as disease-specific surrogate and clinical endpoints…"[100]

The FDA has yet to establish such a program. The "procedural" guidance that the agency issued in May 2014 (following the issuance of a draft procedural guidance in June 2013) discusses the agency's interpretation of fast-track designation, breakthrough therapy designation, and accelerated approval. Instead of outlining a program to encourage development of surrogate endpoints—or providing clear substantive guidance on how it would interpret FDASIA's surrogate endpoint provisions—the guidance offers a brief "overview of some of the important factors to consider in identifying and assessing the predictive potential of surrogate or intermediate clinical endpoints."[101]

The draft guidance stated that the acceptability of surrogate endpoints is "a matter of judgment" that the FDA would continue to exercise, case by case. The final guidance omits the "case-by-case" wording

BOX 5. BIOMARKERS AND RARE DISEASES

Biotechnology companies have encountered development difficulties because of the lack of clear qualification criteria for surrogate endpoints due to the belief that each must be evaluated on a case-by-case basis. This unpredictable process significantly hinders the initiation of development of many programs that might require a novel surrogate endpoint. As an example, the use of the surrogate endpoint of kidney biopsy to gain approval for the treatment of Fabry was initially resisted by FDA, which sought greater assurance that the pathologic surrogate was predictive of clinically meaningful benefit. (p. 10)

These biomarkers are directly related to the disease pathophysiology and also to the mechanism of drug action, and so should more accurately assess whether a drug has a beneficial treatment effect. This holds true even if the ability of the endpoint to predict clinical outcome is yet unproven. It is plausible that some of these drugs may not demonstrate clinical efficacy in Phase 4, but given that the drugs should be reasonably safe through the required clinical evaluation, we believe that families will accept the possibility that the drugs' efficacy may be less than expected. To date, no rare disease drugs approved on biochemical endpoints have been withdrawn for lack of efficacy or safety issues. Our analyses do require minimum patient exposure in clinical trials to ensure a reasonable degree of safety, even if efficacy using the surrogate endpoint could be proven with smaller patient numbers. (p. 10)

If a patient has been permanently changed by disease, a small clinical improvement may appear to be a failure, even if the degree of improvement was the maximum possible for that patient. Surrogate endpoints may be more effective than clinical endpoints in detecting efficacy in these situations because they can indicate that the drug is having the correct metabolic reversal effect regardless of the reversibility of the accumulated clinical disease symptoms. (p. 11)

Surrogate endpoints are not simply a convenience, but are a necessary part of the development path for some ultra-rare disorders. Surrogate endpoints may be indispensable for clinical trials when too few patients exist to conduct a large clinical endpoint-driven, double-blind trial. Diseases with substantial heterogeneity or variable irreversibility of disease symptoms, such as bone or neurologic disease, may also require surrogate endpoint-driven trials to ever have the chance to be treated. It is difficult to detect drug efficacy in treating diseases manifested by a variety of symptoms when not every patient expresses each symptom; those who are not affected in one aspect of a disease cannot, with therapy, show substantial improvement in that aspect, even if overall improvement in health is significant. (p. 11)

Brigitta E. Miyamoto & Emil D. Kakkis, *The potential investment impact of improved access to accelerated approval on the development of treatments for low prevalence rare diseases*, Orphanet J. Rare Diseases (July 6, 2011), *available at* http://www.ojrd.com/content/6/1/49.

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but continues to maintain that surrogate endpoint calls are "matters of judgment"—while declining to address how much evidence, and of what kind may be required to support the conclusion that a surrogate endpoint is "reasonably likely" to predict clinical benefits, because "such evidence is case-specific and not readily generalizable."[102] The guidance's treatment of intermediate clinical endpoints is equally cursory and even more dismissive. In short, the latter will rarely be accepted as a basis for accelerated approval, and drug sponsors that hope to use them "should discuss their

development program with the appropriate review division early in drug development."[103]

The guidance addresses the possibility of relying on outside expertise in a single sentence: the FDA "considers all relevant evidence and may consult external experts as needed."[104] A footnote states that the FDA "has established the Biomarker Qualification Program to support work with external scientists and clinicians in developing biomarkers," describes the program as offering "a formal process to guide

submitters as they develop biomarkers and rigorously evaluate them for use in the regulatory process," and refers readers to the FDA's January 2014 guidance. But that guidance is entirely procedural and makes only one brief reference to information supplied by "external expertise, including scientific communities or other international agencies."[105]

One of the few pieces of substantive guidance provided in the ostensibly "procedural" May 2014 guidance attempts to narrow FDASIA's scope. FDASIA defines two separate types of endpoint that may be used for accelerated approval: "surrogate endpoints"; and what are now usually referred to as "intermediate" clinical endpoints "that can be measured earlier than irreversible morbidity or mortality." Each may be used only when deemed "reasonably likely" to predict the attainment of a conventional clinical endpoint—but FDASIA expressly states that accelerated approval may be based on the use of one *or* the other.[106] FDASIA endorses the use of "a broad range of surrogate and clinical endpoints and modern scientific tools earlier in the drug development cycle when appropriate" and authorizes the agency to use "epidemiological, pathophysiological, therapeutic, pharmacologic, or other evidence developed using biomarkers, for example, or other scientific methods or tools"[107] in determining when an endpoint is reasonably likely to predict clinical benefit. FDASIA also singles out two of those evidentiary factors for special attention. The provision that directs the FDA to issue guidance on how it will apply the Act expressly provides that "the Secretary shall consider how to incorporate novel approaches to the review of surrogate endpoints based on pathophysiologic and pharmacologic evidence in such guidance, especially in instances where the low prevalence of a disease renders the existence or collection of other types of data unlikely or impractical."[108]

The FDA's guidance, however, notes that the FDASIA list of types of evidence, which could be considered when evaluating surrogate endpoints, tracks almost identical language incorporated years earlier in the FDA's existing accelerated-approval pathway.[109] The guidance then boldly declares that evidence of "pharmacologic activity" alone will never suffice to meet

the accelerated-approval rule's "reasonably likely" standard.[110] "Clinical data," the guidance continues, "should be provided to support a conclusion that relationship of an effect on the surrogate endpoint … to the clinical outcome is 'reasonably likely.'"[111] As for rare diseases, which received no mention in the 2013 draft guidance, the FDA's final guidance simply acknowledges that they present special challenges and have often been granted expedited review in the past—while declaring that the agency will "continue to apply flexibility" when addressing them.[112]

At the same time, however, the guidance distinguishes surrogate endpoints "known to predict clinical benefit…either because the [drug's] effect is on the causal pathway [of the disease] or correlates with clinical outcomes"[113] and takes the position that these are as good as clinical endpoints and could be used for traditional approval.[114] Further complicating matters, breakthrough therapy designation requires preliminary clinical evidence that the drug can have an effect on a "clinically significant" endpoint. The FDA reads this as a weaker standard than "reasonably likely to predict" and therefore allows that here, a pharmacodynamic biomarker may "in rare cases… be considered a clinically significant endpoint if it strongly suggests the potential for a clinically meaningful effect on the underlying disease."[115]

The guidance's cursory treatment of rare diseases is particularly surprising because, as pointed out by the authors of the 2011 analysis cited earlier, rare diseases are quite often directly linked to specific rare biochemical or pathologic markers that drugs can be designed to target. In these circumstances, the drug's ability to modulate that target may be an excellent demonstration of a drug's likely efficacy—"even if the ability to predict clinical outcome is yet unproven."[116] As of mid-2011, no rare disease drug approved on biochemical endpoints had ever been withdrawn for lack of efficacy or safety issues.[117]

The authors of that paper also cogently argue that there are times when surrogate endpoints are indispensable: insisting on the use of clinical endpoints in conventional trials will only ensure that no treatment gets developed and approved. With very rare

diseases, to begin with, often "too few patients exist to conduct a large clinical endpoint-driven, double-blind trial."[118] Conventional clinical endpoints also present a more fundamental, if rarely noted, problem. Chronic diseases can cause irreversible effects, but when no treatment is available, there is little incentive to diagnose the disease early, so it usually is not diagnosed until clinical effects surface. At that point, a drug may be able to deliver so little clinical improvement to most patients that it is viewed as a failure.[119]

The FDA's January 2014 "procedural" guidance outlines a "Qualification Process for Drug Development Tools" (DDTs) that are "intended for potential use, over time, in multiple drug development programs"—not tools presented for review in specific drug applications.[120] The expectation is that the guidance will be used by individuals, other federal agencies, and collaborative consortia.

The 2014 guidance defines DDTs as "methods, materials, or measures that aid drug development," among them "biomarkers, clinical outcome assessments, and animal models."[121] A "qualified" DDT will be one that "can be used to produce analytically valid measurements that can be relied on to have a specific use and interpretable meaning" within specified "conditions of use" (COU). Submissions for DDT qualification "should contain a complete and detailed description of the studies and analyses providing the evidence to justify qualification of the DDT for the intended COU. In most cases, submission of primary data from studies will be expected."[122]

This being a "procedural" guidance, however, it "explains the kind of data that should be submitted to support qualification…[but] does not address the evidentiary standards or performance requirements needed for purposes of qualification."[123] It makes no attempt to discuss what types of data collection protocols or analytical methods will be acceptable. For substantive guidance, DDT sponsors are urged to consult with the FDA early in the process. When things work out well, the FDA "intends to make public the DDT qualification and the COU statement when those determinations are made in accordance with the process described in this guidance."[124] But

the guidance makes no mention of publicly discussing factors that might lead to the rejection of DDT applications early, or late, in the consultative process—leaving sponsors with the unwelcome prospect of investing significant resources in qualification efforts without any assurance that their efforts will, in fact, meet agency approval.

There is one exception. The 2014 guidance goes out of its way to declare that "pharmacodynamic" biomarkers will almost never be accepted as surrogate endpoints, conceding only that "[a]fter extensive experience, sufficient knowledge of a particular clinical disorder and the biomarker's role in the disorder may accumulate to allow a few of these biomarkers to be used as surrogate endpoints."[125] Here, too, the guidance includes no mention of rare diseases.

The FDA explains this all-but-outright refusal to accept "pharmacologic activity" alone as reasonably likely to predict a drug's clinical effects by pointing to the fact that, when tested in outcome trials, "numerous biomarkers that represented plausible surrogate endpoints …have failed to predict the expected clinical benefit."[126] But relevant FDA guidances express no interest in systematically investigating the possibility that, by collecting large amounts of data and analyzing them with modern statistical tools, medicine now has the ability to identify clusters of molecules that play strong roles in the progression of diseases—as well as those that play little, if any.

Many experts who study and treat complex diseases are successfully using these tools to guide drug design and treatment of patients. The research community continues to launch studies aiming to unravel the etiology of diseases, from molecular cradle to clinical grave. The NIH's Accelerating Medicines project places high priority on identifying Alzheimer's biomarkers that can be used as surrogate endpoints. In a 2011 presentation,[127] Dr. Janet Woodcock acknowledged that concerns raised in the 1980s about the predictive accuracy of surrogate endpoints led to demands that surrogates "completely correlate with the clinical endpoint." She pointed out that, while this is "not possible," such demands led to "serious" (in her view, "misplaced") "disillusionment with

the use of biomarkers." In the discussion following a speech given in April 2014, FDA commissioner Margaret Hamburg declared that, at least in dealing with drugs that treat chronic conditions, "we don't [need] to have studies that have to wait for the whole natural history of the disease to unfold to [assess] how something works."[128]

Dr. Hamburg might have added that there are systematic ways to assess how well large molecular databases and sophisticated analytical tools can be used to identify prognostic biomarkers. When the FDA accepts a surrogate endpoint, the accelerated-approval rule requires drug sponsors to complete conventional trials to validate it after the drug is conditionally approved. In a serious program to modernize and improve the drug-approval process, the FDA would also be equally willing to learn from its own mistakes. When the agency rejects a surrogate endpoint, a retrospective analysis of data gathered during the conventional trial should be conducted to determine how well the rejected endpoint would have predicted the actual clinical outcome—and how much sooner patients would have gained access to a new drug had a good surrogate endpoint been accepted, not rejected.

The FDA also invokes the "substantial risk of adversely affecting the public health if a biomarker is falsely accepted as a surrogate endpoint."[129] The short rejoinder is the one articulated in the PCAST report: while there is "some risk" in using prognostic biomarkers to accelerate drug approvals, it is justified by "the opportunities for progress against serious or life-threatening diseases," while the risk is mitigated by the requirement that conventional trials be completed after the drug is approved. There is little doubt that the rule has spurred rapid and important innovation in the treatment of cancer and HIV, and accelerated access to drugs that have, collectively, done far more good than harm. Relying more heavily on the expertise and consensus views of outside experts, as the PCAST report recommends, would also help insulate the FDA from the political risk and public criticism that it is likely to face if it approves a drug on the basis of a surrogate endpoint and the drug then fails to deliver the predicted clinical effects (see **Box 6**, page 22).[130]

Integrating Biomarker Research Into Clinical Care

The only way to build a complete foundation of biomarker science is to combine pure biological research, of the kind sponsored by the NIH, with ongoing study of how a drug performs—in as many patients as it takes to present all biomarkers affecting its performance, in all combinations occurring in different patients—for as long as the drug continues to be prescribed. This process can, and should, begin in adaptive drug-approval trials but, as noted in the PCAST report: "Most trials … imperfectly represent and capture… the full diversity of patients with a disease or the full diversity of treatment results. Integrating clinical trial research into clinical care through innovative trial designs may provide important information about how specific drugs work in specific patients."[131]

America's competitors have concluded that integrating clinical research with patient care can be done while still maintaining scientific and statistical rigor. These efforts can both accelerate patient access to effective therapies and create a more attractive environment for international biotechnology investment.

The British government recently announced plans to integrate clinical treatment into drug-development efforts on a national scale. As described by life-sciences minister George Freeman, "our hospitals will become more important in the research ecosystem. From being the adopters, purchasers, and users of late-stage drugs, our hospital we see as being a fundamental part of the development process."[132] Britain's National Health Service will become "a partner in innovative testing, proving and adopting new drugs and devices in research studies with real patients."[133] While the details have not yet been made clear, the *Times* of London reports that "Ministers want to bypass traditional clinical trials by using patients as a 'test bed' for promising new drugs, linking [national] health service data to pharmaceutical company records to discover much more quickly how effective treatments are. Firms would be paid different prices depending on how well drugs work for individual patients … Ministers argue that the system of assessing new treatments is no longer up to the job and

BOX 6. RECOMMENDATIONS FROM THE PRESIDENT'S COUNCIL OF ADVISORS ON SCIENCE AND TECHNOLOGY

Intermediate clinical endpoints can be quite powerful, but they can also fail. Broader use of intermediate clinical endpoints for serious or life-threatening diseases with unmet needs should be accompanied by the requirements that (1) post-market trials are conducted to test whether the drug's effect on the endpoint translates into significant clinical benefit, (2) the approved drugs are demonstrated to be safe enough to have a favorable risk-benefit ratio for the patient population, and (3) the FDA has adequate tools to withdraw approval for drugs that fail to meet these criteria. We recognize that there is some risk in employing predictors, but we believe that the opportunities for progress against serious or life-threatening diseases without good treatments justify taking prudent risks.

The biomedical research community should take a more active role in determining whether endpoints are reasonably likely to predict clinical benefit. While the FDA has the authority to decide whether an endpoint is suitable for drug approval, we believe that the decision should largely reflect the consensus of the scientific community. The scientific community should play a more active role in developing and evaluating whether new surrogate endpoints and intermediate clinical endpoints have a reasonable likelihood of predicting clinical benefit for serious or life-threatening diseases with unmet need. The FDA should engage the community in identifying the needs for and weighing the value of possible predictors. The best decisions will emerge from transparent discussion about these judgment calls.

The FDA should clarify its guidance to drug sponsors concerning Accelerated Approval in general, as well as with respect to the acceptability of specific indicators. Drug developers have expressed frustration that it is difficult to get clear and timely answers concerning the acceptability of specific predictors for Accelerated Approval. Without such clarity, the risk of employing such predictors during the lengthy drug-development process is often too great to justify significant investment. While the FDA must proceed thoughtfully in approving predictors, the risks will be mitigated provided that confirmatory studies are performed in a timely manner by drug sponsors.

The FDA should strengthen its enforcement of the requirement for confirmatory studies. If the FDA is to expand the range of endpoints for Accelerated Approval, it must also ensure that sponsors perform the confirmatory studies to verify the clinical benefit and safety of drugs approved under Accelerated Approval and to validate the endpoints for use in future studies…there is evidence that historically the industry has not always fulfilled and/or that the FDA has not adequately tracked and enforced requirements that companies complete confirmatory studies required for Accelerated Approvals to demonstrate efficacy and thereby verify the drug's clinical benefit. The FDA should strengthen its enforcement of these requirements, including using its existing authority to withdraw approval or impose penalties where confirmatory studies have not been completed in a timely fashion. To ensure that post-marketing studies are completed in a timely manner, new mechanisms might be considered—for example, if studies are not completed, the approval will be presumed to sunset or expire (absent an extension by the Agency) or that the sponsor will have a contractual obligation to pay for a third party to carry out the study. (pp. 60–61)

Innovators require greater clarity about general regulatory pathways for innovative products and approaches. For innovative drug developers to take on new approaches and new types of product areas, they need adequate clarity about the pathways and standards of evidence that the FDA will require in evaluating those products. In important emerging areas of science and innovation, the FDA will sometimes lack the resources and expertise to produce clear policies and standards in a timely enough manner to guide innovators in the development of such products. The development of rapid, clear, and thorough guidance documents that

that the National Institute for Health Care Excellence needs to catch up."[134]

The government is also devoting £300 million to sequence the genomes of 100,000 patients with cancer and rare diseases by 2017. It has set up a biobank, with samples and clinical histories from 500,000 patients, to be used by academic and medical researchers in identifying previously unknown disease pathways and potential biomarkers.[135]

For patients, the advantage of integrating the drug-approval process with ongoing clinical treatment is clear: earlier access to life-saving treatments when standard randomized trial protocols can, for many, amount to a death sentence. In one 2010 trial of a targeted cancer medicine for metastatic melanoma, two cousins who developed the disease at almost the same time were randomized, with one receiving the treatment and the other receiving a "notoriously ineffective" chemotherapy. While the former's condition improved, the latter's continued to deteriorate. Not allowed to switch over to the treatment arm of the trial, the latter died, while his cousin survived.[136] Some oncologists have called randomization of patients in such circumstances unethical.[137]

In the U.S., collection of molecular data is becoming an increasingly routine part of many treatments. Doctors can learn a great deal about the etiology of a disease and its response to treatment by studying patient data in depth and sharing what they learn with one another—often in collaboration with companies that specialize in pooling and analyzing molecular and clinical data. In growing numbers, individual doctors are already engaged in patient-by-patient testing of biomarkers when they prescribe drugs off-

label to patients whose disorder presents the target that the drug is known to modulate; or when there is significant variation in patient responses to on-label drug prescriptions, as there often is, for example, in treating cancers and psychiatric disorders. Foundation Medicine "collaborate[s] with drug developers and cancer researchers to identify novel targets and assist in the development of targeted therapies and active clinical trials" and uses its "growing knowledgebase of genomic information about human cancers and … clinical data, to … enable precision medicine."[138] Genomind has partnered with clinicians to develop a saliva-based assay for "genetic markers that best inform patient responses to different psychiatric treatments."[139]

A significant number of experts have concluded that doctors should be free to use data collected by other doctors in routine clinical practice, to help guide how a drug is prescribed, without waiting for the FDA to approve amendments to the drug's label.[140] The NRC report recommends that doctors be given access to new biochemical and clinical data as they are acquired. It also accepts that some doctors would then prescribe drugs on the strength of evidence that Washington does not yet view as proven. "Some patients and clinicians will be more comfortable than others with making decisions that are based on clinical intuition rather than proven evidence. Any physician should be able to interrogate the Knowledge Network … to learn whether others have had to make a similar decision, and, if so, what the consequences were"[141]—while also being informed about whether causal links between molecules and clinical symptoms have been "rigorously validated."[142]

As discussed, researchers and commercial software companies are already actively developing tools to

integrate the development of biomarker science into clinical care and advance "rapid learning health care." There are now proposals to add analytical tools to oncology networks to conduct what are, in effect, open-ended adaptive trials in which "data collection, and data analysis are continuous and integrated, and all available performance data for every rational therapeutic regimen is taken into account to rank treatment options at each decision point for every patient."[143] The authors of the latter proposal note that "classical trials are not efficient enough in either speed or breadth to search the vast space of cancer subtypes and treatments."[144]

The FDA itself has recognized that drug side effects may involve a limitless number of variations in patient chemistry, some of which may surface after a drug is approved. Established in 2008 to monitor the safety of medical products after they have been approved, the FDA's Sentinel System gathers and analyzes data from multiple sources, including 18 data partners and 150 million patient lives.[145]

Unfortunately, side effects aside, the FDA has shown little interest in the possibility of routinely relying on biomarker data gathered in the normal course of treatment in the approval of drugs or diagnostic devices. The Association of Clinical Research Organizations notes that, notwithstanding FDA support for various collaborative projects involving biomarker development, "actual product development remains costly, slow and unproductive".[146]

For the most part, the agency strongly discourages the distribution of information that might promote off-label uses of drugs. But when patents expire and generic versions of a drug are readily available, there is little economic incentive to conduct new clinical trials to get a drug's label amended to cover new uses. Making full use of data developed by medical specialists and hospital systems in the course of treating their patients would address part of that problem and accelerate development of new diagnostic devices and broader acceptance of new uses for existing drugs.[147]

Although the FDA has not expressly acknowledged the fact, recent, revolutionary advances in drug design have already put the agency well on its way toward accepting molecular biomarkers identified during the course of a single patient's treatment.

Oncologists and biochemists are now extracting the patient's own immune-system cells, re-engineering them in a laboratory to home in on a molecular target expressed by the patient's own cancer, and returning them to the patient to attack it. These custom-made "chimeric antigen receptor" therapies have proved stunningly effective in a number of early trials. There is already reason to believe that similar procedures will prove effective against a wide variety of other disorders.[148] They can and almost inevitably will be used to attack rare targets that occur in very small subsets of patients, or even targets uniquely associated with a single patient. Other biochemists have worked out how to manipulate the patient's own immune system, in much the same way conventional vaccines do, but to attack cancer cells that the immune system ordinarily won't attack. The immunity-inducing components of the treatment are extracted from the patient's own tumor.[149] And, because every tumor is biochemically unique, each treatment will be effective only against that specific tumor.[150]

All such treatments hinge on approving treatment protocols premised on the assumption that modulating the chosen target will have clinically desirable effects. When the FDA approves such drugs, it will be approving a biomarker-based manufacturing methodology, not a product with a fixed, rigorously controlled chemical composition. These methods can be investigated in standard clinical trials. But when based on manipulating the patient's cells to modulate targets extracted from the patient's body, their future efficacy depends entirely on the assumption that biochemists and doctors involved know how to select a target that plays a medically significant role in propelling the disease in one specific patient.

Much pharmacology is now headed in that direction because it is becoming increasingly clear that single-letter genetic variations occur frequently, with many seemingly common disorders launched and propelled by these often rare genomic variations. As noted, an early project on the NCI's National Clinical Trials Network will be to investigate the possibility of

"developing drugs for small subsets of molecularly characterized tumors."

Tools for developing many different drugs to target biomarkers found only in small groups of patients or a single patient, are, in fact, already available or very close at hand. Chimeric antigen receptor therapies are manufactured patient by patient. Methods for rapid production of antigen-specific human monoclonal antibodies are being developed and commercialized.[151] In the last two years, researchers have mastered an extremely powerful and flexible method for selectively adding, deleting, or replacing genes inside a live cell's genome.[152] These tools can do in weeks what often required months or years of work using previous gene-editing tools.[153]

To correct flaws in cells that can't easily be harvested and manipulated outside the patient's body, researchers are now investigating a number of different vectors for reprogramming adult cells inside a patient's mature tissues and organs. In a handful of early trials, for example, young adults blinded by a rare genetic flaw experienced significant improvements in vision soon after a viral vector was used to insert a healthy version of the gene directly into their retinal cells.[154] Similar procedures are reportedly being developed to treat cystic fibrosis, brain cancer, and muscular dystrophy.[155] Alnylam, a company co-founded by MIT geneticist, molecular biologist, and Nobelist Phillip Sharp, is developing "RNA interference" drugs that exploit the recent discovery of molecules that can shut down disease-causing genes.[156]

In enacting the Orphan Drug Act in 1983, Congress recognized that developing treatments for rare diseases presents unique economic and regulatory challenges. FDASIA expressly directs the FDA to give such drugs special attention. The FDA has acknowledged the need for "flexibility" in this area and the agency has indeed exercised it: orphan drugs may be licensed on the strength of favorable case reports, animal models, or even in-vitro studies when no good animal model exists.[157]

From a drug developer's perspective, a drug addresses a "rare disease" whenever it targets a rare molecular pathway, even if it is one of many that lead to the clinical symptoms of a seemingly common disorder. Existing rules allow the FDA to designate a drug as an "orphan" if it targets a "medically plausible (orphan) subset of persons with a common … disease or condition,"[158] and the FDA agrees that a drug that targets, say, "a protein found in only a rare subset of breast cancer patients"[159] is entitled to orphan drug designation. The emergence of treatments customdeveloped to treat very small groups or individual patients will require similar flexibility. As discussed earlier, the only practical approach for approving such treatments will often be to use pharmacodynamic markers to ascertain that the drugs do indeed disrupt the targeted pathway.[160]

PART III: HARNESSING EXTERNAL BIOMARKER EXPERTISE AND RESOURCES

Viewed from a strictly scientific perspective, clinical outcomes are the "surrogates." Conventional clinical trials are one way of testing whether we understand the molecular science well enough to design a drug that can interact safely with the molecular biology of a group of patients to produce desired clinical effects and prescribe it accordingly. But when they ignore variations in patient molecular biology these trials can be worse than useless.

Many skilled experts and doctors are devoting enormous amounts of time and effort to the development of a body of molecular biological science that can provide essential guidance on how to prescribe both new and existing drugs to the right patients, and that should also be leading directly to the development of other therapies for use by the patients who do not respond well. But these researchers work with little assurance that their findings will ever be fully used for those purposes because so much hinges on the slow, opaque, unpredictable process of convincing the FDA that the findings are good enough for use in amending labels of existing drugs, or approving new drugs or diagnostic devices.

In this rapidly evolving field, it is no slight to the FDA to note that most of the best biomarker expertise is now dispersed among many different institutions and

private companies, and that biomarker science and standards will almost certainly continue to improve faster than any centralized agency acting at arm's length from the primary research can promulgate appropriate standards for evaluating it. And the FDA should welcome the fact that the development of this essential body of science will accelerate if the experts involved, and those who fund them, can reasonably expect their work to have a good chance of being accepted for use in the approval of new drugs and diagnostic devices.

A Predictable FDA Pathway for Biomarker Submissions

Given the central role that biomarkers should play in the drug-approval process, the biomarker-approval process should be equally efficient and well-grounded in reliable science. The FDA's New Drug Application (NDA) reviews are subject to specific timelines and input from highly qualified external advisors and a non-binding vote from Advisory Committees. These requirements are codified in Prescription Drug User Fee Act (PDUFA) agreements and similar provisions should be extended to biomarker submissions. Timelines and external reviews will also allow Congress to monitor how quickly the FDA approves novel biomarkers and how well its decisions align with the views of the broader scientific community.

Some of the best potential external experts have already expressed interest in helping provide input to the FDA's biomarker-approval process. In 2003, the NIH's response[161] to the FDA's request for comments on its draft *Guidance for Industry: Pharmacogenomic Data Submission,*[162] included a request that the FDA "clarify the criteria that will be used to determine what constitutes a 'valid biomarker' and a 'probable valid biomarker' " and a recommendation that "clear mechanisms for resolving disputes that might arise about the validity of a biomarker be in place and spelled out in the Guidance."

The NIH then declared that it would "welcome the opportunity to assist FDA in the further refinement of the guidance, particularly determining what voluntary data would most be useful and the standards

for determining the validity of [pharmacogenomic data]."[163] The NIH pointed specifically to two of its own programs "of particular relevance that could, respectively, provide a forum for further collaboration and serve as a model for data collection," adding that it would also welcome "less structured opportunities for discussion and development of [pharmacogenomic] policies and practices…e.g., interaction with NIH scientific experts in the relevant research fields."[164] This was a good proposal a decade ago, and it remains so today. As the PCAST report noted in 2012: the agency should promulgate "clear and thorough guidance documents that reflect the consensus of the scientific community" and "may need to more heavily rely upon the biomedical community to collaboratively suggest standards … to clarify its policies and practices"[165] (Box 6).

Congress should take steps to bridge the gap between increasingly systematic, sophisticated, and collaborative biomarker-science projects—in which the NIH, industry, and many other researchers in the U.S. and abroad are already participating—and the FDA's *ad hoc* process for evaluating and approving biomarkers and surrogate endpoints for use in approving drugs and diagnostic devices. To that end, Congress should adopt policies allowing both the FDA and sponsors of new drugs and devices to rely on up-to-date consensus views of members of relevant scientific communities, in deciding which biomarkers and surrogate endpoints should be accepted for use in the approval process. A second objective should be to ensure that the FDA reviews biomarker submissions through a timely, predictable, transparent, and efficient process, incorporating the latest advances in compiling and analyzing large biological databases—while encouraging the scientific community, stakeholders, and the FDA itself to adopt new technologies and tools for identifying and validating biomarkers in a timely way.

Substantive Biomarker Standards Defined by Expert Consensus

Congress should first create a framework for developing substantive standards for biomarker qualification by expert panels convened by a neutral, scientifically-

credible third party. Our suggestion is that these panels be convened under the auspices of the NIH and the IOM. These expert panels would help the FDA incorporate the consensus views of the scientific community into the biomarker-approval process. Given the many, ongoing biomarker efforts already underway through public-private consortiums, or through the NIH and the IOM, we expect that these panels would not require significant new infusions of government funding.

Convened by the NIH and the IOM, separate but coordinated, expert working groups should address the collection and analysis of scientifically reliable, disease-specific biomarker data for the full range of preclinical and clinically meaningful biomarkers—including biomarkers for assessing drug safety and disease state identification and progression. Among the latter, biomarkers that can be used as surrogate endpoints in the accelerated-approval process should be given particular attention to advance the broader use of accelerated approval as recommended by the PCAST report and endorsed by FDASIA. Expert panels should be expressly charged with setting substantive standards for the two different types of endpoints identified in FDASIA for use in the accelerated-approval pathway—surrogate endpoints and intermediate clinical endpoints "that can be measured earlier than irreversible morbidity or mortality."[166]

Separate expert committees should be convened to promulgate standards addressing statistical tools used to analyze biomarker data, with a focus on ensuring that they are reliable enough to provide objective scientific criteria to be used for patient enrichment in clinical trial designs, or as surrogate endpoint markers in the accelerated-approval pathway. For the latter, substantive evidentiary standards should, whenever possible, include statistical confidence interval criteria that the data must meet to satisfy the "reasonably likely to predict clinical outcomes" statutory standard for surrogate endpoints.[167]

These external working groups and the standards they develop should lighten the FDA's workload associated with the timely, predictable qualification of biomarker submissions. Clear, substantive standards for biomark-

er development would allow for faster adjudication of biomarker submissions by agency reviewers.

Additionally, the working groups could provide a large pool of qualified external reviewers to which sponsors could submit biomarker data packages for pre-review clearance. Submissions with evidentiary gaps could be returned to sponsors with detailed suggestions for improvement, with the most complete, convincing packages forwarded to the agency (perhaps with recommendations for qualification). The goal would be to both raise the quality of biomarker submissions reaching the agency and to allow reviewers to focus their energy on the strongest submissions.

The development of clear consensus standards for biomarker qualification would also go a long way towards encouraging industry and academic data pooling and standardization efforts that have delayed the qualification of many potential biomarkers. While the FDA frequently cites the lack of collaboration and standardization among industry and academic researchers as an impediment to biomarker science, the agency overlooks its own role—including an unwillingness to promulgate substantive standards and the long timelines it imposes—in discouraging the investment and collaboration needed to qualify biomarkers for regulatory use.

To ensure that these requirements do not become an unfunded mandate on the FDA that drains staff or funding from other critical agency activities, we strongly recommend that Congress allocate dedicated funding to support permanent staffing and professional development training for the FDA's biomarker review team. Professional development should, among others, include periodic sabbaticals at the NIH, academic medical centers, and private drug and medical device companies working at the forefront of biomarker science. Staff would be recused from reviewing biomarker submissions from sponsors where they had spent sabbaticals.

Congressional funding should be designed to: encourage the retention and recruitment of the best available staff for the agency's biomarker qualification efforts; sustain ongoing engagement with external

scientific-advisory panels on biomarker qualification; and ensure that FDA guidance, based on expert-panel working groups, is finalized swiftly.

To its credit, the FDA is currently engaged in one collaborative effort that could serve as a model for others. Led by a broad coalition of more than 80 experts and other members of the Duchenne's community, the Parent Project Muscular Dystrophy, founded in 1994, assembled a group, including patients, caregivers, medical experts, industry representatives, and academics, that participated in a six-month series of working group meetings to draft a Duchenne research guidance, including standards for Duchenne's biomarker development, and submitted it to the FDA. In September 2014, the agency issued a Federal Register notice stating that it "values the guidance provided by the DMD community and is posting the document to seek additional guidance and public comment," on "all matters relating to … DMD drug development."[168]

This is the kind of structured, collaborative approach to developing substantive standards for including biomarkers in the drug-approval process that experts at the NIH, IOM, PCAST, and others have recommended for many years. As noted, the NIH has established expert panels and standards for reviewing the scientific validity of biomarker discoveries, reported by researchers whom it funds and submitted for inclusion in publicly accessible databases operated under NIH supervision. In dealing with biomarkers and surrogate endpoints, drawing on consensus views of expert scientific, medical, industry, and patient advocacy communities should be a standard, integral part of the FDA's effort to incorporate biomarkers into the drug approval process—rather than a rare occurrence initiated by others. The NIH and the IOM are the federal entities most qualified to convene such consensus groups and to ensure that their views reflect the most up-to-date biomarker science.[169] Congress should create a framework under which they will take the lead in doing so.

The FDA would be a partner in this process throughout, but the standards themselves should reflect consensus views of the scientific community. The standard-setting process should be dynamic and flexible enough to incorporate innovative approaches to developing this body of science going forward. The FDA would retain final authority in the drug approval process to strike the balance between: what is known, and with how much confidence, about the relevant biomarkers and surrogate endpoints used in clinical trials; a drug's safety and efficacy as established in those trials; the seriousness of the disease; and the availability of other therapies. Broader engagement with the external scientific community, however, will ensure that the agency's decisions better reflect the views of experts who specialize in the disease that the drug is intended to treat, and in the use of modern statistical tools used to assess clinical implications of molecular biomarker data.

Congress should strongly encourage the FDA to expand the use of surrogate biomarker for rare diseases, which often face unique challenges due to the extremely small patient populations involved. Often, the agency won't decide on whether to approve a biomarker as a surrogate endpoint for a rare disease until relatively late in the development process (typically after completion of Phase 2 trials); the agency will then decide if clinical data supports the use of biomarkers in Phase 3 trials.

Given the fact that rare diseases often have genetic origins—and that, by the time clinical damage is apparent such effects may be irreversible—effective drugs will not get approved unless they are tested early in the natural history of the disease, with their efficacy judged on the basis of molecular surrogate endpoints.

The FDA should be encouraged to rule on the use of biomarkers as surrogate endpoints before clinical development begins—ideally, during pre-Investigational New Drug (IND) meetings with sponsors—giving investors and industry confidence that a viable biomarker-based pathway to market exists.[170] The viability of surrogate biomarker based drug development would encourage sponsors to invest in the diagnostics needed to identify patients at the earliest possible disease stage, allowing for faster patient recruitment and completion of clinical trials through the accelerated-approval pathway. The FDA

would retain existing authority to withdraw approval of a drug if Phase IV trials fail to validate the surrogate endpoint, or are not completed in a timely manner.

As outlined, the NIH is already playing a large and innovative role in funding and promoting the development of biomarker science. The Biomarkers Consortium's work and other important initiatives funded by the NIH, are overseen by the independent and not-for-profit FNIH, which has made every effort to collaborate closely with all stakeholders, including the FDA. In consultation with industry, academia, and patient groups, the NIH should strongly encourage the researchers it funds to advance their development of biomarker science in a manner consistent with the substantive standards that would have to be met for the FDA to accept its use for patient enrichment in clinical trial designs; for use as surrogate endpoint markers in the accelerated-approval pathway; and for use in other aspects of the procedures used by the FDA to approve drugs and diagnostic devices.

The NIH should also strongly encourage the eight NIH National Centers for Biomedical Computing to continue their "networked effort to build the computational infrastructure for biomedical computing in the nation," to collaborate in the development and validation of modern statistical methods used to analyze large, complex datasets, and to map out causal networks that link molecular processes to clinical effects.[171] Particularly noteworthy is the collaborative effort of 12 centers currently working with the National Cancer Institute to "provide a core framework for applying systems biology approaches to cancer research through the development and implementation of computational models of processes relevant to cancer prevention, diagnostics and therapeutics" and "to integrate experimental biology with mathematical modeling to foster new insights in the biology and new approaches to the management of cancer."[172] The NIH should be encouraged to launch similar programs addressing other diseases.

When researchers—whether or not funded by the NIH—view existing biomarker standards/guidelines as unduly narrow or outdated, they should explain how and why their research has deviated from such standards/guidelines and how that decision has affected their conclusions. This will give researchers and experts involved in promulgating applicable substantive standards and guidance opportunities to address key issues in areas where technology and statistical methods used to create and analyze large, complex data sets are evolving rapidly. This approach would encourage true collaboration and meaningful dialogue among the NIH, NIH-contracted researchers, and the FDA. It would help ensure, too, that acceptance or rejection of biomarker science is made without needless duplication of time and effort at the expense of taxpayers, industry, and, ultimately, patients.

When the FDA receives a biomarker data package—whether from a drug sponsor, the Biomarkers Consortium, or another collaborative consortium such as Coalition Against Major Diseases (CAMD)—the agency should be required to review the submission within a fixed period (say, 30 to 90 days), with allowances perhaps made for how much input the FDA was invited to provide during the formulation of the data package. (As noted, Congress should ensure adequate agency funding to complete timely review of biomarker submissions.) Ideally, the collaborative process will make rapid review straightforward, and most submissions will end up with the FDA designating the biomarkers as qualified. Once clear, substantive evidentiary guidances and standards have been issued to address the collection and analysis of biomarker data, the FDA should be able to approve or reject a biomarker submission based on a fairly quick determination that applicable standards were, or were not, met.

If the FDA identifies evidentiary shortcomings, it should discuss them with the sponsor and reach an agreement on what is required to address them. The review clock for the biomarker data package will be stopped until the sponsor submits the additional data or analyses that the agency requested. The biomarker development agreement should be considered binding on the agency, in the same way as Special Protocol Assessments (SPAs) provided in the drug-approval process are binding, unless the director of the review-

ing division identifies "a substantial scientific issue essential to determining the safety or effectiveness of the drug" that requires amendment of the plan.[173] If the agency deviates from an agreed-upon qualification plan, the sponsor should have the right to have the decision reviewed by a Scientific Advisory Board (SAB), outlined below. Alternatively, the sponsor could request an informal consultation with the SAB before agreeing on a biomarker development plan with the agency, in cases where outstanding issues might be resolved more quickly through such a consultation.

The FDA's biomarker qualification process should also be reformed to ensure that it better reflects the best scientific expertise available within the FDA. Currently, the agency's biomarker Qualification Review Teams (QRTs) are staffed on an *ad hoc* basis from the FDA review division responsible for indication or application, and other offices as needed. Standards for biomarker qualification thus vary, based on membership of the QRT, leading to inconsistent agency decisions and potential confusion among sponsors.

Congress should direct the FDA commissioner to create a permanent QRT support group. It could be staffed with experts in biomarker qualification, biostatistics, informatics, and any other discipline that addresses analytical methods or other matters that can be applied in standard ways to all biomarker submissions and would enhance the QRT's ability to support center reviewers in evaluating proposed biomarkers and surrogate endpoints. On its own initiative or at the sponsor's request, the QRT would also consult members of the relevant SAB, and/or other external subject matter experts, for their views on a biomarker package or surrogate endpoint submitted for qualification.

As noted, the FDA will retain authority to strike a balance between what is known, and with how much confidence; the relevant biomarkers and surrogate endpoints used in clinical trials; the drug's safety and efficacy, as revealed in those trials; the seriousness of the disease; and the availability of other therapies. But biomarker science is largely the science of molecular biology. It is unrealistic to suppose that the FDA has

sufficient resources, in-house, to assess reliability of the science better than the large and growing cohort of specialist researchers. As authors of the PCAST report recommend, decisions about the acceptability of surrogate endpoints, which can have a significant impact on how swiftly new therapies become available, should largely "reflect the consensus of the scientific community."[174]

The FDA's balancing act should also be struck openly, in ways that can be scrutinized by the patients whom it directly affects—as well as by Congress, which retains authority to pass further legislation to align FDA risk-benefit balancing calls with what a substantial majority of patients might prefer. Decisions should not be buried in arcane pronouncements about surrogate endpoints or in FDA ad hoc declarations of a lack of confidence in their ability to predict clinical outcomes. As Dr. Woodcock noted in her 2011 presentation, there has been "confusion" between the desirability of long-term studies needed to expose long-term safety issues and clinical outcomes and use of surrogates. The FDA, she added, should not try to put "too many eggs in the surrogate basket."[175]

If the FDA rejects a biomarker submission, it should be required to convene an SAB, staffed by experts with relevant disease-specific expertise, screened for conflicts of interest, and selected by the Institute of Medicine, or jointly by the FNIH and the Critical Path Institute, or by some other independent body with broad contacts in the field. The biomarker SAB would hear from both the agency and the sponsor, and would vote for, or against, qualifying the biomarker based on evidence presented. The vote would be non-binding but could, at the SAB's discretion, be accompanied by a written explanation of why it disagreed with the FDA.

When the FDA nevertheless rejects the biomarker submission it should do so publicly and in writing, so that the scientific community, sponsors of drugs and diagnostic devices, patients, members of Congress, and the public receive clear explanations of what the FDA considered to be deficient in the submission and how to improve submissions in the future. A clear, public exchange of opposing views would help spur

further research and input by others and would allow patients and lawmakers to observe, in real time, how the agency is handling the very important process of incorporating biomarkers into the regulatory process. Within reasonable bounds, parts of the FDA's response could be kept confidential at the request of the sponsor, insofar as they contain proprietary information.

Congress should expressly declare that no public or private communication relating to an approved drug's molecular mechanism of action, a disorder's molecular etiology, or any other aspect of biomarker science be considered "drug misbranding"—on the grounds that such communication might promote off-label prescription of a drug—provided the information is truthful, non-misleading, and based on a reasonable, good-faith belief that it is supported by reliable, relevant molecular science or clinical experience.

Scientists and doctors routinely share such information in published articles and case reports, on the correct assumption that sharing it accelerates development of the underlying science and the discovery of how existing FDA-approved drugs can effectively treat otherwise untreatable disorders. Drug companies should be allowed to facilitate rapid, orderly distribution of this kind of information, too. As noted, the NRC report broadly endorses sharing of

this kind, notwithstanding the possibility that it will sometimes promote off-label prescriptions.[176]

CONCLUSION

Congress should ensure that the FDA's overarching priority is to catch up and keep pace with rapid advances in biomarker science and the converging, synergistic power of the biochemical and digital revolutions. Together, these revolutions are propelling the most fundamental, broad, and rapid advances ever seen in medical history, and clearly have the potential to do much more.

The drug industry serves a global market, and other countries are quick to adopt the drug-development tools that the U.S. pioneers. The U.K., in particular, is moving rapidly to develop a "unique combination of capabilities at a scale that enables ambitious research to link genes, phenotypes and disease, the selection of patient cohorts to deliver stratified clinical trials and commercial products, and a wide range of opportunities in the fast-growing stratified medicine market."[177] Britain and other members of the European community have recognized that embracing the full potential of molecular medicine gives them the best opportunity to overtake America's biotech industry by simply modernizing their drug approval process faster than we do.

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