

Biopharmaceutical Policy for American Leadership in the 21st Century

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SINCE THE 1980s, the United States has led the world in medical innovation, and our unmatched skill at developing lifesaving medicines has delivered enormous economic value and health improvements to the American economy and patients. In a 2013 report prepared for the Pharmaceutical Research and Manufacturers of America, Battelle, a research organization, estimates that the biopharmaceutical sector adds more than \$789 billion of value into the American economy annually and employs more than 813,000 workers, whose average annual wages exceed \$110,000, more than double the U.S. private-sector average.⁷⁷ Those salaries generate billions in state and federal tax revenues. Further, biopharmaceuticals are one of the country's leading exports, grossing \$50 billion in 2014.

The industry is also — by far — one of the nation's most R&D intensive, with global R&D spending equal to about 18% of sales.⁷⁸ That investment (\$51 billion as of 2014) helps the U.S. maintain its status as home to the world's most prolific life-sciences industry, claiming 53% of global patents granted to pharmaceutical technology — twice that of our nearest competitor, the European Union (26%), and five times that of third-place Japan (10%).

The U.S.'s position at the forefront of global biomedical innovation is, however, far from permanently assured. Europe claimed that position as recently as the 1980s, but was overtaken by the U.S. in the following three decades.⁷⁹ Experts attribute the shift to the greater attractiveness of the U.S. market in a variety of areas, including stronger protections for intellectual property and high levels of funding for basic biomedical research through a competitive grant process operated by the National Institutes of Health (NIH).

But what has undoubtedly made the industry one of the crown jewels of America's high-tech industries has been a relatively free pricing environment for patented medicines. Premium returns from the sale of new and innovative medicines encourages high levels of R&D investment and a vibrant private venture-capital market that funds numerous small start-up biotech companies — an increasing source of groundbreaking new treatments.⁸⁰

Nonetheless, growing financial pressures associated with spending on health-care entitlements at the state and federal level, and a siloed health-care system that focuses on short-term drug prices, rather than the long-term role that medicines play in improving productivity and reducing other health-care costs, are creating a U.S. political environment that is more skeptical of the benefits the industry provides, and more open to European-style price controls, than at any time in recent memory.

Without public-policy reforms designed to sustain and advance biomedical innovation in the U.S. — especially by reducing the cost, time, and risk associated with bringing new medicines to market while also aligning drug prices with real-world outcomes — America could easily cede its leadership of this vital industry to more nimble competitors in Asia or Europe.⁸¹

PRICE CONTROLS ARE NOT THE CURE

The current U.S. drug-pricing regime is certainly not without its flaws. Third-party payment systems can desensitize patients from considering the marginal benefits and costs of new medicines (a criticism equally applicable to medical devices, as well as hospital and physician services). Paying by the pill, rather than the outcome, provides perverse incentives to both manufacturers and insurers to focus on bulk discounting — or, conversely, across-the-board utilization restrictions, such as narrow formularies — that ignore the wide variation in patient responses to medicines. Some patients are thus exposed to potential side effects without the prospect of offsetting benefits, while other patients are denied access to products that produce greater gains than average. The tools are increasingly available for clinicians and patients to customize treatment protocols, but these protocols are discouraged by one-size-fits-all reimbursement schemes.

Of equal concern is the rise of high-deductible health plans, often without offsetting Health Savings Accounts⁸², and narrow or tiered formularies with unified deductibles for hospital, physician, and pharmacy

care that are exposing more patients to higher out-of-pocket costs from medicines used to treat serious chronic ailments.

While most Americans are faced with only modest co-pays, a small number of patients (2%) with serious chronic diseases—cancer, multiple sclerosis, or HIV—account for 30% of all out-of-pocket payments, meaning significant financial pressures are put on the patients who may be least able to bear them. Patients with higher out-of-pocket drug costs (through insurance co-pays, deductibles, and co-insurance) are also much more likely to discontinue drug therapy, leading to higher costs and worse health in the long run.⁸³

As discussed below, aligning insurance payments with patient outcomes—delivering the right treatment, to the right patient, at the right time—in a competitive, consumer-driven market would undoubtedly help lower net costs and lead to better outcomes for patients and payers. It is also likely to promote the path-breaking innovations that the biopharmaceutical industry is uniquely positioned to deliver through precision medicines and diagnostics.

Policymakers routinely decry the fact that drug companies concede larger discounts to public payers outside the U.S., especially in the U.K., Canada, and Europe. However, government intervention in other wealthy nations' pharmaceutical markets effectively creates monopsony pricing power. Without that intervention, it is likely that other wealthy nations would pay prices closer to those of the U.S. (on a GDP per capita basis). The resulting increase in global industry revenues would incentivize even greater investments in innovation. As the U.S. Department of Commerce noted in a 2004 report:

...[I]n the Organization for Economic Cooperation and Development (OECD) countries studied in this report, governments have relied heavily on government fiat rather than competition to set prices, lowering drug spending through price controls applied to new and old drugs alike. Such controls, when applied to new drugs, reduce company compensation to levels closer to direct production costs, leaving less revenue for R&D. As OECD countries individually seek to reduce spending on drugs through price controls, *their collective actions reduce R&D that would provide substantial health benefits to all.*⁸⁴ [emphasis added]

Another study, from the RAND Corporation, found that if the U.S. adopted European-style price controls, the result would be significantly less future drug innovation in return for only marginally lower prices today.⁸⁵ So while the E.U. is undoubtedly free riding on U.S. funding of global R&D, the U.S. could not adopt similar tactics without significantly dampening R&D efforts—and significantly harming future U.S. patients.

Indeed, pharmaceutical innovation—and its benefits—have become so commonplace that we risk taking them for granted. HIV/AIDS—once a death sentence—is now a manageable chronic illness. Beginning in 1996, Highly Active Antiretroviral Therapy led to an eventual 85% decline in HIV mortality rates in the U.S., with an estimated 862,000 premature deaths avoided. The newest combination therapy has been shown to prevent infection in high-risk individuals. One study from Truven, a health-care analytics firm, found that better HIV/AIDS treatments available from 1996-2010 produced more than \$600 billion in economic value, net of costs.⁸⁶

While cancer remains the nation's second leading cause of death, there has been a 23% decline in death rates since the 1990s, with over two-thirds of cancer patients now surviving at least five years. The pace of decline in cancer deaths has also accelerated in recent years, declining by 15.1% from 2000 to 2011 compared to 7.5% between 1990 and 2000, driven by improved treatment and detection efforts.

With some cancers, we can even begin to speak of effective cures. Ninety percent of women diagnosed with breast cancer can now expect to live at least five years—up from just 75% in 1980.⁸⁷ Until the approval of Gleevec (imatinib) in 2001 patients with chronic myelogenous leukemia had a five year survival rate of 31%—after imatinib was approved, it rose to 90%.⁸⁸ CML patients who respond to imatinib can have similar life expectancy to that of the general population.⁸⁹ Second and third line therapies are also available for patients who don't respond, or whose cancers become drug resistant.

Mortality rates for cardiovascular disease have fallen by over 50% since 1980, with much of the gain attributable to better drug treatments for risk factors such as high LDL cholesterol, and blood pressure, and clot-busting drugs designed to reduce future risks for patients who experience a first heart attack.

Hepatitis C, a chronic liver infection that afflicts millions of

Americans and which can eventually cause severe liver scarring and liver cancer or liver failure, has seen its cure rate more than double in just five years—from 40% in 2010, to 95-96% today, thanks to safer and far more powerful antiviral treatments developed by industry.

Ironically, calls for price controls are mounting even as new medicines are having a greater impact on patient prospects for long-term survival and healthier lives. Rather than slowing innovation to a crawl in the hopes of curtailing short-term costs, American policymakers should find ways to lower the costs and risks of drug development, thus accelerating the pace of innovation, while also spreading the costs of new innovations across more lives and longer periods of time.

As we discuss later, the development of biomarker science and its use in developing precision medicine—targeted drugs and protocols for their prescription to precisely selected cohorts of patients—are increasingly allowing companies and researchers to identify and attack the molecular roots of serious and life-threatening ailments, pointing to a future in which we will be able to prevent, delay, or mitigate the impact of life-threatening diseases such as cancer, Alzheimer’s, diabetes, and Parkinson’s—and thus lower the health-care costs associated with prolonged disability and reduced productivity.

Developments like these will have a large positive effect on overall health-care spending because, as the economist Michael Mandel has written, “the single biggest driving force for increased health-care spending in the U.S. is the rising cost of labor, not drugs.”⁹⁰ He goes on to note that “the cost of labor amounts to more than 40% of the increase in the total cost of personal health-care spending since 2007, while the cost of prescription-drugs amounts to only 10% of the increase.”

Accelerating the development and adoption of precision medicines and diagnostics that compress serious disability to an ever shorter portion of the human lifespan is the best and most far reaching cost-control strategy Washington could adopt in the health-care sector.

DRUG DEVELOPMENT AND EXCESSIVE CAUTION

High-profile safety scandals from Thalidomide to Vioxx and Avandia, have left the U.S. Food and Drug Administration institutionally inclined toward risk aversion. That, in turn, has led the FDA to require longer and larger clinical trials designed to identify rare side effects before a new drug is approved, particularly drugs that are used for primary-care

indications, such as heart disease and diabetes, which often must be taken indefinitely by large patient populations.

But longer and more demanding clinical trials come with real costs to industry, patients, and payers. According to the Tufts Center for the Study of Drug Development, including the cost of capital, it now takes \$2.6 billion and approximately 10 years to bring a single new FDA-approved medicine to market. Tufts researchers have also found that, from 2003 to 2011, total procedures per FDA clinical-trial protocol increased by 57%, the investigator site work burden by 64%, eligibility criteria by 48%, and length of trial treatment by 25%.⁹¹

All of these increases make it more difficult, complex, and costly to bring new therapies to patients. Fewer than 12% of medicines that enter Phase I clinical trials (the first phase of human testing for safety required by the FDA) end up being approved. This means that the industry must recoup its costs and profits from a relatively small number of marketed products, often for diseases, such as some cancers or cystic fibrosis, that treat smaller patient populations (at least as compared to previous blockbuster treatments for the primary prevention of heart attacks, i.e., lowering high LDL cholesterol).

Demanding more information and longer trials pre-launch from a relatively small number of approved therapies over small patient populations increases the pricing pressures that payers often decry.

Regulatory costs and barriers sharply limit new entry and market competition, because only a few large pharmaceutical firms have the capital, and regulatory acumen, to navigate ever-expanding FDA evidentiary requirements. In 2011, Michael Rawlins, at the time head of the U.K.'s National Institute for Health and Care Excellence and a frequent critic of industry pricing, noted that the regulatory requirements in both the U.S. and U.K. "[had] increased hugely."⁹² He pointed out that in the 1990s the median number of patients exposed to a new drug in clinical trials was about 1,500; by 2011, that number had grown to 12,000. "It is a huge increase with not much gain, not much benefit from these increased numbers," Rawlins noted. "And of course, it puts up the cost of drug development hugely." He went on to estimate that clinical trials accounted for well over 50% of the cost of new drugs.

International regulators are beginning to recognize that the high costs and obstacles to competition attributable to the regulatory system's trial protocols can and should be sharply scaled back. The executive director

the European Medicines Agency (EMA), Europe's counterpart to the FDA, noted⁹³ that the new "adaptive pathways initiative" that the EMA is developing could reduce "by years" the time it takes to win approval, and EMA's "expectation is that companies will reflect this by reducing the price of medicines for the benefit of patients and for the sustainability of our healthcare systems."⁹⁴ In short, if new medicines are allowed to reach market faster at lower cost, more firms can compete in the field, leading to more pricing competition without reducing incentives to innovate.

The FDA reforms we propose below are particularly important because the regulatory status quo isn't just less than optimal. Failure to develop the science during FDA-mandated drug trials has undesirable consequences for patients. Adaptive trials are considerably more efficient—they can achieve statistically robust results when they involve fewer patients, ensuring that fewer patients are treated with a drug that cannot in fact help them while its side effects may harm them. Recognizing that a drug is ineffective earlier also allows researchers and patients to shift scarce time and resources towards other, potentially more productive treatment strategies.

Smaller adaptive trials can also be shorter than conventional trials—many years shorter according to at least one estimate. The implied lower cost of capital per FDA-approved medicine should allow innovators to embrace more flexible pricing contracts with payers, without reducing net profit margins. Of course, faster trials also mean earlier patient access to successful new life-saving drugs.

The synergies of molecular-biological science and high-power computing discussed below are beginning to deliver rapid-cycle innovation in the biopharmaceutical industry. Ongoing advances in our understanding of human genomics and related disciplines (epigenetics, proteomics, and systems biology) are allowing researchers to test promising new drugs in patient cohorts identified by molecular profiles (biomarkers) that make those patients most likely to respond well to the drug and least likely to experience serious side effects. Integrated into clinical trials, these tools can accelerate and lower the costs of the drug-approval process and place it on a much more solid scientific foundation than is provided by the one-dimensional statistical correlations traditionally relied on by the FDA.

This approach is already being implemented by oncologists on a learn-as-you-go, patient-by-patient basis as oncologists practice truly personalized precision medicine. Tumor biology is carefully analyzed and

drugs designed to home in on specific molecular targets are prescribed only to patients who present them. Data gathered from patients is stored in large databases, and sophisticated analytical algorithms then analyze the data and recommend optimum treatments for future patients. This process allows physicians to prescribe off-label treatment regimens when biologically appropriate regardless of how the drug was tested during the FDA approval process.

The targeted drugs involved in this “rapid learning” pharmacology, however, will remain expensive—or not get approved at all—if the FDA’s drug-approval process isn’t changed to accept the full implications of the advent of biomarker-guided drugs that make precision medicine possible. Ensuring that biomarker-guided drug development is a sustainable path for innovators, payers, and patients will also require rethinking other elements of the U.S. health-care system to better align value with reimbursement.

THE PRECISION MEDICINE REVOLUTION

In our generation, biochemists have acquired the tools to gather reams of molecular data about the rogue human cells and microbes that propel the diseases that kill us. They have also developed a remarkable array of new tools for designing precisely targeted drugs. Advances in structure-based drug design, monoclonal antibodies, and, most recently, gene-editing technologies have given biochemists the tools to design drugs that can modulate specific molecular targets or reprogram immune system T cells and stem cells that protect, repair, spawn, and maintain tissues throughout our bodies.

Using these tools to cure diseases, however, hinges on working out the causal connections between what we can see and control in the lab and the clinically defined disorders that we wish to control in patients.

Recently acquired diagnostic tools have revealed the roots of the safety and efficacy conundrums that often lead regulators—incorrectly—to binary, one-size-fits-all regulatory decisions when reviewing medicines. At the molecular level, many seemingly common disorders—such as diabetes or depression, conventionally defined by their clinical symptoms—are in fact clusters of biochemically distinct disorders.

Understanding how to mine this information is the next challenge—one we are already overcoming.

The National Institute of Health’s 1000 Genomes Project reported in

2012 that its study of 14 population groups in Europe, Africa, East Asia, and the Americas had identified 38 million “single nucleotide polymorphisms” (“SNPs”)—single letter variations—in their DNA. Another study, completed a few months earlier, analyzed SNPs in the potential “drug target genes” of 14 thousand individuals thought to be particularly susceptible to heart attacks, strokes, obesity, and other health problems. On average, each subject was found to carry about 14 thousand SNPs, about 12 thousand of which were exceedingly rare. Each subject carried an estimated 300 genes with variants found in less than 0.5% of the population that would probably disrupt a protein’s structure in ways likely to undermine health and affect how the protein would respond to targeted drugs.

To further complicate the picture, some of our diseases—cancers most notably—involve cells that mutate rapidly and thus quickly learn to evade drugs prescribed to treat them. Late-stage cancers mutate so fast that they are rarely beaten by a single drug—“cocktail cures” are required instead. A drug’s performance can also depend on how it is metabolized in the patient’s liver or interacts with molecular bystanders in other organ systems to cause unwanted side effects. As noted above, the molecular chemistry involved in all of these processes can vary significantly across patients.

Precision medicine depends on systematically working out how a complex array of molecular factors can propel a disease and affect its response to targeted drugs. This strategy hinges on developing and analyzing large databases that include molecular and clinical information collected from large and diverse arrays of patients—not one-off drug trials for regulatory approvals.

The development of those databases is already well underway. The director of the Genetic Variation Program in the National Institutes of Health’s National Human Genome Institute recently estimated that there were “about 2,000 separate databases” addressing genetic links to various diseases.⁹⁵ The NIH itself has compiled a Cancer Genome Atlas.⁹⁶ The NIH is also funding many other studies of genetic variations that affect health, among them a project that pools data supplied by a consortium of genetic researchers from around the world. It is also working directly with ten big drug companies and eight non-profit organizations that focus 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.⁹⁷

The private sector is also deeply involved. Independent researchers and doctors have set up databases of their own in which they pool and analyze molecular and clinical data collected during the treatment of patients with approved drugs. Increasingly, these databases are being analyzed using software designed to recommend drug prescriptions — on label or off — that match the molecular pathway that is propelling the patient’s disorder with the pathway that a drug was designed to modulate. The managers of these systems and services often receive in return information on how things worked out, and the constant feedback steadily improves the quality of future treatment recommendations.

Google and Illumina, the leading supplier of gene-sequencing machines, among others, recognized the converging, synergistic power of the biochemical and digital revolutions some time ago.⁹⁸ And they already have broad access to customers and the tools to collect the data quickly and efficiently — hence their rapidly rising interest in developing huge databases of molecular and clinical information and analytical engines that can unravel the complex causal chains and identify the signaling systems that propel cancers and other diseases.

Given enough data and computing power, modern statistical tools can map out complex causal networks, and assess the importance of key nodes and links. In analyzing genomic databases, they have already demonstrated their ability to deal successfully with “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, provided what has, until recently, been the standard categorization of breast cancers into four subtypes. A more recent analysis of more data revealed at least ten subtypes.^{99,100}

But the FDA has made clear that it will almost never approve a new drug on the basis of a pathophysiological demonstration that the drug can shut down or repair a disease-propelling pathway. The FDA asserts — correctly — that a drug’s demonstrated effect on a single, disease-specific molecular pathway often fails to predict its ultimate clinical effect on patient health. But much of the time we already know why, or can find out if we wish to.

And the analysis of disease-causing molecular pathways will never be complete because it cannot preclude the possibility that we have

not yet identified all possible variations in that pathway nor the development of further variations in that pathway. Bruce Johnson — a researcher at Boston’s Dana-Farber Cancer Institute and one of the doctors involved in the original trials of Iressa, a drug developed to target the epidermal growth factor receptor (EGFR) on non-small-cell lung cancer — remarked in 2005, “For us as investigators, at this point, there are at least 20 different mutations in the EGF receptors in human lung cancers, and we don’t know if the same drug works as well for every mutation . . . which is why we want as many EGFR inhibitor drugs available as possible for testing.”¹⁰¹ And however precisely targeted it may be, a drug’s overall impact will often also depend on how it interacts with other parts of the patient’s body.

In sum, advances in biological science have revealed that the generally accepted symptom-based taxonomy of diseases — still relied on by the FDA in the drug-approval process — is obsolete, and antithetical to the advance of the precision medicine of targeted drugs in the real world of complex patients. As the National Research Council (NRC) put it, we need a “new taxonomy of disease.”¹⁰² We would add that we need a new FDA capable of viewing itself as the curator of that taxonomy, rather than a gatekeeper for drug approvals based on clinical signs and symptoms.

Complex diseases like cancers are among those poorly served by the FDA’s reliance on traditional clinical-trial designs. The National Center for Biotechnology Information has said “cancer research is . . . poorly served because of the many existing clinical trials from which we currently learn almost nothing.” Instead we should “consider the possibility of linking the efforts of physicians, researchers, and patients in advancing cancer research. . . . Increasingly, randomized trials will be forced to share the stage with innovative trials that deeply investigate cancer within individuals.”¹⁰³

What we see emerging here is the inevitable and essential response to the advent of the science and technologies of precision medicine. The only way to develop the science that tells us when a drug will perform well or badly when prescribed is to study patients and their responses to drugs in the real world of clinical practice.

Critics of such an approach would counter that it is unethical to use patients as guinea pigs, but conventional clinical-trial protocols already do so — slowly and at enormous cost. Doctors do so again, when they

don't prescribe medicines according to a drug's FDA-approved label. The difference is between entering into the process blindfolded or with our eyes wide open and determined to learn as much as possible at every step of the process. The unethical option is to cling to outdated drug-trial protocols that, when there are no other good treatments available, rob patients of the possibility of truly informed consent.

LEARN-AS-YOU-GO MEDICINE

Ongoing analysis of how the patient-side chemistry can affect a drug's performance should populate a large database that continues to grow in predictive power and relevance as more patients are treated with the drug and treating doctors continue to gather molecular and clinical data from every patient treated.

Clinical-trial protocols that facilitate the development of such databases and complementary analytical tools can, as noted earlier, not only place the drug-approval process on a much more solid scientific foundation, they can continue to be updated using post-market data-collection tools, creating a seamless interface between the clinic and the research laboratories searching for the next molecular scalpel to attack previously unknown disease variants.

Most of this information can't be obtained until the drug starts getting prescribed to significant numbers of patients—but the first opportunity to frame the right questions to ask begins with the drug-approval clinical trials required by the FDA. Unfortunately, the development of biomarker science does not in fact happen under the agency's existing, narrowly defined clinical-trial protocols.

This creates a Catch-22. Doctors can't take the lead in working out how to prescribe a drug to the right patients until the drug has been approved; but the drug won't perform at its best and get approved until someone works out how to prescribe it to the right patients. For doctors, the one notable exception is their authority to prescribe an already-approved medicine off-label. The high cost of running the FDA's current trial designs ensures that if the medicine fails the first time around, it is often simply discarded.

In well formulated adaptive trials, by contrast, on-the-fly study of patient-side molecular biomarkers that account for different responses can allow progressively better selection of patients who will respond well. This allows the trial to converge much more quickly and effectively

on the patients who do respond and develops scientific criteria for identifying such patients in the clinic. Non-responders can spur additional opportunities for drug development.

Allowing early access to experimental medicines to expert physicians who specialize in the disease of interest (through a strategy called “conditional approval” or “adaptive licensing”) can allow the development of precision prescription protocols through an iterative process that improves at every step—simultaneously lowering the costs and risks facing developers, while expanding access to promising treatments for patients who have no other good options.

Current clinical trials account for over 50% of estimated drug-development costs. Adaptive trials are considerably more efficient—they can achieve statistically robust results when they involve fewer patients and thus cost less. And by homing in progressively on the information needed to prescribe the drug to the patients who are most likely to respond well, they are also more likely to culminate in the approval of the drug.

An additional advantage of these smaller adaptive trials is that fewer patients are treated with a drug that cannot in fact help them while its side effects may harm them. Yet another, often overlooked advantage of trials that focus from the outset on the molecular etiology of the disease being treated is that they can lead to the enormous economies of drug “repurposing”—using a drug that has been approved to treat one particular disease to treat another, quite different disease. This is quite common in oncology, because the same molecular targets and pathways are often involved in driving two or more types of cancers that develop in different tissues or organs. Oncologists know this and quite often investigate repurposing possibilities by prescribing approved drugs off-label.

If adaptive trials are integrated into clinical treatment conducted in centers—such as the major cancer centers and cancer cooperative groups designated by the National Cancer Institute—that specialize in treating particular diseases, the trial protocols can also be flexible enough to exploit the unmatched expertise of these doctors to investigate such things as dosages and combination, multi-drug therapies, and other aspects of how the new drug is used in environments that will better approximate real-world conditions.

Consciously and strategically blurring the line between experimental and FDA-approved medicines will address the tremendous unmet medical need of the millions of patients who do not respond to currently

available therapies for life-threatening diseases such as cancer, Duchenne muscular dystrophy, and Alzheimer's.

Adaptive trials integrated into clinical treatment can have a further salutary effect on costs and prices. It is reasonable to charge patients who are receiving treatment even when the patients are also paying in the other currency of providing data that will help deliver higher-caliber precision medicine. As the precision-medicines databases grow and the analytical tools improve, a novel process for setting drug prices based on outcomes can be systematically explored and eventually become the norm for pricing drugs once they reach the market. The precision-medicine databases will steadily improve their ability to predict how much a patient is likely to benefit from the treatment, and that knowledge can be starting point for outcomes-based pricing.

Another, as-yet-ungrasped opportunity is moving new preventive medicines through adaptive trials in post-market settings. Developing preventive therapies through conventional trial protocols is often prohibitively expensive because the trials must continue for as long as it takes the disease to materialize and progress. Trials focused on the molecular etiology of diseases and ongoing analysis of a drug's ability to disrupt a disease pathway can establish efficacy much more quickly.

Finally, the rise of precision-medicine databases and analytical tools that can tell doctors and patients how best to match a specific drug to a specific disease may well help solve the new drug problem of sticker shock.

Most of the cost of developing a new drug is incurred before the drug comes to market, and must be recovered before applicable patents expire. This means loading the huge front-end costs on early adopters, the first cohort of patients who are treated with the drug. Prices routinely plummet when patents expire and cheap, generic substitutes flood the market. But for doctors to prescribe the generics well, they will need access the precision-medicine database. By imposing a modest fee for access, drug companies or others who have taken charge of assembling and managing the database could spread the up-front costs of drug development over a broader group of patients and thus sharply lower up-front prices.

NEW REGULATORY PARADIGMS
ARE A COMPETITIVE ADVANTAGE

America's international competitors recognize that integrating clinical research with patient care can be done while still maintaining scientific

and statistical rigor. Creating seamless lab-bench-to-bedside protocols can both accelerate patient access to effective therapies and create a more attractive environment for international biotechnology investment.

The United Kingdom has announced plans to dispense with traditional clinical trials by mining genomic information from patients' electronic health records to identify novel targets for drug development and match patients with tailored therapeutics. It is also devoting £300 million to sequencing the genomes of 100,000 patients with cancer and rare diseases by 2017, and has set up a biobank with samples and clinical histories from 500,000 patients as a resource for academic and medical researchers to identify previously unknown disease pathways and potential biomarkers.

At the same time, Innovate UK, a government agency whose mission is to promote economic growth “by working with companies to de-risk, enable and support innovation,” has created innovation centers called Catapults, each designed to “accelerate and simplify the path from research to commercial products,” including one focused on precision medicine. The precision-medicine Catapult operates with the explicit goal of “making the UK the leading place worldwide to develop and launch new solutions” for precision medicine through the use of cutting-edge diagnostics and Big Data algorithms.

The U.K. government recognizes that close cooperation between stakeholders — patients, academic researchers, innovative drug and diagnostic companies, regulators, and payers — will be necessary to create a rapid adoption of precision-medicine technologies by lowering barriers to product commercialization. The precision-medicine Catapult functions as “trusted neutral party...by offering a critical mass of multidisciplinary expertise, infrastructure and services” to companies operating at the cutting edge of science.¹⁰⁴

At the heart the U.K.'s embrace of rapid cycle, patient-focused innovation is database-driven drug development, including the ability to rapidly share knowledge across various health-care providers. In a March 2015 report, the Association for the British Pharmaceutical Industry explained how the approach could work to accelerate innovation while also enhancing pricing flexibility by reducing regulatory costs and risks:

Novel, matched case controlled studies which include real world data of patient relevance can utilise health databases to more quickly identify and recruit subjects, and allow data capture and

analysis in real time. Adaptive designs, with prospective and in-stream stratification, can increase targeting and further personalise medicines development. Time and cost savings are achieved through expedited recruitment, reduced study complexity and use of fewer investigator sites....

As evidence accrues through post-approval continuation of studies, the value proposition will change based on the evidence generated. The price paid for a medicine should thus adapt to account for the value it brings. Ultimately, greater cost-effectiveness and affordability should result. With lowered development costs, a reduced price can maintain profitability, increase development portfolio cost efficiency, and allow the progression of a greater number of promising projects at reduced cost.

The ABPI report calls for the U.K. to seize the opportunity to “set a new [global] regulatory standard and take a lead in enhancing patient care through medicines evaluation and uptake.” Advancing global regulatory standards through database-driven drug development that matches promising medicines to patients in the clinic would enable “wider applicability, including utilization of data generated substantially in the UK at improved speed and cost,” producing a “major incentive for UK life science investment.”¹⁰⁵

Not to be outdone, in 2014 the European Union launched the second phase of its Innovative Medicines Initiative (IMI2), which recognizes that the “availability of the complete sequence of the human genome, the growing body of ‘-omic’ data sets and epigenetic markers in health and disease, the availability of patients’ electronic medical records, next generation genetics for target identification, and sophisticated bioinformatics techniques offer the opportunity to revolutionise the current medicines development process.”¹⁰⁶

Biomarker development is one of the four key priorities identified by IMI2, which will include an effort to “identify and validate biological markers, tools and assays (biochemical, functional and imaging) 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.” IMI2 is intended to run for 10 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.

For patients, the advantage of rapidly incorporating biomarkers and surrogate endpoints into clinical treatment are clear: It allows greater access to targeted treatments by patients who are most likely to benefit, moving beyond the artificial confines of randomized controlled trials in which some patients, even when they fit the molecular profile of the intervention, are randomized to receive the standard of care and are denied access to targeted medicines—which can amount to a death sentence. In one 2010 trial of a targeted cancer medicine for metastatic melanoma, two cousins with the disease were randomized, with one receiving the treatment and the other receiving a “notoriously ineffective” chemotherapy. Even after his disease progressed, the patient was not allowed to switch over to the treatment arm of the trial. The patient who received the drug survived, while his cousin died. Some oncologists have called randomization of patients in such circumstances unethical.¹⁰⁷

America’s competitors recognize that embracing the full potential of molecular medicine to transform both drug development and accelerate the adoption of precision-medicine technologies gives them the best opportunity to overtake the U.S. biotech industry by simply modernizing their drug-approval process faster than we do.

A ROADMAP FOR AMERICAN LEADERSHIP

To encourage the development of precision-medical treatments and biomarker-based diagnostics that can revolutionize the health-care system and lower costs for both private and public payers, Congress and the next administration should focus on four key reforms.

The first and most complicated of these reforms is perhaps the most important: They should advance the FDA’s toolkit for approving new medicines based on biomarkers, surrogate endpoints, adaptive clinical trials, and real-world data. As discussed above, the FDA should give greater deference to the external scientific community in developing evidentiary standards for incorporating biomarkers into the drug-development process and embracing adaptive clinical-trial designs. This approach can significantly lower the cost and time needed to bring new products to patients, expanding the number of therapeutic options available while also increasing competition based on price and outcomes. Congress should also direct the FDA to develop a rapid-learning

drug-approval process that would allow a drug that modulates a known disease-promoting pathway to be used, after initial safety testing, in clinical treatment by expert physicians and medical centers that specialize in treating the condition of interest. These researchers would then take responsibility for gathering data and developing treatment protocols for the use of these products and for identifying patients most likely to benefit, with predefined endpoints that would indicate when enough evidence had been collected to allow for full FDA approval.

Frustration with the current clinical-trials system is also reflected in the “Right to Try” movement, which advocates state-based legislation that would allow terminally ill patients to obtain experimental medicines after Phase I trials, if the manufacturer agrees to grant access. Right to Try¹⁰⁸ legislation has passed in 27 states to date and reflects the fact that patients are determined to take more control of their own choices when faced with a terminal illness.

One approach that could both expand access for patients without effective treatment options and retain experimental rigor is a conditional-approval pathway or pilot for oncology medicines. This paradigm would rely on expert oncologists learning to use candidate compounds in targeted cohorts of patients using precision-diagnostic and bioinformatics platforms that help them rapidly match patients to treatments they are likely to respond to, based on the patients’ molecular profiles.

Under this approach, compounds would be given conditional approval after demonstrating significant activity in early-stage trials — after demonstrating (through a variety of pre-clinical and clinical tests) their ability to modulate molecular pathways (biomarkers) or surrogate endpoints that are implicated in tumor growth or proliferation in specific cohorts of patients or disease indications.

The compounds would then be made available through the NCI’s network of comprehensive cancer centers or networks of cancer clinical trials like the cancer cooperative groups (such as the Southwest Oncology Group) or any participant with the bioinformatics platforms (EMRs, decision support tools, standardized high-quality assays) and experience in running sophisticated clinical trials. This would rapidly put promising compounds in the hands of oncologists with the requisite expertise and the most experience in treating patients with these characteristics. This infrastructure would allow them to collect real-world outcomes data in a variety of settings and treatment combinations that can be analyzed

to validate the clinical effects predicted by the biomarkers or surrogates. They could then develop precision prescription protocols.

If the candidate medicines fail to meet pre-specified endpoints (in either combination treatment regimens or as single-arm therapy) FDA will have the authority to expeditiously withdraw them from market, but sponsors will be allowed to continue development through the traditional approval pathway. If medicines meet pre-specified endpoints (based on trial designs accepted jointly by the sponsor, NCI, and FDA), they will be given full approval and permission to be marketed outside the cooperative groups.

While oncology has made the most progress towards embracing a precision-medicine paradigm—and can rapidly provide a “proof of concept” that this strategy is viable—conditional approvals should not be confined to it. Heterogeneity is a biological phenomenon that is seen in most, if not all, complex human diseases.

Conditional approvals would not only slash the time and cost needed to bring new treatment options to patients who have run out of options—they would also generate vital data on how new medicines perform in real-world patients, data often lacking today. Ideally, participation in clinical trials should also become the standard of care for off-label treatments, to spur the development of large oncology-patient registries and seamless integration of patients into Phase I studies.

One paradigm for this type of approach is the recently announced PrECISE international consortium for prostate cancer, called the Project to Construct Computational Models to Improve Prostate Cancer Treatment, Care. The members of this consortium include IBM Research, Technikon, Technical University of Darmstadt, Aachen University Hospital, ETH Zurich, University of Zurich, Baylor College of Medicine, Curie Institute, and AstridBio Technologies. The aim of the consortium “is to develop different algorithms that allow us to understand tumor heterogeneity, understand better why drugs work and don’t work, and come up with more effective therapies [and] in particular combination therapies.”¹⁰⁹

Consortium members will also “develop computational approaches that integrate genomic, epigenetic, transcriptomic, proteomic, and clinical information,” including data from publicly available datasets and published in scientific journals. Members will use the resulting models to “investigate prostate cancer’s molecular mechanisms and to try to

predict new targets for therapy.” By homing in on aggressive prostate-cancer subtypes, the consortium will allow clinicians “to classify patients according to risk, minimizing patients exposure to unnecessary surgery or other treatments, reducing spending as a result.”¹¹⁰

Consortia like these allow oncologists to rapidly test and validate new treatment approaches across a variety of disease settings and patient cohorts—learning much more about a drug’s performance than is possible under traditional clinical-trial designs that offer binary succeed-or-fail outcomes. This could also “avoid unnecessary replication of either positive or negative experiments . . . [and] maximize the amount of information obtained from every encounter”¹¹¹ 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.”¹¹²

The only thing missing from this platform—which Congress could supply—is a conditional-approval pathway matching promising cancer-drug candidates with the patients who are likely to respond in a data-rich environment.

Experts have been advocating the adoption of this type of approach for nearly a decade. In 2007, a group of health-care experts convened by the Institute of Medicine coined a phrase for it: “Rapid learning health care.” In brief, the workshop participants proposed a process for continuously improving drug science using data collected by doctors in the course of treating patients, with a particular focus on groups of patients not usually included in drug-approval clinical trials.

Patient access in this environment blurs the line between experimental treatment and FDA approval, but we should also recognize that the high incidence of off-label treatment of cancer has already blurred it substantially. The time has come to make a virtue of necessity and formalize a conditional-approval approach that would grant access to larger cohorts of patients in a structured environment.

Researchers at MIT, who have done pioneering work on conditional approvals for drugs more generally, write that a conditional-approval pathway linked to post-marketing surveillance could have a “profound effect” on drug development by “allowing smaller development programs to achieve greater success.”

They estimate that development costs could be reduced by 90% and development time by 50%, “if the threshold for initial approval

were defined in terms of efficacy and fundamental safety.” “Requiring high-quality and transparent patient registries for independent safety monitoring, would be a more informative and cost-effective approach,” compared to traditional strategies.¹¹³ Christopher McKenna, general manager of discovery science at Thomson Reuters, believes that “identifying targets for drug discovery and identifying patients for clinical studies early in the process will reduce drug development cost and cycle times sufficiently” to enable “biopharma portfolios . . . filled with hundreds of drugs that each generate \$40 million to \$50 million” as opposed to a dozen or so blockbusters that generate \$1 billion or more annually.¹¹⁴

Over the long term, the FDA’s approval system should shift from clinical-symptom-based approvals and labeling to molecular-indication-based labeling, with additional data collected in the post-market environment that would progressively improve clinicians’ ability to prescribe drugs with high precision in the safest and most effective manner concomitant with each patient’s molecular profile.

A slow, smooth transition to integrating drug-approval trials with clinical-patient treatment could begin with the recognition that the high incidence of off-label prescription in treating cancer has already substantially blurred the line between experimental treatment and FDA approval. The doctors and medical centers that have already developed and begun to use rapid-learning databases and analytical systems should review their protocols and analytical tools with the FDA. The medical centers and FDA should then cooperate in the development of uniform standards. Then FDA could formalize a conditional-approval approach that would grant access to new drugs to larger cohorts of patients in a structured environment and that would allow drug companies and the FDA to rely on the work of doctors at medical centers to approve off-label uses and amend labels accordingly.

After the development of new drug-approval pathways, there remain three other key reforms that Congress and the next administration should pursue to support the development of precision-medical treatments and biomarker-based diagnostics. The next should be to encourage a new market-based pricing system for innovation that rewards companies for developing new precision treatments and diagnostics.

Government regulations — such as Medicaid’s “best price” provision and FDA restrictions on the communication of off-label prescription information — often prevent innovator companies from entering into “pay

for performance” contracts with insurers and pharmacy benefit managers (PBMs) that would link reimbursement to real-world outcomes based on molecular biomarkers or other diagnostic criteria. The Centers for Medicare & Medicaid Services should create a safe-harbor for such contracts, and the FDA should promulgate guidance that would allow companies to inform physicians and payers of any relevant molecular information or pharmaco-economic data that would allow them develop more personalized prescription protocols. The free-flow of scientifically reliable information among sophisticated payers and purchasers, along with the freedom to experiment with novel value-based reimbursement contracts, would do much to align drug prices with their value given their overall impact on the total cost of care for a given disease state, the patient’s quality of life and risk preferences, or any other factor that innovators, expert physicians, payers, and patients recognize as valuable.

Under the next administration, Washington’s third step should be to reform the U.S. corporate tax system to make it more attractive to investors and innovative firms. An economic barrier to sustaining and expanding U.S.-based innovation is the country’s corporate tax rate, which ranks among the world’s highest. The United States is unique among developed countries, moreover, in taxing the *worldwide* earnings of its global firms; other countries tax only the earnings from sales within their borders. The U.S. tax on foreign earnings is deferred until the money is repatriated, but that gives life-sciences firms a perverse incentive to keep their profits offshore, rather than use them to fund further investment in the United States. This means that low-tax nations will continue to attract the infrastructure for innovation (labs, manufacturing facilities, and the like) in preference to the U.S., and foreign-based firms will also have greater access to offshore capital in the competition to acquire the most promising U.S.-based companies and their associated technologies and drug pipelines.

Tax reform will become increasingly important as our competitors in Asia and other emerging economies develop the expertise necessary to compete in innovative R&D projects. Congress should ensure that tax policy attracts investors and companies to our shores—instead of driving them away.

Fourth, the next administration should expand the FDA’s platform for crowd-sourcing new regulatory standards. One of the most persistent problems facing innovators in the 21st century is a regulatory structure

and mindset at the FDA that harkens back to the mid-20th century, an era defined by mass manufacturing and hierarchical command-and-control structures — the seeming hallmarks of successful corporate and military organizations that dominated war fighting and international economic competition throughout much of the 20th century.

That regulatory model was defined by two realities: first, the mass delivery of drugs and medical devices to homogenous populations defined by clinical symptoms; and second, the extremely high cost and long timelines associated with conducting “gold standard” medical research, meaning the randomized controlled trial.

The advent of distributed high-performance computing, the rapidly falling cost of whole-genome sequencing and novel gene-editing technologies, and access to high-quality public data sets allow researchers to conduct much more nimble and targeted experiments on the fly, answering far more nuanced (and clinically relevant) questions at far less cost.

But the FDA’s system for developing regulations and regulatory guidance for new technologies remains overly centralized and slow moving — and is sometimes outdated by the time it is completed. It can take between 425 days and 797 days to finalize draft FDA guidance, leaving them “languishing in unfinished form for years, even as new scientific developments or broader shifts in policy render them irrelevant.”¹¹⁵

One approach to closing the gap between regulation and innovation would be to crowd-source regulations through a Wiki-like commons where academic researchers (including the NIH and other federal research agencies), industry, regulators, and patient groups could come together to establish performance standards for novel technology platforms, innovative clinical-trial designs, and even advanced manufacturing technologies.

The prototype for this is the FDA’s existing precisionFDA platform, a public-private venture operated by the FDA and DNA Nexus for developing standards for next-generation sequencing platforms. The FDA’s chief informatics officer explains:

precisionFDA is an online, cloud-based, portal that will allow scientists from industry, academia, government and other partners to come together to foster innovation and develop the science behind a method of “reading” DNA known as next-generation sequencing (or NGS)...

precisionFDA users will have access to a number of important tools..[including] reference genomes, such as “Genome in the Bottle,” a reference sample of DNA for validating human genome sequences developed by the National Institute of Standards and Technology. Users will also be able to compare their results to previously validated reference results as well as share their results with other users, track changes and obtain feedback. . . .

Over the coming months we will engage users in improving the usability, openness and transparency of precisionFDA. One way we’ll achieve that is by placing the code for the precisionFDA portal on the world’s largest open source software repository, GitHub, so the community can further enhance precisionFDA’s features.¹¹⁶

Platforms for rapid-cycle regulatory innovation are increasingly important as we transition from an era of “one test-one disease paradigm” towards simultaneous scans of a patient’s microbiome, genome, transcriptome, and exome that produce massive amounts of data that could “potentially detect multiple conditions in a single test.” DNA Nexus Chief Medical Officer David Shaywitz writes that precisionFDA represents a “novel and forward thinking approach to regulation” in this data-rich environment:

Rather than envisioning governmental regulators as the folks who will define and then impose a specific set of performance standards, precisionFDA instead sees the government as providing the platform that will enable the NGS community to evolve the standards on their own—organically and transparently.

. . . the ability to design, refine, and deploy this platform in such a rapid and agile fashion reflects in part the value of well-conceptualized public-private partnerships, in this case between the FDA and DNAnexus. By intentionally leveraging the skills and capabilities of a company like ours, the FDA was able to implement and realize their exciting and ambitious vision.¹¹⁷ [emphasis in the original]

Importantly, FDA staff will also be able to interact much less formally and more flexibly with the members of the precisionFDA community, which include 23andMe, the Baylor College of Medicine, Intel, the

Human Longevity Institute, and the National Institutes for Standards and Technology (NIST)/Genome in a Bottle consortium, to name just a few platform collaborators.

While the precisionFDA effort is ongoing, Congress should scale up these types of virtual platforms for generating timely regulatory standards for innovative technologies by creating a public-private consortium for regulatory innovation with a remit for developing such standards, particularly for regenerative medicine, biomarkers, nanotechnology, and Bayesian trial designs.

This consortium should also have the authority to pilot promising approaches in a rapid-cycle approach in collaboration with industry, NIH, NCI, NIST, and DARPA for developing breakthrough innovations for unmet medical needs including neurological injuries, Alzheimer's, rare and ultra-rare diseases, and drug-resistant cancers.

A pilot approach would address the FDA's reluctance to promulgate new standards because of its inability to access the needed expertise internally regarding novel technologies, as well as generate funding needed to pilot these approaches in a rigorous way.

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U.S. policy should encourage the development of more paradigm-shifting precision medicines and protocols for approving drugs for off-label use faster and more efficiently, and with more detailed guidance on which patients benefit most from their use. A modernized FDA drug-development and approval framework would improve industry productivity by reducing the risks and costs associated with bringing new medicines to market and allowing more precise prescription of targeted drugs. Washington should also reform or eliminate regulations that currently prevent drug companies and payers from aligning drug prices with the value they deliver to patients and, by extension, the entire health-care system through value-based contracts linked to real-world outcomes. Competition between targeted therapies based on their real-world value would also help to address concerns regarding drug pricing, without reducing incentives to innovate. Reforming FDA trial protocols to accelerate the drug-approval process would allow patients with serious and life-threatening diseases to avoid having to wait in excess of a decade for access to better therapies.

Policy Reforms to Advance Innovation Policy

The platform for 21st century innovation we've outlined looks beyond current drug-pricing controversies and focuses on reforms that would pay dividends for the U.S economy and patients for decades to come. The opportunity remains to be seized, by the U.S.—or by our competitors abroad.

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