



**CULTIVATING INNOVATION IN
PRECISION MEDICINE THROUGH
REGULATORY FLEXIBILITY AT THE
FDA**

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INTRODUCTION

Medical researchers perpetually aspire to a future where an individual's genes will chart the way for the identification and prescription of the right lifesaving drug. The drug will be tailored to a patient's specific genetic profile, assuring that the drug will work safely and effectively for that patient. During the course of care, a physician will extract a biological sample from the patient, run it

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through a diagnostic test, and the test results, along with the patient's medical history, will guide the medical decision on which drug to prescribe. Such an integrative process eliminates the potential for that patient to experience devastating adverse drug events because the drug is not safe or because the treatment is ineffective (and assuredly expensive). Such a future provides benefits not only to the patient but also to countless entities and actors within the public health and medical enterprise.

This scenario may be coming closer to fruition as research initiatives and public support for the field of precision medicine gain momentum. The National Institutes of Health (NIH) describes precision medicine as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."¹ President Obama initially channeled \$215 million into the Precision Medicine Initiative (PMI), with funds to the NIH and the Food and Drug Administration (FDA) "to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients."² In remarks at the White House East Room, Obama touted precision medicine as "delivering the right treatments at the right time, every time to the right person."³ The 21st

¹ LISTER HILL NATIONAL CENTER FOR BIOMEDICAL COMMUNICATIONS, DEP'T OF HEALTH AND HUMAN SERVS., HELP ME UNDERSTAND GENETICS: PRECISION MEDICINE 3 (2017), <https://ghr.nlm.nih.gov/primer/precisionmedicine.pdf>.

² Press Release, White House, Office of the Press Secretary, Fact Sheet: President Obama's Precision Medicine Initiative (Jan. 30, 2015), <https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative> [hereinafter Fact Sheet].

³ Press Release, White House, Office of the Press Secretary, Remarks by the President on Precision Medicine (Jan. 30, 2015), <https://obamawhitehouse.archives.gov/the-press-office/2015/01/30/remarks-president-precision-medicine>.

Century Cures Act, signed into law on December 13, 2016, further supports the PMI and related research with a \$4.8 billion pledge over the next ten years.⁴

The push for precision in the drug context is not new. The PMI and the field of precision medicine build on decades of genomic research and the successful sequencing of the human genome. Many terms have evolved to describe the concept of harnessing genomic information to guide the development of diagnostics and treatment for individuals or subpopulations of patients: pharmacogenomics, personalized medicine, targeted medicine, and most recently, precision medicine.⁵ The PMI emphasizes the need for collaborations

⁴ 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (codified throughout titles 15, 21, 26, 28, 29, 34, and 42 of the U.S.C.); Press Release, U.S. House of Representatives Comm. on Energy and Commerce, The 21st Century Cures Act Fact Sheet, <https://energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/114/analysis/20161128%20Cures%20Fact%20Sheet.pdf> (last visited Oct. 5, 2017) [hereinafter Committee on Energy and Commerce].

⁵ This article examines “precision medicine” in the context of the connection between drug development and genomic information. However, the terms “personalized medicine” and “precision medicine” encompass not only the use of genomic information but also other biological functioning or status of an individual for development of treatments. The FDA offers several examples of personalized medicine outside of the realm of pharmacogenomics, including a custom-made tinnitus masker tailored to an individual patient’s hearing, pedicle screw spinal systems assembled according to a patient’s anatomy and physiology with the aid of MRI/CT imaging, and artificial pancreas device systems that monitor glucose levels and deliver insulin doses based on individual readings for treatment of diabetes. See U.S. FOOD & DRUG ADMIN., PAVING THE WAY FOR PERSONALIZED MEDICINE: FDA’S ROLE IN A NEW ERA OF MEDICAL PRODUCT DEVELOPMENT 10 (Oct. 2013), <https://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf>. Recent developments in 3D printing of medical devices are also examples of personalization (or customization as it is referred in the regulatory scheme) in medicine. See *3D Printing of Medical Devices*, FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/3DPrintinofMedicalDevices/default.htm>.

of academic medical centers, researchers, patients and patient advocates, private foundations, and medical product innovators to achieve its lofty goals.⁶ Coupled with directives to the FDA within the 21st Century Cures Act on aspects of the regulatory science, advancements in precision medicine will introduce fundamental disruptions to the historical structure, support, and contributions in drug research and development. Signals from leaders in the drug industry indicate that there is rapid investment in precision medicine, nearly doubling over the past five years.⁷

Moving innovative research in precision medicine into the medical marketplace will not be easy. Precision medicine poses challenges to traditional FDA regulatory paradigms. Eventual downstream medical products will involve both the initial detection of the presence (or absence) of a specific genetic variant and the subsequent drug treatment tailored to that genetic variant. This diagnosis-treatment spectrum necessarily implicates the regulatory authority of the FDA with regard to both medical devices and new human drugs and biologics. The success of the PMI will inevitably increase pressures on a regulatory system already suffering from a crisis of heavy industry and expert criticism due to its lack of clarity and transparency. Precision medicine also implicates the ongoing

⁶ Emerging concerns surrounding the expansion of players in research and development include the proper role of patient advocate groups, identification and management of complex conflicts of interest, proper incentive structures, access to and sharing of research samples and health information, inventor status and patent rights, payments and contractual agreements, and eventual profit share.

⁷ Reenita Das, *Drug Industry Bets on Precision Medicine: Five Trends Shaping Health Care Delivery*, FORBES (Mar. 8, 2017, 9:35 AM), <https://www.forbes.com/sites/reenitadas/2017/03/08/drug-development-industry-bets-big-on-precision-medicine-5-top-trends-shaping-future-care-delivery/#33f972755d3a>.

debate about FDA oversight of laboratory developed tests.⁸ In a 2013 report assessing scientific promise and related regulatory obstacles, the FDA acknowledged that precision medicine ushers in a “new era of medical product development” for the agency; however, then Commissioner Hamburg emphasized that regulatory adaptation was a priority.⁹ With enactment of the 21st Century Cures Act and other recent legislation, that adaptation may actually be achievable if the FDA is willing to create flexible, dynamic regulatory approaches for innovative new products.¹⁰

This article surveys the current structure of the FDA regulatory regime as it impacts precision medicine and specifically explores a category of FDA-regulated products called companion diagnostics. Part I discusses the field of precision medicine and its relationship to companion diagnostics, highlighting the historical background, incremental funding initiatives, and market trajectory for companion diagnostic products. Part II discusses the FDA institutional frameworks for regulation of traditional drug, biologic, and medical device products, as well as the FDA’s approach to companion

⁸ See generally *Laboratory Developed Tests*, FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/default.htm> (last updated Jan. 13, 2017).

⁹ U.S. FOOD & DRUG ADMIN., *PAVING THE WAY FOR PERSONALIZED MEDICINE: FDA’S ROLE IN A NEW ERA OF MEDICAL PRODUCT DEVELOPMENT 2* (2013), <https://www.fda.gov/downloads/scienceresearch/specialtopics/personalizedmedicine/ucm372421.pdf>.

¹⁰ I have previously written about the need for dynamic FDA regulatory models for emerging technologies. See, e.g., Jordan Paradise et al., *The Challenge of Developing Oversight Approaches to Nanobiotechnology*, 37 J. L., MED. & ETHICS 543, 543-45 (2009); Jordan Paradise et al., *Evaluating Oversight of Human Drugs and Medical Devices: A Case Study of the FDA and Implications for Nanobiotechnology*, 37 J. L., MED. & ETHICS 598, 598-624 (2009); Jordan Paradise et al., *Developing U.S. Oversight Strategies for Nanobiotechnology: Learning from Past Oversight Experiences*, 37 J. L., MED. & ETHICS 688, 688-705 (2009).

diagnostics. Part III identifies key legislative and agency activity supporting innovation in biomedicine, including the Affordable Care Act of 2010, the FDA Safety and Innovation Act of 2012, the 21st Century Cures Act of 2016, and FDA policy on laboratory developed tests. Part III also highlights how these may impact the development of companion diagnostics and possibly help facilitate regulatory flexibility. Part IV concludes.

I. GENOMICS, PRECISION MEDICINE, AND COMPANION DIAGNOSTICS

A. HISTORICAL PERSPECTIVES ON THE GENOME

The moment that the initial three billion base pair sequence of the human genome was published in 2001, the race to fully realize its potential in human health and disease had already begun. Decades of scientific work on the part of countless international cohorts had gone into the endeavor, and the competition to be the first to succeed was fierce.¹¹ Aptly, the article led by Eric S. Lander begins, “The human genome holds an extraordinary trove of information about human development, physiology, medicine and evolution.”¹² Likewise, J. Craig Venter proffered that “[d]ecoding of the DNA that constitutes the human genome has been widely anticipated for the contribution it will make toward understanding human evolution, the causation of disease, and the interplay between the environment

¹¹ Two independent teams, one publicly-funded and one privately-funded, published findings within one day of each other in different journals. Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome*, 409 NATURE 860 (2001); J. Craig Venter et al., *The Sequence of the Human Genome*, 291 SCI. 1304 (2001).

¹² Lander et al., *supra* note 11, at 860.

and heredity in defining the human condition.”¹³ By the time the complete human genome sequence was published in 2004,¹⁴ the new field of pharmacogenomics was fueling tireless research into the utilization of genomic information to inform drug development and medical treatment. Combining the field of pharmacology (studying the mechanisms of action of drugs) and genomics, pharmacogenomics aims to tailor specific drugs and treatments to an individual’s genetic make-up to maximize safety and efficacy.¹⁵

The resulting attention on pharmacogenomics has given rise to a parade of terms to describe the promise of genomics for medicine, including personalized medicine, targeted medicine, and, most recently, precision medicine. The distinctions among these phrases is unclear at best, as they all envision the ability to make treatment “precise”; in other words, treatment tailored to an individual or well-defined group of people sharing particular characteristics. Such an approach challenges the dominant model of blockbuster drug development by narrowing the focus of safety and efficacy to a much smaller, and identifiable, population. The focus on individualization also has relevant implications regarding financial incentives for industry to embark on this type of research and development. This article will use the term precision medicine to encompass these terms, as the difference, if any, resides only in how individualized the drug must be to qualify as “precise.”

Almost two decades following the initial publications of the human genome, that “extraordinary trove of information,” as

¹³ Venter et al., *supra* note 11, at 1305.

¹⁴ See International Human Genome Sequence Consortium, *Finishing the Euchromatic Sequence of the Human Genome*, 431 NATURE 931 (2004).

¹⁵ See Mark A. Rothstein & Phyllis Griffin Epps, *Ethical and Legal Implications of Pharmacogenomics*, 2 NATURE REV. 228, 228 (2001).

described by Lander, continues to hold promise for innovative and life-saving contributions to medicine. However, deciphering the genetic information for its role in drug response has proven more difficult in practice given the complexity of the human genome. There are currently only twenty FDA-approved drugs or biologics on the market that can truly be characterized as pharmacogenomic – that is, they are tailored specifically to a given genetic profile or genetic variant that can be identified by a diagnostic test.¹⁶ The FDA has cleared or approved several dozen *in vitro* diagnostic or imaging tools as medical devices designed to detect whether a given drug or biologic has a relevant safety or efficacy implication for a particular genetic make-up; these several dozen tests correspond to the twenty FDA-approved drugs or biologics.¹⁷ These “companion diagnostics” that provide important information for the safe and effective use of a corresponding therapeutic drug or biologic are distinct from wide-ranging nucleic-acid based tests that are not linked to a particular drug.

¹⁶ See *Personalized Medicine and Companion Diagnostics Go Hand in Hand*, FOOD & DRUG ADMIN., <https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm407328.htm> (last updated Sept. 27, 2017) [hereinafter *Hand in Hand*].

¹⁷ *List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools)*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm> (last updated Aug. 02, 2017) [hereinafter *List of Companion Diagnostic Tests*]. These biologics and/or drugs are the following branded or generic products: ado-trastuzumab emtasine, Erbitux (cetuximab), Exjade (deferasirox), Gleevec (imatinib mesylate), Gilotrif (afatinib), Herceptin (trastuzumab), Iressa (gefitinib), Keytruda (pembrolizumab), Lynparza (olaparib), Mekinist (trametinib), Perjeta (pertuzumab), Rubraca (rucaparib), Rydapt (midostaurin), Tafinlar (dabrafenib), Tagrisso (osimertinib), Tarceva (erlotinib), Venclaxta (venetoclax), Vectibix (pamtopumab), Xalkori (crizotinib), and Zelboraf (vemirafenib). Each may have multiple companion diagnostics on the market. *Id.*

One early example, which progressed alongside scientific advancements during the Human Genome Project (HGP), is the metastatic breast cancer biologic Herceptin (trastuzumab), manufactured by Genentech. Herceptin was developed for women with a genetic variant causing the overproduction of the human epidermal growth hormone receptor 2 protein known as HER2.¹⁸ Approved via biologic license application (BLA) in 1998, Herceptin is an effective treatment in women for whom the diagnostic test shows elevated HER2 protein levels at the cancer site.¹⁹ However, the biologic is ineffective in women without elevated HER2 levels. Herceptin and its corresponding diagnostic test developed collaboratively by DAKO (and approved as a medical device by the FDA) were approved as the first new biologic with a companion diagnostic in the United States.²⁰ There are now ten companion diagnostic tests on the U.S. market for Herceptin.²¹

B. FUNDING INFUSIONS FOR PRECISION MEDICINE

Standing on the shoulders of substantial federal appropriations for scientific research in the realms of genetics (the HGP), nanotechnology (National Nanotechnology Initiative), brain research (BRAIN Initiative), and cancer (Cancer Moonshot 2020), the Precision Medicine Initiative (PMI) shares many features with each of these federally-funded projects. At the core of each has been a goal of fostering multi-disciplinary approaches to research and development that support medical innovation. The PMI identifies

¹⁸ See *Hand in Hand*, *supra* note 16.

¹⁹ See *Id.*

²⁰ See *Hand in Hand*, *supra* note 16.

²¹ See *List of Companion Diagnostic Tests*, *supra* note 17.

five core objectives: (1) discovery of cancer treatments; (2) development of a voluntary, national research cohort; (3) robust privacy protections and interoperability; (4) assessment of regulatory regimes; and (5) strong partnerships in research.²² While all objectives merit attention, this article addresses the issue of regulatory regimes by surveying the recent legislative landscape providing a framework for the FDA.

The PMI is underway. Original plans for a PMI Cohort Program were announced in September 2015, led by NIH Director Francis Collins, with a budget request of \$130 million for NIH.²³ The program, renamed the All of Us Research Program, proposes to recruit over a million new participants to submit blood samples for DNA analysis, undergo a clinical exam, and share their electronic health record.²⁴ The first course of research aims to test participant DNA for single nucleotide polymorphisms (SNPs) that may indicate disease risk genes.²⁵ The driver for starting with SNPs, rather than full genome sequencing, is the cost: \$50 per sample versus over \$1,000.²⁶

Federal funding for precision medicine was enhanced with passage of the 21st Century Cures Act. The 21st Century Cures Act appropriates \$4.8 billion in funding to the NIH for the PMI over the

²² Fact Sheet, *supra* note 2.

²³ THE PRECISION MED. INITIATIVE COHORT PROGRAM, NAT'L INSTS. OF HEALTH, PRECISION MED. INITIATIVE (PMI) WORKING GROUP REPORT TO THE ADVISORY COMMITTEE TO THE DIRECTOR 9 (2015), https://acd.od.nih.gov/documents/reports/PMI_WG_report_2015-09-17-Final.pdf.

²⁴ Jocelyn Kaiser, *NIH Opens Precision Medicine Study to Nation*, 349 SCI. 1433, 1433 (2015). See *All of Us Research Program*, NAT'L INSTS. OF HEALTH, <https://www.nih.gov/research-training/allofus-research-program> (last visited Sept. 28, 2017).

²⁵ Kaiser, *supra* note 24.

²⁶ *Id.*

next decade.²⁷ It remains to be seen how the Trump Administration and Congress will allocate funding; the President's original proposed budget for 2017 included a \$12.6 billion budget decrease to HHS and \$5.8 billion in cuts to NIH.²⁸ Subsequent Congressional action assured a \$2 billion increase in 2017 for NIH, including additional money for the PMI.²⁹ Executive Orders and the federal hiring freeze also contribute uncertainty as to the long-term implementation of the legislation,³⁰ though many remain hopeful that the allocated funds will be appropriated for 2018 and beyond.³¹

Along with targeted funding, the 21st Century Cures Act establishes an organizational framework for the PMI, including authority to the Secretary of the Department of Health and Human Services (HHS) to implement the initiative. The Act amends the Public Health Service Act to "augment efforts to address disease prevention, diagnosis, and treatment."³² The Act establishes the

²⁷ 21st Century Cures Act, Pub. L. No. 114-255, § 1001, 130 Stat. 1033 (codified throughout titles 15, 21, 26, 28, 29, 34, and 42 of the U.S.C.); United States House of Representatives Committee on Energy and Commerce, *supra* note 4.

²⁸ Tal Kopan, *Here's What Trump's Budget Proposes to Cut*, CNN (Mar. 16, 2017, 1:21 PM), <http://www.cnn.com/2017/03/16/politics/trump-budget-cuts/>.

²⁹ Press Release, U.S. Senate Comm. on Appropriations, Labor, Health and Human Servs., and Educ. and Related Agencies Appropriation Bill 2017: Omnibus Agreement Summary, <https://www.appropriations.senate.gov/imo/media/doc/FY17%20Labor%20HHS%20Education%20Conference%20Agreement%20Summary%20-%20Final.pdf> (last visited Sept. 28, 2017).

³⁰ Seth D. Rothman & Jessica Studness, *FDA Faces Uncertainty Implementing 21st Century Cures Act*, LAW360 (Mar. 15, 2017, 12:11 PM), <https://www.law360.com/articles/900882/fda-faces-uncertainty-implementing-21st-century-cures-act>.

³¹ Harlan M. Krumholz & Gregg Gonsalves, *Taking A Ride on the NIH Budget Rollercoaster*, STAT (May 1, 2017), <https://www.statnews.com/2017/05/01/nih-budget-21st-century-cures-act/>.

³² 21st Century Cures Act, Pub. L. No. 114-255, § 2011, 130 Stat. 1033, 1047 (codified as 42 U.S.C. § 289g-5).

general authority of the Secretary of HHS to foster rapid innovation in this realm and also sets forth protections for human research subjects and the data generated by research.³³ The Act lists five components for the initiative, including “developing new approaches for addressing scientific, medical, public health, and regulatory science issues.”³⁴ The Secretary is also expressly required to coordinate with the FDA to achieve the goals of the initiative.³⁵ Part III examines legislative provisions directly impacting the FDA.

C. MARKET TRAJECTORY FOR COMPANION DIAGNOSTICS

Precision medicine necessarily promises innovation not only in the development of lifesaving drugs and biologics for diseases such as cancer, but also in the companion diagnostic field. There is a growing drive on the part of regulators, and entities within industry, to partner drug and biologic development with a diagnostics test; the companion diagnostics market is projected to grow globally from \$3.1 billion in 2014 to \$8.7 billion in 2019.³⁶ Partnering development makes sense for industry, and regulators, as the companion diagnostic serves as a safeguard for appropriate selection and use of the drug or biologic. Co-development can assist with reducing costs to consumers, in that they will not be paying for a drug that does not work for them. Likewise, the certainty of particular drugs’ efficacy for individual patients will compliment current movements toward

³³ 21st Century Cures Act, Pub. L. No. 114-255, §§ 2011-14, 130 Stat. 1033, 1047-51 (codified as 42 U.S.C. § 289g-5 and amending §§ 241 and 282(b)).

³⁴ *Id.* § 2011.

³⁵ *Id.*

³⁶ Arundhati Parmar, *Companion Diagnostics Market Set to Grow to \$8.7B by 2019*, MED. DEVICE & DIAGNOSTIC INDUS. (Sept. 8, 2014), <http://www.mddionline.com/article/companion-diagnostics-market-set-grow-87b-2019>.

comparative effectiveness research and waste reduction in healthcare reimbursement. It will also significantly reduce adverse events: patients will not be prescribed drugs that will cause them harm during the course of normal use. Of course, more personalization means less pay-out for the pharmaceutical industry adhering to the blockbuster drug model; however, it also presents an opportunity for much-needed changes to industry approaches to research and development.

Facilitating the growth of companion diagnostics will be next generation sequencing, or NGS.³⁷ NGS technologies do not rely on conventional DNA sequencing using Sanger biochemistry methods, they instead rely on various emerging high-throughput platforms.³⁸ These developments have dramatically reduced costs over the past decade. Using current sequencing technologies, an individual genome can be sequenced for approximately \$1,000 – down from just over \$1 million in 2008.³⁹ However, many experts caution that although NGS will enable scientists to “find many variants,” these

³⁷ The FDA has expressed that they are “committed to implementing a flexible and adaptive regulatory oversight approach” for NGS *in vitro* diagnostics. See U.S. FOOD & DRUG ADMIN., DRAFT GUIDANCE: USE OF STANDARDS IN FDA REGULATORY OVERSIGHT OF NEXT GENERATION SEQUENCING (NGS)-BASED IN VITRO DIAGNOSTICS (IVDs) USED FOR DIAGNOSING GERMLINE DISEASES 2 (July 8, 2016) [hereinafter NGS IVD DRAFT GUIDANCE], <https://www.fda.gov/downloads/medicaldevices/device%20regulationandguidance/guidancedocuments/ucm509838.pdf>.

³⁸ See Jay Shendure & Hanlee Ji, *Next-generation DNA Sequencing*, 26 NATURE BIOTECH. 1135, 1135 (2008).

³⁹ *The Cost of Sequencing a Human Genome*, NAT'L INSTS. OF HEALTH, <https://www.genome.gov/sequencingcosts/> (last updated July 6, 2016) (Figure 1 approximates the 2008 cost to be higher than \$1 million). The NIH notes that the reduction in costs far exceeds those predicted by Moore's Law. *Id.*

genetic variants “will not always be targets for particular disease.”⁴⁰ During a roundtable hosted by the Institute of Medicine, one commenter offered that “[t]he sheer magnitude of the information that we’ll find on the genetic and molecular level is going to far surpass our capacity to run clinical trials.”⁴¹ Simply put, there will be an ongoing challenge of separating the signal from the noise; NGS may unleash a flood of genetic information without a clear answer for what this information means for therapeutic efficacy and drug response.

In an effort to foster research and discovery in this area, the FDA has launched a website called PrecisionFDA, providing “a community platform for NGS assay evaluation and regulatory science exploration.”⁴² Deciphering information generated and published on this crowd-sourced, cloud-based site will be integral to biomarker identification, standard setting, clinical trial development, and, ultimately, regulatory assessment and adaptability. Users have already been challenged by the FDA to test accuracy and reproducibility of software applied to genetic research through the online portal, and to identify genetic variants within select datasets.⁴³ The FDA has also published draft guidance documents⁴⁴ and

⁴⁰ SARAH H. BEACHY ET AL., INST. OF MED., REFINING PROCESSES FOR THE CO-DEVELOPMENT OF GENOME-BASED THERAPEUTICS AND COMPANION DIAGNOSTICS: WORKSHOP SUMMARY 17 (National Academies Press 2014) (quoting Walter Koch, Roche Molecular Systems) [hereinafter IOM Workshop Summary].

⁴¹ *Id.* at 15 (quoting Felix Frueh, Third Rock Ventures).

⁴² FOOD & DRUG ADMIN., PRECISIONFDA, <https://precision.fda.gov/docs/intro> (last visited Oct. 25, 2017).

⁴³ *Precision FDA Wraps Up Second Challenge*, CLINICAL INFORMATICS NEWS, May 16, 2016, <http://www.clinicalinformaticsnews.com/2016/5/19/precisionfda-wraps-up-second-challenge.aspx>

⁴⁴ NGS IVD DRAFT GUIDANCE, *supra* note 37.

discussion papers⁴⁵ on analytical and clinical strategies to support development of NGS diagnostic tests in the wake of the PMI.

As the FDA and the drug, biologic, and medical device industries embark on research and development in precision medicine, existing legal frameworks and processes provided by Congress and the FDA provide a foundation for oversight. The next Part explores FDA regulation of companion diagnostics and the accompanying drug or biologic product.

II. FDA FRAMEWORKS FOR COMPANION DIAGNOSTICS

A companion diagnostic is characterized by the FDA as “a medical device, often an *in vitro* device, which provides information that is essential for the safe and effective use of a corresponding drug or biological product.”⁴⁶ Companion diagnostics may potentially serve one or more purposes: identify patients who are most likely to benefit from a particular therapeutic product; identify patients likely to be at increased risk for serious side effects as a result of treatment with a particular therapeutic product; or monitor response to

⁴⁵ USE OF DATABASES FOR ESTABLISHING THE CLINICAL RELEVANCE OF HUMAN GENETIC VARIANTS (Food & Drug Admin. Preliminary Discussion Paper, Nov. 13, 2015), <https://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM467421.pdf>; DEVELOPING ANALYTICAL STANDARDS FOR NGS TESTING (Food & Drug Admin. Preliminary Discussion Paper, Nov. 12, 2015), <https://www.fda.gov/downloads/MedicalDevices/NewsEvents/WorkshopsConferences/UCM468521.pdf>; OPTIMIZING FDA’S REGULATORY OVERSIGHT OF NEXT GENERATION SEQUENCING DIAGNOSTIC TESTS-PRELIMINARY DISCUSSION PAPER (Food & Drug Admin. Preliminary Discussion Paper, 2014), <https://www.fda.gov/downloads/medicaldevices/newsevents/workshopsconferences/ucm427869.pdf>.

⁴⁶ *Companion Diagnostics*, FOOD & DRUG ADMIN., <http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407297.htm> (last updated Oct. 5, 2016).

treatment with a particular therapeutic product for the purpose of adjusting treatment to achieve improved safety or effectiveness.⁴⁷ Essentially, the device is the “companion” to the FDA-approved drug or biologic.

The FDA has evaluated and approved companion diagnostics using their drug, biologic and medical device authority. The drug or biologic and the medical device (the companion diagnostic) must gain separate FDA approval in order to enter the market. Distinct statutory and regulatory provisions apply to each of these areas, and the approval processes share similarities but are not uniform. New drugs and new biologic products must undergo clinical investigations and satisfy approval requirements, including full reports of clinical investigations supporting the safety and efficacy of the new product, labeling requirements, adherence to good manufacturing practices, and mandated patent disclosures.⁴⁸ The FDA must affirmatively approve the new drug or biologic product, subject to robust statutory and regulatory procedures. Similarly, medical devices categorized as companion diagnostics are subjected to the FDA’s highest risk classification, Class III pre-market approval (PMA), which requires clinical trials, special controls, and information on labeling, and manufacturing.⁴⁹ This policy decision rests on the position that because the companion diagnostic directs the choice of drug or biologic that a patient ultimately receives, the manufacturer must assure that it is safe and effective for that purpose through clinical trials.⁵⁰

⁴⁷ *Id.*

⁴⁸ See generally 21 U.S.C. § 355 and 42 U.S.C. § 262 (2016).

⁴⁹ See generally, 21 U.S.C. §§ 360c, 360e (2016).

⁵⁰ The medical device premarket approval process is distinguishable from the premarket notification process (also known as the 510(k) clearance process). The

The FDA requires a companion diagnostic test alongside a drug “if a new drug works on a specific gene or biological target that is present in some, but not all, patients with a certain cancer or disease.”⁵¹ Successful co-development depends on a “thorough molecular understanding of both the pathology and drug mechanism of action.”⁵² FDA emphasizes that the approval process works best when the test development begins prior to the drug entering clinical trials, but also recognizes that may not always be feasible.⁵³

Ideally, a therapeutic product and its corresponding IVD [in vitro diagnostic] CD [companion diagnostic] device should be developed contemporaneously with the clinical performance and clinical significance of the IVD CD device established using data from the clinical development program of the corresponding therapeutic product. However, FDA recognizes there may be cases when contemporaneous development may not be possible. An IVD CD may be a novel IVD device, a new version of an existing

premarket notification process is available for lower risk medical devices that may enter the market after demonstrating “substantial equivalence” to a predicate device already on the market. Substantial equivalence means (a) that the device has the same intended use and same technological characteristics as the predicate device or (b) has the same intended use and a different technological characteristics but does not raise novel safety and effectiveness questions and is at least as safe and effective as the predicate device. 21 U.S.C. § 360c(i) (2012).

⁵¹ See *Hand in Hand*, *supra* note 16, at 2. Note that the FDA here uses the term “drug” – the same reasoning applies to biological products as well.

⁵² Dana Olsen & Jan Trøst Jørgensen, *Companion Diagnostics for Targeted Cancer Drugs – Clinical and Regulatory Aspects*, 4 FRONT. ONCOL. 105 (2014).

⁵³ See *Hand in Hand*, *supra* note 16, at 2.

device by a different manufacturer, or an existing device already cleared or approved for another purpose.⁵⁴

The FDA has produced two guidance documents to inform the development of companion diagnostics. However, FDA staff are careful to emphasize that “[n]o two co-development programs are the same” and thus early communications with the FDA are critical.⁵⁵ In August 2014 draft guidance, the FDA provides baseline mechanisms for industry to identify the need for a companion diagnostic at very early stages in drug development in order to allow for successful integration and planning.⁵⁶ It also discusses a requirement to coordinate labeling for co-developed products as a means to provide patients with adequate directions for use.⁵⁷ The FDA released the second draft guidance on July 15, 2016, which is intended as a practical guide to further assist drug and biologic product sponsors and medical device sponsors in developing both a therapeutic product and a companion diagnostic.⁵⁸

A recent drug and companion diagnostic tandem approved by the FDA illustrates successful co-development between drug and

⁵⁴ FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: IN VITRO COMPANION DIAGNOSTIC DEVICES 7 (Aug. 6, 2014). [hereinafter IN VITRO COMPANION DIAGNOSTIC DEVICES]

⁵⁵ IOM Workshop Summary, *supra* note 40, at 12 (quoting Elizabeth Mansfield, Director of Personalized Medicine staff in Office of In Vitro Diagnostics and Radiological Health).

⁵⁶ IN VITRO COMPANION DIAGNOSTIC DEVICES, *supra* note 54, at 10-12.

⁵⁷ “The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.” IN VITRO COMPANION DIAGNOSTIC DEVICES, *supra* note 54, at 7.

⁵⁸ FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: PRINCIPLES FOR CODEVELOPMENT OF AN IN VITRO COMPANION DIAGNOSTIC DEVICE WITH A THERAPEUTIC PRODUCT (July 15, 2016).

medical device sponsors. The drug, Rydapt (midostaurin), is indicated for use in adults with newly diagnosed acute myeloid leukemia (AML) having the genetic mutation FLT3, in combination with chemotherapy.⁵⁹ New drug approval for the AML indication was granted to Novartis through both priority review and breakthrough therapy status.⁶⁰ The approved diagnostic, called the LeukoStrat CDx Mutation Assay, detects the relevant FLT3 mutation, and was granted to Invivoscribe Technologies.⁶¹ The FDA describes the product as,

[A] PCR-based, in vitro diagnostic test designed to detect internal tandem duplication (ITD) mutations and the tyrosine kinase domain mutations D835 and I836 in the FLT3 gene in genomic DNA extracted from mononuclear cells obtained from peripheral blood or bone marrow aspirates of patients diagnosed with acute myelogenous leukemia (AML). The LeukoStrat® CDx FLT3 Mutation Assay is used as an aid in the selection of patients with AML for whom RYDAPT (midostaurin) treatment is being considered.⁶²

⁵⁹ Press Release, FOOD & DRUG ADMIN., FDA APPROVES NEW COMBINATION TREATMENT FOR ACUTE MYELOID LEUKEMIA (Apr. 28, 2017), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm555778.htm>.

⁶⁰ *Id.* Priority review and breakthrough therapy status will be discussed in Part III.

⁶¹ PMA Monthly Approvals 4/1/2017-4/30/2017, FOOD & DRUG ADMIN., <https://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/PMAApprovals/UCM556295.pdf>.

⁶² *Id.* The FDA further provides that the diagnostic assay is only to be performed at a single site laboratory in San Diego, CA. *Id.*

III. RECENT LEGISLATIVE AND AGENCY ACTIVITY SUPPORTING INNOVATION IN BIOMEDICAL REGULATION

Although only a few dozen companion diagnostic products have been reviewed and approved by the FDA, the push toward precision medicine assures that the FDA will continue to assess innovative developments. While the existing regulatory framework is functional, and continuously evolving based on the science, several pieces of recent legislation provide additional authority and flexibility to the FDA to refine the pathway to market. Many of these provisions, including the breakthrough therapy status and biosimilar approval pathway, have been integrated into the regulatory process for companion diagnostics and the accompanying drug and biologic products; others are in early implementation and development stages. The FDA can draw from these authorities and frameworks as they consider how best to design flexible and adaptive strategies for regulation in the realm of precision medicine. This Part briefly details this legislation, as well as the recent activity in the realm of laboratory developed tests (LDTs).

A. THE AFFORDABLE CARE ACT OF 2010

The Patient Protection and Affordable Care Act (ACA) is infamous for establishing the individual mandate for healthcare, expanding Medicaid, introducing state health insurance exchanges, ensuring health insurance for pre-existing conditions, and various other substantial changes to health care law. However, the legislation also created a significant new abbreviated approval process for biological products.⁶³ A biological product is defined as a “virus,

⁶³ 42 U.S.C. § 262(k) (2012).

therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.”⁶⁴ By statutory definition, a biological product is distinct from a drug because of its source (as biological rather than chemically synthesized), yet shares the attribute of serving as a prevention, treatment, or cure.⁶⁵

The Biologics Price Competition and Innovation Act (BPCIA), Title 7 of the ACA, sets forth a “biosimilar”⁶⁶ and “interchangeable”⁶⁷

⁶⁴ 42 U.S.C. § 262(i).

⁶⁵ Historically, the FDA oversees drugs through the Food, Drug and Cosmetic Act and biologics through the Public Health Service Act. Biological products are often referred to as biologic drugs.

⁶⁶ The statute provides that biosimilarity means “(A) that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and (B) there are no clinically meaningful differences between the biological product and the reference product in terms of . . . safety, purity, and potency . . .” 42 U.S.C. § 262(i)(2). The biosimilar BLA (bBLA) must include analytical studies, animal studies, and a clinical study or studies with the following requirements: the biological product must have the same mechanism(s) of action for condition(s) of use that have been previously approved for the reference product; it must have the same route of administration, dosage form, and strength; and the application must demonstrate that the facility assures the development of a “safe, pure, and potent” product. 42 U.S.C. § 262(k)(2)(A)(i).

⁶⁷ Interchangeability requires that the product is biosimilar and that the product “may be substituted for the reference product without the intervention of the health care provider who prescribed the reference product.” 42 U.S.C. § 262(i)(3). Here, the application must demonstrate an expectation to provide the “same clinical result as the reference product in any given patient.” 42 U.S.C. § 262(k)(4)(A)(ii). The application must also show that when the biologic is “administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not

route to market for biologics, creates a twelve year exclusivity period for biologic innovator products, one year exclusivity period for interchangeable products, and introduces a complicated disclosure process for industry dealing with patent rights.⁶⁸ Also included in the ACA of potential relevance to precision medicine and companion diagnostics are provisions aimed at incentivizing drug development⁶⁹ and the creation of entities to examine comparative effectiveness.⁷⁰

greater than the risk of using the reference product without such alteration or switch.” 42 U.S.C. § 262(k)(4)(B).

⁶⁸ This disclosure process is much different than the certification and disclosure process contained in the generic drug approval legislation, or Hatch-Waxman Act. The provisions have been attacked by industry and judges alike as unclear. The Supreme Court granted certiorari in January 2017 in two cases involving the legislation. The first, *Amgen v. Sandoz* asks “is an applicant required by 42 U.S.C. § 262(l)(2)(A) to provide the reference product sponsor with a copy of its biologics license application and related manufacturing information, which the statute says the applicant ‘shall provide;’ and, where an applicant fails to provide that required information, is the Sponsor’s sole recourse to commence a declaratory judgment under 42 U.S.C. § 262(l)(9)(C) and/or a patent-infringement action under 35 U.S.C. § 271(e)(2)(C)(ii)?” Docket No. 15-1195, SUP. CT. OF THE U.S. (Jan. 13, 2017), <https://www.supremecourt.gov/qp/15-01195qp.pdf>. The second, *Sandoz v. Amgen*, asks “[w]hether notice of commercial marketing given before FDA approval can be effective and whether, in any event, treating § 262(l)(8)(A) as a standalone requirement and creating an injunctive remedy that delays all biosimilars by 180 days after approval is improper.” Docket No. 15-1039, SUP. CT. OF THE U.S. (Jan. 13, 2017), <https://www.supremecourt.gov/qp/15-01039qp.pdf>. The two cases have been consolidated; oral arguments were held April 26, 2017.

⁶⁹ The Qualifying Therapeutic Discovery Project contained within the ACA gives tax credit to pharmaceutical and biotech companies that treat unmet medical needs or prevent, detect, or treat chronic or acute diseases and conditions; advance goal of curing cancer; and reduce long-term health care costs in US. This tax credit applies only to companies with 250 people or less and covers up to 50% of qualified investment. 26 U.S.C. §48D (2016).

⁷⁰ The ACA also establishes the Patient Centered Outcomes Research Institute (PCORI), for the evaluation of health and medical technologies and products using a

As a means to implement the new abbreviated approval process, the FDA has formed a Biosimilar Implementation Committee co-chaired by the Directors of CDER and CBER, installed a new Acting Associate Director for Biosimilar within the Office of New Drugs (OND), and created a Biosimilars Review Committee within CDER to advise OND.⁷¹ The FDA published three guidance documents for industry in February 2012 (subsequently revised in 2015),⁷² a fourth

comparative effectiveness approach to clinical efficacy. 42 U.S.C. §1320e (2012). The inclusion of PCORI reflects a movement toward the utilization of comparative research to inform cost and reimbursement decisions. Many question the performance of PCORI specifically but others see the approach appealing to the drug development model. See, e.g., Fred Schulte, *Is Obama's Research Institute Worth the Billions?*, NAT'L PUB. RADIO (Aug. 4, 2015), <http://www.npr.org/sections/health-shots/2015/08/04/428164731/is-obamacares-research-institute-worth-the-billions>. One analyst offers that a comparative effectiveness "process and decision-making algorithm will boost innovation by allowing drug manufacturers to see what product features are valued and rewarded and thereby give companies a better guidance to target medication pipeline." Salil Parab, *Impact of the Affordable Care Act on Pharmaceutical and Biotech Industry*, INST. FOR ADVANCED ANALYTICS, at 6, <http://analytics.ncsu.edu/sesug/2014/PH-08.pdf>. Still others assert that the life science industry has been negatively impacted by the ACA entirely. For example, Avalere Health projects that the ten-year cost of the ACA on brand name pharmaceutical companies will be \$105 billion, mainly from increased Medicaid rebates and net cost or discounts in the Medicare drug coverage gap. J.M. Pickett, *Supreme Court Rules for ACA, Leaving Pharma Fees Intact*, EXPERT BRIEFINGS (June 29, 2012), <http://www.expertbriefings.com/news/supreme-court-rules-for-aca-leaving-pharma-fees-intact/>.

⁷¹ See Food & Drug Admin., *Implementation of the Biologics Price Competition and Innovation Act of 2009*, <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/ucm215089.htm> (last updated Feb. 12, 2016); see also, Jordan Paradise, *The Legal and Regulatory Status of Biosimilars: How Product Naming and State Substitution Laws May Impact the U.S. Healthcare System*, 41 AM. J. OF L. & MED. 49, 50 (2015).

⁷² See FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOSIMILARS: QUESTIONS AND ANSWERS REGARDING IMPLEMENTATION OF THE BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009 (Apr. 2015), <https://www.fda.gov/downloads/drugs/guidances/ucm444661.pdf>; FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: BIOSIMILARS: QUALITY CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A

in May 2014,⁷³ and a fifth and sixth in January 2017.⁷⁴ The FDA also unveiled its *Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations*, or the Purple Book, in September 2014.⁷⁵ The Purple Book identifies innovator biological products approved by the FDA, including any eventual biosimilar and interchangeable products.⁷⁶

REFERENCE PROTEIN PRODUCT (Apr. 2015), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>; FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: SCIENTIFIC CONSIDERATIONS IN DEMONSTRATING BIOSIMILARITY TO A REFERENCE PRODUCT (Apr. 2015), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>.

⁷³ See FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: CLINICAL PHARMACOLOGY DATA TO SUPPORT A DEMONSTRATION OF BIOSIMILARITY TO A REFERENCE PRODUCT (Dec. 2016), <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm397017.pdf>.

⁷⁴ FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: NONPROPRIETARY NAMING FOR BIOLOGICAL PRODUCTS (Jan. 2017), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>; FOOD & DRUG ADMIN., DRAFT GUIDANCE FOR INDUSTRY: CONSIDERATIONS IN DEMONSTRATING INTERCHANGEABILITY WITH A REFERENCE PRODUCT (Jan. 12, 2017), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf>. The naming guidance document establishes that biosimilar products will be given the drug's proper name followed by a hyphen and suffix for biosimilar products. The suffix requires four lowercase letters that are unique and devoid of meaning. For originator products, FDA will use the core name adopted by USAN. There may be a prefix to distinguish a previously licensed biologic where FDA determines necessary for public health (post-market surveillance, tracking, recall ability). FDA is currently contemplating whether interchangeable products will require a unique suffix.

⁷⁵ FOOD & DRUG ADMIN., PURPLE BOOK: LISTS OF LICENSED BIOLOGICAL PRODUCTS WITH REFERENCE PRODUCT EXCLUSIVITY AND BIOSIMILARITY OR INTERCHANGEABILITY EVALUATIONS, <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm> (last updated May 23, 2017).

⁷⁶ The Purple Book operates as an information resource in much the same way that the Orange Book does in the pharmaceutical context. However, unlike the Orange Book,

Seven biosimilar products have been approved by the FDA, as noted in *Figure 1*.⁷⁷ Many other biosimilars are currently under investigation by sponsors and the FDA. This quicker route to market is sure to foster an increase in biologic sponsors willing to pursue products with companion diagnostics.

Figure 1: FDA-Approved Biosimilar Products

<u>Approval</u>	<u>Product & Company</u>	<u>Proper Name</u>	<u>Innovator Product</u>
3/6/15	Zarxio (Sandoz)	Filgrastim -sndz	Neupogen (Amgen)
4/5/15	Inflectra (Celltrion)	Infliximabd -dyyb	Remicade (Janssen)
8/30/16	Erelzi (Sandoz)	Etanercept -szzs	Enbrel (Amgen)
9/23/16	Amjevita (Amgen)	Adalimumab -atto	Humira (Abbvie)
4/21/17	Renflexis (Samsung Bioepis)	Infliximabd -abda	Remicade (Janssen)
8/25/17	Cyltezo (Boehringer Ingelheim)	Adalimumab -adbm	Humira (Abbvie)
9/14/17	Mvasi (Amgen)	Bevacizumab -awwb	Avastin (Genentech)

the Purple Book does not contain patent information, a reflection of the novel patent process laid out in the BPCIA.

⁷⁷ This is the number of approved biosimilar products as of September 28, 2017. The FDA has not yet approved an interchangeable product.

B. THE FOOD AND DRUG ADMINISTRATION SAFETY AND INNOVATION ACT OF 2012

Two years later, Congress passed the Food and Drug Administration Safety and Innovation Act (FDASIA), which, among other things, establishes a statutory process for FDA review of breakthrough therapies.⁷⁸ The FDA defines a breakthrough therapy as a drug

intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.⁷⁹

The provisions create an expedited review mechanism and mandatory timeframes for the FDA to respond to requests for breakthrough therapy designation for either drugs or biologics. FDA published a guidance document in May 2014 detailing the process for industry.⁸⁰ The breakthrough therapy designation joins existing pathways for expedited review at the FDA set forth either through legislation or FDA regulation, including Fast Track designation,

⁷⁸ Food & Drug Admin. Safety & Innovation Act, Pub. L. 112-144, 126 Stat. 993 (2012) (codified in title 21 the U.S.C.). Breakthrough therapy status signals that the drug is progressing through clinical trials subject to the statutory provisions provided for breakthrough therapies, not that the drug has been approved by the FDA.

⁷⁹ Pub. L. 112-144, § 902, 126 Stat. 1086.

⁸⁰ FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: EXPEDITED PROGRAMS FOR SERIOUS CONDITIONS - DRUGS AND BIOLOGICS (May 2014), <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM358301.pdf>.

accelerated approval, and priority review designation.⁸¹ Notably, of the breakthrough therapy designations granted by the FDA in the first year after FDASIA, two-thirds include a companion diagnostic.⁸² This designation further incentivizes investments in precision medicine.

C. THE 21ST CENTURY CURES ACT OF 2016

The first version of the 21st Century Cures Act was introduced to the United States House of Representatives on May 19, 2015,⁸³ and unanimously approved by the House Energy and Commerce Committee two days later.⁸⁴ It passed the full House on July 10, 2015, but died in committee in the Senate.⁸⁵ The major purpose was “to speed up the pace at which FDA approves new medicines” and included topics such as matters affecting the regulation of pharmaceuticals, medical devices, and biotechnology products.⁸⁶ The bill was championed by both industry and patient advocates because it was viewed as an accumulation of ideas to improve drug

⁸¹ A table within the FDA’s breakthrough therapy guidance document compares the four expedited mechanisms. *Id.*, at 11.

⁸² Alexander J. Varond, *Trends in Personalized Medicine*, REGULATORY FOCUS (Oct. 2013), at 2, <http://www.raps.org/WorkArea/DownloadAsset.aspx?id=5275>.

⁸³ H.R. 6, 114th Cong. (2015), <https://www.congress.gov/bill/114th-congress/house-bill/6>.

⁸⁴ Jeannie Baumann, *House Energy/Commerce Unanimously OKs Bill That Would Amend HIPAA Privacy Rule*, PRIVACY LAW WATCH (BNA), May 26, 2015, at 1.

⁸⁵ H.R. 6, 114th Cong. (2015).

⁸⁶ Alexander Gaffney, *Regulatory Explainer: The (Updated) 21st Century Cures Act*, REG. AFF. PROF. SOC’Y (Apr. 30, 2015), <http://www.raps.org/Regulatory-Focus/21st-Century-Cures-Act/>.

development.⁸⁷ The Act was divided into three distinctive sections: discovery, development, and delivery.

Title I regarding discovery included increases to the NIH budget, prize competitions, and administrative provisions; researcher grant increases, capstone awards, and loan repayment for young scientists; facilitation of collaborative research, including standardization of data at the website www.clinicaltrials.gov, sharing and use of clinical trial health data for research; pediatric research promotion; and creation of the Council for 21st Century Cures, a nonprofit, public-private partnership to accelerate discovery, development, and delivery in innovative cures, treatments and preventative measures.⁸⁸

Title II regarding development was largely focused on drug, biologic, and medical device regulation. It included provisions for patient-focused drug development, incorporating patient experience data into risk-benefit assessment frameworks; qualification of drug development tools and accelerated approval development plans; advancement of precision medicine on the part of the FDA, requiring periodic guidance on precision medicine development and accelerated approval; modern trial design and evidence development; antibiotic drug development provisions; orphan product extensions of exclusivity; requirement of final guidance from FDA on combination product responsibilities; breakthrough designation for medical devices; allowance of third party quality assessment for medical devices; allowance of the recognition of

⁸⁷ The bill was described as a “Christmas tree” and “moonshot opportunity for lots of stuff.” Darius Tahir, *Lobbying Groups Eye Fast Moving FDA Bill*, MOD. HEALTHCARE (May 16, 2015), <http://www.modernhealthcare.com/article/20150516/MAGAZINE/305169956/lobbying-groups-hungrily-eye-fast-moving-fda-overhaul-bill>.

⁸⁸ H.R. 6, 114th Cong. (2015).

medical device standards; reduction of regulatory burden for some Class I and II devices; expansion of the humanitarian device exemption patient population; and a requirement for HHS and the FDA to harmonize regulations governing human subjects research.⁸⁹

Title III would have amended the Public Health Service Act, Social Security Act, and the Health Information Technology for Economic and Clinical Health Act to address such topics as interoperability; telehealth under Medicare; disposable medical technologies; local coverage decision reforms; Medicare site-of-service transparency; Medicare Part D patient safety and drug abuse prevention; and various Medicaid, Medicare, and other reform, including exclusion of authorized generics from calculation of average manufacturer price, and civil money penalties for violations related to grants, contracts, and other agreements.⁹⁰

Funding was a large issue voiced by legislators because of the Act's approximately \$13 billion price tag.⁹¹ A news article by Ropes & Gray LLP stated that a key issue discussed at the House Energy and Commerce Committee's hearing was "the need for additional FDA funding to support and implement the legislative proposals."⁹² Critics of the first version of the legislation, including the former FDA commissioner, Margaret Hamburg, worried that the Act's promise to make medications and devices available to the public faster while

⁸⁹ *Id.*

⁹⁰ *Id.*

⁹¹ Steven Ross Johnson, *21 Century Cures Bill Progress Hits Possible Funding Roadblock*, MOD. HEALTHCARE (May 20, 2015), <http://www.modernhealthcare.com/article/20150520/NEWS/150529984>.

⁹² Ropes & Gray LLP, *Progressing Toward a Cure: House Committee Unveils Revised, Streamlined 21st Century Cures Discussion Draft 3* (2015), <https://www.ropesgray.com/news-and-insights/Insights/2015/May/Progressing-Toward-a-Cure-House-Committee-Unveils-Revised-Streamlined-21st-Century-Cures-Discussion.aspx>.

also reducing the cost of product development could “heighten the risk of patients being exposed to inadequately tested and potentially harmful products.”⁹³

The bill was then reintroduced, overhauled, and quickly gained support from professional organizations, lobbyists, and the pharmaceutical industry. Many of the provisions from the previous bill were retained, but much was parsed into the bill from other sources. The bill passed the House and Senate, with only five Senators voting against it; at least one Senator cited objections to the influence of the pharmaceutical industry.⁹⁴ In its final form, signed by President Obama in December 2016, the legislation spans several hundred pages, covering myriad topics impacting health and medical care across 18 titles.⁹⁵ Relevant to this article, the legislation provides several significant changes to the law, and to the FDA’s authority to oversee life science products.

First, the legislation specifically advances Precision Medicine, tasking the Secretary of HHS with developing new approaches, coordinating with other federal agencies, and ensuring the protection of human participants in research.⁹⁶ With regard to clinical trials and participant information, the HHS is directed to issue certificates of confidentiality to researchers receiving federal funding, which prohibits those researchers from disclosing identifiable information except in certain circumstances (including consent and when necessary to treat the individual), grants immunity to this

⁹³ Steven Ross Johnson, *FDA Reform Bill Criticized*, MOD. HEALTHCARE (Apr. 11, 2015), <http://www.modernhealthcare.com/article/20150411/MAGAZINE/304119959>

⁹⁴ Jennifer Steinhauer & Robert Pear, *Sweeping Health Measure, Backed by Obama, Passes Senate*, N.Y. TIMES, Dec. 8, 2016, at A17.

⁹⁵ 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033 (2016).

⁹⁶ *Id.* at § 2011.

identifiable information from the legal process,⁹⁷ and allows the Secretary to exempt individual biomedical research data from disclosure where it is identifiable or could possibly be used to identify.⁹⁸ The Director of NIH is also authorized to require grant recipients to share data generated from federally-funded research in a manner consistent with federal law.⁹⁹

Second, the legislation directs the FDA to make changes in a number of areas for drug and medical device oversight. *Figure 2* identifies the major provisions of the 21st Century Cures Act impacting the FDA. Taken together, these provisions introduce potentially significant changes to the FDA processes involved in product review and approval of drugs, biologics, and medical devices and give much discretion to the FDA to determine how to implement particular requirements. Several provisions will undoubtedly impact drug, biologic, and companion diagnostic development, including the inclusion of patient experience data¹⁰⁰ with drug approvals, new review mechanisms for use of biomarkers¹⁰¹ in clinical trial design for new drugs, use of real world

⁹⁷ *Id.* at § 2012.

⁹⁸ *Id.* at § 2013.

⁹⁹ *Id.* at § 2014.

¹⁰⁰ Patient experience data is defined as data that “are collected by any persons (including patients, family members and caregivers of patients, patient advocacy organizations, disease research foundations, researchers, and drug manufacturers)” and “are intended to provide information about patients’ experience with a disease or conditions, including – (A) the impact of such disease or condition, or a related therapy, on patients’ lives; and (B) patient preferences with respect to treatment of such disease or condition.” *Id.* at § 3001.

¹⁰¹ A biomarker is defined as “a characteristic (such as a physiologic, pathologic, or anatomic characteristic or measurement) that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes, or biological

evidence¹⁰² for support of new drug indications, allowance of centralized institutional review board (IRB) reviews for medical devices,¹⁰³ and the creation of a breakthrough medical device category.¹⁰⁴

The legislation provides momentum to long-standing efforts to reconstruct FDA’s regulatory approach to novel and emerging technologies. While it does not introduce drastic mandates to the FDA to change its existing regulatory frameworks, it does challenge them to consider and integrate more diverse source of information, data collection, and methods of risk assessment in the context of product review and approval.

Figure 2: Select 21st Century Cures Act Provisions Directed to the FDA

Section	Overview
-----	<i>Subpart A: Patient-Focused Drug Development</i>
3001	FDA required to include patient experience data statement at time of drug approval.
3002	FDA required to issue guidance on methods of collecting patient experience data.
3003	FDA exempted from Paperwork Reduction Act when requesting patient information related to patient experience data.
3004	FDA required to report on their review of patient experience data.
-----	<i>Subpart B: Advancing New Drug Therapies</i>

responses to a therapeutic intervention.” 21st Century Cures Act, Pub. L. No. 114-255, § 3011(a), 130 Stat. 1033, 1088-89 (2016).

¹⁰² Real world evidence is defined as “data regarding the usage, or the potential benefits or risks, of a drug derived from sources other than randomized clinical trials.” *Id.* at § 3022.

¹⁰³ *Id.* at § 3056.

¹⁰⁴ *Id.* at § 3051.

3011	Creates review mechanism at FDA for biomarkers and other drug development tools.
3012	Addresses FDA authority over genetically targeted drugs for rare diseases.
3013	Reauthorizes pediatric rare drug disease priority review voucher program.
3014	Requires GAO study on priority review programs regarding impact on drug development.
3015	Allows grants for observational studies for orphan drug development program.
3016	FDA may issue grants for study of continuous manufacturing for drugs.
-----	<i>Subpart C: Modern Trial Design & Evidence Development</i>
3021	FDA required to hold public meeting and issue guidance on adaptive designs and statistical modeling for new drug applications.
3022	FDA required to evaluate use of real world evidence to support new indication of approved drug or post-market requirements.
3023	HHS required to harmonize Common Rule and FDA regulations; revises IRB processes where multiple sites.
3024	FDA may waive or alter informed consent for minimal risk clinical trials.
-----	<i>Subpart D: Patient Access to Therapies & Information</i>
3031	FDA may rely on qualified data summaries to support new indication for approved drug.
3032	Companies must make compassionate use policies publicly available.
3033	FDA may grant accelerated approval for regenerative therapeutics. ¹⁰⁵

¹⁰⁵ The Act defines “regenerative medicine therapy” as including “cell therapy, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, except for those regulated solely under section 361 of the Public Health Service Act and part 1271 of title 21, Code of Federal Regulations.” *Id.* at § 3033.

3034	Devices for use with regenerative therapeutic are deemed moderate risk, unless Secretary determines higher risk.
3035	FDA required to update regulations and guidance on regenerative therapeutics, hold public meeting.
3036	FDA required to consult with NIST and stakeholders to establish regenerative medicine standards and support development.
3037	Scope of permissible communications of health care economic information.
3038	FDA required to meet with sponsors of combination products early in process to agree to plan; clarifies dispute resolution among the Centers; reporting.
-----	<i>Subpart E: Antimicrobial Innovation & Stewardship</i>
3041	FDA and CDC required to report on human resistance to antimicrobial drugs.
3042	FDA may approve antimicrobial drugs based on limited populations where treats life-threatening condition; labeling to identify limited population study; review and approval of promotional materials 30 days prior.
3043	Subpart E provisions impose no restrictions on prescribing or practice of health care.
3044	FDA may rely on third party experts when issuing guidance on use and indications.
-----	<i>Subpart F: Medical Device Innovations</i>
3051	Creates new breakthrough medical device pathway to market.
3052	FDA may apply HDE exemption for devices for conditions affecting 8,000 individuals.
3053	Creates process for use of standards in medical device review.
3054	FDA required to update lists for Class I and II device regulation.
3055	Revises FDA medical device panel review process.
3056	Allows medical device sponsors to use central, rather than local, IRB.
3057	FDA required to update guidance on CLIA waivers.
3058	FDA required to consider least burdensome means for showing reasonable assure of safety and effectiveness.
3059	Emphasizes cleaning and validation data requirements for reusable devices.

3060	Sets forth five types of medical software that are not subject to FDA regulation as a medical device, unless there is a safety concern.
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D. FDA AND LABORATORY DEVELOPED TESTS

FDA policy decisions will also influence precision medicine and product development. One area in which this is unfolding is laboratory developed tests (LDTs). LDTs fall within the spectrum of products categorized by the FDA as medical devices subject to either premarket review or clearance, along with other substantive requirements. The FDA defines an LDT as “an *in vitro* diagnostic (IVD) that is intended for clinical use and designed, manufactured, and used in a single laboratory.”¹⁰⁶ IVD products are “reagents, instruments, and systems intended for use in the diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.”¹⁰⁷

The FDA has historically not enforced premarket review (or clearance) and regulatory requirements for LDTs because they have been relatively simple laboratory tests available on a limited basis.¹⁰⁸

¹⁰⁶ FOOD & DRUG ADMIN., DRAFT GUIDANCE: FDA NOTIFICATION AND MEDICAL DEVICE REPORTING FOR LABORATORY-DEVELOPED TESTS (LDTs) 4 (2014), <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416684.pdf>. Clinical use is defined by FDA regulations in terms of objective intent of the person legally responsible for labeling the device and can be based on aspects such as labeling claims, advertising, oral and written statements by the person or representatives, and particular circumstances. Specifically, intent may be found if the device “is, with the knowledge of such persons or their representatives, offered or used for a purpose for which it is neither labeled nor advertised.” 21 C.F.R. § 201.128 (2016).

¹⁰⁷ 21 C.F.R. § 809.3 (2016).

¹⁰⁸ The Centers for Medicare and Medicaid Services also has overlapping regulatory authority over *in vitro* diagnostics under the Clinical Laboratory Improvement

However, following a July 2014 Notice of Intent to Congress, the FDA released its *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)* in October 2014.¹⁰⁹ Ending decades of enforcement discretion, the FDA guidance highlights the inherent risk of certain LDTs and announced its plan to subject products to medical device requirements.¹¹⁰ The guidance explicitly sets forth that high risk LDTs will be regulated as medical devices subject to premarket review and approval.¹¹¹ The FDA cites changed technological capabilities and the proliferation of advanced marketing and business models as the primary motivation for the change in policy.¹¹² On its website, the FDA emphasizes “[s]ome LDTs are now more complex, have a nation-wide reach and present higher risks.”¹¹³ In addition, the FDA guidance specifically flagged problems with product claims unsupported with adequate evidence and lack of appropriate controls.¹¹⁴

Amendments (CLIA). See *Clinical Laboratory Improvement Amendments*, FOOD & DRUG ADMIN., <https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/IVDRRegulatoryAssistance/ucm124105.htm> (last updated Sept. 29, 2017). CLIA applies to clinical laboratories that test patient specimens, assuring analytical validity and reliability in the test results.

¹⁰⁹ FOOD & DRUG ADMIN., DRAFT GUIDANCE: FRAMEWORK FOR REGULATORY OVERSIGHT OF LABORATORY-DEVELOPED TESTS (LDTs) (2014), <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM416685.pdf> [hereinafter LDT FRAMEWORK].

¹¹⁰ *Id.* at 7-11.

¹¹¹ *Id.* at 13.

¹¹² *Id.* at 7-8.

¹¹³ *Zika Virus Diagnostic Development*, U.S. FOOD & DRUG ADMIN., <http://www.fda.gov/EmergencyPreparedness/Counterterrorism/MedicalCountermeasures/MCMIssues/ucm494615.htm>. (last updated Aug. 21, 2017).

¹¹⁴ LDT FRAMEWORK, *supra* note 109, at 9-10.

The FDA has engaged with stakeholders following the publication of the draft guidance. The FDA hosted a public workshop in January 2015 to vet the framework and has collected public input throughout the process.¹¹⁵ The FDA's flurry of activity has garnered significant legal blog coverage;¹¹⁶ opposing views on the LDT framework were also published in JAMA.¹¹⁷ In March 2015, an independent group of clinical laboratories and diagnostic manufacturers publicly responded to the FDA's position and framed an alternative proposal.¹¹⁸ Many other professional stakeholders shared feedback as well, including the College of American Pathologists, the Association for Molecular Pathology, and the American Clinical Laboratory Association.¹¹⁹

Surprisingly, although likely a result of the impending Administration change, the FDA announced on January 13, 2017, that they would not issue final guidance, at the urging of stakeholders to seek more input and continue dialogue in this area. The FDA

¹¹⁵ *Public Workshop – Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs)*, U.S. FOOD & DRUG ADMIN., <https://www.fda.gov/medicaldevices/news-events/workshopsconferences/ucm423537.htm>. (last updated Jan. 23, 2015) [hereinafter *Public Workshop*].

¹¹⁶ E.g., Jamie Wolzon et al., *FDA Formally Issues Draft LDT Guidance; Provides 120 Day Comment Period and Will Host October Public Meeting*, FDA LAW BLOG (Oct. 2, 2014), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/10/fda-formally-issues-draft-ldt-guidance-documents-provide-120-day-comment-period-and-will-host-octobe.html; Jamie Wolzon, *LDT Battle Lines Drawn*, FDA LAW BLOG (Nov. 24, 2014), http://www.fdalawblog.net/fda_law_blog_hyman_phelps/2014/11/ldt-battle-lines-drawn-fda-announces-jan-8-9-public-meeting-on-ldt-framework-lab-and-medical-groups-.html.

¹¹⁷ James P. Evans & Michael S. Watson, *Viewpoint, Genetic Testing and FDA Regulation: Overregulation Threatens the Emergence of Genomic Medicine*, 313 JAMA 669-70 (2015).

¹¹⁸ Diagnostic Test Working Group, *A Proposed Regulatory Framework for In Vitro Clinical Tests* (2015), http://www.fdalawblog.net/DTWG_final_proposal.pdf.

¹¹⁹ *Public Workshop*, *supra* note 115.

simultaneously issued a discussion paper.¹²⁰ In the discussion paper, FDA reports they

[a]nalyzed more than 300 sets of comments on the draft guidances and discussion from a subsequent public workshop held in 2015 as well as engaged in many meetings and conferences with various stakeholders. In the absence of issuing final guidance and at the request of stakeholders, we feel it is our responsibility to share our synthesis of all the feedback we have received, with the hope that it advances public discussion on future LDT oversight.¹²¹

The FDA noted that a “complementary approach [of both FDA and CMS] in some form is supported by the broadest array of stakeholders.”¹²² Emphasizing that the discussion paper was only a possible approach synthesized from public feedback, the FDA did urge a prospective oversight framework based on a number of core elements. These elements included a process of grandfathering previously marketed LDTs; utilizing risk-based, phased-in oversight; complementary evidence standards of FDA and CMS for clinical and analytical validity; availability of third party review; collaboration with the LDT community, including efforts to develop standards for use; transparency of information; flexibility in product modification without undue burden to industry; and quality system requirements and inspections; and postmarket surveillance.¹²³

¹²⁰ FOOD & DRUG ADMIN., DISCUSSION PAPER ON LABORATORY-DEVELOPED TESTS (LDTs) (2017), <http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/LaboratoryDevelopedTests/UCM536965.pdf>.

¹²¹ *Id.* at 2.

¹²² LDT FRAMEWORK, *supra* note 109, at 2.

¹²³ LDT FRAMEWORK, *supra* note 109.

Current uncertainty in LDT regulation has implications for companion diagnostic research and development. Even where a diagnostic assay is utilized solely to inform individual patient care and is developed in-house (with no intent to commercialize the product), FDA's current position is that its use to detect genetic status is well within the bounds of the agency's medical device authority under the statute. The lack of clarity over LDT regulation may stifle companion diagnostic innovation or at the least cause confusion for sponsors.

CONCLUSION

Precision medicine faces regulatory challenges, as does any emerging area of science and innovation. Many of these challenges have already been identified, others have yet to be confronted. As industry and the FDA move forward, there are also ample opportunities for collaboration, information-sharing, and new approaches. The FDA's PrecisionFDA website is currently facilitating aggregation and comprehension of data generated by genomic sequencing advancements. The FDA has approved drug and companion diagnostic products using breakthrough therapy status, and in May 2017 approved a new indication for a biologic drug based on a biomarker.¹²⁴ Drug, biologic and medical device sponsors, once operating as distinct industries, are actively working together to

¹²⁴ On May 23, 2017, the FDA announced approval of the biologic Keytruda (pembrolizumab) "based on a common biomarker rather than the location in the body where the tumor originated." Press Release, Food & Drug Admin., FDA Approves First Cancer Treatment for Any Solid Tumor with a Specific Genetic Feature (May 23, 2017), <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm560167.htm>.

develop products. And federal infrastructure has been put into place to support continuing innovation in precision medicine. Perhaps these are the proper conditions to spur FDA leadership to embrace more adaptive, flexible, and dynamic regulation that transcends the silo effect of traditional regulatory categories.¹²⁵

¹²⁵ See, e.g., Scott Gottlieb, *FDA Needs to Change How It Regulates Novel Technologies*, FORBES (Jan. 12, 2016), <https://www.forbes.com/sites/scottgottlieb/2016/01/12/fda-needs-tochange-how-it-regulates-novel-technologies/#1beb6116191e> (writing about the need for the FDA to rethink its silo approach for the regulation of novel technologies).