

**Comments on FDA's Draft Guidance:  
Framework for Regulatory Oversight  
of Laboratory Developed Tests (LDTs)**

Submitted by

Russ Altman, MD, PhD; Teri Klein, PhD; and Michelle Whirl-Carrillo, PhD

February 2, 2015

Juelsgaard Intellectual Property  
and Innovation Clinic  
Mills Legal Clinic  
Stanford Law School  
559 Nathan Abbotts Way  
Stanford, CA 94305

Hyosang (Mark) Kim  
Marta Belcher  
Yale Fu  
*Certified Law Students*  
Phil Malone  
Jef Pearlman  
*Counsel for Submitters*

## Introduction

Research and development of precision medicine—drugs and treatments tailored to individual patients' genetic characteristics—is a critical national priority. The recent White House Precision Medicine Initiative recognizes the importance of this vital area of innovation and seeks to accelerate genomics-based research that promises to revolutionize precision medicine.<sup>1</sup> Because pharmacogenomics has played, and will continue to play, a crucial role in precision medicine, we submit these comments to assist the Food and Drug Administration (FDA) in addressing pharmacogenomics in its draft Laboratory Developed Test (LDT) guidance<sup>2</sup> in a way that protects ongoing innovation and maximizes benefits for patients and the public.

Pharmacogenomics<sup>3</sup>—using genomic information to estimate the likely efficacy and side effects of a drug for an individual patient—has been a pioneering field that, according to the White House's initiative, enabled the “initial successes”<sup>4</sup> of precision medicine, with its laboratories at the forefront of innovation. Now, with the support of the national efforts endorsed by the Precision Medicine Initiative, pharmacogenomics can translate these initial successes to a larger scale. *It is therefore crucial that any new regulation arising from FDA's LDT guidance promotes rather than inhibits the development of pharmacogenomics, so that the field can continue to lead in the advancement of precision medicine.*

Pharmacogenomics, by virtue of both its inherent characteristics and established guidelines, already addresses the goals FDA is aiming to ensure with its draft LDT guidance: safety, effectiveness, and reliability.<sup>5</sup> Unnecessary, ill-suited, and burdensome regulation of pharmacogenomics risks stifling innovation in pioneering pharmacogenomics laboratories, reducing pharmacogenomic benefits to patient welfare, and thwarting the imperatives of the Precision Medicine Initiative.

We recognize that FDA's goal is to protect the public without stifling innovation in the burgeoning biomedical field. In these comments, we demonstrate the reasons why FDA should continue to exercise enforcement discretion over pharmacogenomics by explaining: (I) why

---

<sup>1</sup> Pear R., New York Times, Obama Unveils Research Initiative to Develop Tailored Medical Treatments, January 30, 2015, available at <http://www.nytimes.com/2015/01/31/us/obama-to-unveil-research-initiative-aiming-to-develop-tailored-medical-treatments.html>.

<sup>2</sup> Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs), 1-41 (2014).

<sup>3</sup> Our use of the term “pharmacogenomics” in the comments encapsulates the fields of both pharmacogenomics and pharmacogenetics.

<sup>4</sup> The White House, Office of the Press Secretary, FACT SHEET: President Obama's Precision Medicine Initiative, January 30, 2015, available at <http://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>.

<sup>5</sup> Ray T., GenomeWeb, At PMWC, FDA Commissioner Hamburg Discusses LDT Regulation, Personalized Medicine Advancements, 2, 1-4 (2015), available at <https://www.genomeweb.com/regulatory-news/pmwc-fda-commissioner-hamburg-discusses-ldt-regulation-personalized-medicine>.

pharmacogenomics should be exempt from FDA's proposed risk-based classification system or be regulated under a different system; (II) why the proposed adverse event reporting system is ill-suited for pharmacogenomics; (III) why the proposed regulation is particularly problematic for pharmacogenomics; (IV) how the proposed regulation would conflict with national priorities and the Precision Medicine Initiative; and (V) how the safety and effectiveness of pharmacogenomics are already ensured through established guidelines.

As creators of The Pharmacogenomics Knowledgebase (PharmGKB)<sup>6</sup> and as experts in pharmacogenomics, we want to promote the growth of the pharmacogenomics field in a way that maximally benefits patient health and wellbeing. In these comments, we seek to ensure that regulation affecting pharmacogenomics takes into account the field's unique characteristics. We do not intend to address whether or how FDA should regulate disease-risk diagnostic genomics or any other LDT services beyond pharmacogenomics.

### **The Commenters**

The submitters of this comment include the co-creators of PharmGKB and have extensive experience working in pharmacogenomics. PharmGKB is a publicly available pharmacogenomics knowledge resource, sponsored by the National Institute of General Medical Sciences (NIGMS) of the National Institute of Health (NIH). The resource encompasses clinical information including dosing guidelines and drug labels, potentially clinically actionable gene-drug associations, and genotype-phenotype relationships. PharmGKB collects, curates, and disseminates knowledge about the impact of human genetic variation on drug responses.

Russ B. Altman, MD, PhD is the Kenneth Fong Professor of Bioengineering, Genetics, Medicine & (by courtesy) Computer Science at Stanford University. He is the Co-Principal Investigator of PharmGKB. As Co-PI, he is interested in ensuring that the regulatory policies relevant to the implementation of pharmacogenomics allow the field to emerge, with appropriate attention on bringing the benefits to patients, while maintaining safety. Dr. Altman has served as Chair of FDA Science Board advising the Commissioner (2013-2014), and is the Co-PI of FDA-funded UCSF/Stanford Center for Excellence in Regulatory Science and Innovation. He is a member and Co-Chair of the Institute of Medicine's Drug Forum. He is a Past President of the American Society for Clinical Pharmacology & Therapeutics. Dr. Altman is a founder of and stockholder in Personalis, Inc., a company focusing on clinical genomics testing and interpretation.

Teri E. Klein, PhD is a Senior Research Scientist in the Department of Genetics at Stanford University. She is the Co-Principal Investigator and Director of PharmGKB. Dr. Klein is

---

<sup>6</sup> <http://www.pharmgkb.org/>.

co-leader of the Clinical Pharmacogenetics Implementation Consortium (CPIC), whose mission is to develop guidelines that enable the translation of genetic laboratory test results into actionable prescribing decisions for specific drugs. Dr. Klein is also co-leader of the ClinGen PGx working group and is a stockholder in Personalis, Inc., a company focused on clinical genomics testing and interpretation.

Michelle Whirl-Carrillo, PhD is a Research Scientist in the Department of Genetics at Stanford University. She is the Associate Director of PharmGKB. Dr. Whirl-Carrillo has experience in direct-to-consumer genomics, having served as the Manager of Scientific Curation at 23andMe, Inc. from 2008-2009. Dr. Whirl-Carrillo is the co-lead of the Clinical Pharmacogenetics Implementation Consortium (CPIC) Informatics Working Group.

## **The Comments**

### **I. Pharmacogenomics Is Significantly Different from Diagnostic Genomics and Should Not Be Regulated in the Same Manner**

FDA's proposed risk-based classification system should not treat pharmacogenomics and disease-risk diagnostic genomics under the same regulatory framework because of critical differences between the two domains. We define pharmacogenomics as measurements of DNA (genotyping or sequencing, from patients, their tumors, or their infectious pathogens) that are used to estimate the probabilities of efficacy or side effects of specific drugs or classes of drugs. Pharmacogenomics should be exempt from the proposed risk-based classification system. If the already rigorous Clinical Laboratory Improvement Amendments (CLIA) regulations are thought to be insufficient, pharmacogenomics should at most be regulated under a different, appropriately tailored classification system. We submit that FDA should amend its draft LDT guidance to clearly and properly adopt a different regulatory approach tailored to pharmacogenomics, recognizing its critical distinctions from diagnostic genomics.

Pharmacogenomics is different from—and by its nature involves less risk than—diagnostic genomics. Diagnostic genomics uses genomic data to estimate disease risk and prognosis,<sup>7</sup> whereas pharmacogenomics uses genomic data to estimate likely efficacy and side effects in drug response.<sup>8</sup> The use of genetic information to estimate disease risk or find the cause of genetic disease raises very different concerns and issues than pharmacogenomics.<sup>9</sup> The draft LDT guidance proposed by FDA, however, remains silent about the guidance's

---

<sup>7</sup> Altman R.B., Pharmacogenomics: “Noninferiority” Is Sufficient for Initial Implementation. *Nature: Clinical Pharmacology & Therapeutics*, Volume 89 Number 3, 348, 348-50 (2011).

<sup>8</sup> Dunnenberger H.M., et al. Preemptive Clinical Pharmacogenetics Implementation: Current Programs in Five US Medical Centers, *Annu. Rev. Pharmacol. Toxicol.*, 55:89-106, 90, 89-106 (2014). PMID: 2529249.

<sup>9</sup> *Id.*

applicability specifically to pharmacogenomic testing. The lack of clear, explicit provisions regarding how FDA intends to regulate pharmacogenomics is likely to result in pharmacogenomics being regulated identically to the very different field of diagnostic genomics. Treating pharmacogenomics in this manner would be both unnecessary and counterproductive, imposing significant burdens on vital innovation and chilling the development and use of pharmacogenomics without corresponding public benefit.

A critical difference between pharmacogenomics and diagnostic genomics is that pharmacogenomics inherently poses significantly lower risks to patient health and welfare than does diagnostic genomics. Physicians take into consideration many factors when prescribing medication, including the level of confidence in the diagnosis, anticipated side effects, interactions with other substances, and likelihood of patient compliance.<sup>10</sup> Pharmacogenomics provides physicians with additional information, such as the likely efficacy or side effects of the drug based on the individual patient's genetics, to take into account as one factor in their complex decision-making.<sup>11</sup> The additional information provided by pharmacogenomics can increase the quality of medical service and reduce negative side effects, but will rarely result in significantly increased medical risk. Pharmacogenomics simply helps physicians evaluate which available drug is preferable for a particular patient, rather than diagnosing whether that patient has a disease. Thus, incorrect pharmacogenomic test results would be less likely than diagnostic genomic test results to lead to unnecessary treatments (for a false positive) or be harmful due to non-treatment (for a false negative). Where drug prescription decisions pose risks to patients, that risk comes primarily from the drugs themselves—a risk that already exists in the absence of pharmacogenomics and which is already separately regulated by FDA—not in any significant way from the additional information about individual patients that pharmacogenomics provides.

Moreover, in pharmacogenomics, clinical validity is more easily demonstrated than in diagnostic genomics. In diagnostic genomics, clinical validity is a difficult problem because it is often hard to explain the effects of small genetic variations on complex phenotypes. Furthermore, in diagnostic genomics, it can be difficult to analyze the effects of multiple, interacting variations to form a single diagnosis.<sup>12</sup> By contrast, in pharmacogenomics, genetic factors tend to have a clearer impact on drug response, and many important drug responses are modulated by one or a few genetic variations.<sup>13</sup> With a well-implemented delivery system, the benefits of pharmacogenomics can be measured continuously and monitored for evidence of success and failure.<sup>14</sup> Such a system would enable the measurement of the overall

---

<sup>10</sup> *Id.* at 348-49.

<sup>11</sup> *Id.* at 349.

<sup>12</sup> Altman R.B., Pharmacogenomics: “Noninferiority” Is Sufficient for Initial Implementation at 348.

<sup>13</sup> *Id.*

<sup>14</sup> *Id.*

improvements in drug effect, but it could be difficult to tease out the specific contribution of pharmacogenomics without controlled trials. Routine practice for specific patients, however, does not resemble controlled trials, making it very difficult or impossible to separate out the role of pharmacogenomics in individual cases.

Patients are often confused about diagnostic genomic test results that are often delivered directly to the patients, failing to understand the difference between genetic predisposition and a guarantee of a health outcome.<sup>15</sup> Conversely, pharmacogenomic test results inherently require a physician's involvement because the tests are used in determining a drug prescription, which can only be written by a physician.<sup>16</sup> Physician discretion, experience, and vigilance will provide safeguards to prevent patient misinterpretation of pharmacogenomic tests. Moreover, erroneous decisions in drug prescriptions can typically be reversed.<sup>17</sup> Physicians routinely alter or discontinue prescriptions as necessary.

Regulating diagnostic genomics also requires considering methods for protecting individuals and groups from discrimination based on their genetic risk factors for certain diseases, or from the incidental discovery of other likely features of the individuals that may be a cause for discrimination.<sup>18</sup> The propensity to respond to a drug, however, is not a typical target for discrimination,<sup>19</sup> so discrimination does not need to be a factor in regulating pharmacogenomics in the way that it is for diagnostic genomics.

Given these differences, pharmacogenomics warrants a specifically tailored regulatory framework to maintain its expected benefits to the public. This framework should recognize at least the following six key features of pharmacogenomic interventions that separate it from diagnostic evaluations:

- **The level of evidence for any genetic information impacting drug prescribing decisions:** PharmGKB has published a classification (ranging from 1 to 4) based on a standardized set of metrics evaluating how strong the evidence relevant to any pharmacogenomic intervention is, and this is the source of prioritizing the Clinical Pharmacogenetics Implementation Consortium (CPIC) activities.<sup>20</sup> CPIC established guidelines addressing how to interpret genotypes and use that information to alter prescription decisions.
- **The expected magnitude of change in drug efficacy and side effect rates when using genetic information in prescribing:** Some pharmacogenomic interventions are expected to

---

<sup>15</sup> *Id.*

<sup>16</sup> *Id.*

<sup>17</sup> *Id.*

<sup>18</sup> *Id.*

<sup>19</sup> *Id.*

<sup>20</sup> See <http://www.pharmgkb.org/page/cpicStatusLegend>; see e.g., Caudle, K.E., et al., Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process, *Curr. Drug. Metab.* (2014). PMID: 24479687.

have major implications for the selection and dosing of drugs, while others are expected to have more of a moderate optimization of drug use.

- **The inherent risks and benefits of using the drug at baseline (without any pharmacogenomics information):** Pharmacogenomics has the most to offer in optimizing selection and use of the drugs whose routine use is already treacherous due to their long list of serious side effects. Pharmacogenomics may be relatively less impactful for other drugs that have a very wide safety margin.
- **The degree to which “bad” prescribing decisions can be recognized and reversed:** Very rarely are drug prescription decisions irreversible; the decisions can be altered. The degree to which a patient can be monitored for response helps mitigate worries about mistakes in the use of pharmacogenomics.
- **The risks of the underlying patient diagnosis and comorbidities:** Some drugs treat serious and deadly disease (e.g. cancer) and so tolerance for side effects is higher than for more benign conditions.
- **The anticipated degree to which prescribers would depend on the genetic information (ranging from “total reliance” to “likely to be ignored”):** Some medications have an FDA-required “companion genetic diagnostic” that is required or strongly recommended before using the drug (e.g. Herceptin and EGFR status), and physicians rely on this information in selecting the drug. Other medications are well-known and well-tolerated by patients, and physicians may not be interested in the details of pharmacogenomic risk. Still others are generally safe but have a rare serious side effect (e.g. Abacavir), and thus pharmacogenomics promises substantial value to the physician.

We believe it is essential that, if FDA decides that some form of regulation of pharmacogenomics is necessary, it carefully consider the abovementioned factors in establishing a separate regulatory framework.<sup>21</sup>

## **II. The Proposed Adverse Event Reporting System Is Ill-Suited to Pharmacogenomics, and Applying It to Pharmacogenomics Would Not Have the Effects FDA Intends**

FDA should continue to exercise enforcement discretion with respect to the adverse event reporting requirements for pharmacogenomics. We read the draft guidance to mean that many pharmacogenomic tests could be regulated as moderate risk LDTs and subject to the proposed adverse event reporting requirement, among many others, under the risk-based classification system.<sup>22</sup> The intent of the adverse event reporting system is to “detect devices

---

<sup>21</sup> We understand that a future FDA guidance will clarify the definitions of Class I, II, and III for LDT services. We recommend that FDA provide an additional public comments period before finalizing the definition of the classes.

<sup>22</sup> Due to the lack of available definitions of Class I, II, and III for LDT services, we adopted and applied the definitions of Class I, II, and III medical devices to our pharmacogenomic tests.

that are inaccurate, ineffective, or unsafe.”<sup>23</sup> The adverse event reporting system, however, is ill-suited to monitor performance and quality of pharmacogenomics. While some of the issues we raise here may not be exclusive to pharmacogenomics, their potential consequences are likely to be more salient in the particular case of pharmacogenomics for the reasons discussed below. Pharmacogenomic test results are not determinative in prescription decisions, which take into account many additional factors. Such a complex process renders attribution of adverse events to pharmacogenomic testing virtually impossible. The system would also lead to significant commission bias, resulting in skewed data that would fail to reflect any actual problems in pharmacogenomic tests.

The adverse event reporting system would generate little information about the likely role of a pharmacogenomic test in an adverse event. Even with a patient's pharmacogenomic data, a physician must still balance a variety of other factors to reach a final prescribing decision: dosage, patient compliance, manifestation of drugs' inherent side-effects, comorbidity, and interaction with other substances, among others. In addition, the physician must decide how to interpret the pharmacogenomic data in relation to the other factors. A pharmacogenomic test, unlike a diagnostic genomic test, could provide the physician with information regarding a group of recommended drugs along with a recommended dosage range for each potential drug. This multi-factor selection process has been routine for physicians, long before the development and adoption of pharmacogenomics. Pharmacogenomics simply streamlines and individualizes the process for each patient, providing greater accuracy and precision. As part of an organic and dynamic decision-making process, no single individual factor, including pharmacogenomic testing, plays a determinative role. The relationship between a pharmacogenomic test and the ultimate prescription decision is simply not as clear as the relationship between a diagnostic genomic test and a diagnosis based on that test result.

If a prescription were to result in an adverse event, any or all of the factors considered in making that prescription decision in addition to pharmacogenomic testing would be potential causes of that adverse event. For example, warfarin is a common target for pharmacogenomic intervention and is responsible for many adverse bleeding events each year. These events may be traced in large part to the patients' genetics, lifestyle, diet, and medication compliance, as well as the general practices of their provider. Allocating responsibility for a bleeding event to a pharmacogenomic test in the context of all these other factors would be difficult. The proposed adverse event reporting system cannot precisely and accurately identify effects of a pharmacogenomic test—separate from any of the many other factors in prescribing decisions—in reported adverse events.

---

<sup>23</sup> Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) at 9.



Events reported through the adverse event reporting system also are highly likely to be error-prone. While the reporting system would attempt to only measure negative outcomes attributable to pharmacogenomic tests, there would be a tendency to associate pharmacogenomic testing with adverse events resulting from other contemporaneous factors, including poor physician practice, secondary medications, comorbidities, lifestyle elements, and inherent side-effects of a given drug. In the case of warfarin, for example, pharmacogenomics might be blamed for the adverse events that result from a drug that is simply difficult to dose and dangerous to use. Should pharmacogenomic laboratories become aware of adverse events and be required to report the events to FDA, they would not have enough information to report how exactly a physician reached prescription decisions. Despite a lack of resources and first-hand knowledge, the laboratories would still be required to identify, track, and report the way in which the pharmacogenomic data factored into physicians' prescribing decisions. However, accurate attribution in this context is virtually impossible given the complex nature of physicians' use of pharmacogenomics. Adverse events data full of speculation and potential errors may falsely implicate pharmacogenomic data as the cause, an erroneous conclusion that in turn could suggest nonexistent errors or inaccuracies of pharmacogenomic testing or laboratories.

Adverse event reporting for pharmacogenomics is also vulnerable to commission bias. Adverse events would only be reported if pharmacogenomic data led a physician, as part of a series of inputs into a complex prescribing decision, to ultimately (and erroneously) prescribe a given medication. Adverse events, however, would not be reported if such data led the physician ultimately (and erroneously) *not* to prescribe the medication. Thus, the adverse event reporting data would be skewed to show only those adverse events arising from incidents when pharmacogenomic testing led the physician to decide to actually prescribe a particular medication or a particular dosage.

Regulation that isolates the impact of pharmacogenomic tests from the impact of many other factors and subsequent physician interpretation of the tests would be more effective in ensuring the safety and efficacy of pharmacogenomic testing. Without that feature, adverse event reporting would serve only as a burden on pharmacogenomic laboratories that manufacture or use pharmacogenomic testing and would not further any goal of FDA. Physicians might simply elect not to use pharmacogenomic data in making prescription decisions to avoid the reporting requirements, which could undermine pharmacogenomics' potential benefits to patients.

Because it would be both ineffective and unduly burdensome, pharmacogenomic testing should not be subject to the adverse event reporting requirements.

### III. The Proposed Guidance Would Impose Significant, Unnecessary Burdens on Critical Pharmacogenomic Innovation and Pioneering Laboratories

FDA should continue to exercise enforcement discretion over pharmacogenomics to promote innovation in the rapidly growing and promising field. The proposed regulation would be particularly burdensome to innovation in pharmacogenomics because of the sheer volume of pharmacogenomic tests that can be developed by a single laboratory—potentially hundreds or even thousands. Many companies are now providing whole genome and whole exome sequencing for less than \$5,000, and these implicitly provide genetic information relevant to hundreds of drugs that can then be evaluated for pharmacogenomic interactions.<sup>24</sup>

Pharmacogenomic research laboratories seek to discover associations between certain genetic variations and a patient's resulting response to any number of drugs.<sup>25</sup> There are thousands of FDA-approved drugs,<sup>26</sup> and an ever-growing number of known drug-response genes—often multiple per drug—leading to the possibility of an enormous number of pharmacogenomic tests. While it remains unclear what exactly constitutes a new pharmacogenomic test under FDA's definitions, the sheer volume of tests that could be subject to the proposed regulation is unreasonably high—especially considering a relatively small, individual laboratory may develop thousands of such tests. The cost of facing regulation on thousands of tests could easily put a pharmacogenomic laboratory out of business and discourage the development of new laboratories or tests.

The proposed regulation could also disrupt the gathering of data necessary for the growth of the pharmacogenomics field. On its current trajectory, pharmacogenomics is expected to culminate in a knowledgebase of genomic data and drug responses that would aid physicians in prescribing the most effective drugs in the optimal dosage for individual patients (for example, the Pharmacogenomics Knowledgebase<sup>27</sup> that we are building is a research version of this resource which could be expanded to support clinicians directly). The regulation could threaten scientists' ability to conduct studies with LDTs in order to discover important associations between genetics and drug response. The regulation could also delay development and implementation of pharmacogenomics capabilities within electronic health record systems for analyzing and delivering clinical decision support based on large amounts of

---

<sup>24</sup> Ashley E.A., Clinical Assessment Incorporating a Personal Genome, *Lancet* (2010). PMID: 20435227; Dewey F.E., Phased Whole-Genome Genetic Risk in a Family Quartet Using a Major Allele Reference Sequence, *PLoS Genet.* (2011). PMID: 21935354.

<sup>25</sup> See Wetterstrand K.A., DNA Sequencing Costs: Data from the NHGRI Genome Sequencing Program (GSP), available at <http://www.genome.gov/sequencingcosts/> (2014); see also New Illumina Sequencer Enables \$1,000 Genome, *Genetic Engineering & Biotechnology News (GEN)*, available at <http://www.genengnews.com/gen-news-highlights/new-illumina-sequencer-enables-1-000-genome/81249370/> (2014).

<sup>26</sup> See Orange Book Data Files of the U.S. Food and Drug Administration, available at <http://www.fda.gov/Drugs/InformationOnDrugs/ucm129689.htm>; see also National Drug Code Directory of the U.S. Food and Drug Administration, available at <http://www.fda.gov/Drugs/InformationOnDrugs/ucm142438.htm>.

<sup>27</sup> <http://www.pharmgkb.org/>.

genetic data.<sup>28</sup> Moreover, the regulation could also increase clinicians' resistance to using genetic data in clinical practice,<sup>29</sup> raising concerns about the additional costs of regulatory requirements such as adverse event reporting. The development of necessary infrastructure and the participation of clinicians are both critical for the development of a pharmacogenomic knowledgebase, and therefore also important for laboratories that benefit from such a database. The proposed regulation could undermine these key developments, thereby stunting the young and burgeoning pharmacogenomics field.

Because pharmacogenomics is such a young field, the regulatory hurdles and associated costs could also significantly hinder the development of the industry and the technology. Most of the players in pharmacogenomics are laboratories in academic medical centers or are at the venture capital stage. Although they are at the forefront of innovation, these entities do not yet possess the personnel and resources to comply with the proposed LDT regulation in its current form. Even for larger institutions like the School of Medicine at the University of Pennsylvania, the proposed regulation could require too many resources for them to comply.<sup>30</sup> Professionals at Harvard Medical School hospitals predict that the proposed regulation would privilege commercial laboratories over academic laboratories because commercial ventures, unlike academic laboratories, can afford the additional regulation.<sup>31</sup> If even these well-funded and widely recognized institutions cannot withstand the proposed LDT regulation, the budding pharmacogenomic laboratories and start-ups, in a weaker financial position, do not stand a chance. These smaller entities are crucial to the advancement of pharmacogenomics because they tend to be more disruptive and innovative, and their achievements fuel competition that drives innovation. Furthermore, with so many of these ventures at the venture capital funding stage, the regulation threatens to deter investors who are already potentially taking a financial risk on a new technological frontier.<sup>32</sup> Ultimately, as described above, the minimal or nonexistent public benefit the proposed regulations would provide does not outweigh the damage they are likely to cause to the developing field of pharmacogenomics.

---

<sup>28</sup> Dunnenberger H.M. at 93.

<sup>29</sup> *Id.* at 90.

<sup>30</sup> Roth, et al., RE: Framework for Regulatory Oversight of Laboratory Developed Tests; Public Workshop; Request for Comments (2015). [Docket ID: FDA-2011-D-0360 and FDA-2011-D-0357].

<sup>31</sup> Golden and Louis, RE: Laboratory Developed Tests (2014). [Docket ID: FDA-2011-D-0360, 4, 1-5].

<sup>32</sup> See Goswami, S. and Vorhaus, D., Genomics Law Report by Robinson Bradshaw & Hinson, News Roundup: Biotech Funding and LDT Regulation, available at <http://www.genomicslawreport.com/index.php/2011/05/05/news-roundup-biotech-funding-and-ldt-regulation/> (2011).

#### **IV. The Proposed Regulation Would Undermine Innovation and the Goals of the Precision Medicine Initiative by Impeding the Development of Pharmacogenomics**

FDA should continue to exercise enforcement discretion over pharmacogenomics to facilitate realization of the objectives of the new White House Precision Medicine Initiative (the Initiative). The proposed regulation in its current form is likely to undermine the goals of the Initiative,<sup>33</sup> including (I) more and better treatments for cancer, (II) creation of a voluntary national research cohort, (III) commitment to protecting privacy, (IV) regulatory modernization, and (V) public-private partnerships. In pursuit of these objectives, the Initiative “seeks to accelerate biomedical discoveries and provide clinicians with new tools, knowledge, and therapies to select which treatments will work best for which patients,” beginning with a \$215 million investment from the President’s 2016 Budget in agencies, including FDA.<sup>34</sup>

Pharmacogenomics directly implicates the critical innovation the White House is aiming to promote; it is “an innovative approach to disease prevention and treatment that takes into account individual differences in people's genes . . .”<sup>35</sup> Pharmacogenomics “gives clinicians tools to better understand the complex mechanisms underlying a patient's health, disease, or condition, and to better predict which treatments will be most effective.”<sup>36</sup> The proposed regulation, however, would be at odds with the Initiative’s pro-innovation and patient-benefit goals by slowing or stopping the development of and discouraging the use of pharmacogenomics, one of the key fields for realization of the objectives. The proposed regulation would delay or halt progress toward each of these objectives (except for privacy protection).

First, the proposed regulation would delay the design and testing of effective, tailored treatments for cancer. The White House seeks to improve cancer treatments by expanding genetically based clinical cancer trials and developing a national “cancer knowledge network”<sup>37</sup> that generates and shares new knowledge to guide treatment decisions. But the proposed regulation, with its additional burdens, would discourage pharmacogenomic laboratories from conducting trials, including genetically based clinical cancer trials. Moreover, pharmacogenomic knowledgebases like PharmGKB have the potential to play a critical role in establishing the cancer knowledge network by contributing its treatment guides to such a database. The proposed regulation would inhibit pharmacogenomics from making this contribution.

---

<sup>33</sup> The White House, Office of the Press Secretary, FACT SHEET: President Obama’s Precision Medicine Initiative.

<sup>34</sup> *Id.*

<sup>35</sup> *Id.*

<sup>36</sup> *Id.*

<sup>37</sup> *Id.*

Second, the proposed regulation would hinder creation of a voluntary national research cohort that could fuel medical and scientific innovation. The project—a national, patient-powered research cohort of one million or more American volunteers—will collect necessary data to establish the platform of precision medicine: patients’ genetic profiles, metabolites (chemical makeup), and microorganisms in and on the body, among many others. Such efforts “will leverage existing research and clinical networks and build on innovative research models that enable patients to be active participants and partners.”<sup>38</sup> Pharmacogenomics is one of the existing research and clinical networks to be leveraged. By reducing the development and use of pharmacogenomics and stunting its development through unnecessary requirements and burdens, the proposed regulation would damage one of the most prominent resources for realization of this ambitious and beneficial project.

Third, the proposed regulation would conflict with the intended benefits of the planned regulatory modernization. The Initiative seeks to support the development of new research, and FDA will facilitate “generation of knowledge about which genetic changes are important to patient care . . . while ensuring that the tests are accurate and reliable”<sup>39</sup> by developing a new approach for evaluating Next Generation Sequencing technologies. The potential effects of the proposed regulation, however, would hamper development of and impede generation of knowledge from pharmacogenomics, whose accuracy and reliability are under active scientific evaluation for effectiveness, robustness, and cost.

Lastly, the proposed regulation would prevent the Administration from forging strong partnerships with existing research cohorts for testing pharmacogenomics. Burdens from the proposed regulation would discourage or prevent pharmacogenomics laboratories from contributing their resources, efforts, and knowledge to development of the infrastructure for expansion of cancer genomics and launching of the voluntary million-person cohort. Pharmacogenomics could be unnecessarily marginalized or excluded from establishment of the foundation.

The potential effects of the proposed regulation pose threats to valuable innovation generally, and specifically to the national priority of developing precision medicine. The disconnect between this Initiative and FDA guidance would create more uncertainty among laboratories and stakeholders in pharmacogenomics, hampering development, investment, and new efforts. We request that FDA carefully consider the full consequences of its proposed regulation and ensure that any revised guidance complement, rather than conflict with, the objectives of the Precision Medicine Initiative.

---

<sup>38</sup> *Id.*

<sup>39</sup> *Id.*

## V. The Pharmacogenomics Sector Has Already Established Reliable Guidelines that Address FDA’s Legitimate Concerns without Unnecessarily Burdening Innovation or Implementation

FDA should continue to exercise enforcement discretion over pharmacogenomics in light of the Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines that are written to consider and balance the safety and effectiveness of pharmacogenomic testing. An FDA partnership with CPIC would seem to be far preferable to the creation of redundant and cumbersome rules not specifically tailored to pharmacogenomics because FDA's proposed regulation does not confer any additional benefits over the *de facto* utility of CPIC guidelines. CPIC was established in 2009 through a collaboration between PharmGKB and NIH’s Pharmacogenomics Research Network (PGRN) to address the clinical implementation of pharmacogenetic information.<sup>40</sup> Upholding its goal of producing peer-reviewed and evidence-based guidelines, CPIC carefully established guidelines addressing how to interpret genotypes and use that information to alter prescription decisions. The guideline development process includes a rigorous review and grading of the relevant scientific literature; input of a writing committee composed of clinicians and basic researchers with expertise in the subject; formatting standards; and an extensive pre- and post-submission peer review approval process.<sup>41</sup> To ensure that the guidelines respond quickly to important new information, the guidelines are subject to a regular review and updating process.<sup>42</sup>

The resulting CPIC guidelines are rigorous and trustworthy standards that align with the Institute of Medicine (IOM)'s standards.<sup>43</sup> Even though adoption of CPIC guidelines is voluntary, medical and scientific professionals, including the American Society for Clinical Pharmacology and Therapeutics (ASCPT) and the American Society of Health Systems Pharmacists (ASHP), take the guidelines very seriously. The provisional acceptance of CPIC guidelines for “Practice Guideline” status in the ClinVar project of the National Center for Biotechnology Information (NCBI) of NIH indicates the professional societies’ strong support of the guidelines. The CPIC community has prioritized the evaluation and publication of guidelines for 174 genes/drugs.<sup>44</sup> These clear, curated, and peer-reviewed guidelines already address the quality and safety concerns that the proposed LDT regulation seeks to address, and do so in a way tailored to the unique goals and challenges of pharmacogenomics. Additional and burdensome regulation is therefore unnecessary. If more is needed, further integration of the CPIC process or a CPIC-style process would allow innovative pharmacogenomic research and

---

<sup>40</sup> Caudle, K.E., et al., Incorporation of Pharmacogenomics into Routine Clinical Practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) Guideline Development Process, *Curr. Drug. Metab.*, 15, 209, 209-17 (2014). PMID: 24479687.

<sup>41</sup> *Id.*

<sup>42</sup> *Id.*

<sup>43</sup> *Id.*

<sup>44</sup> The list is available at <http://www.pharmgkb.org/cpic/pairs>.

implementation to advance while not imposing burdens on it that are not needed for public or patient safety.

## **Conclusion**

In sum, we submit that FDA should continue to exercise enforcement discretion over pharmacogenomics, specifically with respect to the proposed risk-based classification system and the adverse event reporting system. Should the already-rigorous Clinical Laboratory Improvement Amendments (CLIA) regulations be deemed to be insufficient, pharmacogenomics should at most be regulated under a different, specifically tailored classification system that takes into account at least the following six factors for pharmacogenomics: (I) the level of evidence for any genetic information impacting drug prescribing decisions, (II) the expected magnitude of change in drug efficacy and side effect rates when using genetic information in prescribing, (III) the inherent risks and benefits of using the drug at baseline (without any pharmacogenomics information), (IV) the degree to which “bad” prescribing decisions can be recognized and reversed, (V) the risks of the underlying patient diagnosis and comorbidities, and (VI) the anticipated degree to which prescribers would depend on the genetic information (ranging from “total reliance” to “likely to be ignored”).

Although we endorse FDA’s efforts to ensure the safety and effectiveness of LDT services through its guidance, the current draft guidance compromises innovation in and public benefits flowing from pharmacogenomics. The guidance does not take account of the critical differences between pharmacogenomic testing and testing for disease risk. As a result, it would impose significant and unnecessary burdens on pharmacogenomic innovation and on pioneering laboratories and would undermine the objectives of the Precision Medicine Initiative. The CPIC guidelines already address safety, effectiveness, and reliability of pharmacogenomics.

We urge FDA to revise the proposed LDT guidance so that it serves its intended purposes of ensuring safety, effectiveness, and reliability to protect patient welfare, without stifling innovation in pharmacogenomics that could revolutionize precision medicine. By exercising continued enforcement discretion over pharmacogenomics or taking a tailored approach to pharmacogenomics regulation, FDA can achieve these important public safety goals while fostering innovation in this critical field.