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BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, Maryland 20852

CITIZEN PETITION

I. INTRODUCTION

Hyman, Phelps & McNamara, P.C. submits this Petition to the U.S. Food and Drug Administration (FDA or the agency) on behalf of the Coalition to Preserve Access to Pharmacogenomics (PGx) Information (Coalition or Petitioner) in accordance with 21 C.F.R. § 10.25(a) and § 10.30. The Coalition is a group of diverse stakeholders committed to providing access to accurate information to health care providers about the impact of genetic variants on drug response (hereinafter "PGx" or "gene-drug association" information). Coalition members include laboratories providing PGx testing, companies that provide support to laboratories to enable testing, including software, and clinicians who utilize the PGx information to optimize therapies for their patients. The Coalition submits this Petition in response to recent unprecedented and unlawful actions taken by FDA to suppress communications by clinical laboratories and software providers about the role of PGx in the metabolism of, and response to, specific drugs.

On October 31, 2018, FDA issued a Safety Communication warning health care providers and consumers about alleged dangers associated with PGx tests.[1] The focus of the Safety Communication was "genetic tests with claims to predict how a person will respond to specific medications in cases where the relationship between genetic (DNA)

[1] FDA, *The FDA Warns Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications: FDA Safety Communication* (Oct. 31, 2018), https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-many-genetic-tests-unapproved-claims-predict-patient-response-specific [hereinafter "Safety Communication"].

variations and the medication's effects has not been determined" and "software programs that interpret genetic information from a separate source that claim to provide this same type of information." The Safety Communication asserted that "clinical evidence is not currently available . . . and, therefore, these claims are not supported for most medications." On November 1, 2018, the Center for Devices and Radiological Health (CDRH) and the Center for Drug Evaluation and Research issued a joint statement on the same topic.[2]

Concurrently, FDA engaged in private communications with a number of clinical laboratories in which the agency directed them to cease including information about specific medications in laboratory reports for PGx tests unless and until such tests have been authorized by FDA in the context of a premarket submission. FDA has also contacted software companies that provide services that facilitate laboratories in generating PGx reports. In these communications, FDA officials did not distinguish between medications whose FDA-approved labeling included information about PGx interactions and those that did not; rather, companies were directed to remove all drug information even if it was derived directly from FDA-approved drug labeling. Similarly, FDA directed laboratories that they could not inform health care providers of clinical guidelines relevant to a patient's genetic test results if such guidelines referenced the impact of such results on response to a specific medication. Nor did FDA officials, in these communications, identify a specific regulatory violation associated with communicating PGx information relevant to a patient's test results, even when requested to do so by the regulated entities.

On April 4, 2019, CDRH issued a Warning Letter to Inova Genomics Laboratory, which marketed PGx tests for predicting medication response and reducing negative side effects, after that laboratory apparently declined to make the requested changes to its test reports.[3] The Warning Letter stated that Inova's tests "pose significant public health concerns as inaccurate test results could impact the decision-making of healthcare providers and patients in ways that are seriously detrimental to patient health." In a news release about the Warning Letter, FDA stated that it is "unaware of any data establishing

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[2] FDA, Press Statement, *Jeffrey Shuren, M.D., J.D., director of the FDA's Center for Devices and Radiological Health and Janet Woodcock, M.D., director of the FDA's Center for Drug Evaluation and Research on agency's warning to consumers about genetic tests that claim to predict patients' responses to specific medications* (Nov. 1, 2018), https://www.fda.gov/news-events/press-announcements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md [hereinafter "FDA Statement"].

[3] FDA, Warning Letter to Inova Genomics Laboratory (Apr. 4, 2019), https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/inova-genomics-laboratory-577422-04042019.

that Inova's tests can help patients or health care providers make appropriate treatment decisions for the listed drugs."[4]

Subsequently, FDA contacted additional laboratories providing the results of PGx testing, or software used in PGx testing, and demanded that they discontinue communicating PGx interpretive information in test reports. FDA repeated these same demands in a face-to-face meeting with members of the Coalition and other companies that had been told they must stop offering PGx interpretive services.

On December 10, 2019, Timothy Stenzel, Director of the Office of In Vitro Diagnostics and Radiological Health within CDRH gave a presentation at a policy meeting of the Personalized Medicine Coalition regarding FDA's communications to laboratories offering PGx interpretation. Dr. Stenzel did not provide any new information about FDA's planned approach to PGx testing, but he recommended the formation of a "Collaborative Community" on the topic of PGx. However, Dr. Stenzel stated that the role of a Collaborative Community would be limited to discussing with and making recommendations to FDA about PGx, and would not be a mechanism to develop binding evidentiary standards for PGx. More important, the formation of a Collaborative Community process would not address the Coalition's immediate concern with FDA's restrictions on PGx testing that are in effect today.

For the reasons discussed herein, FDA's precipitous, unilateral, and non-transparent approach is unlawful and, moreover, poses a significant risk to public health by denying physicians access to truthful scientific information that can help them treat their patients. FDA's approach is also incompatible with the goals and principles of personalized medicine. FDA has publicly espoused the value of personalized medicine generally and PGx in particular.[5] FDA's repeated attacks on PGx, however, are incompatible with the goal of increased utilization of PGx data in clinical decision-making. FDA's prohibition on providing PGx information will have the perverse effect of stunting the growth of a discipline that FDA has acknowledged is vital to the practice of medicine in the 21st century. FDA should conduct any future policy development with full participation of stakeholders and consider the impact of preventing access to this

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[4] FDA, News Release, *FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications* (Apr. 4, 2019), https://www.fda.gov/news-events/press-announcements/fda-issues-warning-letter-genomics-lab-illegally-marketing-genetic-test-claims-predict-patients.

[5] *See, e.g.*, FDA, Table of Pharmacogenomic Biomarkers in Drug Labeling, https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling ("Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose.") (last visited Jan. 6, 2020).

important information by physicians and patients, including information that comes directly from FDA-approved drug labeling.

II. ACTIONS REQUESTED

Petitioner respectfully requests the following actions:

1. FDA should issue a revised Safety Communication clarifying that laboratories and software providers may communicate information about gene-drug interactions as part of genetic test reports to the extent such information is supported by adequate evidence and is not contraindicated by information in drug labels with PGx information.

2. As required by the First Amendment and the practice of medicine provision of the Federal Food, Drug, and Cosmetic Act (FDC Act), FDA should permit clinical laboratories to include medication-specific information in PGx test reports that is (1) included in FDA-approved drug labels or (2) that is supported by adequate evidence of PGx gene-drug associations without clearance or approval of a premarket submission.

3. FDA should conduct any future policy development related to PGx tests in compliance with the Administrative Procedure Act (APA), which allows for the participation of stakeholders through notice-and-comment rulemaking. FDA should also hold a public hearing before the Commissioner pursuant to 21 C.F.R Part 15, because this is a matter pending before FDA and a hearing is in the public interest.[6]

III. STATEMENT OF GROUNDS

A. FDA's Actions to Suppress Communications About PGx Testing Violate the Administrative Procedure Act.

i. FDA's Actions Have Circumvented the Requirements in Section 553 of the Administrative Procedure Act.

A fundamental principle of administrative law is that "new rules that work substantive changes in prior regulations are subject to the APA's [notice-and-comment] procedures."[7] Agencies may not use guidance or sub-regulatory documents to create new

[6] 21 C.F.R. § 15.1(a).

[7] *Sprint Corp. v. FCC*, 315 F.3d 369, 374 (D.C. Cir. 2003).

substantive changes to regulatory requirements.[8] In the case of PGx tests, FDA has made substantive changes to the law governing a category of laboratory-developed tests (LDTs) without first engaging in public notice-and-comment rulemaking; this improperly circumvents the requirements of the APA and renders the agency's actions void.

The Safety Communication and subsequent FDA Statement created duties and imposed obligations on the Coalition members that are not set out in a binding statute or regulation. Rather than following the notice-and-comment rulemaking procedure, FDA simply arrogated to itself the full authority to regulate PGx tests and to enforce penalties against entities that do not comply with the agency's new requirements. By going far beyond the plain language of the statute or any regulation addressing diagnostic tests, these two documents adopted new standards and made substantive changes that are impermissible.[9]

The absence of any compliance with Section 553 of the APA is vividly illustrated by FDA's choice to post the Safety Communication and FDA Statement without first engaging in any process with stakeholders. The impact of these pronouncements is substantive because they create new duties and obligations that are not contained in the FDC Act or existing regulations. They cannot be classified as interpretive rules because their purpose is not simply to clarify an existing regulatory term or requirement[10] or to interpret an ambiguous term in the existing statute or regulations.[11] Rather, their effect is to impose a wholly new substantive obligation, which FDA can accomplish only by following the requirements of Section 553.

ii. FDA's Decision Not to Apply LDT Enforcement Discretion to PGx Tests Violates the Administrative Procedure Act.

1. FDA Has Exercised LDT Enforcement Discretion in an Arbitrary and Capricious Manner.

FDA's actions with PGx tests are only the latest example of an approach to LDT oversight that is arbitrary and capricious in violation of Section 706(2) of the APA.

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8 *Christensen v. Harris Cty.*, 529 U.S. 576, 588 (2000).

9 *See, e.g., Syncor Int'l Corp. v. Shalala*, 127 F.3d 90, 95 (D.C. Cir. 1997) (FDA publication that it was regulating PET radiopharmaceuticals and would impose remedies for noncompliance was substantive but failed to comply with the APA).

10 *Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 99 (1995); *Elec. Privacy Info. Ctr. v. Dep't of Homeland Sec.*, 653 F.3d 1, 6-7 (D.C. Cir. 2011).

11 *See, e.g., Hoctor v. U.S. Dep't of Agric.*, 82 F.3d 165 (7th Cir. 1996).

FDA's approach to LDT oversight has, for decades, been marked by confusing, inconsistent, and contradictory pronouncements that has left laboratories, health care providers, and patients without clarity as to the agency's intentions. FDA maintains that LDTs fall under the agency's medical device authority but has never engaged in notice-and-comment rulemaking as would be required under Section 553. Nor has FDA issued any final guidance on point, while the agency has on more than one occasion issued draft LDT proposals and guidance documents only to abandon them mid-development.

Instead of a coherent regulatory approach, in the vast majority of cases, FDA has generally not enforced the requirements of the FDC Act under the rubric of "enforcement discretion." However, according to FDA, enforcement discretion is not an exemption from the agency's requirements but simply the agency's decision to "look the other way" on behavior that otherwise would be the basis for agency enforcement. In other words, the agency's official position is that clinical laboratories are device manufacturers and therefore serial, persistent lawbreakers. As such, they are subject to the imposition of civil and even criminal penalties and are absolved only by the agency's grace, which FDA may withdraw "when appropriate, such as *when the tests pose significant public health concerns*."[12]

This phrase captures the essence of FDA's arbitrary and capricious approach to LDTs. Determining whether or not something is "appropriate" necessarily requires decision-making. FDA does not provide any criteria for this exercise of broad discretion, nor has FDA ever articulated such criteria over these many years. The Safety Communication provides a single example: "significant public health concerns."[13] This phrase is vague and not a statutorily authorized basis for distinguishing this class of LDTs from the vast majority of LDTs against which the statute is not enforced.

The Supreme Court has cautioned that administrative agencies must give fair notice of prohibited conduct. It explained that "first, that regulated parties should know what is required of them so they may act accordingly; second, precision and guidance are necessary so that those enforcing the law do not act in an arbitrary or discriminatory way."[14] By failing to do so, FDA "invites arbitrary enforcement, which is antithetical to our system of criminal justice."[15] While federal agencies have some discretion to make

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12 Safety Communication, *supra* note 1 (emphasis added).

13 *Id.*, *supra* note 1.

14 *FCC v. Fox Television Stations, Inc.*, 132 S. Ct. 2307, 2317 (2012)

15 *United States v. Franck's Lab, Inc.*, 816 F. Supp. 2d 1209, 1255 (M.D. Fla. 2011). In this case, the court held that FDA was precluded from bringing enforcement action against a bulk compounder of animal medications after claiming for 70 years that state-licensed pharmacies were subject to enforcement discretion. (This case was vacated on appeal on joint motion of the

case-by-case determinations regarding enforcement, an agency cannot invoke the doctrine of enforcement discretion as a "magical incantation which automatically provides a shield for arbitrariness."[16]

FDA's disregard for process with respect to LDT oversight is the epitome of arbitrary and capricious agency behavior. FDA has repeatedly acknowledged the need for a comprehensive, prospective, "risk based" framework for LDTs. In 2014, FDA appeared poised to establish such framework, albeit through guidance rather than rulemaking. Two years later, however, FDA announced that it would not be finalizing the previously issued draft guidance documents, after the House Committee on Appropriations asked FDA to "suspend further efforts to finalize the LDT guidance and continue working with Congress to pass legislation that addresses a new pathway for regulation of LDTs in a transparent manner."[17]

Instead, in a "discussion paper" FDA announced it was not pursuing the draft guidance further "to give our congressional authorizing committees the opportunity to develop a legislative solution." The discussion paper further suggested that a possible approach to FDA oversight of LDTs would be to grandfather all existing LDTs and then begin applying the FDC Act in a prospective, phased approach. FDA's willingness to consider grandfathering for existing LDTs strongly signaled FDA's confidence of the basic safety and effectiveness of LDTs under the existing system of oversight based on the Clinical Laboratory Improvement Amendments (CLIA). As a consequence of these events, since late 2016, clinical laboratories have had every reason to believe that FDA would not regulate LDTs unless and until Congress issued new legislation.

2. FDA's PGx-Specific Actions Have Been Undertaken in an Arbitrary and Capricious Manner.

Once again, however, FDA threw into disarray the settled expectations of clinical laboratories and health care providers by releasing the Safety Communication and FDA Statement without warning and, moreover, by subsequently making demands on individual stakeholders that far exceeded the plain language of these documents.

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party. *United States v. Franck's Lab, Inc.,* No. 11-15350, 2012 U.S. App. LEXIS 27100 (11th Cir. Oct. 18, 2012)). While not precedential, this case nevertheless has persuasive value.

16 *Med. Comm. for Human Rights v. SEC,* 432 F.2d 659, 673 (D.C. Cir. 1970) (vacated on other grounds).

17 H.R. Rep. No. 114-531 at 72-73 (2016).

FDA's ostensible justification for imposing a ban on laboratory communications of gene-drug interactions to physicians is the need to protect patients from harm—both self-harm through unilateral changes to medication and physician-caused harm should doctors make incorrect prescribing decisions. As discussed below, this assertion is unfounded. Moreover, FDA's sudden assertion of possible harm cannot justify an *ad hoc* departure from basic requirements of administrative law.[18]

Furthermore, FDA has refused to disclose specific examples of harm from providing information about gene-drug interaction, even when stakeholders have expressly requested such information. When instructing laboratories to discontinue providing PGx report interpretations, FDA has refused to say whether the tests have been linked to an injury. If FDA in fact has concrete examples of harm caused to patients as a consequence of laboratories providing gene-drug information, then the agency has a duty to disclose them, just as FDA publicly discloses adverse events associated with other medical devices, as well as drugs. At a recent Personalized Medicine Coalition meeting in Boston, former FDA Commissioner Scott Gottlieb stated that FDA's actions were driven "by a view, among other things, that there was variable quality in terms of the [PGx] tests that were being promulgated." However, he immediately backed off of this statement and added, "there might have been variable quality; I won't make an assertion that there was."[19] The lack of concrete examples of harm suggests that the purported risks are entirely hypothetical.

FDA's hypothesis is itself subject to question given the countervailing data supporting the use of gene-drug information in many prescribing decisions. Nevertheless, FDA has ignored evidence of benefit and used hypothetical risks to establish a ban on all communications about gene-drug interactions (even for those expressly mentioned in approved drug labeling). The agency's arbitrary overreach is compounded by its inconsistent—indeed illogical—policy that, on the one hand, incorporates gene-drug associations in the labeling of hundreds of drugs and allows the use of PGx tests to identify genes but, on the other, threatens laboratories that communicate any information that would enable proper interpretation of the results of such tests.

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[18] *See, e.g.*, *Reuters, Ltd. v. FCC*, 781 F.2d 946, 950–51 (D.C. Cir. 1986) ("*[a]d hoc* departures from those rules, even to achieve laudable aims, cannot be sanctioned . . . for therein lies the seeds of destruction of the orderliness and predictability which are the hallmarks of lawful administrative action. Simply stated, rules are rules, and fidelity to the rules which have been properly promulgated, consistent with applicable statutory requirements, is required of those to whom Congress has entrusted the regulatory missions of modern life.")

[19] Turna Ray, *Employee Benefits Programs Share Early Experiences Implementing Genetic Testing*, GenomeWeb (Nov. 15, 2019).

It is well established that internally inconsistent agency actions are inherently arbitrary.[20] FDA's current stance towards PGx tests falls well short of the obligation that FDA provide a reasoned basis for any change in policy and explain why the policy is permissible under the statute.[21] FDA's refusal – or inability – to provide a reasoned justification for its abrupt change in policy is a further basis for concluding that the agency has acted in an arbitrary and capricious manner.

The lack of prior notice and absence of an evidence-based rationale in the context of PGx tests foreseeably may adversely affect the development of other important LDTs. As FDA has acknowledged, LDTs "are important to the continued development of personalized medicine."[22] Laboratories have developed numerous LDTs to meet clinical needs in reliance upon FDA's expressed policy that it would exercise enforcement discretion. At the time FDA proposed "grandfathering" as a possible approach to the regulation of LDTs, multiple PGx tests, including tests offered by Coalition members, were already available. Nothing in the LDT discussion paper (described above in Section III.A.ii.1.) suggested that FDA would single out PGx from all the types of LDTs during the pendency of legislation; rather, the implication of the discussion paper is quite the opposite. Yet, FDA is now enforcing the FDC Act against PGx tests, a prime example of novel LDT technologies, without waiting for the legislation FDA has stated it needed.[23] FDA's precipitous ban of one application of LDTs based on a generalized claim of risk creates regulatory unpredictability and may well have a chilling effect on the development of new LDTs that play a clinically important role.

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20 *ANR Storage Co. v. FERC*, 904 F.3d 1020, 1024 (D.C. Cir. 2018) (and citations therein).

21 *See, e.g., FCC v. Fox Television Stations, Inc.*, 556 U.S. 502 (2009).

22 FDA, Laboratory Developed Tests, https://www.fda.gov/medical-devices/vitro-diagnostics/laboratory-developed-tests (last visited Jan. 6, 2020).

23 *Franck's Lab*, 816 F. Supp. 2d at 1252 ("[t]he FDA promised that it would publish new guidance, then it didn't").

B. FDA Has Effectively Banned Clinical Laboratories From Providing Physicians with Truthful, Non-misleading Scientific Information that Could Benefit Their Patients, to the Detriment of Patients and in Violation of the First Amendment.

i. Providing Physicians with PGx Information That is Consistent With FDA-Approved Labeling Benefits Patients.

FDA has repeatedly acknowledged that LDTs generally, and PGx information specifically, are important to the continued development of personalized medicine. For example, a prominently placed statement on FDA's website reads: "Pharmacogenomics can play an important role in identifying responders and non-responders to medications, avoiding adverse events, and optimizing drug dose."[24] Additionally, in the Office of In Vitro Diagnostics and Radiological Health (Office of Health Technology 7), CDRH has established a Personalized Medicine branch.[25] FDA officials have also written and spoken about the value of personalized medicine.[26]

As noted by FDA, the goal of personalized medicine "is to target the right treatments to the right patients at the right time."[27] There are hundreds of FDA-approved drugs with gene-drug associations included in the Prescribing Information. There are currently 385 such drugs listed in FDA's Table of Pharmacogenomic Biomarkers in Drug Labeling.[28] These drugs cover a wide array of therapeutic areas, including oncology,

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[24] FDA, Table of Pharmacogenomic Biomarkers in Drug Labeling, https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling (last visited Jan. 9, 2020).

[25] FDA, CDRH Management Directory by Organization, https://www.fda.gov/about-fda/cdrh-offices/cdrh-management-directory-organization (Office of Product Evaluation and Quality; Office of Health Technology 7); *see also* FDA, In Vitro Diagnostics, https://www.fda.gov/medical-devices/products-and-medical-procedures/vitro-diagnostics ("In vitro diagnostics may also be used in precision medicine to identify patients who are likely to benefit from specific treatments of therapies.").

[26] *See, e.g.*, J. Woodcock & P. Marks, *Drug Regulation in the Era of Individualized Therapies*, 381(17) NEJM 1678 (Oct. 9, 2019); R. Nagourney, *Every Cancer Patient is One in a Billion*, Wall Street J. (July 22, 2019); Scott Gottlieb, Speech, *Leveraging Innovation for the Treatment of Cancer* (Apr. 12, 2018); FDA, Report, Paving the Way for Personalized Medicine: FDA's Role in a New Era of Medical Product Development (Oct. 2013).

[27] FDA, Precision Medicine, https://www.fda.gov/medical-devices/vitro-diagnostics/precision-medicine (last visited Jan. 9, 2020).

[28] FDA, Table of Pharmacogenomic Biomarkers in Drug Labeling, https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-

infectious disease, neurology, psychiatry, pulmonary, anesthesiology, gastroenterology, hematology, rheumatology, cardiology, and inborn errors of metabolism.

FDA-approved drug labeling includes information about the effect of genetic variants on the metabolism of drugs and increased risk of adverse events, including risks that rise to the level of a black box warning. An example of a drug with important gene-drug safety information in the approved labeling is Tegretol (carbamazepine). Tegretol has a black box warning about "serious and sometimes fatal" dermatologic reactions in patients with the HLA-B*15:02 allele. However, in private, verbal communications, FDA directed clinical laboratories to cease providing any information referencing specific medications, including information in FDA-approved drug labeling.

Furthermore, although drug labeling is essential to accurate prescribing, it is not sufficient to provide timely access to new information. The PGx field is constantly evolving, as new research is conducted.[29] Drug labels lag behind the current state of knowledge. Once a drug is approved, the contents of the drug label are rarely updated to reflect new knowledge. For example, the most recent update to the citalopram labeling that included PGx information was in 2011. The labeling was most recently updated in January of this year, but despite significant information in literature between 2011 and January 2019 about ultrarapid metabolizer exposure, that information is still not included in the citalopram labeling. While providing information on drug labeling is necessary, it is not sufficient to provide timely access to new information.

In contrast, clinical laboratories have the tools and resources to remain up-to-date on current PGx research and to transmit that information. Individual physicians do not. As stated by the Association for Molecular Pathology: "As the prevalence of pharmocogenetic testing continues to increase, so will the need for laboratory professionals to translate genetic laboratory results to healthcare providers who make prescribing decisions for patient care."[30] PGx laboratories and software providers play a crucial role in providing access to important PGx information. Furthermore, there are reliable sources of current PGx information beyond FDA-approved drug-labeling, such as the National Institutes of Health (NIH)-supported Clinical Pharmacogenetics Implementation Consortium (CPIC).[31] Yet FDA's PGx policy blocks clinical

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labeling (last visited Jan. 9, 2020).

29 *See* J. Kevin Hicks et al., *Precision Pharmacotherapy: Integrating Pharmacogenomics Into Clinical Pharmacy Practice*, 2 J. Am. Coll. Clin. Pharm. 303, 310 (2019).

30 Association for Molecular Pathology, *Position Statement: Best Practices for Clinical Pharmacogenomic Testing*, 1 (Sept. 4, 2019), https://www.amp.org/AMP/assets/File/position-statements/2019/Best_Practices_for_PGx_9_4_2019.pdf?pass=96.

31 *See* CPIC, https://cpicpgx.org/ ("CPIC guidelines follow standardized formats, include systematic grading of evidence and clinical recommendations, use standardized terminology, are peer-

laboratories from providing information about well-known gene-drug associations that are supported by literature, academic consortia, treatment guidelines, or other authoritative sources of clinically relevant information.

Without the ability to reference specific medications in PGx test reports, the test reports are limited to the listing of genetic variants and do not provide additional information to clinicians to aid in the translation of test results to clinical care. Listing gene variant information in a laboratory report, but withholding other important information about the potential impact of those variants on response to specific medications (e.g., increased risk of serious adverse events), is of limited value to the physician. The failure to provide necessary contextual information about the implications of the PGx results for a patient is inconsistent with the responsibilities of clinical laboratory directors because, as explained below, the CLIA regulations require directors to ensure that pertinent information required for clinical interpretation of the results is included in test reports.[32]

Contrary to FDA's assertion that PGx information reduces patient safety and presents risks,[33] the converse is actually true. PGx information can help doctors avoid multiple risks, such as decreased or elevated serum drug levels, QT prolongation, serious skin reactions, weight gain, and undesired metabolic changes. This information appears in FDA-approved drug labeling. Thus, there cannot be any questions about its accuracy. FDA will not permit information to appear in drug labeling unless it is accurate.[34]

The practical effect of precluding laboratories from providing PGx information is that it makes it vastly harder for physicians to use this information in caring for patients. FDA has said that the ban on PGx information is needed to address safety concerns. When asked to identify those safety issues or provide examples, FDA has demurred or provided dubious examples.[35] In fact, blocking providers from accessing this information is much more likely to cause harm than allowing doctors to get access to truthful, non-misleading information.

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reviewed, and are published in a leading journal (in partnership with Clinical Pharmacology and Therapeutics) with simultaneous posting to cpicpgx.org, where they are regularly updated.").

32 42 C.F.R. § 493.1291.

33 *See* FDA Statement, *supra* note 2.

34 21 C.F.R. § 201.56(a)(2).

35 *See also* Association for Molecular Pathology, *Facts FDA Ignored: An Analysis of the FDA Report, "The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies"* (Dec. 13, 2015).

For example, a physician who is not well-versed in PGx and who receives a laboratory report disclosing only that a patient is a carrier of HLA-B*15:02, without further context, may not appreciate that the patient has a high risk of developing a potentially fatal reaction to the drugs carbamezapine and phenytoin. Prohibiting clinical laboratories from communicating such information as part of the test report increases the likelihood that the physician (or another physician to whom the patient is referred) will prescribe one of these drugs and thereby place the patient at a risk that could easily have been avoided. The prohibition also interferes with the clinical laboratory's responsibilities under CLIA to give health care providers information sufficient to allow them to interpret the clinical significance of the test results.[36]

Most physicians and other health care professionals do not have the time and resources to review each genetic variant result and then compare it against all relevant individual drug labels, not to mention conducting research to find relevant PGx information from literature and clinical guidelines. Furthermore, physicians are not reimbursed for that activity. Nor do many physicians have the knowledge or expertise to do the research or interpret the results. In sharp contrast, the Coalition's members enable physicians to easily review and understand the relevant PGx information.

By making it more difficult for physicians to access this important information, FDA's actions have the effect of disproportionately hampering access to underserved patients. Patients who have access to specialists or treatment at well-funded academic research centers are more likely to have a physician, or a team of physicians, with the resources to research potential gene-drug interactions. Patients who only have access to generalists or family medicine doctors, or who receive treatment in rural or under-funded facilities, are unlikely to have a physician with the time, expertise, and resources to research PGx information. The benefits of PGx insights should be available to everyone, not just the limited set of patients who have access to major research institutions.

As noted above, there are currently 385 drugs that have PGx information in their labeling. FDA's policy blocks doctors from getting meaningful access to that information. Beyond that, FDA is also blocking access to newer, scientifically valid information that is of critical significance to the well-being of patients.

Several patient advocacy, academic, and industry groups have expressed their concerns about the detrimental impact of FDA's policy. On September 18, the American

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[36] The College of American Pathologists (CAP) also has specific checklist requirements with regard to clinical interpretation. *See, e.g.*, CAP Accreditation Program, Molecular Pathology Checklist (Aug. 2017), http://elss.cap.org/elss/ShowProperty?nodePath=/UCMCON/Contribution%20Folders/DctmContent/education/OnlineCourseContent/2017/LAP-TLTM/checklists/cl-mol.pdf.

Clinical Laboratory Association (ACLA) sent a letter to HHS and FDA.[37] The letter states that "ACLA is deeply concerned about FDA's actions, which will have the practical effect of taking away actionable information relied upon by health care professionals every day to make informed prescribing decisions."[38] ACLA describes the practical effects of FDA's actions as follows:

> Without necessary context about the relationship of genetic variants to specific drugs, prescribers and patients are left without clinically vital information. Patients whose genetic makeup indicates that a specific drug will be effective – or will cause an adverse reaction – will be directly and immediately harmed by FDA's actions. Furthermore, FDA compounds the harm by requiring laboratories to withhold information even about drug classes, which can guide a physician towards or away from a broad group of drugs that will help or harm the patient. What FDA is doing will result in more patients getting a less effective or the wrong medication, with negative consequences for patient care and health care costs.[39]

FDA's actions will have adverse repercussions in a variety of disciplines. For example, it is hampering the treatment of depression. The suicide rate among adolescents aged 10 to 24 years old has increased 56% between 2007 and 2017, so this is a time when FDA should prioritize increasing access to information that could lead to better prescribing, not block that information.[40] Experts in the academic community have stated that "[d]ecades of research have established associations between genetic variation and drug response phenotypes, with evidence sufficiently strong for some antidepressant gene-drug pairs to warrant consideration of translation into clinical practice."[41]

On September 25, a group of four mental health advocacy organizations sent a letter to FDA and the U.S. Department of Health and Human Services (HHS).[42] The

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37 Letter to HHS and FDA from ACLA (Sept. 18, 2019), https://www.acla.com/wp-content/uploads/2019/09/ACLA-Letter-to-FDA-re_-PGx-Test-Policy-Sept-18-2019.pdf.

38 *Id.* at 1.

39 *Id.* at 2-3.

40 Brianna Abbott, *Youth Suicide Up 56% in Decade*, Wall Street J., at A3 (Oct. 17, 2019).

41 J. Kevin Hicks et al., *A Call for Clear and Consistent Communications Regarding the Role of Pharmacogenetics in Antidepressant Pharmacotherapy*, Perspectives, 107(1) Clin. Pharm. & Thera. 50 (2019); *see also* Fran Lowry, *Genetic Testing May Help Identify Best Antidepressant*, MedScape (June 6, 2019), https://www.medscape.com/viewarticle/914010?src=WNL_infoc_191119_MSCPEDIT_TEMP2&uac=33981DT&impID=2166851&faf=1.

42 Letter to HHS and FDA from the National Alliance on Mental Illness, National Council for Behavioral Health, Depression and Bipolar Support Alliance, and Mental Health America (Sept.

letter states that these organizations are "troubled by how this policy change will impede the ability of psychiatrists and other front-line health care professionals to personalize medication decisions to most effectively treat patients with Major Depressive Disorder (MDD)."[43] The letter further states that "[c]linical studies have shown that physicians using genetic information as part of the treatment decision process are seeing more patients achieve remission than treatment as usual," and "FDA actions against laboratories offering pharmacogenomic testing will cause a dramatic scientific and clinical setback for the treatment of mental illness."[44]

During meetings, FDA has stated that there is no adverse effect because physicians can use the results of genetic testing to independently research whether a particular variant may have an impact on a drug that a doctor is considering prescribing. Howard McLeod, medical director of Moffitt Cancer Center's personalized medicine institute, stated: "The lab reports no longer give adequate guidance, [and] that's resulting in physicians having to rely on Google to make recommendations."[45] Forcing doctors to rely on Google for their PGx information is wholly unrealistic, impracticable, and less safe for patients.

ii. FDA's Actions Impermissibly Encroach on the Practice of Medicine.

The FDC Act states it must not be "construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease within a legitimate health care practitioner-patient relationship."[46] In clear contravention of this provision, FDA is interfering with the authority of a health care practitioner to prescribe and administer PGx tests within a legitimate health care practitioner-patient relationship.

Clinical laboratory directors and licensed health care practitioners employed by clinical laboratories have a duty under the CLIA regulations and/or applicable state practice of medicine laws to provide information regarding potential safety concerns. For example, pursuant to CLIA, one of the enumerated responsibilities of a laboratory director is to "[e]nsure that reports of test results include pertinent information required

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25, 2019), https://www.politico.com/f/?id=0000016d-6eda-d9fa-a36f-eedacfea0000.

43 *Id.* at 1.

44 *Id.* at 2.

45 Turna Ray, *New Coalition, Stakeholder Groups Push Back Against FDA 'Backdoor' Attempts to Regulate PGx Tests*, GenomeWeb (Oct. 11, 2019).

46 21 U.S.C. § 396.

for interpretation."[47] A laboratory director may determine that information about known gene-drug interactions that will have a direct impact on patient safety is essential to the interpretation of genetic testing results and must be included in a test report to comply with CLIA. However, the laboratory director cannot provide this information under FDA's PGx policy.

Similarly, clinical laboratories frequently employ physicians and other health care providers to consult with patients and other health care providers about test results. Licensed health care providers have certain duties under state practice of medicine laws to provide information to patients to protect patient safety. FDA's directive to withhold information about specific medications conflicts with the responsibility of a licensed provider to, for example, inform a patient that his/her medication may be unsafe due to the presence of a genetic variant.

iii. The Prohibition on Providing Truthful and Non-Misleading PGx Information is Contrary to the First Amendment.

FDA's prohibition on the provision of PGx information relating to specific gene-drug interactions implicates significant First Amendment concerns. Specifically, through threat of undefined "compliance action," FDA is chilling the lawful commercial speech of clinical laboratories seeking to provide truthful and non-misleading information about gene-drug associations. Some of this information comes directly from the FDA-approved drug labeling, while other information is fully consistent with but more current than the drug labeling.

FDA-approved drug labeling is already freely and publicly available to physicians and the public at large. FDA has told Coalition members that doctors can look this information up by themselves. To prevent laboratories from providing the same data is to restrict the free flow of information based on the status of the speaker, which is prohibited by the First Amendment.[48]

Furthermore, by prohibiting clinical laboratories from providing information that is consistent with the approved drug labeling but that also reflects clinical guidelines and other authoritative sources of information developed post-approval, FDA is actively suppressing the free flow of information that could be of benefit to physicians. FDA is effectively asserting that, to be truthful and non-misleading, claims about gene-drug

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47 42 C.F.R. §§ 493.1407(e)(8); 493.1445(e)(8).

48 *Citizens United v. FEC*, 558 U.S. 310, 394 (2010) (Stevens, J., dissenting) (the government's reliance on the speaker's identity is "[t]he basic premise underlying the Court's ruling").

associations must first be reviewed and approved by FDA. Ironically, as noted above, many such gene-drug associations have already been reviewed and approved by FDA. The consequence of FDA's position is to hinder physicians from obtaining information that could be clinically relevant to their patients. As FDA well knows, the content of drug labeling is controlled by the New Drug Application (NDA) holder, and there can be significant lag time between the emergence of new gene-drug information and the submission of a supplemental application to update the labeling – or the labeling may never be updated. Clinical laboratories bridge this gap and serve an important role in physician education when they include clinically valid information derived from authoritative sources in the laboratory report.

FDA's efforts to restrict the flow of scientifically valuable, truthful, and accurate information clearly violates established commercial speech jurisprudence as it applies to the dissemination of scientific information.

Whether the government may restrict commercial speech requires consideration of four factors articulated by the Supreme Court nearly 40 years ago, namely: (1) whether the speech concerns a lawful activity and is not misleading, (2) whether the government's interest is substantial, (3) whether the restriction directly and materially serves the asserted interest, and (4) whether the restriction is no more extensive than necessary.[49] FDA, as the party seeking to uphold a restriction on commercial speech, carries the burden of justifying its implementation.[50]

FDA's ban on the provision of information about gene-drug associations cannot pass this test. To the extent FDA's comprehensive ban on sharing any gene-drug information is motivated by concern about "bad actors," FDA's remedy is grossly overbroad. Moreover, in seeking to avoid one potential risk, FDA has created the certainty of an even greater one, i.e., the risk that physicians will not learn of clinically relevant information that could result in more targeted drug prescribing and dosing decisions. Banning all clinical laboratories from communicating information that is identical to or consistent with FDA-approved drug labels is far more extensive than necessary to address the "bad actor" concern.

Furthermore, to the extent FDA seeks to prohibit clinical laboratories from informing physicians about accurate, well-supported PGx information contained in published scientific literature and/or clinical guidelines solely because such information is not contained within the four corners of the approved drug labeling, FDA once again

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[49] *Cent. Hudson Gas & Elec. Corp. v. Pub. Serv. Comm'n,* 447 U.S. 557, 557 (1980).

[50] *Thompson v. W. States Med. Ctr.,* 535 U.S. 357 (2002).

"exaggerates its overall place in the universe."[51] FDA appears to take the position that PGx claims "are presumptively untruthful or misleading until the FDA has had the opportunity to evaluate them."[52] This position "'paternalistically' interferes with the ability of physicians and patients to receive potentially relevant treatment information."[53] Creating such barriers inhibits the ability of physicians to make "informed and intelligent treatment decisions," to the public's detriment.[54]

IV. CONCLUSION

For the above reasons, we respectfully urge FDA to issue a statement clarifying the original Safety Communication so as to permit clinical laboratories to include in PGx test reports medication-specific information that is included in FDA-approved drug labeling or that is supported by adequate evidence and is not inconsistent with FDA-approved drug labeling. Further, we urge that FDA conduct any future policy development related to PGx tests in compliance with the APA, which allows for the participation of stakeholders through notice-and-comment rulemaking; and hold a public hearing before the Commissioner pursuant to 21 C.F.R Part 15.

V. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.30(h).

VI. ECONOMIC IMPACT STATEMENT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

VII. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner that are unfavorable to the Petition.

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51 *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998).

52 *Id.*

53 *United States v. Caronia*, 703 F.3d 149, 166 (2d Cir. 2012).

54 *Id.*

Sincerely,

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