



ASSOCIATION FOR MOLECULAR PATHOLOGY

Education. Innovation & Improved Patient Care. Advocacy.

6120 Executive Blvd., Suite 700, Rockville, MD 20852

Tel: 301-634-7939 | Fax: 301-634-7995 | amp@amp.org | www.amp.org

May 4, 2020

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

Re: Docket No. FDA-2020-P-0152, Citizen Petition from Hyman, Phelps & McNamara, P.C. on behalf of Coalition to Preserve Access to PGx Information

Submitted electronically via [regulations.gov](https://www.regulations.gov)

To Whom It May Concern:

The Association for Molecular Pathology (AMP), offers these comments in response to the Citizen Petition from Hyman, Phelps & McNamara, P.C. on behalf of the Coalition to Preserve Access to Pharmacogenomics (PGx) Information. AMP is an international medical and professional association representing approximately 2,500 physicians, doctoral scientists, and medical technologists who perform or are involved with laboratory testing based on knowledge derived from molecular biology, genetics, and genomics. Membership includes professionals from academic medicine, hospital-based and private clinical laboratories, the government and the in vitro diagnostics industry.

We are pleased that the Coalition to Preserve Access to PGx Information is bringing much needed attention to the recent actions of the Food and Drug Administration (FDA) to “suppress communications by clinical laboratories and software providers about the role of PGx in the metabolism of, and response to, specific drugs.”¹ Many AMP professionals, using their education, training, and clinical experience, work as part of a medical team to provide information about the role of a person’s genetic makeup in predicting the likelihood of medication response and/or risk for adverse medication reactions. This information can often be critical in nature and it is imperative that those receiving it understand the test result’s implications and limitations. Our concerns about the recent FDA actions to disrupt the transmission of test interpretation information to treating healthcare providers and their patients are outlined below, including specific recommendations to remedy these concerning actions that have the potential to jeopardize patient safety.

1. FDA’s Recent Actions Infringe on the Practice of Medicine

a. Molecular Professional Qualifications

¹ <https://www.regulations.gov/contentStreamer?documentId=FDA-2020-P-0152-0001&attachmentNumber=1&contentType=pdf>

Molecular pathology physicians and doctoral professionals are qualified to offer their interpretative services because they have completed extensive post-graduate education and clinical training, and have mastered certification examinations administered by professional boards, such as the American Board of Pathology or the American Board of Medical Genetics and Genomics under the umbrella of the Accreditation Council for Graduate Medical Education, to demonstrate their expert knowledge. They also continue to maintain their certification as required. Moreover, part of molecular pathology professionals' medical practice involves using their education and training to evaluate scientific evidence in support of the clinical validity of molecular testing, including claims of gene-drug interactions relevant to pharmacogenetic testing. Communicating information about the clinical relevance of a genotype is a professional service of molecular pathology physicians and doctoral professionals. Preventing laboratories from performing this professional service prevents the very individuals that are specifically trained to understand the implications of that information from having a key role in a patient's medical care.

b. Inclusion of Clinical Interpretation in Molecular Pathology Test Reports

i. Requirements and Recommendations by Federal Agencies and Accrediting Bodies

In addition to performing and interpreting molecular tests, clinical laboratory directors are required by the Clinical Laboratory Improvement Amendments (CLIA) to ensure that pertinent information required for clinical interpretation of the results is included in the test reports². Additionally, the Center for Disease Control and Prevention (CDC) Morbidity and Mortality Weekly Report (MMWR) "Good Laboratory Practices for Molecular Genetic Testing for Heritable Diseases and Conditions" agrees that molecular genetic test reports must comply with the CLIA general test report requirements described above and should include information to ensure accurate understanding and interpretation of test results.³ The MMWR Good Practices document further recommends that test reports of molecular genetic testing for heritable conditions should contain "additional information to ensure accurate results interpretation, patient management, and, the ordering of any needed additional tests by persons receiving or using the test results". PGx tests assess a patient's genetic makeup, which is inherited and can be passed along to offspring. Therefore, PGx-related responses to medications are heritable; and the MMWR Good Practices document requires that interpretation for heritable conditions include the following:

"Laboratories should provide information on interpretation of test results in a clinically relevant manner that is relative to the purpose for the testing and should explain how technical limitations might affect the clinical use of the test results. When appropriate and necessary, test results can be explained in reference to family members (e.g., mutations previously detected in a family member that was used for selection of the test method) to ensure appropriate interpretation of results and understanding of their implications by the persons receiving or using the test result."

Additionally, in order for clinical laboratories to maintain their CLIA-certified status, they must comply with inspections by third party accreditors, such as the College of American Pathologists (CAP). The CAP Accreditation Program uses an extensive on-site inspection check-list with requirements for molecular pathology results reporting.⁴ During the inspection, laboratories provide a sampling of their molecular genetic test reporting

² CLIA - 42 CFR §493.1291 (e)

³ <https://www.cdc.gov/mmwr/preview/mmwrhtml/rr5806a1.htm>

⁴ <http://elss.cap.org/elss/ShowProperty?nodePath=/UCMCON/Contribution%20Folders/DctmContent/education/OnlineCourseContent/2017/LAP-TLTM/checklists/cl-mol.pdf>

policies and procedures, as well as a sampling of patient test reports for evaluation. The CAP Accreditation Program requires that molecular pathology reports include both analytic interpretation (the test result or the genotype) and clinical interpretation, when appropriate, and notes that “laboratory reports should be designed to convey patient results effectively to a non-expert physician.” CAP defines clinical interpretation as “reaching a conclusion about the implications of the result for the patient” and “may be stated in general terms, or may be based on specific knowledge of a patient’s situation.”

Laboratories engage in best practice by issuing molecular pathology reports that are compliant with CLIA regulations, CAP requirements, and the CDC’s recommendations. Unfortunately, recent FDA actions prevent such compliance and put clinical laboratory professionals in the untenable position of choosing between compliance with CMS regulations or avoiding punitive FDA actions. Recent FDA actions recommend restricting laboratory directors to include only the analytic interpretation, while withholding the crucial clinical interpretation. This restriction by FDA both prevents the results from being conveyed to a non-expert ordering physician, which might lead to patient harm, and prevents the laboratory director from providing molecular pathology reports at the level that is required by their accrediting body. Additionally, if a patient is harmed because the physician did not receive the proper interpretive information, clinical laboratorians may incur risk for malpractice for not following CLIA and CAP regulations and the standards of care established by professional organizations.

ii. AMP’s Best Practices for Clinical Pharmacogenomic Testing Statement

In 2019, we convened a group of members with expertise in PGx testing to examine the current environment of PGx testing and determined that clinically meaningful pharmacogenomic tests can improve patient care and professional practice⁵, provided the following conditions are met:

- All health-related pharmacogenomic claims must have well-established clinical validity.
- The pharmacogenomic testing provider must comply with the CLIA statute and regulations, as is required for all other clinical laboratory tests, including having documented analytical validity, a robust quality management system, and appropriately licensed or credentialed laboratory personnel.
- The pharmacogenomic test report should be comprehensible by healthcare providers without medical genetics or pharmacogenomics training and include the interpretation of the findings, the significance of the results, as well as the limitations of the test.
- AMP strongly recommends that patients should not change their treatment plan without first talking to their healthcare provider.

One key criterion we identified is the inclusion of information in the test report that is comprehensible by healthcare providers without medical genetics or pharmacogenomics training. The working group found that test report information should include a statement of the metabolizer status, a list of drugs for which responsiveness might be affected by the genotype, a generalized statement to alert healthcare providers when alternate dosage or drug treatment may be considered, and a list of resources that the healthcare provider can use to learn more about the genotyping result, the drug-gene association, and the best manner in which to incorporate the result into actionable decisions.

Our Best Practices in Clinical Pharmacogenomic Testing Statement has been extensively recognized by several professional organizations and laboratories within the PGx testing community. Regrettably, at a time when the PGx community is working to ensure that patients receive the highest quality of care from this emerging field,

⁵ <https://www.amp.org/PGxBestPracticesStatement/>

FDA is thwarting these activities. The Agency's actions directly impede molecular pathology professionals from practicing medicine, and threaten to reverse the positive progress in the PGx field.

Request: We reiterate the first request of the Citizen's Petition that 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 that such information is supported by adequate evidence and is not contraindicated by information in drug labels with PGx information. As per CMS regulations, laboratories are mandated to provide this clinical interpretation information in genetic test reports, which are approved by licensed laboratory professionals in order to care for their patients.

2. FDA Actions Disregard Well-Established Valid Clinical Evidence that Supports PGx Testing

In our Best Practice document, we recommend that the clinical evidence of gene-drug interactions should be supported by peer-reviewed literature, FDA-approved drug labels, and/or clinical practice guidelines, such as those created by Clinical Pharmacogenetics Implementation Consortium (CPIC). All of these resources can provide valuable information and should be available for use by a molecular pathology professional when constructing interpretative findings in a PGx testing report. Yet, FDA recent actions, including the release of their statement on PGx testing on February 20, 2020⁶, indicate that the Agency views none of these sources for scientific evidence as being adequate.

Moreover, the lack of information about which evidence FDA views as adequate for reporting on PGx findings, and the lack of reasoning behind its views and actions, is problematic for several reasons. Specifically, there are over 350 approved drugs with pharmacogenomic information in their labels.⁷ This information has been vetted by FDA, yet the Agency is preventing the appropriate communication of this information to healthcare providers and patients.

FDA's recent release of their new web-based resource, which aims to communicate their view of the current evidence on PGx associations, only causes more confusion. First, the information the new resource provides is incomplete and sometimes conflicts with the information on PGx biomarkers that are contained in drug labeling. Additionally, FDA states that this new resource is intended for "clinicians, patients, and test developers"⁸, but conversely notes that the table is not "intended to make an assessment on the safe and effective use of, or regulatory requirements for, tests that detect variants in the referenced genes, or to provide comprehensive information on the described gene-drug interactions."⁹ The lack of information about the significance of the table from a regulatory and clinical care perspective only compounds the problems associated with FDA taking enforcement actions without grounding its activities in clear policy positions.

FDA's current regulatory system frequently results in labels that can quickly become outdated as additional research is conducted by both industry and academic institutions, therefore molecular pathology professionals

⁶ <https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic>

⁷ <https://www.fda.gov/drugs/science-research-drugs/table-pharmacogenomic-biomarkers-drug-labeling>

⁸ <https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic>

⁹ <https://www.fda.gov/medical-devices/precision-medicine/table-pharmacogenetic-associations>

may employ other valid and important resources in order to ensure that their test result findings represent the most up-to-date scientific information that is relevant to patient care. We recognize CPIC as one such resource -- we endorsed CPIC's Term Standardization for Clinical Pharmacogenetics Test Results Project¹⁰ and encouraged the use of CPIC's gene-drug practice guidelines in our Best Practices document. Yet, through its statements and actions, FDA has essentially communicated to the public that such professional evidence-based guidelines on PGx are not sufficient to demonstrate clinical validity. Professional guidelines are an essential part of the rigorously reviewed information that healthcare providers factor in when making decisions that can impact patient care. FDA is setting a dangerous precedent by rejecting the merit of professional guidelines and their role in healthcare decision-making.

FDA actions undermine the expertise of molecular pathology professionals and create mistrust in and devalue the information they communicate to healthcare providers. In addition, these regulatory actions erroneously suggest to the healthcare community that there is little evidence to support the use of PGx testing in patient care, and even more concerning, contradict FDA's mission to assure the safety of medical devices by placing patients' health in serious jeopardy. For example, specific variants in the *DPYD* gene, which encodes dihydropyrimidine dehydrogenase (DPD), can lead to DPD deficiency, resulting in severe 5-fluorouracil-associated toxicity and even death in some cancer patients.¹¹ If the implications of a positive test result for *DYPD* testing are not immediately clear with regards to how it might influence fluoropyrimidine treatment decisions, then this might lead to significant patient harm.

Request: We support and reiterate the second request of the Citizen's Petition that FDA should permit clinical laboratories to include medication-specific information in PGx test reports that is (1) included in FDA-approved drug labels and/or (2) that is supported by adequate evidence of PGx gene-drug associations without clearance or approval of a premarket submission.

3. FDA's Recent Actions Threaten Patient Safety

As the example above indicates, while FDA claims they are acting to prevent harm to patients, instead we find that FDA actions will likely lead to patient harm by preventing molecular pathology professionals from using their expertise to inform patient care. Another example of patients who could be harmed due to FDA's actions include those with specific variants in the *CYP2C19* gene which result in poor or intermediate metabolizer status that can lead to decreased clopidogrel efficacy. In fact, the FDA drug label for clopidogrel (Plavix) contains a warning about diminished antiplatelet activity in poor metabolizers, and further indicates that tests are available to identify patients who are *CYP2C19* poor metabolizers. For these patients, instead of clopidogrel, alternative drugs such as prasugrel (Effient™) or ticagrelor (Brilinta®) may be indicated.

In another example, the FDA drug label for carbamazepine (Tegretol) warns of serious and sometimes fatal dermatologic reactions that have a strong association with the presence of HLA-B*15:02, an inherited allelic variant of the HLA-B gene. The label recommends that patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*15:02 prior to initiating treatment with carbamazepine.

Moreover, FDA's actions hinder the translation of PGx evidence into clinical testing options, which prevents molecular pathology professionals from working to further improve patient care. Even more concerning, this threat to the public health was introduced by FDA without the Agency providing any evidence of the need for these actions, i.e. public harm as a result of the use of PGx testing.

¹⁰ <https://cpicpgx.org/endorsements/>

¹¹ https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/020896s036lbl.pdf

Request: We request that the FDA disclose any reported adverse events or specific examples of harm that have resulted from providing PGx report interpretations.

4. FDA's Recent Actions Are Unlawful

a. FDA's Actions Violate the Requirements of the Administrative Procedure Act

We agree with the Citizen Petition that FDA's actions are not in compliance with the Administrative Procedure Act (APA). We urge FDA to develop future policies impacting the development and marketing of PGx in vitro diagnostic kits via the notice and comment rule-making process. FDA should provide manufacturers the legal certainty and weight of regulations. Additionally, notice and comment rule-making would allow stakeholders, including our expert members, to provide constructive and informed feedback while giving FDA the opportunity to address the widespread concern regarding their enforcement actions.

b. FDA is Overstepping Its Authority on Laboratory Developed Testing Procedures

While we request that FDA develop any future policies impacting the development and marketing of manufactured PGx in vitro diagnostic kits via the notice and comment rule-making process, we maintain that any actions taken by FDA to regulate laboratory developed testing procedures (LDPs), including the PGx tests currently under consideration, should cease immediately. FDA's actions on PGx LDPs conflict with several indications from FDA leadership that FDA will work with Congress to find common ground regarding diagnostic regulation instead of pursuing the institution of a device-based framework on their own.¹² Additionally, House appropriators directed the Agency to work with Congress instead of executing their own plans to regulate LDPs.¹³ The recent FDA action directly contradicts these previous agreements and the Agency should instead continue to work with Congress on developing legislation on the matter.

We continue to advocate that the most efficient and cost-effective way to modernize the oversight of LDPs is through modernizing CLIA¹⁴ and the recent, inflammatory actions taken by FDA on PGx tests underscores our position. FDA's actions on PGx tests serve as an example of the Agency taking arbitrary actions against laboratories without clearly defining the problems it aims to solve in absence of a clear policy. For laboratories, especially in the academic sector, this has served as a chilling example of a potential future under FDA jurisdiction and the uncertainty they might face taking their tests through the regulatory process proposed in the discussion draft of the Verifying Accurate Leading-edge IVCT Development Act (VALID) of 2020.¹⁵ We are concerned that even if clear policy existed for FDA, FDA may regulate in an apparently capricious, opaque way similar to recent PGx activity. For example, VALID gives wide discretion to the Secretary, via the Special Rule, to revoke any exception set forth in VALID. The drastic changes allowed by this language create uncertainty and raise significant concerns. Thus, recent FDA actions have reignited grave concerns that FDA regulation of LDPs

¹² As examples: 1) <https://www.fda.gov/news-events/fda-voices-perspectives-fda-leadership-and-experts/fda-proposes-new-steps-advance-clinical-testing-deliver-new-cures>, 2) <https://www.congress.gov/115/chr/CHRG-115shrg25027/CHRG-115shrg25027.htm>, 3) and most recently <https://www.fda.gov/news-events/press-announcements/fda-announces-collaborative-review-scientific-evidence-support-associations-between-genetic>

¹³ <https://www.congress.gov/congressional-report/114th-congress/house-report/531/1>

¹⁴ http://www.amp.org/AMP/assets/File/advocacy/AMPCLIAmodernizationproposalFINAL8_14_15.pdf?pass=13

¹⁵ <https://www.congress.gov/bill/116th-congress/house-bill/6102/text?r=6&s=1>

will slow innovation, impede patient access to appropriate testing, and constrain flexibility and adaptability for laboratories.

Request: We reiterate the second request of the Citizen's Petition that 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 rule-making. 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.

Thank you for considering these comments in response to the submitted Citizen Petition. Once again, we fully support the requests made within the Citizen Petition and urge FDA to act swiftly to clarify that molecular pathology professionals may relay PGx information that is either included in FDA-approved drug labels or supported by adequate scientific evidence of PGx gene-drug associations without clearance or approval of a premarket submission. If we can provide additional information or if the Agency has any questions, please direct your correspondence to Tara Burke, AMP Senior Director of Public Policy and Advocacy, at tburke@amp.org.

Sincerely,

Karen E. Weck, MD, FCAP
President, Association for Molecular Pathology