FDA and pharmacogenomics

Guidances and information



Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products— Content and Format

Guidance for Industry

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

https://www.fda.gov/drugs/science-research-drugs/other-fda-resources-related-pharmacogenomics#FDAGuidances

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-public-human-genetic-variant-databases-support-clinical-validity-genetic-and-genomic-based-vitro

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pharmacogenetic-tests-and-genetic-tests-heritable-markers

FDA: recent activity



January 23, 2019

23andMe, Inc. Adam Odeh Regulatory Affairs Manager 899 W. Evelyn Ave., Mountain View, California 94041

Re: DEN180028

Trade/Device Name: 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports

Regulation Number: 21 CFR 862.3364

Regulation Name: Pharmacogenetic assessment system

Regulatory Class: Class II Product Code: QDJ Dated: June 4, 2018 Received: June 5, 2018

Dear Adam Odeh:

This letter corrects our letter dated October 31, 2018.

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your De Novo request for classification of the 23andMe Personal Genome Service (PGS) Pharmacogenetic Reports, an over-the-counter device with the following indications for use:

FDA authorizes first direct-to-consumer test for detecting genetic variants that may be associated with medication metabolism



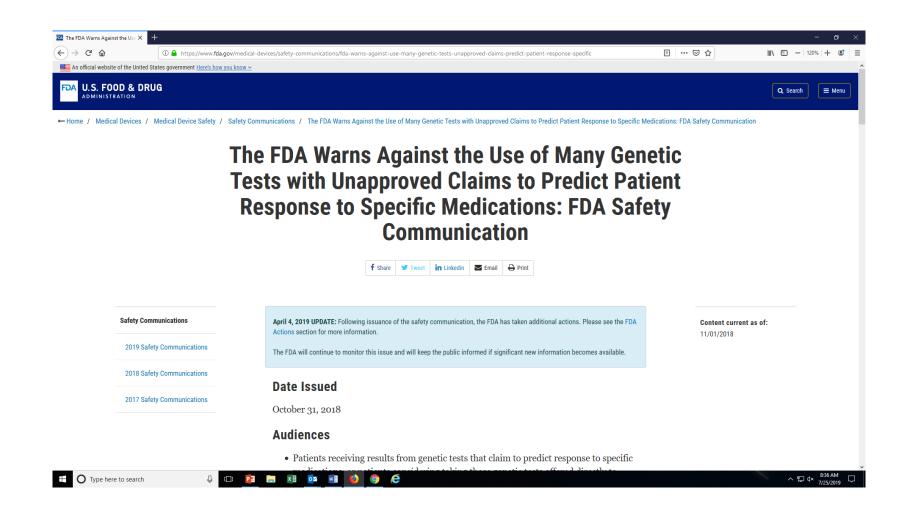
For Immediate Release: October 31, 2018

Nov 1, 2018

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

- https://www.fda.gov/news-events/press-announcements/jeffrey-shuren-md-jd-director-fdas-center-devices-and-radiological-health-and-janet-woodcock-md
- Safety communication on pgx tests "we note our concern about health care providers and patients inappropriately selecting or changing drug treatment based on the results from insufficiently substantiated genetic tests, which could lead to potentially serious health consequences for patients."
- "It is important to note that there are some drugs whose use can be aided by the results of pharmacogenetic information. In those cases, there is scientific evidence to support relationships between the genetic variant and how a patient responds to a drug, which has been reviewed by the FDA. The FDA-approved labeling for such a drug and genetic test provide health care providers with adequate information on how to use genetic information reported by the genetic test to manage medication treatment using the drug."
- "For example, the FDA has evaluated and authorized for marketing, tests that alert patients to drug metabolizing enzymes, such as for warfarin sensitivity. Another example is the direct-to-consumer genetic variant test authorized for marketing yesterday, which is intended to provide information regarding genetic variants that may play a role in the metabolism of some medicines. However, we have required that the test label make clear that it is not intended to provide information on a patient's ability to respond to any specific medication. Furthermore, health care providers should not use the test to make any treatment decisions, without additional testing. This application was granted with limited indications and is subject to special controls."

Oct 31, 2018



"Recommendations for Genetic Test Manufacturers and Developers Oct 31, 2018

- If your test claims to predict a patient's response to specific medications, confirm that the FDA-approved drug labels for medications included in your test labeling describe how genetic information can be used in determining therapeutic treatment. Know that information regarding therapeutic treatment recommendations for patients with certain genetic variations can be found in the warnings (Boxed Warning, or Warnings and Precautions), Indications and usage, Dosage and Administration, or Use in Specific Populations sections of the FDA approved drug labeling, as appropriate.
- Assure your test report and any labeling support an intended use that is consistent with the FDA-approved use of the medication.
- Contact the FDA if you have any questions about genetic tests that are intended to be used to direct use of specific medications."

FDA issues warning letter to genomics lab for illegally marketing genetic test that claims to predict patients' responses to specific medications

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For Immediate Release:	April 04 201	0			
For immediate Release.	April 04, 201	9			

"The FDA issued a warning letter to Inova for marketing pharmacogenetic tests that have not been reviewed by the FDA and that claim to predict patients' clinical responses to specific named drugs, including antidepressants, opioids, cancer treatments, anesthesia and diabetes medications. The FDA has not reviewed and is unaware of any data establishing that Inova's tests can help patients or health care providers use the listed drugs more safely or effectively. The warning letter requests that Inova respond.... Any violations not corrected could lead to enforcement action such as seizure, injunction or civil money penalties."

"Last year, the agency issued a safety communication warning consumers and health care professionals about pharmacogenetic tests being marketed directly to consumers or offered through health care providers that claim to predict how a patient will respond to specific medications."

"Following issuance of the safety communication, the FDA reached out to several firms marketing pharmacogenetic tests with claims to predict how a person will respond to specific medications in cases where the relationship between genetic (DNA) variations and the medication's effects has not been established. Most firms addressed the FDA's concerns by removing specific medication names from their labeling, including promotional material and patient test reports."

WARNING LETTER

Inova Genomics Laboratory

MARCS-CMS 577422 - APR 04, 2019

"FDA is concerned that the clinical validity[1] of your MediMap tests has not been established for their intended uses. Specifically, we are unaware of data establishing the relationships between the genotypes assessed by your tests and your assertions regarding drug response for multiple drugs. For example, the relationship between CYP2C19 genotype and drug response to escitalopram and sertraline is not established and this relationship is not described in the FDA-approved labeling for these drugs. "

"Based on the above, FDA has determined that the MediMap tests are adulterated under section 501(f)(1)(B) of the Act, 21 U.S.C. § 351(f)(1)(B), because your firm does not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, 21 U.S.C. § 360e(a), or an approved application for an investigational device exemption under section 520(g) of the Act, 21 U.S.C. § 360j(g). The MediMap tests are also misbranded under section 502(o) of the Act, 21 U.S.C. § 352(o), because your firm did not notify the Agency of its intent to introduce the devices into commercial distribution, as required by section 510(k) of the Act, 21 U.S.C. § 360(k). For a device requiring premarket approval, the notification required by section 510(k) is deemed satisfied when a PMA is pending before the Agency. (See 21 CFR 807.81(b)). ...The FDA will evaluate the information that your firm submits and decide whether the test may be legally marketed."



Business & Policy Technology Research Diagnostics Disease Areas Applied Markets Resources

Home » Business, Policy & Funding » Business News » Inova Decides to End PGx Test Offerings in Response to FDA Warning Letter

Inova Decides to End PGx Test Offerings in Response to FDA Warning Letter

Apr 15, 2019 | staff reporter

Save for later Save

This article has been updated with a statement from the Clinical Pharmacogenetics Implementation Consortium.

NEW YORK (GenomeWeb) – Inova Health System has decided to completely stop performing its suite of pharmacogenetic tests in response to a US Food and Drug Administration warning letter.

"After thoroughly reviewing the letter, which clarified the FDA's approach to laboratory developed tests (LDT) for pharmacogenomics, Inova has decided to end MediMap tests," an Inova spokesperson said in a statement.

https://pharmgkb.blogspot.com/search/label/cpic

MONDAY, APRIL 15, 2019

CYP2C19 testing may assist with prescribing sertraline and escitalopram

Mary Relling (St. Jude Children's Research Hospital) and I (Teri Klein) as Co-Principal Investigators of the Clinical Pharmacogenetics Implementation Consortium (CPIC) have been discussing the letter that the FDA recently sent to a genomics laboratory expressing concern that "providers may make inappropriate treatment decisions based" on pharmacogenetic testing offered by that lab. The FDA specifically highlighted that "the relationship between CYP2C19 genotype and drug response to escitalopram and sertraline is not established."

"While it is true that some pharmacogenomic testing laboratories may be including genetic variants in their tests, along with prescribing advice, that do not have adequate evidence for clinical utility, testing for variants in this particular gene does have utility for prescribing decisions for escitalopram and sertraline. In fact, CYP2C19 phenotypes are specifically included as actionable for these 2 drugs in CPIC's Guideline for SSRIs."

FDA Warning Letter to Inova Raises Questions About Agency Overreach Into Practice of Medicine

Apr 10, 2019 | Turna Ray

""To say there is no data when there is enough data for CPIC to issue guidelines is really disappointing," said (Howard) McLeod, who is widely recognized for his expertise in pharmacogenomics."

"It remains to be seen how the lab industry and pathologists groups historically opposed to FDA oversight of LDTs react to this language. The American Clinical Laboratory Association and the Association for Molecular Pathology declined to comment for this article."

"The FDA seems to be coming down squarely on the idea that it is within its domain to decide" what are "established" drug/gene relationships, observed Jeff Gibbs, a lawyer at Hyman, Phelps & McNamara .. "That is certainly something people can question in an area as fast moving as these drug/gene associations, and given the regulatory process, it can take a while before information makes it into drug labeling, if it ever does."

FDA Warning Letter to Inova Raises Questions About Agency Overreach Into Practice of Medicine

Apr 10, 2019 | Turna Ray

https://www.genomeweb.com/clinical-lab-management/fda-warning-letter-inova-raises-questions-about-agency-overreach-practice#.XTnCKEFOmUk

"What really got industry insiders worked up, however, is the agency's emphasis in the warning letter that FDA-approved drug labeling is the only source of "established" information on drug/gene relationships. Even when tests aren't approved by the FDA, labs can only make claims supported by FDA-approved labeling, the agency seems to be saying.

"In answers to questions for this article, the FDA elaborated that in its November safety alert it was warning doctors about pharmacogenetic tests without sufficient evidence of clinical validity, but not about FDA-approved or -cleared companion and complementary diagnostics. The agency considers these PGx tests to have sufficient data supporting their use in clinical decision making because it has reviewed the evidence on the underlying drug/gene relationships."

"During FDA review of tests intended to predict a patient's response to specific drugs, FDA reviews scientific and clinical data to determine if the provided data support the claims being made about the relationship of the test and the listed drug(s) such that the use of the test is consistent with the safe and effective use of the listed drug(s)," an agency spokesperson said over email. "FDA would consider the relationship between genetic variants detected by the test and a claim for predicting drug response of specific drugs established if it is demonstrated that the test is safe and effective for its intended use for each listed drug."

"As to whether guidelines from CPIC or another expert body can also be a source of "established" drug/gene relationships for doctors, the spokesperson said that the FDA "doesn't typically endorse consensus guidelines," but companies can use information in such guidelines as part of the data package they submit for test approval."

"The agency's reasoning in this regard reminded Gibbs of a 1999 Washington Legal Foundation lawsuit against the FDA, challenging its ability to restrict drugmakers from disseminating information regarding off-label or unapproved uses of FDA-approved drugs. A district court determined that the FDA's policy of barring drugmakers from sharing truthful information with doctors about off-label use of drugs was an unconstitutional restriction of commercial speech."

"I think people can go back and look at that Washington Legal Foundation case, and other subsequent First Amendment cases involving the FDA," Gibbs said. "I think that same kind of allegation could be made here since FDA is saying that only the agency can determine these drug/gene variant relationships and that CPIC or other authorities cannot.""

FDA feedback to All of Us; June, 2019

"As you are aware, FDA issued a safety communication in November 2018 regarding pharmacogenetic tests that claim to predict patients' responses to specific medications but do not have clinical evidence to support this use and may be inconsistent with the FDA approved drug labeling, which could adversely impact the safe use of the drug. Returning results that include pharmacogenetic associations for specific medications for which there is insufficient evidence to establish the relationship between the variants assessed by the test and the clinical interpretation provided present significant risks to study subjects.

In your pre-submission you state, "out of an abundance of concern that participants may change or stop drug regimens without consulting their healthcare provider, we will initially not include warfarin pharmacogenetics, as these results are difficult to appropriately interpret and apply even for trained professionals." We agree that results from pharmacogenetic tests for warfarin are difficult to appropriately interpret and apply even for trained professionals and providing these results directly to patients poses significant risks if the patient were to stop or change the dose of their medication without a physician's involvement; however, this is also true for the other drugs you propose to include in your test report.

For example, providing the proposed information for escitalopram, an antidepressant, directly to a patient, who may be severely depressed or psychotic poses significant risks to the patient since the results may lead to the patient abruptly ceasing their medication that would typically cause relapse of their condition, induce withdrawal symptoms, and incurs a significant risk of reduced effectiveness if the medication needs to be re-started."

FDA feedback to All of Us; June, 2019

"Furthermore, for most of the drugs you propose to include in your test report, the information you propose to provide to study participants is inconsistent with the FDA approved drug labeling and may not be supported by adequate clinical evidence.

For example, the relationship between CYP2C19 and clinical efficacy has not been established for any antidepressant and FDA has not reviewed any clinical data to support that variants in CYP2C19 may result in a lack of efficacy for antidepressants such as escitalopram and citalopram. In fact, you acknowledge this in your report by stating, "While the FDA labels for these medications acknowledge the role that genetics can have, the exact impact of genetic variations on drug response may not yet be completely understood."

In the absence of sufficient and supportive clinical data, we do not agree that it is reasonably safe to provide information that is inconsistent with the FDA approved drug labeling to study subjects and we are unable to identify any risk mitigations that would adequately mitigate these risks.

Therefore, if you intend to return pharmacogenetic assessments to study participants, information conveyed to study participants should be limited to drugs for which there is information in the FDA approved drug labeling that describes how genetic information can be used. Please keep in mind that a general description of drug metabolism or a difference in drug exposure due to enzyme inhibition is not sufficient to support that the relationship between DNA variation and drug response (e.g., increased adverse events) has been established. The information that is supportive of clinical validity for reporting pharmacogenetic associations for drug response should clearly describe the relationship between DNA variation and drug response. In the drug labeling, this type of information is typically included in the warnings, Indications and Usage, Dosage and Administration, or Use in Specific Populations, as appropriate.

It would not be appropriate to include drugs in your report for which there is an approved companion diagnostic that is essential for the safe and effective use of the medication."



Every patient deserves the GOLD STANDARD ...

Molecular Pathology Checklist

MOL.49615 Report Criteria

Phase II

At a level appropriate for the particular test, the report includes a discussion of the limitations of the findings and the clinical implications of the detected mutation (or negative result) for complex disorders with regard to recessive or dominant inheritance, recurrence risk, penetrance, severity and other aspects of genotype-phenotype correlation.

NOTE: Because of the complexity of genotype-phenotype correlations for many genetic diseases, simply reporting a molecular genetic test as positive for a mutation is not acceptable since it conveys no information to the referring physician and patient as to the clinical ramifications of the result. Since major and often irreversible surgical or obstetric interventions may be initiated based on the test result, it is essential that the report convey the most current and accurate understanding of penetrance and recurrence risks.

REFERENCES

 Clinical and Laboratory Standards Institute (CLSI). Establishing Molecular Testing in Clinical Laboratory Environments: CLSI document MM19-A (ISBN 1-56238-773-1). Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA. 2011.

http://webapps.cap.org/apps/docs/education/OnlineCourseContent/2014/TLTM/MOL04212014.PDF

GUIDANCE DOCUMENT

Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-Based In Vitro Diagnostics

Guidance for Stakeholders and Food and Drug Administration Staff

APRIL 2018

Download the Final Guidance Document

This guidance document describes one part of FDA's efforts to create a flexible and adaptive regulatory approach to the oversight of next generation sequencing (NGS)-based tests. The goal of this effort is to help ensure patients receive accurate, reliable, and clinically meaningful test results, while promoting innovation in test development. This guidance document describes how publicly accessible databases of human genetic variants can serve as sources of valid scientific evidence to support the clinical validity of genotype-phenotype relationships in FDA's regulatory review of both NGS-based tests and genetic and genomic tests based on other technologies. Publicly accessible genetic databases may be useful to support the clinical validity of NGS tests as well as single gene or panel tests that use other technology.

FDA takes new action to advance the development of reliable and beneficial genetic tests that can improve patient care



For Immediate Release: December 04, 2018

Genetic Database Recognition Decision Summary for

ClinGen Expert Curated Human Variant Data

Genetic Database Name: ClinGen Expert Curated Human Variant Data

Submission Number: Q181150

Summary of FDA Review to Support Recognition

The ClinGen Expert Curated Human Variant Data qualifies as a database per FDA's guidance document, "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-based In Vitro Diagnostics".

To support recognition of the Clinical Genome Resource (ClinGen) Expert Curated Human Variant Data, ClinGen submitted variant assertions and the evidence that supports them as well as the oversight and governance procedures for creating, maintaining, and expanding the currently available variant assertions within the scope described below. These assertions and procedures are publicly available. FDA evaluated whether these procedures provide reasonable assurance that the variant assertions made using the procedures are accurate and could be used as a source of valid scientific evidence in support of clinical validity of genetic and genomic-based tests in regulatory submissions. This evaluation was based upon whether ClinGen demonstrated conformance with the recommendations described in FDA's guidance document, "Use of Public Human Genetic Variant Databases to Support Clinical Validity for Genetic and Genomic-based In Vitro Diagnostics". Based upon the information reviewed, the FDA determined that the ClinGen Expert Curated Human Variant Data conforms to the recommendations described in the guidance. FDA's review of the information provided is described herein.

The FDA concludes that the ClinGen Expert Curated Human Variant Data procedures provide reasonable assurance that assertions from the database constitute valid scientific evidence that can be used to support clinical validity of genetic tests in future premarket submissions and therefore, FDA recognizes the ClinGen Expert Curated Human Variant Data for the scope described below.

Scope of Recognition

This recognition is for the ClinGen Expert Curated Human Variant Data variant classifications and the processes that support them for germline variants for hereditary disease where there is a high likelihood that the disease or condition will materialize given a deleterious variant (i.e., high penetrance).

Summary of Genetic Database Operations and Procedures to Support Recognition

ClinGen is a National Institutes of Health (NIH)-funded resource intended to aggregate, curate, and making publicly available information pertaining to the clinical significance of genotype-phenotype associations.



Documents & Announcements

FDA Recognizes ClinGen Assertions in ClinVar - Frequently Asked Questions

FDA Recognizes ClinGen Assertions in ClinVar - Frequently Asked Questions

What is the Clinical Genome Resource (ClinGen) and why is this U.S. Food & Drug Administration (FDA) recognition important?

ClinGen is a research initiative funded by National Institutes of Health (NIH) and managed by the National Human Genome Research Institute (NHGRI). We are dedicated to identifying genes and variants of clinical relevance for use in precision medicine and research. The purpose of the FDA Variant Database Program is to support an easier path for marketing clearance or approval for clinical gene test developers. The ClinGen Variant Curation Expert Panel (VCEP) curated variants are a resource of human variants that have been interpreted for their potential association with disease. Test developers can use expert variant interpretations from ClinGen to support clinical validity.

Date

February 1, 2019

Related Group