Warning Against the Use of Many Genetic Tests with Unapproved Claims to Predict Patient Response to Specific Medications (FDA Safety Communication)

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The Policy

Synopsis

The Food and Drug Administration (FDA) issued a warning on November 1, 2018, "against the use of many genetic tests with unapproved claims to predict patient response to specific medications." The warning, which was a collaboration between the FDA’s Center for Devices and Radiological Health and the Center for Drug Evaluation and Research, was announced via safety communication. The FDA noted that it has become aware of the growing presence of pharmacogenetic tests — tests that predict drug response in relation to specific genes. However, most of these tests have not been reviewed or approved by the FDA because “sufficient clinical evidence is not currently available.” The concerns are that consumers and/or health care providers will change medication, either type or dosage, based on results from these tests. Given the concern that most of these tests lack scientific grounding, this action might result in serious health consequences.

The FDA pointed out that there are a “limited number of cases” in which the FDA had cleared and approved labeling of genetic tests and medications as correlated. This occurs only when sufficient evidence supports a correlation between a genetic variant and drug levels within the body. In these cases, patients and health care providers can find description for “how to use genetic information and manage therapeutic treatment” in either the Warnings, Indications and Usage, Dosage and Administration or Use in Specific Populations sections of drug labels.

The warning repeatedly mentions that the "relationship between DNA variations and [a] medication’s effects [have] not been established" in most cases. As a result, patients and healthcare providers should be cautious when interpreting these reports. The FDA also urges consumers to report to MedWatch -- the FDA Safety Information and Adverse Event Reporting program -- if they experience a problem with a pharmacogenetic test.

Context

The FDA has the authority to regulate medical devices, including in vitro diagnostics (IVDs), which are "reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae.” Pharmacogenetic testing falls within the definition of IVDs, and thus are regulated by the FDA. Regulation on each IVD depends on the risk classification of the device. Currently, pharmacogenetic tests have been approved under the Class III classification, meaning that the device requires a premarket approval application (PMA). Currently approved IVDs can be found within the list of cleared or approved companion diagnostic devise on the FDA website.

The warning mentioned direct-to-consumer tests (DTC) which are IVDs "marketed directly to consumers without the involvement of a health care provider." Pharmacogenetic tests that are DTC could result in serious health consequences if consumers either switch their medication without physician's care or demand that physicians switch their medication based on the results of these pharmacogenetic tests.

One day before the release of this warning, the FDA announced that it has approved pharmacogenetic tests by 23andMe, a landmark approval as these were the first DTC pharmacogenetic tests to be approved. 23andMe is the only company offering DTC pharmacogenetic test currently. The warning points out an increasing use of DTC genetic tests which concerns the FDA because the increase results in a growing prevalence of DTC pharmacogenetic tests.

Currently, pharmacogenetic testing is new to many healthcare providers. The majority of physicians also “have limited training and knowledge of genetics” to use these tests. Thus, pharmacogenetic testing is still in its initial implementation phase, which explains the reason that the warning is the FDA’s first issuance on
Pharmacogenetic testing.

Policy History

This is the first version of a FDA warning regarding pharmacogenetic tests to determine medication requirements or dosage.

The Science

Science Synopsis

According to [27] the National Institute of General Medical Science [28], “[p]harmacogenomics is the study of how genes affect a person's response to drugs.” This relatively new field combines pharmacology (the science of drugs) and genomics (the study of genes and their functions) to develop effective, safe medication regimens and doses that are tailored to a person’s specific genetic makeup. The terms pharmacogenetics and pharmacogenomics are interchangeable [29].

Researchers agree [30] that variation in an individual’s genome can significantly affect their responses to drugs. Pharmacogenetics is hence used to understand [31] the link between genetic variants and an individual’s drug response, and could ultimately decrease the likelihood of adverse drug reactions [32] (ADRs). Current clinical trials provide information on the average response of drug therapies at standard doses in relatively small, specific populations. [33] However, certain individuals could experience no adverse effect while others develop serious ADRs from taking the same dosage of the same drug.

ADRs represent a serious health burden in the United States [34]: approximately 3 to 7% of hospital admissions in the United States are for treatment of ADRs [35]. ADRs result in over 100,000 deaths and over $30-$100 billion dollars annually [36] according to a 2013 study.

The study of pharmacogenetics depends on the association of genotypes and phenotypes. Genotypes [37] are the “DNA sequence variation at specific genetic loci or regions.” A phenotype [37] is “an outward characteristic or trait.” Pharmacogenetics associates genetic data with phenotypes related to drug effects. Gene variants affecting an individual’s drug response are assessed the same way scientists assess gene variants associated with diseases—by first identifying genetic loci [38] associated with known drug responses, and then testing this against individuals whose response is unknown. Current approaches involve multigene analysis or whole-genome single nucleotide polymorphism profiles [39]. Further, advances in these tools such as genome-wide profiling technologies [40] now make possible new analyses such as genome-wide scans for genetic determinants responsible for drug response. This is in direct comparison to the traditional candidate gene approach [41] which aims at genes for certain drug with a priori knowledge [42].

Scientific Assumptions

Pharmacogenomics has clinical utility: Researchers have investigated the role of pharmacogenomics in personalized medicine [43], or the ability of physicians to use genetic profiles to inform treatment choices. There is growing consensus [44] on clinical utility [26] of this approach.

Relevant Experts

Susanne B. Haga, PhD [45], is an associate professor of medicine at Duke University School of Medicine. Her research lies at the intersection of genomics and clinical practice. She has deep expertise in pharmacogenetic testing, specifically the challenges associated with clinical integration.

Relevant publications:


The Debate

Scientific Controversies / Uncertainties

The FDA warned against using pharmacogenetic tests that either “have not been reviewed by the FDA [or] may not be supported by clinical evidence.” One example given in the warning is genetic tests that claim to help physicians to compare effectiveness and side effects between certain antidepressant medications. However, studies (Bousman et al. [46], Tonozzi et al. [47], Rosenblat et al. [48], and others) have suggested association between certain genes and antidepressant medications. Similarly, other gene-drug associations have been identified and compiled by Clinical Pharmacogenetics Implementation Consortium (CPIC) [49].

The CPIC provides a list [50] of gene/drug associations. These associations are listed because of either pharmacogenomics Knowledgebase (PharmGKB) is a data base that provides information about how variations in human genetic information affects responses to medications. The associations that are FDA-approved are specified by the drug labels of “actionable pgx,” “genetic testing recommended,” or “genetic testing required.” Those that are based on PharmGKB are categorized by levels of evidence [52]. The rest are based on CPIC’s own evidence level [53]. This site is helpful for physicians to utilize pharmacogenetic tests. It also revealed that there are an abundance of gene/drug associations that have not been approved by the FDA but have been proven by research. For example, CPIC identified significant association between IFNL3 genotype and PEG interferon-alpha-based Regimens. [54] However, the association is not approved by the FDA. Since the field of pharmacogenetic testing is new and many tests lack clinical evidence, the efficacy of these tests with gene-drug association that the FDA has not approved of is debatable as shown by the discrepancy of recommendations between the FDA and CPIC/PharmGKB.

Endorsements & Opposition

- Dr. Jeffrey Shuren, J.D. and Dr. Janet Woodcock (directors of CDRH and CDER) joint statement [55] November 1, 2018: “While we are committed to supporting innovation in this area, we will also be vigilant in protecting against the potential risks.”

Potential Impacts

The impact is threefold as the warning impacts patients, physicians, and genetic test manufacturers. First, patients are warned against using genetic test report to alter their medication. The FDA recommends patients discussing results with their physicians from genetic test reports before making any decisions about their medications.
Second, physicians are cautioned against using tests that have not been approved by the FDA. The FDA repeatedly warns the physicians to check FDA approved drug label or the label of FDA cleared test for information regarding genetic information before taking action.

Genetic manufacturers are also warned to ensure their test claims adhere to FDA regulation and FDA approved gene-drug association.

Status
The FDA released this warning on November 1, 2018.

Related Policies
is approval of 23 and Me direct-to-consumer pharmacogenetic testing was granted one day before the FDA warning on pharmacogenetic tests.

Recommended Citation

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