

Proposed FDA Regulation of Clinical Laboratories and Clinical Implementation of Pharmacogenetics

Editorial

Recent FDA initiatives relating to the regulation of laboratory developed tests (LDTs) have resulted in a flurry of articles in the lay media and scientific press discussing the clinical utility and accuracy of such tests, and, in particular, tests based on genetic information. Unfortunately, the vast majority of these articles have failed to differentiate between the different types of genetic tests, and the very different levels of evidence of clinical utility and potential harm to the public to be found among the different types of genetic tests. In particular, the media reports have failed to differentiate between genetic tests for disease diagnosis, genetic tests for disease risk, and genetic tests that are useful in understanding an individual's biology as it relates to impact on response to specific drugs, also known as pharmacogenetic testing. By not differentiating between these different types of genetic tests, these articles have been misleading due to conflation of very different attributes among the different types of genetic tests. An understanding of the differences between these tests allows one to stratify them according to the degree of scientific evidence supporting their utility, as well as the degree of risk they pose to public safety.

It is in the interest of public safety that any test that is used to make medical decisions be accurate and FDA is justifiably concerned regarding the potential harm an inaccurate genetic test result could cause. The draft guidance outlining FDA's proposed regulatory framework for oversight of LDTs acknowledges that the risks posed by the wide varieties of LDTs varies greatly, and the proposed regulatory framework is based on the degree of risk that a particular LDT presents, i.e. a risk-based approach [1]. This is a well-reasoned approach that is consistent with FDA's responsibilities to protect the public health while the regulatory framework is being developed and implemented, without denying access to this information to patients during this implementation period. While there are a wide range of risk levels associated within any of the classes of genetic tests, it is generally recognized that genetic tests that diagnose a disease or risk of disease, especially if the disease is potentially life-threatening, pose a greater risk to the public due to a false result because of the harmful actions that may be taken, or beneficial actions which may not be taken, based on the inaccurate test result (e.g. inaccurate ovarian cancer diagnosis leading to unneeded major medical procedures [2] misdiagnosis and lack of care in the case of a false negative result for HER2 breast cancer [3] etc.). In contrast, genetic information that can help inform the patient (and healthcare provider) about their genetic predisposition for an array of drug metabolizing enzymes poses much less risk, as it does not result in unnecessary treatment, does not put the patient at risk of undergoing unnecessary medical treatment, or just as troubling, does not result in the patient not receiving treatment due to false negative misdiagnosis. These differences

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Volume 5 Issue 1 - 2017

Bill W Massey*

Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University and Essense Laboratory, USA

***Corresponding author:** Bill W Massey, Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, USA, Tel: 1-760-443-3782; Email: bmassey@bwmassage.com

Received: January 13, 2017 | **Published:** January 18, 2017

in the potential harm that can result from inaccurate test results makes pharmacogenetic tests much safer, from a public health standpoint, than the above-mentioned genetic tests for cancer (disease) diagnosis.

In an FDA assessment of any LDT, the potential benefit of the test must also be taken into account so that the relative risk or risk-benefit relationship can be considered in the context of current medical practice. The clinical benefit of pharmacogenetics is explicitly stated by FDA on its own website, where a list of pharmacogenetic markers that appear in the FDA-approved prescribing information of over 100 drugs is posted [4]. FDA provides information that suggests that adverse drug reactions are the 4th leading cause of death in the US, cost the nation billions of dollars annually, and that the majority of these adverse drug reactions have a genetic basis, many of which are known and listed in the drug label [5]. It is reasonable to presume that knowledge of a patient's pharmacogenetic profile, when shared with their prescribing physician, could reduce the risk of adverse drug reactions, lower healthcare costs, and potentially save lives.

Clinically-useful pharmacogenetic information is derived from known associations between genetic variation in a gene that codes for a protein that affects how the body metabolizes or responds to a particular drug. These genes can be classified into two major categories: metabolic genes and response genes. Metabolic genes code for proteins that change the drug's chemical structure (biotransformation) into either an active or inactive metabolite. Genetic variants of metabolic genes can result in metabolic enzymes with altered function (e.g. non-functional, impaired function, or over-functioning) which can greatly affect the amount of the drug or its metabolites in the body and the rate of their elimination from the body. The amount of drug in the body affects the magnitude of the response (also known as the dose-response relationship), and thus metabolic abnormalities can produce

under- or over-response to a given dose. Response genes code for proteins that either transport the drug to its site of action, or are the protein with which the drug interacts to produce its effect (e.g. a receptor). Genetic variation in response genes can result in impaired interactions between the drug and the effector protein, non-production of the effector protein, or over-expression of the effector protein. Thus, response genes affect the body's ability to respond to a drug. For reviews that describe these relationships in detail, please see these reviews [6,7].

Much has been written about the relative lack of prospective clinical outcomes data showing the utility of pharmacogenetics in clinical practice. While there is some truth behind this assertion, the evidence is continually mounting and overwhelmingly supports the clinical utility of pharmacogenetics. Thus, it can be argued that the assertion of lack of clinical utility data is based more on the lack of such studies having been conducted, than on a lack of benefit observed in the studies that have been conducted. Improvements in pharmacogenetic clinical study design are being implemented, and data of better quality is now being published. The majority of earlier study designs examined a narrow objective, such as looking at only the relationship between a single gene variant of a single gene and a single outcome measure. It has been demonstrated that considering all relevant genes for a particular drug when using pharmacogenetically-guided drug selection, also known as combinatorial pharmacogenetics, results in better outcomes than when compared to either no pharmacogenetic guidance or single gene/single drug-based pharmacogenetic guidance [8,9]. It is reasonable to expect that adoption of combinatorial pharmacogenetic approaches in clinical practice will continue to show superior clinical benefit and become best practice in pharmacogenetic testing.

It is not necessary to have an overwhelming number of clinical studies to justify implementing pharmacogenetics into clinical practice. The perceived "data gap" is easily crossed by conservative extrapolation of pharmacogenetic data to drug selection using well-established general principles of pharmacology (e.g. pharmacokinetics, elimination, metabolism, dose-response, etc.). Prescribing decisions are regularly made by conservative extrapolation information that impacts well-known biological processes that can affect inter-patient variability in drug response [10], such as the general principles of pharmacology listed above. In fact, in the same Discussion Paper from the Institute of Medicine of the National Academies, the authors state "for many pharmacogenetic traits, the mechanisms are well understood, and randomized controlled trials are not necessary. Many actionable genetic variants affect drugs on a pharmacokinetic basis, analogous to the effects measured by using creatinine to assess renal or bilirubin to assess hepatic function. Thus, many pharmacogenetic prescribing recommendations can be based on underlying pharmacokinetic evidence." Due to the understanding of these underlying and well-understood processes that can affect drug response in a predictable manner, there is no valid reason against using pharmacogenetic information, in combination with clinical judgement, to inform prescribing decisions in a responsible manner compatible with the current practice of medicine.

The health care industry in the US is undergoing rapid changes, such as rapid technological advances, changes in how care is delivered, and the increasing financial burden of care being shifted toward the patient. With insurance deductibles steadily increasing, for the most part patients that do not qualify for Federal health insurance coverage (i.e. Medicare and Medicaid) have to directly pay out of pocket (and in addition to their insurance premiums) for all but catastrophic care. It only seems fair that if citizens are required by law to participate in health insurance, and still end up paying for the majority of the costs of their care, then they should be granted more choice and access to medical information that they believe can be of help to them. It follows that citizens should have the right to know their genetic information so that they may have that information available to present to each of their healthcare providers. Knowing a patient's pharmacogenetic profile can increase the interaction between physician and patient, making the patient a more active participant in their care, and more confident that the prescribed treatment will work. It becomes part of their personal medical history to be shared with healthcare professionals. If the use of a patient's pharmacogenetic information improves their chance of a good clinical response, or reduces their side effects and improves tolerability, then the patient is more likely to take their medication, with compliance being crucial to positive treatment outcomes [11]. It seems inevitable that pharmacogenetics and its core role in personalized medicine will become the standard of care in the future. However, for the patients that may benefit from pharmacogenetic-guided drug selection there is no need to wait. Their future is now.

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