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Before the House Energy and Commerce Subcommittee on Health
21st Century Cures: Examining the Regulation of Laboratory Developed Tests

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Introduction

Chairman Pitts, Ranking Member Pallone, and Members of the Subcommittee.

Thank you for giving me the opportunity to testify before you today.

My name is Christopher Newton-Cheh. I am a cardiologist at Massachusetts General Hospital, specializing in heart failure and cardiac transplantation, and an Assistant Professor of Medicine at Harvard Medical School.

I am also a cardiovascular geneticist and spend a considerable amount of time in the laboratory investigating the root causes of cardiovascular disease, a leading cause of morbidity and mortality worldwide. My colleagues and I are focused on using clinical research to translate genetic discoveries into an improved understanding of human disease, identification of new therapies, and the ability to predict individual patient's risk of disease, as well as positive and negative responses to drugs. In particular, we are seeking to identify genetic variants that underlie sudden cardiac death and hypertension.

Today, I speak to you not only as a clinician and researcher, but also as a volunteer for the American Heart Association, a non-profit organization dedicated to building healthier lives, free of cardiovascular diseases and stroke. I am concerned about the lack of enforcement of regulation on laboratory-developed tests (LDTs). It is important to note that many of these tests have not been clinically validated and are used by patients and providers to make important treatment decisions that can result in further adverse events if the information is neither accurate nor reliable.

Promise of personalized medicine

The potential for personalized medicine to improve health and improve the practice of medicine is great. Our evolving knowledge of how genes and lifestyle combine to affect our health is transformational. As we continue to develop a greater understanding of the genetics of cardiovascular disease and stroke in particular, we will move away from "one-size-fits-all" medicine to more targeted and effective prevention, treatments, and even cures.

Genetic tools are increasingly being integrated into health care in the United States, including their use in the diagnosis and treatment of cardiovascular disease. Biomedical research, including that funded by the American Heart Association and the National Institutes of Health, continues to build on the sequencing of the human genome to better understand the genetic component of cardiovascular disease, notably in the discovery of new genetic markers associated with disease risk as well as drug efficacy and toxicity. As our knowledge of the genetic underpinnings of cardiovascular disease expands, we anticipate there will be many opportunities to use genetic tests to predict or preempt disease, and to treat it more effectively. However, it is imperative that these tests are scientifically credible.

Modern market of laboratory-developed tests

As a result of our increased understanding of the role genetics plays in disease, many new tests are now on the market and are promoted to predict, prevent, and treat cardiovascular disease more effectively. Many scientists, including myself, have expressed concern that advertised claims may not be supported by science. Nevertheless, these genetic tests remain on the market and are inadequately regulated. A lack of oversight means there is no guarantee of test quality and performance and that doctors – attempting to make an accurate diagnosis or prediction of risk– and patients – interested in reducing their risk for disease – may receive and take action based on an inaccurate or misleading result.

Over the past few years a greater number of laboratory-developed tests have come onto the market—without FDA review—that purport to inform individuals of their risk for cardiovascular disease, the likelihood that they will develop risk factors for cardiovascular disease, and which medicines and dosages will be most efficacious or ineffective in treating their cardiovascular disease. Unfortunately, these tests typically come to market without any independent verification by a government agency of their clinical validity. Expert consensus guidelines summarize research evidence but there is no regulatory mechanism enforced that attempts to compare such evidence to claims made in marketing such tests. Whereas testing kits are required to be cleared or

approved by the FDA prior to marketing, the vast majority of tests are laboratory-developed tests, marketed without such review. The current CLIA approval process ensures only the analytical validity, or accurate measurement, but fails to address clinical validity, whether a test result is clinically important to a patient's health decision-making. In the absence of such an independent examination, health care professionals, patients and payors have no assurance of the value and limits of each test.

Particularly alarming has been the growth of a market directly selling genetic tests of unknown clinical validity, rather than patients being offered genetic testing services from qualified health care professionals. Such tests purport to analyze a customer's DNA to establish their risk for myocardial infarction, hypertension, atrial fibrillation, as well as a host of other diseases.

I am greatly concerned that the test claims made by companies marketing them may not reflect current science. The genetics of some relatively rare cardiovascular conditions caused by single mutations - like Marfan syndrome, Long QT Syndrome and hypertrophic cardiomyopathy - has been well characterized, and LDTs have been critical components of medical care, family screening and development of therapeutics for such diseases. However, we are in the early stages of understanding how each person's risk for common heart diseases and stroke is influenced by their DNA. An individual's risk of myocardial infarction, heart failure or atrial fibrillation is a complex interaction of their genetics, their behavior and their environment.

As you know, the American Heart Association is not alone in expressing these concerns. A 2006 investigative study by the U.S. Government Accountability Office (GAO) observed that genetic testing companies they investigated "mislead consumers by making predictions that are medically unproven and so ambiguous that they do not provide meaningful information to consumers". Responding to the GAO report, the Federal Trade Commission issued a statement warning the public to be "…wary of claims about the benefits these products supposedly offer." The public is not equipped to do this on its own.

In 2010 the GAO investigated four companies that market genetic tests directly to consumers and provide direct access to genetic testing services. The GAO again found the companies to be misleading customers, concluding that the test results offered by these companies are of "little or no practical use". With the tests offered by companies investigated in this and the 2006 report, I am especially concerned about the claimed predictive value of tests sold directly to consumers for determining risk of cardiovascular disease. Despite the remarkably rapid progress that has been made in our understanding of the genetics of heart disease and stroke in recent years, it is not yet

possible to assess a person's DNA to evaluate their risk for most common diseases with sufficient accuracy on which to base treatment decisions.

It is clear that some genetic tests lack scientific credibility. Allowing these tests to continue to be marketed without rigorous oversight increases the risk of undermining public and health care provider confidence in the utility of employing genetic tools to improve health care.

Need for oversight of laboratory-developed tests

Ultimately, we may be able to achieve significant medical advances with the development of new genetic tools that assist with preventing and treating heart disease and stroke. But, for this to come to fruition, health care providers need accurate and reliable tests they can interpret to guide shared decision-making with patients. The success of this effort to personalize medicine is also dependent upon acceptance by the American public that undergoing genetic testing will lead to improved health outcomes. The independent review by the FDA of laboratory-developed tests will help establish whether tests are valid, and ensure that information from tests is accurately communicated to physicians and patients.

I recognize that there are differences between a test kit shipped out to laboratories and a laboratory-developed test that is performed in a single laboratory. However, regardless of how and where the test is performed, the interests of health care providers and patients remain the same. They need to have the same degree of confidence that it is a high quality test, where the claims of its validity are substantiated by science, and its application to improve patient health established. Genetic tests therefore need to be independently evaluated by the FDA with the same rigor as tests marketed as kits. Such a level of scrutiny is especially important when tests are being used for guiding critical medical decisions, such as drug selection or dosage.

The oversight of laboratory-developed tests is all the more urgent as new types of testing come onto the market. Whereas genetic testing previously involved looking for a single, well-characterized mutation or chromosomal abnormality known to be associated with a rare disorder, a much wider variety of testing methodologies is now employed. It is now possible to genotyped millions of genetic variants or sequence all 20,000 genes at once, uncovering scores of variants of uncertain clinical relevance. One type of test examines one letter changes in DNA sequence (known as single nucleotide polymorphisms [SNPs]), to obtain a result. Little may be known about the SNPs beyond the observation that their presence or absence correlates with slightly increased or decreased disease risk. Another type of test detects not sequence but gene expression, where levels of activity of a number of genes are tested. In such scenarios, the analysis of the raw data and interpretation is more complex than, for example, the simple

inheritance of a well-characterized point mutation known to cause a disease. The clinical validity of such tests is often not clear to health care providers or patients.

Impact of unregulated laboratory-developed tests on patient care

I have had patients come to me with genetic tests that suggest slightly increased risks of atrial fibrillation or myocardial infarction but they are totally confused because their regular physicians do not know how to interpret results. They ask me whether they should take aspirin, beta blockers, cholesterol-lowering statins or blood thinners. These are medications with risks and benefits that must be carefully matched to individual patient risks. Statins have been well established to lower risk of heart attack in people with coronary artery disease or at high risk of it. A currently marketed genetic test purports to determine whether they are likely not to respond to a statin or to have higher risk of heart attack. The small studies that initially supported this claim have been completely debunked by much larger studies but the marketing continues. Not taking a statin because a patient or their doctor believes falsely that they will not respond could contribute to a potentially fatal outcome. This cannot continue.

FDA's proposed regulatory framework for laboratory-developed tests

The American Heart Association applauds the Food and Drug Administration (FDA) for its decision to reconsider its enforcement discretion with regard to the regulation of laboratory-developed tests—this is an important step in the right direction for patients.

The American Heart Association has long been concerned by the unregulated marketing of genetic laboratory-developed tests. In a 2012 Association policy statement on genetics and cardiovascular disease, the Association notes that "all genetic tests, including laboratory-developed genetic tests, should be required to undergo independent review to confirm their analytic and clinical validity". For some time now, the Association has expressed concern that there are significant gaps in the oversight of genetic testing, and that enhanced oversight is fundamental to ensure that new discoveries are translated into reliable informational tools for healthcare professionals and improved health outcomes for patients.

The Association believes that ultimately it will be in the best interests of patients for laboratory-developed tests to be approved or cleared just as tests marketed as kits are currently regulated. One of the challenges the agency faces in regulating LDTs, of course, is that numerous tests are already on the market, and many are utilized as part of patient care. The Association recognizes that the agency may not currently have all the resources it would need to quickly review all currently marketed tests to determine through an approval or clearance process their safety and effectiveness.

I would urge the FDA to release the draft guidance as soon as the 60-day notice window expires so that all stakeholders have the ability to review and begin a public dialogue about how best to proceed. This is the right thing to do for patients.

Conclusion

Advanced diagnostics hold tremendous promise for patients, but the increasingly pivotal role of these diagnostics in patient care makes it imperative that their safety and effectiveness is assured by the FDA prior to use. The FDA standards are intended to reassure patients and providers on the reliability and usefulness of diagnostic tests and set clear parameters for developers of new tests.

I sincerely thank you for giving me this opportunity to testify before you today. I would be happy to answer any questions you may have.