American Heart Association | American Stroke Association
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January 30, 2015

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
RM. 1061
Rockville, MD 20852

Re: FDA-2011-D-0360; FDA-2011-D-0357

Dear Sir or Madam:

On behalf of the American Heart Association (AHA), including the American Stroke Association (ASA) and over 22.5 million volunteers and supporters across the country, we appreciate the opportunity to comment on the Food and Drug Administration's (FDA) proposed framework for the regulatory oversight of laboratory developed tests (LDTs) and notification and medical device reporting for LDTs.

We applaud the FDA for reconsidering its policy of enforcement discretion with regards to LDTs and issuing its draft guidance documents to begin phased-in oversight of these tests. This step will ensure an appropriate level of oversight for LDTs in order to reassure patients and providers on the reliability and usefulness of these tests. Overall, we support the draft guidance documents and agree that the proposed risk-based approach is the best way to ensure the validity of the highest-risk tests while setting clear parameters for manufacturers to develop new and better tests.

Genetic and genomic tests have become increasingly integrated into health care in the United States for the diagnosis and treatment of cardiovascular disease (CVD), as well as disease prediction and identification of therapeutic targets. For instance, there have been significant advances in identifying pharmacogenetic biomarkers to reduce adverse reactions to specific cardiovascular drugs, including warfarin used as an anticoagulant for patients with atrial fibrillation.[1,2] As biomedical research continues to

[1] Arnett et al. *Circulation*. 2007; 115: 2878-2901.
[2] Ganesh et al. *Circulation*. 2013; 128: 2813-2851.

build on the sequencing of the human genome to better understand the genetic component of CVD and to discover new genetic markers associated with disease risk, we anticipate there will be even more opportunities to use genetic tests to predict or preempt disease and treat it more effectively.

While genetic and genomic tests have become increasingly determinative of critical treatment decisions for patients and for identifying whether or not a particular patient would benefit from a course of therapy, device, or advanced imaging, there is still work to be done in developing testing for complex forms of CVD – one of the leading causes of death in the United States – because individual common variants have only a modest impact on risk. In addition, CVDs in the general population are often diseases with many genetic and environmental factors.[3] For example, genetic testing for mendelian diseases which result from a single gene mutation that have been well studied and characterized, such as the long-QT syndrome and cardiomyopathies, are becoming increasingly available and useful as diagnostic tests in clinical practice. On the other hand, it remains challenging to use genetic testing to assess risk and diagnose complex CVDs, such as hypertension, due to the difficulty in assessing the contribution a single gene mutation makes towards the disease; the possibility that many gene variants may play a role; and, the contribution of non-genetic factors.[4] This complexity warrants the need for the FDA to review claims about testing accuracy, safety, and effectiveness for certain CVDs, particularly as patients and doctors become more reliant on genetic and genomic tests.

The AHA has long expressed concern that there are significant gaps in the oversight of such testing and has consistently supported that genetic tests undergo independent review to confirm their analytic and clinical validity by the FDA. In comments to the Secretary's Advisory Committee on Genetic Health and Society (SACGHS) in 2007, the AHA supported enhanced oversight as a way to ensure that new discoveries are translated into reliable informational tools for medical professionals and improved health outcomes for patients.[5] In 2010 at the FDA's request, the AHA again expressed concerns that some genetic tests lack scientific credibility; that claims made by certain manufacturers do not reflect current science; and that we supported a phased-in, risk-based approach by the FDA to establish whether tests are valid and would ensure that information on tests is accurately communicated to physicians and patients.[6] In a 2012 policy statement, we recommended that LDTs "undergo independent review to confirm their analytic and clinical validity and that this information should be made available to healthcare professionals and the public at large."[7] We argued that the FDA would be best suited to serve as the agency to regulate these tests due to its clear statutory authority, scientific expertise, and experience in regulating genetic tests.[8]

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[3] Ibid.
[4] Ibid.
[5] American Heart Association. Response to Draft Report on Oversight of Genetic Testing. 2007.
[6] American Heart Association. Response to FDA call for comment on laboratory developed tests. 2010.
[7] Ashley et. al. *Circulation*. 2012; 126:142-157.
[8] Ibid.

The AHA is not alone in expressing these views on LDTs and the need for increased oversight by the FDA. A report issued in 2000 from the Secretary of the Department of Health and Human Services' (HHS) Advisory Committee on Genetic Testing concluded that genetic tests should not be introduced in the market before they can be established that they can be used to diagnose or predict health-related conditions.[9] A 2006 Government Accountability Office (GAO) report found that tests from four companies that offered genetic testing services directly to the market and consumers without independent verification provided results – which included future risk of heart disease and high blood pressure – that were medically unproven, meaningless, and misleading.[10] A 2008 SACGHS report also expressed concerns about gaps in oversight and recommended that the FDA should "assess all laboratory tests, regardless of how they are produced (i.e., as a commercial test kit or a LDT), in a manner that takes advantage of its current risk-based regulatory approach."[11] In 2010, the GAO again found companies that marketed genetic tests directly to consumers and provided direct access to genetic testing services – including those that predicted risk for heart attack – found that the companies misled consumers and their tests offered results that were of "little or no practical use."[12]

The lack of appropriate oversight described throughout each of these reports demonstrates there is no guarantee of test quality and performance for LDTs 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. In other words, allowing LDTs to continue to be marketed without rigorous oversight increases the risk of undermining public and health care provider confidence in the utility of employing genomic tools to improve patient care. Additionally, new research and the development of complex blood-based multi-analyte genomic tests based on the measurement of several markers, including ribonucleic acid (RNA) and proteins, as well as deoxyribonucleic acid (DNA) polymorphisms, has led to innovative approaches to diagnostic questions. A lack of a clear regulatory framework impedes the adoption of these advances.

The release of the FDA's draft oversight guidance is a step towards addressing these problems and balancing the needs of protecting patients while allowing developers to innovate and discover potentially groundbreaking advances in the diagnosis and treatment of cardiovascular disease. We support the enhanced oversight proposed in the draft guidance documents and believe it is fundamental to ensuring that new discoveries are translated into reliable informational tools for health care professionals that can ultimately improve health outcomes for patients.

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[9] Secretary's Advisory Committee on Genetic Testing. Enhancing the oversight of genetic tests: recommendations of the SACGT. Bethesda, MD: National Institutes of health. 2000.
[10] US Government Accountability Office. "Nutrigenetic testing: tests purchased from four websites mislead consumers [testimony before the Special Committee on Aging, US Senate]." Washington, DC: US Government Accountability Office. 2006.
[11] Ferreira-Gonzalez et al. *Personalized Medicine.* 2008; 5:521-528.
[12] US Government Accountability Office. "Direct-to-consumer genetic tests: misleading test results are further complicated by deceptive marketing and other questionable practices." Washington, DC: US Government Accountability Office. 2010.

Notification to the FDA of LDTs Manufactured by a Laboratory or Registration and Listing

The AHA agrees that the FDA should require all manufacturers of LDTs to provide the FDA with information about the tests they make and market within the timeframes proposed by the agency. In addition to the required notification data elements proposed by the FDA, the agency should also require manufacturers to include a review of the scientific literature demonstrating the validity and utility of their LDTs. This additional information would ensure that the FDA not only has knowledge of all tests marketed, it would also help the agency identify tests where the risk is likely to be greatest or where the claims appear questionable during its classification process.

We also strongly encourage the FDA to make this information public so that health care professionals and patients alike can also evaluate these tests. The FDA could make this information public either by launching its own public registry or by requiring LDT manufacturers to submit all relevant information about each test to the National Institute of Health's (NIH) Genetic Testing Registry with coordination from the FDA to ensure that the NIH collects all required data elements.

Premarket Review Requirements

The AHA supports the FDA's use of the same risk and complexity-based classification for LDTs as is currently applied to regulated medical devices. We also recognize that the agency may not currently have all the resources it would need to quickly review all currently marketed tests to determine their safety and effectiveness. This is one reason why we believe the proposed phased-in, risk-based approach would provide the appropriate balance of prioritizing current FDA resources to quickly bring those LDTs that pose the highest risk to patients under the FDA's oversight while maintaining flexibility for other LDTs that present lower risks.

The AHA would also support an expedited review process when laboratories identify ways to improve or modify their tests that have already been cleared or approved by the FDA. The FDA should also consider an expedited review process when LDT manufacturers seek to enter an LDT into the market that would modify or improve a previously FDA cleared or approved LDT for the same intended use. An expedited review process would help provide flexibility for LDT manufacturers to bring LDTs to the clinical setting when new advances in genetic technologies and new discoveries and research happen quickly while at the same ensuring patients and providers of their validity.

In addition, for genetic tests intended to assist in the prevention of chronic disease, it may take many years to perform the research demonstrating improved patient outcomes. The AHA would encourage the FDA to allow these types of tests with clear consensus in the scientific literature and clinical validity for disease risk diagnosis to be marketed even if their use has not been shown to result in improved clinical outcomes.

Traditional LDTs

According to the draft guidance, the FDA is considering a number of factors in order to determine whether an LDT is a "traditional LDT" and consequently would not be subject to premarket review requirements. It is our understanding that an important characteristic of early LDTs, in order to ensure their accuracy, was that the test was administered and interpreted by the expert or group of experts who originally developed the tests. The location where a patient was being seen was not a relevant factor. It appears that the FDA is also questioning whether or not the location of where a patient is being treated is necessary for the definition of a "traditional LDT." The AHA agrees that it may not be necessary to include the proposed criteria that states "the LDT is both manufactured and used by a health care facility laboratory (such as one located in a hospital or clinic) for a patient that is being diagnosed and/or treated at that same health care facility or within the facility's healthcare system." The AHA believes it would be unnecessarily burdensome and restrictive to limit patients to a specific institution where a test was developed to consider it a "traditional LDT." The other criteria should be sufficient to mitigate risks and protect patient safety.

Class I Devices and Lower Risk LDTs

We also support the FDA's decision to continue enforcement discretion with respect to applicable premarket submission requirements for devices classified as Class I devices. The AHA suggests the FDA reserve the Class I category for LDTs where there is well-established scientific consensus on the clinical validity and utility of the test, where the agency believes that the probability of a false result is low, the probable benefit from using a test outweighs the risks from its use, and the test is ordered, administered, and interpreted by qualified health care professionals in a health care setting.

We would also like to note that the genetics of some relatively rare cardiovascular conditions caused by single mutations has been well characterized. These diseases include heritable arrhythmias such as long-QT syndrome; cardiomyopathies such as hypertrophic cardiomyopathy (HCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), and dilated cardiomyopathy (DCM); some congenital heart defects, and Marfan syndrome and others. For these types of disorders, LDTs often have been critical components of medical care, family screening, and the development of therapeutics for such diseases, particularly as consensus continues to emerge that genetic testing may have a major impact on the diagnosis, prognosis, and management of these conditions.[13]

While we recognize that testing for the detection of some of these conditions can help determine whether or not to pursue certain treatment options which can include medications or surgical interventions, we do not believe the FDA should highly prioritize these LDTs for immediate oversight when the testing is completed as part of a comprehensive clinical evaluation and incorporates other cardiovascular diagnostic tests. Using these tests do not expose patients to significant risks of harm when patients using them are treated at cardiovascular genetic centers, their results are interpreted by and

[13] Ganesh et al.

discussed with a health care professional or team of health care professionals which can include a trained genetics counselor or pathologists, and the patient is often treated within the same health system or facility administering the LDT. In addition, there currently exists clear scientific consensus that has proven them useful in clinical practice and demonstrated the validity of LDTs for these types of genetic testing.

As noted above, we have also seen scientific advances that have led to clinically useful companion diagnostic tests that help inform the management of patients with certain CVDs. Clopidogrel, an antiplatelet agent, is another example of this recent progress and how identifying pharmacogenetic biomarkers can help better understand risks of adverse reactions to specific drugs. Currently, testing can be done to determine decreased or loss-of *CYP2C19* function in patients. This testing is useful since patients taking clopidogrel with decreased or loss-of *CYP2C19* function can have higher rates of cardiovascular events after acute coronary syndrome and percutaneous coronary interventions compared to patients with normal *CYP2C19* function. As a result, this testing could also lead to alternative treatment strategies.[14]

While there may be consensus that it is important for clinicians to be aware of this effect on clopidogrel and its potential for adverse outcomes in certain types of patients, more data is still needed to determine whether or not testing should be routine prior to clopidogrel use.[15] FDA oversight would ensure that LDTs that claim to predict or guide therapeutic responses must prove these claims prior to entering the market, particularly in instances when our understanding of genetic and non-genetic variants associated with drug actions is not well defined.

Classification of LDTs

The AHA also appreciates that the FDA will provide additional guidance to describe what it generally considers to be Class I, II or III within 24 months from finalization of the guidance documents and that the FDA plans to use advisory panels as part of the process for prioritizing and categorizing LDTs. We look forward to providing additional feedback to the FDA when the agency issues the guidance for public comment. We encourage the FDA to include representation of patients suffering from common chronic diseases, to whom genetic tests are being aggressively marketed, along with health care professionals, test developers, and academic scientists, on expert advisory panels that would classify LDTs.

[14] Holmes DR Jr, et al. ACCF/AHA clopidogrel clinical alert: approaches to the FDA "boxed warning": a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents and the American Heart Association. Circulation. 2010; 122:537–557.
[15] Ganesh et al.

Devices Subject to FDA Oversight

The AHA has been particularly alarmed by the growth of a market directly selling to consumers genetic tests of unknown clinical validity, rather than patients being provided genetic testing services from qualified health care professionals in a health care setting. We understand that, according to the proposed framework, "the enforcement policies in this guidance do not apply to DTC [direct-to-consumer] tests, and FDA's usual enforcement policies apply to DTC tests."[16] It is important to emphasize that many of these DTC tests claim to analyze a customer's DNA to establish their risk of myocardial infarction, hypertension, atrial fibrillation, as well as a host of other diseases. This makes it critical for these tests to undergo independent review and to receive verification from the FDA of their clinical validity prior to entering into the market. Allowing DTC tests to continue to be marketed without rigorous oversight increases the risk of undermining public health and health care provider confidence in the utility of employing genetic tools to improve health care. Aggressive oversight of these tests is critical to protecting patient safety. The FDA either needs to explicitly include DTC tests in its final guidance document subject to premarket review requirements or more aggressively assert its current regulatory authority over these tests that provide results based on unsubstantiated claims.

Oversight of DTC tests is especially important given new research that indicates that many Americans would take some sort of action – including taking medications or having surgery – if they learned they had a genetic risk for a disease, including heart disease, regardless if they are healthy or of their family history for disease.[17] Without oversight of these tests, consumers and patients that use a DTC test may be likely to make misinformed health care decisions as a result of an inaccurate test that does not reflect current science.

In addition to the concerns expressed above related to DTC tests, the AHA generally has concerns with genetic tests based on single nucleotide polymorphisms (SNPs) which claim to assign lifetime risk estimates for common cardiovascular diseases or guide pharmacological intervention. Little may be known about the SNPs beyond the observation that their presence or absence correlates with an increased or decreased disease risk, and this should not be the basis for a test. As noted above, common adult CVDs have both genetic and environmental components, with some having useful treatment options while others do not. As a result, genetic testing in these cases will yield unclear results that should not be used to determine particular courses of treatments or actions.[18] For these types of LDTs, we would encourage the FDA to consider them as Class III devices for which premarket review would be required at the end of the 12-month period after the FDA's guidance is finalized.

[16] FDA. Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories. Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). Draft Guidance. October 3, 2014, pg. 5.
[17] Almeling, Rene and Gadarian, Shana. *Journal of Health and Social Behavior*. 2014; 55(4): 482-503.
[18] Ormond et al. *Lancet.* 2010; 375: 1749-51.

Demonstrated Need for Regulatory Oversight

KIF6 testing is an example that illustrates how tests can continue to remain in the market despite our growing scientific understandings of genetics and disease. In 2008, researchers announced the discovery of a variation in a gene called KIF6. Researchers claimed this gene variation was linked to both an increased risk for heart attack and to an individual's chances of preventing a heart attack by taking statins.[19] At the time, this discovery was noted as "unexpected" with "a lot of question marks surrounding it" by some cardiologists.[20]

Despite these initial concerns, KIF6 testing was marketed to cardiologists and primary care physicians over the course of two years following the initial discovery before additional research found that the variation was not associated with the risk of clinical coronary artery disease.[21,22] Subsequently, the FDA later rejected an application for premarket approval of the KIF6 test; however, the test remains on the market as an LDT.[23,24]

We strongly encourage the FDA to enforce oversight of these types of tests – which have not been proven to impact disease prediction or where there is no proven genetic connection to disease – especially tests used in critical decision-making and not ordered by a health care professional, and consider them as high-risk tests needing premarket review to ensure their clinical validity, as soon as possible.

FDA oversight, however, has proven to not impede the introduction of new test products related to CVD on to the market. For example, the FDA recently approved a screening test that predicts a patient's risk of future coronary heart disease in adults with no history of heart disease. This test, known as the PLAC Test, measures the activity of lipoprotein-associated phospholipase A_2 (Lp-PLA_2) in a patient's blood that can help a doctor identify whether or not a patient has a risk for heart attack and stroke.[25] We believe that the framework proposed by the FDA will continue to allow LDTs into the market that advance our ability to diagnosis and predict CVD risk to improve patient care without unduly burdening makers of LDTs.

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[19] Winslow, Rob. "Gene Variant Is Said to Be Linked to Heart Attack and Prevention." *Wall Street Journal*. Jan. 22, 2008. Accessed Dec. 16, 2014: http://www.wsj.com/news/articles/SB120096559471905225?mg=reno64-wsj&url=http%3A%2F%2Fonline.wsj.com%2Farticle%2FSB120096559471905225.html

[20] Ibid.

[21] Topol et al. *The Journal of the American College of Cardiology*. 2010; 56(19): 1564-1566.

[22] Assimes et al. *The Journal of the American College Cardiology*. 2010; 56(19):1552-1563.

[23] Winnick, Ed. "Genetic, Genomic Testing to Play Key Role in Quest Diagnostics' Growth Efforts." GenomeWeb News. Nov. 21, 2012. Accessed Dec. 16, 2014: https://www.genomeweb.com/clinical-genomics/genetic-genomic-testing-play-key-role-quest-diagnostics-growth-efforts

[24] Description of the test on the market: http://www.bhlinc.com/clinicians/test-descriptions/KIF6

[25] FDA. FDA clears test that helps predict the risk of coronary heart disease. Dec. 15, 2014. Accessed Jan. 2, 2015: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm426799.htm

Conclusion

The AHA thanks the FDA for the opportunity to provide our input to its proposed oversight of LDTs. We are at the beginning of an exciting time of genetic discovery and understanding of how genes and lifestyle combine to affect cardiovascular health. The potential for this knowledge – combined with continued education of healthcare professionals on the advantages and limitations of new genetic tests – to treat and improve health outcomes for patients with CVD and impact the practice of cardiovascular medicine is great. However, it is imperative that the safety and effectiveness of an LDT and genetic tests are assured by the FDA prior to use.

The AHA believes the FDA's proposed framework for oversight is not only in the best interest of patients, but it is essential for assuring providers that health care decisions are based on diagnostic tests that are reliable and useful. The proposed framework also sets clear parameters for developers of new tests that would allow for the continued advancement of highly complicated, potentially groundbreaking discoveries while ensuring their clinical validity and reducing risks to patients. Regardless of an LDT manufacturer's compliance with the guidance document, we strongly believe that the FDA must be prepared to take action against any LDT that presents a significant risk to public health. As described above, we encourage the FDA to include our following recommendations in its final guidance documents:

- Require manufacturers to include a review of the scientific literature demonstrating the validity and utility of their LDTs when providing notice to the FDA.
- Include an expedited review process when laboratories identify ways to improve or modify their tests that have already been cleared or approved by the FDA.
- Include an expedited review process when new LDTs seek to enter into the market that would modify or improve a previously FDA cleared or approved LDT for the same intended use.
- Allow tests with clear consensus in the scientific literature and clinical validity for disease risk diagnosis to be marketed even if their use has not been shown to result in improved clinical outcomes.
- Reserve the Class I category for LDTs when there is well-established scientific consensus on the clinical validity and utility of the test, where the agency believes that the probability of a false result is low, the probable benefit from using a test outweighs the risks from its use, and the test is ordered, administered, and interpreted by qualified health care professionals in a health care setting.
- Include representation of patients suffering from common chronic diseases, to whom genetic tests are being aggressively marketed, along with health care professionals, test developers, and academic scientists, on expert advisory panels that will classify LDTs.
- Include DTC tests in its final guidance document as LDTs subject to premarket review requirements.

Again, we are encouraged by the steps taken by the FDA to oversee LDTs and encourage the agency to act swiftly to finalize its guidance and phase-in regulation of these tests. The American Heart Association looks forward to providing continued assistance to the FDA in support of this endeavor. If you have any questions or need any additional information, please do not hesitate to contact Kevin Kaiser, Government Relations Manager, at 202-785-7931 or via email at kevin.kaiser@heart.org.

Sincerely,

Elliott M. Antman, MD, FAHA
President
American Heart Association