American Association for Cancer Research
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January 5, 2015

The Honorable Fred Upton
Chairman
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Diana DeGette
Member
House Energy & Commerce Committee
2125 Rayburn House Office Building
Washington, DC 20515

Sent via e-mail: Cures@house.mail.gov

Re: Request for Information Regarding 21st Cures – Request for Feedback: A Modernized Framework for Innovative Diagnostic Tests

Attachments:

1. AACR's Policy Statement on Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care.
2. "21st Century Cures: Examining the Regulation of Laboratory Developed Tests." Testimony by Dr. Charles Sawyer before the Committee on Energy and Commerce, Subcommittee on Health, United States House of Representatives. September 9th, 2014.
3. AACR's comments to FDA on "Expedited Access for Premarket Approval of Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions" Docket No. FDA-2014-D-0363.

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Dear Chairman Upton and Representative DeGette:

Thank you for spearheading the 21st Century Cures initiative- an extraordinary, bipartisan initiative aimed at reviewing the steps that can be taken to accelerate the pace of medical innovation in America- from basic science discovery, to streamlining medical product development processes, as well as harnessing digital technologies to improve health-care delivery.

The American Association for Cancer Research (AACR) was honored to testify in front of the committee on September 9, 2014, in order to provide our perspective on the proposed framework by the Food and Drug Administration regarding the regulation of Laboratory Developed Tests (LDTs). We continue to be extremely engaged on this specific issue and welcome this additional opportunity to address specific concerns regarding the regulation of innovative diagnostic tests. We believe that the proposed framework for regulatory oversight will protect patients, instill physician confidence in the validity of the test results, incentivize innovation, and advance the practice of personalized or precision medicine.

The mission of the AACR is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest cancer organization dedicated to accelerating advances in cancer research to benefit patients. The AACR's membership includes more than 35,000 basic, translational, and clinical researchers, health care professionals, patients and patient advocates residing in the U.S. as well as 96 other countries. Since the AACR encompasses the entire continuum of cancer research and biomedical science – from the laboratory to the clinic including public policy – we are able to marshal the full spectrum of expertise in the cancer community to accelerate progress in the prevention, detection, diagnosis, and treatment of cancer.

Indeed, cancer researchers today are leading the way in the exciting area of personalized or precision medicine, where scientists are increasingly developing treatments that are precisely targeted to the unique molecular and genetic characteristics of an individual's cancer. However, the success of these personalized treatments depends in no small measure on diagnostic tests that are able to reliably detect specific molecular or genetic mutations necessary to ensure that a drug or treatment is ultimately effective.

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We greatly appreciate the thoughtful questions in *A Modernized Framework for Innovative Diagnostic Tests* and are pleased to provide the following feedback to the Committee on this important issue.

1. Multiple stakeholders have expressed the urgent need to have clear and logical lines separating the practice of medicine, the actual conduct of a diagnostic test and the development and manufacturing of diagnostic tests. How should these lines be defined and what are the key criteria separating each of these activities?

- The AACR holds that while LDTs should be regulated by the FDA based on the level of risk posed by the test to the patient, the practice of medicine should NOT be regulated or overseen by the Agency. Therefore, it will be crucial to have clear and precise separation between what will constitute the development and manufacturing of diagnostic tests, which will be subject to oversight by the FDA, the actual conduct of the test in a laboratory that is regulated by the Centers for Medicare & Medicaid Services (CMS) through the Clinical Laboratory Improvement Amendments (CLIA)[1], and the practice of medicine which will continue to be the purview of professional medical associations that rely on the expertise of individual medical practitioners.

- The AACR believes that it is important that both the diagnostic tests components, as well as the precise protocol for using the diagnostic test, are standardized to ensure consistency of test quality and test results. This particular recommendation applies to those diagnostic tests that are classified as high-risk, as well as certain moderate risk tests, regardless of origin and including instances wherein laboratories significantly modify a manufactured test kit. The current lack of oversight of LDTs by the FDA has led to discrepancies in testing procedures and results which could directly impact patient safety and treatment outcomes[2,3].

- The interpretation of diagnostic test results relies on the judgment of qualified medical personnel and therefore, should continue to be considered the practice of medicine which is not and should not be subject to regulation by the FDA.

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[1] Standards and Certification: Laboratory Requirements (42 CFR 493) http://www.ecfr.gov/cgi-bin/text-idx?SID=1248e3189da5e5f936e55315402bc38b&node=pt42.5.493&rgn=div5, Accessed on Dec. 16th, 2014

[2] Peikoff, Kara. December 30, 2013. I Had My DNA Picture Taken, With Varying Results. The New York Times. December 30, 2013 http://www.nytimes.com/2013/12/31/science/i-had-my-dna-picture-taken-with-varying-results.html?pagewanted=all&_r=0#commentsContainer , Accessed on Dec. 16th, 2014

[3] Daley, Beth. December 14th, 2014. Oversold prenatal tests spur some to choose abortions. The Boston Globe. http://www.bostonglobe.com/metro/2014/12/14/oversold-and-unregulated-flawed-prenatal-tests-leading-abortions-healthy-fetuses/aKFAOCP5N0Kr8S1HirL7EN/story.html?event=event25, Accessed on Dec. 16th, 2014

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- For example, in the case of an LDT that utilizes the ImmunoHistoChemical (IHC) staining technique protocol for a companion diagnostic test, which would be categorized as a high-risk test, the equipment, reagents and precise protocol (e.g. sample collection and storage protocols, antigen retrieval procedure, incubation time) used to stain a sample should be subject to FDA regulation. The implementation of the test protocol should continue to be subject to CLIA oversight, while the pathologist's interpretation of the test results and expert opinion would continue to not be subject to FDA's oversight since it constitutes the practice of medicine.

2. In FDA's draft regulatory framework, the agency describes the extent to which it proposes to regulate LDTs as medical devices under the Federal Food, Drug, and Cosmetic Act (FFDCA). It is relatively clear with respect to distributed test kits what constitutes a "device," but less clear when considering a test developed and performed in a laboratory. What should comprise the "device" subject to regulation?

- The AACR applauds the FDA's proposal to phase-in a risk-based approach to regulating LDTs as medical devices and agrees that in the absence of a marketed test kit, the exact constituents of a "device" may lead to confusion.

- The diagnostic test should be considered the regulated device, including the test protocol and any and all equipment including software, General Purpose Reagents (GSRs), and Analyte-Specific Reagents (ASRs) used to perform the test.

3. FDA intends its regulation of diagnostics to be risk-based. How should risk be defined? Are the types of risks posed by diagnostic tests different from therapeutic medical devices? Are these risks different with LDTs compared to distributed test kits? Is the traditional medical device classification system appropriate for these products?

- The AACR believes that risk classification should be based on the overall risk to patient safety from an erroneous test result or the risk posed to patients from an invasive test procedure. Further, we believe that the current risk classification system used by the FDA for devices and *In Vitro* Diagnostics (IVDs) is appropriate and applicable to LDTs as well since the types of risks posed by diagnostic tests do not differ based on the origin of the diagnostic test.

- Therefore those LDTs in which erroneous test results pose the greatest threat to patient safety should be designated Class III or the highest risk category tests. For example, LDTs that are offered *in lieu* of FDA approved companion diagnostic tests and used to

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directly determine a patient's course of treatment (or non-treatment) should be classified as Class III or high-risk diagnostic tests. In addition, other LDTs such as prognostic tests, which are used to predict a patient's disease risk or the risk of disease recurrence may be classified as Class II (moderate risk) or Class III (high risk) depending on the specific intended uses, claims and limitations of the individual tests, and the availability of other clinical or informational evidence to assist in the determination addressed by the LDT.

- The AACR believes that risk should not be defined based on the technical or technological complexity of the test, but should be based on the risk posed to patients. For example; all diagnostic tests utilizing a complex technology or technique such as Next Generation Sequencing (NGS) should not be classified under the same risk designation if they confer different risks to patient safety. Rather, the safety and efficacy of each individual test should be considered independently.

- The AACR agrees with the FDA that the risk posed to patients by tests does not differ based on the origin of tests- LDTs are *in vitro* diagnostics (IVDs) and should therefore be subject to the same regulatory risk guidelines as all medical devices.

- The types of risks to patients from inaccurate diagnostic tests are akin to those posed by faulty therapeutic medical devices. For example, an erroneous test result could lead to misdiagnosis leading to unnecessary or over-treatment. Likewise, an erroneous test result could lead to a failure to diagnose a disease or condition leading to the patient not being treated. Both of these situations would be equally unacceptable. Therefore, we believe that the FDA's current risk classification system for medical devices is appropriate and sufficient to be applied to LDTs.

4. The current pre-market review standards that apply to in vitro diagnostics use the same terminology of safety and effectiveness that apply to all medical devices. Should the medical device concepts of safety and effectiveness apply to test kits and LDTs?

- The same safety and effectiveness standards should apply to both LDTs and test kits because they are both IVDs, which section 210(h) of the Federal Food, Drug, and Cosmetic Act (FFDCA) classifies as medical devices[4].

[4] Federal Food, Drug, and Cosmetic Act. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?FR=809.3, Accessed on Dec. 16th, 2014

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5. Are there areas where the balance between pre-market review versus post-market controls should be reconsidered? How can post market processes be used to reduce barriers to patient access to new diagnostic tests?

- The AACR believes that premarket review of high risk and certain moderate risk LDTs is important to ensuring patient safety. CLIA validation of LDTs, which is limited to analytic validation, occurs only after the test is available to the public (post-market).

- The FDA has released draft guidance on Expedited Access PMA, which would serve to hasten the pre-market approval for medical devices, including diagnostic tests, for unmet medical needs by relying on some level of post-market data for assessing safety and effectiveness[5]. The AACR welcomed this proposal and offered comments in response to the draft guidance document (attached).

6. A number of stakeholders have expressed concerns about uncertainty as to when a supplemental premarket submission is required for a modification. When should they be required prior to implementing modifications? Should the requirements for submission of a supplemental clearance or approval differ between LDTs and distributed test kits?

- One of the hallmarks of LDTs is their adaptability- they can be easily experimentally modified by laboratories, often leading to the development of a better diagnostic. However, *significant changes* to existing LDTs and marketed test kits, including significant changes to the protocol could alter the outcome of the test. Therefore, we believe supplemental pre-market submissions would be warranted in these situations.

- The requirements for submission and approval of supplemental clearance should be the same for both high risk and certain moderate risk LDTs and distributed test kits because they are both IVDs.

7. We have heard a lot about the practice of medicine and its relationship with medical product "labeling." What should comprise "labeling" for diagnostic tests? Should different standards for dissemination of scientific information apply to diagnostic tests versus traditional medical devices? What about for laboratories that develop, perform, and

[5] U.S. Food and Drug Administration. Draft Guidance for Expedited Access for Premarket Approved Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm393879.htm Accessed on Dec. 16th, 2014

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improve these tests? Should there be regulatory oversight of the information that is provided to the individual patient or health care provider or is that the practice of medicine?

- The AACR agrees that medical product "labeling" regulations present a challenge with regard to LDTs.

- The standards for dissemination of scientific information should apply to diagnostic tests based on the level of risk they pose to patients. For example, a Class III test should have different standards in the test-specific information conveyed to the ordering physician compared to a Class I test.

- There should be regulatory oversight in determining whether information pertinent to the test itself is provided to patients and health care providers. For example, it is appropriate to require that information on the limitations or caveats for high risk and certain moderate risk LDTs, especially information that would affect the interpretation of the test results, be provided to the ordering physician. However, the considered opinion of a pathologist and his/her interpretation of the test result is part of the practice of medicine and should continue to not be regulated by the FDA.

8. The Section 1143 guidance documents raise important questions about the relationship between the FFDCA and the Clinical Laboratory Improvement Amendments (CLIA), administered by the Centers for Medicare & Medicaid Services (CMS). Is there overlap between the requirements of the guidance documents and CLIA? For instance, how do FDA's quality systems regulations compare with CLIA quality systems requirements? Are there areas of duplication where there would be efficiencies to having either CLIA or FDA regulate, rather than both?

- The AACR views CLIA and FDA guidelines as complementary systems of regulation, both integral and important for patient safety. CLIA guidelines ensure that LDTs are performed in the appropriate laboratory conditions, but do not ensure the clinical relevance or validity of the tests.

- The AACR agrees with the FDA's assessment that CLIA regulations might be sufficient for certain LDTs, such as those tests designated as "*Traditional LDTs*", and for which the FDA will "*exercise enforcement discretion*." However, for high risk and certain moderate risk LDTs it is essential to have active FDA oversight of tests to ensure patient safety and product efficacy.

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9. How should any regulatory system address diagnostic tests used for rare diseases or conditions, customized diagnostic tests and diagnostic tests needed for emergency or unmet needs (e.g. Ebola)?

- The Humanitarian Use Devices (HUD)/Humanitarian Device Exemption (HDE) provisions (FFDCA) regulations (21 CFR 814, Subpart H) provide an expedited regulatory pathway for the development of IVDs for rare diseases (fewer than 4000 patients per year tested).

- The AACR agrees with the FDA that LDTs that would test greater than 4,000 patients per year do not qualify as HUDs, even if prevalence of that disease is below 4,000 patients per year.

- Section 564 of the FFDCA (21 U.S.C. 360bbb-3) permits the FDA to authorize the use of an unapproved medical device in the case of an emergency. The FDA recently issued an Emergency Use Authorization (EUA) for unapproved IVDs in diagnosing Ebola this past August. The AACR believes that the EUA policy works well for IVDs including LDTs that are needed for emergency needs.

10. Any new regulatory system will create transition challenges. How should existing products be handled? Should all current diagnostic tests be "grandfathered" into the marketplace? What transition process should be used for new product introductions?

- The AACR acknowledges that there will be challenges in implementing the new guideline for LDTs, but believes that the phased-in implementation plan proposed by the FDA, with initial action directed toward high-risk tests, is appropriate and reasonable.

- The AACR does not believe that all current diagnostic tests should be "grandfathered" into the marketplace because of concerns involving clinical efficacy and patient safety.

- Further, the AACR acknowledges the FDA's efforts at ameliorating the challenges for laboratories during the transition period by proposing that laboratories will continue to be allowed to offer current LDTs during the pre-market review process, at least until the FDA completes its review of applications.

- New LDT products should follow the IVDs pre-market guidelines[6].

[6] U.S. Food and Drug Administration. In Vitro Diagnostic (IVD) Device Studies – Frequently Asked Questions. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM071230.pdf Accessed Dec. 16th, 2014

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11. What incentives can be put in place to encourage the development of new, more accurate or more efficient diagnostic tests?

- Ensuring the safety, reliability and accuracy of diagnostic tests is vital to safeguard patients, instill physician confidence in the validity of test results, advance personalized medicine and promote innovation.

- Having a predictable and reliable regulatory environment is important to encourage an innovative biomedical ecosystem in the United States.

- Implementing a single, strict regulatory pathway through the FDA will help reassure clinicians, patients and the public that the tests used to make treatment decisions are safe, accurate and effective.

- Implementation of a risk-based framework by the FDA that would provide for the evaluation of all high risk and certain moderate risk molecular diagnostic tests would balance the importance of encouraging innovative medical product development with the need for ensuring patient safety.

We would like to take this opportunity to once again thank the subcommittee for recognizing the importance of LDTs in our health care system, especially in the delivery of modern cancer care, and for taking the initiative to examine the FDA's proposal to phase–in a risk-based oversight framework for LDTs. The AACR is pleased to extend its resources and broad expertise to you and your colleagues as you consider further action on this matter. If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Director, Regulatory Science and Policy at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,

Margaret Foti, PhD, MD (hc)

Chief Executive Officer

American Association for Cancer Research

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Clinical Cancer Research

Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research

Charles L. Sawyers and Laura J. van 't Veer

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Clinical Cancer Research

Policy Statement

Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research

Charles L. Sawyers[1] and Laura J. van 't Veer[2]

Diagnostics are enabling physicians to make more informed treatment decisions by tailoring treatments based on each patient's unique molecular profile. Diagnostics are also an increasingly vital tool for translating the state-of-the-art advances made in basic research into improved clinical outcomes for patients. Some of the most exciting scientific advances of our time—genomics, proteomics, and other "omics" technologies—are propelling the development of novel, rapid, sensitive, less invasive, and more accurate molecular diagnostic tests, which in turn is dramatically improving our ability to detect and treat various cancers earlier and with greater precision.

Diagnostics Are Integral to the Practice of Personalized Medicine

The goal of personalized medicine is to customize healthcare to fit the needs of the individual—with medical decisions, practices, and products tailored to the specific patient. Personalized therapies for cancer are rapidly increasing in number, as exemplified by drugs such as crizotinib (1) for the treatment of patients with metastatic non–small cell lung cancer (NSCLC) whose tumors have a specific rearrangement of the *ALK* gene, and vemurafenib (2) for patients with late-stage melanoma whose tumors carry the V600E mutation in the BRAF protein. These new drugs, sometimes referred to as targeted therapies, are designed to target specific mutations or genes in a patient's tumor.

The success of personalized medicine treatments, therefore, depends on accurately identifying patients with a particular mutation before treating them. In fact, the U.S. Food and Drug Administration (FDA) approves targeted therapies along with a diagnostic tool (called a *companion diagnostic*), which provides physicians with information that is essential for the safe and effective use of the therapy (3). More specifically, drugs that are effective in a specific subpopulation of patients are approved with the stipulation that the corresponding diagnostic test must be used to identify the appropriate patients for treatment. Thus, it follows that the diagnostic tools used to detect the molecular alterations that form the basis of tailored cancer treatments are crucial for the safe and effective practice of personalized medicine. This further underscores the importance of ensuring the accuracy and reliability of these diagnostic assays that physicians and clinicians utilize when making medical decisions.

Recognizing the central role of diagnostics tests to current cancer care, on October 29, 2013, the American Association for Cancer Research (AACR) and AdvaMedDx (4) organized a symposium on "*Transforming Cancer Care through Diagnostics and Personalized Medicine* (5)". The purpose of the symposium was to highlight the importance of diagnostics in improving care for cancer patients and to call attention to some of the scientific, regulatory, and policy issues that are central to ensuring a thriving molecular diagnostics industry (see box). The audience of more than 300 people comprised a diverse group of stakeholders, including researchers, clinicians, patients and patient advocacy leaders, drug and diagnostic industry representatives, regulators, and policymakers.

FDA Regulation to Ensure the Reliability and Safety of Molecular Diagnostics

It is widely recognized that the process of seeking approval from the FDA for a diagnostic test is grounded in sound scientific evidence that physicians can rely on for clinical decision-making. Tests developed by a manufacturer and sold to laboratories (often referred to as test "kits") must go through rigorous pre-market analysis, evaluation of its safety and effectiveness, and an approval or clearance process from the FDA before it can be marketed. These test kits are also subject to post-market oversight, including mandatory adverse event reporting and the FDA's recall authority.

The FDA typically assesses and evaluates diagnostic tests on the following three measures (6):

- *analytic validity* to ensure the accuracy, sensitivity, specificity, and reproducibility of the test;
- *clinical validity* to demonstrate that the results of the test are linked to a biological function or a specific disease state of interest (e.g., presence of the V600E mutation in the *BRAF* gene is associated with aggressive melanoma); and
- *clinical utility*, if applicable, to demonstrate whether use of the information obtained from the test improves patient

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Highlights from the October 29, 2013, AACR-AdvaMedDx symposium "Transforming Cancer Care through Diagnostics and Personalized Medicine"

- AACR president and chair of the symposium planning committee, Charles L. Sawyers, MD, noted that the goal for the day was to discuss how to most effectively utilize and speed the translation of information gleaned from investments in basic research into commercial diagnostic products that result in more tailored treatments and better patient outcomes for cancer patients.
- In his opening keynote, National Cancer Institute Director and Nobel laureate Harold E. Varmus, MD, talked about the importance of molecular diagnostics and noted how crucial they are to tailoring therapies to patients based on the unique molecular signatures of their cancers. He stressed the need to incentivize development of validated and accepted diagnostics in order to keep pace with the explosion of new, targeted cancer drugs that are in the pipeline.
- During a special lunchtime conversation, National Institutes of Health Director, Francis S. Collins, MD, and Commissioner of the U.S. Food and Drug Administration, Margaret A. Hamburg, MD, were enthusiastic about the promise of new "omics"-based technologies to comprehensively examine the entire genome of patients, leading to improvements in patient care. They also emphasized the need to optimize and align the scientific enterprise and the regulatory framework for these technologies of the future.
- Commissioner Hamburg stressed that regulating these complex medical products (including companion diagnostics) and coordinating their review and oversight in a manner that efficiently incorporates current regulatory science standards while upholding patient safety present unique challenges, such as requiring the Agency to rethink its approach to clinical trial design; scientific computing; data mining etc. The Agency's new approach to regulating these products cuts across regulatory frameworks and involves multi-disciplinary, cross-collaborative review, she said.
- Dr. Collins predicted that the coming era of whole genome sequencing would soon eclipse our current system of examining just one or a few genes at a time to decide on a treatment course for a patient. He cautioned, however, that whole–genome sequencing presents new ethical and regulatory challenges, such as defining risk and addressing how health care providers should approach incidental findings, which is genetic information discovered unintentionally.
- The Director of the Coverage and Analysis Group at the Centers for Medicare and Medicaid Services, Louis B. Jacques, MD, stressed the need for transparency and unbiased review of tests and mentioned that having a third-party reviewer like the FDA's stamp of approval reassures payors of the utility of tests. During a discussion about valuation of these tests, he suggested that superior tests could realize better value if reimbursement decisions were linked to evidentiary standards that recognize meaningful performance differences between tests.

treatment and management of the disease and how well it relates to the clinical outcome of interest, such as increased survival or a positive response to the drug (e.g., melanoma patients with the BRAF V600E mutation are more likely to benefit when treated with the drug vemurafenib).

Laboratory-Developed Tests—A Vastly Different Regulatory Standard for Molecular Diagnostics

There are also many molecular diagnostic tests that are currently available to physicians but have not undergone an FDA review and approval process. This is because molecular diagnostic tests can ultimately reach the marketplace (and be utilized by the physician and patient) through an alternative to the FDA review and approval process.

This alternative involves laboratory-developed tests or LDTs, which are tests that are designed, manufactured, and offered within a single laboratory. Currently, LDTs are not required to obtain FDA approval before marketing as long as they are designed, manufactured, and used in a single laboratory that meets the Clinical Laboratory Improvement Amendments (CLIA) certification requirements (7). The standards for CLIA certification of a laboratory and CLIA requirements for offering a non–FDA approved test are very different from FDA approval of a test, particularly because CLIA oversight does not assess or evaluate the safety and/or clinical efficacy of a test. Therefore, an LDT developed in a CLIA-certified laboratory can be utilized by a physician to make treatment decisions without any independent verification of the test's clinical validity or utility.

The FDA's Evolving Position on Exercising Enforcement Discretion over LDTs

While the FDA has authority over all diagnostic tests, the agency had historically chosen not to enforce its authority in the case of LDTs (8). The FDA chose not to exercise its regulatory authority in the past largely because LDTs were typically well-established diagnostic test procedures [e.g., urine analysis, microbiology cultures, blood analysis. (9)]. However, some LDTs being developed today run the risk of being ineffective and exposing patients to inappropriate clinical decision-making if they are not subject to the same scrutiny given to FDA-approved tests (10). Examples include germline DNA tests that claim to predict the likelihood for developing certain cancers or their clinical outcome, and LDTs offered and used *in lieu* of FDA-

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approved companion diagnostic tests to identify specific tumor mutations and channel patients toward treatment with targeted therapies. Tests are typically classified as "high-risk" if the test result will directly determine the course of treatment offered (or not) to the patient. Yet these LDTs are widely considered as equivalent to FDA-approved diagnostic tests, and physicians, patients, and payors are often unaware of the regulatory review status of the specific test (FDA-approved test or LDT) being used. The FDA has recently informed Congress of its intent to regulate LDTs using a risk-based, phased-in approach to ensure the safety, accuracy, and reliability of test results used to make treatment decisions by physicians and patients (9).

AACR Policy Statement—Balancing Innovation with Safety by Adopting a Risk-Based Regulatory Framework

In vitro diagnostic tests can be used to determine the likelihood of developing cancers, screen for cancers, gain information about existing cancers, predict the likelihood of recurrence of certain cancers, predict a patient's response and tolerance for treatments, predict patient benefit, estimate side effects, and monitor patients while they undergo treatment. Therefore, the AACR believes it is imperative that all diagnostic tests used to make high-risk treatment decisions, including the tailoring of an individual's cancer treatment regimen, must be FDA-approved to ensure that these diagnostic tests are held to the highest regulatory and approval standards. Having a single, strict, regulatory approval standard would reassure the public that the tests used in high-risk health care decision-making, whether developed by a laboratory or other manufacturer, are safe, accurate, and effective.

Diagnostic tests are evolving to become more complex. These tests are not only technically challenging to perform, but also return results that are complicated to interpret. Further, clinicians are increasingly relying on these complex test results to make treatment decisions. Therefore, patients and physicians should be able to rely on the test results that are forming the basis of high-risk treatment decisions, whether these tests are developed as an LDT or are kits approved by the FDA. Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety. A focus on high-risk tests would also help channel the FDA's limited resources toward those products that pose the greatest health risks for patients. Having a predictable and reliable regulatory environment is important for patients and for diagnostic and drug developers, since the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. Therefore, a single regulatory standard for high-risk diagnostic tests is key to ensuring the safety and efficacy of molecular diagnostic tests.

Recognizing the importance of reliable and safe diagnostics to propel continued innovation of personalized cancer treatments, the AACR has convened a diagnostics guiding principles committee that includes stakeholders from academia and industry to offer policy proposals that will accelerate development of innovative diagnostics by advocating for a more predictable regulatory (and investment) climate for the industry, while simultaneously ensuring patient safety. When a test provider claims that evidence-based information can be used to associate a patient's tumor biomarker status to treatment agents with potential clinical benefit (or lack thereof), physicians and patients should be able to proceed with confidence.

Disclosure of Potential Conflicts of Interest

L.J. van 't Veer is a co-founder, stockholder, and part-time employee of Agendia Inc. C.L. Sawyers is a co-inventor of patents on drug resistance mutations in BCR-ABL, filed by the University of California Los Angeles and licensed to Housey Pharmaceuticals.

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July 22, 2014
Division of Dockets Management
HFA-305
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2014-D-0363 "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions"

To whom it may concern:

On behalf of the American Association for Cancer Research (AACR), the oldest and largest scientific organization in the world dedicated to the prevention and cure of cancer through research, education, communication and collaboration, we sincerely thank the U.S. Food and Drug Administration (FDA) for the opportunity to provide comments in response to the April 2014 draft guidance on "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions."

The AACR applauds the FDA for developing a draft guidance outlining a new, voluntary program to help patients have more timely access to life-saving medical devices including *in-vitro* diagnostic devices. There are, however, a few areas in which we believe additional guidance would be beneficial. Specifically, the AACR requests FDA to provide greater clarity and detail on the definition of "breakthrough technologies", acceptable post-approval studies, alternative mechanisms of evidence gathering, use of surrogate end points, use of the EAP pathway in conjunction with other expedited pathways for medical products and the logistics of implementing this ambitious new program in a potentially resource constrained environment among other issues. We have elaborated on these concerns below.

With these additions, we believe the guidance document will clarify the pathway to expedite development and approval of novel medical devices intended to fulfill an unmet medical need for life threatening diseases like cancer and create new hope for cancer patients worldwide.

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Pathway nomenclature

The pathway as currently named is the "Expedited Access PMA" or EAP pathway. We would like to draw the Agency's attention to an existing pathway that shares this exact acronym namely the "**E**xpanded **A**ccess **P**rogram" (EAP) which allows patient access to experimental drugs outside a clinical trial through a single patient Investigational New Drug (IND) mechanism. To avoid confusion, we suggest the Agency rename the pathway the "**Accelerated Access Pathway**" or AAP. As the draft states, the proposed new pathway is based in part on existing expedited development programs at the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER), namely the Accelerated Approval pathway for drugs and biologics. Thus, we urge the Agency to consider AAP as a viable alternate name for the pathway since it would be parallel and analogous to the mechanism and nomenclature of the existing pathway for drugs and biologics and would help avoid confusion.

Explicitly define "breakthrough technology"

The draft guidance states that a product may qualify for the Expedited Access PMA or EAP designation if "*The device represents a breakthrough technology that provides a clinically meaningful advantage over existing technology*".

It would be helpful if the Agency could clarify what it means by a "breakthrough technology". For example, could an assay based on existing and commonly used technology (such as immunohistochemistry) be considered breakthrough if it provided a clinically meaningful advantage when used with a highly effective therapeutic?
Multiple *in vitro* diagnostic devices or IVDs could be developed using a breakthrough technology such as next generation sequencing or NGS technology. In such a case, the Agency should clarify whether all IVDs that utilize the same underlying cutting-edge technology, such as NGS, could qualify for the EAP designation or whether the designation could only be given to the first application of the technology.
Further technology is constantly evolving and what is considered innovative today will eventually become a routine and common procedure. Therefore, it would help if the Agency could provide some broad, high-level guidelines on its thinking about how it would define and designate a "breakthrough technology".

Provide clarity on the implementation of the EAP pathway

The draft states that "*FDA may approve more than one EAP device for the same condition because of the possibility that the data from the post-approval study may not*

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confirm certain safety or effectiveness aspects of the device under the conditions of use. FDA may therefore consider devices as offering a "significant, clinically meaningful" advantage over existing approved alternatives, notwithstanding the availability of an EAP Device approved on the condition of a post-approval study."

It would be helpful if the Agency could elaborate on how it would interpret and implement this section of the guidance. For example, a plausible scenario is as follows: two products receive EAP designation for the same condition and one product gains approval before the other.
This above situation raises several questions including but not limited to the following:

- Would the second EAP designated product subsequently have to demonstrate evidence of "*significant, clinically meaningful advantage"* over the first EAP designated product?
- Would the details of the data development plan change for the second EAP designated product, even if previously agreed upon by both the sponsor and the Agency?
- If so, would the Agency continue to work with the sponsor to aid in revising the data development plan? and
- Would the burden of proof for demonstrating *significant, clinically meaningful advantage* differ from proving safety and effectiveness?

With respect to the concern that the "*…data from the post-approval study may not confirm certain safety or effectiveness aspects of the device…",* it would be helpful if the Agency could clarify whether this would result in a "revision" to a specific aspect of the device in question or whether it would entail something more. For example, perhaps a cutoff value for a biomarker based *in vitro* diagnostic assay would change based on data obtained in the post-marketing setting which may necessitate recalibration of the device. It would also help if the Agency could elaborate on how the data obtained from post-approval studies would be used to refine or revise the product in the post-marketing setting including the logistics of informing the sponsor of changes to the product, ensuring implementation of these changes while the product is on market, timeline for implementation of changes etc.

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Clarify use of EAP pathway in conjunction with existing expedited pathways for approval of drugs and biologics

The EAP draft guidance states that "…*certain companion diagnostics, when appropriate, and with consultation from CDER or CBER, may be considered for the Expedited Access PMA. For example, if a drug is reviewed via the accelerated drug approval pathway based on a surrogate endpoint, the companion diagnostic may be considered for the Expedited Access PMA*."

We welcome the Agency's willingness to consider a companion diagnostic for the EAP designation if its corresponding therapeutic partner is granted expedited review via the accelerated approval pathway. However, the Agency should clarify the status of the companion diagnostic in a situation wherein the therapeutic product fails its confirmatory study since an investigational drug or biologic is granted accelerated approval on the condition that the sponsor will conduct post-market confirmatory studies and with the understanding that the Agency has authority to withdraw approval for the drug or biologic if the confirmatory studies fail to meet the appropriate clinical end point. We also request that the Agency provide more details on the processes and procedures whereby sponsors can coordinate filing requests for accelerated approval of the therapeutic product and the EAP designation for its companion diagnostic.

Given that the recent "Breakthrough Therapy designation" has provided a great opportunity to expedite approval of therapies especially in oncology, the Agency should clearly state whether companion diagnostics to Breakthrough Therapy designated products may also be considered for the Expedited Access PMA. Further, given that most oncology therapies under current development are targeted therapies with a companion diagnostic, the Agency may want to consider automatically granting EAP designation to the companion diagnostic of breakthrough designated and accelerated approval pathway products.

Provide greater details on acceptable post-marketing studies

The EAP program will rely heavily on post-marketing studies to provide additional evidence of the safety and efficacy of the device. However, the guidance fails to give details of situations or examples of post-market studies that may be appropriate. We note that the Agency has released draft guidance on *Balancing Premarket and Postmarket*

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Data Collection for Devices Subject to Premarket Approval[1] in which there is one example of a situation where postmarket data collection may be appropriate for an IVD.

"Example: *HPV testing devices have two distinct intended use populations with inherently different risk levels for cervical pre-cancer and cancer. Approval for both populations was based on full analytical data and agreement of clinical samples against a valid comparator, and clinical evidence of safety and effectiveness for the high risk population. A post-approval study assessed the longitudinal risk of cervical cancer in the population with lower risk*."

However, given the diversity of IVD products it would be helpful for the Agency to give more examples of situations where post-market data studies would be appropriate for an IVD seeking EAP approval. It would also be helpful if the Agency could provide details on what kinds of information can be relegated to post-market studies by sponsors who are planning to file for an EAP designation. In other words, it would be helpful if the Agency could clarify whether they are primarily interested in collection of serious adverse effects or long-term safety or product effectiveness etc.

The draft states that "…*FDA may require a bridging study to evaluate the potential impact of various changes (e.g., specimen processing or storage, device or software modifications) on analytical and clinical performance*."

The Agency should clarify whether these bridging studies should be conducted in the pre or post marketing setting. We also refer the Agency to our concerns about interpretation of data from post-approval studies not confirming certain safety or effectiveness aspects of the device detailed earlier in this comment letter. We request the Agency to clarify whether bridging studies can be carried out and/ or may suffice in cases where post-approval studies raise concerns about the quality of a product.

Establishing safety and efficacy of IVDs requires establishing not just analytic and clinical validity, but most importantly clinical utility. Collecting clinical utility data often involves conducting clinical studies which can be expensive and time consuming. The

[1] Balancing Premarket and Postmarket Data Collection for Devices Subject to Premarket Approval: FDA Draft Guidance issued on April 23, 2014. http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393994.pdf

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draft guidance, however, does not mention collection of clinical utility data. Therefore, it would be helpful if the Agency could clarify whether clinical utility data may be collected in the post-market setting if the IVD qualifies for an EAP designation and elaborate on how data collection in the post-market setting should be implemented.

Provide greater detail on acceptable evidence

The draft states that "*In the absence of a new prospective clinical study, FDA may in some cases accept alternative experimental designs unique to diagnostics to generate evidence demonstrating the analytical and clinical validity of an IVD for premarket approval*." One of the examples given is: "*In cases where the clinical validity of a biomarker test may be fully established in the literature, only analytical data that demonstrate a genetic test can accurately detect the variant may be necessary*."

Given that studies in literature span the gamut from early observational studies to studies in validated animal models to reports of clinical trials, it would be helpful if the Agency could clarify, detail and elaborate on what level of evidence and what methodology of study constitutes "*fully established clinical validity of a biomarker test*" in the literature.

With respect to Companion Diagnostics, the draft states that "*In some situations (e.g. a test that combines multiple analytes into a score), a reference method may not exist for direct analytical comparison. In these instances, alternative approaches to address analytical performance may be appropriate*."

We commend the Agency for including this forward-looking concept in the draft. However, it would be helpful if the Agency could provide concrete examples of methodologies and/or kinds of studies that would be acceptable "alternate approaches" to address analytical performance of IVDs and companion diagnostics. We acknowledge the difficulty of providing such comprehensive information *a priori*, therefore, we urge the Agency to provide as much detail and clarity as possible on this issue which is of great importance and concern to the field.

Clarity on the use of surrogate end points

The draft states: "*FDA may, as a basis for PMA approval, rely on assessments of a device's effect on an intermediate or surrogate endpoint that is reasonably likely to predict clinical benefit...*"

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As an example, the draft provides the following: "*Early pathophysiologic analysis of biopsied breast lesions is not a direct measure of clinical benefit but has been shown to correlate with and predict morbidity and mortality associated with breast cancer. Pathophysiological analysis of biopsied breast lesions could serve as a surrogate endpoint for device trials, provided there is sufficient evidence of a known or reasonably likely predictive relationship with clinical benefit such as survival.*"

It would be helpful if more examples of acceptable surrogate and intermediate endpoints could be provided. It would also be helpful if the Agency could provide details of currently accepted surrogate and/or intermediate endpoints for approval of IVDs and companion diagnostics especially in oncology. The Agency should also clarify the conditions as well as the process by which a sponsor could use a novel surrogate or intermediate end point to provide evidence of a device's efficacy and/or safety.

An important consideration for researchers and developers of oncology products is the use of surrogate end points to qualify a therapeutic and its companion diagnostics. We request the Agency to clarify whether the "clinical benefit" of a companion diagnostic demonstrated using a surrogate end point or otherwise, will be judged or considered independently of its corresponding therapeutic product.

Logistics of implementing the EAP program

The draft states that "*As part of this EAP program, FDA intends to provide, **as resources permit**, more interactive communications during device development and more interactive review of Investigational Device Exemption (IDE) applications and PMA applications. In addition, FDA intends to work interactively with the sponsor to create a data development plan specific to the device ("Data Development Plan"). This Data Development Plan should outline all data the sponsor intends to collect in support of device approval, including what data will be collected premarket and postmarket.*"

We enthusiastically welcome the Agency's willingness to consider a pathway to expedite development of life-saving medical devices. However, it is concerning that the Agency uses the phrase "**as resources permit**" to qualify its ability to provide more interactive communications. It would be helpful if the Agency could elaborate on its thinking around how it plans to implement this exciting new, albeit potentially resource intensive program. We specifically request that the Agency clarify the meaning and intent behind the phrase "**as resources permit**" and elaborate on how it plans to determine whether it has adequate resources to man the program and further whether and how it plans to

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communicate its resource availability to researchers and developers who wish to avail themselves of the EAP program. Of concern to us is, whether the Agency can deny a potential EAP designation to a product that fully merits the designation, solely on the basis of a lack of Agency resources. This also leads to a concern that EAP designations will be limited by the Agency's resource constraints or EAP designations will only be considered when and if the Agency decides it can spare adequate resources, which we acknowledge may fluctuate from time to time. The question of resource availability also poses concerns about the Agency's ability to work with sponsors on the "data determination plan" which is a central and crucial component of obtaining the EAP designation. Since the main advantage to sponsors granted the EAP designation is the ability to work with the Agency to create the Data Development Plan and have interactive communications during product development, it is unclear how a sponsor may benefit from the EAP designation if the Agency grants the designation, but subsequently decides it is resource constrained and therefore cannot offer the above benefits to the sponsor.

The AACR commends the FDA for its commitment to incorporating scientific advances into its regulatory framework. The AACR is pleased to extend its resources and broad expertise to the FDA as the Agency further considers revisions to the April 2014 draft guidance on "Expedited Access for Premarket Approval Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Disease or Conditions". If you have any further questions or require follow up, please contact Rasika Kalamegham, PhD, Director, Regulatory Science and Policy at 267-765-1029 or rasika.kalamegham@aacr.org.

Sincerely,

Frank McCormick, PhD, FRS
Chair, Regulatory Science & Policy Subcommittee

Margaret Foti, PhD, MD (h.c.)
Chief Executive Officer

American Association for Cancer Research

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21st Century Cures: Examining the Regulation of Laboratory Developed Tests

Testimony Before
Committee on Energy and Commerce
Subcommittee on Health
United States House of Representatives

Charles L. Sawyers, MD

Immediate Past President of the AACR

Chair, Human Oncology and Pathogenesis Program

Memorial Sloan Kettering Cancer Center

New York, NY

September 9, 2014

21st Century Cures: Examining the Regulation of Laboratory Developed Tests

Testimony of Charles L. Sawyers, MD, Chair, Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center

Good morning, Mr. Chairman and distinguished Members of the Subcommittee. I am the immediate past president of the American Association for Cancer Research (AACR), and serve as Chair of the Human Oncology and Pathogenesis Program at Memorial Sloan Kettering Cancer Center. I am honored to appear before you today to provide you with a perspective from the AACR on the recent notification offered by the Food and Drug Administration regarding the regulation of Laboratory Developed Tests (LDTs). Specifically, I will address the ways in which we believe this potential framework for regulatory oversight will protect patients, incentivize innovation, and advance the practice of personalized or precision medicine.

The mission of the AACR is to prevent and cure cancer through research, education, communication, and collaboration. Founded in 1907, the AACR is the world's oldest and largest cancer organization dedicated to accelerating advances in cancer research to benefit patients. The AACR's membership includes more than 35,000 basic, translational, and clinical researchers, health care professionals, patients and patient advocates residing in the U.S. as well as 96 other countries.

Because the AACR encompasses the entire continuum of cancer research and biomedical science – from the laboratory to the clinic including public policy – we are able to marshal the full

spectrum of expertise in the cancer community to accelerate progress in the prevention, detection, diagnosis, and treatment of cancer.

Cancer researchers today are leading the way in the exciting area of personalized or precision medicine, where scientists are increasingly developing treatments that are precisely targeted to the unique molecular and genetic characteristics of an individual's cancer. However, the success of these personalized treatments depends in no small measure on diagnostic tests that are reliable.

The Promise of Personalized or Precision Medicine

The knowledge of cancer's underlying biological causes, enabled through sustained investment by the federal government, primarily through the National Institutes of Health, has catalyzed a shift from the classification of cancer by site of origin, like lung or breast cancer, to classification by molecular subtype. This means that we are rapidly moving away from the era of one-size-fits-all cancer treatments that involve surgery, radiation, and chemotherapy, and are instead utilizing more sophisticated and highly innovative DNA sequencing technologies to provide patients with more opportunities for targeted treatments and personalized or precision medicine. More and more, we are treating cancer patients based on the specific molecular characteristics of his or her tumor(s), which is increasingly determined using highly complex DNA sequencing technologies. The promise of this approach is immense, and we are now ensuring that these advances are being applied to various forms of cancer with increasing speed and success.

I know the impact of molecularly targeted cancer therapy from firsthand experience, having led the first clinical trial of a drug called Gleevec that is highly effective in a form of blood cancer known as chronic myeloid leukemia. Patients with this formerly devastating disease now live for decades simply by taking a pill once a day that precisely targets the cancer cells. In fact, many of the patients I treated on the first clinical trial in 1999 are still alive and well today.

Since the approval of Gleevec in 2001, many additional targeted therapies have been developed and approved for a range of cancers; including previously deadly cancers -45 such personalized or precision medicines have gained FDA approval as of July 31 this year[1]. The benefit of targeted cancer therapy is that we are able to hone in on specific mutations that drive the growth of a patient's tumor cells, thereby enhancing the chance of a successful treatment response without the side effects of chemotherapy or radiation. However, this sophisticated mechanism of action also means that these drugs are only effective in those patients whose tumors carry these mutations. Therefore, the success of these personalized or precision medicine treatments depends on accurately identifying patients with a particular mutation before treating them with the appropriately matched drug. This is why the sophisticated new diagnostic tests that enable physicians to match the right drugs to the right patients play such a critical role in cutting-edge cancer care.

Importance of Accurate and Effective Diagnostics in Cancer Care

That over 40 targeted cancer therapies have gained FDA approval over the past 10 years is a testament to the fact that we have a streamlined and effective regulatory process in the U.S. To ensure that the right patients receive a targeted drug, the FDA approves targeted therapies in

[1] US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals; accessed on Sep. 5, 2014 http://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm279174.htm

conjunction with a diagnostic tool called a *companion diagnostic*, which provides physicians and patients with information that is essential for the safe and effective use of the therapy[2]. Drugs that are effective in a specific sub-population of patients are approved with the stipulation that the corresponding diagnostic test must be used to identify the appropriate patients for treatment. Thus, it follows that the diagnostic tools used to detect the molecular alterations that form the basis of tailored or personalized cancer treatments are crucial for the safe and effective practice of personalized medicine. A safe, reliable, accurate, and sensitive diagnostic test is as important as a safe, reliable, and effective drug.

Different Paths to Market for Diagnostics

In contrast to the single regulatory path to market for drugs, there are two very different paths to market for a diagnostic[3]. The first path is by gaining approval or clearance from the FDA which requires a sponsor to demonstrate proof of analytic and clinical validity as well as clinical utility of the test in some cases. *This is the path by which companion diagnostics are currently approved, in conjunction with approval of a targeted therapy*. The second path to market is when a test developer designs, manufactures and offers the test within a single laboratory as a laboratory developed test or an LDT. Because LDTs are not subject to the same level of scrutiny as diagnostics approved through the first regulatory path, there is less certainty and confidence in the accuracy of these products. This is particularly relevant for the highly sophisticated DNA sequencing technology based tests that generate the information from tumor cells that form the basis for many companion diagnostic tests.

[2] US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools); accessed on Sep. 5, 2014

[3] Sawyers CL, and van 't Veer, LJ. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research. Clin Can Res; Published Online First September 9, 2014; doi: 10.1158/1078-0432.CCR-14-2295.

For a cancer patient, the consequences of an incorrect treatment recommendation made on the basis of a faulty diagnostic test are unacceptable, since the patient may lose the opportunity to receive an effective treatment or may be exposed to side effects from a treatment that has little to no chance of benefit. Physicians and patients must be able to trust the claims made by developers of health care products, especially products that determine the treatment regimen for a cancer patient.

A Single Regulatory Standard to Ensure Patient Safety and Reliability of Diagnostics

Given the importance of diagnostic tests to personalized cancer treatments, the AACR believes it is imperative that all diagnostic tests used to make high-risk treatment decisions, including the tailoring of an individual's cancer treatment regimen, must be FDA-approved to ensure that these diagnostic tests are held to the highest regulatory and approval standards[4]. Having a single, strict regulatory approval standard will reassure the American public that the tests used in high-risk health care decision-making, regardless of origin, are safe, accurate, and effective.

The FDA's Proposed Framework for Regulatory Oversight of LDTs

The AACR welcomes the recent notification to Congress by FDA of its intent to phase-in a risk-based framework for regulatory oversight of laboratory developed tests[5]. We commend the FDA for taking a regulatory approach that puts patients first by proposing a classification of LDTs

[4] Sawyers CL, and van 't Veer, LJ. Reliable and Effective Diagnostics Are Keys to Accelerating Personalized Cancer Medicine and Transforming Cancer Care: A Policy Statement from the American Association for Cancer Research. Clin Can Res; Published Online First September 9, 2014; doi: 10.1158/1078-0432.CCR-14-2295.

[5] US Food and Drug Administration. Notification to Congress and Anticipated Details of the Draft Guidance for Industry, Food and Drug Administration Staff and Clinical Laboratories; Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs); accessed on Sep 5, 2014 http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm407409.pdf

based on the risk posed by the test to the *patient*. We also note that the FDA plans to focus its efforts and appropriately utilize its resources by continuing to exert its policy of enforcement discretion over low-risk and routine laboratory procedures such as blood and urine analysis. As an organization of cancer scientists and physicians, we strongly support efficient and evidence-based regulatory policy making, and we look forward to doing the same with this proposal.

The proposed framework strikes a thoughtful balance between protecting patient safety while promoting research and innovation in this rapidly evolving field in the following ways:

- By prioritizing FDA's initial oversight efforts to ensure that high-risk LDTs undergo pre-market review to assess the accuracy and safety of the test especially when there is an FDA-approved/cleared equivalent currently on the market;
- By ensuring that this proposal will not adversely affect the ability of researchers at academic medical research centers to develop new tests or conduct clinical research;
- By ensuring that patient access to tests that have not yet undergone FDA review will not be obstructed in cases where there is not an equivalent FDA-approved or cleared test
- By requiring adverse event reporting of LDTs and
- By providing adequate time for laboratories and providers to be in compliance by phasing in the requirements over a period of nine years after the guidance is finalized.

Conclusion

Diagnostic tests are evolving to become more technically complex, and the complexity of these tests will only grow with the increasing use of next-generation sequencing or NGS-based tests. Further, clinicians are increasingly relying on these complex test results to make treatment

decisions. Therefore, patients and physicians should be confident in the test results that are forming the basis of high-risk treatment decisions, whether these tests are developed as an LDT or are kits approved by the FDA. Implementation of a risk-based framework by the FDA that would provide for evaluation of all high-risk molecular diagnostic tests would balance the need for encouraging innovative medical product development with the need for ensuring patient safety. Having a predictable and reliable regulatory environment is important for patients and for developers of diagnostic and drugs, since the success of a targeted therapy is inextricably linked to the successful development of its companion diagnostic test. Therefore, a single regulatory standard for high-risk diagnostic tests is crucial to ensuring the safety and efficacy of molecular diagnostic tests and the key to advancing personalized medicine. We are in the midst of an extremely promising age of innovative new cancer treatments. Genome sequencing and targeted treatments are revolutionizing the way we treat cancer patients and the way we develop cancer treatments. A robust, predictable, and reliable evidence-based regulatory framework will ensure that these 21st century cures will reach patients in an efficient and expeditious manner.

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About the American Association for Cancer Research

Founded in 1907, the American Association for Cancer Research (AACR) is the world's oldest and largest professional organization dedicated to advancing cancer research and its mission to prevent and cure cancer. AACR membership includes more than 35,000 laboratory, translational, and clinical researchers; population scientists; other health care professionals; and cancer advocates residing in more than 90 countries. The AACR marshals the full spectrum of expertise of the cancer community to accelerate progress in the prevention, biology, diagnosis, and treatment of cancer by annually convening more than 20 conferences and educational workshops, the largest of which is the AACR Annual Meeting with more than 18,000 attendees. In addition, the AACR publishes eight peer-reviewed scientific journals and a magazine for cancer survivors, patients, and their caregivers. The AACR funds meritorious research directly as

well as in cooperation with numerous cancer organizations. As the scientific partner of Stand Up To Cancer, the AACR provides expert peer review, grants administration, and scientific oversight of team science and individual grants in cancer research that have the potential for near-term patient benefit. The AACR actively communicates with legislators and policymakers about the value of cancer research and related biomedical science in saving lives from cancer. For more information about the AACR, visit www.AACR.org.