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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

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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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References

1. US Food and Drug Administration. Crizotinib accelerated approval letter; accessed on Aug 5, 2014 http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/202570s000ltr.pdf.
2. US Food and Drug Administration. Vemurafenib approval package; accessed on Aug 5, 2014 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/202429Orig1s000Approv.pdf.
3. US Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools); accessed on Aug 5, 2014 http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/ucm301431.htm.
4. Transforming cancer care through diagnostics and personalized medicine- Agenda of symposium sponsored by AACR and AdvaMedDx; accessed on Aug 5, 2014 http://www.aacr.org/AdvocacyPolicy/GovernmentAffairs/Pages/aacr-advameddx-symposium-on-cancer-diagnostics-agenda___EF0C4F.aspx.
5. Transforming cancer care through diagnostics and personalized medicine- symposium sponsored by AACR and AdvaMedDx; video archive of the event; accessed on Aug 5, 2014 http://www.youtube.com/playlist?feature=edit_ok&list=PLBR9hdykU9fZQpJGvd9IFvXyAYgln2ON0.
6. IOM (Institute of Medicine). 2012. Evolution of Translational Omics: Lessons Learned and the Path Forward. Washington, DC: The National Academies Press.
7. Parkinson DR, McCormack RT, Keating SM, Gutman SI, Hamilton SR, Mansfield EA, et al. Evidence of clinical utility: an unmet need in molecular diagnostics for patients with cancer. Clin Cancer Res 2014;20:1428–44.

Published OnlineFirst September 9, 2014; DOI: 10.1158/1078-0432.CCR-14-2295

8. Centers for Medicare and Medicaid Services. Clinical Laboratory Improvements Amendments accessed on Aug 5, 2014. http://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/Downloads/LDT-and-CLIA_FAQs.pdf.
9. US Food and Drug Administration. Notification to Congress and Anticipated details of the draft guidance to industry, Food and Drug Administration Staff and Clinical Laboratories, Framework for regulatory oversight of Laboratory Developed Tests (LDTs); accessed on Aug. 5, 2014 http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/InVitroDiagnostics/UCM407409.pdf.
10. Buchen L. Cancer: missing the mark. Nature 2011;471:428–32.