



Laboratory Testing in the Era of Precision Medicine

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Good morning, Chairman Alexander, Ranking Member Murray, and Members of the committee. I am Dr. Jeff Allen, President & CEO of Friends of Cancer Research, an advocacy organization that drives collaboration among every healthcare sector to power advances in science, policy, and regulation that speed life-saving treatments to patients. I would like to thank all Members and the staff of this committee for putting together this important hearing. It is an honor to testify before you today and provide the perspective of my organization, and on behalf of patients, as you continue this committee's efforts to examine how laboratory testing can best support the future of medicine and patient care.

Advancements in basic science have never been more profound. The remarkable advancements being made at the National Institutes of Health (NIH), at medical and academic centers all across the country and within private sector industry are rapidly changing how we look at disease, and are in some cases leading to new and markedly improved treatments for patients. Exciting new initiatives like the President's Personalized Medicine Initiative (PMI) and the Vice President's Cancer Moonshot are important opportunities to continue along this promising trajectory and build on the remarkable progress to date.

The therapies patients have access to today to treat many different diseases are far more effective, but also more complex than their predecessors. Adding to this complexity, and the more exacting nature of science today, is the increased reliance on molecular tests for providing optimal medical care. It's not unusual for a variety of tests to be used by healthcare providers to help identify elevated risks, diagnose certain conditions, inform the best treatment option, or even measure if a treatment is working. In some cases, entire treatment regimens are being prescribed based upon the results of such tests.

Given the role that medical tests play in optimizing and determining patient care, it's imperative that these tests' performance and accuracy be well characterized before placing important treatment decisions on the results that they provide. The ramifications of uncertainty or inaccuracy can be quite significant. An inaccurate test could result in a patient not receiving the most appropriate treatment or expose them to an unnecessary or potentially harmful treatment. A recent report from the National Academies concluded that diagnostic errors, including some from molecular tests, account for 6-17% adverse events in hospitals, and played a role in 10% of patient deaths.¹ I don't raise these statistics to be alarmist, to suggest that medical tests are not vital to the future of patient health, or to ignore that there are currently numerous, highly beneficial tests that facilitate the use of life-saving treatments. But as this field rapidly moves forward and becomes more complex, it is important to create policies that can help patients and medical professionals be confident in the results that a test provides.

When a patient is told that they have cancer, or any other debilitating disease, they are flooded with confusion, fear, anger, and the thought, often times, of losing the life of a loved one, or their own. While their journey will undoubtedly include periods of confusion and uncertainty, they shouldn't be left to wonder if the results of a test, which their physician used to decide the course of their treatment, was right or not. Molecular tests may indeed be the key to precision medicine. I, and millions of people across this country, hope that the work of this committee will be a catalyst to accelerate getting the right medicines to the right patients at the right time.

Scientific Progress Facilitated by Molecular Tests

¹ Balogh, EP et al. Improving Diagnosis in Healthcare. Committee on Diagnostic Error in Health Care; Board on Health Care Services; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine. 2015

Past scientific and technological advancements have helped to demonstrate the potential promise of precision medicine in oncology. For example, decades ago many hematologic malignancies were classified as either simply leukemia or lymphoma. At that time the 5-year survival rate for patients diagnosed with those diseases was in the single digits. Through the advancement of microscopy techniques, researchers and physicians are now able to identify different cells and unique characteristics of cells that contribute to their abnormal growth and reclassify specific diseases. Today, there are nearly one hundred different histologically defined leukemia and lymphomas. This ability to identify different subsets of diseases allowed for treatments to be developed that were in some cases more tailored toward those specific cells and were more effective in the subgroup. Today, the number of patients that are still alive five years after their highly specified diagnosis is greater than 70%.²

While the technology is more complex, today a similar phenomenon is occurring based on the improved ability to identify molecular alterations and in some cases to develop treatments to target them accordingly. Many cancers and other diseases that had previously been grouped together are now being characterized based on the presence or absence of different molecular indicators, or biomarkers. The identification of certain biomarkers may indicate elevated risk for developing a disease, the presence of a disease, or the likelihood (or not) of responding to a treatment. In most cases, the assessment of a biomarker requires the use of a molecular test. As more and more reliance is placed upon molecular tests, both in research and routine clinical care, the importance of their accuracy cannot be understated.

Molecular Tests Are Changing the Approach to R&D

The rapid evolution of precision medicine through the identification of biomarkers and the increased utilization of molecular testing has brought a paradigm shift to the biomedical research enterprise. Molecularly defining diseases and developing new drugs that are targeted toward specific alterations

² Allison, M. Is Personalized Medicine Finally Arriving? Nature Biotech. Vol. 26 N. 5; May 2008.

has resulted in numerous compelling examples of new and more effective treatments for previously untreatable conditions.

Products such as imatinib for patients with Ph+ chronic myelogenous leukemia, trastuzumab for treating patients with HER2+ breast cancer, and crizotinib or other inhibitors toward ALK-translocated non-small cell lung cancer are all examples of targeted therapies that have transformed different types of cancers. This provides the motivation and rationale for researchers to pursue new potential drug targets, and great hope for patients waiting for potential cures. In a relatively short period of time, the movement toward precision medicine has resulted in the rapid expansion of a high-quality diagnostic testing industry, impacted care delivery practices in terms to tests that are provided to patients, changed patients' awareness of their health data, are affecting economic models for payment for medical services, and significantly shifted both the opportunities and challenges associated with developing and regulating new medicines.

It has been estimated that 87% of the oncology research pipeline is devoted to targeted therapies, of which a large proportion are used with a biomarker test.³ Among some of the most potentially transformative new therapies – those that have received FDA Breakthrough Therapy Designation – 64% have a biomarker associated with their research program.⁴ Among some of the most transformative therapies in recent years – those that have been approved after being designated as a Breakthrough Therapy – 38% have biomarker selection criteria as part of their indication.⁵

³ IMS HealthGlobal Oncology Trend Report 2015:
https://www.imshealth.com/files/web/IMSH%20Institute/Reports/Global_Oncology_Trend_Report_2015_2020/MSH_The_Oncology_Pipeline.pdf Accessed 9/14/16

⁴ Brookings Center for Health Policy – Breakthrough Therapy Designation: Exploring the Qualifying Criteria 4/24/15: <https://www.brookings.edu/wp-content/uploads/2015/03/Breakthrough-therapy-slide-deck.pdf> Accessed 9/14/16

⁵ Breakthrough Therapy Designations: <http://www.focr.org/breakthrough-therapies> Accessed 9/14/16

While the shift toward a more personalized approach to medical research and care has been enabled by molecular diagnostics, it has also presented challenges that require modifications to traditional R&D. For example, by identifying molecularly-defined subsets of disease, it is hoped that tailoring treatment to these subsets rather than the broader disease will result in the reduction of non-responders to treatment. However, due to the increasing number of disease subsets that have been identified, many of which represent less than 5% of patients with a particular cancer, this significantly reduces the number of patients who are eligible to receive a targeted therapy. When a molecular subset of a disease is a small fraction of the total number patients, it requires broad screening to identify the patients for existing targeted treatments and novel approaches to study new drugs in those settings.

To begin to address this issue directly, drawing on advances in molecular testing that enable researchers to identify clinically meaningful alterations in dozens of genes, Friends of Cancer Research is currently working with a large, diverse set of partners from academia, industry, government and advocacy to develop a modern day, innovative precision medicine clinical trial. In this project, called Lung-MAP, a “master protocol” governs how multiple drugs, from multiple companies, each targeting a different biomarker, are tested as potential treatments for lung cancer. Each arm of the study tests a different therapy that has been determined to target a unique genetic alteration. Lung-MAP utilizes cutting-edge screening technology to help identify which patient may better match each arm. This trial is creating a rapidly evolving infrastructure that can simultaneously examine the safety and efficacy of multiple new drugs.⁶ Lung-MAP provides a model for future research designs that can efficiently incorporate cutting-edge molecular testing and facilitate clinical trials that support the future of personalized medicine. This

⁶ Herbst, RS, et al. Lung Master Protocol (Lung-MAP)-A Biomarker-Driven Protocol for Accelerating Development of Therapies for Squamous Cell Lung Cancer: SWOG S1400. Clin Cancer Res. 2015 Apr 1;21(7):1514-24. doi: 10.1158/1078-0432.CCR-13-3473. Epub 2015 Feb 13.

approach will have the ability to improve enrollment, enhance consistency, increase efficiency, reduce costs, and most importantly improve patients' lives.

Current Regulation of Molecular Tests

In the case of new therapies, the Food & Drug Administration (FDA) is responsible for regulatory oversight of new drugs and to approve them before they enter the market. For molecular tests, however, the regulatory paradigm is more complex. Two broad categories of tests—those manufactured and sold as “diagnostic kits” by companies and those made and performed within a single laboratory, often called laboratory developed tests (LDTs)—have historically been treated differently by regulatory authorities. Since the 1970s, the FDA has provided regulatory oversight for kits that are manufactured and sold by companies to health professionals. Conversely, the Agency has exercised enforcement discretion in requiring premarket review for LDTs. For much of the period of FDA’s enforcement discretion, LDTs were typically manufactured in small volumes and used by laboratories housed within the same institution where patients were treated. They were largely intended for rare diseases and were a lot less prevalent in the healthcare system.

Laboratories themselves are subject to CMS regulation under the Clinical Laboratory Improvement Amendments (CLIA).⁷ The FDA approval process is designed to ensure that individual tests are properly designed and validated so that they are accurate, reliable, and clinically valid, before they are used in clinical practice whereas CLIA is designed to assure that tests are properly performed, largely through the oversight of laboratory personnel and procedures. Although both rigorous in their oversight

⁷ Weiss RL. The Long and Winding Regulatory Road for Laboratory-Developed Tests. *Am J Clin Pathol.* 2012; 138: 20-6.

processes, FDA and CLIA regulations serve very different purposes and so have different sets of regulatory requirements addressing different aspects of the quality of tests.

When this division of responsibility was set up, the methodologies and intended use of the data generated by tests regulated by FDA and those under CLIA was different.⁸ More recently, with the expansion of molecular testing and increased technical capabilities, the breadth of analytes and biomarkers for which there are LDTs and manufactured kits continues to grow. The intended use of the information generated from different tests has also evolved. Any test that produces a result that is intended to be used to guide medical decision-making should be evaluated in its clinical context for risks that may be incurred. For patients, consumers, and healthcare providers it is the information provided by the test that is important, not the place it is manufactured or how it is distributed. The regulatory framework and standards used to ensure the safety and quality of tests should reflect this principle. It is important to acknowledge concerns that have been raised about the potential consequences of an increase in oversight of molecular testing. These concerns raise the possibility that small laboratories will not have the means to handle the administrative burden of complying with new regulations. However, it is worth noting that many molecular tests are not subject to a full FDA pre-market approval application (PMA) and instead go through the FDA de novo process, which provides significant flexibility. Moreover, patients and healthcare providers need to confidently rely on a tests' results, no matter the test's origin. The presence of two separate regulatory processes and incongruent requirements has resulted in a system where certain tests with known high quality, that ought to be trusted, exist alongside a vast array of tests that remain relatively uncharacterized. This is not the reliable path to precision medicine.

⁸ US Food and Drug Administration. Draft Guidance for Industry, Food and Drug Administration Staff, and Clinical Laboratories: Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs). October, 2014.

Use Trends of Molecular Tests

An additional challenge encountered as use of molecular testing expands is the growing number of cases in which analytes being assessed by LDTs developed and performed in single labs may be identical to the analytes assessed with kits manufactured to be marketed. To better understand this current landscape, our research team, in conjunction with the Deerfield Policy Institute, conducted a study to examine trends in molecular testing of non-small cell lung cancer (NSCLC) patients with advanced-stage adenocarcinoma, with a focus on testing to detect *EGFR* mutations and *ALK*-rearrangements. Testing for these alterations is recommended by medical guidelines and both LDTs and FDA-approved tests are available. The study was just published yesterday and provides several key findings. Overall rates of testing of patients with advanced non-small cell lung cancer (NSCLC) were high: 95% (550 of 579) of patients were tested for *EGFR*, and 84% (489 of 579) were tested for *ALK*. Our study also showed that large number of patients who underwent molecular testing were tested with a non-FDA approved test. Specifically, 87% (369 of 424) for *EGFR* and 49% (195 of 399) for *ALK* were tested with an LDT, despite the availability FDA approved assays for those alterations.

While our study was not intended to assess any differences between FDA-approved tests and LDTs that are used to detect *EGFR* or *ALK* alterations, it does reveal a high prevalence of use of tests that have not been subject of FDA review. There are pros and cons to the widespread use of LDTs. On the one hand, LDTs may offer rapid technical advances and facilitate innovation in molecular testing, and have been demonstrated in some cases to offer advantages beyond existing FDA regulated alternatives.^{9,10} On the other hand, concerns exist that LDTs are not currently subjected to pre-market review by the FDA

⁹ Association for Molecular Pathology: Facts FDA Ignored: An analysis of the FDA report, “The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies” (2015). <<http://amp.org/emailads/documents/AMPResponseFDACaseReportFinal.pdf>> Accessed 9/15/16.

¹⁰ Evans J, Watson M. Genetic testing and FDA regulation: overregulation threatens the emergence of genomic medicine. *JAMA*. 2015; 313: 669-70.

and thus are not required to meet the same evidentiary standards as FDA regulated tests. Additionally, LDTs have in at least some instances been reported to perform poorly, as noted in a report of case studies released by the FDA.¹¹ The FDA's most recent safety communication warning against use of ovarian cancer screening tests is one more case where FDA premarket review would have been critical to prevent women from being exposed to tests that simply do not perform as claimed.¹² Given the large number of tests currently in use, some which have been subjected to pre-market review by FDA while others have not, there exists the potential for wide variability in test performance and claims, and the reality that some patients making major medical decisions based on inaccurate test results.^{13,14, 15}

Without a uniform regulatory approach for molecular tests, the potential for uncharacterized variability is likely to be exacerbated by rapidly advancing technology. This situation is further complicated by the fact that the traditional approach of developing a single drug with an individual test may be becoming obsolete. Testing many analytes simultaneously on a single platform is greatly preferred to testing one analyte at a time due to limitations in the quantity of patient tumor tissue available for testing and the potential for streamlining previously separate workflows. Indeed, next-generation sequencing (NGS) technology and other genomic analysis platforms that can analyze hundreds of genetic markers from the same sample are being developed and widely used at hospitals around the country. The information generated by NGS testing in clinical laboratories may be used to identify potential risk factors,

¹¹ US Food and Drug Administration: The Public Health Evidence for FDA Oversight of Laboratory Developed Tests: 20 Case Studies. <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Reports/UCM472777.pdf> Accessed 9/15/16

¹² FDA Safety Communication: <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/ucm519413.htm> Issued 9/7/15. Accessed 9/15/16

¹³ Conway P: Congressional Testimony before the Committee on Energy and Commerce, Subcommittee on Health U.S. House of Representatives. "Examining the regulation of diagnostic tests and laboratory operations." Nov 17, 2015.

¹⁴ Yorczyk A, Robinson LS, Ross TS. Use of panel tests in place of single gene tests in the cancer genetics clinic. Clin Genet 2015; 88: 278-82.

¹⁵ Polley MY, Leung SC, McShane LM, et al: An International Ki67 Reproducibility Study. J Natl Cancer Inst 2013; 105: 1897-906.

prognostic information, or predictors of adverse reactions to drugs, all of which may contribute to a larger body of evidence used by physicians to manage patient care. These powerful NGS technologies are being developed and performed in clinical laboratories whose operations are subject to oversight and accreditation, but are not subject to FDA review, meaning that a thorough review of the accuracy and reliability of the test results is not performed.

While NGS and other emerging technologies present transformational opportunities, steps should be identified to understand variability and improve consistency among different testing platforms. Several studies have shown that different platforms can frequently yield different results.^{16, 17} Due to technological capabilities and expertise residing at clinical laboratories, numerous institutions are developing and utilizing their own genetic screening platforms. While this may present the opportunity to improve time and resource efficiencies, there currently is no requirement to assess inter-institutional variability of genetic platforms. Therefore, the results of tumor molecular analysis may differ from hospital to hospital. Without new approaches to oversight it will remain difficult to assess and optimize clinical outcomes. Therefore, appropriate standards and requirements should be identified and implemented to ensure that patients are being tested with high-quality, reliable tests regardless of where the test are performed.

FDA has taken steps to begin to work with stakeholders to identify new approaches and explore how data obtained from different genetic screening platforms may be able to be compared and potential variations between platforms be better understood. This effort is part of the Obama Administration's Personalized Medicine Initiative and two draft guidance documents were recently made available for public comment.¹⁸ The agency plays a critical role in PMI; its flexible approach on NGS and work to

¹⁶ Boland, JF et al. Hum Genet 2013; 132: 1153-1163

¹⁷ Dickson, DJ, Pfeifer JD. Clin Pharmacol Ther 2016 Feb; 99(2): 186-97. Epub 2016 Jan 12

¹⁸ FDA Draft Guidances Designed to Streamline Regulatory Oversight for Next-Generation Sequencing Tests : <http://www.fda.gov/ScienceResearch/SpecialTopics/PrecisionMedicine/ucm510027.htm> Accessed 9/15/16

convene all sectors of the community will support advancing the science so innovative new NGS tests come to market, and have accurate results for patients.

Conclusion

As the members of this committee decide how best to address the regulation of molecular tests, I would like to lay out a few points that I believe are important to consider. First, the primary basis for regulations governing molecular testing should not be where a test is performed but rather what medical decisions the test is used to inform. Thus, tests that are used to guide the same medical decision making ought to be subject to the same regulatory oversight and requirements no matter where they are developed or performed. Second, medical professionals need to be able to compare the strengths and weaknesses of tests that claim to measure the same analyte(s). Currently there is no means for them to complete this task. The FDA should work with the laboratory and diagnostics industry to standardize techniques to characterize variability between tests. Third, advanced genomic screening technologies may require a regulatory framework of their own, which takes into consideration the rapid pace of technological advancement and ensures that patients have access to high quality, reliable testing. The future of precision medicine and the health and lives of patients depends on the accuracy of these tests.

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About Friends of Cancer Research



Friends of Cancer Research drives collaboration among partners from every healthcare sector to power advances in science, policy and regulation that speed life-saving treatments to patients. www.focr.org

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