"Evaluating Approaches to Diagnostic Test Regulation and the Impact of the FDA's Proposed Rule."

Testimony Before
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United States House of Representatives

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Good morning, Chair Rodgers, Chair Guthrie, Ranking Member Pallone, Ranking Member Eshoo, and Members of the Committee.

I am Jeff Allen, President & CEO, of Friends of Cancer Research, an advocacy organization dedicated to accelerating science & technology from bench to bedside. Thank you for holding this important hearing.

Complexity and Opportunity for the Future of Oncology

Over several decades, remarkable progress has been made to improve cancer research and care. In the mid-1970s, technologies were not readily available to diagnose cancer at its early and more treatable stages. Patients diagnosed with cancer were most frequently given cytotoxic chemotherapies that interrupted cell proliferation and caused cell death in attempt to manage further tumor growth to the extent possible. These treatments were unable to distinguish between cancerous cells and normal cells. The theory was that due to the hyperproliferation of cancer cells, chemotherapy would have a disproportionate impact on abnormally growing cells versus normal cells. While these medicines at times slowed the cancer's progression, the benefits were often limited and accompanied by significant toxicities for the patients. The average 5-year survival rate for those diagnosed with cancer at that time was less than 50%.[1]

By the 1990s, there was an improved understanding of the biology of cancer. Leading scientists identified molecular characteristics that were directly involved with cancerous formation and unchecked cell growth. Understanding the molecular mechanisms presented new opportunities for disrupting irregular processes by directly targeting these abnormalities to treat the cancer and spare healthy cells.

[1] Ahmedin J, Ward EM, et al. Annual Report to the Nation on the Status of Cancer, 1975–2014, Featuring Survival, *JNCI: Journal of the National Cancer Institute*,109 (9), Sept 2017 doi: 10.1093/jnci/djx030. PMID: 28376154; PMCID: PMC5409140.

This approach became the foundation for the future of precision oncology. New drugs, like imatinib (Gleevec) to treat patients with chronic myelogenous leukemia with detectable BRC-ABL1 kinase in the cancer cells or trastuzumab (Herceptin) to treat patients with breast cancer whose tumors harbored HER2 overexpression, successfully targeted cancerous cells with the specific genetic alteration. These new therapies have since demonstrated 10-year survival rates of 83%[2] and 84%[3], respectively. A unique component to these treatment modalities was the need to first correctly identify which patients had these molecular alterations through use of a diagnostic test, as those without the alteration did not respond as well. In both cases, these targeted therapies provide a substantial improvement in survival and set forth a paradigm shift in oncology.

Today's cancer research and care has significantly evolved due to the investment in biomedical research and the advancement of the technological capability focused on interrogating cancer biology at a molecular level. The therapies that patients with cancer have access to today are far more effective, but also more complex than their predecessors. In addition to chemotherapy and targeted therapies, the establishment of immunotherapies able to stimulate and enhance a patient's immune system to recognize and respond to cancerous cells has become an important part of cancer treatment. Adding to the complexity of therapeutic options, it is not unusual for a variety of diagnostic tests to be used by healthcare providers to identify elevated risks, diagnose certain conditions, inform the best treatment option, or even measure if a treatment is working.

The role of identifying patient subsets based on their genetic characteristics and tumor biology is a critical component of developing new treatments and determining which therapy or combination of

[2] Hochhaus A, Larson RA, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. *N Engl J Med*. 376(10), Mar 9, 2017. doi: 10.1056/NEJMoa1609324. PMID: 28273028; PMCID: PMC5901965.
[3] Perez EA, Romond EH, et al. Trastuzumab plus adjuvant chemotherapy for human epidermal growth factor receptor 2-positive breast cancer: planned joint analysis of overall survival from NSABP B-31 and NCCTG N9831. *J Clin Oncol*. 32(33), Nov 20, 2014. doi: 10.1200/JCO.2014.55.5730. PMID: 25332249; PMCID: PMC4226805.

therapies a patient should receive. The necessary incorporation of diagnostic testing to identify molecular alteration or biologic indicators, or biomarkers, in cancer continues to grow. For example, the proportion of patients diagnosed with lung cancer that received biomarker testing within the first 6 months of diagnosis increased from 55.3% in 2011 to 88.1% in 2021.[4] Evaluation of biomarkers in clinicals trials is also rapidly expanding. In 2000, approximately 15% of all cancer clinical trials incorporated biomarker testing compared to 55% in 2018.[5] It should also be noted that in over a quarter of all clinical trials, multiple biomarkers are included in research studies, adding to the complexity of diagnostic testing procedures required (Figure 1). The incorporation of biomarker testing has significant economic impact as well, with a current market size near $3B annually and estimated to grow to over $8B in 2032 in the U.S. alone ($34B globally) (Figure 2).[6] These technological advancements in biomarker science have led to numerous new classes of drugs, enabled access to modern diagnostics tests and treatments, and improved ability to identify patients upfront that may benefit most from a targeted therapy. Most importantly, this has coincided with an improvement in the 5-year overall survival rate among all cancers, rising 18% since the 1970s, and a reduction in U.S. cancer death rates by 33%.[7] The pace of progress has yielded increased complexity in cancer care, coupled with great hope for the future.

[4] Yan JT, Jin Y, et al. Real-World Biomarker Test Utilization and Subsequent Treatment in Patients with Early-Stage Non-small Cell Lung Cancer in the United States, 2011-2021. *Oncol Ther.* 11(3) Sept 2023. doi: 10.1007/s40487-023-00234-7. PMID: 37330972; PMCID: PMC10447355.
[5] Vadas A, Bilodeau TJ, and Oza C. Special Report: The Evolution of Biomarker Use in Clinical Trials for Cancer Treatments. https://www.thejournalofprecisionmedicine.com/the-journal-of-precision-medicine/special-report-the-evolution-of-biomarker-use-in-clinical-trials-for-cancer-treatments/ Accessed 3/15/24.
[6] Cancer Biomarkers Market Size, Growth, Trends Report 2023-2032. *Precedence Research*. https://www.precedenceresearch.com/cancer-biomarkers-market Accessed 3/15/24.
[7] Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. *CA Cancer J Clin*. 73(1) Jan 12, 2023. doi:10.3322/caac.21763

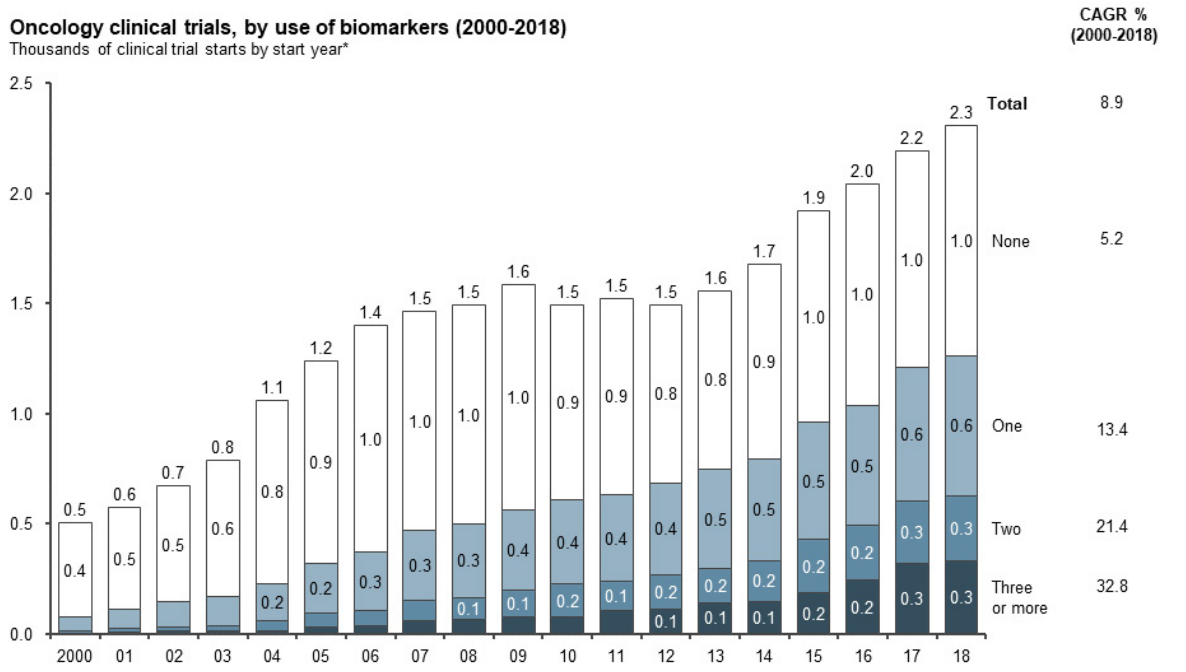

Figure 1. Incorporation of biomarker evaluation in cancer clinical trials (in thousands) by year

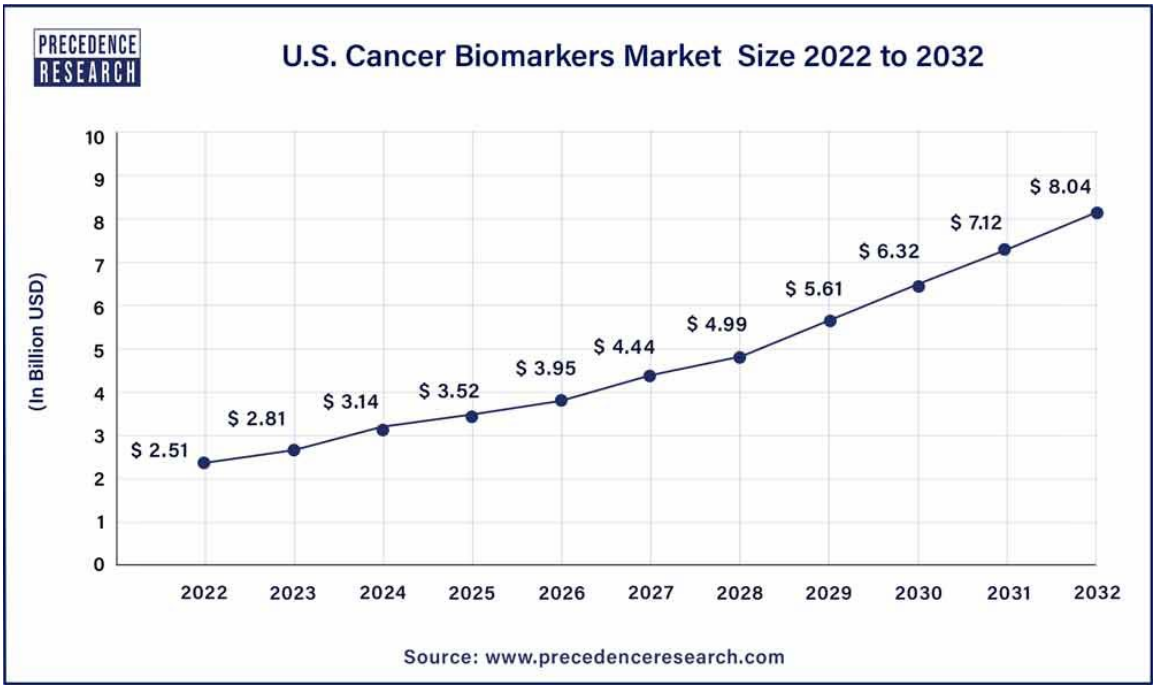

Figure 2. Projected market size for biomarker testing in the United States

Current Regulatory Paradigm

Given the role that diagnostic tests play in optimizing and determining patient care, it is imperative that these tests' performance and accuracy be well characterized before their results are used for important treatment decisions. The ramifications of uncertainty or inaccuracy can be quite significant. An inaccurate test could result in a patient not receiving the most appropriate therapy 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.[8] As the field of oncology, and precision medicine more broadly, continues to advance 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.

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 diagnostic tests, however, the regulatory paradigm was originally designed based on a different, less complex, set of technologies. 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) — are both types of in vitro diagnostics, or IVDs, but 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 healthcare professionals. Conversely, the Agency has exercised enforcement discretion for most LDTs. For much of the period of FDA's enforcement discretion, LDTs were typically manufactured in

[8] 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

small volumes and used by laboratories housed within the same institution where patients were treated. They were largely intended for rare diseases and were far less prevalent in the healthcare system.

The laboratories that establish and run LDTs are subject to CMS regulation under the Clinical Laboratory Improvement Amendments (CLIA).[9] The FDA regulatory framework under the Federal Food, Drug, and Cosmetic Act 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 laboratories properly perform tests, largely through the oversight of laboratory personnel and procedures. Although both rigorous in their oversight processes, FDA and CLIA regulations serve different purposes and as such have different sets of regulatory requirements addressing different aspects of the quality of test performance and procedures. CMS reinforced this in a recent statement it issued, emphasizing that "CMS does not have the expertise to assure that tests work."[10]

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 were different.[11] More recently, with the expansion of molecular testing and increased technical capabilities, the breadth of analytes and biomarkers for which there are LDTs continues to grow. The intended use of the information generated from different tests has also evolved. Any test that produces a result intended to guide medical decision-making should be evaluated in its clinical context for risks incurred. However, our own research indicates that there are many tests used every day for which performance and accuracy have not been independently verified. Specifically, an audit of hundreds of medical records from across the country found that nearly 30% of patients with lung cancer were evaluated for two critical biomarkers with tests

[9] Weiss RL. The Long and Winding Regulatory Road for Laboratory-Developed Tests. *Am J Clin Pathol*. 2012; 138: 20-6. PMID: 22706853 DOI:10.1309/AJCP6OAULC3CMFEJ.
[10] FDA and CMS Statement: Americans Deserve Accurate and Reliable Diagnostic Tests, Wherever They Are Made | CMS Jan 2024. Accessed 3/16/24.
[11] 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.

that had not gone through premarket review, despite the availability of an FDA approved assay for the same intended use.[12] These findings highlight that while there is increased testing for recommended biomarkers, providers may use tests with unknown performance or accuracy for treatment decisions. 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 marketed. The regulatory framework and standards used to ensure the safety and quality of tests should reflect this principle of FDA oversight for all tests.

It is important to acknowledge concerns that have been raised about the potential consequences of an increase in oversight of molecular testing. Small laboratories express concerns that they will not have the means to handle the administrative burden of complying with new regulations. Understanding the important role these results play in determining treatment for patients and their overall health in the U.S., laboratories large and small that are appropriately validating their tests should still be able to submit their tests to FDA, as many labs are submitting tests to New York State for review already. Moreover, most molecular tests are not subject to a FDA pre-market approval application (PMA) and instead go through the 510(k) and de novo process, which provides significant flexibility. 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. Without centralized oversight of all tests, it is not known how many different tests are being offered, let alone how they may perform.[13] This is not the reliable path to precision medicine.

[12] Wempe MM, Stewart MD, et. al. A National Assessment of Diagnostic Test Use for Patients with Advanced NSCLC and Factors Influencing Physician Decision-Making. *Am Health Drug Benefits*. June 2020;13(3):110-119. PMID: 32699571; PMCID: PMC7370822.

[13] Pew Charitable Trusts. 2021. The role of lab-developed tests in the in vitro diagnostics market. Available from: https://pew.org/3vuO3qC. Accessed 3/16/24.

Are all Diagnostic Tests the Same?

There is the potential for wide variability in test performance and claims given the large number of tests currently in use and a system in which some diagnostic tests have been subjected to pre-market review by FDA while others have not. The reality is that some patients may be making major medical decisions based on inaccurate test results.[14,15,16]

Without a uniform regulatory approach for molecular tests, the potential for uncharacterized variability is likely to be exacerbated by rapidly advancing and increasingly complex 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 biomarker at a time due to limitations in the quantity of patient tumor tissue available for testing, the potential for streamlining previously separate workflows, and the time lag associated with serial testing while patients wait to make important treatment decisions. 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.

Due to technological capabilities and expertise residing at clinical laboratories, numerous institutions develop and use their own molecular testing 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 analyses may differ from

[14] 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.
[15] Yorczyk A, Robinson LS, Ross TS. Use of panel tests in place of single gene tests in the cancer genetics clinic. *Clin Genet* Sept 2015; 88: 278-82. doi: 10.1111/cge.12488. Epub 2014 Oct 16. PMID: 25318351.
[16] Polley MY, Leung SC, McShane LM, et al: An International Ki67 Reproducibility Study. *J Natl Cancer Inst.* Dec 2013; 105: 1897-906. doi: 10.1093/jnci/djt306. Epub 2013 Nov 7. PMID: 24203987; PMCID: PMC3888090.

institution to institution. Without novel approaches to oversight, it will remain difficult to assess and optimize clinical outcomes. Several studies have shown that different diagnostic testing platforms can yield different results.[17,18,19] This has been observed in recent research studies designed to help provide alignment in test results.

Case Study: **TMB Testing for Patients with Cancer**

Tumor Mutational Burden (TMB) is a measure of the number of mutations in a tumor and is determined by genomic testing. TMB is increasingly being used in clinical trials and cancer care to help predict which patients are most likely to benefit from an immunotherapy. Recently, FDA approved the use of pembrolizumab, an immunotherapy, for use in patients with high TMB (defined as greater than or equal to 10 mutations per mega base) across multiple cancer types.

However, different methods for measuring and reporting TMB can lead to variability between diagnostic tests and ultimately impact treatment decisions. With unaccounted variability in tests, one test may determine that a patient is a good candidate for treatment based on test results, while the same patient could receive the opposite result from a different test and potentially not receive the treatment.

Friends of Cancer Research recently brought together 17 leading diagnostic test developers and clinical laboratories to determine and define differences in how each of their test measures and reports TMB.

[17] Boland JF, Chung CC, et al. The new sequencer on the block: comparison of Life Technology's Proton sequencer to an Illumina HiSeq for whole-exome sequencing. Hum Genet. Oct 2013;132(10):1153-63. doi: 10.1007/s00439-013-1321-4. Epub 2013 Jun 12. PMID: 23757002; PMCID: PMC4564298.
[18] Dickson DJ, Pfeifer JD. Real-world data in the molecular era-finding the reality in the real world. *Clin Pharmacol Ther.* Feb 2016;99(2):186-97. doi: 10.1002/cpt.300. Epub 2016 Jan 12. PMID: 26565654.
[19] Pfeifer JD, Loberg R, et al. Reference Samples to Compare Next-Generation Sequencing Test Performance for Oncology Therapeutics and Diagnostics. *Am J Clin Pathol.* Apr 2022;157(4):628-638. doi: 10.1093/ajcp/aqab164. PMID: 34871357.

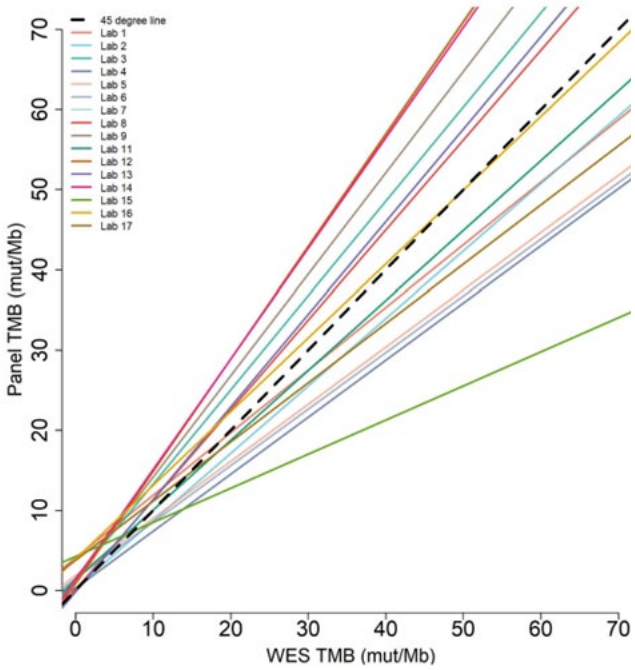

Figure 3. TMB scores reported by 17 different tests across a range of TMB values[20]

Based on the recent approval for use of an immunotherapy for cancers with a TMB score higher than 10 mut/Mb, our pilot demonstrates that some tests may underreport the number of mutations compared to other tests; and therefore, patients may unknowingly be determined as ineligible for immunotherapy from which they could benefit based on the diagnostic test rather than biology.

This pilot project demonstrated that there is variability in TMB estimates across different tests and multiple factors including panel size, gene content, and bioinformatics pipelines contribute to this

[20] Each colored line represents the results produced by different tests currently being used to assess TMB. The values on the horizontal axis are TMB levels based on a series of tumor samples that were evaluated with a uniform calculation of TMB (this was the common reference standard). The corresponding TMB for the same samples as determined by each participating test is on the vertical axis. If each test matched the reference TMB all lines would overlap at the black-dashed line.

variability.[21,22] The results from this study are not meant to indicate that any of the participating tests are inaccurate, but rather utilize different methodologies for estimating TMB levels that may need to be accounted for. Furthermore, with improved transparency in performance metrics, calibration of different tests and alignment of validation studies could ensure accurate interpretation of data from multiple tests based on how they relate to one another and not the assumption that all test results are the same.

Harmonization of TMB assessment across tests and laboratories is essential for reliable and reproducible use of TMB as a clinical biomarker of response to immunotherapy.

Case Study: **HRD Testing for Patients with Ovarian Cancer**

Homologous Recombination Deficiency (HRD) is a biomarker with promise in identifying patients with certain cancers who are more likely to benefit from PARP inhibitors and other DNA repair targeting drugs. Assay developers may use and combine different factors to define HRD using NGS testing. It is essential that tests determining HRD status provide consistent results for providers and patients to ensure patients receive appropriate treatments.

The HRD Harmonization Project is a unique research partnership focused on understanding the variability in HRD assay outputs and developing strategies to align methodology for measuring and using HRD to determine the treatment a patient receives. This collaborative project compared outputs from 17 HRD assays performed on a common set of ovarian cancer samples to measure HRD status. These

[21] Merino DM, et al. Establishing guidelines to harmonize tumor mutational burden (TMB): in silico assessment of variation in TMB quantification across diagnostic platforms: phase I of the Friends of Cancer Research TMB Harmonization Project. *J Immunother Cancer*. 2020 Mar;8(1):e000147. doi: 10.1136/jitc-2019-000147. PMID: 32217756; PMCID: PMC7174078.

[22] Vega DM, et al. Aligning tumor mutational burden (TMB) quantification across diagnostic platforms: phase II of the Friends of Cancer Research TMB Harmonization Project. *Ann Oncol*. 2021 Oct 1:S0923-7534(21)04495-1. doi: 10.1016/j.annonc.2021.09.016. Epub ahead of print. PMID: 34606929.

findings provide an initial step toward understanding the extent of variability in HRD assays and serve as a foundation for HRD assay alignment and optimal use.

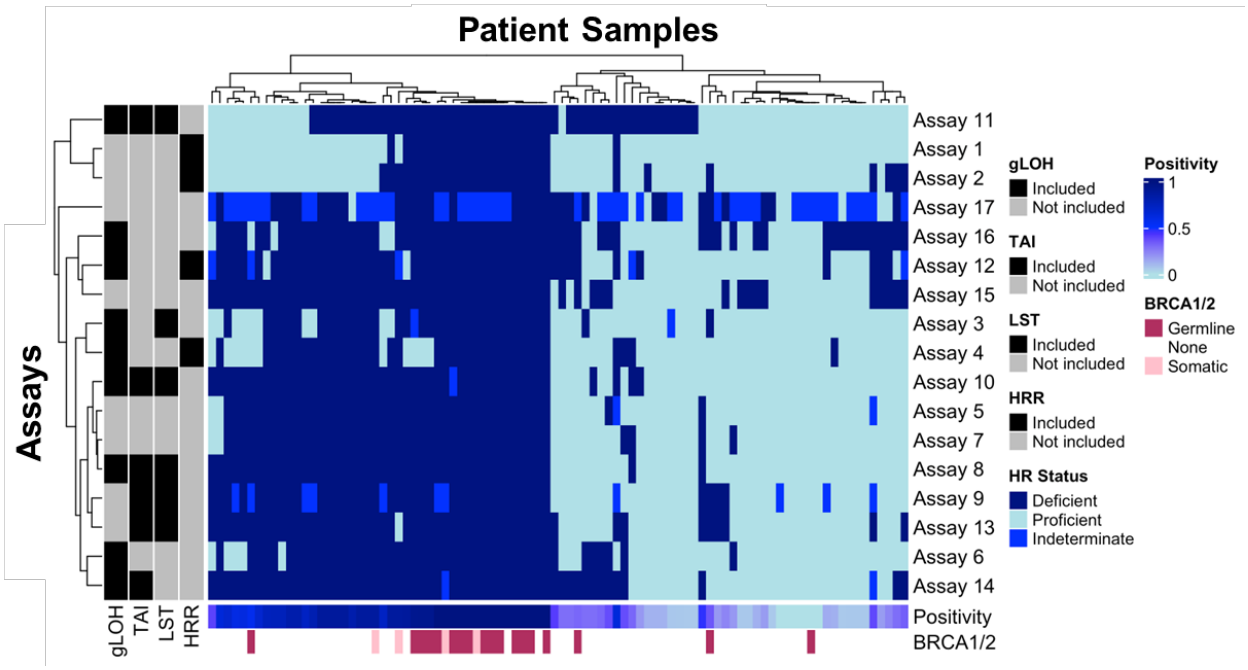

Figure 4. HRD determination reported by 17 different tests evaluating a common set of ovarian cancer tumor samples[23]

Each of these pilot projects were collaborative partnerships among leading experts from academic and clinical research, diagnostic test developers, drug developers, government, laboratories, and patient advocates. The purpose of each project was not to identify if one test had improved performance versus another. It also was not designed to evaluate performance as it related to test status (LDT or FDA approved). Instead, they were intended to describe whether different tests with similar intended use produced variability in results based upon a common set of samples. This transparency in performance

[23] Each column represents an individual in silico patient sample with the results produced by different tests that assess HRD. Each horizontal row is the results from one of 17 different assays. Dark blue represents HRD(+) and light blue indicates samples estimated to be HRD(-) If all assays reported the same result for a sample, the column would be the same shade of blue from top to bottom.

could allow for identification of potential sources of variability, estimation of the potential significance of expected/unexpected variability, and presents the opportunity for future alignment, as appropriate. Each represents significant collaboration and a joint commitment to science, optimal test performance, and patient care. As future policies are considered, improved transparency of test performance would help identify and manage potential variability in results and ensure consistency in the information being utilized by patients and healthcare providers.

Diagnostic Test Assurance for the Future

Over the last several years, the need for modernizing the regulatory framework for quality assurance of diagnostic testing has been acknowledged and attempted to be addressed. Most recently the Verifying Accurate Leading-Edge IVCT Development Act (VALID Act) has been considered, iterations of which have been introduced under bipartisan leadership (2020[24], 2021[25], 2022[26] and 2023[27]). Consideration of this approach saw extensive and transparent discussions for several years, multiple rounds of review from interested stakeholders, and deliberations were complete with thoughtfulness and compromise. The approach is intended to set forth a flexible framework specifically tailored to the subset of medical devices of diagnostic testing technologies and create a level playing field for all tests independent of where they are developed, based upon the risk associated with the diagnostic test and the results it provides. It would also set forth a series of innovative mechanisms, such as a pre-certification program, that would be available to the many highly qualified clinical laboratories across the country to establish a minimally burdensome mechanism for test quality assurance. There would be requirements for listing all

[24] S.3404 - 116th Congress (2019-2020): VALID Act of 2020 | Congress.gov | Library of Congress
[25] S.2209 - 117th Congress (2021-2022): VALID Act of 2021 | Congress.gov | Library of Congress
[26] Text - S.4348 - 117th Congress (2021-2022): FDASLA Act of 2022 | Congress.gov | Library of Congress
[27] H.R.2369 - 118th Congress (2023-2024): VALID Act of 2023 | Congress.gov | Library of Congress

tests to finally provide FDA with a clear understanding of the tests that are used in medical practice in conjunction with the necessary authorities to request additional information or take steps to mitigate potential risks, should such action be necessary. This approach would provide the framework for the future by establishing a quality assurance floor for the performance of all tests, while ensuring an open ceiling to foster future innovation in diagnostic testing.

In the absence of a modern framework established by Congress, and the public health risk mounting without action, FDA moved forward with the public process for rulemaking to clarify the existing authority and regulatory requirements to help ensure the safety and effectiveness of LDTs through the Proposed Rule Medical Devices; Laboratory Developed Tests.[28] This should come as no surprise, as FDA has made it clear for years that if Congressional action did not occur, the complexity of diagnostic testing and potential public health implications warrants FDA action. It should be noted that nothing precludes Congress from continuing to work on a legislative approach, as FDA continues working to finalize its proposed rule.

As future policy is developed, we encourage policymakers to consider several key areas:

- Establish uniform performance standards, regulatory processes, and transparency for all diagnostic tests to ensure accuracy of results.
- Ensure that efficient and timely access to clinical trials is supported for instances that a diagnostic test is required for patient identification, particularly for patients with rare cancers.
- Implement processes that enable efficient incorporation of modifications to tests.
- Identify strategies to streamline validation of tests in instances of well characterized biomarkers and/or the existence of numerous tests with a similar intended use.

[28] Docket No. FDA-2023-N-2177

It is a period of remarkable opportunity and advancement to improve the lives of patients with cancer and many other diseases. However, maintaining the status quo will propagate uncertainty, risk inconsistency, and further an environment where potentially underperforming tests are unknowingly undetected at the detriment to patients and future innovations due to a lack of transparent processes. Furthermore, we urge Congress to provide the resources necessary for FDA to effectively implement the necessary oversight and policy modifications that reflect the current state science, are conducive to the rapid pace of technological advancement, and ensures that patients have access to high quality, reliable testing. Action to ensure performance quality and test accuracy is needed, and progress to that end can no longer be stalled. The future of precision medicine and the health and lives of patients depends on the accuracy of these tests.

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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. We are working to accelerate policy change, support groundbreaking science, and deliver new therapies to patients quickly and safely.

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