Attachment — Additional Questions for the Record

Jeff Allen – Friends of Cancer Research

The Honorable Gus Bilirakis

1. How do you believe this rule could negatively impact the development and production of LDT screening solutions for cancer patients?

The FDA Final Rule on Laboratory Developed Tests (LDTs) clarifies the FDA's approach to regulating such products. Because most LDTs have been subject to enforcement discretion for many years, FDA's intention to phase out enforcement discretion may result in concerns about new processes and the potential burdens of compliance. However, I don't believe that the rule will result in a net negative for the development of screening solutions for patients for several reasons:

1) Multiple developers of cancer screening tools (labs and test kit developers) have been successfully approved through the FDA and/or developers are currently working with the Agency toward that goal.
2) While FDA approval is not an automatic qualifier for public or private payers to cover a technology, it does provide a level of quality assurance that can help support coverage decisions for reimbursement.
3) Patients and providers should have greater confidence in the results provided by screening tests that have been reviewed by the FDA. Reliable accuracy can help boost broad utilization by individuals to receive the best, most tailored treatment, and help clinical programs effectively implement screening programs for preventive services.

The Honorable Frank Pallone, Jr.

1. FDA previously used enforcement discretion, meaning that the agency generally has not enforced applicable requirements with respect to most LDTs. Can you explain why that approach was appropriate at that time and why this is no longer the appropriate approach?
    a. What consequences do you think patients will face if the status quo remains?

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 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.

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 number of LDTs used in clinical practice far exceeds those that have gone through independent review for performance

standards (e.g. FDA, NY State CLEP). While this is not an immediate indicator of problematic tests, the lack of uniform quality assurance regarding tests regularly used to guide medical decision-making leaves the potential for suboptimal tests to unknowingly be used in practice with no way of identifying when an inaccurate result is provided or the ability for any regulatory authority to take corrective action.

The intended use of the information generated from different tests has also evolved. Because increasingly complex tests are more regularly part of diagnosis, evaluation, and treatment determination for many health conditions, such as cancer, the risks associated with a potentially inaccurate test result is generally higher than it was in the past. Any test that produces a result intended to guide medical decision-making should be evaluated in its clinical context for risks incurred. To protect patients relying on these results, there should be uniform standards and policies for all tests regardless of where they are developed.

The Honorable Nanette Barragán

1. Dr. Allen, inaccurate test results can lead to delays in necessary treatments or a misdiagnosis and unnecessary treatment. How have the use and volume of laboratory developed tests changed over time such that the regulation of these tests also needs to change?
    a. What are the gaps in CMS's current regulatory ability to evaluate laboratory developed tests and how would FDA regulation fill in these gaps?

The total volume of laboratory developed tests (LDTs) is difficult to estimate across the U.S. because there is no centralized agency or organization with access to that information. This also exemplifies the challenge of identifying any underperforming tests and significantly impedes the ability for corrective action or protective measures to be taken. Having a reporting system and registration process as described in the FDA Final Rule (and proposed in the VALID Act) would fill this significant void in public health oversight. In addition, the intended use of the information generated from different tests, including LDTs, has become increasingly complex. For example, tests that can evaluate numerous molecular alterations are regularly a part of diagnosis, evaluation, and treatment determination for many health conditions, such as cancer. The risks associated with a potentially inaccurate test result is generally higher than it was in the past, therefore the regulatory processes to assure the accuracy of tests needs to reflect the current state of testing technology and application of their results.

The laboratories that establish and run LDTs are subject to CMS regulation under the Clinical Laboratory Improvement Amendments (CLIA). CLIA is designed to assure that laboratories operate properly, largely through the oversight of laboratory personnel and procedures. The FDA regulatory framework under the Federal Food, Drug, and Cosmetic Act is designed to ensure that individual tests performed within these laboratories are properly designed and validated so that they are accurate, reliable, and clinically valid, before they are used in clinical practice. 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." The regulations in the FDA Final Rule would ensure that medical and technical experts at the FDA who have experience with evaluating diagnostic test performance (for IVDs and the subset of LDTs that have been submitted to FDA) and assisting developers during development will be able to ensure that all tests, no matter where they are developed, are held to the same performance standards.

2. Dr. Allen, you noted in your testimony that there has been an increase in the use of biomarker testing in clinical trials. These biomarkers help predict which patients are most likely to benefit from a particular treatment. Can you explain why there are wide differences between certain biomarker tests, and therefore differences in research results?
    a. How can FDA regulation of laboratory developed tests help improve standardization of biomarker tests and improve healthcare research?

As biomarkers and tests used to identify them become increasingly complex, there may be an increased chance for variability in the results provided. For example, in two recent pilot projects that we conducted, the assays used to calculate biomarker levels, [1,2] or the genetic variants that were measured as part of determining biomarker status, were different across tests with a similar intended use.[3]

Establishing uniform policies that apply to all tests will improve the transparency of performance metrics and allow the identification of tests that yield different results. It should be noted that a different result is not always an indicator of an inaccurate result but highlights the need for test results to be interpreted in the appropriate context. Improving transparency and assurance of accuracy will ensure that the important results yielded by diagnostics tests will be best applied to patient care.

3. Dr. Allen, there are concerns that the current system actually disincentivizes innovation. A developer can develop and validate a test and face immediate competition from an LDT that makes the same claims, or even claims superior performance, without having to demonstrate that these claims are true. In the case of CellMax, a diagnostics company, they were forced to discontinue tests for colon cancer screening because it faced competition from a flood of LDTs. What incentive do developers have to develop tests given the non-level playing field that CalMac and others are experiencing?

A level playing field as created by the FDA Final Rule can help install predictability for test compliance and reduce uncertainty in the marketplace. With FDA having comprehensive overview of all tests being used in practice, it will raise the floor regarding test performance and ensure that appropriate communication of test performance is

[1] 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.
[2] 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.
[3] Homologous Recombination Deficiency (HRD) Harmonization Project: https://friendsofcancerresearch.org/hrd/ *Results presented publicly and in progress to submit for publication.*

conducted. This can help reduce misinformation from being used as a marketing technique to displace competition and allow tests that are successfully validated to be able to compete on their merits, and most importantly protect the people that are relying on the results of tests being used in clinical care.